



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/976,279	04/09/2019	10251875	102843.0006US2	1256

149344 7590 03/20/2019
Umberg Zipser LLP
1920 Main Street Suite 750
Irvine, CA 92614

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (<http://pair.uspto.gov>).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site <http://pair.uspto.gov> for additional applicants):

Navneet Puri, Lebanon, NJ;
Nevakar Inc., Bridgewater, NJ;
Prem Sagar Akasapu, Edison, NJ;
Irfan A. Mohammed, Cherry Hill, NJ;
Kumaresh Soppimath, Skillman, NJ;
Iouri V. Ilitchev, Hillsborough, NJ;
Tao Zhang, Towaco, NJ;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

149344 7590 01/31/2019
Umberg Zipser LLP
1920 Main Street Suite 750
Irvine, CA 92614

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/976.279	05/10/2018	Navneet Puri	102843.0006US2	1256

TITLE OF INVENTION: Atropine Pharmaceutical Compositions

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$500	\$0.00	\$0.00	\$500	04/30/2019

EXAMINER	ART UNIT	CLASS-SUBCLASS
CHU, YONG LIANG	1629	514-304000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Umberg Zipser LLP
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Nevakar Inc.

Bridgewater, NJ

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. Fees submitted: ☒ Issue Fee ☒ Publication Fee (if required) ☐ Advance Order - # of Copies _____

4b. Method of Payment: (Please first reapply any previously paid fee shown above)

☒ Electronic Payment via EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Martin Fessenmaier/

Date February 7, 2019

Typed or printed name Martin Fessenmaier

Registration No. 46697

Electronic Patent Application Fee Transmittal

Application Number:	15976279			
Filing Date:	10-May-2018			
Title of Invention:	Atropine Pharmaceutical Compositions			
First Named Inventor/Applicant Name:	Navneet Puri			
Filer:	Martin Fessenmaier/Danielle Moroz			
Attorney Docket Number:	102843.0006US2			
Filed as Small Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	2501	1	500	500

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				500

Electronic Acknowledgement Receipt

EFS ID:	35091387
Application Number:	15976279
International Application Number:	
Confirmation Number:	1256
Title of Invention:	Atropine Pharmaceutical Compositions
First Named Inventor/Applicant Name:	Navneet Puri
Customer Number:	149344
Filer:	Martin Fessenmaier/Danielle Moroz
Filer Authorized By:	Martin Fessenmaier
Attorney Docket Number:	102843.0006US2
Receipt Date:	07-FEB-2019
Filing Date:	10-MAY-2018
Time Stamp:	16:53:32
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	\$ 500
RAM confirmation Number	020819INTEFSW16535500
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	IssueFee_PartB.pdf	121436	no	1
			6fae4483fc00d46e8fbbc1d209877451eca39640		
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30029	no	2
			aa3346c6cfb07c33baceec5e434dc2434eaccf810		
Warnings:					
Information:					
Total Files Size (in bytes):			151465		
This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503. <u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application. <u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course. <u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.					



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www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

149344 7590 01/31/2019
Umberg Zipser LLP
1920 Main Street Suite 750
Irvine, CA 92614

EXAMINER

CHU, YONG LIANG

ART UNIT

PAPER NUMBER

1629

DATE MAILED: 01/31/2019

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/976,279	05/10/2018	Navneet Puri	102843.0006US2	1256

TITLE OF INVENTION: Atropine Pharmaceutical Compositions

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$500	\$0.00	\$0.00	\$500	04/30/2019

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

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Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

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149344 7590 01/31/2019
Umberg Zipser LLP
1920 Main Street Suite 750
Irvine, CA 92614

Certificate of Mailing or Transmission

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(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/976.279	05/10/2018	Navneet Puri	102843.0006US2	1256

TITLE OF INVENTION: Atropine Pharmaceutical Compositions

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EXAMINER	ART UNIT	CLASS-SUBCLASS
CHU, YONG LIANG	1629	514-304000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,

1 _____

(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. Fees submitted: ☐ Issue Fee ☐ Publication Fee (if required) ☐ Advance Order - # of Copies _____

4b. Method of Payment: (Please first reapply any previously paid fee shown above)

☐ Electronic Payment via EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. Change in Entity Status (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

☐ Applicant changing to regular undiscounted fee status.

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NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____

Date _____

Typed or printed name _____

Registration No. _____



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/976,279	05/10/2018	Navneet Puri	102843.0006US2	1256
149344	7590	01/31/2019	EXAMINER	
Umberg Zipser LLP 1920 Main Street Suite 750 Irvine, CA 92614			CHU, YONG LIANG	
			ART UNIT	PAPER NUMBER
			1629	
DATE MAILED: 01/31/2019				

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 15/976,279	Applicant(s) Puri et al.	
	Examiner YONG L CHU	Art Unit 1629	AIA Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to teh amendment filed 12/19/2018.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☒ The allowed claim(s) is/are 1-20. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a) ☐ All b) ☐ Some *c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. _____.

3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file areply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892) 2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____. 3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____. 4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.	5. ☒ Examiner's Amendment/Comment 6. ☐ Examiner's Statement of Reasons for Allowance 7. ☐ Other _____.

/YONG L CHU/
Primary Examiner, Art Unit 1629

DETAILED ACTION

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Claims 1 and 18-20 have been amended. Claims 1-20 are pending in the instant application and under examination on the merits.

Declaration under Rule 37 C.F.R. §1.132

Applicants' submission of the Declaration under Rule 37 C.F.R. §1.132, filed on 12/19/2018 has been entered.

Response to Amendment

The Amendments by Applicants' representative Dr. Martin Fessenmaier filed on 12/19/2018 has been entered.

Response to Arguments/Amendments

Claim rejection under 35 U.S.C. §112(b)

Applicants' amendments to claims 1 and 18-20 obviates the rejection. The rejection is hereby **withdrawn**.

Claim rejection under 35 U.S.C. §103(a)

Applicants' arguments with support of the 132 Declaration and the amendment have been fully considered, and are sufficient to overcome the rejection. The rejection is hereby **withdrawn**.

Examiner's Amendment

An Examiner's amendment to the record with the authorization by Applicants' representative Dr. Martin Fessenmaier on 01/25/2019 appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37

CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

The application has been amended as following:

Claim 1, the last two lines of the claim, **after** "0.35% tropic acid formed from degradation of the atropine", **DELETE** "and has a pH of between 5.0 and 6.0".

Conclusions

- Claims 1-20 are allowed.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Chu, whose telephone number is (571)272-5759. The examiner can normally be reached on M-F 7:00am-4:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey S. Lundgren can be reached on 571-272-5541. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Status Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/YONG L CHU/
Primary Examiner, Art Unit 1629

<i>Search Notes</i> 	Application/Control No. 15/976,279	Applicant(s)/Patent Under Reexamination Puri et al.
	Examiner YONG L CHU	Art Unit 1629

CPC - Searched*		
Symbol	Date	Examiner
A61K31/46	01/25/2019	YC
A61K9/0048	01/25/2019	YC
A61K9/08	01/25/2019	YC
A61K47/02; 38; 183	01/25/2019	YC

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
514	304	01/25/2019	YC

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
EAST	11/27/2018	YC
STN	11/27/2018	YC
ODP search	11/27/2018	YC
Google search	11/27/2018	YC
EAST	01/25/2019	YC
Google search	01/25/2019	YC

/YONG L CHU/ Primary Examiner, Art Unit 1629	

<i>Search Notes</i> 	Application/Control No. 15/976,279	Applicant(s)/Patent Under Reexamination Puri et al.
	Examiner YONG L CHU	Art Unit 1629

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
See search report		01/25/2019	YC

/YONG L CHU/ Primary Examiner, Art Unit 1629	

Issue Classification 	Application/Control No. 15/976,279	Applicant(s)/Patent Under Reexamination Puri et al.
	Examiner YONG L CHU	Art Unit 1629

CPC						
Symbol					Type	Version
A61K	/	31	/	46	F	2013-01-01
A61K	/	9	/	0048	I	2013-01-01
A61K	/	47	/	38	I	2013-01-01
A61K	/	47	/	02	I	2013-01-01
A61K	/	47	/	183	I	2013-01-01
A61K	/	9	/	08	I	2013-01-01

CPC Combination Sets					
Symbol				Type	Version
	/		/		

NONE (Assistant Examiner) _____ (Date) _____		Total Claims Allowed: 20	
/YONG L CHU/ Primary Examiner, Art Unit 1629 (Primary Examiner) _____ (Date) _____		O.G. Print Claim(s) 1	O.G. Print Figure None

Issue Classification 	Application/Control No. 15/976,279	Applicant(s)/Patent Under Reexamination Puri et al.
	Examiner YONG L CHU	Art Unit 1629

INTERNATIONAL CLASSIFICATION					
CLAIMED					
A61K	/	31	/	46	
A61K	/	9	/	00	
A61K	/	9	/	08	
A61K	/	47	/	02	
A61K	/	47	/	18	
A61K	/	47	/	38	
NON-CLAIMED					
	/		/		

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS
514	304

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

NONE (Assistant Examiner) _____ (Date) _____		Total Claims Allowed: 20	
/YONG L CHU/ Primary Examiner, Art Unit 1629 (Primary Examiner) _____ (Date) _____		O.G. Print Claim(s) 1	O.G. Print Figure None

Issue Classification 	Application/Control No. 15/976,279	Applicant(s)/Patent Under Reexamination Puri et al.
	Examiner YONG L CHU	Art Unit 1629

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47															
CLAIMS															
Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original

NONE (Assistant Examiner) _____ (Date) _____		Total Claims Allowed: 20	
/YONG L CHU/ Primary Examiner, Art Unit 1629 (Primary Examiner) _____ (Date) 25 January 2019		O.G. Print Claim(s) 1	O.G. Print Figure None



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BIB DATA SHEET

CONFIRMATION NO. 1256

SERIAL NUMBER 15/976,279	FILING or 371(c) DATE 05/10/2018 RULE	CLASS 514	GROUP ART UNIT 1629	ATTORNEY DOCKET NO. 102843.0006US2
APPLICANTS Nevakar Inc., Bridgewater, NJ; INVENTORS Navneet Puri, Lebanon, NJ; Prem Sagar Akasapu, Edison, NJ; Irfan A. Mohammed, Cherry Hill, NJ; Kumaresh Soppimath, Skillman, NJ; Iouri V. Ilitchev, Hillsborough, NJ; Tao Zhang, Towaco, NJ;				
** CONTINUING DATA ***** This appin claims benefit of 62/505,027 05/11/2017 ** FOREIGN APPLICATIONS ***** ** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** ** SMALL ENTITY ** 06/04/2018				
Foreign Priority claimed ☐ Yes ☒ No 35 USC 119(a-d) conditions met ☐ Yes ☐ No Verified and Acknowledged <u>/YONG LIANG CHU/</u> Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY NJ	SHEETS DRAWINGS 1	TOTAL CLAIMS 20
ADDRESS Umberg Zipser LLP 1920 Main Street Suite 750 Irvine, CA 92614 UNITED STATES		**The Drawings are accepted.** /YONG CHU/ 01-25-2019		
TITLE Atropine Pharmaceutical Compositions				
FILING FEE RECEIVED 865	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:		☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit	

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
P.O. BOX 1450
ALEXANDRIA, VA 22313-1450**

Appl No.: **15/976,279**
Applicant: **Navneet Puri**
Filing Date: **05/10/2018**
Art Unit: **1629**
Examiner: **CHU, YONG LIANG**
Attorney Docket No.: **102039.0006US2**

Title **Atropine Pharmaceutical Compositions**

Mail Stop Amendments
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO OFFICE ACTION

Sir:

This paper responds to the Office Action dated December 4, 2018. Please enter the amendments shown herein.

- Claim amendments begin on page 2.
- Remarks begin on page 5.
- A declaration under 37 CFR1.132 is attached to this submission.

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
P.O. BOX 1450
ALEXANDRIA, VA 22313-1450**

**Appl No.: 15/976,279
Inventor: Navneet Puri
Filing Date: 05/10/2018
Art Unit: 1629
Examiner: CHU, YONG LIANG
Attorney Docket No.: 102039.0006US2**

Title Atropine Pharmaceutical Compositions

**Mail Stop Amendments
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450**

DECLARATION UNDER 37 C.F.R. § 1.132

I, the undersigned, Valentino J. Stella hereby declare as follows:

1. I am a Distinguished Professor Emeritus in Pharmaceutical Chemistry at the University of Kansas, where I taught from 1973 until December 2016. I am presently retired but continue to consult and write scholarly papers.
2. I have a B. Pharm. degree from the Victorian College of Pharmacy (now Monash University), Melbourne, Australia, which I received in 1968, and a Ph.D. in Analytical Pharmaceutical Chemistry and Pharmaceutics from the University of Kansas, Lawrence, Kansas, which I received in 1971.
3. Since graduating with my PhD from the University of Kansas in 1971, I spent my entire career studying and teaching physical and organic chemistry in Schools of Pharmacy at both the UG and graduate level, particularly as they affect drug stability and delivery. I

am considered one of the most knowledgeable people in the world on drug stability issues.

4. Two of the primary issues affecting drug delivery are the solubility and stability of the molecule. I have reviewed thousands of molecules and drug formulations over the years in an effort to ensure or improve their solubility/stability profile, on an academic basis, as a consultant to the pharmaceutical industry (>200 companies) and for the three drug companies that I co-founded.
5. I have authored or co-authored numerous peer reviewed articles on subjects relating to drug stability and solubility, in addition to the following text books on the subject, among others:

Prodrugs: Challenges and Rewards, Stella V. et al. (Springer 2007)

Stability of Drugs and Dosage Forms, Yoshioka S. and Stella V.J. (Klewer Academic/Plenum Pub. 2000), now published by Springer.

Chemical Stability of Pharmaceuticals: A Handbook for Pharmacists, Connors K. et al. (2d Ed.) (Wiley & Sons 1986)

6. In addition, I have over 45 US issued patents and am the inventor or co-inventor of the approved FDA drugs fosphenytoin (Cerebyx[®]), Viread[®], Lusedra[®], the formulation covering Velcade[®], fosnetupitent (Akyneo[®] injectable) and Tavalisse[®], as well as Captisol[®], the solubilizer used in the injectable forms of Vfend[®], Geodon[®], Abilify[®], Nexterone[®], Kyprolis (carfilzomib)[®], Noxafil-IV[®] and Cerenia and four other products.
7. I am not an inventor in the above referenced application, nor have a position at Nevakar, Inc., the assignee of this application. I have, on occasions, provided consulting for Nevakar on a number of projects.
8. In connection with this declaration, I have reviewed the above noted patent application, the Office Action, and the cited reference (WO 2016/172712) in detail, bringing to bear my knowledge of one who is skilled in the relevant art of all aspects of the pharmaceutical chemistry, especially in the field of stability of pharmaceutically active ingredients.

9. With respect to the above referenced examination, I hereby declare the following:
10. Chemical stability of atropine in unbuffered aqueous solutions is problematic since its chemical stability is highly pH dependent, particularly where the atropine is present at pH values higher than 4.0.
11. The WO 2016/172712 publication teaches that the chemical stability of atropine is improved by use of D₂O (or heavy water) in place of H₂O. The greater chemical stability of atropine is likely due to significantly reduced base catalyzed hydrolysis in the presence of D₂O. The WO 2016/172712 publication does not give any other indication how atropine can be stabilized at low concentrations in the absence of D₂O.
12. D₂O, often referred to as heavy water, is not an "aqueous" solution as that term is used by both those skilled in the art or by experts. When one refers to an aqueous solution, one is referring to H₂O.
13. The skilled artisan would have little to no expectation of success that chemical stability of atropine at a low concentration could be improved in aqueous solutions by use of low buffer concentration and the presence of a chelator in the absence of D₂O. Such is particularly true where the buffer has a low concentration and the chelator has a low concentration.
14. Upon review of the WO 2016/172712 publication and given the known stability problems of atropine at higher pH (such as pH5.0-6.0), the skilled artisan would not have been motivated to engage in routine experimentation to find a buffer and a chelator at respective concentrations that would increase atropine stability, let alone in the presence of a viscosity modifier. The data in the WO 2016/172712 publication clearly establish that D₂O is the critical factor in atropine stability since no data is presented in its absence.

///

Executed at Lawrence, KS, this 18th day of December, 2018.

By: 
(Valentino J. Stella, Distinguished Professor Emeritus and Consultant)

Electronic Acknowledgement Receipt

EFS ID:	34646740
Application Number:	15976279
International Application Number:	
Confirmation Number:	1256
Title of Invention:	Atropine Pharmaceutical Compositions
First Named Inventor/Applicant Name:	Navneet Puri
Customer Number:	149344
Filer:	Martin Fessenmaier/olimpia jakubowska
Filer Authorized By:	Martin Fessenmaier
Attorney Docket Number:	102843.0006US2
Receipt Date:	19-DEC-2018
Filing Date:	10-MAY-2018
Time Stamp:	21:41:36
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		2018_12_18Response_02_nonfinal_12_04_18_OA.pdf	152686	yes	10
			558eab535f08fc8cd0a3babe2b87469aa1fb102		

Multipart Description/PDF files in .zip description					
Document Description			Start	End	
Applicant Arguments/Remarks Made in an Amendment			5	10	
Claims			2	4	
Amendment/Req. Reconsideration-After Non-Final Reject			1	1	
Warnings:					
Information:					
2	Miscellaneous Incoming Letter	2018_12_18_Executed_Declaration_under_37_CFR_1_132.pdf	257056	no	3
			459c321000dd06e4e8af377d348cee085a27db8b		
Warnings:					
Information:					
Total Files Size (in bytes):			409742		
This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503. <u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application. <u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course. <u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.					

REMARKS/ARGUMENTS

Claim Amendments

By this amendment, claims 1 and 18-20 are amended. No new matter has been added by these amendments. After entry of these amendments, Claims 1-20 will be pending.

35 USC §112 (Claims 18-20)

The Office rejected claims 18-20 as being indefinite for failing to particularly point out and distinctly claim the subject matter as it relates to the phrase “substantially free of a preservative”. Applicant amended claims 18-20 to recite a specific numeric value as expressed in the specification and noted by the Office. Support for the amendment can be found in [0056] of the specification as originally filed. The rejection should therefore be overcome.

35 USC §103 (Claims 1-20)

The Office rejected claims 1-20 as being obvious over WO 2016/172712 ("the ‘712 publication"), which claims priority to U.S. Provisional Patent Application 62/151,926 (filing date April 23, 2015), and which issued as U.S. Patent No. 9,421, 199. The Applicant respectfully disagrees, especially in view of amendments herein.

(a) At the outset, applicant wishes to point out that the PHOSITA would have known at the time of filing that atropine sulfate is subjected to a greater degree of hydrolysis in solutions that are closer to neutral and basic pH conditions. Moreover, the PHOSITA would also have known that degradation of atropine to tropic acid in aqueous solution is notably accelerated with reduced concentrations of atropine (*e.g.*, US 9421 199; see specification [0008]; see Declaration at ¶ 10).

Such stability issues were also well known to the inventors of the ‘712 publication. More specifically, on [00370] that inventors of the ‘712 publication state that “...more degradation is observed in the formulations that start at a higher pH. This degradation is predominantly the growth of tropic acid...”

To address the difficulties associated with stability of atropine in low concentrations, inventors of the ‘712 publication unexpectedly discovered that D₂O in place of H₂O as a solvent

for such low dose formulations provided superior stability. The '712 publication is replete with teachings and examples that establish that D₂O is *the* determinant factor in increasing atropine stability. For example, the '712 publication reads in pertinent parts: "...the present disclosure recognizes that deuterated water stabilizes ophthalmic compositions..." or "...deuterated water also stabilizes atropine sulfate...". The '712 publication does not give any other indication how atropine can be stabilized at low concentrations in the absence of D₂O. See *e.g.*, Abstract, [0003], [0079-0080], [0108], [0138], [0141-0142], [0380], [0406], claims 1-20, etc. See also Declaration at ¶ 11.

In other words, the atropine stability problem known to the PHOSITA was addressed by the inventors of the '712 publication by replacement of H₂O with D₂O, and the '712 publication provides ample examples to that effect. See *e.g.*, Tables 16 and 25A/B depicting comparative results between of H₂O with D₂O with regard to formation of tropic acid.

(b) With respect to the fact that the '712 publication does not teach a formulation that also includes, *inter alia*, a buffer agent and EDTA as presently claimed, the Examiner noted that the '712 publication would teach

"...an aqueous low-dose ophthalmic atropine composition comprising atropine at 0.001-0.05 wt%, a buffer, a tonicity agent of NaCl, and a preservative such as benzalkonium chloride, or cetrimonium sodium perborate sufficient to prevent the growth of or destroy microorganism induced into the solution, wherein the amount of buffer in the composition is sufficient to maintain pD at range of 4.2-7.9, see TABLEs 1-3...."

Applicant agrees that formulations of Tables 1-3 indeed include a preservative, a buffer agent, and a tonicity agent, it must be appreciated that these (and indeed the other formulations of Tables 1-8) expressly contain D₂O instead of H₂O. In this context it should be recognized that the PHOSITA does not consider D₂O to be an aqueous solvent. See also Declaration at ¶ 12. As already noted above, such difference is not trivial, and indeed the replacement of H₂O with D₂O is attributed to the increase in stability. Consequently, after consulting the '712 publication, the PHOSITA would not be motivated to start at the formulations as described in the '712 publication and then exchange D₂O with H₂O to so arrive at the formulation as presently

claimed. The examples in the '712 publication simply do not provide any reasonable expectation of success. See also Declaration at ¶ 11, ¶ 13, and ¶ 14.

(c) With respect to the examiner's reference to Examples 2-4, it is once more noted that Example 2 is directed to use of D₂O in the preparation of an atropine stock solution. Where the stock solution is diluted in Example 2, no reference to H₂O and stability of the diluted solutions is made. In contrast, Example 3 is directed to use of H₂O in the preparation of an atropine stock solution. Where the stock solution is diluted in Example 3, no reference to stability of the diluted solutions is made.

With respect to Example 4, it should be appreciated that the experiments were performed with the D₂O solutions of Example 2. Interestingly, Table 11 provides exemplary results for the stability tests using the solutions of Example 2 (*i.e.*, solutions without EDTA and without buffer) and it can be readily taken from the 2-month data (as compared to the claimed 2-mo data of the applicant) that not only significant degradation is observed at comparable conditions (*i.e.*, 25 °C, 60RH), but that the final pH of the atropine solution is well above the claimed value. Moreover, as can be seen from the further results in table 12 of the '712 publication, the main degradation species (tropic acid) after 2 months is substantially higher than the claimed tropic acid (equal or less than 0.35%).

As such, it should be recognized that applicant's added chelator and buffer at the claimed pH contribute unexpectedly to the stability of atropine, even in the absence of D₂O. Such advantage is neither taught nor suggested by the '712 publication, or known to the skilled artisan. See also Declaration at ¶ 11, and the PHOSITA would have no expectation of success that chemical stability of atropine at a low concentration could be improved in aqueous solutions by use of low buffer concentration and the presence of a chelator in the absence of D₂O. Such is particularly true where the buffer has a low concentration and the chelator has a low concentration. See also Declaration at ¶ 13. Notably, the '712 publication expressly teaches against use of a buffer as can be seen in [0094] and [0107]: "...the lowered buffering capacity of the ophthalmic formulations or solutions when administered into the eye allows the ophthalmic formulation or solution to reach physiological pH at a faster rate than compared to an equivalent ophthalmic formulation or solution formulated in H₂O..." and "...the lowered buffering capacity

allows the composition to induce less tear reflex than an equivalent composition comprising H₂O...”. Once more, starting from the ‘712 publication, the skilled artisan would not be motivated to use a buffer agent, let alone a buffer agent at the concentrations as presently claimed. See Declaration at ¶ 13 and ¶ 14.

(d) With respect to the examiner’s reference to Examples 6-8, the Examiner noted that the ‘712 publication would teach a

“...viscosity enhancing agent such as hydroxypropyl methylcellulose, buffer agent such as sodium acetate, and stabilizer such as EDTA for keeping low degradation of atropine sulfate, see TABLES 6-8...”

While applicant agrees that the formulations of the examples in tables 6-8 include EDTA, a viscosity enhancing agent, and/or a buffer agent, it must be appreciated that these (and indeed the other formulations of Tables 1-5) expressly contain D₂O instead of H₂O. As already noted above, such difference is not trivial and indeed replacement of H₂O with D₂O is attributed to the increase in stability. Moreover, there are no data presented in the ‘712 publication that would establish that the viscosity enhancing agent such as hydroxypropyl methylcellulose, buffer agent such as sodium acetate, and the stabilizer such as EDTA would ensure low degradation of atropine sulfate. In contrast, and as already noted above, the use of D₂O instead of H₂O is the reason for increased stability.

Consequently, after consulting the ‘712 publication, the PHOSITA would not be motivated to start at the formulations as described in the ‘712 publication and then exchange D₂O with H₂O to so arrive at the formulation as presently claimed. The examples in the ‘712 publication simply provide no reasonable expectation of success. See also Declaration at ¶ 11, ¶ 13, and ¶ 14.

(e) With respect to the examiner’s reference to buffer concentration, there is no teaching or suggestion in the ‘712 publication that would establish that a specific low concentration buffer at a specific pH and in combination with a chelator would indeed increase atropine stability. In contrast, applicant has established such unexpected advantage. The only guideline for improving stability of atropine is with regard to adjustment of the pD of the solution, [0141-0142] and

[0180-0193]. It is clearly the use of D₂O instead of H₂O that drives the stability in the '712 publication. See also Declaration at ¶ 11.

(f) The applicant also respectfully points out with regard to the examiner's assertion that the

“...difference between the compositions of instant claims and the compositions of Example 1 at TABLEs 1-3 of the '712 publication is that the prior art does not teach the composition contains a chelator and a viscosity modifier...”,

a further significant difference between the compositions of the present claims and the examples in the '712 publication is that the solvent is D₂O instead of H₂O. Tables 16 and 25A and 25B provide clear and convincing factual evidence that the use of D₂O in the solvent system of the '712 publication is the critical factor in stability improvements. There is absolutely no indication or knowledge of the skilled artisan that would establish that the formulations as claimed would provide any advantage with regard to stability of atropine. As such, the claimed composition is not a function of optimization of ranges. Moreover, the simple appreciation of a normal desire to improve on what is already generally known does not provide any reasonable expectation that one could arrive at a stabilized formulation. See also Declaration at ¶ 13 and ¶ 14.

In conclusion, the '712 publication fails to recognize or suggest (alone or in combination with the knowledge of the PHOSITA) the improvements in atropine stability as claimed by the inventors. These unexpected advantages were neither predictable from the '712 publication and knowledge in the art. See also [0036], [0046], [0049] as originally filed and Declaration at ¶ 13 and ¶ 14.

For at least the reasons above and further of the expert declaration submitted herewith, the claims should not be deemed obvious over the '712 publication. The Applicant respectfully requests the rejection to be withdrawn.

///

Request For Allowance

Claims 1-20 are pending in this application. Applicant requests allowance of all pending claims.

Respectfully submitted,
Umberg Zipser LLP

Date: December 19, 2018

By /Martin Fessenmaier/
Martin Fessenmaier, Ph.D.
Reg. No. 46697

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Telephone (949) 679-0052
Fax (949) 679-0461

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (currently amended) A liquid storage-stable low-dose ophthalmic atropine composition, consisting essentially of:
 - an aqueous solution comprising a buffer, a tonicity agent, a chelator, a viscosity modifier, and atropine or a pharmaceutically acceptable salt thereof;
 - wherein the atropine or the pharmaceutically acceptable salt thereof is present in the ophthalmic atropine composition in an amount of equal or less than 0.05 wt%;
 - wherein the buffer has a concentration of equal or less than 75mM, and wherein the ophthalmic atropine composition has a pH of between 5.0 and 6.0; and
 - wherein the ophthalmic atropine composition is ~~formulated such that~~ after storage over at least two months at 25 °C and 60% relative humidity contains equal or less than 0.35% tropic acid [[is]] formed from degradation of the atropine and has a pH of between 5.0 and 6.0.
2. (original) The composition of claim 1, wherein the atropine or the pharmaceutically acceptable salt thereof is atropine sulfate.
3. (original) The composition of claim 1, wherein the atropine or a pharmaceutically acceptable salt thereof is present in the ophthalmic atropine composition in an amount of equal or less than 0.02 wt%.
4. (original) The composition of claim 1, wherein the atropine or a pharmaceutically acceptable salt thereof is present in the ophthalmic atropine composition in an amount of equal or less than 0.01 wt%.
5. (original) The composition of claim 1, wherein the atropine or a pharmaceutically acceptable salt thereof is present in the ophthalmic atropine composition in an amount of between 0.001 wt% and 0.01 wt%.

6. (original) The composition of claim 2, wherein the buffer has a concentration of equal or less than 60mM.
7. (original) The composition of claim 5, wherein the buffer has a concentration of equal or less than 50mM.
8. (original) The composition of claim 6, wherein the buffer comprises monobasic and dibasic sodium phosphate.
9. (original) The composition of claim 7, wherein the buffer comprises monobasic and dibasic sodium phosphate.
10. (original) The composition of claim 1, wherein the chelator is selected from the group consisting of a bicarboxylic acid, a tricarboxylic acid, and an aminopolycarboxylic acid.
11. (original) The composition of claim 8, wherein the chelator is ethylenediaminetetraacetic acid (EDTA).
12. (original) The composition of claim 9, wherein the chelator is ethylenediaminetetraacetic acid (EDTA).
13. (original) The composition of claim 10 wherein the chelator is present in the ophthalmic atropine composition in an amount of equal or less than 0.01 wt%.
14. (original) The composition of claim 1, wherein the ophthalmic atropine composition has a pH of between 5.0 (+/- 0.2) and 5.5 (+/- 0.2).
15. (original) The composition of claim 1, wherein the ophthalmic atropine composition has a pH of between 5.5 (+/- 0.2) and 6.0 (+/- 0.2).
16. (original) The composition of claim 1, wherein the tonicity agent is a pharmaceutically acceptable salt and wherein the salt is present in the ophthalmic atropine composition in an amount of between 0.2 wt% and 0.8 wt%.

17. (original) The composition of claim 1, wherein the viscosity modifier is a hydroxyethyl cellulose, a hydroxypropyl cellulose, or a hydroxypropyl methylcellulose.
18. (currently amended) The composition of claim 1, wherein the ophthalmic atropine composition ~~is substantially free of~~ includes a preservative in an amount of no more than 0.01 wt%.
19. (currently amended) The composition of claim 1, wherein the atropine or a pharmaceutically acceptable salt thereof is present in the ophthalmic atropine composition in an amount of between 0.001 wt% and 0.01 wt%, wherein the buffer comprises monobasic and dibasic sodium phosphate and has a concentration of equal or less than 50mM, wherein the viscosity modifier is a hydroxyethyl cellulose, a hydroxypropyl cellulose, or a hydroxypropyl methylcellulose, and wherein the ophthalmic atropine composition ~~is substantially free of~~ includes a preservative in an amount of no more than 0.01 wt%.
20. (currently amended) The composition of claim 1, wherein the atropine or a pharmaceutically acceptable salt thereof is present in the ophthalmic atropine composition in an amount of between 0.01 wt% and 0.05 wt%, wherein the buffer comprises monobasic and dibasic sodium phosphate and has a concentration of equal or less than 50mM, wherein the viscosity modifier is a hydroxyethyl cellulose, a hydroxypropyl cellulose, or a hydroxypropyl methylcellulose, and wherein the ophthalmic atropine composition ~~is substantially free of~~ includes a preservative in an amount of no more than 0.01 wt%.

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875				Application or Docket Number 15/976,279		Filing Date 05/10/2018		☐ To be Mailed	
ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO									
APPLICATION AS FILED - PART I									
		(Column 1)	(Column 2)						
FOR		NUMBER FILED	NUMBER EXTRA		RATE (\$)		FEE (\$)		
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))		N/A	N/A		N/A				
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))		N/A	N/A		N/A				
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))		N/A	N/A		N/A				
TOTAL CLAIMS (37 CFR 1.16(i))		minus 20 = *		x \$50 =					
INDEPENDENT CLAIMS (37 CFR 1.16(h))		minus 3 = *		x \$230 =					
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))		If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).							
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))									
* If the difference in column 1 is less than zero, enter "0" in column 2.					TOTAL				
APPLICATION AS AMENDED - PART II									
		(Column 1)		(Column 2)	(Column 3)				
AMENDMENT	12/19/2018	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)		ADDITIONAL FEE (\$)	
	Total (37 CFR 1.16(i))	* 20	Minus	** 20	= 0	x \$50 =		0	
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0	x \$230 =		0	
	☐ Application Size Fee (37 CFR 1.16(s))								
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))								
						TOTAL ADD'L FEE		0	
		(Column 1)		(Column 2)	(Column 3)				
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)		ADDITIONAL FEE (\$)	
	Total (37 CFR 1.16(i))	*	Minus	**	=	x \$0 =			
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x \$0 =			
	☐ Application Size Fee (37 CFR 1.16(s))								
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))								
						TOTAL ADD'L FEE			
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.						LIE			
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".						/MOLIKI I MAY/			
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".									
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.									

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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**Courtesy Reminder for
Application Serial No: 15/976,279**

Attorney Docket No: 102843.0006US2
Customer Number: 149344
Date of Electronic Notification: 12/04/2018

This is a courtesy reminder that new correspondence is available for this application. If you have not done so already, please review the correspondence. The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/976,279	05/10/2018	Navneet Puri	102843.0006US2	1256
149344	7590	12/04/2018	EXAMINER	
Umberg Zipser LLP			CHU, YONG LIANG	
1920 Main Street Suite 750			ART UNIT	PAPER NUMBER
Irvine, CA 92614			1629	
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The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@umbergzipser.com
rdean@umbergzipser.com

DETAILED ACTION

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Claims 1-20 are pending in the instant application.

Priority

This application, filed May 10, 2018, claims priority to a copending US provisional application with serial number 62/505,027, which was filed May 11, 2017.

Information Disclosure Statements

Applicants' Information Disclosure Statements, filed on 10/19/2018 and 08/09/2018, have been considered. Please refer to Applicants' copies of the PTO-1449 submitted herewith.

Response to Restriction Requirement

Applicant's election without traverse of the elected species of (A) phosphate buffer at a concentration of equal or less than 50mM; (B) NaCl as tonicity agent; (C) hydroxypropyl methylcellulose as the viscosity modifier; (D) EDTA as the chelator; and (E) atropine at a concentration of equal or less than 0.02 wt% in the reply by Applicants' representative Dr. Martin Fessenmaier on 11/05/2018 is acknowledged. Claims 1-20 are under examination on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of 35 U.S.C. 112(b):

(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18-20 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention. Specifically, said claims contain a phrase “wherein the ophthalmic atropine composition is substantially free of a preservative”. However, the claims do not define the term “substantially free of a preservative”. The specification at paragraph [0056] describes the term “substantially free of a preservative” as “not more than 0.01 wt %, and more typically not more than 0.005 wt %”. It seems that the term “substantially free of a preservative” can be interpreted as either “not more than 0.01 wt %”, or “not more than 0.005 wt %”. Therefore, metes and bounds of the term are not clear. Accordingly, the claims 18-20 are indefinite. The Examiner gives the term a broadest interpretation in light of the specification as “not more than 0.01 wt %”.

Claim Rejections - 35 USC § 103

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102 of this title, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-20 are rejected under 35 U.S.C. 103 as being unpatentable over WO2016/172712 ("the 712 publication"), claiming priority to U.S. Provision Patent Application 62/151,926 (filing date April 23, 2015), and issued as U.S. Patent No. 9,421,199.

Applicants' claim 1 is drawn to a liquid storage-stable low-dose ophthalmic atropine composition, consisting essentially of an aqueous solution comprising a buffer, a tonicity agent, a chelator, a viscosity modifier, and atropine or a pharmaceutically acceptable salt thereof; wherein the atropine or the pharmaceutically acceptable salt thereof is present in the ophthalmic atropine composition in an amount of equal or less than 0.05 wt%; wherein the buffer has a concentration of equal or less than 75mM, and wherein the ophthalmic atropine composition has a pH of between 5.0 and 6.0; and wherein the ophthalmic atropine composition is formulated such that after storage over at least two months at 25 °C and 60% relative humidity equal or less than 0.35% tropic acid is formed from degradation of the atropine.

Claims 18-20 further limit the ophthalmic atropine composition is substantially free of a preservative.

Claim 1 contains the functional language “wherein the ophthalmic atropine composition is formulated such that after storage over at least two months at 25 °C and 60% relative humidity equal or less than 0.35% tropic acid is formed from degradation of the atropine”. The functional language does not define what the ophthalmic atropine composition is, but what property of the composition would be. This functional language does not further limit the composition. Instead, it is interpreted as an *inherited property* of the ophthalmic atropine composition as defined by the structural limitations (i.e. what the composition is) in claim 1.

In terms of claims 18-20, the term “the ophthalmic atropine composition is substantially free of a preservative” is interpreted as “the preservative is not more than 0.01 wt %”, also see the above 112(b) rejection.

The '712 publication teaches an aqueous low-dose ophthalmic atropine composition comprising atropine at 0.001-0.05 wt%, a buffer, a tonicity agent of NaCl, and a preservative such as benzalkonium chloride, or cetrimonium sodium perborate sufficient to prevent the growth of or destroy microorganism induced into the solution, wherein the amount of buffer in the composition is sufficient to maintain pD at range of 4.2-7.9, see TABLEs 1-3. A pD is for D₂O, deuterated H₂O of pH. In addition, Examples 2-4 teaches preparation of five atropine aqueous solutions containing 0.01% atropine sulfate, buffer agent q.s. (sufficient) for pD at range of 4.2-7.9 and tonicity agent NaCl, wherein pH of the aqueous solutions were 5.87, 5.97, 5.90, 6.24, and 6.16 (Example 4). No preservative was present in the five aqueous solutions. In addition, the '712 publication teaches the atropine sulfate formulations can also contain viscosity enhancing agent such as hydroxypropyl methylcellulose, buffer agent such as sodium acetate, and stabilizer such as EDTA for keeping low degradation of atropine sulfate, see TABLES 6-8. In terms of the concentration of the buffer, the '712 publication teaches the

buffer as borates in an amount of from about 0.01 to about 2.0% w/v, and one or more polyols in an amount of from about 0.01% to about 5.0% w/v, see "Aqueous Solution Stability". More importantly, the '712 publication teaches guideline for optimization of buffer to make stable ophthalmic atropine composition for clinical application. In terms of preservative, the '712 publication teaches the concentration of preservative is at range of about 0.001%, 0.002%, 0.003%, 0.004%, 0.005%, 0.006%, 0.008%, 0.009%, 0.009%, below the instantly claimed limitation of substantially free of a preservative, which is not more than 0.01 wt %, according to paragraph [0056] of Applicants' specification.

The difference between the compositions of instant claims and the compositions of Example 1 at TABLEs 1-3 of the '712 publication is that the prior art does not teach the composition contains a chelator and a viscosity modifier.

However, the differences are further taught in the other examples of the same prior art at TABLES 6-8, wherein a chelator of EDTA as a stabilizer (of the aqueous atropine ophthalmic composition) and a viscosity modifier of hydroxypropyl methylcellulose are used in the formulations substantially free of a preservative. In addition, the '712 publication teaches the formulations are stable enough for clinical use based on the stability test results, see Figs 1-2 and TABLE 16 of the '712 publication. Instant claims would have been obvious over the '712 publication, because optimization of the range of each active agents in the combined composition is a routine practice, not inventive practice. It has been well established that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233,235 (CCPA 1955). The rationale for determining the optimal parameters for prior art result effective variables "flows from the 'normal desire of scientists or artisans to improve upon what is already generally known.'" *Id.* (quoting *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003)). "Only if the results of optimizing a variable are unexpectedly good can a

patent be obtained for the claimed critical range." In re Geisler, 116 F.3d 1465, 1470 (Fed. Cir. 1997) (quotations omitted).

Conclusions

- Claims 1-20 are rejected.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Chu, whose telephone number is (571)272-5759. The examiner can normally be reached on M-F 7:00am-4:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey S. Lundgren can be reached on 571-272-5541. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

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/YONG L CHU/
Primary Examiner, Art Unit 1629

Notice of References Cited	Application/Control No. 15/976,279	Applicant(s)/Patent Under Reexamination Puri et al.	
	Examiner YONG L CHU	Art Unit 1629	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
	A					
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FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
*	N	WO-2016172712-A2	10-2016	WO	WIDDER KENNETH J	A61K9/08
	O					
	P					
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	Examiner YONG L CHU	Art Unit 1629

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
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Search Notes	Date	Examiner
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STN	11/27/2018	YC
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US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

<i>Index of Claims</i> 	Application/Control No. 15/976,279	Applicant(s)/Patent Under Reexamination Puri et al.
	Examiner YONG L CHU	Art Unit 1629

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

CLAIMS										
☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47										
CLAIM		DATE								
Final	Original	09/11/2018	11/27/2018							
	1	÷	✓							
	2	÷	✓							
	3	÷	✓							
	4	÷	✓							
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	18	÷	✓							
	19	÷	✓							
	20	÷	✓							

15/976,279 Yong Chu 11-26-2018

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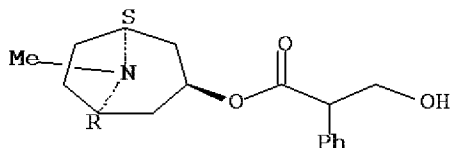
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CN Benzeneacetic acid, α -(hydroxymethyl)-
(3-endo)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl ester (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN (3-endo)-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl
 α -(hydroxymethyl)benzeneacetate
CN 1 α H,5 α H-Tropan-3 α -ol ($\pm$)-tropate (ester) (8CI)
CN Benzeneacetic acid, α -(hydroxymethyl)-,
8-methyl-8-azabicyclo[3.2.1]oct-3-yl ester, endo-
OTHER NAMES:
CN ($\pm$)-Atropine
CN ($\pm$)-Hyoscyamine
CN Atropin
CN Atropine
CN Atropinum sulphuricum
CN dl-Hyoscyamine
CN DL-Hyoscyamine
CN dl-Tropyl tropate
CN Tropine ($\pm$)-tropate
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Relative stereochemistry.



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DICTIONARY FILE UPDATES: 25 NOV 2018 HIGHEST RN 2249944-55-4

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TSCA INFORMATION NOW CURRENT THROUGH April 2018.

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REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

<http://www.cas.org/training/stn/database-specific>

=> 9004-65-3/rn

9004-65-3 IS NOT A RECOGNIZED COMMAND

The previous command name entered was not recognized by the system.

For a list of commands available to you in the current file, enter

"HELP COMMANDS" at an arrow prompt (=>).

=> s 9004-65-3/rn

L4 1 9004-65-3/RN

=> d

L4 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2018 ACS on STN

RN ~~9004-65-3~~ REGISTRY

ED Entered STN: 16 Nov 1984

CN Cellulose, 2-hydroxypropyl methyl ether (CA INDEX NAME)

OTHER NAMES:

CN 2-Hydroxypropyl methyl cellulose

CN 2-Hydroxypropyl methyl cellulose ether

CN 35SK

CN 40US

CN 60HD20000

CN 60MP4000

CN 60RT50

CN 60SH06

CN 60SH100

CN 60SH4000
 CN 60SH4000F
 CN 60SH5
 CN 65HD50
 CN 65SH-4000
 CN 65SH5
 CN 65SH50
 CN 90SH100
 CN 90SH100000
 CN 90SH15000S
 CN 90SH400
 CN Accel R 100
 CN Affinisol 100
 CN Affinisol 15cP
 CN Affinisol 4M
 CN Affinisol HPMC 100
 CN Affinisol HPMC 100LV
 CN Affinisol HPMC 4M
 CN Anyaddy AN 50
 CN Anyaddy BN 40H
 CN Anyaddy CN 40H
 CN AnyCoat-C AN 6
 CN AnyCoat-C BN 4
 CN AnyCoat-C CN 10T
 CN AW 4
 CN Benecel 324
 CN Benecel 363
 CN Benecel 424
 CN Benecel A 4C
 CN Benecel E 15
 CN Benecel K 100LV
 CN Benecel K 100M
 CN Benecel K 35M
 CN Benecel MP 3
 CN Benecel MP 363C
 CN Benecel MP 824
 CN Benecel MP 843
 CN Benecel MP 9
 CN Benecel MP 943
 CN Benecel MP 943W
 CN BN 4

ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for
 DISPLAY

DR 8063-82-9, 11106-33-5, 12673-53-9, 37341-76-7, 39363-71-8, 59029-31-1,
 62683-26-5, 65607-39-8, 68073-10-9, 71373-07-4, 98112-80-2, 125053-98-7,
 125857-43-4, 137397-89-8, 137397-90-1, 137397-91-2, 171544-38-0,
 173080-61-0, 194615-25-3, 876407-53-3, 1262284-64-9

MF C3 H8 O2 . x C H4 O . x Unspecified

CI COM

PCT Manual registration, Polyother, Polyother only

LC STN Files: ADISNEWS, ANABSTR, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT,
 CHEMCATS, CHEMLIST, CIN, DDFU, DRUGU, EMBASE, IFIALL, IPA, MEDLINE,
 MSDS-OHS, PIRA, RTECS*, TOXCENTER, USPAT2, USPATFULL, USPATOLD

(*File contains numerically searchable property data)

Other Sources: DSL**, TSCA**, WHO

(**Enter CHEMLIST File for up-to-date regulatory information)

CM 1

CRN 9004-34-6

CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2
CRN 67-56-1
CMF C H4 O

H₃C—OH

CM 3
CRN 57-55-6
CMF C3 H8 O2

OH
|
H₃C—CH—CH₂—OH

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

50310 REFERENCES IN FILE CA (1907 TO DATE)
454 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
50735 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> s 60-00-4/rn
L5 1 60-00-4/RN

=> d

L5 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2018 ACS on STN
RN 60-00-4 REGISTRY
ED Entered STN: 16 Nov 1984
CN Glycine, N,N'-1,2-ethanediylbis[N-(carboxymethyl)- (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Acetic acid, (ethylenedinitrilo)tetra- (8CI)
CN N,N'-1,2-Ethanediylbis[N-(carboxymethyl)glycine]
OTHER NAMES:
CN 2,2',2'',2'''-(ethane-1,2-diylbis(azanetriyl))tetraacetic acid
CN 3,6-Diazaoctanedioic acid, 3,6-bis(carboxymethyl)-
CN Acetic acid, 2,2',2'',2'''-(1,2-ethanediyl dinitrilo)tetrakis-
CN Acroma DH 700
CN Celon A
CN Celon ATH
CN Cheelox
CN Chelest 3A
CN Chelest A
CN Chemcolox 340

CN Clewat TAA
 CN Clewat TTA
 CN Complexon II
 CN Dissolvine E
 CN Dissolvine NA-X
 CN Dissolvine Z
 CN Dotite 4H
 CN Edathamil
 CN EDETA B
 CN Edetic acid
 CN EDTA
 CN EDTA (chelating agent)
 CN Endrate
 CN Ethylene-N,N'-biscarboxymethyl-N,N'-diglycine
 CN Ethylenediamine-N,N,N',N'-tetraacetic acid
 CN Ethylenediaminetetraacetate
 CN Ethylenediaminetetraacetic acid
 CN Ethylenedinitrilotetraacetic acid
 CN Gluma Cleanser
 CN Havidote
 CN ICRF 185
 CN Kurewat-N
 CN Metaquest A
 CN Nervanaid B acid
 CN NSC 97243
 CN NSC 97404
 CN Nullapon B acid
 CN Nullapon BF acid
 CN Perma Kleer 50 acid
 CN PrefGel
 CN Quastal Special
 CN Sequestrene AA
 CN Sequestrene K 4
 CN Sequestric acid
 CN Sequestrol
 CN Techrun DO
 CN Titriplex
 CN Titriplex II

ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for DISPLAY

DR 13440-78-3, 20539-27-9, 26627-46-3, 30485-87-1, 30485-88-2, 30485-90-6,
 32757-10-1, 94108-75-5, 161122-33-4, 402925-67-1, 675141-16-9,
 1586747-13-8, 1799367-75-1

MF C10 H16 N2 O8

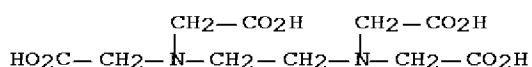
CI COM

SR CA

LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BIOSIS, BIOTECHNO, CA, CABA,
 CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CIN, DDFU, DRUGU, ENCOMPLIT,
 ENCOMPLIT2, ENCOMPPAT, ENCOMPPAT2, IFIALI, IPA, MEDLINE, MSDS-OHS, PIRA,
 PS, REAXYSFILE*, RTECS*, TOXCENTER, USPAT2, USPATFULL, VETU
 (*File contains numerically searchable property data)

Other Sources: DSL**, EINECS**, TSCA**, WHO

(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

67991 REFERENCES IN FILE CA (1907 TO DATE)
5317 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
69232 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> s 7647-14-5/rn
L6 1 7647-14-5/RN

=> d

L6 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2018 ACS on STN
RN 7647-14-5 REGISTRY
ED Entered STN: 16 Nov 1984
CN Sodium chloride (NaCl) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Sodium chloride (8CI)
OTHER NAMES:
CN 2: PN: WO2014001822 PAGE: 45 claimed sequence
CN Adios Ambros
CN Adsorbanac
CN Alberger salt
CN Arm-A-Vial
CN Ayr
CN BCD
CN Brinewate Superfine
CN Cannery 999
CN Cap-Shure 70 Salt
CN Cap-Shure 85 Salt
CN Common salt
CN Culinox 999 Salt
CN D 02056
CN Dendritic salt
CN Dendritis
CN EF 40
CN EF 40 (salt)
CN Esco PDV Table Salt
CN Extra Fine 200 Salt
CN Extra Fine 325 Salt
CN Flexivial
CN Gingivyl
CN H.G. Blending
CN Hypersal
CN Iodised salt
CN Iodized salt
CN Kochsalz
CN LS 1700
CN Mafiron
CN MARSEL
CN Mediterra salt
CN Nakuru N
CN Nakuru UM 5
CN Naruto Shokuen
CN Natritope chloride
CN Natrum mur
CN Natrum muriaticum
CN Nissei-no Yakishio S

CN NSC 77364
 CN Salt
 CN Slow Sodium
 CN Sodium chloric
 CN Sodium monochloride
 CN Soft Salt S 50
 CN Solsel
 CN Special Salt 100/95
 CN SS Salt
 CN Suprasel
 ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for
 DISPLAY
 DR 8028-77-1, 11062-32-1, 11062-43-4, 418758-90-4
 MF Cl Na
 CI COM
 LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BIOSIS, BIOTECHNO, CA, CABA,
 CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CIN, DDFU, DRUGU, ENCOMPLIT,
 ENCOMPLIT2, ENCOMPPAT, ENCOMPPAT2, IPA, MEDLINE, MSDS-OHS, PATDPASPC,
 PIRA, RTECS*, TOXCENTER, USPAT2, USPATFULL, USPATOLD, VETU
 (*File contains numerically searchable property data)
 Other Sources: DSL**, EINECS**, TSCA**
 (**Enter CHEMLIST File for up-to-date regulatory information)

Cl—Na

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

326298 REFERENCES IN FILE CA (1907 TO DATE)
 607 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 333797 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	14.30	24.01

FILE 'CAPLUS' ENTERED AT 16:24:02 ON 26 NOV 2018
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FILE COVERS 1907 - 26 Nov 2018 VOL 169 ISS 24
 FILE LAST UPDATED: 25 Nov 2018 (20181125/ED)

REVISED CLASS FIELDS (/NCL) LAST RELOADED: Dec 2015
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Dec 2015

CAPLUS now includes the comprehensive Cooperative Patent Classification (CPC). See HELP CPC for details.

CAS Information Use Policies apply and are available at:

<http://www.cas.org/legal/infopolicy>

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s 14 and 15 and 16

50735 L4

69232 L5

333797 L6

L7 176 L4 AND L5 AND L6

=> s 13 and 17

L8 1 L3 AND L7

=> d ibib abs hitstr tot

****Closest art****

L8 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2018 ACS on STN

ACCESSION NUMBER: 2008:1448380 CAPLUS Full-text

DOCUMENT NUMBER: 150:2326

TITLE: Ophthalmic formulations of Chrysamine G derivative
contrast agents for detecting amyloid- β plaques

INVENTOR(S): Goldstein, Lee E.; Smith, Francis X.; Sullivan, Kevin
R.; Hartung, Paul D.; Sherr, Evan A.

PATENT ASSIGNEE(S): Neuroptix Corporation, USA

SOURCE: PCT Int. Appl., 44pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

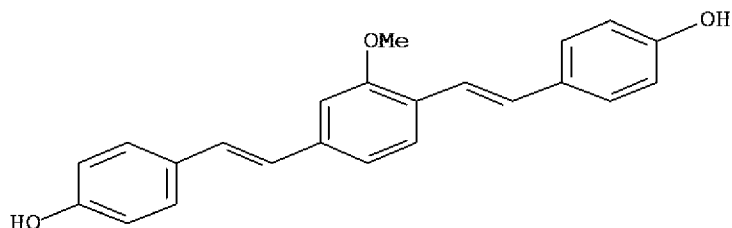
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

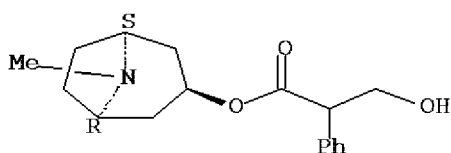
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008144065	A1	20081127	WO 2008-US6490	20080521
W:	AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
AU 2008254428	A1	20081127	AU 2008-254428	20080521
CA 2688811	A1	20081127	CA 2008-2688811	20080521
US 20090041666	A1	20090212	US 2008-154226	20080521
EP 2152255	A1	20100217	EP 2008-754603	20080521
R:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, AL, BA, MK, RS			

JP 2010528010 T 20100819 JP 2010-509369 20080521
 PRIORITY APPLN. INFO.: US 2007-60931189 P 20070521
 US 2008-61062170 P 20080123
 WO 2008-US6490 W 20080521
 ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
 OTHER SOURCE(S): MARPAT 150:2326
 GI

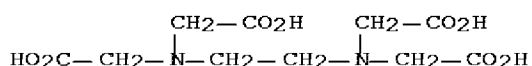


AB The invention provides ophthalmic formulations of Chrysamine G derivs. as amyloid- β contrast agents. Also provided are methods of using such formulations in the diagnosis of Alzheimer's disease or a predisposition thereto as well as methods for the prognosis of Alzheimer's Disease.
 IT 51-55-8, Atropine, biological studies
 RL: BSU (Biological study, unclassified); BIOL (Biological study) (ophthalmic formulations of Chrysamine G derivative contrast agents for detecting amyloid- β plaques)
 RN 51-55-8 CAPLUS
 CN Benzeneacetic acid, α -(hydroxymethyl)-(3-endo)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl ester (CA INDEX NAME)

Relative stereochemistry.



IT 60-00-4, EDTA, uses 7647-14-5, Sodium chloride, uses 9004-65-3, Hydroxypropyl methyl cellulose
 RL: MOA (Modifier or additive use); USES (Uses) (ophthalmic formulations of Chrysamine G derivative contrast agents for detecting amyloid- β plaques)
 RN 60-00-4 CAPLUS
 CN Glycine, N,N'-1,2-ethanediylbis[N-(carboxymethyl)- (CA INDEX NAME)



RN 7647-14-5 CAPLUS
CN Sodium chloride (NaCl) (CA INDEX NAME)

Cl—Na

RN 9004-65-3 CAPLUS
CN Cellulose, 2-hydroxypropyl methyl ether (CA INDEX NAME)

CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 67-56-1
CMF C H4 O

H₃C—OH

CM 3

CRN 57-55-6
CMF C3 H8 O2

OH
|
H₃C—CH—CH₂—OH

OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD
(3 CITINGS)
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s 17 and ophthalmic
32381 OPHTHALMIC
82 OPHTHALMICS
32422 OPHTHALMIC
(OPHTHALMIC OR OPHTHALMICS)
L9 64 L7 AND OPHTHALMIC

=> s 19 and atropine
39419 ATROPINE
40 ATROPINES
39424 ATROPINE
(ATROPINE OR ATROPINES)
L10 1 L9 AND ATROPINE

=> s 13 and 14
50735 L4
L11 18 L3 AND L4

=> s 13 and 15
69232 L5
L12 6 L3 AND L5

=> s 13 and 16
333797 L6
L13 15 L3 AND L6

=> s l11 or l12 or l13
L14 31 L11 OR L12 OR L13

=> s l11 and l12 and l13
L15 1 L11 AND L12 AND L13

=> s l15 not l10
L16 0 L15 NOT L10

=> s 19 and buffer
420724 BUFFER
72599 BUFFERS
460028 BUFFER
(BUFFER OR BUFFERS)
L17 27 L9 AND BUFFER

=> s 117 and tonicity agent
2103 TONICITY
89 TONICITIES
2144 TONICITY
(TONICITY OR TONICITIES)
1932662 AGENT
2941526 AGENTS
4047908 AGENT
(AGENT OR AGENTS)
156 TONICITY AGENT
(TONICITY(W) AGENT)
L18 2 L17 AND TONICITY AGENT

=> s 118 not l10
L19 2 L18 NOT L10

=> d ibib abs hitstr tot

L19 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2018 ACS on STN
ACCESSION NUMBER: 2008:590194 CAPLUS Full-text
DOCUMENT NUMBER: 148:509920
TITLE: Methods of treating an ocular allergy with low-dose
dexamethasone
INVENTOR(S): Freidlaender, Mitchell H.
PATENT ASSIGNEE(S): Riolan Technologies, Inc., USA

SOURCE: PCT Int. Appl., 19pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008057360	A1	20080515	WO 2007-US23024	20071101
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM US 20080119448 A1 20080522 US 2007-979356 20071101 EP 2089036 A1 20090819 EP 2007-861615 20071101 R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR PRIORITY APPLN. INFO.: US 2006-60856026 P 20061102 WO 2007-US23024 W 20071101				

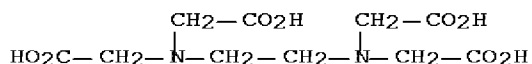
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The invention discloses a method for treating an ocular allergy with a composition comprising a low dose of dexamethasone. In some embodiments, the invention discloses a method for treating an ocular allergy, the method comprising administering to an ocular surface of a subject in need thereof a composition comprising about 0.001 % to about 0.01% (w/v) dexamethasone.

IT 60-00-4, biological studies 60-00-4D, salts
 7647-14-5, Sodium chloride (NaCl), biological studies
 9004-65-3
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (low-dose dexamethasone for ocular allergy treatment)

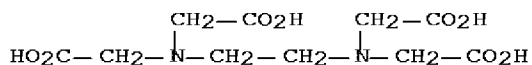
RN 60-00-4 CAPLUS

CN Glycine, N,N'-1,2-ethanediylbis[N-(carboxymethyl)- (CA INDEX NAME)]



RN 60-00-4 CAPLUS

CN Glycine, N,N'-1,2-ethanediylbis[N-(carboxymethyl)- (CA INDEX NAME)]



RN 7647-14-5 CAPLUS

CN Sodium chloride (NaCl) (CA INDEX NAME)

Cl-Na

RN 9004-65-3 CAPLUS
CN Cellulose, 2-hydroxypropyl methyl ether (CA INDEX NAME)

CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 67-56-1
CMF C H4 O

H₃C-OH

CM 3

CRN 57-55-6
CMF C3 H8 O2

OH
|
H₃C-CH-CH₂-OH

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2018 ACS on STN
ACCESSION NUMBER: 2008:589485 CAPLUS Full-text
DOCUMENT NUMBER: 148:554069
TITLE: Method and composition using dexamethasone and an
antibiotic for treatment of blepharitis
INVENTOR(S): Friedlaender, Mitchell H.
PATENT ASSIGNEE(S): Riolan Technologies, Inc., USA
SOURCE: PCT Int. Appl., 23pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:
PATENT NO. KIND DATE APPLICATION NO. DATE

WO 2008057364	A1	20080515	WO 2007-US23031	20071101
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
US 20090023668	A1	20090122	US 2007-979354	20071101
EP 2089035	A1	20090819	EP 2007-861619	20071101
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR				
PRIORITY APPLN. INFO.:			US 2006-60856009	P 20061102
			WO 2007-US23031	W 20071101

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

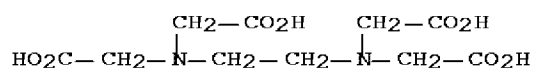
AB The invention is related to a method for treating blepharitis, the method comprising administering to an ocular area of a subject in need thereof a composition comprising about 0.001% to about 0.01% (w/v) dexamethasone and an antibiotic, wherein the composition is substantially free of lipids, and wherein the composition is ophthalmically acceptable.

IT 60-00-4, Ethylenediaminetetraacetic acid, biological studies
60-00-4D, Ethylenediaminetetraacetic acid, salts
7647-14-5, Sodium chloride, biological studies 9004-65-3
, Hydroxypropylmethyl cellulose

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dexamethasone and antibiotic for treatment of blepharitis)

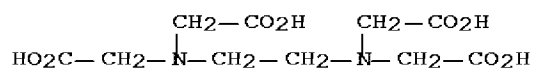
RN 60-00-4 CAPLUS

CN Glycine, N,N'-1,2-ethanediylbis[N-(carboxymethyl)- (CA INDEX NAME)]



RN 60-00-4 CAPLUS

CN Glycine, N,N'-1,2-ethanediylbis[N-(carboxymethyl)- (CA INDEX NAME)]



RN 7647-14-5 CAPLUS

CN Sodium chloride (NaCl) (CA INDEX NAME)

Cl-Na

RN 9004-65-3 CAPLUS
CN Cellulose, 2-hydroxypropyl methyl ether (CA INDEX NAME)

CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 67-56-1
CMF C H4 O

$\text{H}_3\text{C}-\text{OH}$

CM 3

CRN 57-55-6
CMF C3 H8 O2

$\begin{array}{c} \text{OH} \\ | \\ \text{H}_3\text{C}-\text{CH}-\text{CH}_2-\text{OH} \end{array}$

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s 11 and 17
13933 L1
L20 3 L1 AND L7

=> s 120 not 110
L21 2 L20 NOT L10

=> s 121 not 119
L22 2 L21 NOT L19

=> d ibib abs hitstr tot

L22 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2018 ACS on STN
ACCESSION NUMBER: 2007:771975 CAPLUS Full-text
DOCUMENT NUMBER: 148:128090
TITLE: Oral soluble medicated membrane (os2m)
INVENTOR(S): Chaudhuri, Avijit
PATENT ASSIGNEE(S): Pac Med Biotech Private Limited, India
SOURCE: Indian Pat. Appl., 48pp.

CODEN: INXXBQ
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
IN 2006KO00351	A	20070706	IN 2006-KO351	20060419
PRIORITY APPLN. INFO.:			IN 2006-KO351	20060419

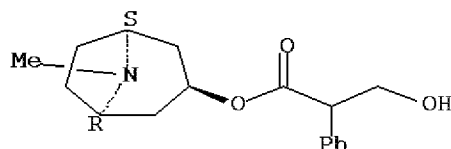
AB The present invention is related to the composition and methods of manufacture of orally soluble medicated membrane as a vehicle for the non-invasive administration of nitroglycerin as well as other therapeutic agents either with or without nitroglycerin through the mucosal tissues of the oral cavity. The medicated membrane includes a water soluble film-forming polymer such as pullulan. Methods for producing the medicated membrane are also disclosed.

IT 51-55-8, Atropine, biological studies 60-00-4, EDTA, biological studies 7647-14-5, Sodium chloride, biological studies 9004-65-3, Hydroxypropyl methyl cellulose
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral soluble medicated membrane)

RN 51-55-8 CAPLUS

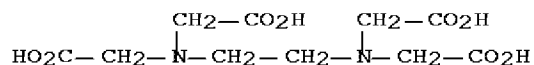
CN Benzeneacetic acid, α -(hydroxymethyl)-(3-endo)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl ester (CA INDEX NAME)

Relative stereochemistry.



RN 60-00-4 CAPLUS

CN Glycine, N,N'-1,2-ethanediylbis[N-(carboxymethyl)- (CA INDEX NAME)



RN 7647-14-5 CAPLUS

CN Sodium chloride (NaCl) (CA INDEX NAME)

Cl-Na

RN 9004-65-3 CAPLUS

CN Cellulose, 2-hydroxypropyl methyl ether (CA INDEX NAME)

CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 67-56-1
CMF C H4 O

$\text{H}_3\text{C}-\text{OH}$

CM 3

CRN 57-55-6
CMF C3 H8 O2

$\begin{array}{c} \text{OH} \\ | \\ \text{H}_3\text{C}-\text{CH}-\text{CH}_2-\text{OH} \end{array}$

L22 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2018 ACS on STN
ACCESSION NUMBER: 2005:55116 CAPLUS Full-text
DOCUMENT NUMBER: 142:141267
TITLE: Film comprising therapeutic agents
INVENTOR(S): Maibach, Todd
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 49 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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WO 2005004989	A2	20050120	WO 2004-US21038	20040630
WO 2005004989	A3	20050616		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
CA 2530843	A1	20050120	CA 2004-2530843	20040630
EP 1648362	A2	20060426	EP 2004-777314	20040630

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK

CN 1829490	A	20060906	CN 2004-80022053	20040630
US 20070059346	A1	20070315	US 2006-562633	20060609
US 20120121724	A1	20120517	US 2012-13355414	20120120
PRIORITY APPLN. INFO.:			US 2003-60484009	P 20030701
			US 2003-60497426	P 20030821
			WO 2004-US21038	W 20040630
			US 2006-562633	B1 20060609

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The present invention is related to the composition and methods of manufacture of orally-dissolvable, edible films as a vehicle for the non-invasive administration of nitroglycerin, as well as other therapeutic agents either with or without nitroglycerin, through the mucosal tissues of the oral cavity. The films include a water-soluble film-forming polymer, such as pullulan. Methods for producing the films are also disclosed.

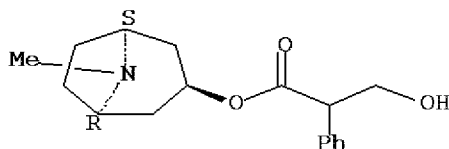
IT 51-55-8, Atropine, biological studies 60-00-4, EDTA, biological studies 7647-14-5, Sodium chloride, biological studies 9004-65-3, Hydroxypropylmethyl cellulose

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (buccal tapes comprising therapeutic agents)

RN 51-55-8 CAPLUS

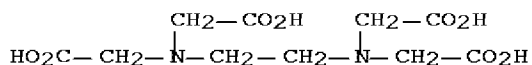
CN Benzeneacetic acid, α -(hydroxymethyl)-(3-endo)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl ester (CA INDEX NAME)

Relative stereochemistry.



RN 60-00-4 CAPLUS

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CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 67-56-1
CMF C H4 O

H₃C—OH

CM 3

CRN 57-55-6
CMF C3 H8 O2

OH
|
H₃C—CH—CH₂—OH

OS.CITING REF COUNT: 9 THERE ARE 9 CAPLUS RECORDS THAT CITE THIS RECORD
(11 CITINGS)
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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Executing the logoff script...

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(FILE 'HOME' ENTERED AT 16:19:43 ON 26 NOV 2018)

FILE 'REGISTRY' ENTERED AT 16:19:50 ON 26 NOV 2018

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L3 173 SEA FILE=CAPLUS ABB=ON PLU=ON L2 AND OPHTHALMIC

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D
 L6 1 SEA FILE=REGISTRY ABB=ON PLU=ON 7647-14-5/RN
 D
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 L8 1 SEA FILE=CAPLUS ABB=ON PLU=ON L3 AND L7
 D IBIB ABS HITSTR TOT
 L9 64 SEA FILE=CAPLUS ABB=ON PLU=ON L7 AND OPHTHALMIC
 L10 1 SEA FILE=CAPLUS ABB=ON PLU=ON L9 AND ATROPINE
 L11 18 SEA FILE=CAPLUS ABB=ON PLU=ON L3 AND L4
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 L13 15 SEA FILE=CAPLUS ABB=ON PLU=ON L3 AND L6
 L14 31 SEA FILE=CAPLUS ABB=ON PLU=ON L11 OR L12 OR L13
 L15 1 SEA FILE=CAPLUS ABB=ON PLU=ON L11 AND L12 AND L13
 L16 0 SEA FILE=CAPLUS ABB=ON PLU=ON L15 NOT L10
 L17 27 SEA FILE=CAPLUS ABB=ON PLU=ON L9 AND BUFFER
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 D IBIB ABS HITSTR TOT
 L20 3 SEA FILE=CAPLUS ABB=ON PLU=ON L1 AND L7
 L21 2 SEA FILE=CAPLUS ABB=ON PLU=ON L20 NOT L10
 L22 2 SEA FILE=CAPLUS ABB=ON PLU=ON L21 NOT L19
 D IBIB ABS HITSTR TOT

COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	93.79	117.80

SESSION WILL BE HELD FOR 120 MINUTES
 STN INTERNATIONAL SESSION SUSPENDED AT 16:40:04 ON 26 NOV 2018

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	20809	atropine	US-PGPUB; USPAT; USOCR	OR	ON	2018/11/26 15:46
S2	18	atropine NEAR ophthalmic	US-PGPUB; USPAT; USOCR	OR	ON	2018/11/26 15:47
S3	1	S2 SAME buffer	US-PGPUB; USPAT; USOCR	OR	ON	2018/11/26 15:48
S4	11	S2 and buffer	US-PGPUB; USPAT; USOCR	OR	ON	2018/11/26 15:48
S5	2	S2 and nacl	US-PGPUB; USPAT; USOCR	OR	ON	2018/11/26 15:48
S6	11	S2 and sodium ADJ1 chloride	US-PGPUB; USPAT; USOCR	OR	ON	2018/11/26 15:49
S7	1	S6 and EDTA	US-PGPUB; USPAT; USOCR	OR	ON	2018/11/26 15:49
S8	1	S6 and EDTA	US-PGPUB; USPAT; USOCR	OR	ON	2018/11/26 15:49
S9	11	S6 and cellulose	US-PGPUB; USPAT; USOCR	OR	ON	2018/11/26 15:50
S10	0	S6 and hyprocellulose	US-PGPUB; USPAT; USOCR	OR	ON	2018/11/26 15:50
S11	1	S6 and hypromellose	US-PGPUB; USPAT; USOCR	OR	ON	2018/11/26 15:50
S12	1	S7 and S11	US-PGPUB; USPAT; USOCR	OR	ON	2018/11/26 15:51
S13	11	S6 and S9	US-PGPUB; USPAT; USOCR	OR	ON	2018/11/26 15:59
S14	1606	A61K31/46.cpc.	US-PGPUB; USPAT; USOCR	OR	ON	2018/11/26 16:12
S15	1530	514/304	US-PGPUB; USPAT; USOCR	OR	ON	2018/11/26 16:13
S16	340	S14 and S15	US-PGPUB; USPAT; USOCR	OR	ON	2018/11/26 16:13
S17	2039	A61K9/48.cpc.	US-PGPUB; USPAT; USOCR	OR	ON	2018/11/26 16:14
S18	6328	A61K9/0048.cpc.	US-PGPUB; USPAT; USOCR	OR	ON	2018/11/26 16:14
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S21	2	S16 and S20	US-PGPUB; USPAT; USOCR	OR	ON	2018/11/26 16:14
S22	6883	A61K47/02.cpc.	US-PGPUB; USPAT; USOCR	OR	ON	2018/11/26 16:15

S23	3988	A61K47/183.cpc.	US-PGPUB; USPAT; USOCR	OR	ON	2018/11/26 16:15
S24	4415	A61K47/38.cpc.	US-PGPUB; USPAT; USOCR	OR	ON	2018/11/26 16:15
S25	3	S16 and S22	US-PGPUB; USPAT; USOCR	OR	ON	2018/11/26 16:15
S26	2	S16 and S23	US-PGPUB; USPAT; USOCR	OR	ON	2018/11/26 16:16
S27	1	S16 and S24	US-PGPUB; USPAT; USOCR	OR	ON	2018/11/26 16:16
S28	6	S21 or S25 or S26 or S27	US-PGPUB; USPAT; USOCR	OR	ON	2018/11/26 16:16
S29	1	"20090041666".pn.	US-PGPUB; USPAT; USOCR	OR	ON	2018/11/26 16:26
S30	1	"20080119448".pn.	US-PGPUB; USPAT; USOCR	OR	ON	2018/11/26 16:36
S31	4	WO-2016172712-\$.did.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2018/11/27 09:33
S32	1	"9421199".pn.	US-PGPUB; USPAT; USOCR	OR	ON	2018/11/27 09:33
S33	25	("20070254914" "20160009705" "20160067238" "20160338947" "20180042911" "6164282" "7491383" "8758816" "9421199").PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2018/11/27 15:29
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S35	13	"976279".ap.	US-PGPUB; USPAT; USOCR	OR	ON	2018/11/27 15:37

11/ 27/ 2018 10:07:55 PM
C:\ Users\ ychu\ Documents\ EAST\ Workspaces\ 15976279.wsp

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)

Application Number	15976279
Filing Date	2018-05-10
First Named Inventor	Navneet PURI
Art Unit	1629
Examiner Name	CHU, YONG LIANG
Attorney Docket Number	102843.0006US2

U.S.PATENTS

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Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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/Y.L.C/	1	JP1-203320	JP		1988-02-05			
/Y.L.C/	2	WO2016/205069	WO	A1	2016-12-22	Presbyopia Therapies, LLC		

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**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	15976279
Filing Date	2018-05-10
First Named Inventor	Navneet PURI
Art Unit	1629
Examiner Name	CHU, YONG LIANG
Attorney Docket Number	102843.0006US2

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T ⁵
	1		
	2		
	3		

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EXAMINER SIGNATURE

Examiner Signature	/YONG L CHU/	Date Considered	11/27/2018

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. ² Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). ³ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁴ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁵ Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)

Application Number	15976279
Filing Date	2018-05-10
First Named Inventor	Navneet Puri
Art Unit	1629
Examiner Name	
Attorney Docket Number	102843.0006US2

U.S.PATENTS						Remove
Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	6164282		2000-12-26	Gwon et al.	
	2	7491383	B2	2009-02-17	Woodward et al.	
	3	8758816	B2	2014-06-24	Fuge et al.	
	4	9421199	B2	2016-08-23	Ostrow et al.	
If you wish to add additional U.S. Patent citation information please click the Add button.						Add

U.S.PATENT APPLICATION PUBLICATIONS						Remove
Examiner Initial*	Cite No	Publication Number	Kind Code ¹	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20070254914	A1	2007-11-01	Wu et al.	
	2	20160009705	A1	2016-01-14	Ostrow et al.	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /Y.L.C/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)

Application Number	15976279
Filing Date	2018-05-10
First Named Inventor	Navneet Puri
Art Unit	1629
Examiner Name	
Attorney Docket Number	102843.0006US2

3	20160067238	A1	2016-03-10	Wu et al.
4	20160338947	A1	2016-11-24	Leahy et al.
5	20180042911	A1	2018-02-15	Ostrow et al.

If you wish to add additional U.S. Published Application citation information please click the Add button.

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number ³	Country Code ²	Kind Code ⁴	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T ⁵
	1	2012161655	WO	A1	2012-11-29	Singapore Health Services PTE LTD		
	2	2015200361	WO	A1	2015-12-30	Sydnexis, Inc.		
	3	2016172712	WO	A2	2016-10-27	Sydnexis, Inc.		
	4	2017204262	WO	A1	2017-11-30	Singapore Health Services PTE LTD		

If you wish to add additional Foreign Patent Document citation information please click the Add button.

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T ⁵

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**INFORMATION DISCLOSURE
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Application Number	15976279
Filing Date	2018-05-10
First Named Inventor	Navneet Puri
Art Unit	1629
Examiner Name	
Attorney Docket Number	102843.0006US2

1	Lund, Walter, et al. "The Kinetics of Atropine and Apotatropine in Aqueous Solutions." Acta Chemica Scandinavica, vol. 22, 1968, pp. 3085–3097.
2	Parry, Nicola, et al. "How to Use Low-Dose Atropine to Slow Myopic Progression in Kids." Eyenet Magazine, Dec 2016, pages 29-31
3	Schier, Joshua G., et al. "Preparing for Chemical Terrorism: Stability of Injectable Atropine Sulfate." Academic Emergency Medicine, vol. 11, no. 4, 2004, pp. 329–334.

If you wish to add additional non-patent literature document citation information please click the Add button

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EXAMINER SIGNATURE

Examiner Signature	/YONG L CHU/	Date Considered	11/27/2018

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. ² Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). ³ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁴ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁵ Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /Y.L.C/



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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/976,279	05/10/2018	Navneet Puri	102843.0006US2

CONFIRMATION NO. 1256

PUBLICATION NOTICE



OC000000103831006

149344
Umberg Zipser LLP
1920 Main Street Suite 750
Irvine, CA 92614

Title:Atropine Pharmaceutical Compositions

Publication No.US-2018-0325888-A1

Publication Date:11/15/2018

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently <http://www.uspto.gov/patft/>.

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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
P.O. BOX 1450
ALEXANDRIA, VA 22313-1450**

Appl No.:	15/976,279	Confirmation No. 1256
Applicant:	Navneet Puri	
Filed:	05/10/2018	
TC/A.U.:	1629	
Examiner:	CHU, YONG LIANG	
Docket No.:	102843.0006US2	
Customer No.:	149344	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT

Sir:

In response to the Office action of September 17, 2018, please amend the above-identified application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Amendments to the Specification -/-

Remarks/Arguments begin on page 7 of this paper.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (original) A liquid storage-stable low-dose ophthalmic atropine composition, consisting essentially of:
 - an aqueous solution comprising a buffer, a tonicity agent, a chelator, a viscosity modifier, and atropine or a pharmaceutically acceptable salt thereof;
 - wherein the atropine or the pharmaceutically acceptable salt thereof is present in the ophthalmic atropine composition in an amount of equal or less than 0.05 wt%;
 - wherein the buffer has a concentration of equal or less than 75mM, and wherein the ophthalmic atropine composition has a pH of between 5.0 and 6.0; and
 - wherein the ophthalmic atropine composition is formulated such that after storage over at least two months at 25 °C and 60% relative humidity equal or less than 0.35% tropic acid is formed from degradation of the atropine.
2. (original) The composition of claim 1, wherein the atropine or the pharmaceutically acceptable salt thereof is atropine sulfate.
3. (original) The composition of claim 1, wherein the atropine or a pharmaceutically acceptable salt thereof is present in the ophthalmic atropine composition in an amount of equal or less than 0.02 wt%.
4. (original) The composition of claim 1, wherein the atropine or a pharmaceutically acceptable salt thereof is present in the ophthalmic atropine composition in an amount of equal or less than 0.01 wt%.
5. (original) The composition of claim 1, wherein the atropine or a pharmaceutically acceptable salt thereof is present in the ophthalmic atropine composition in an amount of between 0.001 wt% and 0.01 wt%.
6. (original) The composition of claim 2, wherein the buffer has a concentration of equal or less than 60mM.

7. (original) The composition of claim 5, wherein the buffer has a concentration of equal or less than 50mM.
8. (original) The composition of claim 6, wherein the buffer comprises monobasic and dibasic sodium phosphate.
9. (original) The composition of claim 7, wherein the buffer comprises monobasic and dibasic sodium phosphate.
10. (original) The composition of claim 1, wherein the chelator is selected from the group consisting of a bicarboxylic acid, a tricarboxylic acid, and an aminopolycarboxylic acid.
11. (original) The composition of claim 8, wherein the chelator is ethylenediaminetetraacetic acid (EDTA).
12. (original) The composition of claim 9, wherein the chelator is ethylenediaminetetraacetic acid (EDTA).
13. (original) The composition of claim 10 wherein the chelator is present in the ophthalmic atropine composition in an amount of equal or less than 0.01 wt%.
14. (original) The composition of claim 1, wherein the ophthalmic atropine composition has a pH of between 5.0 (+/- 0.2) and 5.5 (+/- 0.2).
15. (original) The composition of claim 1, wherein the ophthalmic atropine composition has a pH of between 5.5 (+/- 0.2) and 6.0 (+/- 0.2).
16. (original) The composition of claim 1, wherein the tonicity agent is a pharmaceutically acceptable salt and wherein the salt is present in the ophthalmic atropine composition in an amount of between 0.2 wt% and 0.8 wt%.
17. (original) The composition of claim 1, wherein the viscosity modifier is a hydroxyethyl cellulose, a hydroxypropyl cellulose, or a hydroxypropyl methylcellulose.
18. (original) The composition of claim 1, wherein the ophthalmic atropine composition is substantially free of a preservative.

19. (original) The composition of claim 1, wherein the atropine or a pharmaceutically acceptable salt thereof is present in the ophthalmic atropine composition in an amount of between 0.001 wt% and 0.01 wt%, wherein the buffer comprises monobasic and dibasic sodium phosphate and has a concentration of equal or less than 50mM, wherein the viscosity modifier is a hydroxyethyl cellulose, a hydroxypropyl cellulose, or a hydroxypropyl methylcellulose, and wherein the ophthalmic atropine composition is substantially free of a preservative.
20. (original) The composition of claim 1, wherein the atropine or a pharmaceutically acceptable salt thereof is present in the ophthalmic atropine composition in an amount of between 0.01 wt% and 0.05 wt%, wherein the buffer comprises monobasic and dibasic sodium phosphate and has a concentration of equal or less than 50mM, wherein the viscosity modifier is a hydroxyethyl cellulose, a hydroxypropyl cellulose, or a hydroxypropyl methylcellulose, and wherein the ophthalmic atropine composition is substantially free of a preservative.

REMARKS/ARGUMENTS

Restriction/Election

The Office required restriction/election to a single species invention as the application would contain claims directed to the following patentably distinct species of a liquid atropine composition consisting essentially of an aqueous solution comprising (A) a buffer, (B) a tonicity agent, (C) a chelator, (D) a viscosity modifier, (E) atropine or a pharmaceutically acceptable salt thereof at various concentrations, identifiable in claims 2-20:

(A) a buffer and concentration identifiable in claims 6-8;

(B) a tonicity agent identifiable in claim 16;

(C) a chelator identifiable in claims 10-13;

(D) a viscosity modifier identifiable in claims 17, 19, and 20; and

(E) atropine or a pharmaceutically acceptable salt thereof at a specific range of concentrations identifiable in claims 2-5, 19, and 20.

The applicant respectfully disagrees. Nevertheless, the applicant elects without traverse the following species: (A) phosphate buffer at a concentration of equal or less than 50mM; (B) NaCl as tonicity agent; (C) hydroxypropyl methylcellulose as the viscosity modifier; (D) EDTA as the chelator; and (E) atropine at a concentration of equal or less than 0.02 wt%.

Request For Allowance

Claims 1-20 are pending in this application. The applicant requests allowance of all pending claims.

///

Respectfully submitted,
Umberg/Zipser, LLP

Date: November 5, 2018

By /Martin Fessenmaier/
Martin Fessenmaier, Ph.D.
Reg. No. 46697

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Fax (949) 679-0461

Electronic Acknowledgement Receipt

EFS ID:	34216587
Application Number:	15976279
International Application Number:	
Confirmation Number:	1256
Title of Invention:	Atropine Pharmaceutical Compositions
First Named Inventor/Applicant Name:	Navneet Puri
Customer Number:	149344
Filer:	Martin Fessenmaier
Filer Authorized By:	
Attorney Docket Number:	102843.0006US2
Receipt Date:	05-NOV-2018
Filing Date:	10-MAY-2018
Time Stamp:	17:58:45
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		2018_10_22Response_01_restr iction_election.pdf	100951	yes	6
			28ed62d528b5809031a51f0cfb64436f9f19 497c		

Multipart Description/PDF files in .zip description			
Document Description	Start	End	
Response to Election / Restriction Filed	1	1	
Claims	2	5	
Applicant Arguments/Remarks Made in an Amendment	6	6	

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Information:

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National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/976,279	Filing Date 05/10/2018	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO**APPLICATION AS FILED – PART I**

(Column 1)

(Column 2)

FOR	NUMBER FILED	NUMBER EXTRA	RATE (\$)	FEE (\$)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X \$ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X \$ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

(Column 1)

(Column 2)

(Column 3)

AMENDMENT	11/05/2018	CLAIMS REMAINING AFTER AMENDMENT	MINUS	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)
	Total (37 CFR 1.16(i))	* 20	Minus	** 20	= 0	X \$50 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X \$230 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
TOTAL ADD'L FEE						0	

(Column 1)

(Column 2)

(Column 3)

AMENDMENT	CLAIMS REMAINING AFTER AMENDMENT	MINUS	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X \$ =
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X \$ =
	☐ Application Size Fee (37 CFR 1.16(s))					
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					
TOTAL ADD'L FEE						

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	15976279
	Filing Date	2018-05-10
	First Named Inventor	Navneet PURI
	Art Unit	1629
	Examiner Name	CHU, YONG LIANG
	Attorney Docket Number	102843.0006US2

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	1	JP1-203320	JP		1988-02-05			
	2	WO2016/205069	WO	A1	2016-12-22	Presbyopia Therapies, LLC		

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**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	15976279
Filing Date	2018-05-10
First Named Inventor	Navneet PURI
Art Unit	1629
Examiner Name	CHU, YONG LIANG
Attorney Docket Number	102843.0006US2

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T ⁵
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EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	15976279
Filing Date	2018-05-10
First Named Inventor	Navneet PURI
Art Unit	1629
Examiner Name	CHU, YONG LIANG
Attorney Docket Number	102843.0006US2

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Martin Fessenmaier/	Date (YYYY-MM-DD)	2018-10-19
Name/Print	Martin Fessenmaier	Registration Number	46697

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The information provided by you in this form will be subject to the following routine uses:

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2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
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4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

⑩ 日本国特許庁(JP)

⑪ 特許出願公開

⑫ 公開特許公報(A) 平1-203320

⑬ Int.Cl.⁴

A 61 K 31/135
9/08
31/135
47/00

識別記号

ABF

AEM
3 3 2

庁内整理番号

7330-4C
G-7417-4C

⑭ 公開 平成1年(1989)8月16日

審査請求 未請求 請求項の数 4 (全4頁)

⑮ 発明の名称 安定なジフェンヒドラミン含有水溶液

⑯ 特 願 昭63-25506

⑰ 出 願 昭63(1988)2月5日

⑱ 発 明 者 黒 部 俊 夫 埼玉県熊谷市大字柿沼1000-7
⑱ 発 明 者 立 石 公 男 埼玉県本庄市栄2-4-2
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⑲ 出 願 人 エーザイ株式会社 東京都文京区小石川4丁目6番10号
⑳ 代 理 人 弁理士 古 谷 馨

明 細 書

1. 発明の名称

安定なジフェンヒドラミン含有水溶液

2. 特許請求の範囲

1. pH3～5においてポリビニルピロリドンを含む必須成分として配合してなることを特徴とするジフェンヒドラミン含有水溶液。
2. pH3～5においてポリビニルピロリドンを含む必須成分として配合し、更にグリセリン及び／又はソルビットを配合してなることを特徴とするジフェンヒドラミン含有水溶液。
3. pH3～5においてポリビニルピロリドンを含む必須成分として配合し、更にグリシン、アスパラギン酸、水溶性ポリペプチドから選ばれる1種又は2種以上を配合してなることを特徴とするジフェンヒドラミン含有水溶液。
4. pH3～5においてポリビニルピロリドンを含む必須成分として配合し、更にグリセリン及び／又はソルビットと、グリシン、アスパラギン酸、水溶性ポリペプチドから選ばれる1

種又は2種以上とを配合してなることを特徴とするジフェンヒドラミン含有水溶液。

3. 発明の詳細な説明

(産業上の利用分野)

本発明は、安定なジフェンヒドラミン含有水溶液に関する。従って本発明は医薬品の製剤技術の分野において利用される。即ち、本発明は抗ヒスタミン作用及び抗アレルギー鎮痛作用を有するジフェンヒドラミンを安定に含有する水溶液を提供する製剤技術の発明である。

(従来の技術)

ジフェンヒドラミン含有水溶液は、注射剤、シロップ剤、点眼剤として従来から調製されてきた。これらの製剤において水溶液のpHは一般に中性域に調節されるのが従来技術であった。即ち下記の文献(a)～(b)に示されるとおり、ジフェンヒドラミンは水溶液のpHによってその安定性が著しく変動することが知られているので、水溶液の調製にあたっては、安定なpH域、即ち中性pH域6～7に調節されるのが通常である。

(a) 堀岡ら、薬誌、31(1), 79 (1960)

(b) 日本薬局方第10版(広川書店) C427の「塩酸ジフェンヒドラミン」の注1の項。

しかしながら、ジフェンヒドラミン含有水溶液のpHを酸性域に調節しなければならない場合がある。例えば、ジフェンヒドラミンの外に中性pH域で不安定な臭化水素酸スコポラミン、硫酸アトロピンのごとき他の薬剤を配合する必要があるときに、該薬剤の要請に基づき水溶液のpHを酸性域に調節しなければならない場合がある。またジフェンヒドラミンは、ドリンク剤においては中性pH域で飲用した場合、苦味と同時に口腔内、特に舌上に麻痺感を与え、これが比較的持続性が長いこと、飲用者にとって不快感を生ずることになる。これはジフェンヒドラミンの水溶液中での溶存型が、大部分分子型ジフェンヒドラミンとして、存在するため、この分子型ジフェンヒドラミン量を減少させる方向、即ち酸性pH域とし解離型ジフェンヒドラミンとすることにより軽減することができる。これら

の目的のために、水溶液のpHを安定性の許す限りにおいて酸性域に調節したいとする場合がある。

しかし、これらの場合における要請はジフェンヒドラミンの安定性、とりわけ加水分解に対する安定性との間で矛盾するものであり、それらを損なう結果となることは既に前記したところにより明らかな如くである。この要請が可能となるためには、酸性域のpHにおいてジフェンヒドラミンの安定性を高めるための特別の手段が工夫されなくてはならない。しかし従来の技術において未だ上記の問題を解決するための特別な手段が完成されていない。

(発明が解決しようとする課題)

前記したところにより明らかな如く、本発明が解決しようとする課題は、酸性域のpHであるpH3~5においてジフェンヒドラミンの安定性を高めるための特別の手段を提供することである。

(課題を解決するための手段)

上記課題に対し、本発明者は種々の検討を行った結果、ポリビニルピロリドン必須成分として配合することにより上記課題が解決されることを見出し、本発明を完成するに至った。

即ち、本発明は、pH3~5においてポリビニルピロリドン必須成分として配合してなることを特徴とするジフェンヒドラミン含有水溶液に係わるものである。

本発明においては、ポリビニルピロリドンと共にグリセリン及び／又はソルビット、あるいはグリシン、アスパラギン酸、水溶性ポリペプチドから選ばれる1種又は2種以上を配合することによって、pH3~5において加水分解に対してより安定なジフェンヒドラミン含有水溶液を得ることができる。

更に、pH3~5においてポリビニルピロリドン必須成分として配合し、更にグリセリン及び／又はソルビットと、グリシン、アスパラギン酸、水溶性ポリペプチドから選ばれる1種又は2種以上とを配合してなるジフェンヒドラ

ミン含有水溶液が加水分解に対する安定化において一層好ましい。

以下に本発明を詳細に説明する。

本発明においてジフェンヒドラミンは、抗ヒスタミン剤のための医薬品として通常に入手されるものを使用すればよく、塩酸塩等の塩の形で用いても良い。

通常は経口投与されるが、抗ヒスタミン剤として10~30mgが皮下又は筋肉注射により、また2%軟膏が外用されている。

本発明の水溶液中のジフェンヒドラミン量については特に限定はされないが、本発明が医薬品として使用される関係から通常は0.01~5重量%の濃度が好ましい。

本発明においてポリビニルピロリドンは、PVP K-15, 30, 60, 90 (GAF Corp社製)として入手されるものを使用すればよい。本発明の水溶液中のポリビニルピロリドンの量は、水溶液の必要な保存条件及び投与剤型に応じて適宜に実験により選定すればよいが、例えば0.01~10重量

%の範囲が好ましい。

また、本発明において、ソルビット及びグリセリンは通常に入手されるものを使用すればよく、本発明の水溶液中のそれぞれの量は5～50重量%の範囲が好ましい。

本発明において、グリシン及びアスパラギン酸は、通常に入手されるものを使用すればよく、本発明の水溶液中のそれぞれの量は0.05～5重量%の範囲が好ましい。

本発明において、水溶性ポリペプチドとしては、卵白加水分解物、ゼラチン加水分解物などを使用すればよい。本発明の水溶液中のこれらの量は0.1～5重量%の範囲が好ましい。

本発明の水溶液のpHは3～5である。一般にpHの調整には最大0.5程度の測定誤差が伴うので該pH範囲は厳密に規定されるべきではなく、本発明の技術課題にそって大約3～5の意味に解釈されなければならない。測定誤差の発生を回避するため好ましくは緩衝剤を加えるのがよい。緩衝剤としては、例えばクエン酸緩衝液、

酒石酸緩衝液、リン酸緩衝液等を使用するのが望ましい。

本発明の水溶液に、ジフェンヒドラミン以外の医薬品を含有せしめることは自由である。ジフェンヒドラミン以外の医薬品としては、例えば、臭化水素酸スコボラミン、硫酸アトロピン、マレイン酸クロルフェニラミン、塩酸ピリドキシン、テオフィリン、8-ヒドロキシテオフィリン等を挙げることができる。又、ジフェンヒドラミンの塩酸塩以外にジフェンヒドラミンのサリチル酸塩、タンニン酸塩等を含有せしめることも自由である。

本発明の水溶液は、主にドリンク剤、注射剤、点眼剤として使用される。従って、本発明の水溶液の製造は、これら製剤に応じてそれぞれにおける常法に従って行えばよい。又、本発明の水溶液には、上記の成分の他に、従来のドリンク剤、注射剤、点眼剤等に使用されている公知の添加剤を添加しても良い。

(作 用)

本発明の水溶液における作用は加水分解の抑制であり、具体的にはジフェンヒドラミンの加水分解反応の反応速度定数の低下により示される。即ちポリビニルピロリドンの配合あるいはポリビニルピロリドンとグリセリン等の配合によって、pH3～5における反応速度定数が低下することををもって示される。

(実施例)

以下、実施例により本発明を更に詳細に説明するが、本発明はこれらの実施例に限定されるものではない。

実施例1 (注射剤)

pH 5.0の0.05M クエン酸緩衝液80mlに塩酸ジフェンヒドラミン3g、臭化水素酸スコボラミン0.001g、ポリビニルピロリドン(重合度30)0.1g、ソルビット(結晶)7gを逐次加えて溶解後、全量を100mlとし常法により注射剤を製造する。

実施例2 (点眼剤)

pH 5.0の0.01M リン酸緩衝液90mlに塩酸ジフ

ェンヒドラミン1g、硫酸アトロピン0.001g、ポリビニルピロリドン(重合度30)0.3g、グリシン0.1g、塩化ナトリウム0.8gを逐次加えて溶解する。必要により防腐剤を加えて全量を100mlとし、常法により点眼剤とする。

実施例3 (ドリンク剤)

pH 3.0の0.01M 酒石酸緩衝液50mlに、塩酸ジフェンヒドラミン0.2g、臭化水素酸スコボラミン0.5mg、ポリビニルピロリドン5g、アスパラギン酸1g、パラオキシ安息香酸メチル10mg、フレーバー100mgを逐次加えて溶解し全量を150mlとし、常法によりドリンク剤を製造する。

(発明の効果)

以下の実験例によって本発明の効果を説明する。

実験例1

試 料

pH 2.0, 3.0, 4.0, 5.0の0.01M クエン酸緩衝液に塩酸ジフェンヒドラミンを0.1g/100ml

特開平1-203320 (4)

となるように溶解し、更にポリビニルピロリドン、グリセリン、ソルビット、アミノ酸（グリシン、アラニン、アスパラギン酸）又は水溶性ポリペプチド（卵白加水分解物）をそれぞれ、1%、40%、40%、0.1%、0.1%となるように添加して全量とし、検体試料とした。別に何も添加しないものを用意して対照試料とした。

方 法

各試料を120℃で20分間加熱し、塩酸ジフェンヒドラミンの残存量を測定した。

結 果

いずれの場合も一次反応の形式で塩酸ジフェンヒドラミンの残存量低下が見られたので、下記式によりそれぞれ反応速度定数 K を求めた。

$$K = 2.303 / t \times \log a / (a - x)$$

a = 塩酸ジフェンヒドラミンの初期濃度 (%)

x = t 日後の加水分解された塩酸ジフェンヒドラミンの濃度 (%)

t = day (日)

結果を表1に示す。

表中の値は、反応速度定数 (day^{-1}) を示す。

表1よりポリビニルピロリドン、グリシン、アスパラギン酸、水溶性ポリペプチド、グリセリン又はソルビットを配合することによって pH 3～5 において、塩酸ジフェンヒドラミンの加水分解が抑制されることがわかった。

表 1

添 加 剤 \ pH	2.0	3.0	4.0	5.0
緩 衝 液 の み	1.7×10^{-3}	1.2×10^{-3}	3.8×10^{-4}	1.3×10^{-4}
グ リ セ リ ン	6.0×10^{-3}	4.6×10^{-4}	1.8×10^{-5}	6.1×10^{-6}
ソ ル ビ ッ ト	7.2×10^{-3}	5.3×10^{-4}	7.0×10^{-5}	1.8×10^{-5}
ポリビニルピロリドン	7.4×10^{-3}	9.2×10^{-5}	6.1×10^{-5}	6.1×10^{-5}
グ リ シ ン	—	3.6×10^{-4}	6.1×10^{-5}	6.1×10^{-5}
ア ラ ニ ン	8.9×10^{-3}	8.8×10^{-4}	1.2×10^{-4}	1.1×10^{-4}
アスパラギン酸	—	4.6×10^{-4}	6.0×10^{-5}	6.1×10^{-5}
水溶性ポリペプチド (卵白加水分解物)	—	4.0×10^{-4}	1.2×10^{-5}	1.8×10^{-5}

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(43) International Publication Date
22 December 2016 (22.12.2016)

(10) International Publication Number
WO 2016/205069 A1

- (51) **International Patent Classification:**
A61K 31/439 (2006.01) *A61P 27/02* (2006.01)
A61K 31/165 (2006.01)
- (21) **International Application Number:**
PCT/US2016/036692
- (22) **International Filing Date:**
9 June 2016 (09.06.2016)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
14/742,921 18 June 2015 (18.06.2015) US
14/742,903 18 June 2015 (18.06.2015) US
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- (81) **Designated States** (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.
- (84) **Designated States** (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) **Title:** COMPOSITIONS FOR THE IMPROVEMENT OF DISTANCE VISION AND THE TREATMENT OF REFRACTIVE ERRORS OF THE EYE

(57) **Abstract:** The invention provides compositions and methods for the improvement of distance vision. The invention further provides compositions and methods for the treatment of refractive errors of the eye. The invention further provides compositions that preferably comprise aceclidine lyophilized with a cryoprecipitate separate or together with a diluent comprising a cycloplegic agent, a surfactant, and optionally a viscosity enhancer.

Compositions for the Improvement of Distance Vision and the Treatment of Refractive Errors of the Eye

Background of the Invention

[001] As a person ages the minimum distance from the eye at which an object will come into focus, provided distance vision is corrected or is excellent unaided, increases. For example, a 10 year-old can focus on an object at a “focal point” only three inches (0.072 meters) from their eye while still retaining excellent distance vision; a 40 year-old at six inches (0.15 meters); and a 60 year-old at an inconvenient 39 inches (1.0 meter). This condition of increasing minimum focal length in individuals with excellent unaided distance vision is called presbyopia, loosely translated as “old-man eye”.

[002] Excellent unaided distance vision is also known as emmetropia. The inability to focus on distant focal points is known as myopia and the inability to focus on near focal points is known as hyperopia. Specifically, “distance” vision is considered any focal point 1 meter or more from the eye and near vision is any focal point less than 1 meter from the eye. The minimum focal length at which an object will come into focus is known as the “near point”. The change in focus from distance to the near point and any focal point in between is called accommodation. Accommodation is often measured in diopters. Diopters are calculated by taking the reciprocal of the focal length (in meters). For example, the decrease in accommodation from a 10 year-old eye to a 60 year-old eye is about 13 diopters ($1 \div 0.072 \text{ meters} = 13.89 \text{ diopters}$; $1 \div 1 \text{ meter} = 1 \text{ diopter}$).

[003] The highest incidence of first complaint of presbyopia occurs in people ages 42-44. Presbyopia occurs because as a person ages the eye’s accommodative ability, which uses near reflex-pupil constriction, convergence of the eyes and particularly ciliary muscle contraction, decreases. This reduction in accommodation results in an inadequate change in the normal thickening and increased curvature of the anterior surface of the lens that is necessary for the shift in focus from distant objects to near objects. Important near focus tasks affected by presbyopia include viewing computer screens (21 inches) and reading print (16 inches).

[004] Presbyopia is a normal and inevitable effect of ageing and is the first unmistakable sign for many in their forties that they are getting older. One study found that more than 1 billion people worldwide were presbyopic in 2005. This same study predicted that number to almost double by the year 2050. If everyone over the age of 45 is considered to be presbyopic, then an

estimated 122 million people in the United States alone had presbyopia in 2010. As baby boomers reach the critical age, this number is only going to increase.

[005] Presbyopia carries with it a stigma resulting from the limitation in ability to quickly function at many tasks requiring focusing at both distant and near points, which once occurred almost immediately. In the presbyopic patient, these tasks can be performed only by the use of eyeglasses, contact lenses or after undergoing invasive surgery. One such optical modification, the monovision procedure, can be executed with the use of glasses, contact lenses or even surgery. The monovision procedure corrects one eye for near focus and the other eye for distance focus. However, monovision correction is normally accompanied by loss of depth perception and distance vision particularly in dim light (e.g. night). Other surgical procedures that have been developed to relieve presbyopia include: (1) the implantation of intraocular lenses (INTRACOR®; registered trademark of Technolas Perfect Vision GMBH); (2) reshaping of the cornea (PresbyLASIK and conductive keratoplasty); (3) scleral band expansion; and (4) implantation of corneal inlays (Flexivue MicroLens®; registered trademark of PresbiBio LLC, Kamra®; registered trademark of Acufocus, Inc. and Vue+). Kamra® corneal inlays manufactured by Acufocuswork by inlaying a pinhole on the cornea to increase the depth of focus. A similar effect can be achieved with general miotic agents, such as pilocarpine (a non-selective muscarinic acetylcholine receptor agonist), carbachol (a non-selective muscarinic acetylcholine receptor agonist), and phospholine iodide (an acetylcholinesterase inhibitor). These general miotic agents trigger increased ciliary muscle contraction and induce accommodation of any remaining reserves, improving near vision at the expense of distance vision in individuals who still retain some accommodative function. While these general miotic agents also create improved depth of focus via a pinhole effect induced by pupillary miosis (i.e. constriction), to the degree accommodation occurs, the pinhole effect only partially offsets the induced accommodative myopia for distance. In some cases, such as with pilocarpine or carbachol, the induced accommodation may create up to 5 diopters or more of induced myopia resulting in induced myopia causing blurred distance vision generally and during shift of the focal point from distance to near. These general miotic agents also cause substantial redness, severe nasal congestion and create ciliary muscle spasms, which commonly induces discomfort that can be severe and long-lasting. In extreme cases, such ciliary muscle spasms can result in retinal detachment.

[006] Miotic agents have been described in various patent and patent applications for the treatment of presbyopia. US Patent Nos. 6,291,466 and 6,410,544 describe the use of pilocarpine to regulate the contraction of ciliary muscles to restore the eye to its resting state and potentially restore its accommodative abilities.

[007] US Patent Application Publication No. 2010/0016395 describes the use of pilocarpine with the non-steroidal anti-inflammatory, diclofenac, to reduce brow ache from ciliary spasm and increase the time in which the ciliary muscle contraction is regulated. International PCT Application Publication WO/2013/041967 describes the use of pilocarpine with oxymetazoline or meloxicam to temporarily overcome ocular conditions such as presbyopia.

[008] US Patent No. 8,299,079 (HEK Development LLC) describes the use of direct acting general miotic agents such as pilocarpine, carbachol and phospholine iodide with brimonidine at a concentration from 0.05% to 3.0% w/v. However, the use of brimonidine concentrations at or above 0.05% w/v results in increased rebound hyperemia. For example, rebound redness occurs in 25% of patients using brimonidine 0.20% w/v (Alphagan®, registered trademark of Allergan, Inc.) twice daily.

[009] These attempts at miotic treatment for presbyopia all induce transient myopia of several diopters reducing distance vision to about legal blindness or worse at the expense of improved near vision for the full duration of their action, typically lasting several hours.

[010] Thus, there is a need in the art for a treatment of presbyopia that is non-invasive and convenient with minimal side effects. Specifically, there is a need for an ophthalmological composition that will allow a person suffering from presbyopia to focus on near objects without significant side effects such as diminished distance vision, blurred vision, pain, redness, impaired night driving or incapacitating dim light vision, induced nasal congestion, or risk of retinal detachment. Further, such treatment should provide quick onset in minutes and a duration of full effect of several hours during which a pupillary miosis of between about 1.65 – 2.40 mm and more preferably 1.80 mm – about 2.2 mm is achieved.

Summary of the Invention

[011] In certain embodiments, the present invention is directed to compositions and methods for the treatment of presbyopia.

[012] In certain embodiments, the present invention is directed to compositions and methods for the treatment of presbyopia comprising a muscarinic agonist, wherein the muscarinic agonist

preferentially activates M1 and M3 muscarinic acetylcholine receptors. In still more preferred embodiments the muscarinic agonist is more highly selective for M1 than M3.

[013] In certain embodiments, the present invention is directed to compositions and methods for the treatment of presbyopia comprising a muscarinic agonist that preferentially activates M1 and M3 muscarinic acetylcholine receptors.

[014] In certain embodiments, the present invention is directed to compositions and methods for the treatment of presbyopia comprising a muscarinic agonist selected from the group consisting of aceclidine, talsaclidine, sabcomeline, cevimeline, WAY-132983, AFB267B (NGX267), AC-42, AC-260584, 77-LH-28-1, and LY593039 or any pharmaceutically acceptable salts, esters, analogues, prodrugs or derivatives thereof.

[015] In certain embodiments, the present invention is directed to compositions and methods for the treatment of presbyopia comprising a muscarinic agonist that activates only M1 muscarinic acetylcholine receptors.

[016] In certain other embodiments, the present invention is directed to an ophthalmological composition for the treatment of presbyopia comprising aceclidine.

[017] In certain other embodiments the present invention is directed to an ophthalmological composition for the treatment of presbyopia comprising aceclidine and a cycloplegic agent.

[018] In certain other embodiments, the present invention is directed to an ophthalmological composition for the treatment of presbyopia comprising aceclidine and a selective α -2 adrenergic receptor agonist.

[019] In certain other embodiments, the present invention is directed to an ophthalmological composition for the treatment of presbyopia comprising aceclidine, a cycloplegic agent and a selective α -2 adrenergic receptor agonist.

[020] In certain other embodiments, the present invention is directed to an ophthalmological composition for the treatment of presbyopia comprising a general miotic agent and a cycloplegic agent.

[021] In certain other embodiments, the present invention is directed to an ophthalmological composition of the present invention comprising:

[022] a general miotic agent, a muscarinic agonist or aceclidine;

optionally a cycloplegic agent;

optionally a selective α -2 adrenergic receptor agonist;

a viscosity enhancer; and

a surfactant selected from the group consisting of an anionic surfactant, a nonionic surfactant, and a combination thereof.

[023] The present invention is further directed to a method of improving distance vision comprising administering to a subject in need thereof a composition comprising aceclidine at a concentration from about 0.25% to about 2.0 % w/v and a cycloplegic agent at a concentration from about 0.025% to about 0.1% w/v.

[024] The present invention is further directed to a method of improving depth of focus comprising administering to a subject in need thereof a composition comprising aceclidine at a concentration from about 0.25% to about 2.0 % w/v and a cycloplegic agent at a concentration from about 0.025% to about 0.1% w/v.

[025] The present invention is further directed to a method of improving distance vision comprising administering to a subject in need thereof a composition comprising aceclidine at a concentration from about 0.25% to about 2.0 % w/v and a cycloplegic agent at a concentration from about 0.025% to about 0.1% w/v, wherein the subject has less than 20.20 distance vision prior to the administration of the composition.

[026] The present invention is further directed to a method of improving distance vision comprising administering to a subject in need thereof a composition comprising aceclidine at a concentration from about 0.25% to about 2.0 % w/v and a cycloplegic agent at a concentration from about 0.025% to about 0.1% w/v, wherein the subject has less than 20.20 distance vision prior to the administration of the composition and 20.20 or better distance vision after administration of the composition.

[027] The present invention is further directed to a method of improving distance vision comprising administering to a subject in need thereof a composition comprising aceclidine at a concentration from about 0.25% to about 2.0 % w/v and a cycloplegic agent at a concentration from about 0.025% to about 0.1% w/v, wherein the subject has less than 20.40 distance vision prior to the administration of the composition.

[028] The present invention is further directed to a method of improving distance vision comprising administering to a subject in need thereof a composition comprising aceclidine at a concentration from about 0.25% to about 2.0 % w/v and a cycloplegic agent at a concentration from about 0.025% to about 0.1% w/v, wherein the subject has less than 20.40 distance vision

prior to the administration of the composition and 20.40 or better distance vision after administration of the composition.

[029] The present invention is further directed to a method of improving distance vision comprising administering to a subject in need thereof a composition comprising aceclidine at a concentration from about 0.25% to about 2.0 % w/v and a cycloplegic agent at a concentration from about 0.025% to about 0.1% w/v, a surfactant, a tonicity adjustor, optionally an antioxidant and optionally a viscosity enhancer.

[030] The present invention is further directed to a method of improving distance vision comprising administering to a subject in need thereof a composition comprising aceclidine at a concentration from about 0.25% to about 2.0 % w/v and a cycloplegic agent selected from pirenzepine, tropicamide, cyclopentolate hydrochloride, 4-diphenylacetoxy-N-methylpiperidine methiodide (4-DAMP), AF-DX 384, methocitramine, tripitramine, darifenacin, solifenacin, tolterodine, oxybutynin, ipratropium, oxitropium, tiotropium, otenzepad and a combination thereof, at a concentration from about 0.025% to about 0.1% w/v, preferably tropicamide, a surfactant selected from polyoxyl stearate, a gamma cyclodextrin, sulfobutylether β -cyclodextrin, 2-hydroxypropyl cyclodextrin, sodium lauryl sulfate, sodium ester lauryl sulfate, a poloxamer, a polysorbate, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan monooleate, a polyoxyl alkyl, a cyclodextrin and combinations thereof, preferably polyoxyl 40 stearate, a tonicity adjustor selected from mannitol, sodium chloride, potassium chloride, glycerin and combinations thereof, preferably mannitol, optionally an antioxidant and optionally a viscosity enhancer.

[031] The present invention is further directed to a method of improving distance vision comprising administering to a subject in need thereof a composition comprising aceclidine at a concentration from about 0.25% to about 2.0 % w/v and a cycloplegic agent selected from pirenzepine, tropicamide, cyclopentolate hydrochloride, 4-diphenylacetoxy-N-methylpiperidine methiodide (4-DAMP), AF-DX 384, methocitramine, tripitramine, darifenacin, solifenacin, tolterodine, oxybutynin, ipratropium, oxitropium, tiotropium, otenzepad and a combination thereof, at a concentration from about 0.025% to about 0.1% w/v, preferably tropicamide, a surfactant selected from polyoxyl stearate, a gamma cyclodextrin, sulfobutylether β -cyclodextrin, 2-hydroxypropyl cyclodextrin, sodium lauryl sulfate, sodium ester lauryl sulfate, a poloxamer, a polysorbate, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan

monooleate, a polyoxyl alkyl, a cyclodextrin and combinations thereof, preferably polyoxyl 40 stearate, a tonicity adjustor selected from mannitol, sodium chloride, potassium chloride, glycerin and combinations thereof, preferably mannitol, a viscosity enhancer selected from guar gum, hydroxypropyl-guar, xanthan gum, alginate, chitosan, gelrite, hyaluronic acid, dextran, and a carbomer, preferably carbomer 934 or carbomer 940, wherein the viscosity is from about 1 to about 5000 centipoise ("cps") prior to topical topical instillation and from about 1 to about 50 cps upon topical topical instillation, preferably from about 15 to about 35 cps upon topical topical instillation and optionally an antioxidant.

[032] The present invention is further directed to a method of improving distance vision comprising administering to a subject in need thereof a composition comprising aceclidine at a concentration from about 0.25% to about 2.0 % w/v and a cycloplegic agent selected from pirenzepine, tropicamide, cyclopentolate hydrochloride, 4-diphenylacetoxy-N-methylpiperidine methiodide (4-DAMP), AF-DX 384, methocitramine, tripitramine, darifenacin, solifenacin, tolterodine, oxybutynin, ipratropium, oxitropium, tiotropium, otenzepad and a combination thereof, at a concentration from about 0.025% to about 0.1% w/v, preferably tropicamide, a surfactant selected from polyoxyl stearate, a gamma cyclodextrin, sulfobutylether β -cyclodextrin, 2-hydroxypropyl cyclodextrin, sodium lauryl sulfate, sodium ester lauryl sulfate, a poloxamer, a polysorbate, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan monooleate, a polyoxyl alkyl, a cyclodextrin and combinations thereof, preferably polyoxyl 40 stearate, a tonicity adjustor selected from mannitol, sodium chloride, potassium chloride, glycerin and combinations thereof, preferably mannitol, an antioxidant selected from citrate, citric acid monohydrate, ethylenediaminetetraacetic acid, disodium ethylenediaminetetraacetic acid, dicalcium diethylenetriamine pentaacetic acid and combinations thereof, preferably citrate and optionally a viscosity enhancer.

[033] In a preferred embodiment, the present invention is directed to an ophthalmological composition for the treatment of presbyopia comprising aceclidine at a concentration from about 0.25% to about 2.0% w/v, a polyol selected from mannitol, xylitol, sorbitol, isosorbide, and maltitol as a cryoprecipitate, and tropicamide at a concentration from about 0.025% to about 0.10% w/v.

[034] In another preferred embodiment, the present invention is directed to a method of treating presbyopia or myopia comprising administering to a subject in need thereof a first composition

comprising aceclidine at a concentration from about 0.25% to about 2.0% w/v and mannitol as a cryoprecipitate at a concentration from about 2.5% to about 4.0% w/v and further comprising administering concurrently or sequentially a second composition comprising tropicamide at a concentration from about 0.025% to about 0.1% w/v, polyoxyl 40 stearate at a concentration from about 4.0% to about 5.5% w/v, citrate at a concentration from about 0.01% to about 1.0% w/v, a buffer selected from citrate, phosphate or acetate buffer at a concentration from about 3 mM to about 100 mM and benzalkonium chloride (BAK) at a concentration from about 0.01% to about 0.02% w/v.

[035] In another preferred embodiment, the present invention is directed to a method of treating presbyopia or myopia comprising administering to a subject in need thereof a first composition comprising aceclidine at a concentration from about 1.65% to about 1.75% w/v and mannitol as a cryoprecipitate at a concentration of about 2.5% w/v and further comprising administering concurrently or sequentially a second composition comprising tropicamide at a concentration of about 0.042% w/v, polyoxyl 40 stearate at a concentration of about 5.5% w/v, citrate at a concentration of about 0.1% w/v, acetate buffer at a concentration of about 3 mM and BAK at a concentration of about 0.01% w/v.

[036] In another preferred embodiment, the present invention is directed to a method of treating presbyopia or myopia or hyperopia comprising administering to a subject in need thereof a first composition comprising aceclidine at a concentration from about 1.48% w/v and mannitol as a cryoprecipitate at a concentration of about 4.0% w/v and further comprising administering concurrently or sequentially a second composition comprising tropicamide at a concentration of about 0.042% w/v, polyoxyl 40 stearate at a concentration of about 5.5% w/v, citrate at a concentration of about 0.1% w/v, carbomer 940 at a concentration from about 0.09% to about 0.5% w/v, preferably 0.09% w/v, acetate buffer at a concentration of about 3 mM and BAK at a concentration of about 0.01% w/v.

[037] In another preferred embodiment, the present invention is directed to a method of treating presbyopia or myopia or hyperopia comprising administering to a subject in need thereof a first composition comprising aceclidine at a concentration from about 0.25% to about 2.0% w/v and mannitol as a cryoprecipitate at a concentration from about 2.5% w/v to about 4.0% w/v and further comprising administering concurrently or sequentially a second composition comprising tropicamide at a concentration from about 0.025% to about 0.1% w/v, polyoxyl 40 stearate at a

concentration from about 4.0% to about 5.5% w/v, citrate at a concentration from about 0.01% to about 1.0% w/v, a buffer selected from citrate, phosphate or acetate buffer at a concentration from about 3 mM to about 100 mM and benzalkonium chloride (BAK) at a concentration from about 0.01% to about 0.02% w/v, wherein the first composition and the second composition are administered from one device with at least two chambers and wherein the first composition resides in a first chamber and the second composition resides in a second chamber and wherein the first composition first contacts the second composition at the time of administration.

[038] In another preferred embodiment, the present invention is directed to a method of treating presbyopia or myopia comprising administering to a subject in need thereof a first composition comprising aceclidine at a concentration from about 0.25% to about 2.0% w/v and mannitol as a cryoprecipitate at a concentration from about 2.5% w/v to about 4.0% w/v and further comprising administering concurrently or sequentially a second composition comprising tropicamide at a concentration from about 0.025% to about 0.1% w/v, polyoxyl 40 stearate at a concentration from about 4.0% to about 5.5% w/v, citrate at a concentration from about 0.01% to about 1.0% w/v, a buffer selected from citrate, phosphate or acetate buffer at a concentration from about 3 mM to about 100 mM and benzalkonium chloride (BAK) at a concentration from about 0.01% to about 0.02% w/v, wherein the first composition resides in a first vial and the second composition resides in a second vial and the first composition first contacts the second composition at the time of administration.

[039] It has been surprisingly discovered there is an inverse relationship between aceclidine concentration and mannitol - particularly in the absence of a viscosity enhancer and most particularly in the absence of Carbopol® such that 1.75% aceclidine with 2.5% mannitol and no viscosity agent provides similar therapeutic efficacy to aceclidine 1.48% with 4.0% mannitol and 0.09% Carbopol®; yet aceclidine even at 1.75% with 4.0% mannitol without Carbopol® shows the least efficacy of all three.

[040] It is a further discovery of the present invention that formulations containing polyoxyls and related nonionic surfactants, such as in a preferred embodiment polyoxyl 40 stearate, in the presence of certain viscosity enhancers may in certain concentration combinations result in phase separation, particularly with polysaccharide based viscosity agents such as cellulose derivatives including methyl cellulose, hydroxypropyl cellulose and hydroxypropylmethyl cellulose ("HPMC"). It is prophetically discovered that this insoluble combination is primarily restricted

to polysaccharide based viscosity enhancers, where nonpolysaccharide viscosity enhancers, such as polyacrylic acid derivatives (e.g. carbomers), in a preferred embodiment Carbopol® (carbomer) 934 or Carbopol® (carbomer) 940, may be used in place of polysaccharide based viscosity enhancers in such situations without phase separation.

[041] The present invention is further directed to a method for treating presbyopia comprising administering to a patient in need thereof a composition of the present invention.

[042] The present invention is further directed to a method for treating presbyopia or myopia comprising administering to a patient in need thereof a composition comprising aceclidine and optionally, an α -2 adrenergic agonist and/or a cycloplegic agent, wherein the treatment can be combined in a single formulation or multiple formulations or by co-administration or a sequential administration of an α -2 adrenergic agonist and/or co-administration or a sequential administration of a cycloplegic agent, or preferably co-administration or sequential administration of both.

[043] The present invention is further directed to a method of increasing the visual depth of field (i.e. depth of focus) comprising administering to a subject in need thereof a pharmaceutically effective amount of an ophthalmological composition of the present invention.

[044] The present invention is further directed to a method of increasing the visual depth perception upon improving near vision unaided comprising administering to a subject in need thereof a pharmaceutically effective amount of an ophthalmological composition of the present invention in both eyes (binocular vision), wherein such binocularity further enhances near vision beyond that of either eye separately, and beyond that of monocular corneal inlays such as the Kamra®.

[045] The present invention is further directed to a method of increasing the visual depth perception upon improving near vision unaided comprising administering to a subject in need thereof a pharmaceutically effective amount of an ophthalmological composition of the present invention in both eyes (binocular vision), wherein such binocularity and location of the pin hole at the pupil further enhances quality of distance and near vision beyond that of monocular inlays which may induce light scattering, and require pupil constriction of about 1.60 mm which at the cornea results in increased monocular dimming and loss of optical resolution believed to be due to Rayleigh scattering.

[046] The present invention is further directed to a method of improving vision in a subject with ammetropia (vision abnormality), comprising administering to a subject in need thereof a pharmaceutically effective amount of a composition of the present invention.

[047] The present invention is further directed to a method of improving vision in a subject with ammetropia, comprising administering to a subject in need thereof a pharmaceutically effective amount of a composition of the present invention, wherein ammetropia is selected from the group consisting of nearsightedness, farsightedness, regular astigmatism, irregular astigmatism and high degrees of regular astigmatism.

[048] The present invention is further directed at eliminating optical aberrations induced by corneal irregularity, opacities, or very high degrees of regular astigmatism that include regions adjacent or peripheral to the central 1.5 mm optical zone, and thereby inducing improved visual acuity and quality of vision by filtering out these aberrant optics in those suffering from irregular astigmatism or high degrees of more regular astigmatism, such as occurs in conditions such as keratoconus, photorefractive keratectomy induced corneal haze, diffuse lamellar keratitis ("DLK") (post-lasik DLK), other iatrogenic corneal induced irregularity such as cataract incision, glaucoma filtering blebs, implanted glaucoma valves, corneal inlays with or without removal, ectasia post corneal surgery (lasik), and secondary to infection.

[049] The present invention is further directed at improving acuity relative to existing uncorrected refractive error. Upon this improved acuity, patients now requiring toric contact lenses for astigmatism with reduced comfort and optics that may shift during each blink may in many cases require only non-toric soft contact lenses or no contact lenses. Further, those requiring gas permeable contact lenses may no longer require contact lenses or only require much more comfortable soft contact lenses. Patients with high degrees of astigmatism may now require no correction or reduced astigmatic correction. Patients with small to moderate degrees of nearsightedness may require less correction or no longer require correction. Patients with small to moderate degrees of hyperopia (farsightedness) may require no correction or reduced correction.

[050] The present invention is directed to methods and ophthalmological compositions for improving eye sight. In a preferred embodiment the present invention is directed to methods and ophthalmological compositions for the treatment of presbyopia. In a more preferred embodiment the present invention is directed to ophthalmological compositions comprising aceclidine. In a

yet more preferred embodiment present invention is directed to ophthalmological compositions comprising aceclidine and a low-dose cycloplegic agent. In a most preferred embodiment the present invention is directed to ophthalmological compositions comprising aceclidine, a low-dose cycloplegic agent and a combination of inactive ingredients that make effective and/or enhance aceclidine.

[051] In another embodiment the present invention is directed to a composition comprising aceclidine at a concentration from about 0.25% to about 2.0% w/v, a polyol selected from mannitol, xylitol, sorbitol, isosorbide, and maltitol as a cryoprecipitate and tropicamide at a concentration from about 0.025% to about 0.10% w/v.

[052] In another more preferred embodiment the present invention is directed to a composition comprising aceclidine at a concentration from about 0.25% to about 2.0% w/v, mannitol as a cryoprecipitate at a concentration from about 0.5% to about 6.0%, tropicamide at a concentration from about 0.025% to about 0.10% w/v, polyoxyl 40 stearate at a concentration of about 2.0% w/v or 10.0% w/v, a buffer selected from acetate buffer, phosphate buffer and citrophosphate buffer at a concentration of about 3 millimolar, optionally citric acid monohydrate at a concentration from about 0.1% to about 0.2% w/v, optionally a viscosity enhancer selected from carbomer 934 and carbomer 940 at a concentration from about 0.01% to about 1.0% w/v; and optionally benzalkonium chloride (BAK) at a concentration of about 0.02% w/v, wherein the pH of the composition is from about 4.75 to about 5.0 and wherein the viscosity of the composition is from about 1 to about 5,000 centipoise (cps) at about 10 to about 30 °C.

[053] In another embodiment the present invention is directed to a method for treating a refractive error of the eye comprising administering to a patient in need thereof a pharmaceutically acceptable amount of a composition comprising aceclidine at a concentration from about 0.25% to about 2.0% w/v and a cycloplegic agent at a concentration from about 0.025% to about 0.1% w/v, wherein w/v denotes weight by volume, wherein the size of the pupil is reduced to from about 1.5 to about 2.5 millimeters, preferably from about 1.7 to about 2.0 millimeters, and wherein the refractive error is selected from the group consisting of corneal irregular astigmatism, an ectasia induced corneal irregularity, a pellucid induced corneal irregularity, a higher order aberration and a refractive surgery induced higher order aberration.

Brief Description of the Figures

[054] Figure 1 is a graphical representation of the effects of pilocarpine and aceclidine with or without tropicamide and with or without a carrier on near and distance vision in a patient over the age of 45.

Detailed Description of the Invention

[055] The present invention is directed to compositions and methods of treating presbyopia, irregular astigmatism, and/or refractive error, comprising administering to a patient in need thereof a pharmaceutical composition comprising a muscarinic agonist that preferentially activates M1 and M3 muscarinic acetylcholine receptors, preferably activate M1 more than M3 and most preferably aceclidine or its derivatives. Aceclidine has been surprisingly and unexpectedly discovered to provide enhanced presbyopic reversal with negligible side effects day or night (when viewing includes one or more direct or reflected light sources) using compositions of the present invention.

[056] Aceclidine is traditionally used as a treatment for glaucoma. When aceclidine is used to treat glaucoma it is normally stored in a two-bottle system; one bottle containing the lyophilized aceclidine and the second bottle containing the diluent necessary to reconstitute the lyophilized aceclidine before topical topical instillation. It is a further aspect of the present invention to provide an aqueous aceclidine composition that is stable in combination with cold chain storage. It is yet a further aspect of the present invention to provide a method of stabilizing aqueous aceclidine by combining effective excipients, pH ranges and temperature ranges.

[057] The compositions and methods of the present invention treat presbyopia by improving depth of focus in patients with presbyopia by administering an ophthalmological composition to the eye that reduces pupil dilation in the dark or in dim light, produces a particular degree and duration of miosis without accommodation, provides cosmetic whitening and/or induce redness prophylaxis. The compositions and methods of the present invention also do not cause significant pupil rebound, tachyphylaxis, ciliary spasms, induction of myopia or reduction in distance vision. Additionally, the compositions and methods of the present invention allow for the further improvement in visual acuity and depth perception of binocular (both eyes) treatment. The ophthalmological composition of the present invention surprisingly creates a pupil of from about 1.5 to about 2.4 mm at the anterior iris plane and about 2.0 mm at the corneal surface with negligible increase in accommodative tone and with a reduction or ablation of the redness that is otherwise a hallmark of the use of miotic agents. This pupil miosis with greatly diminished or

absent accommodative tone is superior to the pinhole effect of the Kamra® and Flexivue MicroLens® corneal inlays. Pupil miosis is superior because the constriction of the actual pupil does not result in the attendant severe night vision disturbance caused by the light scattering borders of the pre-corneal pinholes created by the inlays. Further pupil miosis provides a greater field of vision and transmission of more focused light. The use of aceclidine has a minimal effect on the longitudinal ciliary muscle, thus reducing risk of retinal detachment when compared to the use of general muscarinic agonists such as pilocarpine and carbachol. The further inclusion of a cycloplegic agent resulted in only 0.04 mm of anterior chamber shallowing. Aceclidine particularly as enhanced for the present invention also has greater magnitude, duration, and control of minimum pupil diameter. Compositions of the present invention achieve these advantages while having negligible effects on accommodation, thus avoiding the distance blur typically seen in patients as a response to pilocarpine and/or carbachol induced miosis. Any effects on accommodation may be further reduced or totally eliminated in preferred embodiments with a cycloplegic agent. Aceclidine is capable of producing the increased depth of focus by pupil miosis described in the present invention without the need of a selective α -2 adrenergic receptor agonist (" α -2 agonist"). Particularly enhanced miosis occurs with use of compositions of the present invention, thus making it possible to use an α -2 agonist at low concentrations to reduce eye redness. Further, due to the apparent and surprisingly selective nature of aceclidine, administration to the eye almost exclusively affects pupil miosis rather than ciliary muscle contraction. Thus, the administration of aceclidine results in pupil miosis without accommodation and attendant distance blur. However, aceclidine may cause some redness and brow ache, and without formulation enhancement of the present invention may produce less than optimal pupil miosis or at extremely high concentration more than desired peak miosis with added dimming of vision in dim or absent lighting.

[058] Certain embodiments of the present invention enhance the discovered preferred degree of pupillary miosis by providing a consistent range of effect of about 1.50 – 2.20 mm for most patients using a preferred embodiment of a nonionic surfactant and viscosity enhancer. Similar benefit may be achieved using other permeation enhancers, particularly Carbopol®(polyacrylic acid or carbomer), and various viscosity additives that increase drug residence time, such as xanthan gums, guar gum, alginate, and other *in situ* gels well known to experts in the art. The present invention further prevents nasal congestion otherwise occurring when substantial

aceclidine levels reach the nasal mucosa, due to the rheologic properties of the preferred embodiment.

[059] The combination of aceclidine and a low concentration of a selective α -2 adrenergic receptor agonist (α -2 agonist or α -2 adrenergic agonist), such as fadolmidine, brimonidine or guanfacine, allows for the desired miotic effect with diminished or no redness. The use of low concentrations of a selective α -2 agonist results in substantial reduction of hyperemia with greatly reduced risk of rebound hyperemia that is found in concentrations of about 0.06% w/v or more. Furthermore, the use of low concentrations of selective α -2 agonist does not adversely modify the pupil constriction caused by aceclidine. In contrast, the use of brimonidine 0.20% w/v, when topically applied for pupil modulation for night vision, result in tachyphylaxis of pupil modulation due to α -2 receptor upregulation in almost 100% of treated subjects within four weeks of use.

[060] Unexpectedly, the addition of a cycloplegic agent results in reduction of any brow ache or associated discomfort by further reducing the degree of ciliary spasms on topical instillation without impairing the miotic response. This lack of impairment of the miotic response is an unexpected surprising discovery, as particular cycloplegic agents, such as tropicamide, have known pupil dilating effects at concentrations as low as 0.01% w/v (Grünberger J. et al., The pupillary response test as a method to differentiate various types of dementia, Neuropsychiatr, 2009, 23(1), pg 57). More specifically cycloplegic agents cause pupil mydriasis (i.e. dilation of the radial muscle of the iris). Further, the addition of a cycloplegic agent to the miotic agent unexpectedly increases the time at which the pupil maintains the desired size range without becoming too restricted. Peak miotic effect at 30 – 60 minutes can be titrated in inverse relation to the cycloplegic concentration. The concentrations of tropicamide discovered in the present invention apparently cause more relaxation of the ciliary muscle than the iris radial musculature. In fact, iris mydriasis is discovered to be suppressed by the addition of tropicamide to compositions containing concentrations of aceclidine used in the present invention, with instead a more consistent level of miosis for the duration of the miotic effect. Additionally and quite surprisingly, unexpectedly, and beneficially the addition of tropicamide can reduce the degree of peak pupil miosis without inducing mydriasis thereby creating a more constant and ideal pupil size throughout the drug induced miosis. This more consistent pupil size allows for beneficial

near and distance vision without the adverse dimming or loss of resolution due to diffraction limits at the very reduced pupil sizes seen at peak pupil miosis (e.g. 1.25 mm).

[061] Normal distance vision as determined by a Snellen Chart vision exam is 20.20. The legal limit for driving in most states is 20.50 or better and in some states is 20.40 or better. In one aspect of the invention the compositions of the invention are capable upon administration to improve the distance vision of a subject to that within the legal limit for driving in most and even all states. In another aspect of the invention the administration of compositions of the invention causes a subject to have better than normal distance vision.

[062] General miotic agents, such as pilocarpine, carbachol and phospholine diesterase, are capable of causing pupil miosis resulting in improved near vision of presbyopic patients. However, there is an inverse reduction in distance vision associated with these general miotic agents from miosis at peak effect and accommodation that is not seen with aceclidine. The co-administration of a cycloplegic agent with aceclidine surprisingly results in an attenuation of this reduction in distance vision.

[063] Comfort, safety, and efficacy of a preferred embodiment of an ophthalmological composition of the present invention results from the presence of a nonionic surfactant, such as cyclodextrin alpha, beta, or gamma chains, preferably 2-hydroxypropyl beta-cyclodextrin ("HP β CD"), and or sulfobutyl ether derivative of β -cyclodextrin (Captisol[®]), polyoxyl 40 stearate or poloxamer 407; a viscosity enhancing agent, such as carboxymethyl cellulose ("CMC"); a tonicity adjustor, such as sodium chloride; a preservative, such as benzalkonium chloride and a pH from about 5.0 to about 8.0. Further, an increase in the concentration of the viscosity agent and the electrolyte may result in reduced redness. Specifically, increasing CMC from 0.50% to 0.75% w/v (preferably 0.80% w/v) and sodium chloride from 0.25% to 0.50% w/v results in reduced redness.

[064] It has been surprisingly discovered there is an inverse relationship between aceclidine and mannitol such that an increase in mannitol suppresses clinical effectiveness and pupil constriction for a given aceclidine concentration. For example, aceclidine 1.50% with 4% mannitol results in a pupil size of about 2.5 mm and no significant near vision improvement. Aceclidine 1.50% with 2.5 % mannitol achieves a pupil size of about 2.1 mm and significant depth of focus near vision improvement. This difference is attributable to the concentration of aceclidine and mannitol as the remaining components are identical. It has been found through

testing at a variety of aceclidine concentrations in the absence of mannitol that a pupil constricted range of about 1.7-1.9 mm appears to provide best near vision improvement, and 1.60 and below substantial increase in dimming with loss of acuity resolution negating further near vision depth of focus enhancement.

[065] Viscosity enhancement, such as with HPMC, to 35 cps provides enhanced pupil constriction especially in the presence of mannitol. However, it was unexpectedly discovered that HPMC and most other viscosity enhancers result in eventual phase separation with formulations containing nonionic surfactants, most particularly with polyoxyl 40 stearate. Surprisingly and unexpectedly when a non-polysaccharide based viscosity enhancer (e.g. carbomer) was added pupil constriction and depth of focus enhancement resulted. For example, a composition comprising 1.48% aceclidine, 4% mannitol and 0.09% carbomer 940 results in a pupil range of about 1.8 – 1.9 mm and optimum near vision / depth of focus improvement.

In yet another preferred embodiment the formulation may be stored in separate containers, such as separate bottles or a dual chamber bottle. The formulation is then mixed at the time of first use to one solution such that at least one month stability at 25 °C results. In such cases the first container or chamber contains a lyophilized aceclidine with a cryoprecipitate, in a preferred embodiment mannitol. The second container or chamber contains a diluent containing remainder of preferred formulation(s).

[066] The viscosity of compositions of the present invention comprising a viscosity enhancer may be from about 1 to about 5,000 cps prior to topical instillation in the eye. As a result of the shear force applied to the composition as it exits the device used for administration the viscosity is lowered to a range from about 1 to about 50 cps upon topical instillation, preferably from about 15 to about 35 cps.

Definitions

[067] As used herein, the term “composition” is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from a combination of the specified ingredients in the specified amounts.

[068] The term “stabilizing”, as used herein, refers to any process which facilitates and/or enables an active agent to remain in solution. The term “stabilizing”, as used herein, also refers to any means or process which inhibits and/or reduces the tendency of a muscarinic agonist, including aceclidine, to degrade.

[069] As used herein, all numerical values relating to amounts, weights, and the like, that are defined as “about” each particular value is plus or minus 10%. For example, the phrase “about 5% w/v” is to be understood as “4.5% to 5.5% w/v.” Therefore, amounts within 10% of the claimed value are encompassed by the scope of the claims.

[070] As used herein “% w/v” refers to the percent weight of the total composition.

[071] As used herein the term “subject” refers but is not limited to a person or other animal.

[072] The term muscarinic receptor agonist (“muscarinic agonist”) encompasses agonists that activate muscarinic acetylcholine receptors (“muscarinic receptors”). Muscarinic receptors are divided into five subtypes named M1-M5. Muscarinic agonists of the present invention include those muscarinic agonists that preferentially activate M1 and M3 receptors over M2, M4 and M5 receptors (“M1/M3 agonists”). M1/M3 agonists include but are not limited to aceclidine, xanomeline, talsaclidine, sabcomeline, cevimeline, alvameline, arecoline, milameline, SDZ-210-086, YM-796, RS-86, CDD-0102A (5-[3-ethyl-1,2,4-oxadiazol-5-yl]-1,4,5,6-tetrahydropyrimidine hydrochloride), N-arylurea-substituted 3-morpholine arecolines, VUO255-035 (N-[3-oxo-3-[4-(4-pyridinyl)-1-piperazinyl]propyl]-2,1,3-benzothiadiazole-4-sulfonamide), benzylquinolone carboxylic acid (BQCA), WAY-132983, AFB267B (NGX267), AC-42, AC-260584, chloropyrazines including but not limited to L-687, 306, L-689-660, 77-LH-28-1, LY593039, and any quinclidine ring with one or more carbon substitutions particularly that include an ester, sulfur, or 5 or 6 carbon ring structure including with substituted nitrogen(s) and or oxygen(s), or any pharmaceutically acceptable salts, esters, analogues, prodrugs or derivatives thereof. A preferred M1/M3 agonist is aceclidine. In a preferred embodiment, muscarinic agonist of the present invention include those muscarinic agonist that preferentially activate M1 and M3 over M2, M4, and M5; and even more preferably activate M1 over M3.

[073] The term “aceclidine” encompasses its salts, esters, analogues, prodrugs and derivatives including, but not limited to, aceclidine as a racemic mixture, aceclidine (+) enantiomer, aceclidine (-) enantiomer, aceclidine analogues, including, but not limited to, highly M1 selective 1,2,5 thiadiazole substituted analogues like those disclosed in Ward, J.S. et al., 1,2,5-Thiadiazole analogues of aceclidine as potent m1 muscarinic agonists, *J Med Chem*, 1998, Jan. 29, 41(3), 379-392 and aceclidine prodrugs including but not limited to carbamate esters.

[074] The term “selective α -2 adrenergic receptor agonists” or “ α -2 agonist” encompasses all α -2 adrenergic receptor agonists which have a binding affinity of 900 fold or greater for α -2 over

α -1 adrenergic receptors, or 300 fold or greater for α -2a or α -2b over α -1 adrenergic receptors. The term also encompasses pharmaceutically acceptable salts, esters, prodrugs, and other derivatives of selective α -2 adrenergic receptor agonists.

[075] The term "low concentrations" or "low-dose" refers to concentrations from between about 0.0001% to about 0.065% w/v; more preferably, from about 0.001% to about 0.035% w/v; even more preferably, from about 0.01% to about 0.035% w/v; and even more preferably, from about 0.03% to about 0.035% w/v.

[076] The term "brimonidine" encompasses, without limitation, brimonidine salts and other derivatives, and specifically includes, but is not limited to, brimonidine tartrate, 5-bromo-6-(2-imidazolin-2-ylamino)quinoxaline D-tartrate, and Alphagan®.

[077] The terms "treating" and "treatment" refer to reversing, alleviating, inhibiting, or slowing the progress of the disease, disorder, or condition to which such terms apply, or one or more symptoms of such disease, disorder, or condition.

[078] The term "pharmaceutically acceptable" describes a material that is not biologically or otherwise undesirable (i.e. without causing an unacceptable level of undesirable biological effects or interacting in a deleterious manner).

[079] As used herein, the term "pharmaceutically effective amount" refers to an amount sufficient to effect a desired biological effect, such as a beneficial result, including, without limitation, prevention, diminution, amelioration or elimination of signs or symptoms of a disease or disorder. Thus, the total amount of each active component of the pharmaceutical composition or method is sufficient to show a meaningful subject benefit. Thus, a "pharmaceutically effective amount" will depend upon the context in which it is being administered. A pharmaceutically effective amount may be administered in one or more prophylactic or therapeutic administrations.

[080] The term "higher order aberrations" refers to aberrations in the visual field selected from starbursts, halos (spherical aberration), double vision, multiple images, smeared vision, coma and trefoil.

[081] The term "prodrugs" refers to compounds, including, but not limited to, monomers and dimers of the compounds of the invention, which have cleavable groups and become, under physiological conditions, compounds which are pharmaceutically active *in vivo*.

[082] As used herein "salts" refers to those salts which retain the biological effectiveness and properties of the parent compounds and which are not biologically or otherwise harmful at the dosage administered. Salts of the compounds of the present inventions may be prepared from inorganic or organic acids or bases.

[083] The compounds of the present invention can be used in the form of pharmaceutically acceptable salts derived from inorganic or organic acids or bases. The phrase "pharmaceutically acceptable salt" means those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well-known in the art. For example, S. M. Berge et al. describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, 66: 1 *et seq.*

[084] The salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention or separately by reacting a free base function with a suitable organic acid. Representative acid addition salts include, but are not limited to acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate (isothionate), lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmitoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, phosphate, glutamate, bicarbonate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; arylalkyl halides like benzyl and phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained. Examples of acids which can be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, hydrobromic acid, hyaluronic acid, malic acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, malic acid, maleic acid, methanesulfonic acid, succinic acid and citric acid.

[085] Basic addition salts can be prepared *in situ* during the final isolation and purification of compounds of this invention by reacting a carboxylic acid-containing moiety with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia or an organic primary, secondary or tertiary amine. Pharmaceutically acceptable salts include, but are not limited to, cations based on alkali metals or alkaline earth metals such as lithium, sodium, potassium, calcium, magnesium and aluminum salts and the like and nontoxic quaternary ammonia and amine cations including ammonium, tetramethylammonium, tetraethylammonium, methylammonium, dimethylammonium, trimethylammonium, triethylammonium, diethylammonium, and ethylammonium among others. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, piperazine and the like.

[086] The term “ester” as used herein is represented by the formula ---OC(O)A^1 or ---C(O)OA^1 , where A^1 can be alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, a heteroaryl group or other suitable substituent.

[087] As used herein the term “20.X”, wherein X is a whole number, refers to a subject’s score on the Snellen Chart vision exam. For example, 20.15 refers to a score wherein the smallest letters a subject can read on the chart at 20 feet distance are the same letters that a subject of normal visual acuity could read from no more than 15 feet distance from the chart. In further example, refers to a score wherein the smallest letters a subject can read on the chart at 20 feet distance are the same letters that a subject of normal visual acuity could read from 200 feet distance from the chart. Thus, a score of 20.15 represents better distance vision than a score of 20.200.

[088] As used herein, the term “improving distance vision” refers to causing a subject to have improved visual acuity at distances of 1 meter or more. The term “improving distance vision” also refers to causing a subject to have the ability to obtain a better score on the Snellen Chart vision exam.

Compositions of the Invention

[089] In one embodiment, the present invention is directed to an ophthalmological composition comprising aceclidine. In a preferred embodiment, aceclidine is at a concentration from about 0.25% to about 2.0% w/v, more preferably from about 0.50% to about 1.90% w/v, still more preferably from about 1.25% to about 1.85% w/v, and most preferably from about 1.35% to

about 1.65% w/v. As aceclidine is a tertiary amine with asymmetry, both a + and – optical isomer exist (where in some studies (+) is more potent and in others it is felt (-) may be more potent). For the above concentrations polarimetry demonstrated an exactly equal ratio of (+) and (–) isomer for these concentrations. Altering this ratio could therefore alter this concentration range proportional to a change in ratio.

[090] The present invention is further directed to an ophthalmological composition comprising a muscarinic agonist, preferably a nonionic surfactant above its critical micellar concentration for the composition, and a viscosity enhancing agent; or alternatively an *in situ* gelling agent. In preferred embodiments the initial viscosity of the composition on topical application is above 20 cps, preferably 50 cps, and more preferably above 70 cps at low shear (1/s).

[091] Nonionic surfactants suitable for the present invention include cyclodextrins, polyoxyl alkyls, poloxamers or combinations thereof, and may include in addition combinations with other nonionic surfactants such as polysorbates. Preferred embodiments include polyoxyl 40 stearate and optionally Poloxamer 188, Poloxamer 407, Polysorbate 20, Polysorbate 80, ionically charged (e.g. anionic) beta - cyclodextrins with or without a butyrate salt (Captisol®)2-hydroxypropyl beta cyclodextrin (“HPβCD”), alpha cyclodextrins, gamma cyclodextrins, Polyoxyl 35 castor oil, and Polyoxyl 40 hydrogenated castor oil or combinations thereof. Further, substitution of other nonionic surfactants compatible with ophthalmological use allows for similar formulation advantages, which may included but is not limited to one or more of a nonionizing surfactant such as poloxamer, poloxamer 103, poloxamer 123, and poloxamer 124, poloxamer 407, poloxamer 188, and poloxamer 338, any poloxamer analogue or derivative, polysorbate, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, any polysorbate analogue or derivative, cyclodextrin, hydroxypropyl-β- cyclodextrin, hydroxypropyl- γ- cyclodextrin, randomly methylated β-cyclodextrin, β-cyclodextrin sulfobutyl ether, γ- cyclodextrin sulfobutyl ether or glucosyl- β- cyclodextrin, any cyclodextrin analogue or derivative, polyoxyethylene, polyoxypropylene glycol, an polysorbate analogue or derivative, polyoxyethylene hydrogenated castor oil 60, polyoxyethylene (200) , polyoxypropylene glycol (70), polyoxyethylene hydrogenated castor oil, polyoxyethylene hydrogenated castor oil 60, polyoxyl, polyoxyl stearate, nonoxynol, octyphenol ethoxylates, nonyl phenol ethoxylates, capryls, lauroglycol, PEG, Brij®35(polyoxyethyleneglycol dodecyl ether; Brij is a registered trademark of Uniqema Americas LLC), glyceryl laurate, lauryl glucoside, decyl glucoside, or

cetyl alcohol; or zwitterion surfactants such as palmitoyl carnitine, cocamide DEA, cocamide DEA derivatives cocamidopropyl betaine, or trimethyl glycine betaine, N-2(2-acetamido)-2-aminoethane sulfonic acid (ACES), N-2-acetamido iminodiacetic acid (ADA), N,N-bis(2-hydroxyethyl)-2-aminoethane sulfonic acid (BES), 2-[Bis-(2-hydroxyethyl)-amino]-2-hydroxymethyl-propane-1,3-diol (Bis-Tris), 3-cyclohexylamino-1-propane sulfonic acid (CAPS), 2-cyclohexylamino-1-ethane sulfonic acid (CHES), N,N-bis(2-hydroxyethyl)-3-amino-2-hydroxypropane sulfonic acid (DIPSO), 4-(2-hydroxyethyl)-1-piperazine propane sulfonic acid (EPPS), N-2-hydroxyethylpiperazine-N'-2-ethane sulfonic acid (HEPES), 2-(N-morpholino)-ethane sulfonic acid (MES), 4-(N-morpholino)-butane sulfonic acid (MOBS), 2-(N-morpholino)-propane sulfonic acid (MOPS), 3-morpholino-2-hydroxypropanesulfonic acid (MOPSO), 1,4-piperazine-bis-(ethane sulfonic acid) (PIPES), piperazine-N,N'-bis(2-hydroxypropane sulfonic acid) (POPSO), N-tris(hydroxymethyl)methyl-2-aminopropane sulfonic acid (TAPS), N-[tris(hydroxymethyl)methyl]-3-amino-2-hydroxypropane sulfonic acid (TAPSO), N-tris(hydroxymethyl) methyl-2-aminoethane sulfonic acid (TES), 2-Amino-2-hydroxymethyl-propane-1,3-diol (Tris), tyloxapol, and Span[®] 20-80(sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, and sorbitan monooleate). In certain embodiments the addition of an anionic surfactant such as sodium lauryl sulfate and or sodium ester lauryl sulfate may be preferred.

[092] Ophthalmological *in situ* gels which may be added to or substituted for non-gelling viscosity enhancers, or added in addition to one or more nonionic surfactants include but are not limited to gelatin, xanthan gums, alginic acid (alginate), guar gums, locust bean gum, chitosan, pectins and other gelling agents well known to experts in the art. Preferred *in situ* gels include carbomers of various molecular weights including carbomer 934 P and 940 P,

[093] In preferred embodiments the nonionic surfactant is polyoxyl 40 stearate at a concentration from about 1 to about 15% w/v, more preferably at about 5.5% w/v.

[094] In such preferred embodiment, polyoxyl 40 stearate is found to enhance the redness reduction effect preferentially over aqueous solutions and other nonionic surfactants such as poloxamer 407 and β -cyclodextrin.

[095] Viscosity enhancers suitable for the present invention include, but are not limited to, guar gum, hydroxypropyl-guar ("hp-guar"), xanthan gum, alginate, chitosan, gelrite, hyaluronic acid, dextran, Carbopol[®](polyacrylic acid or carbomer) including Carbopol[®] 900 series including

Carbopol® 940 (carbomer 940), Carbopol® 910 (carbomer 910) and Carbopol® 934 (carbomer 934), carboxymethyl cellulose ("CMC"), methylcellulose, methyl cellulose 4000, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxyl propyl methyl cellulose 2906, carboxypropylmethyl cellulose, hydroxyethyl cellulose, or hydroxyethyl cellulose, hyaluronic acid, dextran, polyethylene glycol, polyvinyl alcohol, polyvinyl pyrrolidone, gellan, carrageenan, alginate, carboxyvinyl polymer or combinations thereof. In a preferred embodiment the viscosity enhancer will have an equilibration viscosity less than 100 cps, preferably from about 15 to about 35 cps, and most preferably at about 30 cps. In a preferred embodiment the viscosity enhancer is Carbopol® 934 (carbomer 934) or Carbopol® 940 (carbomer 940) at a concentration from about 0.5% to about 6.0% w/v, preferably from about 0.09% to about 1.0% w/v, more preferably at 0.09%, 0.25%, 0.5%, 0.75%, 0.9% or 1.0% w/v. In another preferred embodiment the viscosity enhancer is guar gum.

[096] Cryoprecipitates suitable for the present invention include, but are not limited to, polyols, which include but are not limited to, mannitol, xylitol, sorbitol, isosorbide, and maltitol, preferably mannitol at a concentration from about 2.5% to about 6.0% w/v, more preferably at 2.5% or 4.0% w/v.

[097] Not wishing to be held to particularly theory, it appears the combination of nonionic surfactant and viscosity enhancer results in nanometer diameter particles that are, for example, spheroid, other geometric shaped rods or ellipsoids, that aggregate such as in bilayers. These particles are at low surface tension and may be at relatively high viscosity, both allowing prolonged residence time with minimal flow with tears exiting the lacrimal puncta thus allowing better penetration of the tear mucosal layer and cornea and reduced nasal mucosal penetration and local effect as well as reduced systemic absorption. Once applied topically an initial viscosity well above 20 cps prevents nasolacrimal drainage and nasal congestion from the aceclidine, which is a direct vasodilating cholinergic drug and may otherwise cause some degree of nasal congestion. Viscosities well above 20 cps may be achieved with the use of carbomer 940 in preferred embodiments. This comfort is achieved without systemic side from nasolacrimal vascular entry into the circulation, suppressing direct effects on nasal mucosa leading to nasal congestion as results from aceclidine aqueous compositions.

[098] The selective α -2 agonist may be included within the composition of the present invention or applied topically preferably just minutes before or just minutes afterward if

additional means to reduce nasal congestion or redness is desired for sensitive subjects. Selective α -2 agonists suitable for the present invention have minimal α -1 agonist activity at low concentrations. For example, for brimonidine, 1% to 2% w/v is considered extremely high, 0.5% to 1.0% w/v still highly inductive of α -1 receptors and toxic for purposes of the present invention. Further, 0.10% to 0.5% w/v is still too high and even 0.070% to 0.10% w/v is associated with a higher than preferred incidence of rebound hyperemia. For most α -2 agonists with a high degree of selectivity (1:900 or greater), 0.050% w/v or even more preferably 0.035% w/v or less is desired. On the other hand some degree of useful activity may occur at one or more orders of magnitude further reduction of concentration. Brimonidine, fadolmidine, guanfacine and other highly selective α -2 agonists of the present invention preferentially stimulate α -2 adrenergic receptors, and even more preferably α -2b adrenergic receptors so that α -1 adrenergic receptors are not stimulated sufficiently enough to cause excessive large vessel arteriolar constriction and vasoconstrictive ischemia. The α -2 agonist may optionally be applied separately or in certain preferred embodiments with formulations of the present invention that do not include an α -2 agonist, such as those formulas with polyoxyl 40 stearate 5.5% w/v as the non-ionic surfactant, although the α -2 agonist is not required except for occasional sensitive subjects. Fadolmidine represents the α -2 agonist with highest hydrophilicity and therefore high surface retention for the present invention. Guanfacine is also highly selective and hydrophilic. Brimonidine is highly selective with moderate lipophilicity. Finally, dexmedetomidine has high selectivity with high lipophilicity that may be used with less efficacy for reducing redness for the purposes of the present invention (although more likely inducing fatigue as a side effect in some patients). In an embodiment using polyoxyl 40 stearate 5.5% w/v; CMC 0.80% w/v; NaCl 0.037% w/v; EDTA 0.015% w/v, borate buffer 5 mM and BAK 0.007% w/v results in redness of about 1.0 to 1.5 out of 4 which is transient lasting about ten minutes, and by 30 minutes returns to about baseline.

[099] In one embodiment, the selective α -2 adrenergic receptor agonist is a compound which has binding affinity of about 900 fold or greater, even more preferably about 1000 fold or greater, and most preferably, about 1500 fold or greater.

[0100] The selective α -2 adrenergic receptor agonist may be present at a concentration from between about 0.0001% to about 0.065% w/v; more preferably, from about 0.001% to about

0.035% w/v; even more preferably, from about 0.01% to about 0.035% w/v; and even more preferably, from about 0.020% to about 0.035% w/v.

[0101] In one embodiment, the selective α -2 adrenergic receptor is selected from the group consisting of brimonidine, guanfacine, fadolmidine, dexmedetomidine, (+)-(S)-4-[1-(2,3-dimethyl-phenyl)-ethyl]-1,3-dihydro-imidazole-2-thione, 1-[(imidazolidin-2-yl)imino]indazole, and mixtures of these compounds. Analogues of these compounds that function as highly selective α -2 agonists may also be used in compositions and methods of the present invention.

[0102] In a more preferred embodiment, the selective α -2 agonist is selected from the group consisting of fadolmidine, guanfacine and brimonidine. In a yet more preferred embodiment the selective α -2 agonist is brimonidine in the form of a salt at a concentration of 0.025% to 0.065% w/v, more preferably from 0.03% to 0.035% w/v. In a preferred embodiment, the salt is a tartrate salt.

[0103] In another yet more preferred embodiment, the selective α -2 agonist is fadolmidine at a concentration from about 0.005% to about 0.05% w/v, more preferably from 0.02% to about 0.035% w/v in the form of a hydrochloride ("HCl") salt.

[0104] In another yet more preferred embodiment, the selective α -2 agonist is guanfacine at a concentration from about 0.005% to about 0.05% w/v, more preferably from 0.02% to about 0.035% w/v in the form of an HCl salt.

[0105] In another yet more preferred embodiment, the selective α -2 agonist is dexmedetomidine at a concentration from about 0.005% to about 0.05% w/v, more preferably from 0.04% to about 0.05% w/v in the form of an HCl salt.

[0106] In another preferred embodiment a pH less than physiologic pH is found to enhance the whitening effect for brimonidine, preferably pH 4.5 to 6.5, and more preferably pH 5.5 to 6.0. However, redness reduction is achieved at all pHs, and enhancement of aceclidine absorption occurs at alkaline pH, such that more effect occurs from a given concentration, and therefore while effective at pH ranges from 4.5 to 8.0, pH range of 6.5 to 7.5 is preferred for the present invention, and 7.0 to 7.5 most preferred.

[0107] The present invention is further directed to an ophthalmological composition further comprising a cycloplegic agent. It is a surprising and totally unexpected discovery of the present invention that certain cycloplegic agents can be combined with miotic agents, particularly for the present invention, aceclidine, without reducing miotic onset, magnitude, or duration; and further

blunt the normally attendant spike in miotic effect coinciding with time of peak absorption in aqueous formulations to provide a constant miosis versus time after onset from 15 to 30 minutes to 6 to 10 hours depending on the desired formulation. The addition of the cycloplegic agent also reduces any residual associated discomfort that may otherwise occur soon after topical instillation, which presumably is a result of ciliary spasms or excessive pupillary miosis.

[0108] Cycloplegic agents suitable for the present invention include, but are not limited to, atropine, Cyclogyl® (cyclopentolate hydrochloride), hyoscine, pirenzepine, tropicamide, atropine, 4-diphenylacetoxy-N-methylpiperidine methobromide (4-DAMP), AF-DX 384, methoctramine, tripitramine, darifenacin, solifenacin (Vesicare), tolterodine, oxybutynin, ipratropium, oxitropium, tiotropium (Spriva), and otenzepad (a.k.a. AF-DX116 or 11-([2-(diethylamino)methyl]-1-piperidinyl)acetyl]-5,11-dihydro-6H-pyrido[2,3b][1,4]benzodiazepine-6-one). In a preferred embodiment the cycloplegic agent is tropicamide at a concentration from about 0.01% to about 0.10% w/v, more preferably from about 0.025% to about 0.080% w/v and still more preferably from about 0.04% to about 0.06% w/v. In another preferred embodiment the cycloplegic agent is a mixture of tropicamide at a concentration from about 0.04% to about 0.07% w/v or pirenzepine or otenzepad at a concentration from about 0.002% to about 0.05% w/v.

[0109] In a preferred embodiment, tropicamide 0.01% w/v was found to slightly reduce brow ache, 0.030% w/v to further reduce and possibly eliminate brow ache and from greater than 0.03% to about 0.07% w/v to completely eliminate brow ache without reduction of the average pupillary miosis diameter over duration of effect. Not to be held to particular theory, it is believed the short onset and weak pupil cycloplegic effect of tropicamide offsets the peak onset of aceclidine's pupillary constriction. This offset creates an essentially constant pupil constriction effect after a short onset period eliminating large depth of focus fluctuation. This offset also accounts for some component of reduced to absent brow ache, and reduced or eliminated excessive dimming that may be undesirable particularly in certain low light conditions.

[0110] Tropicamide in preferred embodiments has demonstrated completely unexpected sensitivity of effect, where at about 0.04% w/v unexpectedly and very effectively reduces or eliminates brow ache and ciliary spasm pain, becoming very noticeably further reduced at 0.042% w/v and absent at 0.044% w/v in a preferred embodiment with no cycloplegia (surprising

due to its common use as a pupil dilating agent). Yet, tropicamide did not reduce the mean degree of pupil miosis, the time of onset of pupil miosis or the subsequent visual benefits. On the contrary, tropicamide blunted the peak miosis seen in aqueous formulations to create a smooth consistent miotic effect over time. It allowed modulation of peak pupil miosis to achieve a more even effect over time with no dilation as has been found with its prior use. Specifically, tropicamide is useful to prevent transient constriction below 1.50 mm at 30 to 60 minutes following aceclidine in some embodiments and to reduce transient excessive and undesirable dimming of vision that may otherwise occur at peak onset of about 30 minutes. As an example, an ophthalmological composition comprising 1.53% w/v aceclidine, 5% w/v HP β CD, 0.75% w/v CMC, 0.25% w/v NaCl, 0.01% w/v BAK and a phosphate buffer at pH 7.0; or 1.45% w/v aceclidine; 5.5% w/v polyoxyl 40 stearate; 0.80% w/v CMC; 0.037% w/v NaCl; 0.015% w/v EDTA; 0.007% w/v BAK and 5mM phosphate buffer at a pH 7.0; was varied from 0.040% w/v tropicamide, where moderate dimming was noted, to 0.044% w/v tropicamide where dimming became almost undetectable other than in extremely dim light conditions. This additional pupil size modulation with a cycloplegic agent allows aceclidine concentrations sufficient for prolonged effect while blunting the attendant peak excessive constriction that is undesirable as well as any uncomfortable brow ache. Surprisingly and due to its short-acting nature, tropicamide achieves this blunting effect without causing mydriasis. Further, in a preferred embodiment, tropicamide 0.014% w/v was found to reduce brow ache, 0.021% w/v to further reduce brow ache and from 0.028% to 0.060% w/v and in some embodiments up to 0.09% w/v to completely eliminate brow ache without cycloplegia (i.e. paralysis of ciliary muscle of the eye).

[0111] It has been found for a racemic 50:50 mixture of (+) and (-) aceclidine optical isomers (where in some studies (+) is more potent and in others it is felt (-) may be more potent) tropicamide effects may vary depending on the ratio of aceclidine to tropicamide. For example, in an ophthalmological composition of the present invention comprising 1.55% w/v aceclidine, 5.5% w/v HP β CD or in a preferred embodiment polyoxyl 40 stearate, 0.75% w/v CMC (1% = 2,500 centipoise), 0.25% w/v NaCl, and 0.01% w/v BAK and at pH 7.5, 0.042% w/v tropicamide can be differentiated from even 0.035% w/v, with the former demonstrating normal indoor night vision and the latter slight dimming that becomes more noticeable at still lower concentrations. At higher concentrations, such as from about 0.075% to about 0.090% w/v tropicamide, loss of optimal range pupil constriction 1.50 mm to 1.80 mm range begins, and

frank mydriasis at higher concentrations begins to occur. As isomer ratio may alter the effective concentration, this must be factored into the clinical efficacy anticipated using aceclidine; for preferred embodiments of the present invention a polarimeter was used to determine an exact 50:50 isomer ratio was used (personal communication Toronto Research Chemicals).

[0112] FIG. 1 shows the effect of a miotic agent with or without a cycloplegic agent and with or without a carrier. Subject is an emmetrope over the age of 45 with a baseline near vision of 20.100 and baseline distance vision of 20.20. Topical administration to the eye of 1% w/v pilocarpine in saline solution results in an improvement of near vision to 20.40 (8a), however this improvement comes at the expense of a reduction in distance vision to 20.100 (8b). The addition of 0.015% w/v tropicamide results in an improvement of near vision to 20.25 (9a) and a lessening of the reduction of distance vision to 20.55 (9b), though in certain instances with some induced irregular astigmatism (mildly blotched areas in reading field of vision). Topical administration of 1.55% w/v aceclidine in saline solution results in an improvement of near vision to 20.40 for an extended time period of 6 hrs (10a) without any effect on the baseline distance vision (10b). 10c and 10d show the effects of administering aceclidine in a carrier composed of 5.5% w/v 2-hydroxypropyl beta cyclodextrin, 0.75% w/v CMC (1% = 2,500 centipoise), 0.25% w/v NaCl, and 0.01% w/v BAK. As seen in 10c the carrier increases the beneficial effect of aceclidine resulting in better than 20.20 near vision. As seen in 10d a similar increase in distance vision occurs. 10e and 10f show the effects of adding 0.042% w/v tropicamide to the aceclidine in the carrier. As seen in 10e near vision is improved to 20.15 with a quicker onset of maximum visual acuity. As seen in 10f a similar improvement is seen in distance vision. Taken together, FIG. 1 shows that aceclidine is capable of temporarily correcting near vision in a presbyopic subject without affecting the baseline distance vision. Similar results can be achieved with a different miotic agent, pilocarpine, with the addition of a cycloplegic agent such as tropicamide. A proper drug carrier can also have a beneficial effect.

[0113] The present invention is further directed to an ophthalmological composition further comprising a tonicity adjustor and a preservative.

[0114] A tonicity adjustor can be, without limitation, a salt such as sodium chloride ("NaCl"), potassium chloride, mannitol or glycerin, or another pharmaceutically or ophthalmologically acceptable tonicity adjustor. In certain embodiments the tonicity adjustor is 0.037% w/v NaCl,

[0115] Preservatives that can be used with the present invention include, but are not limited to, benzalkonium chloride ("BAK"), chlorobutanol, thimerosal, phenylmercuric acetate, disodium ethylenediaminetetraacetic acid, phenylmercuric nitrate, perborate or benzyl alcohol. In a preferred embodiment the preservative is BAK at a concentration of about 0.001% to about 0.02% w/v. In another preferred embodiment the preservative is perborate at a concentration of 0.01% to about 1.0% w/v, more preferably at a concentration of about 0.02% w/v.

[0116] Various buffers and means for adjusting pH can be used to prepare ophthalmological compositions of the invention. Such buffers include, but are not limited to, acetate buffers, citrate buffers, phosphate buffers and borate buffers. It is understood that acids or bases can be used to adjust the pH of the composition as needed, preferably of 1 to 10 mM concentration, and more preferably about 5 mM. In a preferred embodiment the pH is from about 4.0 to about 8.0, in a more preferred embodiment the pH is from about 4.5 to about 5.0.

[0117] The present invention is further directed to an ophthalmological composition further comprising an antioxidant. Antioxidants that can be used with the present invention include but are not limited to disodium ethylenediaminetetraacetic acid at a concentration from about 0.005% to about 0.50% w/v, citrate at a concentration from about 0.01% to about 0.3% w/w, dicalcium diethylenetriamine pentaacetic acid ("Ca2DTPA") at a concentration from about 0.001% to about 0.2% w/v, preferably about 0.01% w/v Ca2DTPA which can be formulated by adding 0.0084% w/v $\text{Ca}(\text{OH})_2$ and 0.0032% w/v pentetic acid to the formulation and mixing slowly. Further combinations of antioxidants can be used. Other antioxidants that can be used with the present invention include those well known to experts in the art such as ethylenediaminetetraacetic acid at a concentration from about 0.0001% to about 0.015% w/v.

[0118] It is a surprising and unexpected discovery that topical formulations of the present invention, particularly one of the preferred embodiments comprising aceclidine 1.35% to 1.55% w/v; 5.5% w/v polyoxyl 40 stearate; 0.80% w/v CMC; 0.037% w/v NaCl; 0.015% w/v EDTA; 0.007% w/v BAK; and 5mM phosphate buffer at pH 7.0 result in considerably prolonged contact lens wear and comfort after a single topical instillation daily. The single daily use of the preferred embodiments allowed a subject with dry eye to sleep in his lenses for one week periods where previously even after a single night vision would be blurred and contact lenses coated with film requiring removal and cleaning or replacement (see Example 7).

[0119] The following representative embodiments are provided solely for illustrative purposes and are not meant to limit the invention in any way.

Representative Embodiments

[0120] In another embodiment, the ophthalmological composition comprises:

- aceclidine at a concentration of about 1.42% w/v;
- tropicamide at a concentration of about 0.042% w/v;
- polyoxyl 40 stearate at a concentration of about 5.5% w/v;
- mannitol at a concentration of about 4.0% w/v;
- citrate at a concentration of about 0.2% w/v;
- acetate buffer at a concentration of about 3.0 mM;
- wherein said composition has a pH of about 5.0.

[0121] In another embodiment, the ophthalmological composition comprises:

- aceclidine at a concentration of about 1.50% w/v;
- tropicamide at a concentration of about 0.042% w/v;
- polyoxyl 40 stearate at a concentration of about 4.0% w/v;
- mannitol at a concentration of about 4.0% w/v;
- Carbopol® 934 (carbomer 934) at an amount effective to achieve 30-33 cps upon topical topical instillation;
- citrate at a concentration of about 0.2% w/v;
- acetate buffer at a concentration of about 3.0 mM;
- wherein said composition has a pH of about 4.75.

[0122] In another embodiment, the ophthalmological composition comprises:

- aceclidine at a concentration of about 1.50% w/v;
- tropicamide at a concentration of about 0.042% w/v;
- polyoxyl 40 stearate at a concentration of about 5.5% w/v;
- mannitol at a concentration of about 4.0% w/v;
- Carbopol® 934 or 940 (carbomer 934 or 940) at an amount effective to achieve 30-33 cps upon topical topical instillation;
- acetate buffer at a concentration of about 3.0 mM;
- wherein said composition has a pH of about 5.0.

[0123] In another embodiment, the ophthalmological composition comprises:

aceclidine at a concentration of about 1.48% w/v;
tropicamide at a concentration of about 0.042% w/v;
polyoxyl 40 stearate at a concentration of about 5.5% w/v;
mannitol at a concentration of about 4.0% w/v;
citrate at a concentration of about 0.2% w/v;
guar gum at an amount effective to achieve 30-33 cps;
acetate buffer at a concentration of about 3.0 mM;
wherein said composition has a pH of about 4.75.

[0124] In another embodiment, the ophthalmological composition comprises:

aceclidine at a concentration of about 1.75% w/v;
tropicamide at a concentration of about 0.042% w/v;
polyoxyl stearate at a concentration of about 5.5% w/v;
mannitol at a concentration of about 2.5% w/v;
acetate buffer at a concentration of about 3.0 mM;
wherein said composition has a pH of about 4.75.

[0125] In another embodiment, the ophthalmological composition comprises:

aceclidine at a concentration of about 1.75% w/v;
tropicamide at a concentration of about 0.042% w/v;
polyoxyl 40 stearate at a concentration of about 4.5% w/v;
mannitol at a concentration of about 2.5% w/v;
acetate, citrophosphate, or phosphate buffer at a concentration of about 3.0 mM; and
BAK at a concentration of about 0.02% w/v,
wherein said composition has a pH of about 4.75.

[0126] In another embodiment, the ophthalmological composition comprises:

aceclidine at a concentration of about 1.55% w/v;
tropicamide at a concentration of about 0.042% w/v;
polyoxyl 40 stearate at a concentration of about 5.5% w/v;
citric acid monohydrate at a concentration of about 0.1% w/v;
mannitol at a concentration of about 4.0% w/v;
Carbopol® (carbomer) 940 at a concentration of 0.09% w/v;
acetate buffer at a concentration of about 3.0 mM; and

BAK at a concentration of about 0.02% w/v,
wherein said composition has a pH of about 4.75.

[0127] In another embodiment, the ophthalmological composition comprises:

aceclidine at a concentration of about 1.50% w/v;
tropicamide at a concentration of about 0.042% w/v;
polyoxyl 40 stearate at a concentration of about 5.5% w/v;
mannitol at a concentration of about 2.5% w/v;
phosphate buffer at a concentration of about 3.0 mM;
Carbopol® (carbomer) 940 at a concentration of about 0.25% w/v; and
BAK at a concentration of about 0.02% w/v,
wherein said composition has a pH of about 4.75.

[0128] In another embodiment, the ophthalmological composition comprises:

aceclidine at a concentration of about 1.45% w/v;
tropicamide at a concentration of about 0.042% w/v;
polyoxyl 40 stearate at a concentration of about 5.5% w/v;
mannitol at a concentration of about 4.0% w/v;
citric acid monohydrate at a concentration of about 0.1% w/v;
acetate buffer at a concentration of about 3.0 mM; and
Carbopol® (carbomer) 940 at a concentration of about 0.75% w/v,
wherein said composition has a pH of about 4.75.

[0129] In another embodiment, the ophthalmological composition comprises:

aceclidine at a concentration of about 1.45% w/v;
tropicamide at a concentration of about 0.042% w/v;
polyoxyl 40 stearate at a concentration of about 5.5% w/v;
mannitol at a concentration of about 4.0% w/v;
citric acid monohydrate at a concentration of about 0.1% w/v;
phosphate buffer at a concentration of about 3.0 mM; and
Carbopol® (carbomer) 940 at a concentration of about 1.0% w/v,
wherein said composition has a pH of about 4.75.

[0130] In another embodiment, the ophthalmological composition comprises:

aceclidine at a concentration of 1.5% w/v, mannitol at a concentration of 2.5% w/v,

[0131] In another embodiment, the ophthalmological composition comprises:

aceclidine at a concentration of 1.55% w/v, mannitol at a concentration of 2.5% w/v.

[0132] In another embodiment, the ophthalmological composition comprises:

aceclidine at a concentration of 1.6% w/v, mannitol at a concentration of 2.5% w/v.

[0133] In another embodiment, the ophthalmological composition comprises:

aceclidine at a concentration of 1.65% w/v, mannitol at a concentration of 2.5% w/v.

[0134] In another embodiment, the ophthalmological composition comprises:

aceclidine at a concentration of 1.7% w/v, mannitol at a concentration of 2.5% w/v.

[0135] In another embodiment, the ophthalmological composition comprises:

aceclidine at a concentration of 1.75% w/v, mannitol at a concentration of 2.5% w/v.

[0136] In another embodiment, the ophthalmological composition comprises:

aceclidine at a concentration of 1.48% w/v, mannitol at a concentration of 4.0% w/v and
Carbopol® (carbomer) 940 at a concentration of 0.09% w/v.

[0137] In another embodiment, the ophthalmological composition comprises:

aceclidine at a concentration of 1.48% w/v, mannitol at a concentration of 4.0% w/v and
Carbopol® (carbomer) 940 at a concentration of 0.50% w/v.

[0138] In another embodiment, the ophthalmological composition comprises:

aceclidine at a concentration of 1.48% w/v, mannitol at a concentration of 4.0% w/v and
Carbopol® (carbomer) 940 at a concentration of 0.9% w/v.

[0139] The following Examples are provided solely for illustrative purposes and are not meant to limit the invention in any way.

Examples

Example 1-Effect of aceclidine on vision of subjects aged 47 to 67 years

[0140] Table 1 demonstrates the effect on the near focus ability of presbyopic subjects before and after ophthalmological administration of a composition containing aceclidine. Each composition included aceclidine in the concentrations indicated and 5.5% w/v HPβCD, 0.75% w/v CMC, 0.25% w/v NaCl and 0.01% w/v BAK. Additionally compositions administered to

subjects 4 and 5 included 0.125% w/v tropicamide. As aceclidine is an enantiomer, the clinical effectiveness may vary with different ratios. For the present studies a nearly exact 50:50 ratio of stereoisomers was measured as best determined by polarimetry.

Table 1. Effects of aceclidine on vision of presbyopic patients.

Date	#	Age	Aceclidine %	Vision Baseline				Post Gtt 15"				Effect (h)
				R Pre Dist	L Pre Dist	R Pre Near	L Pre Near	R Post Dist	L Post Dist	R Post Near	L Post Near	
8/21/2013	1	67	1.5	20.30	20.30	20.50	20.60	20.20	20.20	20.15	20.15	9.00
8/22/2013	2	52	1.5	20.30	20.30	20.50	20.50	20.25	20.25	20.25	20.20	8.00
8/23/2013	3	61	1.5	20.40	20.30	20.60	20.50	20.20	20.25	20.15	20.15	8.00
8/23/2013	4	61	1.1	20.20	20.25	20.80	20.50	20.15	20.15	20.20	20.15	12.00
8/23/2013	5	53	1.1	20.20	20.20	20.60	20.60	20.20	20.20	20.25	20.25	7.00
8/24/2013	6	47	1.5	20.25	20.25	20.100	20.100	20.20	20.20	20.15	20.15	8.00
8/25/2013	7	58	1.5	20.30	20.200	20.100	20.30	20.25	20.30	20.20	20.30	8.00

[0141] As seen in Table 1 all subjects had less than perfect near vision (20.20) in both the left and right eye (object at 15 inches from the eye) and most subjects had less than perfect distance vision before administration of the composition. After administration of the composition all subjects experienced an improvement in their near vision that lasted from 7 to 12 hours. Surprisingly, the majority of subjects also experienced improvement of their distance vision for the same time period. Still more surprisingly the improvement in near point was much closer than 16" typically required for comfortable reading, in some cases to about 8.5" more commonly seen in individuals 30 or less. The addition of tropicamide, a cycloplegic agent, had no additive or deleterious effect on vision correction.

Example 2 Effect of concentration of concentration of aceclidine and tropicamide

	#1	#2	#3	#4	#5 (OD)	#5 (OS)	#6	#7
Brimonidine	0.03%	0.03%	0.03%	0.03%	0.03%	0.03%	0.03%	
Poloxamer 407	5.5%							
HPBCD		5.5%	5.5%	5.5%	5.5%	5.5%	5.5%	5.5%
Aceclidine	1.5%	1.5%	0.75%	1.1%	1.1%	1.1%	1.1%	1.1%
Tropicamide				0.014%	0.021%	0.028%	0.042%	0.062%
NaCl	0.25%	0.25%	0.25%	0.25%	0.25%	0.25%	0.25%	0.25%
CMC	0.75%	0.75%	0.75%	0.75%	0.75%	0.75%	0.75%	0.75%
BAK	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
Redness (15 m)	3+	1	0.5	0.5	0	0	0	0
Redness (30 m)	1.5	0.5	0.25	0.25	0	0	0	0
Brow Ache (60 m)	2+	2+	2	0.5	0.5	0.0	0.0	0.0
Stinging (10 m)	2	2	0.5	0	0	0	0	0
BD-OD	20.20	20.20	20.20	20.20	20.20	20.20	20.20	20.20
BD-OS	20.25	20.25	20.25	20.25	20.25	20.25	20.25	20.25
BN-OD	8 pt	8 pt	8 pt	8 pt	8 pt	8 pt	8 pt	8 pt
BN-OS	7 pt	7 pt	7 pt	7 pt	7 pt	7 pt	7 pt	7 pt
BP-photopic	3 mm	3 mm	3 mm	3 mm	3 mm	3 mm	3 mm	3 mm
BP-mesopic	5 mm	5 mm	5 mm	5 mm	5 mm	5 mm	5 mm	5 mm
Miosis start (m)	15	15	15	15	15	15	15	15
Miosis (OU) (1 hr)	1.63 mm	1.63 mm	2.0-2.5 mm	1.63 mm	1.63 mm	1.63 mm	1.63 mm	1.70 mm
Distance (OU) (20 m)	20.20	20.20	20.20	20.20	20.20	20.20	20.20	20.20
Distance (OD) (1hr)	20.15+2	20.15+2	20.20	20.15+2	20.15+2	20.15+2	20.15+2	20.15+2
Distance (OS) (1hr)	20.15+2	20.15+2	20.20	20.15+2	20.15+2	20.15+2	20.15+2	20.15+2
Distance (OU) (1hr)	20.10-3	20.10-3	20.15	20.10-3	20.10-3	20.10-3	20.10-3	20.10-3
Near (OU) (20 m)	4 pt	4 pt	4pt	4 pt	4 pt	4 pt	4 pt	4 pt
Time (hr)	12.5	12.5	6.5	11	10	10		

Table 2: Effect of concentration of concentration of aceclidine and tropicamide.

[0142] Abbreviations: (C) indicates corrected vision, (m) indicates minutes, (hr) indicates hour, mm indicates millimeters, BD indicates baseline distance vision; BN indicates baseline near vision, BP indicates baseline pupil size, OD indicates right eye; OS indicates left eye and OU indicates both eyes.

[0143] All percentages are w/v. "pt" reflects size of print materials, 4 being equivalent to 20/20 vision and 3 to 20/15 vision.

[0144] "Time" refers to duration of the effect.

[0145] As seen in Table 2 aceclidine at a concentration of at least 1.1% w/v was able to reduce the size of the pupil to 1.63 mm 1 hour after topical instillation resulting in corrected near and distance vision for at least 10 hours. Lowering of the concentration of aceclidine to 0.75% w/v (formula #3) reduced the miotic effect to 2.0-2.5 mm after 1 hour and vision correction lasted

only 6.5 hours. The addition of 0.03% w/v brimonidine reduced redness of the eye (4 out of 4 without brimonidine, not shown) to 1.5 out of 4 within 30 minutes after topical instillation which was maintained for the entire time vision was corrected. Switching the nonionic surfactant to HP β CD (formulas #2-6) further reduced the redness of the eye. Lowering of the concentration of aceclidine to 0.75% w/v (formula #3) further reduced eye redness but as mention above also reduced the vision correction duration of the formula.

[0146] A brow ache and stinging in the eye were noticeable in formulas #1-3 with a 2 out of 4 level of pain which was also associated with feelings of slight nausea, upset stomach and fatigue. Surprisingly, the addition of a cycloplegic agent, tropicamide, reduced brow ache and stinging to 0.5 out of 4 and 0 out of 4 respectively with brow ache dissipating after 60 minutes (formula #4). Further, the raising of the concentration of aceclidine to 1.1% w/v restored the longer duration of corrected vision seen in formulas #1-2 without increasing eye redness. However, upon re-topical instillation of formula #4 at the end of the 10 hours noticeable brow ache occurred. Topical instillation of formula #5 (OD) and (OS), with increased tropicamide concentrations, following formula #4 relieved the brow ache experienced with re-installation of formula #4. Upon a 3rd topical instillation, at the end of the effective duration of formula #5, re-topical instillation of formula #5 again led to considerable brow ache. Once again, in formula #6, raising the concentration of tropicamide was able to overcome the brow ache. Additionally and unexpectedly, tropicamide, despite being a cycloplegic agent, had no effect on pupil miosis or vision correction. Surprisingly, the addition of tropicamide resulted in a prolonged duration of optimal pupil size constriction.

[0147] To determine the effect of brimonidine on pupil miosis, formula #7, was administered. Administration of formula #7 resulted in only a slight decrease in pupil miosis to 1.70 mm with identical distance and near vision improvement to that of formula #5. A 2-3+ conjunctival injection was noted.

[0148] All baseline vision data was based on vision corrected with distance contact lenses. Near vision was noted by subject as outstanding from 8 inches to the horizon at 1.5 hours after installation. A Marco Autorefractor with infrared camera and superimposed pupil calibration scale was used for all pupil size measurements. Once an image was selected it remained on screen allowing accurate calibration.

Example 3 Effect of concentration of aceclidine, brimonidine, guanfacine, fadolmidine, tropicamide and additives

Table 3: Effect of concentration of aceclidine, brimonidine, guanfacine, fadolmidine, tropicamide and additives.

	AB2T	AB4T	AB6T	AB11T	AB12T	PROPH13
Aceclidine	1.55	1.55	1.55	1.55	1.85	1.55
Brimonidine	0.037	0.037	0.037	0.037		
Fadolmidine						0.037
Guanfacine					0.037	
HPBCD	5.5	5.5	5.5	5.5	5.5	5
Tropicamide	0.043	0.043	0.043	0.043	0.042	0.043
CMC*	0.075	0.075	0.075	0.075	0.075	0.075
NaCl	0.025	0.025	0.025	0.025	0.025	0.025
BAK	0.01	0.01	0.01	0.01	0.01	0.01
Glycerin	0.1		0.1			0.1
Poloxamer 188	0.1	0.05				
Polyoxyl 40 stearate		0.05				
pH	6.5	7.5	7.5	7.5	7.0	7.5
nasal congestion	0	0	0	0	0	0
stinging initial	0.75	0	1.5	3.5	0	1.5
stinging, 3 min	0.5	0	0	wash out	0	0
redness initial	0	0	1	D/C	1	1
redness 15 min	0	0	0	D/C	0	0
whitening	0	0	0	D/C	1.5	1.5
pain	0	0	0	D/C	0	0
vision near	20.30	20.15	20.15	D/C	20.15	20.15
vision distance	20.20	20.20	20.20	D/C	20.20	20.20
onset (min)	20	12	16	D/C	12	16
duration (hrs)	5.5	7.5	7.5	D/C	7.5	7.5
color	clear	yellow	yellow	yellow	yellow	yellow
OVERALL	2.5	3.9	3.8	0	4	3.9

[0149] *1% = 2,500 cps

[0150] All percentages are w/v. Scores for nasal congestion, stinging initial, stinging, 3 min, redness initial, redness 15 min, whitening, pain and overall are out of 4.

[0151] "pt" reflects size of print materials, 4 being equivalent to 20/20 vision and 3 to 20/15 vision.

[0152] Baseline vision was 20.20 both eyes for distance; 20.70 right eye unaided for near; 20.80 left eye for near (best @ 16").

[0153] D/C stands for discontinued after eye washing due to intolerable stinging.

[0154] Aceclidine at a concentration of 1.55% w/v was able to reduce the size of the pupil to about 1.63 mm 30 minutes after topical instillation resulting in corrected near and distance vision to 20.20 or better for at least 6 hours, with noticeable affect lasting about 7.5 hours as seen in Table 3. Lowering of the concentration of aceclidine to 1.25% w/v (not shown) resulted in useful near vision improvement to about 20.25 – 20.30, but not as effective as at the higher dose range alkaline pH resulted in quicker onset, longer duration, and greater effect. The addition of 0.037% w/v brimonidine reduced redness of the eye (4 out of 4 without brimonidine, not shown) to baseline within 15 minutes after topical instillation which was maintained for the about the entire time vision was corrected. Adding glycerin 0.10% w/v noticeably reduced stinging. Adding instead poloxamer 188 0.05% w/v and polyoxyl 40 stearate 0.05% w/v however reduced initial stinging further but was more viscous. The combination of glycerin 0.1% w/v, poloxamer 188 0.1% w/v at a pH of 6.5 was noticeably reduced in onset, duration, comfort and effectiveness. AB11T did not include glycerin, poloxamer 188, or polyoxyl 40 stearate, which resulted in substantial stinging and discontinuation of the experiment with eye flush irrigation immediately after topical instillation. Substitution of guanfacine 0.037% w/v in AB12T for brimonidine resulted in minimal initial redness with prolonged redness reduction and some degree of whitening, and appeared to provide overall the best cosmesis though requiring slightly higher aceclidine concentration for optimal effect.

[0155] All baseline vision data was based on vision corrected with distance contact lenses. Near vision was noted by subject as outstanding from 8 to 10 inches to the horizon at 30minutes after installation for AB4T and AB6T.

[0156] AB4T and AB6T were repeated both monocularly and binocularly. Substantial improvement in depth perception, near point acuity to 3 pt (20.15), and near point distance (8", 20.20) was noted when both eyes were treated vs. monocular treatment. Monocular treatment resulted in worsening of vision with both eyes open versus testing only the treated eye.

Example 4 Effect of concentration of aceclidine, brimonidine, tropicamide, and additives

Table 4: Effect of concentration of aceclidine, brimonidine, tropicamide, and additives.

	#8	#9	#10	#11	#12	#13	#14	#15	#16	#17	#18	#19	#20	#21
Aceclidine	1.61%	1.61%	1.61%	1.61%	1.61%	1.53%	1.53%	1.53%	1.53%	1.53%	1.53%	1.45%	1.65%	1.75%
Tropicamide	0.042%	0.042%	0.042%	0.042%	0.042%	0.044%	0.044%	0.044%	0.044%	0.044%	0.044%	0.042%	0.044%	0.035%
Brimonidine	0.042%	0.042%	0.042%	0.042%			0.042%	0.042%	0.042%		0.042%	0.042%	0.042%	0.042%
CMC	0.75%	0.75%	0.80%	0.87%	0.75%	0.75%	0.75%	0.80%	0.80%	0.80%	0.80%	0.75%	0.75%	0.75%
NaCl	0.25%	0.25%	0.50%	0.50%	0.25%	0.50%	0.50%	0.50%	0.75%	0.75%	1.00%	0.25%	0.25%	0.25%
BAK	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%
pH	7.00	7.00	7.00	7.00	8.00	7.00	7.00	7.00	7.00	8.00	7.00	7.00	7.00	8.00
phosphate buffer	5 mM		5 mM	5 mM	6 mM	5 mM	5 mM	5 mM	5 mM	5 mM	5 mM	5 mM	5 mM	6 mM
borate buffer		5 mM												
Onset (min)	15	15	15	15	15	15	15	15	15	15	15	15	15	15
Duration (hrs)	7	7	10-12	10-12	7	9	7	10-12	9	9	7	7	7	7
Pupil range (mm)	1.5-1.7	1.5-1.7	1.5-1.7	1.5-1.7	1.5-1.7	1.8-2.0	1.8-2.0	1.8-2.0	1.8-2.0	1.8-2.0	1.8-2.0	1.8-2.1	1.8-2.1	1.8-2.2
Dimming 0-4	1.5	1.5	1.5	1.5	1.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Sting 0-4	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Ache 0-4	0.25	0.25	0.25	0.25	0.25	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.25	0.00
Redness 0-4	0.5	0.5	0.5	0.5	1.5	1.0	0.5	0.5	0.5	1.0	0.5	0.5	0.5	0.5
Other	watery	watery	sl thicker	sl residue	watery	watery	watery	sl thicker	sl thicker	sl thicker	thicker	watery	watery	watery
Overall 0-5	3.5	3.5	4	4	2.5	4.5	4.75	5	5	5	4	4	4	4

[0157] As seen in Table 4, formulas #8-9, an increase in brimonidine to 0.42% w/v resulted in redness reduction to 0.5, while 0.75% w/v CMC resulted in a watery consistency. Unexpectedly, increasing CMC from 0.75% w/v to a range of 0.80% w/v to 0.87% w/v and increasing NaCl from 0.25% w/v to 0.75% w/v in formulas #10-11 resulted in a thicker consistency and an increased residence time from 7 hours to 10-12 hours and decreased the amount of drug that drained into the nasolacrimal duct. This decreased drug delivery to the nasal passages results in less nasal congestion.

[0158] In formulas #13-18 a decrease in the amount of aceclidine from 1.61% to 1.53% w/v resulted in a pupil size range from 1.8-2.0 mm. Dimming as a result of the restriction of the pupil decreased linearly from 1.5 to 0.5 with the decreased amount of aceclidine. Specifically, the 1.8 to 2.0 mm pupil created 41% more light than the 1.5 to 1.7 mm pupil. Surprisingly, the 1.8 to 2.0 mm pupil had a near depth increase of 1.75 D. This is only a 0.25 D loss from the beneficial 2.00 D seen with the 1.5-1.7 mm range. Thus, the 1.80 to 2.0 mm range produces 41% more light while still allowing the full benefit of increased near vision in individuals under 60 years of age; whereas, individuals 60 years of age and over still experience total computer benefit and some increased near benefit.

[0159] The increase in tropicamide concentration from 0.042% w/v (formulas #8-#11) to 0.044% w/v (formulas #13-#18) resulted in a decrease in ache to negligible amounts. The amount of ache may also be correlated with the age of the individual. For those individuals under the age of 45, an increase of tropicamide concentration to a range from 0.046% to 0.060% w/v may be preferred.

[0160] Further, Table 4 shows an unexpected result seen in formulas #13 and #17 where the increase of NaCl from 0.25% w/v to a range of 0.50 to 0.75% w/v resulted in an acceptable redness score of only 1.0 even without the addition of the redness reducing agent brimonidine.

[0161] Formulas #15, #16 and #17 each result in an overall maximum rating of 5 by combining the benefits of: (1) reduced aceclidine concentrations to improve the amount of light produced without significantly affecting the near vision benefits seen in formulas #8-#12; (2) increased NaCl concentrations resulting in a further reduction in redness even in the absence of brimonidine; and (3) increased CMC concentrations resulting in longer residency time on the eye.

[0162] Formula #19 is an excellent alternative for the minority of individuals that are high responders to formulas #15- #17 and get noticeable dimming with 1.53% w/v aceclidine. Formula #20 is an excellent alternative for the minority of individuals that are low responders to formula #19. Lastly, Formula #21 is an excellent alternative for the minority of individuals that are low responders and get poor pupil response with Formula #20.

Example 5 Comparison of Effects of Polyoxyl 40 Stearate, HP β CD and Poloxamer 407

Table 5. Comparison of Effects of Polyoxyl 40 Stearate, HP β CD and Poloxamer 407.

	#22	#23	#24
Aceclidine	1.45%	1.45%	1.45%
Tropicamide	0.044%	0.044%	0.044%
Brimonidine	0.040%	0.040%	0.040%
Polyoxyl 40 Stearate	5.5%		
HP β CD		5.5%	
Poloxamer 407			5.5%
CMC	0.80%	0.80%	0.80%
NaCl	0.037%	0.037%	0.037%
EDTA	0.015%	0.015%	0.015%
BAK	0.007%	0.007%	0.007%
pH	7.00	7.00	7.00
phosphate buffer	5 mM	5 mM	5 mM
Nasal Congestion	0.00	0.50	1.50
Stinging	0.25	0.25	0.25
Wetting	4.00	4.00	4.00
Redness	0.25	0.50	0.50
Visual Blur (< 15 sec)	0.50	0.50	1.50
Duration	6-8 hrs	6-8 hrs	6-8 hrs
Overall 0-4	4.00	4.00	4.00

Clinical Protocol

[0163] 20 presbyopic patients with full distance correction were each given one of the above formulas (#22 - #23). All patients received pre- and post-drop distance and near acuity measurement, Zeiss Visante® (Visante is a registered trademark of Carl Zeiss Meditec AG) optical adherence tomography, axial length and contrast acuity testing (i.e. Colenbrander-Michelson 10% Lum target) with the following results:

all patient achieved a miotic pupil of 1.5 to 2.20 mm;

no patient experienced ciliary ache, ciliary spasm, or induced accommodation;

all patients achieved 20/30+ visual acuity or better at 14" and were very satisfied with their high contrast near vision results and there was no significant complaint of burning or aching;

the duration of effect lasted 6 -8 hrs in all cases;

binocular vision afforded all patients 1 – 1.5 additional lines of near acuity over monocular testing;

the last 10 patients were tested at 20" (i.e. computer distance, cell phone distance) and all achieved 20/25 or better near visual acuity;

moderately hyperopic (approx. +2.25 sphere) uncorrected presbyopes were very satisfied with distance visual acuity that improved to a 20/25 or better level at distance and near vision in the 20/30 range; and

uncorrected distance acuity was often improved for those patients who chose not to routinely correct a small refractive error.

[0164] As seen in Table 5, the use of polyoxyl 40 stearate provides the most comfortable aceclidine formulation with the least amount of visual blur and redness. To achieve similar results to that of formula #22, formula #23 requires 10-15% higher concentrations of the non-ionic surfactant and formula #24 requires 15-20% higher concentrations of the non-ionic surfactant. HPBCD induced a color change over time, possibly indicative of oxidation. Captisol® (sulfobutylether β -cyclodextrin) was substituted with similar findings.

Example 6 Modulation of Aceclidine Concentrations in a Preferred Embodiment.

[0165] Preferred embodiment:

Aceclidine 1.35% - 1.55% w/v;

Polyoxyl 40 stearate 5.5% w/v;

NaCl 0.037% w/v;
CMC 0.80% w/v;
EDTA 0.015% w/v;
BAK 0.007% w/v;
Phosphate or Borate buffer 5 mM; and
pH 7.0.

[0166] For 1.35% w/v aceclidine —

[0167] Stinging on topical instillation 0.25 / 4.0 (lasting about 2-5 seconds);

[0168] Induced redness at 10 minutes: 1.0 to 1.5 / 4.0;

[0169] Induced redness at 30 minutes: 0.0 to 0.25 / 4.0;

[0170] Comfort: very high.

[0171] Wetting: very high, the eye maintaining sensation of improved wetting for most of a 24 hour period after a single topical instillation.

[0172] Depth of Focus distance: excellent.

[0173] Depth of Focus near: excellent.

[0174] In testing the above formulations on several subjects it was discovered that there is a slight range in clinical effect depending on the concentration of aceclidine, where 1.35% - 1.55% w/v aceclidine is preferred, but for which 1.35% w/v and 1.45% w/v confer the desired benefits on most subjects.

[0175] Further, it is discovered that the clinical effect of 1.35% w/v aceclidine can be improved when instilled as follows:

- 1) baseline effect: 1 drop to each eye.
- 2) enhanced effect: 2 drops to each eye.
- 3) greater effect: after 2) above repeat 1) above.
- 4) maximum effect: after 2) above repeat 2) above.

Example 7 Use of a preferred embodiment to prolong contact lens wear.

[0176] Preferred embodiment:

Aceclidine 1.45% w/v;
Polyoxyl 40 stearate 5.5% w/v;
NaCl 0.037% w/v;
CMC 0.80% w/v;

EDTA 0.015% w/v;

BAK 0.007% w/v;

Phosphate or Borate buffer 5 mM;

pH 7.0

[0177] As a baseline, the subject, who normally wore extended wear lenses (Air Optix®; Air Optix is a registered trademark of Novartis AG) for daily wear only, slept in these lenses overnight. On arising each morning the subject's vision was blurred and the contact lenses required removal and cleaning of film and deposits that had formed overnight. Average vision on arising at distance: 20.60; average vision at near on a Michelson contrast acuity chart: 20.80.

[0178] Then, for seven consecutive days the above formulation was instilled between 7 am and 10 am each day as a single dose. Subject wore the Air Optix® lenses throughout each day and slept in the lenses overnight. Upon arising each morning the subject's vision at distance: 20.20+; vision at near 20.40 unaided (consistent with subject's baseline presbyopia when the subject did not wear the lenses overnight and instead inserted the lenses upon arising).

Example 8 Comparison of Effects of Polyoxyl 40 Stearate and Captisol® (sulfobutylether β -cyclodextrin)

Table 6. Comparison of Effects of Polyoxyl 40 Stearate and Captisol® (sulfobutylether β -cyclodextrin).

	#25	#26	#27	#28	#29	#30	#31	#32	#33
Aceclidine	1.35%	1.35%	1.35%	1.35%	1.35%	1.35%	1.35%	1.35%	1.35%
Tropicamide	0.044%	0.044%	0.044%	0.044%	0.044%	0.044%	0.044%	0.044%	0.044%
Polyoxyl 40 stearate	5.5%	5.5%	5.5%	5.5%	5.5%	5.5%	5.5%		
Captisol [®]								5.5%	5.5%
Cocamidopropyl betaine							0.10%		
EDTA			0.015%	0.015%	0.005%	0.005%	0.005%	0.005%	0.015%
CMC 1%=2,500 cps	0.80%	0.80%	0.80%	0.80%	0.80%	0.80%	0.80%	0.80%	0.80%
NaCl	0.037%	0.037%	0.037%	0.037%	0.037%	0.037%	0.037%	0.037%	0.037%
Mannitol								4%	4%
BAK	0.007%	0.007%	0.007%	0.007%	0.007%	0.007%	0.007%	0.007%	0.007%
Borate buffer (mM)	4		4		4	4	4	4	4
Phosphate buffer (mM)		4		4					
pH	7	7	7	7	7	7	7	7	7
Redness, 10 min	1.25	1.25	2	2	1.75	1.75	0	0	0
Redness, 30 min	0	0	1.5	1.5	1.25	1.25	0	0	0
Pupil, 30 min (mm)	<2	<2	<2	<2	<2	<2	<2	<2	<3
Blur on instill (sec)	10	10	10	10	10	10	10	10	10
Ache	0	0	0	0	0	0	1	0	0
Rating	4.00	4.00	2.00	2.00	2.50	2.50	1.00	5.00	TBD

[0179] As seen in Table 6, when using polyoxyl 40 stearate as the surfactant the exclusion of EDTA results in reduced redness and best overall rating among polyoxyl 40 stearate compositions (Formulas #25 and #26). The addition of cocamidopropyl betaine (“CAPB”) further reduces redness however results in significant ache (Formula #31). Replacing polyoxyl 40 stearate with Captisol[®](sulfobutylether β-cyclodextrin) and adding mannitol achieves similar results in redness reduction as the addition of CAPB to polyoxyl 40 stearate but without the attendant ache resulting in the highest overall rating among aceclidine compositions (Formula #32). After several weeks formulations with Captisol[®](sulfobutylether β-cyclodextrin) had an orange hue, possibly indicative of oxidation.

Example 9 Use of a preferred embodiment

[0180] Composition tested:

- aceclidine at a concentration of about 0.5% w/v; and
- poloxamer 188 at about 0.1% w/v;
- poloxamer 407 at about 0.2% w/v;
- polyoxyl stearate at about 5% w/v;
- polyoxyl 35 castor oil at about 0.25% w/v;
- carboxymethyl cellulose at a concentration of about 0.80% to about 0.85% w/v;

sodium chloride at a concentration of about 0.25% w/v;
optionally, BAK at a concentration of about 0.01% w/v;
citrate buffer at a concentration of about 0.02%;
with and without guanfacine at a concentration of about 0.03% w/v; and
wherein said composition has a pH of about 5.0 to about 8.0; and preferably, about 5.9 to about 6.2; and
wherein w/v denotes weight by volume

The composition as described above was administered to a 61 year old subject and was reinstalled after 1 hour . It resulted in pupils of 1.6 mm ou, 20.20 + reading vision, and 20.20 + distance vision No ciliary spasm or loss of distance vision resulted. Transient redness of about 2+ /out of 4 was noted for about 20 minutes without guanfacine, whereas transient redness of about 0.5+ / out of 4 lasting less than 5 minutes was noted with guanfacine; otherwise the clinical results were identical. The presence or absence of BAK had no clinical effect, and was used to provide an optional preservative.

Example 10-Improved Distance Vision using Separate Aceclidine and Diluent Formulations

[0181] First container or chamber:

aceclidine at a concentration of about 1.50% w/v lyophilized with
mannitol as a cryoprecipitate at a concentration of about 2.5% w/v;

[0182] Second container or chamber:

[0183] tropicamide at a concentration of about 0.042% w/v;

[0184] polyoxyl 40 stearate at a concentration of about 5.5% w/v;

[0185] optionally citrate at a concentration of about 0.1% w/v;

[0186] optionally BAK as a preservative at a concentration of about 0.02% w/v.

[0187] 6 subjects were given a Snellen Chart vision exam and their results were recorded and reproduced in Table 8 below. These 6 subjects were then administered a dose of a composition immediately above. The 6 subject were then retested 10 minutes, 1 hour, 2 hours and 4 hours and 8 hours after administration.

[0188] Table 8. Distance Vision Improvement

Eye	Before		After (10 min)		After (1 hr)		After (2 hrs)		After (4 hrs)		After (8 hrs)	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
#1	20.20	20.20	20.15	20.15	20.15	20.15	20.15	20.15	20.15	20.15	20.15	20.15
#2	20.800	20.400	20.50	20.50	20.50	20.50	20.50	20.50	20.50	20.50	20.50	20.50
#3	20.100	20.200	20.15	20.20	20.15	20.20	20.15	20.20	20.20	20.20	20.20	20.20
#4	20.50	20.40	20.15	20.15	20.15	20.15	20.15	20.15	20.15	20.15	20.15	20.15

[0189] As seen in Table 8 the administration of a composition comprising aceclidine and tropicamide to the eye of subjects with either perfect (20.20) or less than perfect distance vision (20.>20) resulted in improvement of distance vision. Among those with perfect distance vision the improvement was as great as 30% (subject #1). Among those with less than perfect distance vision the improvement was as great as 1500% (subject #2).

Example 11 Effects of Mannitol and Carbopol® 940 on Pupil Size, Distance Vision and Near Vision

[0190] Table 9. Effects of Mannitol and Carbopol® 940

	A	B	C	D	E	F
Aceclidine	1.42%	1.50%	1.50%	1.48%	1.65%	1.75%
Tropicamide	0.042%	0.042%	0.042%	0.042%	0.042%	0.042%
Polyoxyl 40 stearate	5.50%	5.50%	5.50%	5.50%	5.50%	5.50%
Mannitol		2.50%	4.00%	4.00%	2.50%	2.50%
Citrate Buffer		pH 5.0				
Citrate only	0.10%		0.10%	0.10%	0.10%	0.10%
Acetate buffer pH 4.75	3 mM		3 mM	3 mM	3 mM	3 mM
BAK *	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%
Carbopol® 940				0.09%		
HPMC	0.30%					
Pupil (mm) 1 hr	1.8	2.1	2.4	1.9	2	1.9
VA cc D						
Pre	20.20	20.20	20.20	20.20	20.20	20.20
Post	20.15+	20.20+	20.20	20.15+	20.15+	20.15+
VA sc N						
Pre	8 pt	8 pt	8 pt	8 pt	8 pt	8 pt
Post	5 pt	6 pt	8 pt	5 pt	6 pt	5 pt
Duration (hrs)	6.5	5.5	5.5	6.5	6	6

VA = visual acuity

cc = with correction

sc = without correction

D = distance vision

N = near vision

* BAK may also be at 0.02%

[0191] Pupil size based on direct Orbscan and Marco pupillometry video screen calibration

[0192] As shown when comparing formulas A, B and C the addition of mannitol resulted in reduced pupil miosis and less distance and near unaided vision improvement; but this suppression was largely neutralized by addition of Carbopol® 940 (formula D; 0.18% and 0.50% Carbopol® 940 resulted in similar effects as 0.09%, data not shown) or increasing the aceclidine concentration from about 1.40% to about 1.60% - 1.75%.

*Example 12 Predicted 25 °C Stable Aceclidine Formulations***[0193]** Composition:

aceclidine at a concentration of about 1.48% w/v;
tropicamide at a concentration of about 0.042% w/v;
polyoxyl 40 stearate at a concentration of about 5.5% w/v;
mannitol at a concentration of about 2.5% w/v;
Carbopol® 940 (carbomer 940) at a concentration of about 0.09% w/v;
optionally citrate at a concentration of about 0.2% w/v;
optionally acetate or phosphate buffer at a concentration of about 3.0 mM;
optionally a preservative such as BAK at a concentration of about 0.02% w/v;
wherein said composition has a pH of about 4.75.

[0194] Composition:

aceclidine at a concentration of about 1.48% w/v;
tropicamide at a concentration of about 0.042% w/v;
polyoxyl stearate at a concentration of about 4.0% w/v;
mannitol at a concentration of about 4.0% w/v;
Carbopol® 940 (carbomer 940) at a concentration of about 0.09% w/v;
optionally citrate at a concentration of about 0.2% w/v;
optionally acetate buffer at a concentration of about 3.0 mM;
optionally a preservative such as BAK at a concentration of about 0.02% w/v;
wherein said composition has a pH of about 4.75.

*Example 13 Dual-Chamber Delivery***[0195]** General Formula:

Lyophilized composition:

Aceclidine 1.55%-1.75% w/v

Mannitol 2.5% w/v

Diluent composition:

Tropicamide 0.042% w/v

Polyoxyl 40 stearate 5.5% w/v

Carbopol® 940 0.09% to 1.0% w/v, preferably 0.5% to 0.9% w/v

BAK 0.02% w/v

Citrate, phosphate or acetate buffer at pH 4.75 - 5.0 3 mM – 100 mM.

[0196] Formula II:

Lyophilized composition:

Aceclidine 1.65% w/v

Mannitol 2.5% w/v

Diluent composition:

Tropicamide 0.042% w/v

Polyoxyl 40 stearate 5.5% w/v

Optionally BAK 0.02% w/v

Citrate buffer at 3 mM

pH of 5.0

[0197] Formula III:

Lyophilized composition:

Aceclidine 1.75% w/v

Mannitol 2.5% w/v

Diluent composition:

Tropicamide 0.042% w/v

Polyoxyl 40 stearate 5.5% w/v

Optionally citrate 0.1% w/v

Optionally BAK 0.02% w/v

Optionally acetate, citrate, citrophosphate or phosphate buffer at 3 to 10 mM

pH of 4.75 to 5.5.

[0198] Method

[0199] Aceclidine can be packaged in a convenient dual chamber unit dose pack allowing complete mixing prior to installation. An assembly comprising two chambers of a unit-dose container are separated by an impermeable thin membrane, or thick membrane with thin central region. Aceclidine is lyophilized with mannitol as a cryoprecipitate and placed within the base of the unit dose container and sealed at its end creating a lyophilized chamber (first chamber). Preferably the lyophilized chamber is vacuum sealed and/or purged of air with nitrogen gas both before and while being sealed. An ophthalmologically effective diluent formulation as listed above is placed at the apex of the unit dose and sealed at its end creating a diluent chamber

(second chamber). The user may then simply pinch the diluent chamber firmly, creating a break in the impermeable membrane between the lyophilized chamber and diluent chamber and releasing the lyophilized aceclidine into the diluent chamber with premixing resulting in a suspension or a solubilized solution prior to subject topical instillation.

[0200] The assembly may be optionally designed to effect an automatic compression of the diluent chamber causing the impermeable membrane to rupture and deliver the drug into the diluent chamber. An example of such an automatic compression may occur by placing the unit dose packs in a rack assembly where an upper plastic planar assembly is designed with a smaller opening than the diameter of the unit dose pack at its apex (i.e. the diluent chamber), wherein pulling a tab of the unit dose may then squeeze the upper chamber and effect its internal rupture and mixing of the lyophilized tyrosine kinase inhibitor and ophthalmologically effective diluent. Alternatively, the puncturing of the impermeable membrane is effected by the turning of a screw cap thus mixing the lyophilized aceclidine with the preferred diluent.

Example 14 Use of Preferred Embodiment for Dual-Chamber Delivery

[0201] Formula

Vial A: Lyophilized Powder

1.65% w/v aceclidine

2.5% w/v mannitol

Vial B: Diluent

0.042% w/v tropicamide

5.5% w/v polyoxyl 40 stearate

0.01% w/v BAK

3 mM citrate buffer

pH 5.0

Method

[0202] One cubic centimeter ("cc") of diluent from Vial B was injected into Vial A and the lyophilized powder was allowed to completely solubilize over several minutes. Two drops were then administered to each eye via a 3 cc syringe with the needle removed. Acuity measurements were then taken in a room whose sole illumination was produced by the backlit visual acuity charting, where pupil measurement was taken 3 meters back with fellow eye viewing the illuminated chart. A Neuroptix pupillometer was used for all pupil readings. A neutral density

filter of 3 cd/m was placed over the illumination chart for dim illumination low contrast acuity testing. Distance vision was tested at 3 meters (m) using a chart designed for that distance. Near vision was tested at 40 cm, 66 cm, and 100 cm binocularly.

[0203] Table 10. Visual Acuity after Topical Instillation of Dual-Chamber Aceclidine Composition

Test	LogMAR		
	OD	OS	OU
Baseline Pupil Size (mm)	4.20	4.3	-
15 min after instillation	1.90	1.9	-
30 min after instillation	2.10	- *	-
Baseline Distance (3 m)	0.14	0	-
0.25h Distance (3 m)	-0.08	-0.1	-
0.5h Distance (3 m)	-0.1	0	-
1h Distance (3 m)	-0.18	-0.1	-
Baseline Low-luminance	0.3	0.14	-
0.25h Low-luminance	0.08	0.08	-
0.5h Low-luminance	0.12	0.08	-
1h Low-luminance	0.02	0.08	-
Baseline 40cm	0.46	0.18	0.2
0.25h 40cm	-	-	0.12
0.5h 40cm	-	-	0.02
1h 40cm	-	-	0
Baseline 66cm	0.08	0.04	-0.02
0.25h 66cm	-	-	-0.12
0.5h 66cm	-	-	-0.14
1h 66cm	-	-	-0.12
Baseline 100cm	0.06	0.02	-0.08
0.25h 100cm	-	-	-0.14
0.5h 100cm	-	-	-0.18
1h 100cm	-	-	-0.2

[0204] Abbreviations: m indicates meters, mm indicates millimeters, cm indicates centimeters, h indicates hour, OD indicates right eye; OS indicates left eye and OU indicates both eyes. LogMAR is a visual acuity chart specialized for research settings. LogMAR values approximate

to Snellen Chart values as follows: 1.00 (20/200), 0.90 (20.160), 0.80 (20.125), 0.70 (20.100), 0.60 (20.80), 0.50, (20.63), 0.40 (20.50), 0.30 (20.40), 0.20 (20.32), 0.10 (20.25), 0.00 (20.20), -0.10 (20.16), -0.20 (20.13), -0.30 (20.10). * indicates failure of the Neuroptix pupillometer.

Results

[0205] As indicated in Table 10 instillation of the dual-chamber aceclidine composition resulted in improved distance vision, near vision and low-light vision. Specifically, distance vision gradually improved from 0.14 (about 20.28) in the left eye to -0.18 (about 20.13) and from 0.00 (20.20) in the right eye to -0.1 (20.16). Distance vision in low light improved from 0.3 (20.40) in the left eye to 0.02 (about 20.21) and from 0.14 (about 20.28) in the right eye to 0.08 (about 20.24). Near vision at 40 cm (16 inches) improved from about 0.2 (20.32) to 0 (20.20). Near vision at 66 cm (26 inches) improved from about -0.02 (about 20.19) to -0.12 (about 20.15). Near vision at 100 cm (39 inches) improved from about -0.08 (about 20/17) to -0.2 (20.13).

WHAT IS CLAIMED IS:

1. A method of improving distance vision comprising administering to a subject in need thereof a composition comprising aceclidine at a concentration from about 0.25% to about 2.0 % w/v and a cycloplegic agent at a concentration from about 0.025% to about 0.1% w/v, wherein w/v denotes weight by volume.
2. The method of claim 1 wherein the subject has less than 20.20 distance vision prior to the administration of the composition.
3. The method of claim 3 wherein the distance vision of the subject after administration of the composition is 20.20 or better.
4. The method of claim 1 wherein the subject has less than 20.40 distance vision prior to the administration of the composition.
5. The method of claim 4 wherein the distance vision of the subject after administration of the composition is 20.40 or better.
6. The method of claim 1 wherein the composition further comprises a surfactant, a tonicity adjustor, optionally an antioxidant and optionally a viscosity enhancer.
7. The method of claim 6 wherein:

the cycloplegic agent is selected from pirenzepine, tropicamide, cyclopentolate hydrochloride, 4-diphenylacetoxy-N-methylpiperidine methiodide (4-DAMP), AF-DX 384, methoctramine, tripitramine, darifenacin, solifenacin, tolterodine, oxybutynin, ipratropium, oxitropium, tiotropium, otenzepad and a combination thereof;

the surfactant is selected from polyoxyl stearate, a gamma cyclodextrin, sulfobutylether β -cyclodextrin, 2-hydroxypropyl cyclodextrin, sodium lauryl sulfate, sodium ester lauryl sulfate, a poloxamer, a polysorbate, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan monooleate, a polyoxyl alkyl, a cyclodextrin and combinations thereof; and

the tonicity adjustor is selected from mannitol, sodium chloride, potassium chloride, glycerin and combinations thereof.

8. The method of claim 7 wherein:

the cycloplegic agent is tropicamide;

the surfactant is polyoxyl stearate; and

the tonicity adjustor is mannitol.

9. The method of claim 6 wherein the composition comprises a viscosity enhancer selected from guar gum, hydroxypropyl-guar, xanthan gum, alginate, chitosan, gelrite, hyauluronic acid, dextran, and a carbomer, and the viscosity is from about 1 to about 5000 centipoise ("cps") prior to topical topical instillation and from about 1 to about 50 cps upon topical topical instillation.

10. The method of claim 9 wherein the viscosity enhancer is selected from guar gum, carbomer 934 and carbomer 940 and the viscosity is from about 15 to about 35 cps upon topical topical instillation.

11. The composition of claim 6 comprising an antioxidant selected from citrate, ethylenediaminetetraacetic acid, disodium ethylenediaminetetraacetic acid, dicalcium diethylenetriamine pentaacetic acid and combinations thereof.

12. The composition of claim 11 wherein the antioxidant is citrate.

13. An ophthalmological composition for the treatment of presbyopia comprising:
aceclidine at a concentration from about 0.25% to about 2.0% w/v;
a polyol selected from mannitol, xylitol, sorbitol, isosorbide, and maltitol as a cryoprecipitate;
and tropicamide at a concentration from about 0.025% to about 0.10% w/v,
wherein w/v denotes weight by volume.

14. The composition of claim 13 further comprising:

polyoxyl 40 stearate at a concentration of about 2.0% w/v or 10.0% w/v;

a buffer selected from acetate buffer, phosphate buffer and citrophosphate buffer at a concentration of about 3 millimolar;

optionally citric acid monohydrate at a concentration from about 0.1% to about 0.2% w/v;

optionally a viscosity enhancer selected from carbomer 934 and carbomer 940 at a concentration from about 0.01% to about 1.0% w/v; and

optionally benzalkonium chloride (BAK) at a concentration of about 0.02% w/v,

wherein the polyol is mannitol at a concentration from about 0.5% to about 6.0% w/v and

the pH of the composition is from about 4.75 to about 5.0 and wherein the viscosity of the composition is from about 1 to about 5,000 centipoise (cps) at about 10 to about 30 °C and wherein w/v denotes weight by volume.

15. The claim of 14, further comprising from about 0.09% to about 1.0% w/v carbomer 940.

16. A method of treating a refractive error of the eye in a subject in need thereof comprising administering to a subject in need thereof a first composition comprising lyophilized aceclidine at a concentration from about 0.25% to about 2.5% w/v and a cryoprecipitate at a concentration from about 2.5% w/v to about 6.0% w/v and further comprising administering concurrently or sequentially a second composition comprising a cycloplegic agent at a concentration from about 0.025% to about 0.1% w/v and optionally one or more excipients selected from a nonionic surfactant at a concentration from about 0.25% to about 10% w/v, a viscosity enhancer, a buffer and a preservative, wherein w/v denotes weight by volume, wherein the refractive error of the eye is selected from presbyopia, myopia, hyperopia, astigmatism or a combination thereof.

17. The method of claim 16 wherein the aceclidine is at a concentration from about 1.45% to about 1.75% w/v, the cryoprecipitate is mannitol is at a concentration from about 2.5% to about

4.0% w/v, the cycloplegic agent is tropicamide at a concentration of about 0.042% w/v and wherein the second composition further comprises polyoxyl 40 stearate as a nonionic surfactant at a concentration of 5.5% w/v, carbomer 940 as a viscosity enhancer at a concentration from about 0.09% w/v to about 1.0% w/v, citrate as an antioxidant at a concentration of about 0.1% w/v, acetate as a buffer at a concentration of about 3 mM and benzalkonium chloride as a preservative at a concentration of about 0.02% w/v and wherein the pH is from about 4.75 to about 5.0.

18. The method of claim 16 wherein the first composition and the second composition are administered from one device with at least two chambers and wherein the first composition resides in a first chamber and the second composition resides in a second chamber and wherein the first composition first contacts the second composition at the time of administration.

19. The method of claim 16 wherein the first composition resides in a first vial and the second composition resides in a second vial and the first composition first contacts the second composition at the time of administration.

20. A method for treating a refractive error of the eye comprising administering to a patient in need thereof a pharmaceutically acceptable amount of a composition comprising aceclidine at a concentration from about 0.25% to about 2.0% w/v and a cycloplegic agent at a concentration from about 0.025% to about 0.1% w/v, wherein w/v denotes weight by volume, wherein the size of the pupil is reduced to from about 1.5 to about 2.5 millimeters and wherein the refractive error is selected from the group consisting of corneal irregular astigmatism, an ectasia induced corneal irregularity, a pellucid induced corneal irregularity, a higher order aberration and a refractive surgery induced higher order aberration.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 16/36692

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/439; A61K 31/165; A61P 27/02 (2016.01)

CPC - A61K9/0048; A61K31/439; A61K31/165

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8): A61K 31/439; A61K 31/165; A61P 27/02 (2016.01)

CPC: A61K9/0048; A61K31/439; A61K31/165

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/305 (Keyword limited, terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Patents, Google Scholar (NPL); Keywords: ophthalmic, aceclidine, cycloplegic agent, tropicamide, distance vision, myopia, mannitol, polyoxyl stearate

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2015/0065511 A1 (Horn et al.) 05 March 2015 (05.03.2015) para [0010], [0088]-[0092], [0110], [0112], [0117], [0165], [0170], [0366], [0168], [0373], Table 1	1-12, 20 ----- 13-19
Y	US 2015/0010634 A1 (Knappe et al.) 08 January 2015 (08.01.2015) para [0002]-[0003], [0012], [0107], [0700], [0734]	13-19
A	US 2014/0378401 A1 (Horn) 25 December 2014 (25.12.2014) para [0012]-[0018], [0022], [0030], [0033], [0035], [0044]-[0050], [0052], [0299], [0302]-[0311], Table 2	1-20
A	US 2006/0177430 A1 (Bushan et al.) 10 August 2006 (10.08.2006) entire document	1-20

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

29 August 2016 (29.08.2016)

Date of mailing of the international search report

22 SEP 2016

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-8300

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

Electronic Acknowledgement Receipt

EFS ID:	34067782
Application Number:	15976279
International Application Number:	
Confirmation Number:	1256
Title of Invention:	Atropine Pharmaceutical Compositions
First Named Inventor/Applicant Name:	Navneet Puri
Customer Number:	149344
Filer:	Martin Fessenmaier/olimpia jakubowska
Filer Authorized By:	Martin Fessenmaier
Attorney Docket Number:	102843.0006US2
Receipt Date:	19-OCT-2018
Filing Date:	10-MAY-2018
Time Stamp:	21:18:55
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	IDS_2.pdf	636481	no	4
			7cf315ac02db4fa4b269b32df0475da449f64687		

Warnings:

Information:					
A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
2	Foreign Reference	JP1203320.pdf	120179	no	4
			e7218731e0f455655cb5b18073ffb5ca8f720ac8		
Warnings:					
Information:					
3	Foreign Reference	WO2016205069.pdf	4599216	no	59
			0d7cc349075e87a89e1df103d111667838cf139c		
Warnings:					
Information:					
Total Files Size (in bytes):			5355876		
This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503. <u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application. <u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course. <u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.					

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Umberg Zipser LLP
1920 Main Street Suite 750
Irvine, CA 92614



**Courtesy Reminder for
Application Serial No: 15/976,279**

Attorney Docket No: 102843.0006US2
Customer Number: 149344
Date of Electronic Notification: 09/17/2018

This is a courtesy reminder that new correspondence is available for this application. If you have not done so already, please review the correspondence. The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

An email notification regarding the correspondence was sent to the following email address(es) associated with your customer number:

rdean@umbergzipser.com
patents@umbergzipser.com

To view your correspondence online or update your email addresses, please visit us anytime at <https://sportal.uspto.gov/secure/myportal/privatepair>. If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov or call 1-866-217-9197.



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Address: COMMISSIONER FOR PATENTS
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Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/976,279	05/10/2018	Navneet Puri	102843.0006US2	1256
149344	7590	09/17/2018	EXAMINER	
Umberg Zipser LLP			CHU, YONG LIANG	
1920 Main Street Suite 750				
Irvine, CA 92614				
			ART UNIT	PAPER NUMBER
			1629	
			NOTIFICATION DATE	DELIVERY MODE
			09/17/2018	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@umbergzipser.com
rdean@umbergzipser.com

DETAILED ACTION

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Claims 1-20 are pending in this application.

Species Election/Restrictions

This application contains claims directed to the following patentably distinct species of a liquid atropine composition consisting essentially of an aqueous solution comprising (A) a buffer, (B) a tonicity agent, (C) a chelator, (D) a viscosity modifier, (E) atropine or a pharmaceutically acceptable salt thereof at various concentrations, identifiable in claims 2-20.

Applicant is required under 35 U.S.C. 121 to elect a particular liquid composition consisting essentially of an aqueous solution comprising (A) a buffer and concentration identifiable in claims 6-8, (B) a tonicity agent identifiable in claim 16, (C) a chelator identifiable in claims 10-13, (D) a viscosity modifier identifiable in claims 17, 19, and 20, (E) atropine or a pharmaceutically acceptable salt thereof at a specific range of concentrations identifiable in claims 2-5, 19, and 20, for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claim 1 is generic.

The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record. In this case, the species of the compositions comprising distinct ingredients and concentrations. These species require a different field of search (e.g., searching different CPC classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Conclusion

No telephone communication was made to request an oral election due to the complexity of the compositions.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Chu, whose telephone number is (571)272-5759. The examiner can normally be reached on M-F 7:00am-4:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey S. Lundgren can be reached on 571-272-5541. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Status Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

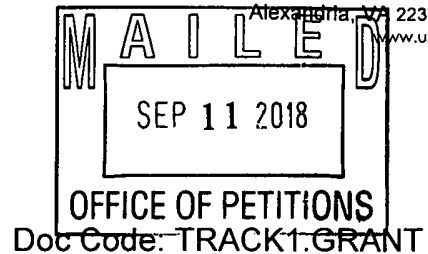
/YONG L CHU/
Primary Examiner, Art Unit 1629



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Umberg Zipser LLP
1920 Main Street Suite 750
Irvine CA 92614



**Decision Granting Request for
Prioritized Examination
(Track I or After RCE)**

Application No.: 15/976,279

The Petition, filed September 7, 2018, requesting reconsideration of the decision, mailed August 27, 2018, which initially dismissed the Request for Prioritized Examination, Track 1, is **GRANTED**. In view of the specific circumstances surrounding this application and, in particular, the filing of the Track 1 Request requirements including irregularities with EFS-Web involving payment of the Processing Fee, the Office, in this specific instance, hereby waives, *sua sponte*, the Processing Fee date requirement of the Prioritized Examination, Track 1, program to the extent necessary to render the processing fee as timely paid and sufficient to fulfill such requirement.

1. THE REQUEST FILED May 10, 2018 IS **GRANTED**.

The above-identified application has met the requirements for prioritized examination

- A. ☒ for an original nonprovisional application (Track I).
B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

- A. filing a **petition for extension of time** to extend the time period for filing a reply;
B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims**, or a multiple dependent claim;
C. filing a **request for continued examination**;
D. filing a notice of appeal;
E. filing a request for suspension of action;
F. mailing of a notice of allowance;
G. mailing of a final Office action;
H. completion of examination as defined in 37 CFR 41.102; or
I. abandonment of the application

Telephone inquiries with regard to this decision should be directed to Brian W. Brown at 571-272-5338.

/Brian W. Brown/
[Signature]

Petitions Examiner, Office of Petitions
(Title)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
P.O. BOX 1450
ALEXANDRIA, VA 22313-1450**

Appl No.: 15/976,279
Inventor: Navneet Puri, et al.
Applicant: Nevakar Inc.
Filing Date: May 10, 2018
Art Unit: 1629
Examiner: Yong Liang Chu
Attorney Docket No.: 102843.0006US2
Title: Atropine Pharmaceutical Compositions

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Request for Reconsideration of Request for Prioritized Examination

Sir:

In response to the Decision Dismissing Applicant's Request for Prioritized Examination (Track I), dated August 27, 2018, Applicant submits herewith the required processing fee in the amount of \$70. While in process of filing the application, a technical difficulty occurred; which led to the nonpayment of the fee. Applicant respectfully requests reconsideration of the Request for Prioritized Examination (Track I).

Respectfully submitted,
Umberg Zipser LLP

Date: September 7, 2018

By: /Martin Fessenmaier/
Martin Fessenmaier
Reg. No. 46697

Umberg Zipser LLP
1920 Main Street, Suite 750
Irvine, CA 92614
Telephone (949) 679-0052
Fax (949) 679-0461

Electronic Patent Application Fee Transmittal

Application Number:	15976279			
Filing Date:	10-May-2018			
Title of Invention:	Atropine Pharmaceutical Compositions			
First Named Inventor/Applicant Name:	Navneet Puri			
Filer:	Martin Fessenmaier/Dani Moroz			
Attorney Docket Number:	102843.0006US2			
Filed as Small Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
PROCESSING FEE, EXCEPT PROV. APPLS.	2830	1	70	70
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				70

Electronic Acknowledgement Receipt

EFS ID:	33659940
Application Number:	15976279
International Application Number:	
Confirmation Number:	1256
Title of Invention:	Atropine Pharmaceutical Compositions
First Named Inventor/Applicant Name:	Navneet Puri
Customer Number:	149344
Filer:	Martin Fessenmaier/Dani Moroz
Filer Authorized By:	Martin Fessenmaier
Attorney Docket Number:	102843.0006US2
Receipt Date:	07-SEP-2018
Filing Date:	10-MAY-2018
Time Stamp:	15:28:09
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	\$ 70
RAM confirmation Number	091018INTEFSW15290800
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	Request_Reconsideration.pdf	456007	no	1
			24a298d8d4f40d688931501f85cbc10ff1d920be		
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30456	no	2
			846e15e9c836ee836a44851cf2b833f0fd19af8f		
Warnings:					
Information:					
Total Files Size (in bytes):			486463		
This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503. <u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application. <u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course. <u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.					



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/976,279	05/10/2018	Navneet Puri	102843.0006US2	1256
149344	7590	08/27/2018	EXAMINER	
Umberg Zipser LLP 1920 Main Street Suite 750 Irvine, CA 92614			CHU, YONG LIANG	
			ART UNIT	PAPER NUMBER
			1629	
			NOTIFICATION DATE	DELIVERY MODE
			08/27/2018	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

rdean@umbergzipser.com
patents@umbergzipser.com



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United States Patent and Trademark Office
P.O. Box 1450
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Doc Code: TRACK1.DENY

**Decision Dismissing Request for
Prioritized Examination (Track I)**

Application No.: 15/976,279

1. THE REQUEST FILED May 10, 2018 IS **DISMISSED** BECAUSE:

- A. ☐ The application is not a utility application under 35 U.S.C. 111(a) filed by EFS-Web or a plant application under 35 U.S.C. 111(a) filed by paper:
- i. ☐ The application is a utility application that was not filed by EFS-Web.
 - ii. ☐ The application is neither a utility application nor a plant application, but rather is a _____, which is excluded from the Track I program.
- B. ☐ The request was not filed with the application or on the same date the application was filed.
- C. ☒ One or more of the following fees were not filed with the application or on the same date the application was filed:
- i. ☐ Basic filing fee, as set forth in 37 CFR 1.16(a), or for a plant application, 37 CFR 1.16(c).
 - ii. ☐ Search fee, as set forth in 37 CFR 1.16(k), or for a plant application, 37 CFR 1.16(m).
 - iii. ☐ Examination fee, as set forth in 37 CFR 1.16(o), or for a plant application, 37 CFR 1.16(q).
 - iv. ☐ Publication fee, as set forth in 37 CFR 1.18(d).
 - v. ☒ Track I processing fee, as set forth in 37 CFR 1.17(i).
 - vi. ☐ Track I prioritized examination fee, as set forth in 37 CFR 1.17(c).
- D. ☐ The executed inventor's oath or declaration, **or** an application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) was not filed with the application or on the same date the application was filed.
- E. ☐ The application contains or has been amended to contain:
- i. ☐ More than four independent claims.
 - ii. ☐ More than thirty total claims.
 - iii. ☐ One or more multiple dependent claims.
- F. ☐ The Track I program has exceeded its limit of 10,000 requests for the current fiscal year.
- G. ☐ Other: _____

Art Unit: OPET

2. CONCLUSION

☐ **ALL** of the above defect(s) consist only of one or more of items E (i-iii). Applicant is hereby accorded a **non-extendable ONE MONTH** time period from the mailing date of this Decision to (1) correct the subject defect(s) and (2) file a petition under 37 CFR 1.181 requesting reconsideration of prioritized examination. If no such petition is timely filed, the application will not undergo prioritized examination.

-OR-

☒ **The application will not undergo prioritized examination, because the request was not accompanied by all of the required items.**

Telephone inquiries with regard to this decision should be directed to Michelle R. Eason at 571-272-4231.

In his/her absence, calls may be directed to Brian W. Brown at (571) 272-5338.

/Michelle R. Eason/
(Signature)

Paralegal Specialist, Office of Petitions
(Title)

Office of Petitions: Routing Sheet



Application No.

This application is being forwarded to your office for further processing. A decision has been rendered on a petition filed in this application, as indicated below. For details of this decision, please see the document PET.OP.DEC filed on the same date as this document.

☐ **GRANTED**

☒ **DISMISSED**

☐ **DENIED**

Office of Petitions: Decision Count Sheet

Mailing Month

8

Application No.

15976279



For US serial numbers: enter number only, no slashes or commas. Ex: 10123456

For PCT: enter "51+single digit of year of filing+last 5 numbers", Ex. for PCT/US05/12345, enter 51512345

Deciding Official:

Eason, Michelle

Count (1) - Palm Credit

15976279

Decision:

DISMISSED

FINANCE WORK NEEDED

☐ Select Check Box for YES

Decision Type:

643 - Track One request



Notes:

Count (2)

Decision:

n/a

FINANCE WORK NEEDED

☐ Select Check Box for YES

Decision Type:

NONE

Notes:

Count (3)

Decision:

n/a

FINANCE WORK NEEDED

☐ Select Check Box for YES

Decision Type:

NONE

Notes:

Initials of Approving Official (if required)

If more than 3 decisions, attach
2nd count sheet & mark this box

Printed on: 8/23/2018

Office of Petitions Internal Document - Ver. 5.0

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		15976279
	Filing Date		2018-05-10
	First Named Inventor	Navneet Puri	
	Art Unit	1629	
	Examiner Name		
	Attorney Docket Number	102843.0006US2	

U.S.PATENTS						Remove
Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	6164282		2000-12-26	Gwon et al.	
	2	7491383	B2	2009-02-17	Woodward et al.	
	3	8758816	B2	2014-06-24	Fuge et al.	
	4	9421199	B2	2016-08-23	Ostrow et al.	
If you wish to add additional U.S. Patent citation information please click the Add button.						Add

U.S.PATENT APPLICATION PUBLICATIONS						Remove
Examiner Initial*	Cite No	Publication Number	Kind Code ¹	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20070254914	A1	2007-11-01	Wu et al.	
	2	20160009705	A1	2016-01-14	Ostrow et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	15976279
Filing Date	2018-05-10
First Named Inventor	Navneet Puri
Art Unit	1629
Examiner Name	
Attorney Docket Number	102843.0006US2

3	20160067238	A1	2016-03-10	Wu et al.
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5	20180042911	A1	2018-02-15	Ostrow et al.

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FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number ³	Country Code ²	Kind Code ⁴	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T ⁵
	1	2012161655	WO	A1	2012-11-29	Singapore Health Services PTE LTD		
	2	2015200361	WO	A1	2015-12-30	Sydnexis, Inc.		
	3	2016172712	WO	A2	2016-10-27	Sydnexis, Inc.		
	4	2017204262	WO	A1	2017-11-30	Singapore Health Services PTE LTD		

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NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T ⁵

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		15976279
Filing Date		2018-05-10
First Named Inventor	Navneet Puri	
Art Unit	1629	
Examiner Name		
Attorney Docket Number	102843.0006US2	

1	Lund, Walter, et al. "The Kinetics of Atropine and Apotatropine in Aqueous Solutions." Acta Chemica Scandinavica, vol. 22, 1968, pp. 3085–3097.
2	Parry, Nicola, et al. "How to Use Low-Dose Atropine to Slow Myopic Progression in Kids." Eyenet Magazine, Dec 2016, pages 29-31
3	Schier, Joshua G., et al. "Preparing for Chemical Terrorism: Stability of Injectable Atropine Sulfate." Academic Emergency Medicine, vol. 11, no. 4, 2004, pp. 329–334.

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☒ A certification statement is not submitted herewith.

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Signature	/Martin Fessenmaier/	Date (YYYY-MM-DD)	2018-08-09
Name/Print	Martin Fessenmaier	Registration Number	46697

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(10) International Publication Number
WO 2015/200361 A1(43) International Publication Date
30 December 2015 (30.12.2015)

(51) International Patent Classification:

A61K 31/46 (2006.01) A61K 9/08 (2006.01)
A61K 31/245 (2006.01) A61P 27/02 (2006.01)

(21) International Application Number:

PCT/US20 15/037249

(22) International Filing Date:

23 June 2015 (23.06.2015)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/016,502 24 June 2014 (24.06.2014) US
62/096,433 23 December 2014 (23.12.2014) US
62/151,926 23 April 2015 (23.04.2015) US
14/726,139 29 May 2015 (29.05.2015) US

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

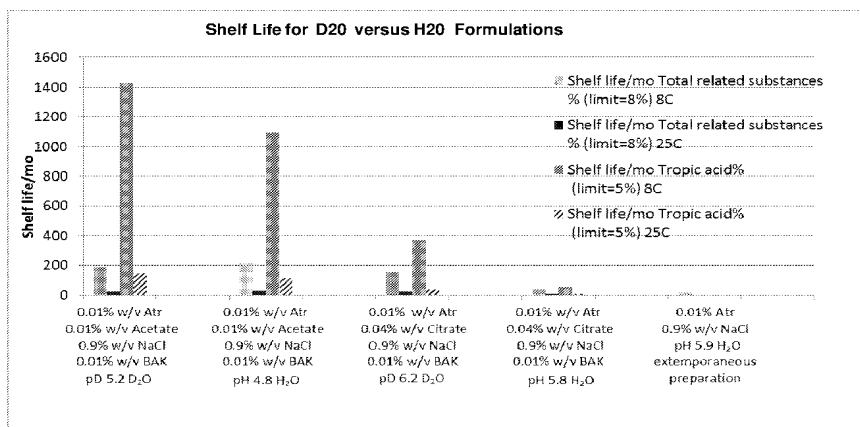
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: OPHTHALMIC COMPOSITION

Fig. 10



(57) Abstract: Provided herein is an ophthalmic composition. In some embodiments, the ophthalmic composition includes a low concentration of an ophthalmic agent for treatment of an ophthalmic disorder or condition; and an ophthalmically acceptable carrier, wherein the ophthalmic agent is distributed with substantial uniformity throughout the ophthalmically acceptable carrier. Further disclosed herein include an ophthalmic composition including a low concentration of an ophthalmic agent and deuterated water. Also disclosed herein are methods of arresting or preventing myopia development by administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition as described herein.

OPHTHALMIC COMPOSITION**CROSS-REFERENCE**

[0001] This application claims the benefit of U.S. Provisional Application Nos. 62/016,502, filed June 24, 2014; 62/096,433, filed December 23, 2014; and 62/151,926, filed April 23, 2015; and is a continuation in part of U.S. Application No. 14/726,139, filed May 29, 2015, which are incorporated herein by reference in their entirety.

BACKGROUND OF THE DISCLOSURE

[0002] Pharmaceutical formulations have an expiration date which is based on the degradation of the active ingredient.

SUMMARY OF THE DISCLOSURE

[0003] Provided herein are ophthalmic compositions. In some embodiments, disclosed herein is an ophthalmic composition, comprising from about 0.001 wt% to about 0.05 wt% of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9.

[0004] In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine -N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine. In some embodiments, the muscarinic antagonist is atropine sulfate.

[0005] In some embodiments, the ophthalmic composition has a pD of one of: less than about 7.3, less than about 7.2, less than about 7.1, less than about 7, less than about 6.8, less than about 6.5, less than about 6.4, less than about 6.3, less than about 6.2, less than about 6.1, less than about 6, less than about 5.9, less than about 5.8, less than about 5.2, or less than about 4.8 after extended period of time under storage condition.

[0006] In some embodiments, the ophthalmic composition comprises one of: at least about 80%, at least about 85%>, at least about 90%>, at least about 93%>, at least about 95%>, at least about 97%>, at least about 98%>, or at least about 99%> of the muscarinic antagonist based on initial concentration after extended period of time under storage condition. As described in this disclosure, the percentage of the ophthalmic agent in the composition after storage is based on the amount of ophthalmic agent that is initially present in the composition (i.e. prior to the storage condition).

[0007] In some embodiments, the ophthalmic composition further has a potency of one of: at least 80%, at least 85%, at least 90%, at least 93%, at least 95%, at least 97%, at least 98%, or at least 99% after extended period of time under storage condition. As described in this disclosure, the potency of the ophthalmic agent in the composition after storage is based on the potency of ophthalmic agent that is initially present in the composition (i.e. prior to the storage condition).

[0008] In some embodiments, the extended period of time is one of: about 1 week, about 2 weeks, about 3 weeks, about 1 month, about 2 months, about 3 months, about 4 months, about 5 months,

about 6 months, about 8 months, about 10 months, about 12 months, about 18 months, about 24 months, about 36 months, about 4 years, or about 5 years.

[0009] In some embodiments, the storage condition has a storage temperature of from about 2°C to about 10°C or from about 16°C to about 26°C. In some embodiments, the storage condition has a storage temperature of about 25°C. In some embodiments, the storage condition has a storage temperature of about 40°C. In some embodiments, the storage condition has a storage temperature of about 60°C.

[0010] In some embodiments, the storage condition has a relative humidity of about 60%. In some embodiments, the storage condition has a relative humidity of about 75%.

[0011] In some embodiments, the muscarinic antagonist is present in the composition at a concentration of one of: from about 0.001 wt% to about 0.04 wt%, from about 0.001 wt% to about 0.03 wt%, from about 0.001 wt% to about 0.025 wt%, from about 0.001 wt% to about 0.02 wt%, from about 0.001 wt% to about 0.01 wt%, from about 0.001 wt% to about 0.008 wt%, or from about 0.001 wt% to about 0.005 wt%.

[0012] In some embodiments, the composition comprises less than 20% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 15% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition.

[0013] In some embodiments, the composition comprises less than 10% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 5% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 2.5% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 2.0% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 1.5% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 1.0% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.5% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.4% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.3% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.2% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the

composition comprises less than 0.1% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the major degradant is tropic acid. As described in this disclosure, the percentage of the primary degradant in the composition after storage is based on the amount of ophthalmic agent that is initially present in the composition (i.e. prior to the storage condition).

[0014] In some embodiments, the composition is in a form of an aqueous solution.

[0015] In some embodiments, the composition further comprises an osmolality adjusting agent. In some embodiments, the osmolality adjusting agent is sodium chloride.

[0016] In some embodiments, the ophthalmic composition further comprises a preservative. In some embodiments, the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof.

[0017] In some embodiments, the ophthalmic composition further comprises a buffer agent. In some embodiments, the buffer agent is selected from borates, borate-polyol complexes, phosphate buffering agents, citrate buffering agents, acetate buffering agents, carbonate buffering agents, organic buffering agents, amino acid buffering agents, or combinations thereof.

[0018] In some embodiments, the ophthalmic composition further comprises a tonicity adjusting agent. In some embodiments, the tonicity adjusting agent is selected from sodium chloride, sodium nitrate, sodium sulfate, sodium bisulfate, potassium chloride, calcium chloride, magnesium chloride, zinc chloride, potassium acetate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium thiosulfate, magnesium sulfate, disodium hydrogen phosphate, sodium dihydrogen phosphate, potassium dihydrogen phosphate, dextrose, mannitol, sorbitol, dextrose, sucrose, urea, propylene glycol, glycerin, or a combination thereof.

[0019] In some embodiments, the composition is stored in a plastic container. In some embodiments, the material of the plastic container comprises low-density polyethylene (LDPE).

[0020] In some embodiments, the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof.

[0021] In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 50%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 40%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 30%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 20%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 10%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 5%. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 10 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 8 consecutive doses. In some embodiments, the dose-to-dose

ophthalmic agent concentration variation is based on 5 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 3 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 2 consecutive doses.

[0022] In some embodiments, the composition further comprises a pD adjusting agent. In some embodiments, the pD adjusting agent comprises DCI, NaOD, CD_3COOD , or $\text{C}_6\text{D}_8\text{O}_7$.

[0023] In some embodiments, the composition further comprises a pharmaceutically acceptable carrier. In some embodiments, the ophthalmically acceptable carrier further comprises at least one viscosity-enhancing agent. In some embodiments, the viscosity-enhancing agent is selected from cellulose-based polymers, polyoxyethylene-polyoxypropylene triblock copolymers, dextran-based polymers, polyvinyl alcohol, dextrin, polyvinylpyrrolidone, polyalkylene glycols, chitosan, collagen, gelatin, hyaluronic acid, or combinations thereof.

[0024] In some embodiments, the ophthalmic composition comprises one of: less than 60% of H_2O , less than 55% of H_2O , less than 50% of H_2O , less than 45% of H_2O , less than 40% of H_2O , less than 35% of H_2O , less than 30% of H_2O , less than 25% of H_2O , less than 20% of H_2O , less than 15% of H_2O , or less than 10% of H_2O .

[0025] In some embodiments, the ophthalmic composition comprises one of: less than 5% of H_2O , less than 4% of H_2O , less than 3% of H_2O , less than 2% of H_2O , less than 1% of H_2O , less than 0.5% of H_2O , less than 0.1% of H_2O , or 0% of H_2O .

[0026] In some embodiments, the ophthalmic composition is stored below room temperature prior to first use. In some embodiments, the ophthalmic composition is stored at between about 2 °C to about 10 °C prior to first use. In some embodiments, the ophthalmic composition is stored at between about 4 °C to about 8 °C prior to first use.

[0027] In some embodiments, the ophthalmic composition is stored at room temperature after first use. In some embodiments, the ophthalmic composition is stored at between about 16 °C to about 26 °C after first use.

[0028] In some embodiments, the ophthalmic composition is not formulated as an injectable formulation.

[0029] In some embodiments, the ophthalmic composition is formulated as an ophthalmic solution for the treatment of an ophthalmic disorder. In some embodiments, the ophthalmic disorder or condition is pre-myopia, myopia, or progression of myopia. In some embodiments, the ophthalmic composition is formulated as an ophthalmic solution for the treatment of pre-myopia, myopia, or progression of myopia.

[0030] In some embodiments, the ophthalmic composition is a solution.

[0031] In some embodiments, disclosed herein is a method of arresting myopia development that comprises administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition described herein. Also described herein is a method of preventing myopia development that comprises administering to an eye of an individual in need thereof an effective amount

of an ophthalmic composition described herein. In some embodiments, described herein is a method of arresting or preventing myopia development, comprising administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition comprising from about 0.001 wt% to about 0.05 wt% of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9. In some embodiments, the ophthalmic composition is administered at predetermined time intervals over an extended period of time. In some embodiments, the ophthalmic composition is administered once every day. In some embodiments, the ophthalmic composition is administered every other day. In some embodiments, the ophthalmic composition is administered over 1 week, 2 weeks, 1 month, 2 months, 3 months, 6 months, 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 11 years, or 12-15 years. In some embodiments, the ophthalmic composition is stored below room temperature prior to first use. In some embodiments, the ophthalmic composition is stored at between about 2 °C to about 10 °C prior to first use. In some embodiments, the ophthalmic composition is stored at between about 4 °C to about 8 °C prior to first use. In some embodiments, the ophthalmic composition is stored at room temperature after first use. In some embodiments, the ophthalmic composition is stored at between about 16 °C to about 26 °C after first use.

[0032] In some embodiments, disclosed herein is an ophthalmic solution that comprises from about 0.001 wt% to about 0.05 wt% of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9. In some embodiments, the ophthalmic solution has a pD of one of: less than about 7.3, less than about 7.2, less than about 7.1, less than about 7, less than about 6.8, less than about 6.5, less than about 6.4, less than about 6.3, less than about 6.2, less than about 6.1, less than about 6, less than about 5.9, less than about 5.8, less than about 5.2, or less than about 4.8 after extended period of time under storage condition. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the ophthalmic solution comprises one of: less than 5% of H₂O, less than 4% of H₂O, less than 3% of H₂O, less than 2% of H₂O, less than 1% of H₂O, less than 0.5% of H₂O, less than 0.1% of H₂O, or 0% of H₂O. In some embodiments, the ophthalmic composition comprises one of: at least about 80%, at least about 85%, at least about 90%, at least about 93%, at least about 95%, at least about 97%, at least about 98%, or at least about 99% of the muscarinic antagonist based on initial concentration after extended period of time under storage condition. In some embodiments, the ophthalmic composition further has a potency of one of: at least 80%, at least 85%, at least 90%, at least 93%, at least 95%, at least 97%, at least 98%, or at least 99% after extended period of time under storage condition. In some embodiments, the extended period of time is one of: about 1 week, about 2 weeks, about 3 weeks, about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 8 months, about 10 months, about 12 months, about 18 months, about 24 months, about 36 months, about 4 years, or about 5 years. In some embodiments, the muscarinic antagonist is present in the composition at a concentration of one of: from about 0.001 wt% to about 0.04 wt%, from about 0.001 wt% to about 0.03 wt%, from about 0.001

wt% to about 0.025 wt%, from about 0.001 wt% to about 0.02 wt%, from about 0.001 wt% to about 0.01 wt%, from about 0.001 wt% to about 0.008 wt%, or from about 0.001 wt% to about 0.005 wt%. In some embodiments, the storage condition has a storage temperature of from about 2°C to about 10°C or from about 16°C to about 26°C. In some embodiments, the ophthalmic composition has a dose-to-dose muscarinic antagonist concentration variation of one of: less than 50%, less than 40%>, less than 30%>, less than 20%>, less than 10%>, or less than 5%>. In some embodiments, the dose-to-dose muscarinic antagonist concentration variation is based on one of: 10 consecutive doses, 8 consecutive doses, 5 consecutive doses, 3 consecutive doses, or 2 consecutive doses.

[0033] In some embodiments, disclosed herein is an ophthalmic composition, comprising from about 0.001 wt%> to about 0.05 wt%> of a muscarinic antagonist and water, at a pH of from about 3.8 to about 7.5.

[0034] In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine -N-oxide, tropine, tropic acid, hyoscyne, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine or atropine sulfate.

[0035] In some embodiments, the ophthalmic composition comprises one of: at least about 80%>, at least about 85%>, at least about 90%>, at least about 93%>, at least about 95%>, at least about 97%>, at least about 98%>, or at least about 99%> of the muscarinic antagonist based on initial concentration after extended period of time under storage condition.

[0036] In some embodiments, the ophthalmic composition has a pH of one of: less than about 7.3, less than about 7.2, less than about 7.1, less than about 7, less than about 6.8, less than about 6.5, less than about 6.4, less than about 6.3, less than about 6.2, less than about 6.1, less than about 6, less than about 5.9, less than about 5.8, less than about 5.2, less than about 4.8, or less than about 4.2 after extended period of time under storage condition.

[0037] In some embodiments, the ophthalmic composition further has a potency of one of: at least 80%, at least 85%, at least 90%, at least 93%, at least 95%, at least 97%, at least 98%, or at least 99%> after extended period of time under storage condition.

[0038] In some embodiments, the extended period of time is one of: about 1 week, about 2 weeks, about 3 weeks, about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 8 months, about 10 months, about 12 months, about 18 months, about 24 months, about 36 months, about 4 years, or about 5 years.

[0039] In some embodiments, the storage condition has a storage temperature of one of: about 25°C, about 40°C, or about 60°C. In some embodiments, the storage condition has a storage temperature of from about 2°C to about 10°C or from about 16°C to about 26°C.

[0040] In some embodiments, the storage condition has a relative humidity of about 60%> or about 75%.

[0041] In some embodiments, the muscarinic antagonist is present in the composition at a concentration of one of: from about 0.001 wt% to about 0.04 wt%, from about 0.001 wt% to about 0.03 wt%, from about 0.001 wt% to about 0.025 wt%, from about 0.001 wt% to about 0.02 wt%, from about 0.001 wt% to about 0.01 wt%, from about 0.001 wt% to about 0.008 wt%, or from about 0.001 wt% to about 0.005 wt%.

[0042] In some embodiments, the ophthalmic composition further comprises an osmolality adjusting agent. In some embodiments, the osmolality adjusting agent is sodium chloride.

[0043] In some embodiments, the ophthalmic composition further comprises a preservative. In some embodiments, the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof.

[0044] In some embodiments, the ophthalmic composition further comprises a buffer agent. In some embodiments, the buffer agent is selected from borates, borate-polyol complexes, phosphate buffering agents, citrate buffering agents, acetate buffering agents, carbonate buffering agents, organic buffering agents, amino acid buffering agents, or combinations thereof.

[0045] In some embodiments, the ophthalmic composition further comprises a tonicity adjusting agent. In some embodiments, the tonicity adjusting agent is selected from sodium chloride, sodium nitrate, sodium sulfate, sodium bisulfate, potassium chloride, calcium chloride, magnesium chloride, zinc chloride, potassium acetate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium thiosulfate, magnesium sulfate, disodium hydrogen phosphate, sodium dihydrogen phosphate, potassium dihydrogen phosphate, dextrose, mannitol, sorbitol, dextrose, sucrose, urea, propylene glycol, glycerin, or a combination thereof.

[0046] In some embodiments, the ophthalmic composition is stored in a plastic container. In some embodiments, the material of the plastic container comprises low-density polyethylene (LDPE).

[0047] In some embodiments, the ophthalmic composition has a dose-to-dose muscarinic antagonist concentration variation of one of: less than 50%, less than 40%, less than 30%, less than 20%, less than 10%, or less than 5%.

[0048] In some embodiments, the dose-to-dose muscarinic antagonist concentration variation is based on one of: 10 consecutive doses, 8 consecutive doses, 5 consecutive doses, 3 consecutive doses, or 2 consecutive doses.

[0049] In some embodiments, the ophthalmic composition has a pH of one of: from about 3.8 to about 7.5, from about 4.2 to about 7.5, from about 4.8 to about 7.3, from about 5.2 to about 7.2, from about 5.8 to about 7.1, from about 6.0 to about 7.0, or from about 6.2 to about 6.8.

[0050] In some embodiments, the ophthalmic composition further comprises a pH adjusting agent. In some embodiments, the pH adjusting agent comprises HCl, NaOH, CH₃COOH, or C₆H₈O₇.

[0051] In some embodiments, the ophthalmic composition comprises one of: less than 60% of D₂O, less than 55% of D₂O, less than 50% of D₂O, less than 45% of D₂O, less than 40% of D₂O, less than

35% of D₂O , less than 30% of D₂O , less than 25% of D₂O , less than 20% of D₂O , less than 15% of D₂O , or less than 10% of D₂O .

[0052] In some embodiments, the ophthalmic composition comprises one of: less than 5% of D₂O , less than 4% of D₂O , less than 3% of D₂O , less than 2% of D₂O , less than 1% of D₂O , less than 0.5% of D₂O , less than 0.1% of D₂O , or 0% of D₂O . In some embodiments, ophthalmic composition is essentially free of D₂O .

[0053] In some embodiments, the composition further comprises a pharmaceutically acceptable carrier.

[0054] In some embodiments, the ophthalmic composition is formulated as an ophthalmic solution for the treatment of an ophthalmic disorder. In some embodiments, the ophthalmic disorder or condition is pre-myopia, myopia, or progression of myopia.

[0055] In some embodiments, the ophthalmic composition is not formulated as an injectable formulation.

[0056] Other features and technical effects of the methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only.

BRIEF DESCRIPTION OF THE DRAWINGS

[0057] The novel features of the disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the disclosure are utilized, and the accompanying drawings of which:

[0058] Fig. 1A-Fig. 1C show the shelf life prediction of 0.01% atropine sulfate solution with a primary degradant RRT 0.87-0.89, and a n.m.t. of 0.5% area, based on data obtained from samples stored at 25°C and 40°C. The pH range of the atropine sulfate solution is from 5.9-6.2.

[0059] Fig. 2A-Fig. 2C show the shelf life prediction of 0.01% atropine sulfate solution with a primary degradant RRT 0.87-0.89, and a n.m.t. of 0.5% area, based on data obtained from samples stored at 25°C and 60°C. The pH range of the atropine sulfate solution is from 5.9-6.2.

[0060] Fig. 3 illustrates mass balance at 4 weeks and at 60°C condition for atropine sulfate formulations disclosed in Example 9.

[0061] Fig. 4 illustrates atropine sulfate (0.010%) formulation stability in acetic acid. The atropine sulfate formulation is formulated with acetic acid and either with H₂O (top panel, Formulation 3) or D₂O (bottom panel, Formulation 7). Formulation 3 has a pH of 4.8 and Formulation 7 has a pD of 5.2. Both formulations are stored at 60 °C for 4 weeks prior to analysis.

[0062] Fig. 5 illustrates atropine sulfate (0.01%) formulation stability in citric acid. The atropine sulfate formulation is formulated with citric acid and either with H₂O (top panel, Formulation 5) or D₂O

(bottom panel, Formulation 8). Formulation 5 has a pH of 5.8 and Formulation 8 has a pD of 6.2. Both formulations are stored at 60 °C for 4 weeks prior to analysis.

[0063] Fig. 6 illustrates comparison of total RS and tropic acid for atropine sulfate (0.025%) formulation (Formulation 4) at pH 4.8 in H₂O .

[0064] Fig. 7 illustrates comparison of total RS and tropic acid for atropine sulfate (0.01%) formulation (Formulation 7) at pD 5.2 in D₂O .

[0065] Fig. 8 illustrates comparison of total RS and tropic acid for atropine sulfate (0.01%) formulation (Formulation 5) at pH 5.8 in H₂O .

[0066] Fig. 9 illustrates comparison of total RS and tropic acid for atropine sulfate (0.025%) formulation (Formulation 6) at pH 5.8 in H₂O .

[0067] Fig. 10 illustrates estimated shelf lives for D₂O and H₂O formulations disclosed in Examples 11 and 12.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0068] The present disclosure recognizes that there is a need for a stabilized ophthalmic composition with extended shelf life upon storage. The present disclosure also recognizes that there is a need for stabilizing an ophthalmic composition through arresting or reducing hydrolysis of at least some of its active agents. The present disclosure further recognizes that there is a need for an ophthalmic composition that provides convenient and effective delivery of a muscarinic antagonist such as atropine in the eye of a patient.

[0069] The present disclosure recognizes that muscarinic antagonist (e.g. atropine or its pharmaceutically acceptable salts) prevents or arrests the development of myopia in humans, for example as evidenced by reduction of the rate of increase of myopia in young people. The present disclosure also recognizes the effects of muscarinic antagonist (e.g. atropine or its pharmaceutically acceptable salts) on reduction of axial elongation and myopia in visually impaired chick eyes, and on ocular growth and muscarinic cholinergic receptors in young rhesus monkeys.

[0070] In addition, the present disclosure recognizes that systemic absorption of muscarinic antagonist (e.g. atropine) sometimes leads to undesirable side effect, and that localized delivery of muscarinic antagonist (e.g. atropine or its pharmaceutically acceptable salts) reduces or prevents the aforementioned systemic exposure.

[0071] Further, the present disclosure recognizes that some liquid muscarinic antagonist (e.g. atropine) compositions are formulated at a relatively lower pH range (e.g. less than 4.5) for stability of muscarinic antagonist (e.g. atropine or its pharmaceutically acceptable salts). For some individuals, the lower pH range in some instances causes discomfort or other side effects such as pain or burning sensation in the eye, which is prevented or alleviated by formulating muscarinic antagonist (e.g. atropine) compositions at higher pH ranges. For some individuals, the lower pH in some instances elicits a tear response which reduces the absorption of the drug in the eye and therefore the effectiveness.

[0072] Still further, the present disclosure recognizes that some muscarinic antagonist (e.g. atropine) liquid compositions formulated at lower concentrations (e.g. 0.001% to 0.05%) present stability challenges that are less so in higher concentrations (e.g. 0.1-1%>). Without wishing to be bound by any particular theory, it is contemplated that the some muscarinic antagonist (e.g. atropine) contributes to the stability of an ophthalmic composition, such as an aqueous solution. For example, the concentration of the muscarinic antagonist (e.g. atropine) in some embodiments affects the pH or pD of the ophthalmic composition, such as with the muscarinic antagonist acting as a buffering agent. Furthermore, the concentration of the muscarinic antagonist (e.g. atropine) in some embodiments affects the interaction between the muscarinic antagonist and other ingredients of the ophthalmic composition, which in turn affects the stability of the ophthalmic composition.

[0073] Finally, the present disclosure recognizes that deuterated water stabilizes ophthalmic compositions. In some cases, the deuterated water is a weak acid as compared to H_2O , as such deuterated water comprises a lower concentration of the reactive species (e.g., -OD) which in some instances leads to base catalyzed hydrolysis of an active agent in the ophthalmic composition. As such, in some instances compositions comprising deuterated water leads to reduced base catalyzed hydrolysis when compared to compositions comprising H_2O . In some instances, deuterated water further lowers the buffering capacity of an ophthalmic composition, leading to less tear reflex in the eye.

[0074] Myopia, axial elongation of the eye, affects a large proportion of the population. The onset of myopia is generally during the grade school years and progresses until growth of the eye is completed. The present disclosure recognizes the importance of compositions and treatments for preventing or arresting the development of myopia, especially compositions and treatments that allow convenient administration, reduce potential side effects, has suitable stability, and/or provide relatively consistent therapeutic effects.

[0075] **Ophthalmic Muscarinic Antagonist Composition**

[0076] Provided herein is an ophthalmic composition containing low concentrations of an ophthalmic agent. In some embodiments, the ophthalmic composition includes from about 0.001 wt% to about 0.05 wt% of an ophthalmic agent for treatment of an ophthalmic disorder or condition; and an ophthalmically acceptable carrier, wherein the ophthalmic agent is distributed with substantial uniformity throughout the ophthalmically acceptable carrier. In some instances, the ophthalmic agent is a muscarinic antagonist.

[0077] Provided herein is an ophthalmic composition containing low concentrations of a muscarinic antagonist. In some embodiments, the ophthalmic composition includes from about 0.001 wt% to about 0.05 wt%> of a muscarinic antagonist for treatment of an ophthalmic disorder or condition; and an ophthalmically acceptable carrier, wherein the muscarinic antagonist is distributed with substantial uniformity throughout the ophthalmically acceptable carrier.

[0078] In some instances, the muscarinic antagonist includes atropine, atropine sulfate, noratropine, atropine -N-oxide, tropine, tropic acid, atropine methonitrate, diphenhydramine,

dimenhydrinate, dicyclomine, flavoxate, oxybutynin, tiotropium, hyoscine, scopolomine (L-hyoscine), hydroxyzine, ipratropium, tropicamide, cyclopentolate, pirenzapine, homatropine, solifenacin, darifenacin, benztropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, tolterodine, or a combination thereof. In some instances, the muscarinic antagonist includes atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt or prodrug thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

[0079] In some embodiments, the ophthalmic composition comprise a muscarinic antagonist selected from atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, atropine methonitrate, diphenhydramine, dimenhydrinate, dicyclomine, flavoxate, oxybutynin, tiotropium, hyoscine, scopolomine (L-hyoscine), hydroxyzine, ipratropium, tropicamide, cyclopentolate, pirenzapine, homatropine, solifenacin, darifenacin, benztropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, tolterodine, or a combination thereof. In some instances, the muscarinic antagonist includes atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, or homatropine.

[0080] In some embodiments, the ophthalmic composition comprise two or more muscarinic antagonists in which the two or more muscarinic antagonists comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, atropine methonitrate, diphenhydramine, dimenhydrinate, dicyclomine, flavoxate, oxybutynin, tiotropium, hyoscine, scopolomine (L-hyoscine), hydroxyzine, ipratropium, tropicamide, cyclopentolate, pirenzapine, homatropine, solifenacin, darifenacin, benztropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, tolterodine, or a combination thereof. In some instances, the muscarinic antagonist includes atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or any combination thereof.

[0081] In some embodiments, the ophthalmic composition comprises one or more muscarinic antagonist in combination with one or more sympathetic agonists. In some embodiments, the sympathetic agonist is selected from phenylephrine or hydroxyamphetamine. In some embodiments, the ophthalmic composition comprises one or more of muscarinic antagonist: atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, atropine methonitrate, diphenhydramine, dimenhydrinate, dicyclomine, flavoxate, oxybutynin, tiotropium, hyoscine, scopolomine (L-hyoscine), hydroxyzine, ipratropium, tropicamide, cyclopentolate, pirenzapine, homatropine, solifenacin, darifenacin, benztropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, or tolterodine; in combination with one or more of sympathetic agonists: phenylephrine or hydroxyamphetamine.

[0082] Provided herein is an ophthalmic composition containing low concentrations of atropine or its pharmaceutically acceptable salts. In some embodiments, the ophthalmic composition includes from about 0.001 wt% to about 0.05 wt% of atropine or its pharmaceutically acceptable salts for

treatment of an ophthalmic disorder or condition; and an ophthalmically acceptable carrier, wherein the ophthalmic agent is distributed with substantial uniformity throughout the ophthalmically acceptable carrier.

[0083] Provided herein is an ophthalmic composition containing low concentrations of atropine sulfate. In some embodiments, the ophthalmic composition includes from about 0.001 wt% to about 0.05 wt% of atropine sulfate for treatment of an ophthalmic disorder or condition; and an ophthalmically acceptable carrier, wherein the ophthalmic agent is distributed with substantial uniformity throughout the ophthalmically acceptable carrier.

[0084] In some embodiments, the ophthalmic disorder or condition is pre-myopia, myopia or progression of myopia.

[0085] The present disclosure further recognizes that the clinical use of atropine as a therapy has been limited due to its ocular side effects including glare from pupillary dilation and blurred vision due to loss of accommodation. Without wishing to be bound by any particular theory, it is contemplated that the limited use of atropine against myopia development, include its ocular side effects, is attributable to the concentration of atropine used in known ophthalmic formulations (e.g. 1wt% or higher).

[0086] The present disclosure further recognizes the challenges present in formulation of compositions that contain low concentrations, especially very low concentrations (e.g. from about 0.001 wt% to about 0.5 wt%), of ophthalmic agents, such as muscarinic antagonist (e.g. atropine or its pharmaceutically acceptable salts). In particular, pharmaceutical compositions with ophthalmic agent at such low concentrations are difficult to maintain dose-to-dose uniformity in term of ophthalmic agent content and/or distribution.

[0087] In some aspects, described herein are formulations or solutions of muscarinic antagonist (e.g., atropine) formulated in deuterated water. In some aspects, formulations or solutions of muscarinic antagonist (e.g., atropine) formulated in deuterated water are stable at different temperatures, at different relative humidity, with an acidic pD, and with a potency of at least 80% relative to the ophthalmic agent. In additional aspects, formulations or solutions of muscarinic antagonist (e.g., atropine) formulated in deuterated water has a lowered buffering capacity. In such instances, the lowered buffering capacity of the ophthalmic formulations or solutions when administered into the eye allows the ophthalmic formulation or solution to reach physiological pH at a faster rate than compared to an equivalent ophthalmic formulation or solution formulated in H₂O.

[0088] In some aspects, described herein are formulations of muscarinic antagonist (e.g. atropine) at low concentrations that does not have a dose-to-dose variation. In some aspects, described herein are formulations of muscarinic antagonist (e.g. atropine) at low concentrations that are stable at different temperatures, at different relative humidity, with an acidic pD, and with a potency of at least 80% relative to the ophthalmic agent.

[0089] In other aspects, described herein include formulating the ophthalmic composition as an ophthalmic gel or an ophthalmic ointment. For example, some ophthalmic gel or an ophthalmic ointment

described herein allows desirable dose-to-dose uniformity, reduced or limited systemic exposure, or combinations thereof.

[0090] Ophthalmic Solution Muscarinic Antagonist Composition

[0091] Disclosed herein, in certain embodiments, is an ophthalmic composition formulated as an aqueous solution. In some embodiments, the ophthalmic composition comprises from about 0.001 wt% to about 0.05 wt% of a muscarinic antagonist and deuterated water. As used herein, deuterated water refers to D₂O, DHO, heavy water, and/or deuterium oxide.

[0092] In some embodiments, the composition comprises at least about 80% of the ophthalmic agent (e.g. muscarinic antagonist) for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 81% of the ophthalmic agent (e.g. muscarinic antagonist) for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 82% of the ophthalmic agent (e.g. muscarinic antagonist) for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 83% of the ophthalmic agent (e.g. muscarinic antagonist) for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 84% of the ophthalmic agent (e.g. muscarinic antagonist) for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 85% of the ophthalmic agent (e.g. muscarinic antagonist) for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 86% of the ophthalmic agent (e.g. muscarinic antagonist) for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 87% of the ophthalmic agent (e.g. muscarinic antagonist) for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 88% of the ophthalmic agent (e.g. muscarinic antagonist) for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 89% of the ophthalmic agent (e.g. muscarinic antagonist) for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 90% of the ophthalmic agent (e.g. muscarinic antagonist) for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 91% of the ophthalmic agent (e.g. muscarinic antagonist) for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 92% of the ophthalmic agent (e.g. muscarinic antagonist) for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 93% of the ophthalmic agent (e.g. muscarinic antagonist) for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 94% of the ophthalmic agent (e.g. muscarinic antagonist) for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 95% of the ophthalmic agent (e.g. muscarinic antagonist) for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 96% of the ophthalmic agent (e.g. muscarinic antagonist) for an extended period of time under storage condition. In

some embodiments, the composition comprises at least about 97% of the ophthalmic agent (e.g. muscarinic antagonist) for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 98% of the ophthalmic agent (e.g. muscarinic antagonist) for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 99% of the ophthalmic agent (e.g. muscarinic antagonist) for an extended period of time under storage condition.

[0093] In some embodiments, the composition has a potency of at least about 80% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least about 81% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least about 82% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least about 83% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least about 84% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least about 85% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least about 86% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least about 87% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least about 88% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least about 89% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least 90% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least 91% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least 92% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least 93% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least 94% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least 95% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least 96% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least 97% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least 98% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least 99% after extended period of time under storage condition.

[0094] In some embodiments, the extended period of time is at least 1 week. In some embodiments, the extended period of time is at least 2 weeks. In some embodiments, the extended period of time is at least 3 weeks. In some embodiments, the extended period of time is at least 1 month. In some embodiments, the extended period of time is at least 2 months. In some embodiments, the extended period of time is at least 3 months. In some embodiments, the extended period of time is at least 4 months. In some embodiments, the extended period of time is at least 5 months. In some embodiments,

the extended period of time is at least 6 months. In some embodiments, the extended period of time is at least 7 months. In some embodiments, the extended period of time is at least 8 months. In some embodiments, the extended period of time is at least 9 months. In some embodiments, the extended period of time is at least 10 months. In some embodiments, the extended period of time is at least 11 months. In some embodiments, the extended period of time is at least 12 months (i.e. 1 year). In some embodiments, the extended period of time is at least 18 months (i.e. 1.5 years). In some embodiments, the extended period of time is at least 24 months (i.e. 2 years). In some embodiments, the extended period of time is at least 36 months (i.e. 3 years). In some embodiments, the extended period of time is at least 3 years. In some embodiments, the extended period of time is at least 5 years, or more.

[0095] In some embodiments, the temperature of the storage condition is between about 20°C and about 70°C. In some embodiments, the temperature of the storage condition is between about 25°C and about 65°C, about 30°C and about 60°C, about 35°C and about 55°C, or about 40°C and about 50°C. In some embodiments, the temperature of the storage condition is about 25°C. In some embodiments, the temperature of the storage condition is about 40°C. In some embodiments, the temperature of the storage condition is about 60°C.

[0096] In some embodiments, the relative humidity of the storage condition is between about 50% and about 80%, or between about 60% and about 75%. In some embodiments, the relative humidity of the storage condition is about 60%. In some embodiments, the relative humidity of the storage condition is about 75%.

[0097] In some embodiments, the composition comprises less than 60% of H₂O. In some embodiments, the composition comprises less than 55% of H₂O. In some embodiments, the composition comprises less than 50% of H₂O. In some embodiments, the composition comprises less than 45% of H₂O. In some embodiments, the composition comprises less than 40% of H₂O. In some embodiments, the composition comprises less than 35% of H₂O. In some embodiments, the composition comprises less than 30% of H₂O. In some embodiments, the composition comprises less than 25% of H₂O. In some embodiments, the composition comprises less than 20% of H₂O. In some embodiments, the composition comprises less than 15% of H₂O. In some embodiments, the composition comprises less than 10% of H₂O.

[0098] In some embodiments, the composition comprises from less than 5% of H₂O to 0% of H₂O. In some embodiments, the composition comprises less than 5% of H₂O. In some embodiments, the composition comprises less than 4.5% of H₂O. In some embodiments, the composition comprises less than 4% of H₂O. In some embodiments, the composition comprises less than 3.5% of H₂O. In some embodiments, the composition comprises less than 3% of H₂O. In some embodiments, the composition comprises less than 2.5% of H₂O. In some embodiments, the composition comprises less than 2% of H₂O. In some embodiments, the composition comprises less than 1.5% of H₂O. In some embodiments, the composition comprises less than 1% of H₂O. In some embodiments, the composition comprises less than 0.5% of H₂O. In some embodiments, the composition comprises less than 0.4% of H₂O. In some

embodiments, the composition comprises less than 0.3% of H₂O . In some embodiments, the composition comprises less than 0.2% of H₂O . In some embodiments, the composition comprises less than 0.1 % of H₂O . In some embodiments, the composition comprises 0% of H₂O .

[0099] In some embodiments, the composition has a pD of between about 4 and about 8, about 4.5 and about 7.8, about 5 and about 7.5, or about 5.5 and about 7. In some embodiments, the composition has a pD of less than about 7.5. In some embodiments, the composition has a pD of less than about 7.4. In some embodiments, the composition has a pD of less than about 7.3. In some embodiments, the composition has a pD of less than about 7.2. In some embodiments, the composition has a pD of less than about 7.1. In some embodiments, the composition has a pD of less than about 7. In some embodiments, the composition has a pD of less than about 6.9. In some embodiments, the composition has a pD of less than about 6.8. In some embodiments, the composition has a pD of less than about 6.7. In some embodiments, the composition has a pD of less than about 6.6. In some embodiments, the composition has a pD of less than about 6.5. In some embodiments, the composition has a pD of less than about 6.4. In some embodiments, the composition has a pD of less than about 6.3. In some embodiments, the composition has a pD of less than about 6.2. In some embodiments, the composition has a pD of less than about 6.1. In some embodiments, the composition has a pD of less than about 6. In some embodiments, the composition has a pD of less than about 5.9. In some embodiments, the composition has a pD of less than about 5.8. In some embodiments, the composition has a pD of less than about 5.7. In some embodiments, the composition has a pD of less than about 5.6. In some embodiments, the composition has a pD of less than about 5.5. In some embodiments, the composition has a pD of less than about 5.4. In some embodiments, the composition has a pD of less than about 5.3. In some embodiments, the composition has a pD of less than about 5.2. In some embodiments, the composition has a pD of less than about 5.1. In some embodiments, the composition has a pD of less than about 5. In some embodiments, the composition has a pD of less than about 4.9. In some embodiments, the composition has a pD of less than about 4.8. In some embodiments, the composition has a pD of less than about 4.7. In some embodiments, the composition has a pD of less than about 4.6. In some embodiments, the composition has a pD of less than about 4.5. In some embodiments, the composition has a pD of less than about 4.4. In some embodiments, the composition has a pD of less than about 4.3. In some embodiments, the composition has a pD of less than about 4.2. In some embodiments, the composition has a pD of less than about 4.1. In some embodiments, the composition has a pD of less than about 4.

[00100] In some embodiments, the composition comprising deuterated water has a lowered buffering capacity than an equivalent composition comprising H₂O . As described elsewhere herein, in some embodiments, the lowered buffering capacity allows the composition comprising deuterated water to normalize to physiological pH at a faster rate than a composition comprising H₂O . In some embodiments, the lowered buffering capacity allows the composition to induce less tear reflex than an equivalent composition comprising H₂O .

[00101] In some instances, the composition comprising deuterated water stabilizes muscarinic antagonist (e.g., atropine). In some embodiments, this is due to a lower concentration of the reactive species (e.g., -OD) in the D₂O aqueous system compared to the concentration of the reactive species (e.g., -OH) in an equivalent H₂O aqueous system. In some cases, base catalyzed hydrolysis leads to the presence of tropine degradant from atropine. In some cases, with a lower concentration of the reactive species that causes tropine degradant formation, atropine solution is more stable in a D₂O aqueous system than compared to an equivalent H₂O aqueous system. In some embodiments, the ophthalmic composition formulated with deuterated water allows for a more stable ophthalmic composition relative to the ophthalmic composition formulated with H₂O.

[00102] In some embodiments, the composition comprises less than 20% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 15% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition.

[00103] In some embodiments, the composition comprises less than 10% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 5% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 2.0% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 1.5% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 1.0% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.5% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.4% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.3% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.2% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.1% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the major degradant is tropic acid.

[00104] In some embodiments, the primary degradant is an early eluting related substance at RRT of 0.87-0.89 according to the UPLC method described herein (Table 10). In some instances, the early eluting related substance is referred to as RRT 0.87-0.89. In some embodiments, the primary degradant is RRT 0.87-0.89.

[00105] Ophthalmic Muscarinic Antagonist Concentration

[00106] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.050%, between about 0.005% to about 0.050%, between about 0.010% to about 0.050%, between about 0.015% to about 0.050%, between about 0.020% to about 0.050%, between about 0.025% to about 0.050%, between about 0.030% to about 0.050%, between about 0.035% to about 0.050%, between about 0.040% to about 0.050%, or between about 0.045% to about 0.050% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some instances, the prodrug of the ophthalmic agent (e.g. muscarinic antagonist) is chemically converted into the ophthalmic agent (e.g. muscarinic antagonist) after the administration of the ophthalmic composition. In a non-limiting example, the muscarinic antagonist prodrug has a chemical bond that is cleavable by one or more enzymes in tears. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine -N-oxide, tropine, tropic acid, hyoscyne, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate. As described herein, the ophthalmic agent includes optically pure stereoisomers, optically enriched stereoisomers, and a racemic mixture of stereoisomers. For example, some ophthalmic compositions disclosed herein includes atropine or atropine sulfate in which the atropine is a racemic mixture of D- and L-isomers; and some ophthalmic compositions disclosed herein includes atropine or atropine sulfate in which the atropine is a optically enriched in favor of the more ophthalmically active L-isomer.

[00107] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.045%, between about 0.005% to about 0.045%, between about 0.010% to about 0.045%, between about 0.015% to about 0.045%, between about 0.020% to about 0.045%, between about 0.025% to about 0.045%, between about 0.030% to about 0.045%, between about 0.035% to about 0.045%, or between about 0.040% to about 0.045% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine -N-oxide, tropine, tropic acid, hyoscyne, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

[00108] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.040%, between about 0.005% to about 0.040%, between about 0.010% to about 0.040%, between about 0.015% to about 0.040%, between about 0.020% to about 0.040%, between about 0.025% to about 0.040%, between about 0.030% to about 0.040%,

between about 0.035% to about 0.040% of the active ingredient, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine -N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

[00109] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.035%, between about 0.005% to about 0.035%, between about 0.010% to about 0.035%, between about 0.015% to about 0.035%, between about 0.020% to about 0.035%, between about 0.025% to about 0.035%, or between about 0.030% to about 0.035% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine -N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

[00110] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.030%, between about 0.005% to about 0.030%, between about 0.010% to about 0.030%, between about 0.015% to about 0.030%, between about 0.020% to about 0.030%, or between about 0.025% to about 0.030% of the active ingredient, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine -N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

[00111] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.025%, between about 0.005% to about 0.025%, between about 0.010% to about 0.025%, between about 0.015% to about 0.025%, or between about 0.020% to about 0.025% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine -N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a

pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

[00112] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.020%, between about 0.005% to about 0.020%, between about 0.010% to about 0.020%, or between about 0.015% to about 0.020% of the active ingredient, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine -N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

[00113] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.015%, between about 0.005% to about 0.015%, or between about 0.010% to about 0.015% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine -N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

[00114] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.010%, between about 0.005% to about 0.010%, or between about 0.008% to about 0.010% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine -N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

[00115] In some embodiments, the compositions described herein have a concentration of ophthalmic agent about 0.001%, 0.005%, 0.010%, 0.015%, 0.020%, 0.025%, 0.030%, 0.035%, 0.040%, 0.045%, or 0.050% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine -N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a

pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

[00116] Without wishing to be bound by any particular theory, it is contemplated herein that the low concentration of the ophthalmic agent (e.g. muscarinic antagonist such as atropine or atropine sulfate) in the disclosed ophthalmic composition provides sufficient and consistent therapeutic benefits to an individual in need thereof, while reducing or avoiding the ocular side effects including glare from pupillary dilation and blurred vision due to loss of accommodation that are associated with ophthalmic formulations containing higher concentrations of the ophthalmic agent (e.g. muscarinic antagonist such as atropine or atropine sulfate).

[00117] **Aqueous Solution Stability**

[00118] In some embodiments, the composition described herein comprises a buffer. In some embodiments, a buffer is selected from borates, borate-polyol complexes, phosphate buffering agents, citrate buffering agents, acetate buffering agents, carbonate buffering agents, organic buffering agents, amino acid buffering agents, or combinations thereof. In some embodiments, the composition described herein comprises buffer comprising deuterated water. In some embodiments, a deuterated buffer is selected from borates, borate-polyol complexes, phosphate buffering agents, citrate buffering agents, acetate buffering agents, carbonate buffering agents, organic buffering agents, amino acid buffering agents, or combinations thereof, formulated in deuterated water.

[00119] In some instances, borates include boric acid, salts of boric acid, other pharmaceutically acceptable borates, and combinations thereof. In some cases, borates include boric acid, sodium borate, potassium borate, calcium borate, magnesium borate, manganese borate, and other such borate salts.

[00120] As used herein, the term polyol includes any compound having at least one hydroxy! group on each of two adjacent carbon atoms that are not in trans configuration relative to each other. In some embodiments, the polyols is linear or cyclic, substituted or unsubstituted, or mixtures thereof, so long as the resultant complex is water soluble and pharmaceutically acceptable. In some instances, examples of polyol include: sugars, sugar alcohols, sugar acids and uronic acids. In some cases, polyols include, but are not limited to: mannitol, glycerin, xylitol and sorbitol.

[00121] In some embodiments, phosphate buffering agents include phosphoric acid; alkali metal phosphates such as disodium hydrogen phosphate, sodium dihydrogen phosphate, trisodium phosphate, dipotassium hydrogen phosphate, potassium dihydrogen phosphate, and tripotassium phosphate; alkaline earth metal phosphates such as calcium phosphate, calcium hydrogen phosphate, calcium dihydrogen phosphate, monomagnesium phosphate, dimagnesium phosphate (magnesium hydrogen phosphate), and trimagnesium phosphate; ammonium phosphates such as diammonium hydrogen phosphate and ammonium dihydrogen phosphate; or a combination thereof. In some instances, the phosphate buffering agent is an anhydride. In some instances, the phosphate buffering agent is a hydrate.

[00122] In some embodiments, borate-polyol complexes include those described in U.S. Pat. No. 6,503,497. In some instances, the borate-polyol complexes comprise borates in an amount of from about 0.01 to about 2.0% w/v, and one or more polyols in an amount of from about 0.01% to about 5.0% w/v.

[00123] In some cases, citrate buffering agents include citric acid and sodium citrate.

[00124] In some instances, acetate buffering agents include acetic acid, potassium acetate, and sodium acetate.

[00125] In some instances, carbonate buffering agents include sodium bicarbonate and sodium carbonate.

[00126] In some cases, organic buffering agents include Good's Buffer, such as for example 2-(N-morpholino)ethanesulfonic acid (MES), *N*-(2-Acetamido)iminodiacetic acid, *N*-(Carbamoylmethyl)iminodiacetic acid (ADA), piperazine-*N,N'*-bis(2-ethanesulfonic acid (PIPES), *N*-(2-acetamido)-2-aminoethanesulfonic acid (ACES), β -Hydroxy-4-morpholinepropanesulfonic acid, 3-Morpholino-2-hydroxypropanesulfonic acid (MOPSO), choline chloride, 3-(*N*-morpholino)propanesulfonic acid (MOPS), *N,N*-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid (BES), 2-[(2-Hydroxy-1,1-bis(hydroxymethyl)ethyl)amino] ethanesulfonic acid (TES), 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES), 3-(*N,N*-Bis[2-hydroxyethyl]amino)-2-hydroxypropanesulfonic acid (DIPSO), acetamidoglycine, 3-[[1,3-Dihydroxy-2-(hydroxymethyl)-2-propenyl]amino]-2-hydroxy-1-propanesulfonic acid (TAPSO), piperazine-1,4-bis(2-hydroxypropanesulphonic acid) (POPSO), 4-(2-hydroxyethyl)piperazine-1-(2-hydroxypropanesulfonic acid) hydrate (HEPPSO), 3-[4-(2-hydroxyethyl)-1-piperazinyl]propanesulfonic acid (HEPPS), tricine, glycine, bicine or *N*-tris(hydroxymethyl)methyl-3-aminopropanesulfonic acid sodium (TAPS); glycine; and diethanolamine (DEA).

[00127] In some cases, amino acid buffering agents include taurine, aspartic acid and its salts (e.g., potassium salts, etc), γ -aminocaproic acid, and the like.

[00128] In some instances, the composition described herein further comprises a tonicity adjusting agent. Tonicity adjusting agent is an agent introduced into a preparation such as an ophthalmic composition to reduce local irritation by preventing osmotic shock at the site of application. In some instances, buffer solution and/or a pD adjusting agent that broadly maintains the ophthalmic solution at a particular ion concentration and pD are considered as tonicity adjusting agents. In some cases, tonicity adjusting agents include various salts, such as halide salts of a monovalent cation. In some cases, tonicity adjusting agents include mannitol, sorbitol, dextrose, sucrose, urea, and glycerin. In some instances, suitable tonicity adjustors comprise sodium chloride, sodium nitrate, sodium sulfate, sodium bisulfate, potassium chloride, calcium chloride, magnesium chloride, zinc chloride, potassium acetate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium thiosulfate, magnesium sulfate, disodium hydrogen phosphate, sodium dihydrogen phosphate, potassium dihydrogen phosphate, dextrose, mannitol, sorbitol, dextrose, sucrose, urea, propylene glycol, glycerin, or a combination thereof.

[00129] In some instances, the concentration of the tonicity adjusting agent in a composition described herein is between about 0.5% and about 2.0%. In some instances, the concentration of the tonicity adjusting agent in a composition described herein is between about 0.7% and about 1.8%, about 0.8% and about 1.5%, or about 1% and about 1.3%. In some instances, the concentration of the tonicity adjusting agent is about 0.6%, 0.7%, 0.8%, 0.9%, 1.0%, 1.1%, 1.2%, 1.3%, **1.4%**, 1.5%, 1.6%, 1.7%, 1.8%, or 1.9%. In some cases, the percentage is a weight percentage.

[00130] In some cases, the composition described herein further comprises a pD adjusting agent. In some embodiments, the pD adjusting agent used is an acid or a base. In some embodiments, the base is oxides, hydroxides, carbonates, bicarbonates and the likes. In some instances, the oxides are metal oxides such as calcium oxide, magnesium oxide and the likes; hydroxides are of alkali metals and alkaline earth metals such as sodium hydroxide, potassium hydroxide, calcium hydroxide and the likes or their deuterated equivalents, and carbonates are sodium carbonate, sodium bicarbonates, potassium bicarbonates and the likes. In some instances, the acid is mineral acid and organic acids such as hydrochloric acid, nitric acid, phosphoric acid, acetic acid, citric acid, fumaric acid, malic acid tartaric acid and the likes or their deuterated equivalents. In some instances, the pD adjusting agent includes, but is not limited to, acetate, bicarbonate, ammonium chloride, citrate, phosphate, pharmaceutically acceptable salts thereof and combinations or mixtures thereof. In some embodiments, the pD adjusting agent comprises DC1 and NaOD.

[00131] In some instances, the composition has a pD of between about 4 and about 8, about 4.5 and about 7.8, about 5 and about 7.5, or about 5.5 and about 7. In some embodiments, the composition has a pD of less than about 7.5. In some embodiments, the composition has a pD of less than about 7.4. In some embodiments, the composition has a pD of less than about 7.3. In some embodiments, the composition has a pD of less than about 7.2. In some embodiments, the composition has a pD of less than about 7.1. In some embodiments, the composition has a pD of less than about 7. In some embodiments, the composition has a pD of less than about 6.9. In some embodiments, the composition has a pD of less than about 6.8. In some embodiments, the composition has a pD of less than about 6.7. In some embodiments, the composition has a pD of less than about 6.6. In some embodiments, the composition has a pD of less than about 6.5. In some embodiments, the composition has a pD of less than about 6.4. In some embodiments, the composition has a pD of less than about 6.3. In some embodiments, the composition has a pD of less than about 6.2. In some embodiments, the composition has a pD of less than about 6.1. In some embodiments, the composition has a pD of less than about 6. In some embodiments, the composition has a pD of less than about 5.9. In some embodiments, the composition has a pD of less than about 5.8. In some embodiments, the composition has a pD of less than about 5.7. In some embodiments, the composition has a pD of less than about 5.6. In some embodiments, the composition has a pD of less than about 5.5. In some embodiments, the composition has a pD of less than about 5.4. In some embodiments, the composition has a pD of less than about 5.3. In some embodiments, the composition has a pD of less than about 5.2. In some embodiments, the composition has a pD of less

than about 5.1. In some embodiments, the composition has a pD of less than about 5. In some embodiments, the composition has a pD of less than about 4.9. In some embodiments, the composition has a pD of less than about 4.8. In some embodiments, the composition has a pD of less than about 4.7. In some embodiments, the composition has a pD of less than about 4.6. In some embodiments, the composition has a pD of less than about 4.5. In some embodiments, the composition has a pD of less than about 4.4. In some embodiments, the composition has a pD of less than about 4.3. In some embodiments, the composition has a pD of less than about 4.2. In some embodiments, the composition has a pD of less than about 4.1. In some embodiments, the composition has a pD of less than about 4. In some embodiments, the pD is the pD of the composition after extended period of time under storage condition.

[00132] In some instances, the composition has an initial pD of between about 4 and about 8, about 4.5 and about 7.8, about 5 and about 7.5, or about 5.5 and about 7. In some embodiments, the composition has an initial pD of about 7.5. In some embodiments, the composition has an initial pD of about 7.4. In some embodiments, the composition has an initial pD of about 7.3. In some embodiments, the composition has an initial pD of about 7.2. In some embodiments, the composition has an initial pD of about 7.1. In some embodiments, the composition has an initial pD of about 7. In some embodiments, the composition has an initial pD of about 6.9. In some embodiments, the composition has an initial pD of about 6.8. In some embodiments, the composition has an initial pD of about 6.7. In some embodiments, the composition has an initial pD of about 6.6. In some embodiments, the composition has an initial pD of about 6.5. In some embodiments, the composition has an initial pD of about 6.4. In some embodiments, the composition has an initial pD of about 6.3. In some embodiments, the composition has an initial pD of about 6.2. In some embodiments, the composition has an initial pD of about 6.1. In some embodiments, the composition has an initial pD of about 6. In some embodiments, the composition has an initial pD of about 5.9. In some embodiments, the composition has an initial pD of about 5.8. In some embodiments, the composition has an initial pD of about 5.7. In some embodiments, the composition has an initial pD of about 5.6. In some embodiments, the composition has an initial pD of about 5.5. In some embodiments, the composition has an initial pD of about 5.4. In some embodiments, the composition has an initial pD of about 5.3. In some embodiments, the composition has an initial pD of about 5.2. In some embodiments, the composition has an initial pD of about 5.1. In some embodiments, the composition has an initial pD of about 5. In some embodiments, the composition has an initial pD of about 4.9. In some embodiments, the composition has an initial pD of about 4.8. In some embodiments, the composition has an initial pD of about 4.7. In some embodiments, the composition has an initial pD of about 4.6. In some embodiments, the composition has an initial pD of about 4.5. In some embodiments, the composition has an initial pD of about 4.4. In some embodiments, the composition has an initial pD of about 4.3. In some embodiments, the composition has an initial pD of about 4.2. In some embodiments, the composition has an initial pD of about 4.1. In some embodiments, the composition has an initial pD of about 4.

[00133] In some embodiments, the pD of the composition described herein is associated with the stability of the composition. In some embodiments, a stable composition comprises a pD of between about 4 and about 8, about 4.5 and about 7.8, about 5 and about 7.5, or about 5.5 and about 7. In some embodiments, a stable composition comprises a pD of less than about 7.5. In some embodiments, a stable composition comprises a pD of less than about 7.4. In some embodiments, a stable composition comprises a pD of less than about 7.3. In some embodiments, a stable composition comprises a pD of less than about 7.2. In some embodiments, a stable composition comprises a pD of less than about 7.1. In some embodiments, a stable composition comprises a pD of less than about 7. In some embodiments, a stable composition comprises a pD of less than about 6.9. In some embodiments, a stable composition comprises a pD of less than about 6.8. In some embodiments, a stable composition comprises a pD of less than about 6.7. In some embodiments, a stable composition comprises a pD of less than about 6.6. In some embodiments, a stable composition comprises a pD of less than about 6.5. In some embodiments, a stable composition comprises a pD of less than about 6.4. In some embodiments, a stable composition comprises a pD of less than about 6.3. In some embodiments, a stable composition comprises a pD of less than about 6.2. In some embodiments, a stable composition comprises a pD of less than about 6.1. In some embodiments, a stable composition comprises a pD of less than about 6. In some embodiments, a stable composition comprises a pD of less than about 5.9. In some embodiments, a stable composition comprises a pD of less than about 5.8. In some embodiments, a stable composition comprises a pD of less than about 5.7. In some embodiments, a stable composition comprises a pD of less than about 5.6. In some embodiments, a stable composition comprises a pD of less than about 5.5. In some embodiments, a stable composition comprises a pD of less than about 5.4. In some embodiments, a stable composition comprises a pD of less than about 5.3. In some embodiments, a stable composition comprises a pD of less than about 5.2. In some embodiments, a stable composition comprises a pD of less than about 5.1. In some embodiments, a stable composition comprises a pD of less than about 5. In some embodiments, a stable composition comprises a pD of less than about 4.9. In some embodiments, a stable composition comprises a pD of less than about 4.8. In some embodiments, a stable composition comprises a pD of less than about 4.7. In some embodiments, a stable composition comprises a pD of less than about 4.6. In some embodiments, a stable composition comprises a pD of less than about 4.5. In some embodiments, a stable composition comprises a pD of less than about 4.4. In some embodiments, a stable composition comprises a pD of less than about 4.3. In some embodiments, a stable composition comprises a pD of less than about 4.2. In some embodiments, a stable composition comprises a pD of less than about 4.1. In some embodiments, a stable composition comprises a pD of less than about 4.

[00134] As described elsewhere herein, in some instances, the D₂O aqueous system stabilizes a muscarinic antagonist (e.g., atropine). In some embodiments, this is due to a lower concentration of the reactive species (e.g., -OD) in the D₂O aqueous system compared to the concentration of the reactive species (e.g., -OH) in an equivalent H₂O aqueous system. In some instances, the concentration of the reactive species (e.g., -OD) in the D₂O aqueous system is about one third less than the concentration of

the reactive species (e.g., -OH) in the equivalent H₂O aqueous system. In some cases, this is due to a lower or smaller dissociation constant of D₂O than H₂O. For example, the $K_a(\text{H}_2\text{O})$ is 1×10^{-14} , whereas the $K_a(\text{D}_2\text{O})$ is 1×10^{-15} . As such, D₂O is a weaker acid than H₂O. In some cases, base catalyzed hydrolysis leads to the presence of tropine degradant from atropine. In some cases, with a lower concentration of the reactive species that causes tropine degradant formation, atropine solution is more stable in a D₂O aqueous system than compared to an equivalent H₂O aqueous system. In some embodiments, the ophthalmic composition formulated with deuterated water allows for a more stable ophthalmic composition relative to the ophthalmic composition formulated with H₂O.

[00135] In some embodiments, the presence of deuterated water shifts the pK_a of the buffer. In some embodiments, the presence of deuterated water allows for the ophthalmic composition to simulate the stability of a lower pH system. In some instances, the buffer capacity of the ophthalmic composition is lowered, thereby allowing a faster shift in pH. In some instances, the lowered buffering capacity of the ophthalmic composition when administered into the eye allows the ophthalmic composition to reach physiological pH at a faster rate than compared to an ophthalmic composition formulated in H₂O. In some instances, the ophthalmic composition formulated with deuterated water allows for a lower tear production, or less tear reflex in the eye, in comparison with an ophthalmic composition formulated with H₂O.

[00136] In some instances, the composition described herein further comprises a disinfecting agent. In some cases, disinfecting agents include polymeric biguanides, polymeric quarternary ammonium compounds, chlorites, bisbiguanides, chlorite compounds (e.g. potassium chlorite, sodium chlorite, calcium chlorite, magnesium chlorite, or mixtures thereof), and a combination thereof.

[00137] In some instances, the composition described herein further comprises a preservative. In some cases, a preservative is added at a concentration to a composition described herein to prevent the growth of or to destroy a microorganism introduced into the composition. In some instances, microorganisms refer to bacteria (e.g. *Proteus mirabilis*, *Serratia marcesens*), virus (e.g. Herpes simplex virus, herpes zoster virus), fungus (e.g. fungi from the genus *Fusarium*), yeast (e.g. *Candida albicans*), parasites (e.g. *Plasmodium* spp., *Gnathostoma* spp.), protozoan (e.g. *Giardia lamblia*), nematodes (e.g. *Onchocercus volvulus*), worm (e.g. *Dirofilaria immitis*), and/or amoeba (e.g. *Acanthameoba*).

[00138] In some instances, the concentration of the preservative is between about 0.0001% and about 1%, about 0.001% and about 0.8%, about 0.004% and about 0.5%, about 0.008 % and about 0.1%, and about 0.01% and about 0.08%. In some cases, the concentration of the preservatives is about 0.001%, 0.002%, 0.003%, 0.004%, 0.005%, 0.006%, 0.008%, 0.009%, 0.009%, 0.01%, 0.015%, 0.02%, 0.025%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9% or 1.0%.

[00139] In some embodiments, the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia (Alcon), polyquaternium-1, chlorobutanol, edetate disodium, and polyhexamethylene biguanide.

[00140] In some embodiments, the composition described herein is stored in a plastic container. In some embodiments, the material of the plastic container comprises high density polyethylene (HDPE), low density polyethylene (LDPE), polyethylene terephthalate (PET), polyvinyl chloride (PVC), polypropylene (PP), polystyrene (PS), fluorine treated HDPE, post-consumer resin (PCR), K-resine (SBC), or bioplastic. In some embodiments, the material of the plastic container comprises LDPE.

[00141] In some embodiments, the composition described herein is stored in a plastic container. In some embodiments, the composition stored in a plastic container has a pD of between about 4 and about 8, about 4.5 and about 7.9, or about 4.9 and about 7.5. In some embodiments, the composition stored in a plastic container has a pD of less than about 7.4. In some embodiments, the composition stored in a plastic container has a pD of less than about 7.3. In some embodiments, the composition stored in a plastic container has a pD of less than about 7.2. In some embodiments, the composition stored in a plastic container has a pD of less than about 7.1. In some embodiments, the composition stored in a plastic container has a pD of less than about 7. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.9. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.8. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.7. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.6. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.5. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.4. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.3. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.2. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.1. In some embodiments, the composition stored in a plastic container has a pD of less than about 6. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.9. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.8. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.7. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.6. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.5. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.4. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.3. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.2. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.1. In some embodiments, the composition stored in a plastic container has a pD of less than about 5. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.9. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.8. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.7. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.6. In some embodiments, the composition stored in a plastic

container has a pD of less than about 4.5. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.4. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.3. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.2. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.1. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.

[00142] In some embodiments, the composition stored in a plastic container has a potency of at least 80% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 85% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 90% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 93% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 95% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 97% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 98% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 99% after extended period of time under storage condition. In some instances, the storage condition comprises a temperature of about 25°C, about 40°C, or about 60°C. In some instances, the extended period of time is at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months.

[00143] In some embodiments, the composition stored in a plastic container has a potency of at least 80%, at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container has a potency of at least 85% at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container has a potency of at least 90% at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container has a potency of at least 93% at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container has a potency of at least 95% at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container has a potency of at least 97% at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container has a potency of at least 98% at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container has a potency of at least 99% at a temperature of about 25°C, about 40°C, or about 60°C.

[00144] In some embodiments, the composition stored in a plastic container has a potency of at least 80%, for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2

months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container has a potency of at least 85% for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container has a potency of at least 90% for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container has a potency of at least 93% for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container has a potency of at least 95% for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container has a potency of at least 97% for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container has a potency of at least 98% for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container has a potency of at least 99% for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months.

[00145] In some embodiments, the composition stored in a plastic container comprises less than 20% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container comprises less than 15% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container comprises less than 10% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container comprises less than 5% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition.

[00146] In some embodiments, the composition stored in a plastic container comprises from less than 2.5% of primary degradant to less than 0.1 % of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container comprises less than 2.5% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container comprises less than 2.0% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container comprises less than 1.5% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container comprises less than 1.0% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container comprises less than 0.5% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container comprises less than 0.4% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container comprises less than 0.3% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container comprises less than 0.2% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container comprises less than 0.1 % of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some instances, the storage condition comprises a temperature of about 25°C, about 40°C, or about 60°C. In some instances, the extended period of time is at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months.

[00147] In some embodiments, the composition stored in a plastic container comprises less than 20% of primary degradant based on the concentration of the ophthalmic agent at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container comprises less than 15% of primary degradant based on the concentration of the ophthalmic agent at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container comprises less than 10% of primary degradant based on the concentration of the ophthalmic agent at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container comprises less than 5% of primary degradant based on the concentration of the ophthalmic agent at a temperature of about 25°C, about 40°C, or about 60°C.

[00148] In some embodiments, the composition stored in a plastic container comprises from less than 2.5% of primary degradant to less than 0.1 % of primary degradant based on the concentration of the ophthalmic agent at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container comprises less than 2.5% of primary degradant based on the concentration of the ophthalmic agent at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container comprises less than 2.0% of primary degradant based on the concentration of the ophthalmic agent at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container comprises less than 1.5% of primary degradant based on the concentration of the ophthalmic agent at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container comprises less than 1.0% of primary degradant based on the concentration of the ophthalmic agent at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container comprises less than 0.5% of primary degradant based on the concentration of the ophthalmic agent at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container comprises less than 0.4% of primary degradant based on the concentration of the ophthalmic agent at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container comprises less than 0.3% of primary degradant based on the concentration of the ophthalmic agent at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container comprises less than 0.2% of primary degradant based on the concentration of the ophthalmic agent at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container comprises less than 0.1 % of primary degradant based on the concentration of the ophthalmic agent at a temperature of about 25°C, about 40°C, or about 60°C.

[00149] In some embodiments, the composition stored in a plastic container comprises less than 20% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 15% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 10% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 5% of primary

degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months.

[illegible]

least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 0.2% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 0.1% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months.

[00151] In some embodiments, the composition described herein is stored in a glass container. In some embodiments, the glass container is a glass vial, such as for example, a type I, type II or type III glass vial. In some embodiments, the glass container is a type I glass vial. In some embodiments, the type I glass vial is a borasilicate glass vial.

[00152] In some embodiments, the composition stored in a glass container has a pD of higher than about 7. In some embodiments, the composition stored in a glass container has a pD of higher than about 7.5. In some embodiments, the composition stored in a glass container has a pD of higher than about 8. In some embodiments, the composition stored in a glass container has a pD of higher than about 8.5. In some embodiments, the composition stored in a glass container has a pD of higher than about 9.

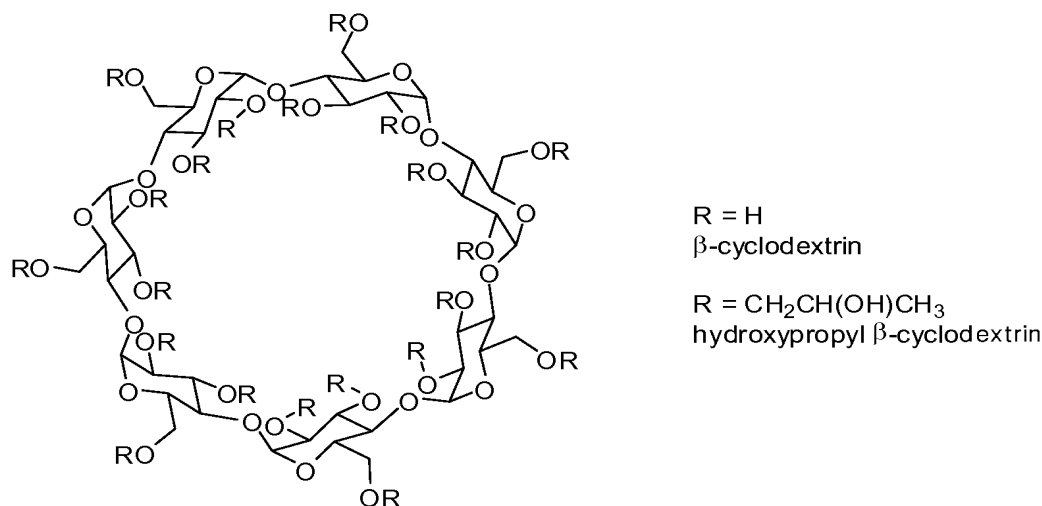
[00153] In some embodiments, the composition stored in a glass container has a potency of less than 60% at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a glass container has a potency of less than 60% for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months.

[00154] In some embodiments, the composition stored in a glass container is less stable than a composition stored in a plastic container.

[00155] In some embodiments, the composition is stored under in the dark. In some instances, the composition is stored in the presence of light. In some instances, the light is indoor light, room light, or sun light. In some instances, the composition is stable while stored in the presence of light.

[00156] In some embodiments, the composition described herein is formulated as an aqueous solution. In some embodiments, the aqueous solution is a stable aqueous solution. In some instances, the aqueous solution is stored in a plastic container as described above. In some instances, the aqueous solution is not stored in a glass container. In some instances, the aqueous solution is stored in the dark. In some instances, the aqueous solution is stored in the presence of light. In some instances, the aqueous solution is stable in the presence of light.

[00157] In a specific embodiment, the ophthalmically acceptable formulations alternatively comprise a cyclodextrin. Cyclodextrins are cyclic oligosaccharides containing 6, 7, or 8 glucopyranose units, referred to as α -cyclodextrin, β -cyclodextrin, or γ -cyclodextrin respectively. Cyclodextrins have a hydrophilic exterior, which enhances water-soluble, and a hydrophobic interior which forms a cavity. In an aqueous environment, hydrophobic portions of other molecules often enter the hydrophobic cavity of cyclodextrin to form inclusion compounds. Additionally, cyclodextrins are also capable of other types of nonbonding interactions with molecules that are not inside the hydrophobic cavity. Cyclodextrins have three free hydroxyl groups for each glucopyranose unit, or 18 hydroxyl groups on α -cyclodextrin, 21 hydroxyl groups on β -cyclodextrin, and 24 hydroxyl groups on γ -cyclodextrin. In some embodiments, one or more of these hydroxyl groups are reacted with any of a number of reagents to form a large variety of cyclodextrin derivatives, including hydroxypropyl ethers, sulfonates, and sulfoalkylethers. Shown below is the structure of β -cyclodextrin and the hydroxypropyl- β -cyclodextrin (HP β CD).



[00158] In some embodiments, the use of cyclodextrins in the pharmaceutical compositions described herein improves the solubility of the drug. Inclusion compounds are involved in many cases of enhanced solubility; however other interactions between cyclodextrins and insoluble compounds also improves solubility. Hydroxypropyl- β -cyclodextrin (HP β CD) is commercially available as a pyrogen free product. It is a nonhygroscopic white powder that readily dissolves in water. HP β CD is thermally stable and does not degrade at neutral pH. Thus, cyclodextrins improve the solubility of a therapeutic agent in a composition or formulation. Accordingly, in some embodiments, cyclodextrins are included to increase the solubility of the ophthalmically acceptable ophthalmic agents within the formulations described herein. In other embodiments, cyclodextrins in addition serve as controlled release excipients within the formulations described herein.

[00159] By way of example only, cyclodextrin derivatives for use include α -cyclodextrin, β -cyclodextrin, γ -cyclodextrin, hydroxyethyl- β -cyclodextrin, hydroxypropyl- γ -cyclodextrin, sulfated β -cyclodextrin, sulfated α -cyclodextrin, sulfoethyl ether β -cyclodextrin.

[00160] The concentration of the cyclodextrin used in the compositions and methods disclosed herein varies according to the physiochemical properties, pharmacokinetic properties, side effect or adverse events, formulation considerations, or other factors associated with the therapeutically ophthalmic agent, or a salt or prodrug thereof, or with the properties of other excipients in the composition. Thus, in certain circumstances, the concentration or amount of cyclodextrin used in accordance with the compositions and methods disclosed herein will vary, depending on the need. When used, the amount of cyclodextrins needed to increase solubility of the ophthalmic agent and/or function as a controlled release excipient in any of the formulations described herein is selected using the principles, examples, and teachings described herein.

[00161] Other stabilizers that are useful in the ophthalmically acceptable formulations disclosed herein include, for example, fatty acids, fatty alcohols, alcohols, long chain fatty acid esters, long chain ethers, hydrophilic derivatives of fatty acids, polyvinyl pyrrolidones, polyvinyl ethers, polyvinyl alcohols, hydrocarbons, hydrophobic polymers, moisture-absorbing polymers, and combinations thereof. In some embodiments, amide analogues of stabilizers are also used. In further embodiments, the chosen stabilizer changes the hydrophobicity of the formulation, improves the mixing of various components in the formulation, controls the moisture level in the formula, or controls the mobility of the phase.

[00162] In other embodiments, stabilizers are present in sufficient amounts to inhibit the degradation of the ophthalmic agent. Examples of such stabilizing agents, include, but are not limited to: glycerol, methionine, monothioglycerol, EDTA, ascorbic acid, polysorbate 80, polysorbate 20, arginine, heparin, dextran sulfate, cyclodextrins, pentosan polysulfate and other heparinoids, divalent cations such as magnesium and zinc, or combinations thereof.

[00163] Additional useful stabilization agents for ophthalmically acceptable formulations include one or more anti-aggregation additives to enhance stability of ophthalmic formulations by reducing the rate of protein aggregation. The anti-aggregation additive selected depends upon the nature of the conditions to which the ophthalmic agents, for example a muscarinic antagonist (e.g. atropine or its pharmaceutically acceptable salts), are exposed. For example, certain formulations undergoing agitation and thermal stress require a different anti-aggregation additive than a formulation undergoing lyophilization and reconstitution. Useful anti-aggregation additives include, by way of example only, urea, guanidinium chloride, simple amino acids such as glycine or arginine, sugars, polyalcohols, polysorbates, polymers such as polyethylene glycol and dextrans, alkyl saccharides, such as alkyl glycoside, and surfactants.

[00164] Other useful formulations optionally include one or more ophthalmically acceptable antioxidants to enhance chemical stability where required. Suitable antioxidants include, by way of example only, ascorbic acid, methionine, sodium thiosulfate and sodium metabisulfite. In one embodiment, antioxidants are selected from metal chelating agents, thiol containing compounds and other general stabilizing agents.

[00165] Still other useful compositions include one or more ophthalmically acceptable surfactants to enhance physical stability or for other purposes. Suitable nonionic surfactants include, but are not limited to, polyoxyethylene fatty acid glycerides and vegetable oils, e.g., polyoxyethylene (60) hydrogenated castor oil; and polyoxyethylene alkylethers and alkylphenyl ethers, e.g., octoxynol 10, octoxynol 40.

[00166] In some embodiments, the ophthalmically acceptable pharmaceutical formulations described herein are stable with respect to compound degradation (e.g. less than 30% degradation, less than 25% degradation, less than 20% degradation, less than 15% degradation, less than 10% degradation, less than 8% degradation, less than 5% degradation, less than 3% degradation, less than 2% degradation, or less than 5% degradation) over a period of any of at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 4 weeks, at least about 5 weeks, at least about 6 weeks, at least about 7 weeks, at least about 8 weeks, at least about 3 months, at least about 4 months, at least about 5 months, or at least about 6 months under storage conditions (e.g. room temperature). In other embodiments, the formulations described herein are stable with respect to compound degradation over a period of at least about 1 week. Also described herein are formulations that are stable with respect to compound degradation over a period of at least about 1 month.

[00167] In other embodiments, an additional surfactant (co-surfactant) and/or buffering agent is combined with one or more of the pharmaceutically acceptable vehicles previously described herein so that the surfactant and/or buffering agent maintains the product at an optimal pD for stability. Suitable co-surfactants include, but are not limited to: a) natural and synthetic lipophilic agents, e.g., phospholipids, cholesterol, and cholesterol fatty acid esters and derivatives thereof; b) nonionic surfactants, which include for example, polyoxyethylene fatty alcohol esters, sorbitan fatty acid esters (Spans), polyoxyethylene sorbitan fatty acid esters (e.g., polyoxyethylene (20) sorbitan monooleate (Tween 80), polyoxyethylene (20) sorbitan monostearate (Tween 60), polyoxyethylene (20) sorbitan monolaurate (Tween 20) and other Tweens, sorbitan esters, glycerol esters, e.g., Myrj and glycerol triacetate (triacetin), polyethylene glycols, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, polysorbate 80, poloxamers, poloxamines, polyoxyethylene castor oil derivatives (e.g., Cremophor® RH40, Cremophor A25, Cremophor A20, Cremophor® EL) and other Cremophors, sulfosuccinates, alkyl sulphates (SLS); PEG glyceryl fatty acid esters such as PEG-8 glyceryl caprylate/caprate (Labrasol), PEG-4 glyceryl caprylate/caprate (Labrafac Hydro WL 1219), PEG-32 glyceryl laurate (Gelucire 444/14), PEG-6 glyceryl mono oleate (Labrafil M 1944 CS), PEG-6 glyceryl linoleate (Labrafil M 2125 CS); propylene glycol mono- and di-fatty acid esters, such as propylene glycol laurate, propylene glycol caprylate/caprate; Brij® 700, ascorbyl-6-palmitate, stearylamine, sodium lauryl sulfate, polyoxethyleneglycerol triiricinoleate, and any combinations or mixtures thereof; c) anionic surfactants include, but are not limited to, calcium carboxymethylcellulose, sodium carboxymethylcellulose, sodium sulfosuccinate, dioctyl, sodium alginate, alkyl polyoxyethylene sulfates, sodium lauryl sulfate,

triethanolamine stearate, potassium laurate, bile salts, and any combinations or mixtures thereof; and d) cationic surfactants such as cetyltrimethylammonium bromide, and lauryldimethylbenzyl-ammonium chloride.

[00168] In a further embodiment, when one or more co-surfactants are utilized in the ophthalmically acceptable formulations of the present disclosure, they are combined, e.g., with a pharmaceutically acceptable vehicle and is present in the final formulation, e.g., in an amount ranging from about 0.1% to about 20%, from about 0.5% to about 10%.

[00169] In one embodiment, the surfactant has an HLB value of 0 to 20. In additional embodiments, the surfactant has an HLB value of 0 to 3, of 4 to 6, of 7 to 9, of 8 to 18, of 13 to 15, of 10 to 18.

[00170] **pD**

[00171] In some embodiments, the pD of a composition described herein is adjusted (e.g., by use of a buffer and/or a pD adjusting agent) to an ophthalmically compatible pD range of from about 4 to about 8, about 4.5 to about 7.5, or about 5 to about 7. In some embodiments, the ophthalmic composition has a pD of from about 5.0 to about 7.0. In some embodiments, the ophthalmic composition has a pD of from about 5.5 to about 7.0. In some embodiments, the ophthalmic composition has a pD of from about 6.0 to about 7.0.

[00172] In some embodiments, useful formulations include one or more pD adjusting agents or buffering agents. Suitable pD adjusting agents or buffers include, but are not limited to acetate, bicarbonate, ammonium chloride, citrate, phosphate, deuterated forms of acetate, bicarbonate, ammonium chloride, citrate, phosphate, pharmaceutically acceptable salts thereof and combinations or mixtures thereof. In some embodiments, the pD adjusting agents or buffers include deuterated hydrochloric acid (DCl_1), deuterated sodium hydroxide (NaOD), deuterated acetic acid (CD_3COOD), or deuterated citric acid ($\text{C}_6\text{D}_8\text{O}_7$).

[00173] In one embodiment, when one or more buffers are utilized in the formulations of the present disclosure, they are combined, e.g., with a pharmaceutically acceptable vehicle and are present in the final formulation, e.g., in an amount ranging from about 0.1% to about 20%, from about 0.5% to about 10%. In certain embodiments of the present disclosure, the amount of buffer included in the gel formulations are an amount such that the pD of the gel formulation does not interfere with the body's natural buffering system.

[00174] In one embodiment, diluents are also used to stabilize compounds because they provide a more stable environment. In some instances, salts dissolved in buffered solutions (which also provides pD control or maintenance) are utilized as diluents in the art, including, but not limited to a phosphate buffered saline solution.

[00175] In some embodiments, the pD is calculated according to the formula disclosed in Glasoe *et al*, "Use of glass electrodes to measure acidities in deuterium oxide," J. Physical Chem. 64(1): 188-190 (1960). In some embodiment, the pD is calculated as $\text{pD} = \text{pH}^* + 0.4$, in which pH^* is the measured

or observed pH of the ophthalmic composition formulated in a solution comprising deuterated water (e.g., D₂O).

[00176] In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4 and about 8, between about 4.5 and about 8, between about 4.9 and about 7.9, between about 5.4 and about 7.9, between about 5.9 and about 7.9, between about 6.4 and about 7.9, or between about 7.4 and about 7.9. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4.5-7.5, between about 5.0 and about 7.5, between about 5.5 and about 7.5, between about 6.0 and about 7.5, or between about 7.0 and about 7.5. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4.5-7.0, between about 5.0 and about 7.0, between about 5.5 and about 7.0, between about 6.0 and about 7.0, or between about 6.5 and about 7.0. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4.9-7.4, between about 5.4 and about 7.4, between about 5.9 and about 7.4, between about 6.4 and about 7.4, or between about 6.9 and about 7.4. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4.5-6.5, between about 5.0 and about 6.5, between about 5.5 and about 6.5, or between about 6.0 and about 6.5. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4.9-6.9, between about 5.4 and about 6.9, between about 5.9 and about 6.9, or between about 6.4 and about 6.9. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4.5-6.0, between about 5.0 and about 6.0, or between about 5.5 and about 6.0. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4.9-6.4, between about 5.4 and about 6.4, or between about 5.9 and about 6.4. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4.5-5.5, or between about 5.0 and about 5.5. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4.9-5.9, or between about 5.4 and about 5.9. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4.5-5.0. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4.9-5.4.

[00177] In some embodiments, the ophthalmic composition is an ophthalmic aqueous composition. In some instances, the ophthalmic aqueous composition has a pD of between about 4 and about 8, about 4.5 and about 7.8, about 5 and about 7.5, or about 5.5 and about 7. In some embodiments, the ophthalmic aqueous composition has a pD of about 7.5. In some embodiments, the ophthalmic aqueous composition has a pD of about 7.4. In some embodiments, the ophthalmic aqueous composition has a pD of about 7.3. In some embodiments, the ophthalmic aqueous composition has a pD of about 7.2. In some embodiments, the ophthalmic aqueous composition has a pD of about 7.1. In some embodiments, the ophthalmic aqueous composition has a pD of about 7. In some embodiments, the ophthalmic aqueous composition has a pD of about 6.9. In some embodiments, the ophthalmic aqueous

composition has a pD of about 6.8. In some embodiments, the ophthalmic aqueous composition has a pD of about 6.7. In some embodiments, the ophthalmic aqueous composition has a pD of about 6.6. In some embodiments, the ophthalmic aqueous composition has a pD of about 6.5. In some embodiments, the ophthalmic aqueous composition has a pD of about 6.4. In some embodiments, the ophthalmic aqueous composition has a pD of about 6.3. In some embodiments, the ophthalmic aqueous composition has a pD of about 6.2. In some embodiments, the ophthalmic aqueous composition has a pD of about 6.1. In some embodiments, the ophthalmic aqueous composition has a pD of about 6. In some embodiments, the ophthalmic aqueous composition has a pD of about 5.9. In some embodiments, the ophthalmic aqueous composition has a pD of about 5.8. In some embodiments, the ophthalmic aqueous composition has a pD of about 5.7. In some embodiments, the ophthalmic aqueous composition has a pD of about 5.6. In some embodiments, the ophthalmic aqueous composition has a pD of about 5.5. In some embodiments, the ophthalmic aqueous composition has a pD of about 5.4. In some embodiments, the ophthalmic aqueous composition has a pD of about 5.3. In some embodiments, the ophthalmic aqueous composition has a pD of about 5.2. In some embodiments, the ophthalmic aqueous composition has a pD of about 5.1. In some embodiments, the ophthalmic aqueous composition has a pD of about 5. In some embodiments, the ophthalmic aqueous composition has a pD of about 4.9. In some embodiments, the ophthalmic aqueous composition has a pD of about 4.8. In some embodiments, the ophthalmic aqueous composition has a pD of about 4.7. In some embodiments, the ophthalmic aqueous composition has a pD of about 4.6. In some embodiments, the ophthalmic aqueous composition has a pD of about 4.5. In some embodiments, the ophthalmic aqueous composition has a pD of about 4.4. In some embodiments, the ophthalmic aqueous composition has a pD of about 4.3. In some embodiments, the ophthalmic aqueous composition has a pD of about 4.2. In some embodiments, the ophthalmic aqueous composition has a pD of about 4.1. In some embodiments, the ophthalmic aqueous composition has a pD of about 4. In some embodiments, the pD is an initial pD of the ophthalmic aqueous composition. In some embodiments, the pD is the pD of the ophthalmic aqueous composition after extended period of time under storage condition.

[00178] In some instances, the ophthalmic aqueous composition has an initial pD of between about 4 and about 8, about 4.5 and about 7.8, about 5 and about 7.5, or about 5.5 and about 7. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7.5. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7.4. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7.3. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7.2. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7.1. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.9. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.8. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.7. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.6. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.5. In some embodiments, the

ophthalmic aqueous composition has an initial pD of about 6.4. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.3. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.2. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.1. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.9. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.8. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.7. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.6. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.5. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.4. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.3. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.2. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.1. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 4.9. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 4.8. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 4.7. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 4.6. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 4.5. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 4.4. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 4.3. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 4.2. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 4.1. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 4.

[00179] In some instances, the ophthalmic aqueous composition has a pD of between about 4 and about 8, about 4.5 and about 7.8, about 5 and about 7.5, or about 5.5 and about 7. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 7.5. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 7.4. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 7.3. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 7.2. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 7.1. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 7. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 6.9. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 6.8. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 6.7. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 6.6. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 6.5. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 6.4. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 6.3. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 6.2. In some

embodiments, the ophthalmic aqueous composition has a pD of less than about 6.1. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 6. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 5.9. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 5.8. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 5.7. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 5.6. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 5.5. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 5.4. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 5.3. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 5.2. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 5.1. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 5. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 4.9. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 4.8. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 4.7. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 4.6. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 4.5. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 4.4. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 4.3. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 4.2. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 4.1. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 4. In some embodiments, the pD is the pD of the ophthalmic aqueous composition after extended period of time under storage condition.

[00180] In some embodiments, the pD of the ophthalmic aqueous composition described herein is associated with the stability of the ophthalmic aqueous composition. In some embodiments, a stable composition comprises a pD of between about 4 and about 8, about 4.5 and about 7.8, about 5 and about 7.5, or about 5.5 and about 7. In some embodiments, a stable composition comprises a pD of less than about 7.5. In some embodiments, a stable composition comprises a pD of less than about 7.4. In some embodiments, a stable composition comprises a pD of less than about 7.3. In some embodiments, a stable composition comprises a pD of less than about 7.2. In some embodiments, a stable composition comprises a pD of less than about 7.1. In some embodiments, a stable composition comprises a pD of less than about 7. In some embodiments, a stable composition comprises a pD of less than about 6.9. In some embodiments, a stable composition comprises a pD of less than about 6.8. In some embodiments, a stable composition comprises a pD of less than about 6.7. In some embodiments, a stable composition comprises a pD of less than about 6.6. In some embodiments, a stable composition comprises a pD of less than about 6.5. In some embodiments, a stable composition comprises a pD of less than about 6.4. In some embodiments, a stable composition comprises a pD of less than about 6.3. In some embodiments, a stable composition comprises a pD of less than about 6.2. In some embodiments, a

stable composition comprises a pD of less than about 6.1. In some embodiments, a stable composition comprises a pD of less than about 6. In some embodiments, a stable composition comprises a pD of less than about 5.9. In some embodiments, a stable composition comprises a pD of less than about 5.8. In some embodiments, a stable composition comprises a pD of less than about 5.7. In some embodiments, a stable composition comprises a pD of less than about 5.6. In some embodiments, a stable composition comprises a pD of less than about 5.5. In some embodiments, a stable composition comprises a pD of less than about 5.4. In some embodiments, a stable composition comprises a pD of less than about 5.3. In some embodiments, a stable composition comprises a pD of less than about 5.2. In some embodiments, a stable composition comprises a pD of less than about 5.1. In some embodiments, a stable composition comprises a pD of less than about 5. In some embodiments, a stable composition comprises a pD of less than about 4.9. In some embodiments, a stable composition comprises a pD of less than about 4.8. In some embodiments, a stable composition comprises a pD of less than about 4.7. In some embodiments, a stable composition comprises a pD of less than about 4.6. In some embodiments, a stable composition comprises a pD of less than about 4.5. In some embodiments, a stable composition comprises a pD of less than about 4.4. In some embodiments, a stable composition comprises a pD of less than about 4.3. In some embodiments, a stable composition comprises a pD of less than about 4.2. In some embodiments, a stable composition comprises a pD of less than about 4.1. In some embodiments, a stable composition comprises a pD of less than about 4.

[00181] In some embodiments, the D₂O aqueous system stabilizes a muscarinic antagonist (e.g., atropine). In some embodiments, this is due to a lower concentration of the reactive species (e.g., -OD) in the D₂O aqueous system compared to the concentration of the reactive species (e.g., -OH) in an equivalent H₂O aqueous system. In some instances, the concentration of the reactive species (e.g., -OD) in the D₂O aqueous system is about one third less than the concentration of the reactive species (e.g., -OH) in the equivalent H₂O aqueous system. In some cases, this is due to a lower or smaller dissociation constant of D₂O than H₂O. For example, the $K_a(H_2O)$ is 1×10^{-14} , whereas the $K_a(D_2O)$ is 1×10^{-15} . As such, D₂O is a weaker acid than H₂O. In some cases, base catalyzed hydrolysis leads to the presence of tropine degradant from atropine. In some cases, with a lower concentration of the reactive species that causes tropine degradant formation, atropine solution is more stable in a D₂O aqueous system than compared to an equivalent H₂O aqueous system. In some embodiments, the ophthalmic composition formulated with deuterated water allows for a more stable ophthalmic composition relative to the ophthalmic composition formulated with H₂O.

[00182] In some embodiments, the presence of deuterated water shifts the pK_a of the buffer. In some embodiments, the presence of deuterated water allows for the ophthalmic composition to simulate the stability of a lower pH system. In some instances, the buffer capacity of the ophthalmic composition is lowered, thereby allowing a faster shift in pH. In some instances, the lowered buffering capacity of the ophthalmic composition when administered into the eye allows the ophthalmic composition to reach physiological pH at a faster rate than compared to an ophthalmic composition formulated in H₂O. In

some instances, the ophthalmic composition formulated with deuterated water allows for a lower tear production, or less tear reflex in the eye, in comparison with an ophthalmic composition formulated with H₂O .

[00183] In some embodiment, the ophthalmic gel or ointment composition described herein has a pD of about 4, about 4.1, about 4.2, about 4.3, about 4.4, about 4.5, about 4.6, about 4.7, about 4.8, about 4.9, about 5.0, about 5.1, about 5.2, about 5.3, about 5.4, about 5.5, about 5.6, about 5.7, about 5.8, about 5.9, about 6.0, about 6.1, about 6.2, about 6.3, about 6.4, about 6.5, about 6.6, about 6.7, about 6.8, about 6.9, about 7.0, about 7.1, about 7.2, about 7.3, about 7.4, about 7.5, about 7.6, about 7.7, about 7.8, or about 7.9.

[00184] In some embodiment, the pD of the ophthalmic aqueous, gel, or ointment composition described herein is suitable for sterilization (e.g., by filtration or aseptic mixing or heat treatment and/or autoclaving (e.g., terminal sterilization)) of ophthalmic formulations described herein. As used in in the present disclosure, the term "aqueous composition" includes compositions that are based on D₂O .

[00185] In some embodiments, the pharmaceutical formulations described herein are stable with respect to pD over a period of any of at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 4 weeks, at least about 5 weeks, at least about 6 weeks, at least about 7 weeks, at least about 8 weeks, at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about 18 months, at least about 24 months, at least about 3 years, at least about 4 years, at least about 5 years, at least about 6 years, at least about 7 years, at least about 8 years, at least about 9 years, at least about 10 years, or more. In other embodiments, the formulations described herein are stable with respect to pD over a period of at least about 1 week. In other embodiments, the formulations described herein are stable with respect to pD over a period of at least about 2 weeks. In other embodiments, the formulations described herein are stable with respect to pD over a period of at least about 3 weeks. In other embodiments, the formulations described herein are stable with respect to pD over a period of at least about 1 month. Also described herein are formulations that are stable with respect to pD over a period of at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 12 months, at least about 18 months, at least about 2 years, or more.

[00186] **Aqueous Solution Dose-To-Dose Uniformity**

[00187] Typical ophthalmic aqueous solutions are packaged in eye drop bottles and administered as drops. For example, a single administration (i.e. a single dose) of an ophthalmic aqueous solution includes a single drop, two drops, three drops or more into the eyes of the patient. In some embodiments, one dose of the ophthalmic aqueous solution described herein is one drop of the aqueous solution composition from the eye drop bottle.

[00188] In some cases, described herein include ophthalmic aqueous compositions which provide a dose-to-dose uniform concentrations. In some instances, the dose-to-dose uniform concentration does not present significant variations of drug content from one dose to another. In some instances, the dose-to-dose uniform concentration does provide consistent drug content from one dose to another.

[00189] In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 50%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 40%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 30%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 20%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 10%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 5%.

[00190] In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 10 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 8 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 5 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 3 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 2 consecutive doses.

[00191] A nonsettling formulation should not require shaking to disperse drug uniformly. A "no-shake" formulation is potentially advantageous over formulations that require shaking for the simple reason that patients' shaking behavior is a major source of variability in the amount of drug dosed. It has been reported that patients often times do not or forget to shake their ophthalmic compositions that requires shaking before administering a dose, despite the instructions to shake that were clearly marked on the label. On the other hand, even for those patients who do shake the product, it is normally not possible to determine whether the shaking is adequate in intensity and/or duration to render the product uniform. In some embodiments, the ophthalmic gel compositions and ophthalmic ointment compositions described herein are "no-shake" formulations that maintained the dose-to-dose uniformity described herein.

[00192] To evaluate the dose-to-dose uniformity, drop bottles or tubes containing the ophthalmic aqueous compositions, the ophthalmic gel compositions, or ophthalmic ointment compositions are stored upright for a minimum of 12 hours prior to the start of the test. To simulate the recommended dosing of these products, predetermined number of drops or strips are dispensed from each commercial bottles or tubes at predetermined time intervals for an extended period of time or until no product was left in the bottle or tube. All drops and strips are dispensed into tared glass vials, capped, and stored at room temperature until analysis. Concentrations of a muscarinic antagonist such as atropine in the expressed drops were determined using a reverse-phase HPLC method.

[00193] Aqueous Solution Viscosity

[00194] In some embodiments, the composition has a Brookfield RVDV viscosity of from about 10 to about 50,000 cps at about 20°C and sheer rate of Is^{-1} . In some embodiments, the composition has a Brookfield RVDV viscosity of from about 100 to about 40,000 cps at about 20°C and sheer rate of Is^{-1} . In some embodiments, the composition has a Brookfield RVDV viscosity of from about 500 to about 30,000 cps at about 20°C and sheer rate of Is^{-1} . In some embodiments, the composition has a Brookfield RVDV viscosity of from about 1000 to about 20,000 cps at about 20°C and sheer rate of Is^{-1} . In some embodiments, the composition has a Brookfield RVDV viscosity of from about 2000 to about 10,000 cps at about 20°C and sheer rate of Is^{-1} . In some embodiments, the composition has a Brookfield RVDV viscosity of from about 4000 to about 8000 cps at about 20°C and sheer rate of Is^{-1} .

[00195] In some embodiments, the ophthalmic aqueous formulation contains a viscosity enhancing agent sufficient to provide a viscosity of between about 500 and 50,000 centipoise, between about 750 and 50,000 centipoise; between about 1000 and 50,000 centipoise; between about 1000 and 40,000 centipoise; between about 2000 and 30,000 centipoise; between about 3000 and 20,000 centipoise; between about 4000 and 10,000 centipoise, or between about 5000 and 8000 centipoise.

[00196] In some embodiments, the compositions described herein are low viscosity compositions at body temperature. In some embodiments, low viscosity compositions contain from about 1% to about 10% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, low viscosity compositions contain from about 2% to about 10% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, low viscosity compositions contain from about 5% to about 10% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, low viscosity compositions are substantially free of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, a low viscosity ophthalmic agent composition described herein provides an apparent viscosity of from about 100 cP to about 10,000 cP. In some embodiments, a low viscosity ophthalmic agent composition described herein provides an apparent viscosity of from about 500 cP to about 10,000 cP. In some embodiments, a low viscosity ophthalmic agent composition described herein provides an apparent viscosity of from about 1000 cP to about 10,000 cP.

[00197] Osmolarity

[00198] In some embodiments, a composition disclosed herein is formulated in order to not disrupt the ionic balance of the eye. In some embodiments, a composition disclosed herein has an ionic balance that is the same as or substantially the same as the eye. In some embodiments, a composition disclosed herein does not does not disrupt the ionic balance of the eye.

[00199] As used herein, "practical osmolarity/osmolality" or "deliverable osmolarity/osmolality" means the osmolarity/osmolality of a composition as determined by measuring the osmolarity/osmolality of the ophthalmic agent and all excipients except the gelling and/or the thickening agent (e.g.,

polyoxyethylene-polyoxypropylene copolymers, carboxymethylcellulose or the like). The practical osmolality of a composition disclosed herein is measured by a suitable method, e.g., a freezing point depression method as described in Viegas et. al., Int. J. Pharm., 1998, 160, 157-162. In some instances, the practical osmolality of a composition disclosed herein is measured by vapor pressure osmometry (e.g., vapor pressure depression method) that allows for determination of the osmolality of a composition at higher temperatures. In some instances, vapor pressure depression method allows for determination of the osmolality of a composition comprising a gelling agent (e.g., a thermoreversible polymer) at a higher temperature wherein the gelling agent is in the form of a gel.

[00200] In some embodiments, the osmolality at a target site of action (e.g., the eye) is about the same as the delivered osmolality of a composition described herein. In some embodiments, a composition described herein has a deliverable osmolality of about 150 mOsm/L to about 500 mOsm/L, about 250 mOsm/L to about 500 mOsm/L, about 250 mOsm/L to about 350 mOsm/L, about 280 mOsm/L to about 370 mOsm/L or about 250 mOsm/L to about 320 mOsm/L.

[00201] The practical osmolality of an ophthalmic composition disclosed herein is from about 100 mOsm/kg to about 1000 mOsm/kg, from about 200 mOsm/kg to about 800 mOsm/kg, from about 250 mOsm/kg to about 500 mOsm/kg, or from about 250 mOsm/kg to about 320 mOsm/kg, or from about 250 mOsm/kg to about 350 mOsm/kg or from about 280 mOsm/kg to about 320 mOsm/kg. In some embodiments, a composition described herein has a practical osmolality of about 100 mOsm/L to about 1000 mOsm/L, about 200 mOsm/L to about 800 mOsm/L, about 250 mOsm/L to about 500 mOsm/L, about 250 mOsm/L to about 350 mOsm/L, about 250 mOsm/L to about 320 mOsm/L, or about 280 mOsm/L to about 320 mOsm/L.

[00202] In some embodiments, suitable tonicity adjusting agents include, but are not limited to any pharmaceutically acceptable sugar, salt or any combinations or mixtures thereof, such as, but not limited to dextrose, glycerin, mannitol, sorbitol, sodium chloride, and other electrolytes. In some instances, the tonicity adjusting agent is selected from sodium chloride, sodium nitrate, sodium sulfate, sodium bisulfate, potassium chloride, calcium chloride, magnesium chloride, zinc chloride, potassium acetate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium thiosulfate, magnesium sulfate, disodium hydrogen phosphate, sodium dihydrogen phosphate, potassium dihydrogen phosphate, dextrose, mannitol, sorbitol, dextrose, sucrose, urea, propylene glycol, glycerin, or a combination thereof.

[00203] In some embodiment, the ophthalmic compositions described herein include one or more salts in an amount required to bring osmolality of the composition into an acceptable range. Such salts include those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or bisulfite anions; suitable salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfite and ammonium sulfate.

[00204] **Sterility**

[00205] In some embodiments, the compositions are sterilized. Included within the embodiments disclosed herein are means and processes for sterilization of a pharmaceutical composition disclosed

herein for use in humans. The goal is to provide a safe pharmaceutical product, relatively free of infection causing micro-organisms. The U. S. Food and Drug Administration has provided regulatory guidance in the publication "Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing" available at: <http://www.fda.gov/cder/guidance/5882f1.htm>, which is incorporated herein by reference in its entirety.

[00206] As used herein, sterilization means a process used to destroy or remove microorganisms that are present in a product or packaging. Any suitable method available for sterilization of objects and compositions is used. Available methods for the inactivation of microorganisms include, but are not limited to, the application of extreme heat, lethal chemicals, or gamma radiation. In some embodiments, a process for the preparation of an ophthalmic formulation comprises subjecting the formulation to a sterilization method selected from heat sterilization, chemical sterilization, radiation sterilization or filtration sterilization. The method used depends largely upon the nature of the device or composition to be sterilized. Detailed descriptions of many methods of sterilization are given in Chapter 40 of Remington: The Science and Practice of Pharmacy published by Lippincott, Williams & Wilkins, and is incorporated by reference with respect to this subject matter.

Filtration

[00207] Filtration sterilization is a method used to remove but not destroy microorganisms from solutions. Membrane filters are used to filter heat-sensitive solutions. Such filters are thin, strong, homogenous polymers of mixed cellulosic esters (MCE), polyvinylidene fluoride (PVF; also known as PVDF), or polytetrafluoroethylene (PTFE) and have pore sizes ranging from 0.1 to 0.22 μm . Solutions of various characteristics are optionally filtered using different filter membranes. For example, PVF and PTFE membranes are well suited to filtering organic solvents while aqueous solutions are filtered through PVF or MCE membranes. Filter apparatus are available for use on many scales ranging from the single point-of-use disposable filter attached to a syringe up to commercial scale filters for use in manufacturing plants. The membrane filters are sterilized by autoclave or chemical sterilization. Validation of membrane filtration systems is performed following standardized protocols (Microbiological Evaluation of Filters for Sterilizing Liquids, Vol 4, No. 3. Washington, D.C: Health Industry Manufacturers Association, 1981) and involve challenging the membrane filter with a known quantity (ca. $10^7/\text{cm}^2$) of unusually small microorganisms, such as *Brevundimonas diminuta* (ATCC 19146).

[00208] Pharmaceutical compositions are optionally sterilized by passing through membrane filters. Formulations comprising nanoparticles (U.S. Pat No. 6,139,870) or multilamellar vesicles (Richard et al., International Journal of Pharmaceutics (2006), 312(1-2): 144-50) are amenable to sterilization by filtration through 0.22 μm filters without destroying their organized structure.

[00209] In some embodiments, the methods disclosed herein comprise sterilizing the formulation (or components thereof) by means of filtration sterilization. In ophthalmic gel compositions that includes thermosetting polymers, filtration is carried out below (e.g. about 5°C) the gel temperature (T_{gel}) of a

formulation described herein and with viscosity that allows for filtration in a reasonable time using a peristaltic pump (e.g. below a theoretical value of 100cP).

[00210] Accordingly, provided herein are methods for sterilization of ophthalmic formulations that prevent degradation of polymeric components (e.g., thermosetting and/or other viscosity enhancing agents) and/or the ophthalmic agent during the process of sterilization. In some embodiments, degradation of the ophthalmic agent (e.g., a muscarinic antagonist such as atropine or atropine sulfate) is reduced or eliminated through the use of specific pH ranges for buffer components and specific proportions of viscosity enhancing agents in the formulations. In some embodiments, the choice of an appropriate viscosity enhancing agents or thermosetting polymer allows for sterilization of formulations described herein by filtration. In some embodiments, the use of an appropriate thermosetting polymer or other viscosity enhancing agents in combination with a specific pH range for the formulation allows for high temperature sterilization of formulations described with substantially no degradation of the therapeutic agent or the polymeric excipients. An advantage of the methods of sterilization provided herein is that, in certain instances, the formulations are subjected to terminal sterilization via autoclaving without any loss of the ophthalmic agent and/or excipients and/or viscosity enhancing agents during the sterilization step and are rendered substantially free of microbes and/or pyrogens.

Radiation Sterilization

[00211] One advantage of radiation sterilization is the ability to sterilize many types of products without heat degradation or other damage. The radiation commonly employed is beta radiation or alternatively, gamma radiation from a ^{60}Co source. The penetrating ability of gamma radiation allows its use in the sterilization of many product types, including solutions, compositions and heterogeneous mixtures. The germicidal effects of irradiation arise from the interaction of gamma radiation with biological macromolecules. This interaction generates charged species and free-radicals. Subsequent chemical reactions, such as rearrangements and cross-linking processes, result in the loss of normal function for these biological macromolecules. The formulations described herein are also optionally sterilized using beta irradiation.

Sterilization by Heat

[00212] Many methods are available for sterilization by the application of high heat. One method is through the use of a saturated steam autoclave. In this method, saturated steam at a temperature of at least 121 °C is allowed to contact the object to be sterilized. The transfer of heat is either directly to the microorganism, in the case of an object to be sterilized, or indirectly to the microorganism by heating the bulk of an aqueous solution to be sterilized. This method is widely practiced as it allows flexibility, safety and economy in the sterilization process.

Microorganisms

[00213] In some embodiments, the compositions are substantially free of microorganisms. Acceptable bioburden or sterility levels are based on applicable standards that define therapeutically acceptable compositions, including but not limited to United States Pharmacopeia Chapters <111> et

seq. For example, acceptable sterility (e.g., bioburden) levels include about 10 colony forming units (cfu) per gram of formulation, about 50 cfu per gram of formulation, about 100 cfu per gram of formulation, about 500 cfu per gram of formulation or about 1000 cfu per gram of formulation. In some embodiments, acceptable bioburden levels or sterility for formulations include less than 10 cfu/mL, less than 50 cfu/mL, less than 500 cfu/mL or less than 1000 cfu/mL microbial agents. In addition, acceptable bioburden levels or sterility include the exclusion of specified objectionable microbiological agents. By way of example, specified objectionable microbiological agents include but are not limited to *Escherichia coli* (*E. coli*), *Salmonella* sp., *Pseudomonas aeruginosa* (*P. aeruginosa*) and/or other specific microbial agents.

[00214] An important component of the sterility assurance quality control, quality assurance and validation process is the method of sterility testing. Sterility testing, by way of example only, is performed by two methods. The first is direct inoculation wherein a sample of the composition to be tested is added to growth medium and incubated for a period of time up to 21 days. Turbidity of the growth medium indicates contamination. Drawbacks to this method include the small sampling size of bulk materials which reduces sensitivity, and detection of microorganism growth based on a visual observation. An alternative method is membrane filtration sterility testing. In this method, a volume of product is passed through a small membrane filter paper. The filter paper is then placed into media to promote the growth of microorganisms. This method has the advantage of greater sensitivity as the entire bulk product is sampled. The commercially available Millipore Steritest sterility testing system is optionally used for determinations by membrane filtration sterility testing. For the filtration testing of creams or ointments Steritest filter system No. TLHVSL210 are used. For the filtration testing of emulsions or viscous products Steritest filter system No. TLAREM210 or TDAREM210 are used. For the filtration testing of pre-filled syringes Steritest filter system No. TTHASY210 are used. For the filtration testing of material dispensed as an aerosol or foam Steritest filter system No. TTHVA210 are used. For the filtration testing of soluble powders in ampoules or vials Steritest filter system No. TTHADA210 or TTHADV210 are used.

[00215] Testing for *E. coli* and *Salmonella* includes the use of lactose broths incubated at 30 - 35 °C for 24-72 hours, incubation in MacConkey and/or EMB agars for 18-24 hours, and/or the use of Rappaport medium. Testing for the detection of *P. aeruginosa* includes the use of NAC agar. United States Pharmacopeia Chapter <62> further enumerates testing procedures for specified objectionable microorganisms.

[00216] In certain embodiments, the ophthalmic formulation described herein has less than about 60 colony forming units (CFU), less than about 50 colony forming units, less than about 40 colony forming units, or less than about 30 colony forming units of microbial agents per gram of formulation. In certain embodiments, the ophthalmic formulations described herein are formulated to be isotonic with the eye.

Endotoxins

[00217] An additional aspect of the sterilization process is the removal of by-products from the killing of microorganisms (hereinafter, "Product"). The process of depyrogenation removes pyrogens from the sample. Pyrogens are endotoxins or exotoxins which induce an immune response. An example of an endotoxin is the lipopolysaccharide (LPS) molecule found in the cell wall of gram-negative bacteria. While sterilization procedures such as autoclaving or treatment with ethylene oxide kill the bacteria, the LPS residue induces a proinflammatory immune response, such as septic shock. Because the molecular size of endotoxins varies widely, the presence of endotoxins is expressed in "endotoxin units" (EU). One EU is equivalent to 100 picograms of *E. coli* LPS. In some cases, humans develop a response to as little as 5 EU/kg of body weight. The bioburden (e.g., microbial limit) and/or sterility (e.g., endotoxin level) is expressed in any units as recognized in the art. In certain embodiments, ophthalmic compositions described herein contain lower endotoxin levels (e.g. < 4 EU/kg of body weight of a subject) when compared to conventionally acceptable endotoxin levels (e.g., 5 EU/kg of body weight of a subject). In some embodiments, the ophthalmic formulation has less than about 5 EU/kg of body weight of a subject. In other embodiments, the ophthalmic formulation has less than about 4 EU/kg of body weight of a subject. In additional embodiments, the ophthalmic formulation has less than about 3 EU/kg of body weight of a subject. In additional embodiments, the ophthalmic formulation has less than about 2 EU/kg of body weight of a subject.

[00218] In some embodiments, the ophthalmic formulation has less than about 5 EU/kg of formulation. In other embodiments, the ophthalmic formulation has less than about 4 EU/kg of formulation. In additional embodiments, the ophthalmic formulation has less than about 3 EU/kg of formulation. In some embodiments, the ophthalmic formulation has less than about 5 EU/kg Product. In other embodiments, the ophthalmic formulation has less than about 1 EU/kg Product. In additional embodiments, the ophthalmic formulation has less than about 0.2 EU/kg Product. In some embodiments, the ophthalmic formulation has less than about 5 EU/g of unit or Product. In other embodiments, the ophthalmic formulation has less than about 4 EU/ g of unit or Product. In additional embodiments, the ophthalmic formulation has less than about 3 EU/g of unit or Product. In some embodiments, the ophthalmic formulation has less than about 5 EU/mg of unit or Product. In other embodiments, the ophthalmic formulation has less than about 4 EU/ mg of unit or Product. In additional embodiments, the ophthalmic formulation has less than about 3 EU/mg of unit or Product. In certain embodiments, ophthalmic formulations described herein contain from about 1 to about 5 EU/mL of formulation. In certain embodiments, ophthalmic formulations described herein contain from about 2 to about 5 EU/mL of formulation, from about 3 to about 5 EU/mL of formulation, or from about 4 to about 5 EU/mL of formulation.

[00219] In certain embodiments, ophthalmic compositions described herein contain lower endotoxin levels (e.g. < 0.5 EU/mL of formulation) when compared to conventionally acceptable endotoxin levels (e.g., 0.5 EU/mL of formulation). In some embodiments, the ophthalmic formulation

has less than about 0.5 EU/mL of formulation. In other embodiments, the ophthalmic formulation has less than about 0.4 EU/mL of formulation. In additional embodiments, the ophthalmic formulation has less than about 0.2 EU/mL of formulation.

[00220] Pyrogen detection, by way of example only, is performed by several methods. Suitable tests for sterility include tests described in United States Pharmacopoeia (USP) <71> Sterility Tests (23rd edition, 1995). The rabbit pyrogen test and the Limulus amoebocyte lysate test are both specified in the United States Pharmacopoeia Chapters <85> and <151> (USP23/NF 18, Biological Tests, The United States Pharmacopoeial Convention, Rockville, MD, 1995). Alternative pyrogen assays have been developed based upon the monocyte activation-cytokine assay. Uniform cell lines suitable for quality control applications have been developed and have demonstrated the ability to detect pyrogenicity in samples that have passed the rabbit pyrogen test and the Limulus amoebocyte lysate test (Taktak et al, J. Pharm. Pharmacol. (1990), 43:578-82). In an additional embodiment, the ophthalmic formulation is subject to depyrogenation. In a further embodiment, the process for the manufacture of the ophthalmic formulation comprises testing the formulation for pyrogenicity. In certain embodiments, the formulations described herein are substantially free of pyrogens.

[00221] Ophthalmic Muscarinic Antagonist-Mucus Penetrating Particle (MPP)

Composition

[00222] Mucus-penetrating particles (MPPs) are particles that rapidly traverse mucus (e.g. human mucus). In some cases, MPPs comprise of a nanoparticle with a particle size of between about 200nm and 500nm. In some instances, the nanoparticle is further coated with a mucus penetrating agent. In some instances, a composition described herein is formulated with MPPs for mucus penetration. In some instances, an ophthalmic agent composition described herein is formulated with MPPs for mucus penetration. In some instances, the ophthalmic agent is a muscarinic antagonist. In some instances, a muscarinic antagonist composition described herein is formulated with MPPs for mucus penetration. In some instances, a muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, atropine methonitrate, diphenhydramine, dimenhydrinate, dicyclomine, flavoxate, oxybutynin, tiotropium, hyoscine, scopolamine (L-hyoscine), hydroxyzine, ipratropium, tropicamide, cyclopentolate, pirenzapine, homatropine, solifenacin, darifenacin, benzatropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, or tolterodine. In some instances, a muscarinic antagonist is atropine or its pharmaceutically acceptable salt thereof. In some instances, a muscarinic antagonist is atropine sulfate. In some instances, an atropine composition described herein is formulated with MPPs for mucus penetration. In some instances, an atropine sulfate composition described herein is formulated with MPPs for mucus penetration. In a non-limiting example, the MPPs for use in the disclosed composition is obtained from Kala Pharmaceuticals, Inc. (100 Beaver Street #201, Waltham, MA 02453).

[00223] In some embodiments, the nanoparticle comprises of any suitable material, such as an organic material, an inorganic material, a polymer, or combinations thereof. In some instances, the

nanoparticle comprises of inorganic material, such as for example, a metal (e.g., Ag, Au, Pt, Fe, Cr, Co, Ni, Cu, Zn, and other transition metals), a semiconductor (e.g., silicon, silicon compounds and alloys, cadmium selenide, cadmium sulfide, indium arsenide, and indium phosphide), or an insulator (e.g., ceramics such as silicon oxide). In some instances, the nanoparticle comprises organic materials such as a synthetic polymer and/or a natural polymer. Examples of synthetic polymers include non-degradable polymers such as polymethacrylate and degradable polymers such as polylactic acid, polyglycolic acid and copolymers thereof. Examples of natural polymers include hyaluronic acid, chitosan, and collagen.

[00224] In some embodiments, the nanoparticle is coated with a mucus penetrating agent. In some instances, the mucus penetrating agent comprises any suitable material, such as a hydrophobic material, a hydrophilic material, and/or an amphiphilic material. In some instances, the mucus penetrating agent is a polymer. In some instances, the polymer is a synthetic polymer (i.e., a polymer not produced in nature). In other embodiments, the polymer is a natural polymer (e.g., a protein, polysaccharide, rubber). In certain embodiments, the polymer is a surface active polymer. In certain embodiments, the polymer is a non-ionic polymer. In certain embodiments, the polymer is a non-ionic block copolymer. In some embodiments, the polymer is a diblock copolymer, a triblock copolymer, e.g., e.g., where one block is a hydrophobic polymer and another block is a hydrophilic polymer. In some embodiments, the polymer is charged or uncharged.

[00225] Additional examples of suitable polymers include, but are not limited to, polyamines, polyethers, polyamides, polyesters, polycarbamates, polyureas, polycarbonates, polystyrenes, polyimides, polysulfones, polyurethanes, polyacetylenes, polyethylenes, polyethyleneimines, polyisocyanates, polyacrylates, polymethacrylates, polyacrylonitriles, and polyarylates. Non-limiting examples of specific polymers include poly(caprolactone) (PCL), ethylene vinyl acetate polymer (EVA), poly(lactic acid) (PLA), poly(L-lactic acid) (PLLA), poly(glycolic acid) (PGA), poly(lactic acid-co-glycolic acid) (PLGA), poly(L-lactic acid-co-glycolic acid) (PLLGA), poly(D,L-lactide) (PDLA), poly(L-lactide) (PLLA), poly(D,L-lactide-co-caprolactone), poly(D,L-lactide-co-caprolactone-co-glycolide), poly(D,L-lactide-co-PEO-co-D,L-lactide), poly(D,L-lactide-co-PPO-co-D,L-lactide), polyalkyl cyanoacrylate, polyurethane, poly-L-lysine (PLL), hydroxypropyl methacrylate (HPMA), poly(ethylene glycol), poly-L-glutamic acid, poly(hydroxy acids), polyanhydrides, polyorthoesters, poly(ester amides), polyamides, poly(ester ethers), polycarbonates, polyalkylenes such as polyethylene and polypropylene, polyalkylene glycols such as poly(ethylene glycol) (PEG), polyalkylene oxides (PEO), polyalkylene terephthalates such as poly(ethylene terephthalate), polyvinyl alcohols (PVA), polyvinyl ethers, polyvinyl esters such as poly(vinyl acetate), polyvinyl halides such as poly(vinyl chloride) (PVC), polyvinylpyrrolidone, polysiloxanes, polystyrene (PS), polyurethanes, derivatized celluloses such as alkyl celluloses, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitro celluloses, hydroxypropylcellulose, carboxymethylcellulose, polymers of acrylic acids, such as poly(methyl(meth)acrylate) (PMMA), poly(ethyl(meth)acrylate), poly(butyl(meth)acrylate), poly(isobutyl(meth)acrylate), poly(hexyl(meth)acrylate), poly(isodecyl(meth)acrylate), poly(lauryl(meth)acrylate),

poly(phenyl(meth)acrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate) (jointly referred to herein as "polyacrylic acids"), and copolymers and mixtures thereof, polydioxanone and its copolymers, polyhydroxyalkanoates, polypropylene fumarate), polyoxymethylene, poloxamers, poly(ortho)esters, poly(butyric acid), poly(valeric acid), poly(lactide-co-caprolactone), and trimethylene carbonate, polyvinylpyrrolidone.

[00226] In some cases, an ophthalmic agent (e.g. a muscarinic antagonist such as atropine or atropine sulfate) is present in the MPP formulation at a concentration of between about 0.001 wt% and about 0.05 wt%, between about 0.005% to about 0.050%, between about 0.010% to about 0.050%, between about 0.015% to about 0.050%, between about 0.020% to about 0.050%, between about 0.025% to about 0.050%, between about 0.030% to about 0.050%, between about 0.035% to about 0.050%, between about 0.040% to about 0.050%, or between about 0.045% to about 0.050% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some instances, additional agents such as buffers, pH adjusting agents, and/or preservatives are formulated in the MPP formulation.

[00227] In some instances, ophthalmic agent-MPP composition is formulated using any suitable method. In some embodiments, a milling process is used to reduce the size of a solid material to form particles in the micrometer to nanometer size range. In some cases, dry and wet milling processes such as jet milling, cryo-milling, ball milling, media milling, and homogenization are known and are used in methods described herein. Generally, in a wet milling process, a suspension of the material to be used as the nanoparticle is mixed with milling media with or without excipients to reduce particle size. Dry milling is a process wherein the material to be used as the nanoparticle is mixed with milling media with or without excipients to reduce particle size. In a cryo-milling process, a suspension of the material to be used as the nanoparticle is mixed with milling media with or without excipients under cooled temperatures.

[00228] In some embodiments, any suitable grinding medium is used for milling. In some embodiments, a ceramic and/or polymeric material and/or a metal is used. Examples of suitable materials include zirconium oxide, silicon carbide, silicon oxide, silicon nitride, zirconium silicate, yttrium oxide, glass, alumina, alpha- alumina, aluminum oxide, polystyrene, poly(methyl methacrylate), titanium, steel. In some cases, a grinding medium has any suitable size. For example, the grinding medium has an average diameter of at least about 0.1 mm, at least about 0.2 mm, at least about 0.5 mm, at least about 0.8 mm, at least about 1 mm, at least about 2 mm, or at least about 5 mm. In some cases, the grinding medium has an average diameter of less than or equal to about 5 mm, less than or equal to about 2 mm, less than or equal to about 1 mm, less than or equal to about 0.8, less than or equal to about 0.5 mm, or less than or equal to about 0.2 mm. Combinations of the above-referenced ranges are also possible (e.g. , an average diameter of at least about 0.5 millimeters and less than or equal to about 1 mm). Other ranges are also possible.

[00229] In some embodiments, any suitable solvent are used for milling. In some cases, the choice of solvent is depend on factors such as the solid material (e.g., a muscarinic antagonist such as atropine) being milled, the particular type of stabilizer/mucus penetrating agent being used (e.g., one that renders the particle mucus penetrating), the grinding material be used, among other factors. In some cases, suitable solvents are ones that do not substantially dissolve the solid material or the grinding material, but dissolve the stabilizer/mucus penetrating agent to a suitable degree. Non-limiting examples of solvents include, but are not limited to, water, buffered solutions, other aqueous solutions, alcohols (e.g., ethanol, methanol, butanol), and mixtures thereof that optionally include other components such as pharmaceutical excipients, polymers, pharmaceutical agents, salts, preservative agents, viscosity modifiers, tonicity modifier, taste masking agents, antioxidants, pH modifier, and other pharmaceutical excipients. In other embodiments, an organic solvent is used. In some cases, a pharmaceutical agent (e.g. a muscarinic antagonist such as atropine) has any suitable solubility in these or other solvents, such as a solubility in one or more of the ranges described above for aqueous solubility or for solubility in a coating solution.

[00230] In some instances, a MPP is a MPP as described in WO2013/166385. In some instances, a MPP is a MPP as described in Lai *et al.*, "Rapid transport of large polymeric nanoparticles in fresh undiluted human mucus," *PNAS* 104(5):1482-1487 (2007). In some instances, an ophthalmic agent-MPP composition is formulated using a method as described in WO2013/166385. In some instances, an ophthalmic agent-MPP composition is formulated using a method as described in Lai *et al.*, "Rapid transport of large polymeric nanoparticles in fresh undiluted human mucus," *PNAS* 104(5):1482-1487 (2007). In some instances, the ophthalmic agent is a muscarinic antagonist such as atropine or atropine sulfate.

[00231] **Ophthalmic Gel Muscarinic Antagonist Composition**

[00232] Gels have been defined in various ways. For example, the United States Pharmacopoeia defines gels as semisolid systems consisting of either suspensions made up of small inorganic particles or large organic molecules interpenetrated by a liquid. Gels include a single-phase or a two-phase system. A single-phase gel consists of organic macromolecules distributed uniformly throughout a liquid in such a manner that no apparent boundaries exist between the dispersed macromolecules and the liquid. Some single-phase gels are prepared from synthetic macromolecules (e.g., carbomer) or from natural gums, (e.g., tragacanth). In some embodiments, single-phase gels are generally aqueous, but will also be made using alcohols and oils. Two-phase gels consist of a network of small discrete particles.

[00233] In some embodiments, gels are also classified as being hydrophobic or hydrophilic. In certain embodiments, the base of a non-limiting example of a hydrophobic gel includes a liquid paraffin with polyethylene or fatty oils gelled with colloidal silica, or aluminum or zinc soaps. In contrast, the base of a non-limiting example of a hydrophilic gel includes water, glycerol, or propylene glycol gelled with a suitable gelling agent (e.g., tragacanth, starch, cellulose derivatives, carboxyvinylpolymers, and

magnesium-aluminum silicates). In certain embodiments, the rheology of the compositions disclosed herein is pseudo plastic, plastic, thixotropic, or dilatant.

[00234] In some embodiments, the ophthalmic composition is an ophthalmic gel, and wherein the ophthalmically acceptable carrier comprises water and at least one viscosity-enhancing agent. In some embodiments, the viscosity-enhancing agent is selected from cellulose-based polymers, polyoxyethylene-polyoxypropylene triblock copolymers, dextran-based polymers, polyvinyl alcohol, dextrin, polyvinylpyrrolidone, polyalkylene glycols, chitosan, collagen, gelatin, hyaluronic acid, or combinations thereof.

[00235] In some embodiment, the ophthalmic gel composition described herein is a semi-solid or id in a gelled state before it is topically administered (e.g. at room temperature). For example, suitable viscosity-enhancing agents for such gels include by way of example only, gelling agents and suspending agents. In one embodiment, the enhanced viscosity formulation does not include a buffer. In other embodiments, the enhanced viscosity formulation includes a pharmaceutically acceptable buffer. Sodium chloride or other tonicity agents are optionally used to adjust tonicity, if necessary.

[00236] By way of example only, the ophthalmically acceptable viscosity agent includes hydroxypropyl methylcellulose, hydroxyethyl cellulose, polyvinylpyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium chondroitin sulfate, sodium hyaluronate. Other viscosity enhancing agents compatible with the targeted ocular site include, but are not limited to, acacia (gum arabic), agar, aluminum magnesium silicate, sodium alginate, sodium stearate, bladderwrack, bentonite, carbomer, carrageenan, Carbopol, xanthan, cellulose, microcrystalline cellulose (MCC), ceratonia, chitin, carboxymethylated chitosan, chondrus, dextrose, furcellaran, gelatin, Ghatti gum, guar gum, hectorite, lactose, sucrose, maltodextrin, mannitol, sorbitol, honey, maize starch, wheat starch, rice starch, potato starch, gelatin, sterculia gum, xanthum gum, gum tragacanth, ethyl cellulose, ethylhydroxyethyl cellulose, ethylmethyl cellulose, methyl cellulose, hydroxyethyl cellulose, hydroxyethylmethyl cellulose, hydroxypropyl cellulose, poly(hydroxyethyl methacrylate), oxypolygelatin, pectin, polygeline, povidone, propylene carbonate, methyl vinyl ether/maleic anhydride copolymer (PVM/MA), poly(methoxyethyl methacrylate), poly(methoxyethoxyethyl methacrylate), hydroxypropyl cellulose, hydroxypropylmethyl-cellulose (HPMC), sodium carboxymethyl-cellulose (CMC), silicon dioxide, polyvinylpyrrolidone (PVP: povidone), Splenda® (dextrose, maltodextrin and sucralose) or combinations thereof. In specific embodiments, the viscosity-enhancing excipient is a combination of MCC and CMC. In another embodiment, the viscosity-enhancing agent is a combination of carboxymethylated chitosan, or chitin, and alginate. The combination of chitin and alginate with the ophthalmic agents disclosed herein acts as a controlled release formulation, restricting the diffusion of the ophthalmic agents from the formulation. Moreover, the combination of carboxymethylated chitosan and alginate is optionally used to assist in increasing the permeability of the ophthalmic agents in the eye.

[00237] In some embodiments is an enhanced viscosity formulation, comprising from about 0.1 mM and about 100 mM of an ophthalmic agent, a pharmaceutically acceptable viscosity agent, and water

for injection, the concentration of the viscosity agent in the water being sufficient to provide an enhanced viscosity formulation with a final viscosity from about 100 to about 100,000 cP. In certain embodiments, the viscosity of the gel is in the range from about 100 to about 50,000 cP, about 100 cP to about 1,000 cP, about 500 cP to about 1500 cP, about 1000 cP to about 3000 cP, about 2000 cP to about 8,000 cP, about 4,000 cP to about 50,000 cP, about 10,000 cP to about 500,000 cP, about 15,000 cP to about 1,000,000 cP. In other embodiments, when an even more viscous medium is desired, the biocompatible gel comprises at least about 35%, at least about 45%, at least about 55%, at least about 65%, at least about 70%, at least about 75%, or even at least about 80% or so by weight of the ophthalmic agent. In highly concentrated samples, the biocompatible enhanced viscosity formulation comprises at least about 25%, at least about 35%, at least about 45%, at least about 55%, at least about 65%, at least about 75%, at least about 85%, at least about 90% or at least about 95% or more by weight of the ophthalmic agent.

[00238] In one embodiment, the pharmaceutically acceptable enhanced viscosity ophthalmically acceptable formulation comprises at least one ophthalmic agent and at least one gelling agent. Suitable gelling agents for use in preparation of the gel formulation include, but are not limited to, celluloses, cellulose derivatives, cellulose ethers (e.g., carboxymethylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxymethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, methylcellulose), guar gum, xanthan gum, locust bean gum, alginates (e.g., alginic acid), silicates, starch, tragacanth, carboxyvinyl polymers, carrageenan, paraffin, petrolatum and any combinations or mixtures thereof. In some other embodiments, hydroxypropylmethylcellulose (Methocel®) is utilized as the gelling agent. In certain embodiments, the viscosity enhancing agents described herein are also utilized as the gelling agent for the gel formulations presented herein.

[00239] In some embodiments, the ophthalmic gel composition described herein is an in situ gel formulation. In some instances, the in situ gel formation is based on increased pre-corneal residence time of the ophthalmic composition which improves ocular bioavailability, corneal mucoadhesion, lysosomal interaction and ionic gelation, improved corneal absorption, thermal gelation, or a combination thereof. In some instances, the in situ gel formulation is activated by pH, temperature, ion, UV, or solvent exchange.

[00240] In some instances, the ophthalmic gel composition comprises a muscarinic antagonist and one or more gelling agents. In some instances, the gelling agent includes, but is not limited to, poloxamer (e.g. Poloxamer 407), tetronics, ethyl (hydroxyethyl) cellulose, cellulose acetate phthalate (CAP), carbopol (e.g. Carbopol 1342P NF, Carbopol 980 NF), alginates (e.g. low acetyl gellan gum (Gelrite®)), gellan, hyaluronic acid, pluronics (e.g. Pluronic F-127), chitosan, polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), dextran, hydroxy propyl methyl cellulose (HPMC), hydroxyethylcellulose (HEC), methylcellulose (MC), thiolated xyloglucan, polymethacrylic acid (PMMA), polyethylene glycol (PEG), pseudolatexes, xyloglucans, or combinations thereof.

[00241] In some instances, the in situ gel formation further comprises a permeation enhancer. In some instances, the permeation enhancer includes surfactants (e.g. non-ionic surfactants), benzalkonium

chloride, EDTA, surface-active heteroglycosides, calcium chelators, hydroxyl propyl beta cyclodextrin (HP beta CD), bile salts, and the like.

[00242] In some embodiments, other gel formulations are useful depending upon the particular ophthalmic agent, other pharmaceutical agent or excipients/additives used, and as such are considered to fall within the scope of the present disclosure. For example, other commercially-available glycerin-based gels, glycerin-derived compounds, conjugated, or crosslinked gels, matrices, hydrogels, and polymers, as well as gelatins and their derivatives, alginates, and alginate-based gels, and even various native and synthetic hydrogel and hydrogel-derived compounds are all expected to be useful in the ophthalmic agent formulations described herein. In some embodiments, ophthalmically acceptable gels include, but are not limited to, alginate hydrogels SAF®-Gel (ConvaTec, Princeton, N.J.), Duoderm® Hydroactive Gel (ConvaTec), Nu-gel ©(Johnson & Johnson Medical, Arlington, Tex.); Carrasyn®(V) Acemannan Hydrogel (Carrington Laboratories, Inc., Irving, Tex.); glycerin gels Elta® Hydrogel (Swiss-American Products, Inc., Dallas, Tex.) and K-Y® Sterile (Johnson & Johnson). In further embodiments, biodegradable biocompatible gels also represent compounds present in ophthalmically acceptable formulations disclosed and described herein.

[00243] In some embodiments, the viscosity-enhancing agent is a cellulose-based polymer selected from cellulose gum, alkylcellulose, hydroxyl-alkyl cellulose, hydroxyl-alkyl alkylcellulose, carboxy-alkyl cellulose, or combinations thereof. In some embodiments, the viscosity-enhancing agent is hydroxyl-alkyl alkylcellulose. In some embodiment, the viscosity-enhancing agent is hydroxypropyl methylcellulose.

[00244] In certain embodiments, the enhanced viscosity formulation is characterized by a phase transition between room temperature and body temperature (including an individual with a serious fever, e.g., up to about 42 °C). In some embodiments, the phase transition occurs at 1 °C below body temperature, at 2 °C below body temperature, at 3 °C below body temperature, at 4 °C below body temperature, at 6 °C below body temperature, at 8 °C below body temperature, or at 10 °C below body temperature. In some embodiments, the phase transition occurs at about 15 °C below body temperature, at about 20 °C below body temperature or at about 25 °C below body temperature. In specific embodiments, the gelation temperature (Tgel) of a formulation described herein is about 20 °C, about 25 °C, or about 30 °C. In certain embodiments, the gelation temperature (Tgel) of a formulation described herein is about 35 °C, or about 40 °C. Included within the definition of body temperature is the body temperature of a healthy individual, or an unhealthy individual, including an individual with a fever (up to -42 °C). In some embodiments, the pharmaceutical compositions described herein are liquids at about room temperature and are administered at or about room temperature.

[00245] Copolymers polyoxypropylene and polyoxyethylene (e.g. polyoxyethylene-polyoxypropylene triblock copolymers) form thermosetting gels when incorporated into aqueous solutions. These polymers have the ability to change from the liquid state to the gel state at temperatures close to body temperature, therefore allowing useful formulations that are applied to the targeted ocular

site. The liquid state-to-gel state phase transition is dependent on the polymer concentration and the ingredients in the solution.

[00246] In some embodiments, the amount of thermosetting polymer in any formulation described herein is about 10%, about 15%, about 20%, about 25%, about 30%, about 35% or about 40% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer in any formulation described herein is about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24% or about 25% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 7.5% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 10% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 11% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 12% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 13% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 14% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 15% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 16% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 17% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 18% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 19% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 20% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 21% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 23% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 25% of the total weight of the formulation. In some embodiments, the amount of thickening agent (e.g., a gelling agent) in any formulation described herein is about 1%, about 5%, about 10%, or about 15% of the total weight of the formulation. In some embodiments, the amount of thickening agent (e.g., a gelling agent) in any formulation described herein is about 0.5%, about 1%,

about 1.5%, about 2%, about 2.5%, about 3%, about 3.5%, about 4%, about 4.5%, or about 5% of the total weight of the formulation.

[00247] In an alternative embodiment, the thermogel is a PEG-PLGA-PEG triblock copolymer (Jeong et al, Nature (1997), 388:860-2; Jeong et al, J. Control. Release (2000), 63:155-63; Jeong et al, Adv. Drug Delivery Rev. (2002), 54:37-51). The polymer exhibits sol-gel behavior over a concentration of about 5% w/w to about 40% w/w. Depending on the properties desired, the lactide/glycolide molar ratio in the PLGA copolymer ranges from about 1:1 to about 20:1. The resulting copolymers are soluble in water and form a free-flowing liquid at room temperature, but form a hydrogel at body temperature. A commercially available PEG-PLGA-PEG triblock copolymer is RESOMER RGP t50106 manufactured by Boehringer Ingelheim. This material is composed of a PLGA copolymer of 50:50 poly(DL-lactide-co-glycolide) and is 10% w/w of PEG and has a molecular weight of about 6000.

[00248] Additional biodegradable thermoplastic polyesters include AtriGel® (provided by Atrix Laboratories, Inc.) and/or those disclosed, e.g., in U.S. Patent Nos. 5,324,519; 4,938,763; 5,702,716; 5,744,153; and 5,990,194; wherein the suitable biodegradable thermoplastic polyester is disclosed as a thermoplastic polymer. Examples of suitable biodegradable thermoplastic polyesters include polylactides, polyglycolides, polycaprolactones, copolymers thereof, terpolymers thereof, and any combinations thereof. In some such embodiments, the suitable biodegradable thermoplastic polyester is a polylactide, a polyglycolide, a copolymer thereof, a terpolymer thereof, or a combination thereof. In one embodiment, the biodegradable thermoplastic polyester is 50/50 poly(DL-lactide-co-glycolide) having a carboxy terminal group; is present in about 30 wt. % to about 40 wt. % of the composition; and has an average molecular weight of about 23,000 to about 45,000. Alternatively, in another embodiment, the biodegradable thermoplastic polyester is 75/25 poly (DL-lactide-co-glycolide) without a carboxy terminal group; is present in about 40 wt. % to about 50 wt. % of the composition; and has an average molecular weight of about 15,000 to about 24,000. In further or alternative embodiments, the terminal groups of the poly(DL-lactide-co-glycolide) are either hydroxyl, carboxyl, or ester depending upon the method of polymerization. Polycondensation of lactic or glycolic acid provides a polymer with terminal hydroxyl and carboxyl groups. Ring-opening polymerization of the cyclic lactide or glycolide monomers with water, lactic acid, or glycolic acid provides polymers with the same terminal groups. However, ring-opening of the cyclic monomers with a monofunctional alcohol such as methanol, ethanol, or 1-dodecanol provides a polymer with one hydroxyl group and one ester terminal groups. Ring-opening polymerization of the cyclic monomers with a diol such as 1,6-hexanediol or polyethylene glycol provides a polymer with only hydroxyl terminal groups.

[00249] Since the polymer systems of thermosetting gels dissolve more completely at reduced temperatures, methods of solubilization include adding the required amount of polymer to the amount of water to be used at reduced temperatures. Generally after wetting the polymer by shaking, the mixture is capped and placed in a cold chamber or in a thermostatic container at about 0-10 °C in order to dissolve the polymer. The mixture is stirred or shaken to bring about a more rapid dissolution of the thermosetting

gel polymer. The ophthalmic agent and various additives such as buffers, salts, and preservatives are subsequently added and dissolved. In some instances the pharmaceutically agent is suspended if it is insoluble in water. The pD is modulated by the addition of appropriate buffering agents.

[00250] Ophthalmic Ointment Muscarinic Antagonist Composition

[00251] An ointment is a homogeneous, viscous, semi-solid preparation, most commonly a greasy, thick oil (e.g. oil 80% - water 20%) with a high viscosity, intended for external application to the skin or mucous membranes. Ointments have a water number that defines the maximum amount of water that it contains. They are used as emollients or for the application of active ingredients to the skin for protective, therapeutic, or prophylactic purposes and where a degree of occlusion is desired. Ointments are used topically on a variety of body surfaces. These include the skin and the mucous membranes of the eye (an eye ointment), vulva, anus, and nose

[00252] The vehicle of an ointment is known as the ointment base. The choice of a base depends upon the clinical indication for the ointment. The different types of ointment bases are: hydrocarbon bases, e.g. hard paraffin, soft paraffin, microcrystalline wax and ceresine; absorption bases, e.g. wool fat, beeswax; water soluble bases, e.g. macrogols 200, 300, 400; emulsifying bases, e.g. emulsifying wax, cetrimide; vegetable oils, e.g. olive oil, coconut oil, sesame oil, almond oil and peanut oil.

[00253] Ointments are formulated using hydrophobic, hydrophilic, or water-emulsifying bases to provide preparations that are immiscible, miscible, or emulsifiable with skin secretions. In some embodiments, they are also derived from hydrocarbon (fatty), absorption, water-removable, or water-soluble bases. The active agents are dispersed in the base, and later they get divided after the drug penetration into the target sites (e.g. membranes, skins, etc.).

[00254] The present disclosure recognizes that it is sometimes difficult to incorporate into the ointment a drug of low concentration with sufficient dose-to-dose uniformity for effectively treating a disorder or disease. In some embodiments, poly(ethylene-glycols), polyethoxylated castor oils (Cremophor®EL), alcohols having 12 to 20 carbon atoms or a mixture of two or more of said components are effective excipients for dispersing and/or dissolving effective amounts of ophthalmic drugs, in particular of ascomycins and staurosporine derivatives, in an ointment base, in particular in an ointment base substantially comprising oleaginous and hydrocarbon components, and that the resulting ointments are excellently tolerated by the skin and by ocular tissue.

[00255] The present disclosure further recognizes that ophthalmic drugs, such as a muscarinic antagonist (e.g. atropine or its pharmaceutically acceptable salts), incorporated in the ointment compositions describes herein target the choroid and/or retina in a patient when the compositions are topically administered to the ocular surface, in particular to the sclera of said patient. In some embodiments, an ophthalmic ointment composition includes an ophthalmic drug, an ointment base and an agent for dispersing and/or dissolving said drug in the ointment base, selected from a poly(ethylene-glycol), a polyethoxylated castor oil, an alcohol having 12 to 20 carbon atoms and a mixture of two or more of said components.

[00256] In some embodiments, the ointment bases include ophthalmically acceptable oil and fat bases, such as natural wax e.g. white and yellow bees wax, carnauba wax, wool wax (wool fat), purified lanolin, anhydrous lanolin; petroleum wax e.g. hard paraffin, microcrystalline wax; hydrocarbons e.g. liquid paraffin, white and yellow soft paraffin, white petrolatum, yellow petrolatum; or combinations thereof.

[00257] The above mentioned oil and fat bases are described in more detail, for instance, in the British Pharmacopoeia, Edition 2001, or the European Pharmacopoeia, 3rd Edition.

[00258] In some embodiments, the ointment base is present in amounts of about 50 to about 95, preferably of 70 to 90% by weight based on the total weight of the composition.

[00259] A preferred ointment base comprises a combination of one or more of one or more natural waxes like those indicated above, preferably wool wax (wool fat), and one or more hydrocarbons like those indicated above, preferably a soft paraffin or a petrolatum, more preferably in combination with liquid paraffin.

[00260] A special embodiment of the aforementioned ointment base comprises e.g. 5 to 17 parts by weight of wool fat, and 50 to 65 parts by weight of white petrolatum as well as 20 to 30 parts by weight of liquid paraffin.

[00261] In some embodiments, the agent for dispersing and/or dissolving the ophthalmic drug in the ointment base is selected from a poly(ethylene-glycol), a polyethoxylated castor oil, an alcohol having 12 to 20 carbon atoms and a mixture of two or more of said components. The agent is preferably used in amounts of 1 to 20 percent, more preferably 1 to 10 percent by weight of the entire semisolid ophthalmic composition.

[00262] Alcohols having 12 to 20 carbon atoms include particularly stearyl alcohol (C₁₈H₃₇O), cetyl alcohol (C₁₆H₃₃O) and mixtures thereof. Preferred are so-called cetostearyl alcohols, mixtures of solid alcohols substantially consisting of stearyl and cetyl alcohol and preferably comprising not less than 40 percent by weight of stearyl alcohol and a sum of stearyl alcohol and cetyl alcohol amounting to at least 90 percent by weight, and compositions comprising not less than 80 percent by weight of cetylstearyl alcohol and an emulsifier, in particular sodium cetostearyl sulfate and/or sodium lauryl sulfate, preferably in amounts not less than 7 percent by weight of emulsifier.

[00263] Polyethoxylated castor oils are reaction products of natural or hydrogenated castor oils and ethylene glycol. In some instances, such products are obtained in known manner, e.g. by reaction of a natural or hydrogenated castor oil or fractions thereof with ethylene oxide, e.g. in a molar ratio of from about 1:30 to about 1:60, with optional removal of free polyethylene glycol components from the product, e.g. in accordance with the methods disclosed in German Auslegeschriften 1,182,388 and 1,518,819. Especially suitable and preferred is a product commercially available under the trade name Cremophor®EL having a molecular weight (by steam osmometry)=ca. 1630, a saponification no.=ca. 65-70, an acid no.=ca. 2, an iodine no.=ca. 28-32 and an nD₂₅=ca. 1.471. Also suitable for use in this category is, for instance, Nikkol®HCO-60, a reaction product of hydrogenated castor oil and ethylene

oxide exhibiting the following characteristics: acid no.=ca. 0.3; saponification no.=ca. 47.4; hydroxy value=ca. 42.5. pH (5%)=ca. 4.6; Color APHA=ca. 40; m.p.=ca. 36.0° C ; Freezing point=ca. 32.4° C ; H₂O content (% , KF)=ca. 0.03.

[00264] Poly(ethylene-glycols) are used in some embodiments as the agent for dispersing and/or dissolving the ophthalmic drug in the ointment base according to the present disclosure. Suitable poly(ethylene-glycol)s are typically mixtures of polymeric compounds of the general formula H—(OCH₂—CH₂)_nOH, wherein the index n typically range from 4 to 230 and the mean molecular weight from about 200 to about 10000. Preferably n is a number from about 6 to about 22 and the mean molecular weight between about 300 and about 1000, more preferably n ranges from about 6 to about 13 and the mean molecular weight from about 300 to about 600, most preferably n has a value of about 8.5 to about 9 and the relative molecular weight is about 400. Suitable poly(ethylene-glycols) are readily available commercially, for example poly(ethylene-glycols) having a mean molecular weight of about 200, 300, 400, 600, 1000, 1500, 2000, 3000, 4000, 6000, 8000 and 10000.

[00265] The poly(ethylene-glycols), in particular the preferred types described in the foregoing paragraph, are preferably used in amounts of 1 to 10, more preferably 1 to 5 percent by weight of the entire semisolid ophthalmic composition.

[00266] An especially preferred embodiment of the compositions according to the instant disclosure comprises an agent for dispersing and/or dissolving of the drug in the ointment base which is selected from a poly(ethylene-glycol), a polyethoxylated castor oil and preferably a mixture of said components.

[00267] Gel/Ointment Viscosity

[00268] In some embodiments, the composition has a Brookfield RVDV viscosity of from about 10,000 to about 300,000 cps at about 20°C and sheer rate of Is^{-1} . In some embodiments, the composition has a Brookfield RVDV viscosity of from about 15,000 to about 200,000 cps at about 20°C and sheer rate of Is^{-1} . In some embodiments, the composition has a Brookfield RVDV viscosity of from about 50,000 to about 150,000 cps at about 20°C and sheer rate of Is^{-1} . In some embodiments, the composition has a Brookfield RVDV viscosity of from about 70,000 to about 130,000 cps at about 20°C and sheer rate of Is^{-1} . In some embodiments, the composition has a Brookfield RVDV viscosity of from about 90,000 to about 110,000 cps at about 20°C and sheer rate of Is^{-1} .

[00269] In some embodiments, the ophthalmic gel formulation contains a viscosity enhancing agent sufficient to provide a viscosity of between about 500 and 1,000,000 centipoise, between about 750 and 1,000,000 centipoise; between about 1000 and 1,000,000 centipoise; between about 1000 and 400,000 centipoise; between about 2000 and 100,000 centipoise; between about 3000 and 50,000 centipoise; between about 4000 and 25,000 centipoise; between about 5000 and 20,000 centipoise; or between about 6000 and 15,000 centipoise. In some embodiments, the ophthalmic gel formulation contains a viscosity enhancing agent sufficient to provide a viscosity of between about 50,000 and 1,000,000 centipoise.

[00270] In some embodiments, the compositions described herein are low viscosity compositions at body temperature. In some embodiments, low viscosity compositions contain from about 1% to about 10% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, low viscosity compositions contain from about 2% to about 10% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, low viscosity compositions contain from about 5% to about 10% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, low viscosity compositions are substantially free of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, a low viscosity ophthalmic agent composition described herein provides an apparent viscosity of from about 100 cP to about 10,000 cP. In some embodiments, a low viscosity ophthalmic agent composition described herein provides an apparent viscosity of from about 500 cP to about 10,000 cP. In some embodiments, a low viscosity ophthalmic agent composition described herein provides an apparent viscosity of from about 1000 cP to about 10,000 cP.

[00271] In some embodiments, the compositions described herein are viscous compositions at body temperature. In some embodiments, viscous compositions contain from about 10% to about 25% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, the viscous compositions contain from about 14% to about 22% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, the viscous compositions contain from about 15% to about 21% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, a viscous ophthalmic composition described herein provides an apparent viscosity of from about 100,000 cP to about 1,000,000 cP. In some embodiments, a viscous ophthalmic composition described herein provides an apparent viscosity of from about 150,000 cP to about 500,000 cP. In some embodiments, a viscous ophthalmic composition described herein provides an apparent viscosity of from about 250,000 cP to about 500,000 cP. In some of such embodiments, a viscous ophthalmic composition is a liquid at room temperature and gels at about between room temperature and body temperature (including an individual with a serious fever, e.g., up to about 42 °C). In some embodiments, a viscous ophthalmic composition is administered as monotherapy for treatment of an ophthalmic disease or condition described herein.

[00272] In some embodiments, the viscosity of the gel formulations presented herein is measured by any means described. For example, in some embodiments, an LVDV-II+CP Cone Plate Viscometer and a Cone Spindle CPE-40 is used to calculate the viscosity of the gel formulation described herein. In other embodiments, a Brookfield (spindle and cup) viscometer is used to calculate the viscosity of the gel formulation described herein. In some embodiments, the viscosity ranges referred to herein are measured at room temperature. In other embodiments, the viscosity ranges referred to herein are measured at body temperature (e.g., at the average body temperature of a healthy human).

[00273] Gel/Ointment Dose-To-Dose Uniformity

[00274] Typical ophthalmic gels are packaged in eye drop bottles and administered as drops. For example, a single administration (i.e. a single dose) of an ophthalmic gel includes a single drop, two drops, three drops or more into the eyes of the patient. Furthermore, typical ophthalmic ointments are packaged in tubes or other squeezable containers with a dispensing nozzle through which strips of the ointment are delivered. For example, a single administration (i.e. a single dose) of an ophthalmic ointment includes a single strip, or multiple strips into the eyes of the patient. In some embodiments, one dose of the ophthalmic gel described herein is one drop of the gel composition from the eye drop bottle. In some embodiments, one dose of the ophthalmic ointment is one strip of the ointment composition dispensed through the nozzle of a dispersing tube.

[00275] In some cases, described herein include ophthalmic gel compositions which provide a dose-to-dose uniform concentrations. In some instances, the dose-to-dose uniform concentration does not present significant variations of drug content from one dose to another. In some instances, the dose-to-dose uniform concentration does provide consistent drug content from one dose to another.

[00276] In some cases, described herein include ophthalmic ointment compositions which provide a dose-to-dose uniform concentrations. In some instances, the dose-to-dose uniform concentration does not present significant variations of drug content from one dose to another. In some instances, the dose-to-dose uniform concentration does provide consistent drug content from one dose to another.

[00277] In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 50%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 40%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 30%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 20%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 10%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 5%.

[00278] In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 10 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 8 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 5 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 3 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 2 consecutive doses.

[00279] A nonsettling formulation should not require shaking to disperse drug uniformly. A "no-shake" formulation is potentially advantageous over formulations that require shaking for the simple reason that patients' shaking behavior is a major source of variability in the amount of drug dosed. It has been reported that patients often times do not or forget to shake their ophthalmic compositions that

requires shaking before administering a dose, despite the instructions to shake that were clearly marked on the label. On the other hand, even for those patients who do shake the product, it is normally not possible to determine whether the shaking is adequate in intensity and/or duration to render the product uniform. In some embodiments, the ophthalmic gel compositions and ophthalmic ointment compositions described herein are "no-shake" formulations that maintained the dose-to-dose uniformity described herein.

[00280] To evaluate the dose-to-dose uniformity, drop bottles or tubes containing the ophthalmic aqueous compositions, the ophthalmic gel compositions, or ophthalmic ointment compositions are stored upright for a minimum of 12 hours prior to the start of the test. To simulate the recommended dosing of these products, predetermined number of drops or strips are dispensed from each commercial bottles or tubes at predetermined time intervals for an extended period of time or until no product was left in the bottle or tube. All drops and strips are dispensed into tared glass vials, capped, and stored at room temperature until analysis. Concentrations of a muscarinic antagonist such as atropine in the expressed drops were determined using a reverse-phase HPLC method.

[00281] **Methods of Treatment**

[00282] Disclosed herein are methods of arresting myopia development by administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition as described above. Also disclosed herein are methods of preventing myopia development by administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition as described above.

[00283] In some embodiments, the ophthalmic aqueous formulations described herein are packaged in eye drop bottles and administered as drops. For example, a single administration (i.e. a single dose) of an ophthalmic aqueous formulation includes a single drop, two drops, three drops or more into the eyes of the patient. In some embodiments, the ophthalmic gel formulations described herein are packaged in eye drop bottles and administered as drops. For example, a single administration (i.e. a single dose) of an ophthalmic gel includes a single drop, two drops, three drops or more into the eyes of the patient. In some embodiments, the ophthalmic ointment formulations described herein are packaged in tubes or other squeezable containers with a dispensing nozzle through which strips of the ointment are delivered. For example, a single administration (i.e. a single dose) of an ophthalmic ointment includes a single strip, or multiple strips into the eyes of the patient. In some embodiments, one dose of the ophthalmic aqueous formulation described herein is one drop of the aqueous composition from the eye drop bottle. In some embodiments, one dose of the ophthalmic gel described herein is one drop of the gel composition from the eye drop bottle. In some embodiments, one dose of the ophthalmic ointment is one strip of the ointment composition dispensed through the nozzle of a dispersing tube.

[00284] In some embodiments of the disclosed method, the ophthalmic composition is stored below room temperature prior to first use. In some embodiments of the disclosed method, the ophthalmic composition is stored at between about 2 °C to about 10 °C prior to first use. In some embodiments of the disclosed method, the ophthalmic composition is stored at about 2 °C, about 3 °C, about 4 °C, about 5 °C,

about 6 °C, about 7 °C, about 8 °C, about 9 °C, or about 10 °C prior to first use. In some embodiments of the disclosed method, the ophthalmic composition is stored at between about 4 °C to about 8 °C prior to first use.

[00285] In some embodiments of the disclosed method, the ophthalmic composition is stored at room temperature after first use. In some embodiments of the disclosed method, the ophthalmic composition is stored at between about 16 °C to about 26 °C after to first use. In some embodiments of the disclosed method, the ophthalmic composition is stored at about 16 °C, about 17 °C, about 18 °C, about 19 °C, about 20 °C, about 21 °C, about 22 °C, about 23 °C, about 24 °C, about 25 °C, or about 26 °C after to first use.

[00286] In some embodiments, the ophthalmic aqueous formulations are administered as follows: the lower lid of the eye to be administered was pulled down and a predetermined amount of the aqueous formulation (e.g. 1-3 drops) is applied to the inside of the eyelid. The ophthalmic tip of the dispensing mechanism does not touch any surface to avoid contamination and/or injury.

[00287] In some embodiments, the ophthalmic gel formulations are administered as follows: the lower lid of the eye to be administered was pulled down and a predetermined amount of gel (e.g. 1-3 drops) is applied to the inside of the eyelid. The ophthalmic tip of the dispensing mechanism does not touch any surface to avoid contamination and/or injury.

[00288] In some embodiments, the ophthalmic ointment formulations are administered as follows: the lower lid of the eye to be administered was pulled down and a small amount of ointment (approximately 0.25 inches) was applied to the inside of the eyelid. The ophthalmic tip of the dispensing mechanism does not touch any surface to avoid contamination and/or injury.

[00289] In some embodiments, the ophthalmic composition is administered at predetermined time intervals over an extended period of time. In some embodiments, the ophthalmic composition is administered once every day. In some embodiments, the ophthalmic composition is administered every other day. In some embodiments, the ophthalmic composition is administered over 1 week, 2 weeks, 1 month, 2 months, 3 months, 6 months, 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 11 years, or 12-15 years.

[00290] In some embodiments, the ophthalmic composition is administered in doses having a dose-to-dose ophthalmic agent concentration variation of less than 50%, less than 40%, less than 30%>, less than 20%>, less than 10%>, or less than 5%>.

[00291] The number of times a composition is administered to an individual in need thereof depends on the discretion of a medical professional, the disorder, the severity of the disorder, and the individual's response to the formulation. In some embodiments, a composition disclosed herein is administered once to an individual in need thereof with a mild acute condition. In some embodiments, a composition disclosed herein is administered more than once to an individual in need thereof with a moderate or severe acute condition. In the case wherein the patient's condition does not improve, upon the doctor's discretion the administration of an ophthalmic agent is administered chronically, that is, for

an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

[00292] In the case wherein the patient's condition does not improve, upon the doctor's discretion the administration of the ophthalmic agent is administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

[00293] In the case wherein the patient's status does improve, upon the doctor's discretion the administration of the ophthalmic agent is given continuously; alternatively, the dose of drug being administered is temporarily reduced or temporarily suspended for a certain length of time (*i.e.*, a "drug holiday"). The length of the drug holiday varies between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, and 365 days. The dose reduction during a drug holiday is from 10%-100%, including by way of example only 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 100%.

[00294] Once improvement of the patient's ophthalmic conditions has occurred, a maintenance ophthalmic agent dose is administered if necessary. Subsequently, the dosage or the frequency of administration, or both, is optionally reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained. In certain embodiments, patients require intermittent treatment on a long-term basis upon any recurrence of symptoms.

[00295] The amount of ophthalmic agent that will correspond to such an amount will vary depending upon factors such as the particular compound, disease condition and its severity, according to the particular circumstances surrounding the case, including, *e.g.*, the specific ophthalmic agent being administered, the route of administration, the condition being treated, the target area being treated, and the subject or host being treated. The desired dose is presented in a single dose or as divided doses administered simultaneously (or over a short period of time) or at appropriate intervals.

[00296] In some embodiments, the initial administration is a particular ophthalmic agent and the subsequent administration a different formulation or ophthalmic agent.

[00297] **Kits/Articles of Manufacture**

[00298] The disclosure also provides kits for preventing or arresting myopia development. Such kits generally will comprise one or more of the ophthalmic compositions disclosed herein, and instructions for using the kit. The disclosure also contemplates the use of one or more of the ophthalmic compositions, in the manufacture of medicaments for treating, abating, reducing, or ameliorating the symptoms of a disease, dysfunction, or disorder in a mammal, such as a human that has, is suspected of having, or at risk for developing myopia.

[00299] In some embodiments, kits include a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the

container(s) including one of the separate elements to be used in a method described herein. Suitable containers include, for example, bottles, vials, syringes, and test tubes. In other embodiments, the containers are formed from a variety of materials such as glass or plastic.

[00300] The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products are also presented herein. See, e.g., U.S. Patent Nos. 5,323,907, 5,052,558 and 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, drop bottles, tubes, pumps, bags, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment. A wide array of ophthalmic compositions provided herein are contemplated as are a variety of treatments for any disease, disorder, or condition that benefits by controlled release administration of an ophthalmic agent to the eye.

[00301] In some embodiments, a kit includes one or more additional containers, each with one or more of various materials (such as rinses, wipes, and/or devices) desirable from a commercial and user standpoint for use of a formulation described herein. Such materials also include labels listing contents and/or instructions for use and package inserts with instructions for use. A set of instructions is optionally included. In a further embodiment, a label is on or associated with the container. In yet a further embodiment, a label is on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label is associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. In other embodiments a label is used to indicate that the contents are to be used for a specific therapeutic application. In yet another embodiment, a label also indicates directions for use of the contents, such as in the methods described herein.

[00302] In certain embodiments, the ophthalmic compositions are presented in a dispenser device which contains one or more unit dosage forms containing a compound provided herein. In a further embodiment, the dispenser device is accompanied by instructions for administration. In yet a further embodiment, the dispenser is also accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. In another embodiment, such notice, for example, is the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. In yet another embodiment, compositions containing a compound provided herein formulated in a compatible pharmaceutical carrier are also prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

EXAMPLES

Example 1 - Ophthalmic Formulations

[00303] Exemplary compositions for preparation of ophthalmic formulations are described in Tables 1-8.

Table 1 —Aqueous Solution Formulation (Atropine)

Ingredient	Quantity (mg/g)	Concentration (wt%)
Atropine	0.01-0.5	0.001-0.05 (wt%)
Buffer agent and/or pD adjusting agent (e.g. , borates and/or DCl)	-	q.s. for pD=4.2-7.9
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	-	q.s. to prevent the growth of or to destroy microorganism introduced into the solution
Tonicity and/or Osmolarity adjustor (e.g. NaCl, mannitol, etc)	-	q.s. to 0.5-2.0 wt%
Deuterated Water	-	q.s. to 100 wt%

Table 2 —Aqueous Solution Formulation (Atropine Sulfate)

Ingredient	Quantity (mg/g)	Concentration (wt%)
Atropine sulfate	0.01-0.5	0.001-0.05 (wt%)
Buffer agent and/or pD adjusting agent (e.g. , borates and/or DCl)	-	q.s. for pD=4.2-7.9
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	-	q.s. to prevent the growth of or to destroy microorganism introduced into the solution
Tonicity and/or Osmolality adjustor (e.g. NaCl, mannitol, etc)	-	q.s. to 0.5-2.0 wt%
Deuterated Water	-	q.s. to 100 wt%

Table 3 —Aqueous Solution Formulation (Atropine Sulfate)

Ingredient	Quantity (mg/g)	Concentration (wt%)
Atropine sulfate	0.05-0.15	0.005-0.015 (wt%)
Buffer agent and/or pD adjusting agent (e.g. , borates and/or DCl)	-	q.s. for pD=4.2-7.9
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	-	q.s. to prevent the growth of or to destroy microorganism introduced into the solution
Tonicity and/or Osmolality adjustor (e.g. - NaCl, mannitol, etc)	-	q.s. to 0.5-2.0 wt%
Deuterated Water	-	q.s. to 100 wt%

Table 4 —Mucus Penetrating Particle Formulation (Atropine)

Ingredient	Quantity (mg/g)	Concentration (wt%)
Atropine	0.01-0.5	0.001-0.05 (wt%)
Buffer agent and/or pD adjusting agent (e.g. , borates and/or DCl)	-	q.s. for pD=4.2-7.9
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	-	q.s. to prevent the growth of or to destroy microorganism introduced into the solution
Mucus penetrating particles	-	q.s. to formulate atropine at 0.001-0.05 wt%
Deuterated Water	-	q.s. to 100 wt%

Table 5 —Mucus Penetrating Particle Formulation (Atropine Sulfate)

Ingredient	Quantity (mg/g)	Concentration (wt%)
Atropine sulfate	0.01-0.5	0.001-0.05 (wt%)
Buffer agent and/or pH adjusting agent (e.g. , borates and/or DCl)	-	q.s. for pH=4.2-7.9
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	-	q.s. to prevent the growth of or to destroy microorganism introduced into the solution
Mucus penetrating particles	-	q.s. to formulate atropine at 0.001-0.05 wt%
Deuterated Water	-	q.s. to 100 wt%

Table 6 —Cellulose Gel Formulation (Atropine Sulfate)

Ingredient	Quantity (mg/g)	Concentration (wt%)
Atropine Sulfate	0.01-0.5	0.001-0.05 (wt%)
Viscosity enhancing agent (e.g. hydroxypropyl methylcellulose)	10-50	1-5 (wt%)
Buffer agent and/or pH adjusting agent (e.g. , sodium acetate and/or DCl)	-	q.s. for pH=4.2-7.9
Stabilizer (e.g. EDTA, cyclodextrin, etc.)	-	q.s. for low degradation of atropine sulfate (e.g. less than 10%, 5% or 1% degradation)
Osmolarity modifier (e.g. NaCl)	-	q.s. 150-500 mOsm/L
Deuterated Water	-	q.s. to 100 wt%

Table 7 —Thermosetting Gel Formulation (Atropine Sulfate)

Ingredient	Quantity (mg/g)	Concentration (wt%)
Atropine sulfate	0.01-0.5	0.001-0.05 (wt%)
Viscosity enhancing agent (e.g. poloxarner 407)	100-250	10-25 (wt%)
Buffer agent and/or pD adjusting agent (e.g. , sodium acetate and/or DC1)	-	q.s. for pH=4.2-7.9
Stabilizer (e.g. EDTA, cyclodextrin, etc.)	-	q.s. for low degradation of atropine sulfate (e.g. less than 10%, 5% or 1% degradation)
Osmolarity modifier (e.g. NaCl)	-	q.s. 150-500 mOsm/L
Deuterated Water	-	q.s. to 100 wt%

Table 8 — Ointment Formulation (Atropine Sulfate)

Ingredient	Quantity (g) for 100g m L. solution	Concentration in 100 m L. aqueous solution
Atropine sulfate	0.01-0.5	0.001-0.05 (wt%)
Dispersing agent (e.g. polyethyleneglycol, and/or polyethoxylated castor oil and/or C12-C20 alcohol	10-200	1-20 (wt%)
Buffering agent pD adjusting agent (e.g. DC1)	-	q.s. for pD=4.2-7.9
Stabilizer (e.g. EDTA, cyclodextrin, etc.)	-	q.s. for low degradation of atropine sulfate (e.g. less than 10%, 5% or 1% degradation)
Osmolarity modifier (e.g. NaCl)	-	q.s. 150-500 mOsm/L
Ointment base (e.g. wool wax and/or petrolatum and/or liquid paraffin)		q.s. to 100 wt%

Example 2 - Preparation of an Aqueous Solution Formulation Containing 0.01% Atropine in D₂O**[00304] Stock 1% Solution**

[00305] In a 100mL solution, 1 gram of atropine, and 0.77 g of NaCl (and other ingredients/components preferably in their dry state) are added along with a quantity sufficient to equal 100mL sterile deuterated water for injection. The solution is mixed in an appropriately sized beaker with a stir bar on a hot plate until all of the solid powders have dissolved and the solution has become clear with no visible particles. Next, the stir bar is removed, and the solution is poured into a filter bottle and vacuum filtered through a 0.22 micron polyethersulfone membrane filter into a sterile bottle. The filter top is removed from the sterile stock bottle and the stock bottle is capped for storage with a sterile bottle cap.

[00306] Diluted 0.01% Solution

[00307] 0.3mL of the 1% solution was combined with a quantity sufficient to achieve 30mL total of sterile 0.9% Sodium Chloride For Injection USP. The solution was thoroughly mixed. The pH of the solution was recorded. A 0.22 micron filter was placed on the tip of the syringe and the solution was aliquotted into separate sterile containers.

Example 3 - Preparation of an Aqueous Solution Formulation Containing 0.01% Atropine Sulfate**[00308] Stock 1% Solution**

[00309] In a 100mL solution, 1 gram of atropine sulfate, and 0.77 g of NaCl (and other ingredients/components preferably in their dry state) were added along with a quantity sufficient to equal 100mL sterile water for injection. The solution was mixed in an appropriately sized beaker with a stir bar on a hot plate until all of the solid powders had dissolved and the solution became clear with no visible particles. Next, the stir bar was removed, and the solution was poured into a filter bottle and vacuum filtered through a 0.22 micron polyethersulfone membrane filter into a sterile bottle. The filter top was removed from the sterile stock bottle and the stock bottle was capped for storage with a sterile bottle cap.

[00310] Diluted 0.01% Solution

[00311] 0.3mL of the 1% solution was combined with a quantity sufficient to achieve 30mL total of sterile 0.9% Sodium Chloride For Injection USP. The solution was thoroughly mixed. The pH of the solution was recorded. A 0.22 micron filter was placed on the tip of the syringe and the solution was aliquotted into separate sterile containers.

Example 4 - Stability Analysis

[00312] Five 0.01% atropine sulfate solutions were prepared from the 1% atropine sulfate stock solution (preparation as described in Example 2). The pH of the five solutions was 5.87, 5.97, 5.90, 6.24, and 6.16 for solutions 1-5, respectively. Each solution was thoroughly mixed. A 0.22 micron filter was placed on the tip of the syringe and the solution was aliquotted into separate sterile containers according to Table 9.

Table 9. Container Filling Outline

Type of Container	Volume of 0.01% Atropine Sulfate Drug Product in Container	Total Containers Filled
Sterile Eyedroppers	5-mL	12
Sterile Glass Vials	5-mL	12

[00313] The samples were then stored at different conditions for stability analysis. The samples were analyzed at different time points up to 2 months. The storage conditions include: 40°C with 75% relative humidity (RH) (samples were transferred from 2-8°C condition after 3 days), 25°C with 60% RH, and 60°C. The time points were 1 week, 2 weeks, 1 month, and 2 months. At each of the time point, one plastic eyedropper (LDPE plastic) and one glass vial from each of the stored condition were removed and allowed to equilibrate to ambient conditions. Once equilibrated, both the plastic eyedropper and the glass vials were inverted 3 times. The solution in the eyedroppers was transferred to an HPLC vial in a drop wise fashion through the dropper. The solution in the glass vial was aliquotted into an HPLC vial using a glass Pasteur pipette. The samples were then tested for purity and potency using the UPLC method listed in Table 10.

Table 10. UPLC Method Parameters

Parameter	Condition
Column	EMD, Hiber HR PurospherSTAR C-18, 100 x 2.1 mm, 2 μ m
Mobile Phase/Diluent	87:13, 50 mM Potassium Phosphate: Acetonitrile, pH 3.5
Flow	Isocratic
Flow Rate	0.5 mL/min
Detection Wavelength	210 nm
Column Temperature	30 $\pm$ 3 °C
Autosampler Temperature	5 $\pm$ 3 °C
Run Time	6.0 minutes
Injection Volume	10 μ L*
Needle Wash Solution	90/10 Water: Acetonitrile

* Modified from original method to maintain sensitivity at 100 μ g/mL nominal.

[00314] Table 11 lists the stability data for the 0.01% atropine sulfate solutions.

Table 11. Stability Data for 0.01% Atropine Sulfate Solutions

Analyst	Container Type	Storage Condition	t=0			t=1 week		t=2 week ¹		t=1 month ²			t=2 month ³		
			Purity	Potency	pH	Purity	Potency	Purity	Potency	Purity	Potency	pH	Purity	Potency	pH
1	Eyedropper, LDPE (Plastic)	25 °C/60% RH	99.5	99.8	5.9	ND	ND	99.1	99.9	ND	ND	ND	95.4	97.4	6.3
		40 °C/75% RH				ND	ND	96.2	97.3	95.1	95.6	5.2	ND	ND	ND
		60 °C				80.8	83.3	86.2	88.6	88.3	91.5	4.2	ND	ND	ND
	Glass Vial	25 °C/60% RH	99.8	100.4	ND	ND	ND	92.2	93.1	80.7	80.5	7.8	73.0	74.5	7.3
		40 °C/75% RH				ND	ND	73.6	74.1	50.1	50.2	7.4	ND	ND	ND
		60 °C				43.1	43.9	28.3	28.4	ND	ND	ND	ND	ND	ND
2	Eyedropper, LDPE (Plastic)	25 °C/60% RH	99.7	99.9	6.0	ND	ND	99.1	99.6	ND	ND	ND	97.0	99.1	6.1
		40 °C/75% RH				ND	ND	96.6	97.2	95.5	95.8	5.6	ND	ND	ND
		60 °C				89.4	92.2	92.2	94.0	90.6	94.4	4.1	ND	ND	ND
	Glass Vial	25 °C/60% RH	99.8	100.2	ND	ND	ND	92.6	92.9	82.5	82.2	7.6	80.2	81.6	7.3
		40 °C/75% RH				ND	ND	74.7	75.1	59.1	59.0	7.2	ND	ND	ND
		60 °C				54.2	55.2	37.3	37.4	ND	ND	ND	ND	ND	ND
3	Eyedropper, LDPE (Plastic)	25 °C/60% RH	99.3	96.3	5.9	ND	ND	98.7	96.1	ND	ND	ND	95.8	94.8	6.3
		40 °C/75% RH				ND	ND	96.7	93.1	94.8	91.8	5.5	ND	ND	ND
		60 °C				88.8	89.0	88.0	86.8	88.6	87.7	4.1	ND	ND	ND
	Glass Vial	25 °C/60% RH	99.4	98.4	ND	ND	ND	94.1	91.2	85.0	81.9	7.5	79.3	78.3	7.3
		40 °C/75% RH				ND	ND	72.2	74.6	61.3	63.0	7.2	ND	ND	ND
		60 °C				48.6	51.1	34.1	34.9	ND	ND	ND	ND	ND	ND
4	Eyedropper, LDPE (Plastic)	25 °C/60% RH	99.8	99.6	6.2	ND	ND	99.1	98.8	ND	ND	ND	96.4	97.6	6.3
		40 °C/75% RH				ND	ND	96.3	97.0	94.5	94.2	5.6	ND	ND	ND
		60 °C				90.5	93.0	89.3	90.6	84.2	85.8	4.2	ND	ND	ND
	Glass Vial	25 °C/60% RH	99.8	98.8	ND	ND	ND	90.7	90.0	76.9	75.1	7.6	72.5	71.6	7.4
		40 °C/75% RH				ND	ND	71.0	68.7	57.0	56.7	7.2	ND	ND	ND
		60 °C				52.4	52.1	29.7	28.6	ND	ND	ND	ND	ND	ND
5	Eyedropper, LDPE (Plastic)	25 °C/60% RH	99.6	100.5	6.2	ND	ND	99.3	100.4	ND	ND	ND	97.8	100.5	6.2
		40 °C/75% RH				ND	ND	95.9	96.7	96.8	97.6	5.5	ND	ND	ND
		60 °C				91.2	94.6	91.4	93.6	90.3	92.8	4.2	ND	ND	ND
	Glass Vial	25 °C/60% RH	99.8	100.7	ND	ND	ND	90.5	91.3	79.3	79.7	7.8	72.8	74.6	7.3
		40 °C/75% RH				ND	ND	71.3	71.9	56.0	56.4	7.3	ND	ND	ND
		60 °C				46.3	47.4	29.5	29.6	ND	ND	ND	ND	ND	ND

¹The 25 °C and the 60 °C samples were pulled at 15 days, the 40 °C samples were pulled at 11 days.

²The 25 °C and the 60 °C samples were pulled at 28 days, the 40 °C samples were pulled at 24 days.

³The 25 °C and the 60 °C samples were pulled at 46 days.

[00315] A change in the pH of the 0.01% Atropine Sulfate solutions was observed over the course of the stability study. The plastic (LDPE) eyedroppers maintained pH around 6.2 when stored at 25 °C for 2 months. However at the same time point, the pH of the 0.01% atropine has increased to 7.2 when stored in glass vials. Additionally, when stored at elevated temperatures (e.g. 40°C and 60°C), the pH in the plastic (LDPE) eyedroppers dropped to approximately 4-5, while the pH maintained around 7.2 when stored in the glass vials.

[00316] There was also a significant difference in the rate of degradation for Atropine Sulfate (0.01%) when stored in plastic (LDPE) eyedroppers versus Type I glass vials. However, in both containers there was an increase of an early eluting related substance at relative retention time (RRT) =0.87-0.89. In some cases, this early eluting related substance is referred to as primary degradant. In some instances, the primary degradant is referred to as RRT 0.87-0.89. This related substance is likely to be the first parameter to fail specification regardless of the container. The amount of this related substance was tracked at each time point and is listed in Table 12.

Table 12. Area (%) of the Main Degradation Species for 0.01% Atropine Sulfate (RRT 0.87-0.89)

Analyst	Temperature °C	t=0	t=1 week	t=2 week	t=1 month	t=2 months
1	25	0.08	NA	0.92	NA	3.98
	40	NA	NA	3.74	4.78	NA
	60	NA	17.78	13.49	11.51	NA
2	25	0.07	NA	0.88	NA	2.46
	40	NA	NA	3.26	4.37	NA
	60	NA	9.38	7.67	9.13	NA
3	25	0.07	NA	1.05	NA	2.88
	40	NA	NA	2.98	4.85	NA
	60	NA	9.59	11.57	10.55	NA
4	25	0.08	NA	0.92	NA	3.09
	40	NA	NA	3.43	5.32	NA
	60	NA	8.30	10.46	15.49	NA
5	25	0.08	NA	0.64	NA	1.66
	40	NA	NA	3.96	3.07	NA
	60	NA	7.61	8.35	9.7	NA
Average 25 °C		0.08	NA	0.88	NA	2.81
Average 40 °C		NA	NA	3.47	4.48	NA
Average 60 °C		NA	10.53	10.31	11.28	NA

[00317] Arrhenius based shelf life predictions were calculated using the related substance data from Table 12. These predictions are based on an assumption that the degradation is first order (linear). These predictions are illustrated in Figs. 1 and 2. Fig. 1 shows the shelf life prediction of 0.01% atropine sulfate solution with a primary degradant RRT 0.87-0.89, and a n.m.t. of 0.5% area, based on data obtained from samples stored at 25°C and 40°C. The pH range of the atropine sulfate solution is from 5.9-6.2. Fig. 2 shows the shelf life prediction of 0.01% atropine sulfate solution with a primary degradant RRT 0.87-0.89, and a n.m.t. of 0.5% area, based on data obtained from samples stored at 25°C and 60°C. The pH range of the atropine sulfate solution is from 5.9-6.2.

Example 5 - 1% Atropine Sulfate (Bausch + Lomb) Sample Analysis

[00318] The 1% atropine sulfate sample was obtained from Bausch + Lomb (Lot 198421). For comparison the pH of the 1% Atropine Sulfate drug product was determined in the neat solution as well as a sample that was diluted to the current nominal concentration (0.01% Atropine Sulfate) using the vehicle. Additionally a sample was diluted to the nominal concentration with method diluent. Both samples diluted to the nominal concentration were analyzed using the RP-UPLC method (Table 10). The results are listed in Table 13.

Table 13. pH and Purity of the Bausch + Lomb Atropine Sulfate Sample

Sample	pH	Purity (% area)
1% Atropine Sulfate	4.89	ND
0.01% Atropine Sulfate, <i>diluted with Vehicle</i>	6.16	99.6%
0.01% Atropine Sulfate, <i>diluted with Diluent</i>	ND	99.6%
Vehicle	7.94	ND

ND= not determined

Example 6 - Dose Uniformity (10-Dose)

[00319] To evaluate the dose-to-dose uniformity, drop bottles containing the ophthalmic aqueous composition are stored upright for a predetermined period of time (e.g. 12 hours) prior to the start of the test. To simulate the recommended dosing of the product, 10 drops of the aqueous composition are dispensed from each bottle at predetermined time intervals (e.g. consecutively, every 1 minute, every 10 minutes, every hour or every 24 hours). All drops are dispensed into tared glass vials, capped, and stored at room temperature until analysis. Concentrations of atropine in the expressed drops are determined using a reverse-phase HPLC method.

Example 7 - Dose Uniformity (5-Dose)

[00320] To evaluate the dose-to-dose uniformity, drop bottles containing the ophthalmic aqueous composition are stored upright for a predetermined period of time (e.g. 12 hours) prior to the start of the test. To simulate the recommended dosing of the product, 5 drops of the aqueous composition are dispensed from each bottle at predetermined time intervals (e.g. consecutively, every 1 minute, every 10 minutes, every hour or every 24 hours). All drops are dispensed into tared glass vials, capped, and stored at room temperature until analysis. Concentrations of atropine in the expressed drops are determined using a reverse-phase HPLC method.

Example 8 - Dose Uniformity (2-Dose)

[00321] To evaluate the dose-to-dose uniformity, drop bottles containing the ophthalmic aqueous composition are stored upright for a predetermined period of time (e.g. 12 hours) prior to the start of the test. To simulate the recommended dosing of the product, 2 drops of the aqueous composition are dispensed from each bottle at predetermined time intervals (e.g. consecutively, every 1 minute, every 10 minutes, every hour or every 24 hours). All drops are dispensed into tared glass vials, capped, and stored at room temperature until analysis. Concentrations of atropine in the expressed drops are determined using a reverse-phase HPLC method.

Example 9 - Formulation Stability Comparison

[00322] Atropine sulfate monohydrate (MP Bio; Lot Number 7825K) and tropic acid (Sigma Aldrich; Lot Number STBD6457V) were used for this experiment. Eight formulations illustrated in Table 14A were analyzed at t=0, 2 weeks, and 4 weeks. A RP-HPLC method was used to carry out the analysis.

Table 14A. Atropine sulfate formulations

Formulation	Atropine Sulfate Monohydrate	Benzalkonium Chloride (BAK)	Sodium Chloride	Acetic Acid	Citric Acid	pH/pD	Aqueous
1	0.010	0.01	0.90	0.01	-	4.2	SWFI
2	0.025	0.01	0.90	0.01	-	4.2	SWFI
3	0.010	0.01	0.90	0.01	-	4.8	SWFI
4	0.025	0.01	0.90	0.01	-	4.8	SWFI
5	0.010	0.01	0.90	-	0.04	5.8	SWFI
6	0.025	0.01	0.90	-	0.04	5.8	SWFI
7	0.010	0.01	0.90	0.01	-	5.2 (pD)	D ₂ O
8	0.010	0.01	0.90	-	0.04	6.2 (pD)	D ₂ O

[00323] The values are % w/v. The formulations were prepared at 100mL scale in volumetric glassware. The pD of Formulation 7 and Formulation 8 are 5.2 and 6.2, respectively. In some instances, the pD is calculated as $pD = 0.4 + pH^*$, in which pH^* is the measured or observed pH of the solution formulated in a solution containing deuterated water.

[00324] Table 14B illustrates analysis time points for the formulations listed in Table 14A.

Table 14B. Schedule for atropine sulfate formulation testing

Storage Condition (Horizontal)	Time Point		
	Initial (t=0)	2 Week	4 Week
25 °C/60%RH	X	X	X
40 °C/75%RH		X	X
60 °C		X	X

[00325] Table 15 illustrates the atropine sulfate purity data associated with each of the eight formulations. Purity is indicated as percentage of area under the curve.

Table 15. Atropine sulfate purity as Area-%

Solvent	Condition	t=0	t=2 weeks	t=4 weeks ¹
Formulation 1 pH 4.2	25/60	97.39	97.76	98.20
	40/75		97.25	97.04
	60 °C		94.98	93.87
Formulation 2 pH 4.2	25/60	98.85	99.03	99.08
	40/75		98.50	98.32
	60 °C		97.47	96.65
Formulation 3 pH 4.8	25/60	98.16	98.16	98.45
	40/75		97.98	97.35
	60 °C		95.94	94.65
Formulation 4 pH 4.8	25/60	98.81	98.75	98.46
	40/75		98.26	98.01
	60 °C		96.22	94.04
Formulation 5 pH 5.8	25/60	98.16	97.92	97.54
	40/75		95.88	93.51
	60 °C		80.94	66.83
Formulation 6 pH 5.8	25/60	99.08	98.91	98.46
	40/75		97.65	96.20
	60 °C		89.15	80.68
Formulation 7 pD 5.2	25/60	98.93	99.07	98.39
	40/75		98.51	97.55
	60 °C		96.70	94.01
Formulation 8 pD 6.2	25/60	98.93	98.95	98.51
	40/75		98.53	97.44
	60 °C		95.97	92.72

¹ Some chromatographic interference were observed to occur late in the run (-27-32 minutes) for many of the t=4 week stability samples and in some instances is proposed to be system related.

[00326] After four weeks of storage at 60 °C, in some instances the atropine sulfate concentration have an impact on the stability for the formulations containing acetic acid at pH 4.2. For example, atropine sulfate concentration at 0.025 % w/v (Formulation 2) showed a 2.8% increase in % purity at pH 4.2 compared to the atropine sulfate concentration at 0.010 % w/v (Formulation 1). This trend was not observed for the acetic acid formulations at pH 4.8 (Formulations 3 and 4); rather a 0.6% decrease in % purity was observed for the higher doses.

[00327] The dose dependent stability trend that was observed at pH=4.2 was also seen in the formulations containing citric acid at pH 5.8 (Formulations 5 and 6). After four weeks of storage at 60 °C there is approximately 14% less degradation in the higher doses than observed in the lower dose.

[00328] At both the high and the low doses, more degradation is observed in the formulations that start at a higher pH. This degradation is predominantly the growth of tropic acid. In some instances, buffer species plays a role in the observed degradation between the different pH values.

[00329] The percentage of tropic acid observed for each of the formulations at t=4 weeks and at 60°C are as follow:

[00330] Formulation 1-Tropic acid observed is 0.54%.

[00331] Formulation 2-Tropic acid observed is 0.93%.

[00332] Formulation 3-Tropic acid observed is 1.58%.

[00333] Formulation 4-Tropic acid observed is 3.03%.

[00334] Formulation 5-Tropic acid observed is 29.13%.

[00335] Formulation 6-Tropic acid observed is 16.84%.

[00336] Formulation 7-Tropic acid observed is 1.07%.

[00337] Formulation 8-Tropic acid observed is 4.03%.

[00338] In some embodiments, switching the water source to deuterated water (D₂O) has an impact on stabilizing the growth of the tropic acid peak for the formulation containing acetic acid at pD 5.2 (Formulation 7), see Fig. 4. In addition, in the formulation containing citric acid at pD 6.2 (Formulation 8), the deuterated water also stabilizes atropine sulfate, see Fig. 5.

[00339] Table 16 illustrates tropic acid as area under the curve for each of the eight formulations. Tropic acid is a degradant of atropine sulfate. In some instances, LOQ was previously found to be 0.05% for the RP-HPLC method.

Table 16. Tropic acid as area-%

Solvent	Condition	t=0	t=2 weeks	t=4 weeks
Formulation 1 pH 4.2	25/60	<LOQ	0.08	<LOQ
	40/75		0.10	0.10
	60 °C		0.37	0.51
Formulation 2 pH 4.2	25/60	<LOQ	0.05	<LOQ
	40/75		0.11	0.12
	60 °C		0.46	0.93
Formulation 3 pH 4.8	25/60	<LOQ	0.12	0.05
	40/75		0.19	0.27
	60 °C		0.90	1.58
Formulation 4 pH 4.8	25/60	<LOQ	0.10	0.13
	40/75		0.31	0.53
	60 °C		1.84	3.03
Formulation 5 pH 5.8	25/60	<LOQ	0.40	0.71
	40/75		2.22	4.35
	60 °C		16.62	29.13
Formulation 6 pH 5.8	25/60	<LOQ	0.24	0.42
	40/75		1.30	2.44
	60 °C		9.32	16.84

Formulation 7 pD 5.2	25/60	<LOQ	0.07	0.08
	40/75		0.14	0.24
	60 °C		0.71	1.07
Formulation 8 pD 6.2	25/60	<LOQ	0.11	0.14
	40/75		0.33	0.65
	60 °C		2.32	4.03

[00340] Table 17 illustrates percentage of potency of atropine in the eight formulations.

Table 17. % Potency

Solvent	Condition	t=0	t=2 weeks	t=4 weeks
Formulation 1 pH 4.2	25/60	109.4	110.3	112.8
	40/75		111.0	112.4
	60 °C		112.8	114.8
Formulation 2 pH 4.2	25/60	102.9	107.1	109.7
	40/75		108.4	109.6
	60 °C		109.4	111.0
Formulation 3 pH 4.8	25/60	106.3	108.0	109.6
	40/75		108.1	110.0
	60 °C		108.0	109.9
Formulation 4 pH 4.8	25/60	102.5	107.9	109.2
	40/75		107.4	108.9
	60 °C		107.9	108.8
Formulation 5 pH 5.8	25/60	105.0	105.9	107.1
	40/75		103.8	103.5
	60 °C		90.2	77.7
Formulation 6 pH 5.8	25/60	107.2	107.1	109.1
	40/75		106.8	107.1
	60 °C		99.0	93.7
Formulation 7 pD 5.2	25/60	107.3	111.3	112.9
	40/75		111.6	113.5
	60 °C		111.8	113.5
Formulation 8 pD 6.2	25/60	99.0	103.0	105.0
	40/75		104.9	104.7
	60 °C		101.6	103.0

[00341] After 4 weeks of storage, the observed potency values were elevated from the t=0 and 2 week time points, with the exception of Formulations 5 and 6 at 60 °C where the potencies dropped due to degradation. In some instances, these potency values are within the error of the HPLC method, but appear to be trending upward. Mass balance was calculated for the 60 °C data and results were consistent

across the formulations and levels of degradation, although skewed lower due to the higher than anticipated potency values at 4 weeks, see Figure 3.

[00342] Table 18 illustrates pH or pD stability of the eight formulations.

Table 18. pH/pD Stability

Solvent	Condition	t=0	t=2 weeks	t=4 weeks
Formulation 1 (pH)	25/60	4.21	3.93	4.02
	40/75		3.86	3.96
	60 °C		3.71	3.86
Formulation 2 (pH)	25/60	4.26	4.11	4.25
	40/75		4.04	4.17
	60 °C		3.93	4.10
Formulation 3 (pH)	25/60	4.85	4.44	4.61
	40/75		4.41	4.54
	60 °C		4.32	4.40
Formulation 4 (pH)	25/60	4.98	4.93	5.05
	40/75		4.89	4.98
	60 °C		4.77	4.77
Formulation 5 (pH)	25/60	5.87	5.93	6.03
	40/75		5.96	5.96
	60 °C		5.82	5.78
Formulation 6 (pH)	25/60	5.80	5.69	5.77
	40/75		5.65	5.67
	60 °C		5.54	5.50
Formulation 7 (pD)	25/60	<i>5.31</i>	<i>5.10</i>	<i>5.24</i>
	40/75		<i>5.08</i>	<i>5.15</i>
	60 °C		<i>5.00</i>	<i>4.93</i>
Formulation 8 (pD)	25/60	6.25	5.72	5.88
	40/75		5.74	5.78
	60 °C		5.58	5.50

[00343] The italicized values are pD values for a deuterated sample. In some embodiments, the pD of the deuterated samples are $pD = pH_{\text{reading}} + 0.4$ (Glasoe, *et al.* "Use of glass electrodes to measure acidities in deuterium oxide" J. Physical Chem. 64(1): 188-190 (1960)).

[00344] At the two lower temperatures, the pH values at t=4 week are slightly elevated from the t=2 week time point. These data were generated using a new glass pH probe. In some instances, the observed differences are due to the probe differences or additional variables such as for example, the age of the standard buffers or temperature gradients within the laboratory environment. The downward pH trend for each formulation with increasing temperatures at t=4 week is consistent with previous data and is consistent with the increase in the amount of tropic acid present in the stability sample.

Example 10-Determination of Shelf Life and Activation Energy

[00345] Activation energy was calculated for the eight formulations disclosed in Example 9 and comparison with a reference standard was made with Formulations 4-7.

[00346] Table 19 illustrates the activation energy (Ea) calculation. The Ea minimum is 17.8 Kcal/mol, the Ea maximum is 21.3 Kcal/mol, and the Ea mean is 19.5 Kcal/mol. Mean is $\pm 3 \times \text{stdev}$. Figs. 6 and 7 illustrate the poor correlation between RS and tropic acid with Formulation 4 and Formulation 7, respectively. Figs. 8 and 9 illustrate improved correlation between RS and tropic acid with Formulation 5 and Formulation 6, respectively. At a lower pH (e.g. pH 4.8 or lower), there was a poor correlation observed (Formulation 4 and Formulation 7). This was due to a slowed hydrolysis and increased alternative degradation pathways. At a higher pH (e.g., pH 5.8 or higher), an improved or better correlation was observed (Formulation 5 and Formulation 6). This was due to the hydrolysis of atropine as the primary degradant. It is noted that the activation energy is for the specific acid catalyzed degradation to tropic acid- the predominant degradation product and degradation mechanism operating at pH 5.8 or higher.

Table 19. Activation energy for total related substance (RS) and tropic acid.

	Total RS	Tropic Acid
1	Poor Corr	Poor Corr
2	12.2	Poor Corr
3	Poor Corr	18.3
4	16.8	18.1
5	19.8	19.7
6	19.2	20.0
ie 7	13.3	15.5
8	Poor Corr	18.9
Mean	16.2	18.4 Kcal/mole
Stdev	3.4	1.6
RSD	21%	9%

[00347] Table 20 illustrates the rate of RS or tropic acid formation per week at 40°C.

Table 20.

	Formulation	Rate 40°C (total RS %/wk)	Rate 40°C (Tropic acid %/wk)
Formulation 5	0.01% Atr Citrate pH5.8	1.16	1.09
Formulation 6	0.025% Atr Citrate pH5.8	0.72	0.61
Formulation 8	0.01% Atr Citrate pD 6.2 D ₂ O		0.163

[00348] Table 21 illustrates the activation energy and predicted shelf life at 30°C calculated based on Table 20. It is assumed for the calculation that tropic acid and total RS is 5% (self-life).

Table 21A.

	Rate @30°C (Total RS %/wk)			Estimated Shelf life @30°C (mo)		
Formulation	Ea min	Ea mean	Ea max	Ea min	Ea mean	Ea max
5	0.45	0.41	0.38	2.78	3.04	3.33
6	0.28	0.26	0.23	4.47	4.90	5.37
8	--	--	--	--	--	--

Table 21B.

	Rate @30°C (Tropic acid %/wk)			Estimated Shelf life @30°C (mo)		
Formulation	Ea min	Ea mean	Ea max	Ea min	Ea mean	Ea max
5	0.42	0.39	0.35	2.95	3.24	3.54
6	0.24	0.22	0.20	5.28	5.78	6.33
8	0.06	0.06	0.05	19.75	21.64	23.70

[00349] At pD 6.2, the deuterated formulation (Formulation 8) has a predicted shelf life of close to 2 years at 30°C.

[00350] Table 22 illustrate the predicted shelf life at temperatures of 40°C, 30°C, 25°C, and 2-8°C for Formulations 4-8 for total RS and tropic acid, respectively.

Table 22

Stability Prediction		RS		Tropic Acid		
Formulation	Temperature (°C)	weeks	months	Temperature (°C)	weeks	months
4	40	16.5	4.1	40	7.7	1.9
	30	40.2	10.1	30	20.0	5.0
	25	64.2	16.0	25	33.0	8.3
	2-8	493.4	123.4	2-8	296.8	74.2

5	40	2.8	0.7	40	0.9	0.2
	30	7.9	2.0	30	2.7	0.7
	25	13.7	3.4	25	4.6	1.2
	2-8	151.1	37.8	2-8	50.5	12.6
6	40	5.8	1.4	40	1.7	0.4
	30	15.9	4.0	30	4.8	1.2
	25	27.3	6.8	25	8.4	2.1
	2-8	281.6	70.4	2-8	95.9	24.0
7	40	11.5	2.9	40	16.9	4.2
	30	23.2	5.8	30	38.4	9.6
	25	33.4	8.4	25	59.1	14.8
	2-8	165.7	41.4	2-8	388.2	97.1
8	40	-	-	40	6.2	1.6
	30	-	-	30	17.0	4.3
	25	-	-	25	28.9	7.2
	2-8	-	-	2-8	287.1	71.8

Example 11-Additional Formulation Stability Comparison

[00351] Atropine sulfate monohydrate (MP Bio; Lot Number 7825K) and tropic acid (Sigma Aldrich; Lot Number STBD6457V) were used for this experiment. Thirteen formulations illustrated in Table 23A were analyzed. Formulations 1-8 had been analyzed at t=0, 2 weeks, 4 weeks, and 8 weeks. Formulations 9-13 had been analyzed at t=0, 2 weeks, and 4 weeks. The pH values reported herein are the measured pH values obtained using the Thermo Scientific, Orion Dual Star pH/ISE benchtop pH meter and the Orion Double Junction Micro pH probe S/N S01-18520 calibrated with H₂O based standards.

Table 23A. Atropine sulfate Formulations

Formulation	Atropine Sulfate Monohydrate	Benzalkonium Chloride (BAK)	Sodium Chloride	Acetic Acid	Citric Acid	pH/pD	Aqueous
1	0.010	0.01	0.90	0.01	-	4.2	SWFI
2	0.025	0.01	0.90	0.01	-	4.2	SWFI
3	0.010	0.01	0.90	0.01	-	4.8	SWFI
4	0.025	0.01	0.90	0.01	-	4.8	SWFI
5	0.010	0.01	0.90	-	0.04	5.8	SWFI
6	0.025	0.01	0.90	-	0.04	5.8	SWFI

7	0.010	0.01	0.90	0.01	-	5.2 (pD)	D ₂ O
8	0.010	0.01	0.90	-	0.04	6.2 (pD)	D ₂ O
9	0.010	-	0.90	-	0.04	6.8 (pD)	D ₂ O
10	0.010	-	0.90	-	0.04	6.4	H ₂ O (control)
11	0.010	-	0.90	-	0.08	6.4	H ₂ O (control)
12	0.010	-	0.90	-	0.04	7.2 (pD)	D ₂ O
13	0.010	-	0.90	-	0.04	6.8	H ₂ O (control)

[00352] The values are % w/v. The formulations were prepared at 100 mL scale in volumetric glassware and filled into LDPE eye droppers. In some instances, the pD is calculated as $pD = 0.4 + pH^*$, in which pH^* is the measured or observed pH of the solution formulated in a solution containing deuterated water.

[00353] Table 23B illustrates analysis time points for the formulations listed in Table 23A.
Table 23B. Schedule for atropine sulfate formulation testing

Storage Condition (Horizontal)	Time Point		
	Initial (t=0)	2 Week	4 Week
25 °C/60%RH	X	X	X
40 °C/75%RH		X	X
60 °C		X	X

[00354] Table 24A and Table 24B illustrate atropine sulfate purity data associated with the atropine sulfate formulations. Purity is indicated as percentage of area under the curve. The † & ↓ indicate the high or low concentration of atropine sulfate monohydrate (0.01% and 0.025%). The A & C indicate the buffer species used, acetic acid and citric acid respectively.

Table 24A. Atropine Sulfate Purity as Area-% for H₂O Formulations

Solvent	Condition	t=0	t=2 weeks	t=4 weeks
Formulation 3 ↓A H ₂ O pH 4.8	25/60	98.16	98.16	98.45
	40/75		97.98	97.35
	60 °C		95.94	94.65
Formulation 5 ↓C H ₂ O pH 5.8	25/60	98.16	97.92	97.54
	40/75		95.88	93.51
	60 °C		80.94	66.83
Formulation 10 ↓C H ₂ O pH 6.4	25/60	98.66	96.67	95.81
	40/75		91.07	85.27
	60 °C		59.77	42.87
Formulation 11 ↓C(2x) H ₂ O pH 6.4	25/60	99.47	97.87	96.69
	40/75		90.97	84.26
	60 °C		54.96	34.40
Formulation 13 ↓C H ₂ O pH 6.8	25/60	97.21	95.42	93.24
	40/75		83.05	73.00
	60 °C		43.99	27.50

Table 24B. Atropine Sulfate Purity as Area-% for D₂O Formulations

Solvent	Condition	t=0	t=2 weeks	t=4 weeks
Formulation 7 ↓A D ₂ O pD 5.2	25/60	98.93	99.07	98.39
	40/75		98.51	97.55
	60 °C		96.70	94.01
Formulation 8 ↓C D ₂ O pD 6.2	25/60	98.93	98.95	98.51
	40/75		98.53	97.44
	60 °C		95.97	92.72
Formulation 9 ↓C D ₂ O pD 6.8	25/60	99.29	98.42	98.07
	40/75		95.20	93.22
	60 °C		75.17	65.97
Formulation 12 ↓C D ₂ O pD 7.2	25/60	98.53	97.17	95.99
	40/75		90.75	84.64
	60 °C		56.78	46.05

[00355] Table 25A and Table 25B illustrate tropic acid formation associated with the atropine sulfate formulations. Tropic acid is a degradant of atropine sulfate, and is indicated as percentage of area under the curve. LOQ was found to be 0.05% for the RP-HPLC method. The † & ↓ indicate the high or low concentration of atropine sulfate monohydrate (0.01% and 0.025%). The A & C indicate the buffer species used, acetic acid and citric acid, respectively.

Table 25A. Tropic Acid as Area-% for H₂O Formulations

Solvent	Condition	t=0	t=2 weeks	t=4 weeks
Formulation 3 ↓A H ₂ O pH 4.8	25/60	<LOQ	0.12	0.05
	40/75		0.19	0.27
	60 °C		0.90	1.58
Formulation 5 ↓C H ₂ O pH 5.8	25/60	<LOQ	0.40	0.71
	40/75		2.22	4.35
	60 °C		16.62	29.13
Formulation 10 ↓C H ₂ O pH 6.4	25/60	0.74	1.90	3.21
	40/75		7.61	13.49
	60 °C		37.44	54.06
Formulation 11 ↓C(2x) H ₂ O pH 6.4	25/60	0.09	1.31	2.64
	40/75		7.61	14.68
	60 °C		42.43	62.23
Formulation 13 ↓C H ₂ O pH 6.8	25/60	2.21	3.66	6.11
	40/75		15.47	25.80
	60 °C		53.24	69.34

Table 25B. Tropic Acid as Area-% for D₂O Formulations

Solvent	Condition	t=0	t=2 weeks	t=4 weeks
Formulation 7 ↓A D ₂ O pD 5.2	25/60	<LOQ	0.07	0.08
	40/75		0.14	0.24
	60 °C		0.71	1.07
Formulation 8 ↓C D ₂ O pD 6.2	25/60	<LOQ	0.11	0.14
	40/75		0.33	0.65
	60 °C		2.32	4.03
Formulation 9 ↓C D ₂ O pD 6.8	25/60	0.06	0.55	1.06
	40/75		3.16	6.29
	60 °C		21.09	29.25
Formulation 12 ↓C D ₂ O pD 7.2	25/60	0.42	1.35	2.62
	40/75		7.27	13.53
	60 °C		38.58	48.15

[00356] Table 26A and Table 26B illustrate the percentage of potency of atropine in the formulations. The † & ↓ indicate the high or low concentration of atropine sulfate monohydrate (0.01% and 0.025%). The A & C indicate the buffer species used, acetic acid and citric acid respectively.

Table 26A. Percentage of potency for H₂O Formulations

Solvent	Condition	t=0	t=2 weeks	t=4 weeks
Formulation 3 ↓A H ₂ O pH 4.8	25/60	106.3	108.0	109.6
	40/75		108.1	110.0
	60 °C		108.0	109.9
Formulation 5 ↓C H ₂ O pH 5.8	25/60	105.0	105.9	107.1
	40/75		103.8	103.5
	60 °C		90.2	77.7
Formulation 10 ↓C H ₂ O pH 6.4	25/60	101.7	100.0	98.0
	40/75		89.4	87.0
	60 °C		63.7	45.7

Formulation 11 <i>iC</i> (2x) H ₂ O pH 6.4	25/60	97.5	96.1	94.3
	40/75		89.4	82.0
	60 °C		55.7	35.20
Formulation 13 ↓ <i>c</i> H ₂ O pH 6.8	25/60	99.4	96.9	94.1
	40/75		85.0	74.0
	60 °C		46.4	29.8

Table 26B. Percentage of potency for D₂O Formulations

Solvent	Condition	t=0	t=2 weeks	t=4 weeks
Formulation 7 ↓ _A D ₂ O pD 5.2	25/60	107.3	111.3	112.9
	40/75		111.6	113.5
	60 °C		111.8	113.5
Formulation 8 ↓ _c D ₂ O pD 6.2	25/60	99.0	103.0	105.0
	40/75		104.9	104.7
	60 °C		101.6	103.0
Formulation 9 ↓ _c D ₂ O pD 6.8	25/60	101.4	99.9	100.1
	40/75		97.4	93.2
	60 °C		78.7	68.9
Formulation 12 ↓ _c D ₂ O pD 7.2	25/60	104.9	103.5	101.6
	40/75		96.9	89.1
	60 °C		62.5	50.9

[00357] Table 27A and Table 27B illustrate the stability of pH or pD for the atropine sulfate formulations. The † & ↓ indicate the high or low concentration of atropine sulfate monohydrate (0.01% and 0.025%). The _A & _c indicate the buffer species used, acetic acid and citric acid respectively.

Table 27A. Stability of pH for H₂O Formulations

Solvent	Condition	t=0	t=2 weeks	t=4 weeks
Formulation 3 ↓ _A H ₂ O pH 4.8	25/60	4.85	4.44	4.61
	40/75		4.41	4.54
	60 °C		4.32	4.40
Formulation 5 ↓ _c H ₂ O pH 5.8	25/60	5.87	5.93	6.03
	40/75		5.96	5.96
	60 °C		5.82	5.78
Formulation 10 ↓ _c H ₂ O pH 6.4	25/60	6.43	6.41	6.46
	40/75		6.62	6.67
	60 °C		6.01	5.92
Formulation 11 <i>iC</i> (2x) H ₂ O pH 6.4	25/60	6.44	6.47	6.72
	40/75		6.66	6.61
	60 °C		6.27	6.23
Formulation 13 ↓ _c H ₂ O pH 6.8	25/60	6.77	6.91	6.91
	40/75		6.65	6.62
	60 °C		6.30	6.19

Table 27B. Stability of pD for D₂O Formulations

Solvent	Condition	t=0	t=2 weeks	t=4 weeks
Formulation 7 ↓A D ₂ O pD 5.2	25/60	5.31	5.10	5.24
	40/75		5.08	5.15
	60 °C		5.00	4.93
Formulation 8 ↓C D ₂ O pD 6.2	25/60	6.25	5.72	5.88
	40/75		5.74	5.78
	60 °C		5.58	5.50
Formulation 9 ↓C D ₂ O pD 6.8	25/60	6.76	6.80	6.81
	40/75		6.78	6.86
	60 °C		6.45	6.24
Formulation 12 ↓C D ₂ O pD 7.2	25/60	7.25	7.18	7.26
	40/75		7.14	7.15
	60 °C		6.52	6.36

Example 12. Determination of shelf life and activation energy for atropine sulfate formulations of**Example 11**

[00358] Activation energy was calculated for the atropine sulfate formulations disclosed in Example 11. Specifically, activation energies were calculated from the total % of related substances (RS) at 40°C and 60°C (2 point calculations) and from tropic acid formation at 40°C and 60°C (2 point calculations). These values were then averaged. Table 28 illustrates the activation energy calculation. Table 29 illustrates estimated shelf-lives from the 40°C rate of formation of %RS and tropic acid, respectively. Figure 10 illustrates estimated shelf lives for D₂O and H₂O formulations.

Table 28. Activation Energy

Atropine Formulations	Total RS	Tropic Acid
7	14	19
3	16	17
8	20	21
5	14	Poor Corr
6	15	16
Mean	16.3	18.7
Stdev	2.68	1.90
RSD	16%	10%
Poor Corr:	One or more curve had $R^2 < 0.95$	

Table 29. Estimated Shelf Life

	Estimated Shelf life/mo			
	Total related substances % (limit=8%)		Tropic acid % (limit=5%)	
Formulation	8°C	25°C	8°C	25°C
0.01% w/v Atr 0.01% w/v Acetate 0.9% w/v NaCl 0.01% w/v BAK pD 5.2 D₂O (Formulation 7)	189	26	1427	147
0.01% w/v Atr 0.01% w/v Acetate 0.9% w/v NaCl 0.01% w/v BAK pH4.8 H₂O (Formulation 3)	211	29	1095	113
0.01% w/v Atr 0.04% w/v Citrate 0.9% w/v NaCl 0.01% w/v BAK pD 6.2 D₂O (Formulation 8)	158	22	369.8	38
0.01% w/v Atr 0.04% w/v Citrate 0.9% w/v NaCl 0.01% w/v BAK pH5.8 H₂O (Formulation 5)	37	5.2	54	5.5
0.01% Atr 0.9% w/v NaCl pH5.9 H₂O extemporaneous preparation	13.6	2.6		

[00359] Tables 30 illustrate the predicted shelf life at temperatures of 40°C, 30°C, 25°C, and 2-8°C for Formulations 2-8 for total RS and tropic acid, respectively.

Table 30

Stability Prediction		RS				Tropic Acid	
Formulation	Temperature (°C)	weeks	months		Temperature (°C)	weeks	months
2	40	64.5	16.1		40	-	-
	30	153.2	38.3		30	-	-
	25	241.2	60.3		25	-	-
	2-8	1747.9	437.0		2-8	-	-
3	40	31.1	7.8		40	99.5	24.9
	30	73.9	18.5		30	268.3	67.1
	25	116.3	29.1		25	451.8	113.0
	2-8	842.9	210.7		2-8	4382.0	1095.5
4	40	30.7	7.7		40	42.1	10.5
	30	73.0	18.2		30	113.7	28.4
	25	114.9	28.7		25	191.5	47.9
	2-8	832.6	208.1		2-8	1857.0	464.2
5	40	5.5	1.4		40	4.9	1.2
	30	13.1	3.3		30	13.2	3.3
	25	20.6	5.2		25	22.2	5.5
	2-8	149.3	37.3		2-8	215.0	53.8
6	40	10.7	2.7		40	8.8	2.2
	30	25.5	6.4		30	23.7	5.9
	25	40.1	10.0		25	39.8	10.0
	2-8	290.5	72.6		2-8	386.5	96.6
7	40	27.9	7.0		40	129.6	32.4
	30	66.4	16.6		30	349.6	87.4
	25	104.5	26.1		25	588.7	147.2
	2-8	757.3	189.3		2-8	5709.4	1427.4
8	40	23.3	5.8		40	33.6	8.4
	30	55.3	13.8		30	90.6	22.6
	25	87.2	21.8		25	152.5	38.1
	2-8	631.6	157.9		2-8	1479.2	369.8

Example 13 - Effect of pH on Ophthalmic Acceptance in Guinea Pigs

[00360] A cohort of guinea pigs is administered 50 μ L of ophthalmic formulations having different pH values described herein. For example, ophthalmic formulations comprising H₂O or deuterated water (e.g., D₂O) are administered to the animals. Animal behavior is recorded at predetermined time intervals to evaluate the acceptance of the ophthalmic formulations

Example 14 - In vivo Rabbit Eye Irritation Test

[00361] The exemplary compositions disclosed herein are subjected to rabbit eye irritation test to evaluate their safety profile. The test composition are tested for eye irritation test in New Zealand Rabbits (see for example Abraham M H, et al., *Draize rabbit eye test compatibility with eye irritation thresholds in humans: a quantitative structure-activity relationship analysis*. Toxicol Sci. 2003 December; 76(2):384-91. Epub 2003 Sep. 26; see also Gettings S D et al., *A comparison of low volume, Draize and in vitro eye irritation test data. III. Surfactant-based formulations*. Food Chem Toxicol. 1998 March; 36(3):209-31). The study involves single ocular administration into the right eye and the same volume of its placebo in the left eye of each of the three rabbits. Rabbits are examined immediately and after instillation of the compositions for 4, 24, 48 and 72 hours post instillation to note the signs/symptoms of eye irritation, if any. The test compositions show no sign of irritancy in cornea, iris and conjunctivae of the rabbit eyes.

Example 15 - In vivo Testing of Ophthalmic Aqueous Formulation in Guinea Pigs

[00362] Focus deprivation myopia (FDM) is achieved using a latex shield to cover one eye. For defocus-induced myopia, a latex-made facemask was held in place by a rubber-band around the head of animals, leaving both eyes, the nose, mouth and ears freely exposed. A -4.00 D lens is glued onto a plastic lens frame. The lens frame is then attached to the facemask around one eye by a fabric hook-and-loop fastener after the optical center of the lens was aligned with the pupil center. The lens is detached and cleaned on both sides with a water-wetted gauze at least once daily followed by re-attachment to the facemask. All the animals are maintained on a cycle of 12-h illumination (500 Lux) and 12-h darkness during the experimental period

[00363] A cohort of guinea pigs at age of 3 weeks are randomly assigned to FDM (a facemask worn monocularly) or defocus-induced myopia (a -4.00 D lens worn monocularly) and control groups. The FDM groups were treated with the ophthalmic aqueous formulation, the ophthalmic carrier (without the ophthalmic agent), or FDM-only. The defocus-induced myopia groups were treated with the ophthalmic aqueous formulation, the ophthalmic carrier (without the ophthalmic agent), or defocus-only. The control groups were treated with the ophthalmic aqueous formulation, the ophthalmic carrier (without the ophthalmic agent), or no treatment. Ocular biometric parameters are measured in both eyes of individual animals before and at 11 days of treatment

[00364] Biometric parameters (e.g. refraction, corneal curvature, and axial components of the eye) are measured by an optometrist, orthoptist, or ophthalmologist with help from an animal care assistant during the light cycle (daytime) after removal of the facemask or lens. The optometrist, orthoptist, or ophthalmologist is masked in regard to the treatment conditions for each animal.

[00365] Refraction is measured by retinoscopy after the pupil is completely dilated by topical administration of 1% cyclopentolate hydrochloride. The results of retinoscopy are recorded as the mean value of the horizontal and vertical meridians.

[00366] Corneal curvature is measured with a keratometer modified by attachment of an +8 D lens onto the anterior surface of the keratometer. A group of stainless steel balls with diameters from 5.5 to 11.0 mm are measured by the modified keratometer. Three readings are recorded for each measurement to provide a mean result. The radius of corneal curvature is then deduced from the readings on the balls with known radii.

[00367] A-scan ultrasonograph is used to measure axial components of the eye (lens thickness and vitreous length and axial length). The conducting velocity was 1,723.3 m/s for measurement of the lens thickness and 1,540 m/s for measurement of the vitreous length as described previously. Each of the axial components is calculated as the mean of 10 repeated measurements.

Example 16 - Safety and Efficacy Studies of Ophthalmic Aqueous Formulation

[00368] A clinical trial is performed to investigate the efficacy and safety of ophthalmic aqueous formulations described herein in patients with myopia. In some instances, the study is open-label, single blind, or double blind study. Patient selection criteria include myopic refraction of at least 1.0D in both eyes, and additional factors such as astigmatism, a documented myopic progression, age, sex, and/or health conditions.

[00369] The patients are randomized to receive 0.05%, 0.01%, or 0.001 atropine aqueous formulation formulated in either H₂O or deuterated water (e.g., D₂O) once nightly in both eyes. Allocation ratio in some instances is defined based the patient population.

[00370] The patients are evaluated on day 0 (baseline), day 14, day 30, and then at 2, 3, 4, 5, 6, 8, 10, 12, 18, 20, 24, and 36 months. At each visit, best-corrected distance logMar visual acuity (BCVA) is assessed by an optometrist, orthoptist, or ophthalmologist using the Early Treatment Diabetic Retinopathy study chart. Near visual acuity is assessed using best-corrected distance spectacle correction with a reduced logMar reading chart placed at 40cm under well-lit conditions. The near point of accommodation (NPA) is measured using a RAF rule using best-corrected distance spectacle correction. Patients are instructed to move the target inwards till the N5 print becomes slightly blurred and then outwards till it just becomes clear. Accommodation amplitude is calculated as the inverse of NPA. Mesopic pupil size is measured with Procyon 3000 pupillometer. Photopic pupil size is measured using the Neuroptics pupillometer.

[00371] Cycloplegic autorefraction is determined 30 minutes after 3 drops of cyclopentolate 1% are administered at 5 minutes apart using a Canon RK-F1 autorefractor. A Zeiss IOL Master, a non-contact partial coherence interferometry, is used to measure the ocular axial length.

[00372] The primary outcome is myopia progression over the time period of the study. Safety is assessed by adverse events including allergic reactions, irritation, or development of blurring of vision in one or both eyes.

Example 17 - Preparation of an Ointment Formulation Containing Atropine Sulfate

[00373] Atropine sulfate is mixed with the dispersing agent (e.g. polyethyleneglycol) under heating and sonication and this mixture is further thoroughly mixed with a molten ointment base (e.g. a mixture of wool wax, white petrolatum, and liquid paraffin). The mixture is placed in a pressure vessel, and sterilized at 125 °C for 30-45 minutes and cooled to room temperature. In another embodiment, autoclaving is conducted under nitrogen. The resulting ophthalmic ointment is aseptically filled into pre-sterilized containers (e.g. tubes).

Example 18 - Atropine-Mucus Penetrating Particle Composition

[00374] A 0.01% atropine-mucus penetrating particle composition was prepared utilizing a milling procedure. An aqueous dispersion containing atropine particles and an MPP-enabling mucus penetrating agent was milled with grinding medium until particle size was reduced to approximately 200nm with a polydispersity index less than 0.15 as measured by dynamic light scattering. Additional agents such as preservatives are also added during the milling procedure. Subsequently, the atropine-MPP composition are be stored at temperatures of between about 15°C and about 25°C.

Example 19 - Atropine Sulfate-Mucus Penetrating Particle Composition

[00375] A 0.01% atropine sulfate-mucus penetrating particle composition was prepared utilizing a milling procedure. An aqueous dispersion containing atropine particles and an MPP-enabling mucus penetrating agent was milled with grinding medium until particle size was reduced to approximately 200nm with a polydispersity index less than 0.15 as measured by dynamic light scattering. Additional agents such as preservatives are also be added during the milling procedure. Subsequently, the atropine-MPP composition are be stored at temperatures of between about 15°C and about 25°C.

[00376] According to another aspect of the disclosure, described herein is an ophthalmic composition that comprises from about 0.001 wt% to about 0.05 wt% of a muscarinic antagonist and water, at a pH of from about 3.8 to about 7.5.

[00377] In some instances, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine -N-oxide, tropine, tropic acid, hyoscyne, scopolomine, tropicamide, cyclopentolate,

pirenzapine, homatropine, or a combination thereof. In some cases, the muscarinic antagonist is atropine. In some cases, the muscarinic antagonist is atropine sulfate.

[00378] In some instances, the ophthalmic composition comprises one of: at least about 80%, at least about 85%, at least about 90%, at least about 93%, at least about 95%, at least about 97%, at least about 98%, or at least about 99% of the muscarinic antagonist based on initial concentration after extended period of time under storage condition.

[00379] In some instances, the ophthalmic composition has a pH of one of: less than about 7.3, less than about 7.2, less than about 7.1, less than about 7, less than about 6.8, less than about 6.5, less than about 6.4, less than about 6.3, less than about 6.2, less than about 6.1, less than about 6, less than about 5.9, less than about 5.8, less than about 5.2, less than about 4.8, or less than about 4.2 after extended period of time under storage condition.

[00380] In some instances, the ophthalmic composition further has a potency of one of: at least 80%, at least 85%, at least 90%, at least 93%, at least 95%, at least 97%, at least 98%, or at least 99% after extended period of time under storage condition.

[00381] In some instances, the extended period of time is one of: about 1 week, about 2 weeks, about 3 weeks, about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 8 months, about 10 months, about 12 months, about 18 months, about 24 months, about 36 months, about 4 years, or about 5 years.

[00382] In some instances, the storage condition has a storage temperature of one of: about 25°C, about 40°C, or about 60°C. In some cases, the storage condition has a storage temperature of from about 2°C to about 10°C or from about 16°C to about 26°C. In some cases, the storage condition has a relative humidity of about 60% or about 75%.

[00383] In some instances, the ophthalmic composition is in the form of an aqueous solution. In some cases, the muscarinic antagonist is present in the composition at a concentration of one of: from about 0.001 wt% to about 0.04 wt%, from about 0.001 wt% to about 0.03 wt%, from about 0.001 wt% to about 0.025 wt%, from about 0.001 wt% to about 0.02 wt%, from about 0.001 wt% to about 0.01 wt%, from about 0.001 wt% to about 0.008 wt%, or from about 0.001 wt% to about 0.005 wt%.

[00384] In some instances, the ophthalmic composition further comprises an osmolality adjusting agent. In some cases, the osmolality adjusting agent is sodium chloride.

[00385] In some instances, the ophthalmic composition further comprises a preservative. In some cases, the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof.

[00386] In some instances, the ophthalmic composition further comprises a buffer agent. In some cases, the buffer agent is selected from borates, borate-polyol complexes, phosphate buffering agents, citrate buffering agents, acetate buffering agents, carbonate buffering agents, organic buffering agents, amino acid buffering agents, or combinations thereof.

[00387] In some instances, the ophthalmic composition further comprises a tonicity adjusting agent. In some cases, the tonicity adjusting agent is selected from sodium chloride, sodium nitrate, sodium sulfate, sodium bisulfate, potassium chloride, calcium chloride, magnesium chloride, zinc chloride, potassium acetate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium thiosulfate, magnesium sulfate, disodium hydrogen phosphate, sodium dihydrogen phosphate, potassium dihydrogen phosphate, dextrose, mannitol, sorbitol, dextrose, sucrose, urea, propylene glycol, glycerin, or a combination thereof.

[00388] In some instances, the ophthalmic composition is stored in a plastic container. In some cases, the material of the plastic container comprises low-density polyethylene (LDPE).

[00389] In some instances, the ophthalmic composition has a dose-to-dose muscarinic antagonist concentration variation of one of: less than 50%, less than 40%>, less than 30%>, less than 20%, less than 10%, or less than 5%. In some cases, the dose-to-dose muscarinic antagonist concentration variation is based on one of: 10 consecutive doses, 8 consecutive doses, 5 consecutive doses, 3 consecutive doses, or 2 consecutive doses.

[00390] In some instances, the ophthalmic composition has a pH of one of: from about 3.8 to about 7.5, from about 4.2 to about 7.5, from about 4.8 to about 7.3, from about 5.2 to about 7.2, from about 5.8 to about 7.1, from about 6.0 to about 7.0, or from about 6.2 to about 6.8.

[00391] In some instances, the ophthalmic composition further comprises a pH adjusting agent. In some cases, the pH adjusting agent comprises HCl, NaOH, CH₃COOH, or C₆H₈O₇.

[00392] In some instances, the ophthalmic composition comprises one of: less than 5% of D₂O, less than 4% of D₂O, less than 3% of D₂O, less than 2% of D₂O, less than 1% of D₂O, less than 0.5% of D₂O, less than 0.1% of D₂O, or 0% D₂O. In some cases, the ophthalmic composition is essentially free of D₂O.

[00393] In some instances, the ophthalmic composition further comprises a pharmaceutically acceptable carrier.

[00394] In some instances, the ophthalmic composition is formulated as an ophthalmic solution for the treatment of an ophthalmic disorder. In some cases, the ophthalmic disorder or condition is pre-myopia, myopia, or progression of myopia.

[00395] In some instances, the ophthalmic composition is not formulated as an injectable formulation.

[00396] While preferred embodiments of the present disclosure have been shown and described herein, such embodiments are provided by way of example only. Various alternatives to the embodiments described herein are optionally employed in practicing the disclosure. It is intended that the following claims define the scope of the disclosure and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

WHAT IS CLAIMED IS:

1. An ophthalmic composition, comprising from about 0.001 wt% to about 0.05 wt% of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9.
2. The ophthalmic composition of claim 1, wherein the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine -N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof.
3. The ophthalmic composition of claim 2, wherein the muscarinic antagonist is atropine or atropine sulfate.
4. The ophthalmic composition of any one of the claims 1-3, wherein the ophthalmic composition has a pD of one of: less than about 7.3, less than about 7.2, less than about 7.1, less than about 7, less than about 6.8, less than about 6.5, less than about 6.4, less than about 6.3, less than about 6.2, less than about 6.1, less than about 6, less than about 5.9, less than about 5.8, less than about 5.2, or less than about 4.8 after extended period of time under storage condition.
5. The ophthalmic composition of any one of the claims 1-4, wherein the ophthalmic composition comprises one of: at least about 80%, at least about 85%, at least about 90%>, at least about 93%>, at least about 95%>, at least about 97%>, at least about 98%>, or at least about 99%> of the muscarinic antagonist based on initial concentration after extended period of time under storage condition.
6. The ophthalmic composition of any one of the claims 1-5, wherein the ophthalmic composition further has a potency of one of: at least 80%>, at least 85%>, at least 90%>, at least 93%>, at least 95%, at least 97%>, at least 98%>, or at least 99%> after extended period of time under storage condition.
7. The ophthalmic composition of any one of the claims 1-6, wherein the storage condition has a storage temperature of from about 2°C to about 10°C or from about 16°C to about 26°C.
8. The ophthalmic composition of any one of the claims 1-7, wherein the muscarinic antagonist is present in the composition at a concentration of one of: from about 0.001 wt%> to about 0.04 wt%, from about 0.001 wt% to about 0.03 wt%, from about 0.001 wt% to about 0.025 wt%, from

about 0.001 wt% to about 0.02 wt%, from about 0.001 wt% to about 0.01 wt%, from about 0.001 wt% to about 0.008 wt%, or from about 0.001 wt% to about 0.005 wt%.

9. The ophthalmic composition of any one of the claims 1-8, wherein the ophthalmic composition further comprises an osmolality adjusting agent, a preservative, a buffer agent, a tonicity adjusting agent, or a combination thereof.
10. The ophthalmic composition of any one of the claims 1-9, wherein the ophthalmic composition has a dose-to-dose muscarinic antagonist concentration variation of one of: less than 50%, less than 40%, less than 30%, less than 20%, less than 10%, or less than 5%.
11. The ophthalmic composition of any one of the claims 1-10, wherein the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof.
12. The ophthalmic composition of any one of the claims 1-11, wherein the ophthalmic composition further comprises a pD adjusting agent.
13. The ophthalmic composition of claim 12, wherein the pD adjusting agent comprises DCl, NaOD, CD_3COOD , or $\text{C}_6\text{D}_8\text{O}_7$.
14. The ophthalmic composition of any one of the claims 1-13, wherein the ophthalmic composition comprises one of: less than 5% of H_2O , less than 4% of H_2O , less than 3% of H_2O , less than 2% of H_2O , less than 1% of H_2O , less than 0.5% of H_2O , less than 0.1% of H_2O , or 0% of H_2O .
15. The ophthalmic composition of any one of the claims 1-14, wherein the ophthalmic composition is a solution.
16. The ophthalmic composition of any one of the claims 1-15, wherein the ophthalmic composition is not formulated as an injectable formulation.
17. The ophthalmic composition of any one of the claims 1-16, wherein the ophthalmic composition is formulated as an ophthalmic solution for the treatment of an ophthalmic disorder.
18. The ophthalmic composition of any one of the claims 1-17, wherein the ophthalmic disorder or condition is pre-myopia, myopia, or progression of myopia.

19. A method of arresting myopia development or preventing myopia development, comprising administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition of claims 1-18.
20. The method of claim 19, wherein the ophthalmic composition is stored at between about 2 °C to about 10 °C prior to first use.
21. The method of claim 19 or 20, wherein the ophthalmic composition is stored at between about 16 °C to about 26 °C after first use.
22. An ophthalmic composition, comprising from about 0.001 wt% to about 0.05 wt% of a muscarinic antagonist and water, at a pH of from about 3.8 to about 7.5.
23. The ophthalmic composition of claim 22, wherein the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof.
24. The ophthalmic composition of claim 22 or 23, wherein the ophthalmic composition comprises one of: at least about 80%, at least about 85%>, at least about 90%>, at least about 93%>, at least about 95%o, at least about 97%>, at least about 98%>, or at least about 99%> of the muscarinic antagonist based on initial concentration after extended period of time under storage condition.
25. The ophthalmic composition of any one of the claims 22-24, wherein the ophthalmic composition has a pH of one of: less than about 7.3, less than about 7.2, less than about 7.1, less than about 7, less than about 6.8, less than about 6.5, less than about 6.4, less than about 6.3, less than about 6.2, less than about 6.1, less than about 6, less than about 5.9, less than about 5.8, less than about 5.2, less than about 4.8, or less than about 4.2 after extended period of time under storage condition.
26. The ophthalmic composition of any one of the claims 22-25, wherein the ophthalmic composition further has a potency of one of: at least 80%>, at least 85%>, at least 90%>, at least 93%o, at least 95%>, at least 97%>, at least 98%>, or at least 99%> after extended period of time under storage condition.
27. The ophthalmic composition of any one of the claims 22-26, wherein the storage condition has a storage temperature of from about 2°C to about 10°C or from about 16°C to about 26°C.

28. The ophthalmic composition of any one of the claims 22-27, wherein the ophthalmic composition further comprises an osmolarity adjusting agent, a preservative, a buffer agent, a tonicity adjusting agent, optionally a pH adjusting agent, or a combination thereof.
29. The ophthalmic composition of any one of the claims 22-28, wherein the ophthalmic composition comprises one of: less than 5% of D₂O , less than 4% of D₂O , less than 3% of D₂O , less than 2% of D₂O , less than 1% of D₂O , less than 0.5% of D₂O , less than 0.1% of D₂O , or 0% of D₂O .
30. The ophthalmic composition of any one of the claims 22-29, wherein the ophthalmic composition is formulated as an ophthalmic solution for the treatment of an ophthalmic disorder.

Fig. 1A

Weeks							
	Temp (°C)	0	1	1.571429	2.142857	3.428571	6.571429
T1	25	0.08			0.88		2.81
T2	40	0.08		3.47		4.48	

Fig. 1B

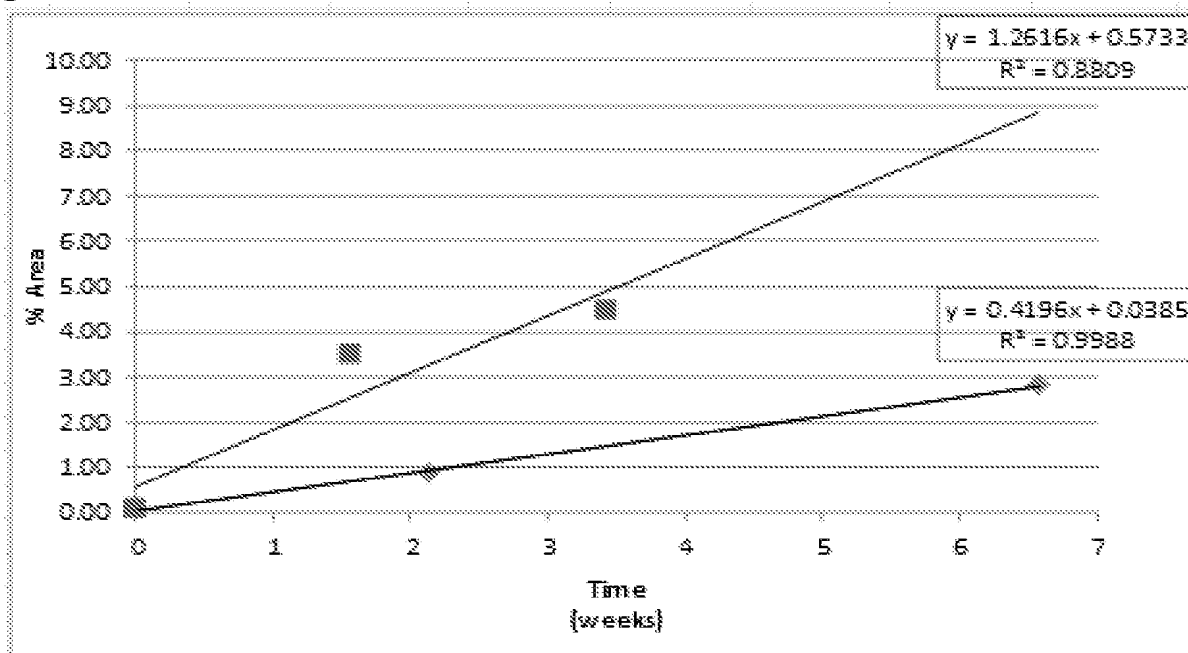


Fig. 1C

Formulation:		Average of Analysts		
Stability Prediction:		RRT 0.87		
	spec limit:	0.50	% (not more than)	
			shelf life	
			weeks	months
rate	1.24844 at 40C		0.4	0.1
rate	0.60617 at 30C		0.8	0.2
rate	0.41477 at 25C		1.2	0.3
rate	0.07932 at 2-8C		6.3	1.6
rate	0.00694 at -20C		N/A	N/A

Fig. 2A

		Weeks				
	Temp (°C)	0	1	2.142857	4	6.571429
T1	25	0.08		0.9		2.8
T2	60	0.08	10.5		11.3	

Fig. 2B

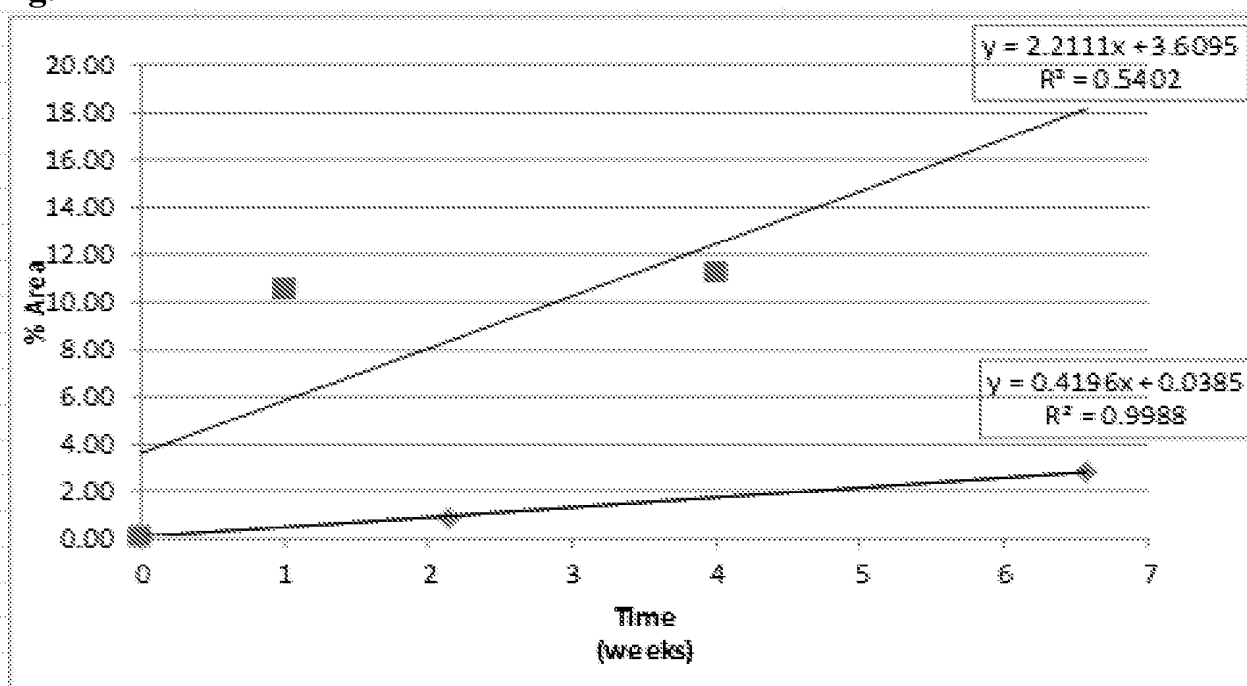


Fig. 2C

Formulation:		Average of Analysts		
Stability Prediction:		FRT 0.87		
	spec limit:	0.50	% (not more than)	
			shelf life	
			weeks	months
rate	0.88876 at 40C		0.6	0.1
rate	0.54051 at 30C		0.9	0.2
rate	0.41627 at 25C		1.2	0.3
rate	0.13331 at 2-8C		3.8	0.9
rate	0.02493 at -20C		N/A	N/A

3/ 10

Fig. 3

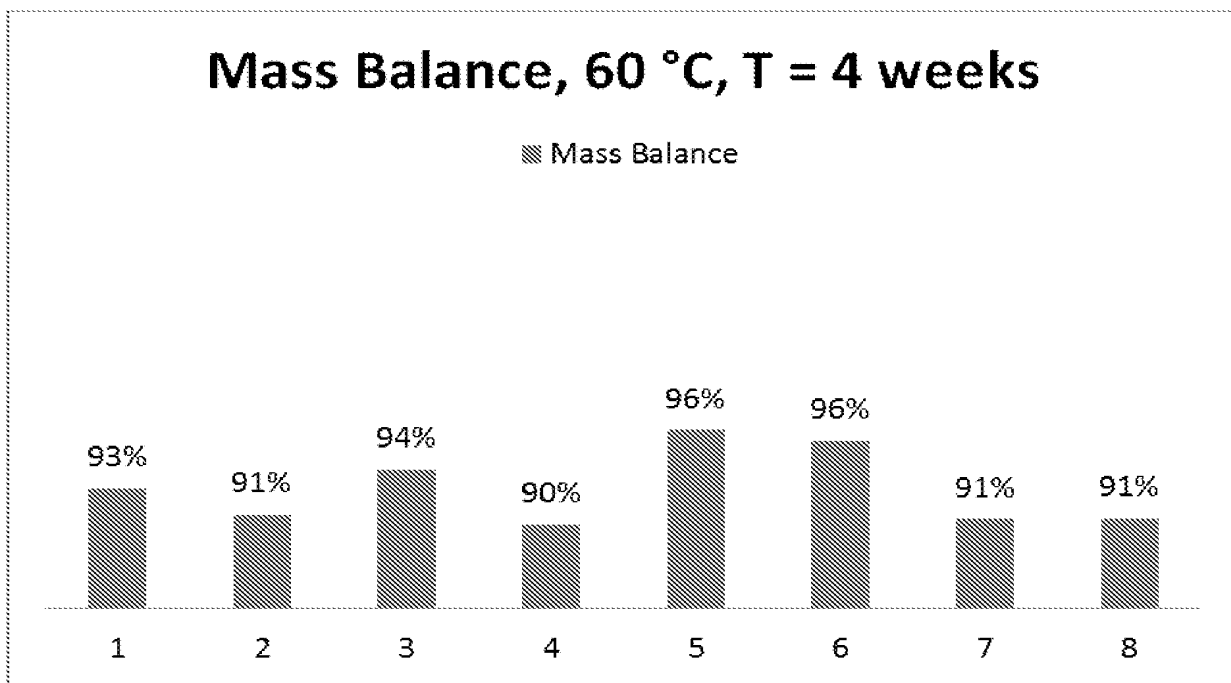


Fig. 4

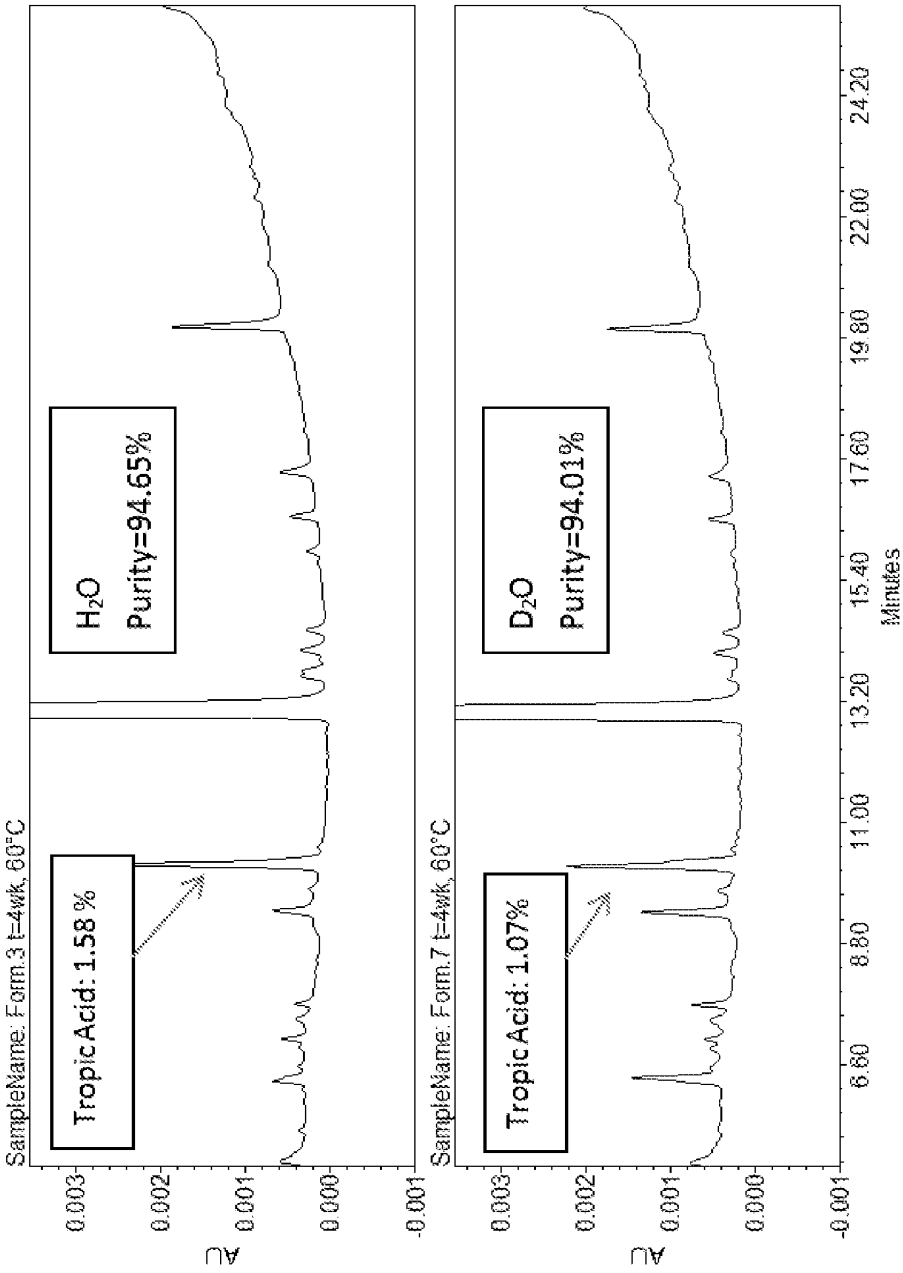


Fig. 5

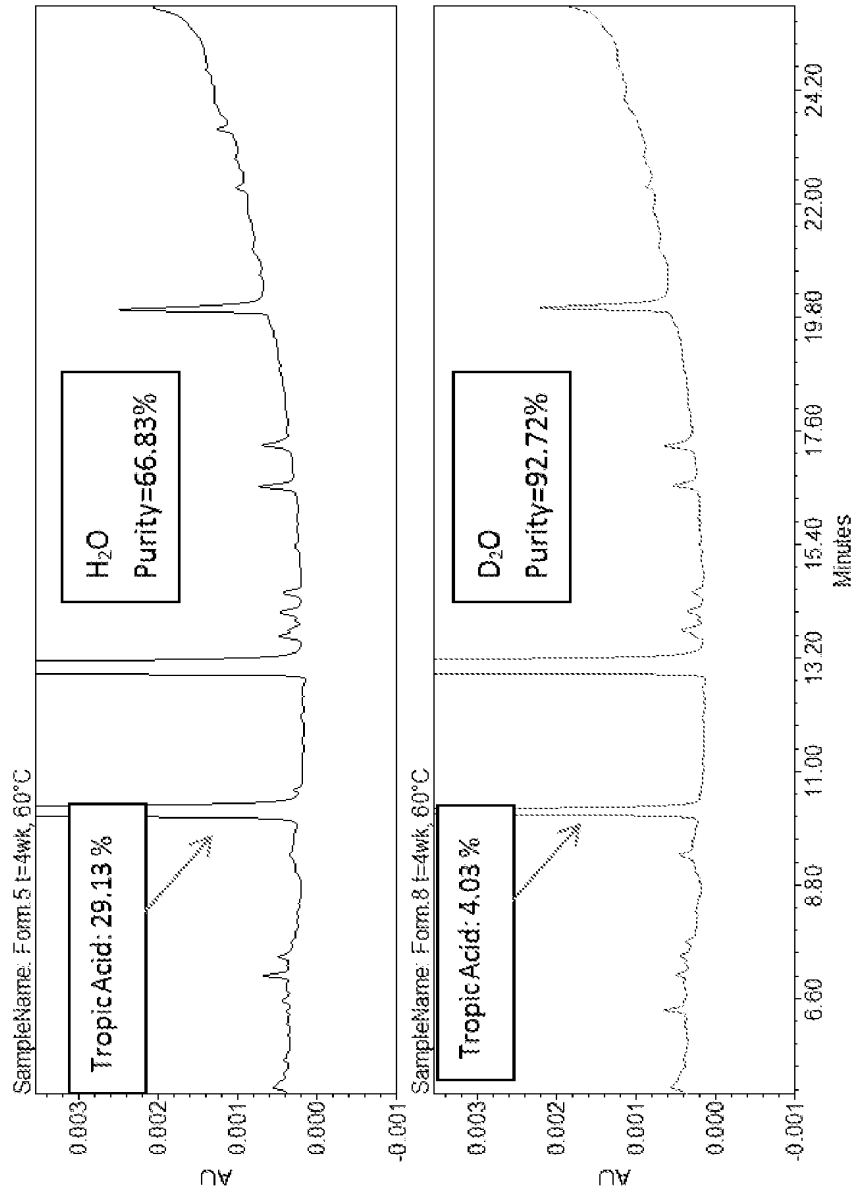


Fig. 6

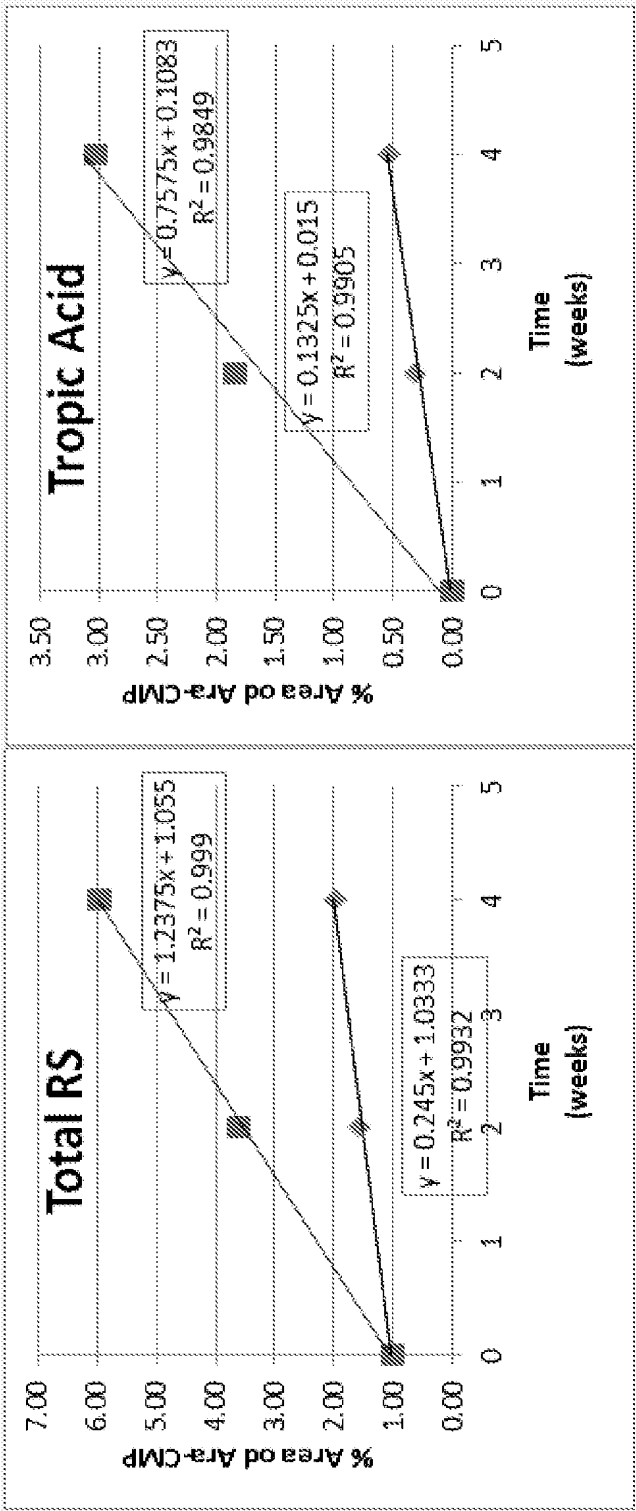


Fig. 7

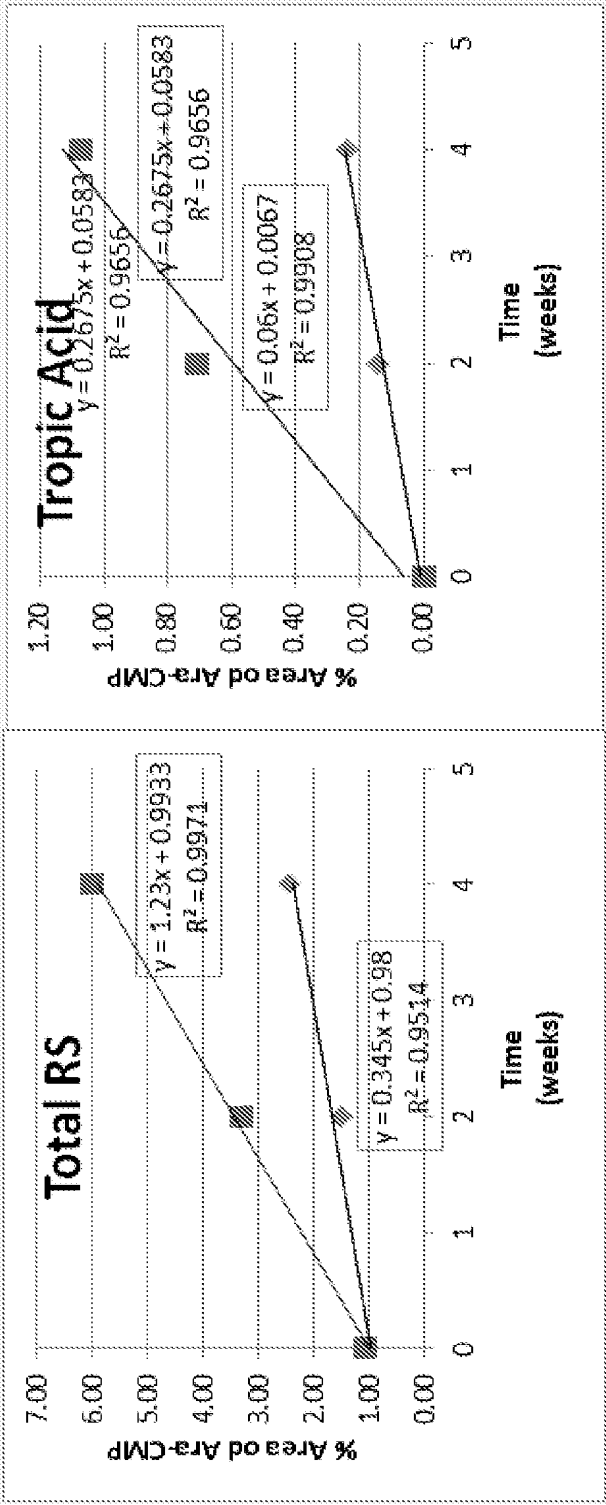


Fig. 8

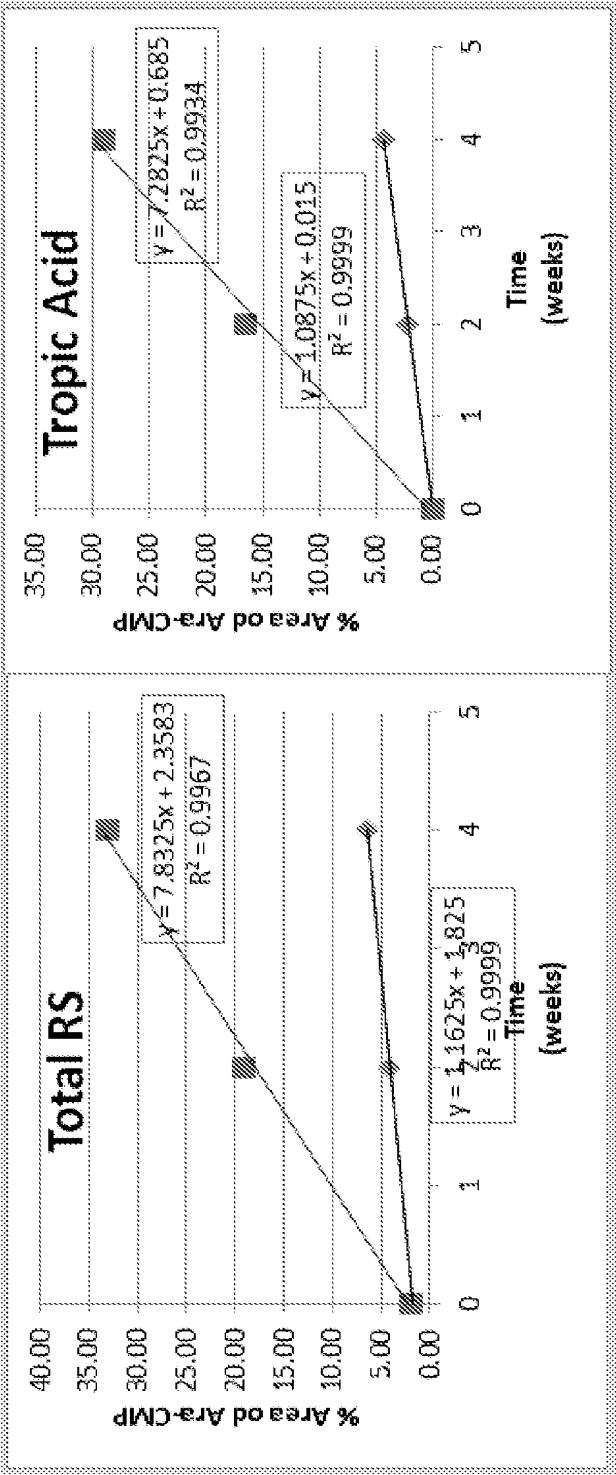


Fig. 9

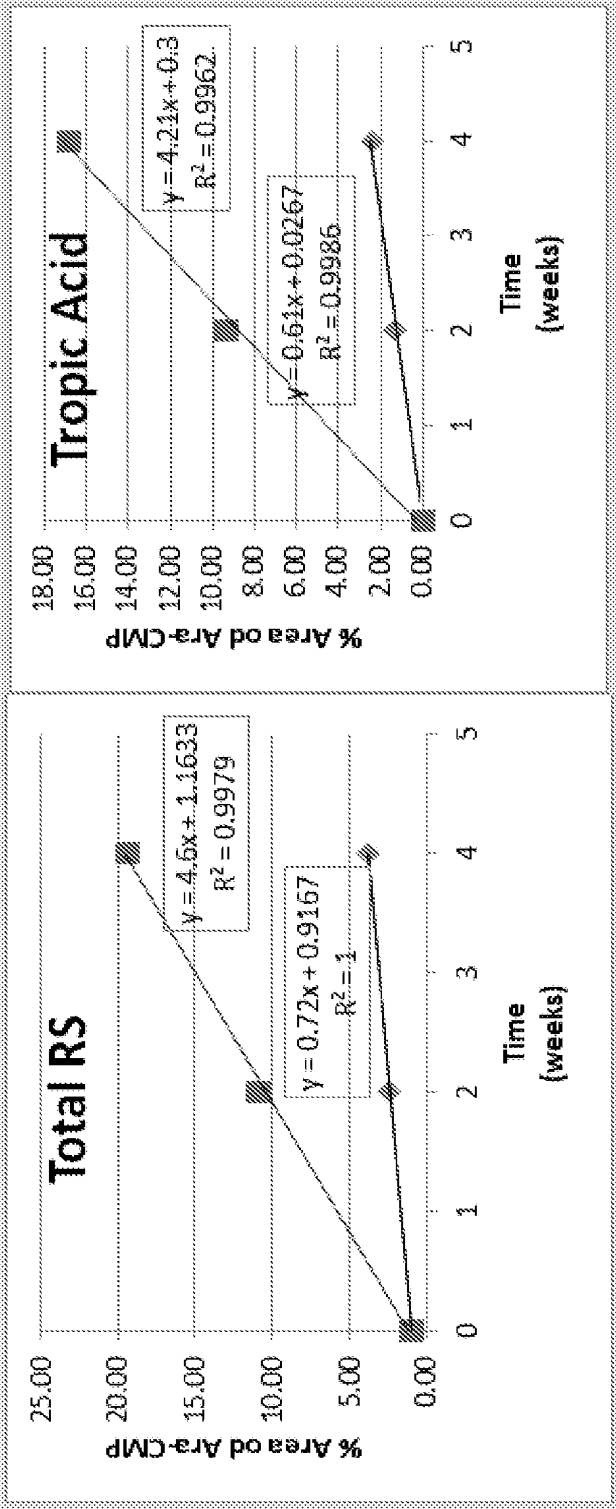
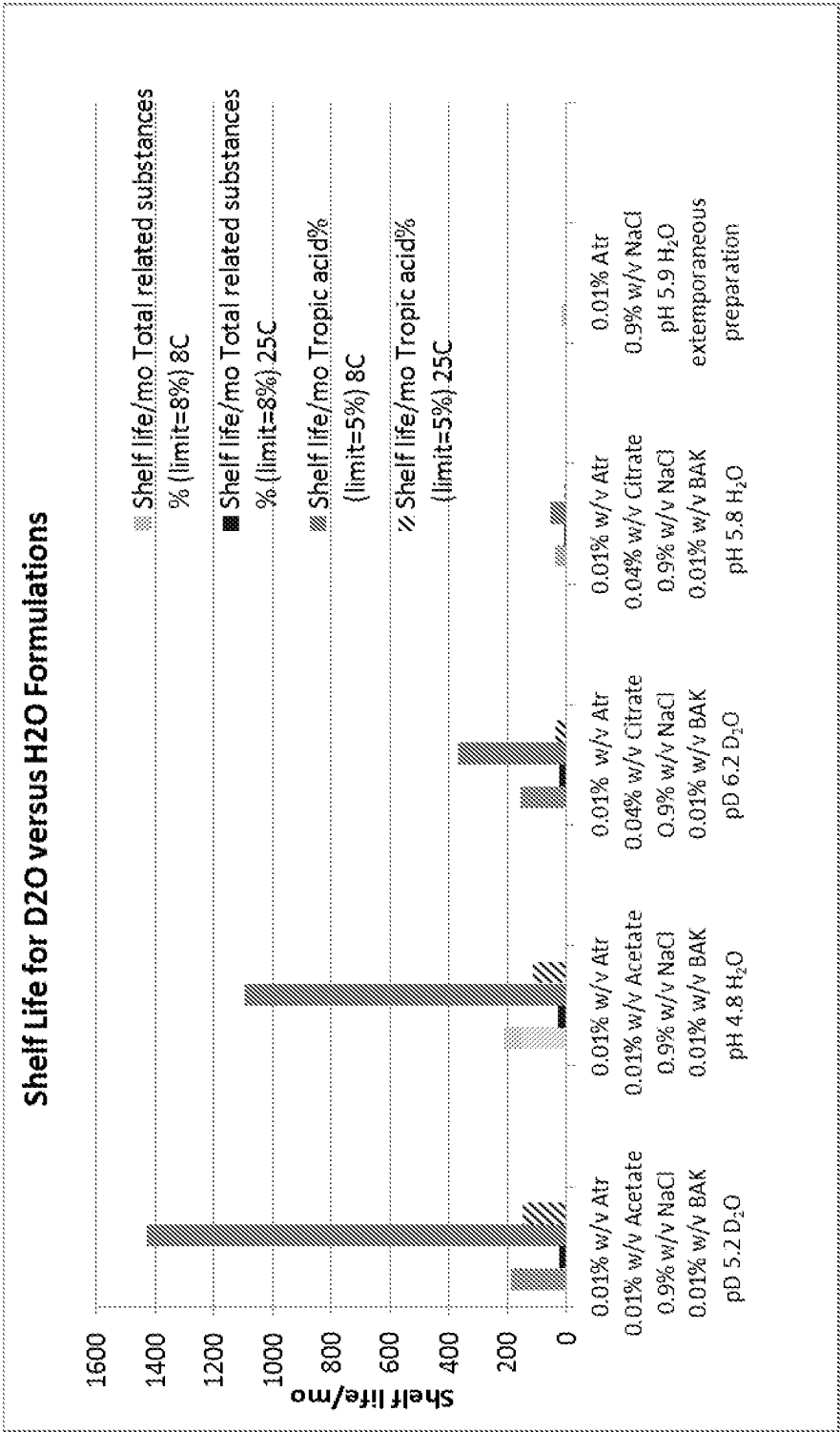


Fig. 10



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2015/037249**A. CLASSIFICATION OF SUBJECT MATTER****A61K 31/46(2006.01)i, A61K 31/245(2006.01)i, A61K 9/08(2006.01)i, A61P 27/02(2006.01)i**

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K 31/46; A61K 31/135; A61P 29/00; A61K 31/55; A61K 31/505; A61K 9/50; A61K 47/32; A61K 47/38; A61K 47/42; A61K 38/13; C07D 401/14; A61K 31/245; A61K 9/08; A61P 27/02

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal) & Keywords: ophthalmic composition, muscarinic antagonist, deuterated water, shelf life, stability

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5716952 A (IOLDEMUSSIE, E. et al.) 10 February 1998 See columns 2, 4; and table 1.	22-24
A		1-4
X	W0 97-16192 AI (MERCK & CO., INC.) 09 May 1997 See pages 2-4, 12.	22-24
X	US 2012-0015035 AI (WILDSOET, C. F. et al.) 19 January 2012 See paragraphs [0030], [0031], [0075]; and claims 1, 13, 14.	22-24
A	wo 2011-019940 A2 (SEROS MEDICAL, LLC) 17 February 2011 See the whole document.	1-4, 22-24
A	US 2012-0028910 AI (COMBAL, J.-P. et al.) 02 February 2012 See the whole document.	1-4, 22-24



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

30 September 2015 (30.09.2015)

Date of mailing of the international search report

30 September 2015 (30.09.2015)

Name and mailing address of the ISA/KR

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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 19-21
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 19-21 pertain to methods for treatment of the human body by therapy, and thus relate to a subject matter which this International Searching Authority is not required, under PCT Article 17(2)(a)(i) and PCT Rule 39.1(iv), to search.
2. ☒ Claims Nos.: 13, 20
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :
Claims 13 and 20 are unclear, since they refer to one of claims which are not drafted in accordance with PCT Rule 6.4(a) (PCT Article 6).
3. ☒ Claims Nos.: 5-12, 14-19, 21, 25-30
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos. :
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2015/037249

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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wo 97-16192 A1	09/05/1997	AU 7528696 A	22/05/1997
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wo 2011-019940 A2	17/02/2011	EP 2464387 A2 EP 2464387 A4 US 2012-0203161 A1 ¥0 2011-019940 A3	20/06/2012 15/05/2013 09/08/2012 16/06/2011
US 2012-0028910 A1	02/02/2012	AU 2008-309923 A1 AU 2008-309923 B2 BR PI0819081 A2 CA 2702082 A1 CN 101820917 A CN 101820917 B EA 019867 B1 EA 201000441 A1 EP 2195033 A1 HK 1147937 A1 JP 2010-540671 A JP 5640207 B2 MX 2010003774 A NZ 584275 A ¥0 2009-046967 A1	16/04/2009 03/04/2014 22/04/2015 16/04/2009 01/09/2010 02/01/2013 30/06/2014 29/10/2010 16/06/2010 13/09/2013 24/12/2010 17/12/2014 27/04/2010 29/06/2012 16/04/2009



(51) International Patent Classification:

A61K 31/46 (2006.01) A61P 27/10 (2006.01)

(21) International Application Number:

PCT/SG2012/000174

(22) International Filing Date:

18 May 2012 (18.05.2012)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/489,016 23 May 2011 (23.05.2011) US

(71) Applicant (for all designated States except US): **SINGAPORE HEALTH SERVICES PTE LTD** [SG/SG]; 31 Third Hospital Avenue, #30-03 Bowyer Block C, Singapore 168753 (SG).

(72) Inventors; and

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(74) Agent: **CHUNG, Jing, Yeng**; Marks & Clerk Singapore LLP, Tanjong Pagar, P.O. Box 636, Singapore 910816 (SG).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— of inventorship (Rule 4.17(iv))

Published:

— with international search report (Art. 21(3))

(54) Title: COMPOSITION AND/OR METHOD FOR REDUCING AND/OR PREVENTING MYOPIA PROGRESSION COMPRISING ATROPINE

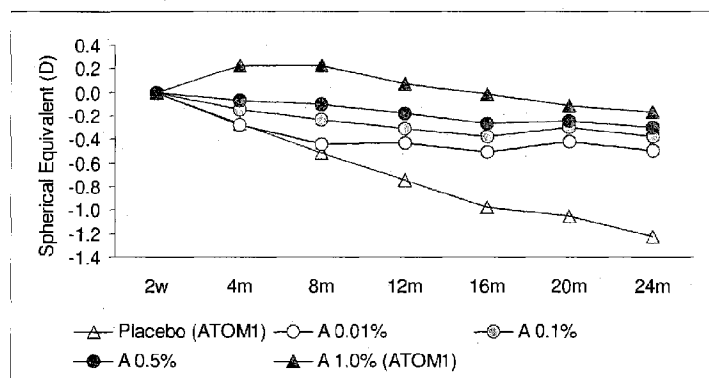


Figure 5

(57) Abstract: The invention relates to a composition and/or method for reducing and/or preventing myopia progression. The composition comprises an ultra-low atropine concentration. The composition comprises less than 0.025% atropine. For example, the composition comprises about 0.01% atropine. The ultra-low atropine composition reduces and/or prevents myopia progression with negligible side effects, such as loss of accommodation, mydriasis, near-vision blur, allergic conjunctivitis and dermatitis.

COMPOSITION AND/OR METHOD FOR REDUCING AND/OR PREVENTING MYOPIA PROGRESSION COMPRISING ATROPINE

Field of the invention

The present invention relates to a composition and/or method for reducing and/or preventing myopia progression. In particular, the invention relates to an ultra-low
5 concentration atropine solution for reducing and/or preventing myopia progression.

Background of the invention

Myopia (nearsightedness or short sightedness) is a type of refractive error of the eye, in which the visual image is focused in front of the retina, typically resulting in blurred vision of distant objects. Myopia is especially prevalent among Asians and has been
10 reported to be as high as 70-90% in Asian countries. Myopia may be corrected by prescription lenses (for example, spectacles or contact lenses) or refractive surgery (for example, LASIK or phakic intraocular lens implantation).

After onset of myopia, which typically occurs during early childhood, its progression is often difficult to control. Atropine is a non-specific muscarinic antagonist. Atropine at
15 1.0% and 0.5% has been demonstrated through randomised trials to be effective in slowing myopia progression (Shih *et al.*, 1999). The safety profile, and associated side-local and systemic effects of atropine (i.e. its effect on pupil size and accommodation), however, has often been a source of concern, and has greatly deterred the use of this medication for myopia control. Every unit increase in pupil size results in an
20 exponential increase in the amount of light entering the eye, and this may cause glare and photophobia. The long term effect of excessive amounts of ultraviolet light entering an eye which has been chronically dilated with atropine may potentially increase the risk of cataract or macular degeneration. Atropine also decreases accommodation amplitude (ability to focus on near objects), thus reducing near vision so that children
25 may require bifocal or progressive glasses to read or see close objects.

In atropine in the treatment of myopia study 1 (ATOM1), 1 % atropine was reported to be effective in slowing the progression of myopia (Chua *et al.*, 2006). Side effects were recognised with 1 % atropine treated eyes, including blurring of near vision in the

atropine-treated eye (likely due to cycloplegia) and anisocoria or uneven pupil size, (likely due to mydriasis).

In a retrospective non-randomized study, Lee *et al.*, (2006) found that myopia in 21 children aged 6-12 years on 0.05% atropine progressed at a rate of 0.28 ± 0.26 D per year, compared to 0.75 ± 0.35 D per year in 36 consecutive untreated clinic patients. Negative side effects including photophobia and hampered near vision were reported in the subjects.

In another retrospective review of 50 pre-myopic children, 24 of whom were started on 0.025% atropine, Fang *et al.*, (2010) noted that subsequent myopia shift was less (-0.14 ± 0.24 D) in the 0.025% atropine group, compared to controls (-0.58 ± 0.34 D). Both the control group and the 0.025% atropine group exhibited photophobia although the difference was not significant. None of the subjects complained of near-vision blur.

It is desirable to provide an atropine composition for reducing and/or preventing myopia progression with negligible or minimal side effects.

15 Summary of the invention

The present composition provides an ultra-low concentration atropine composition for reducing and/or preventing myopia progression.

According to a first aspect, the present invention provides a composition for reducing and/or preventing myopia progression comprising less than 0.025% atropine.

20 According to another aspect, the invention relates to the use of atropine in the preparation of a composition for reducing and/or preventing myopia progression, wherein the composition comprises less than 0.025% atropine.

The invention also provides a method for reducing and/or preventing myopia progression comprising administering to a subject a composition comprising less than 25 0.025% atropine.

Brief description of the figures

Figure 1 is a flow chart illustrating the study design of ATOM1.

Figure 2 is a graph showing mean spherical equivalent change from baseline from ATOM1.

- 5 Figure 3 is a graph showing mean axial length change from baseline from ATOM1.

Figure 4 is a flow chart illustrating the study design of ATOM2.

Figure 5 is a graph showing the mean change in spherical equivalent for groups from baseline 2 to 24 months with 0.01%, 0.1% and 0.5% atropine from ATOM2 and 1% atropine and placebo from ATOM1.

- 10 Figure 6 is a graph illustrating progression of myopia according to severity (pooled eyes) with 0.01%, 0.1% and 0.5% atropine from ATOM2 and 1% atropine and placebo from ATOM1. Myopia progression from baseline 2 is classified as severe (if > 1 D), moderate (0.5-0.99 D) and mild (if < 0.5 D).

- 15 Figure 7 is a graph illustrating the main change in axial lengths from baseline 2 to 24 months from ATOM2.

Figure 8 is a graph illustrating the changes in spherical equivalent in groups from ATOM2 after stopping atropine for 1 year.

Figure 9 is a graph illustrating the changes in axial length in groups from ATOM2 after stopping atropine for 1 year.

20 Definitions

The term "about" when used in conjunction with a value, for example about 0.01%, means a value reasonably close to the value. For example, for 0.01%, 0.006%, 0.007%, 0.008%, 0.009%, 0.0095%, 0.0099%, 0.011%, 0.0115%, 0.012%, 0.013%, 0.014% would be included. In particular, it would include the value itself.

25

"Accommodation" refers to the process by which the eye adjusts to a near focus, to maintain a clear image (focus) on an object as its distance changes.

"Amblyopia" (also known as "lazy eye") refers to a decrease of vision, either unilaterally or bilaterally, with no apparent structural abnormality in the eye. In amblyopia, visual stimulation either fails to transmit or is poorly transmitted through the optic nerve to the brain.

"Anisocoria" refers to a condition where the pupils of the eyes are uneven in size.

"Cycloplegia" refers to paralysis of the ciliary muscle of the eye, resulting in a loss of accommodation.

10 "Mydriasis" refers to a condition where the pupil of the eye is dilated due to disease, trauma or the use of drugs. Mydriasis may be associated with glare intolerance and photophobia.

"Photophobia" refers to a condition of sensitivity to light. In ordinary medical terms, photophobia is not a morbid fear or phobia, but an experience of discomfort or pain to the eyes due to light exposure.

"Strabismus" (also known as "crossed eyes") refers to a condition in which the two eyes do not line up in the same direction, and therefore do not look at the same object at the same time.

Detailed description of the invention

20 The composition of the present invention comprises an ultra-low concentration of atropine, i.e. less than 0.025% atropine. The concentration of atropine in the composition may be any value less than 0.025%, for example, the composition may comprise 0.001 to 0.0249% atropine; 0.005% to 0.0249% atropine, 0.01 to 0.0249% atropine, 0.005 to 0.02% atropine, 0.05 to 0.015% atropine or 0.008 to 0.012% atropine.

25 Accordingly, the composition may comprise 0.001%, 0.002%, 0.003%, 0.004%, 0.005%, 0.006%, 0.007%, 0.008%, 0.009%, 0.01%, 0.011%, 0.012%, 0.013%, 0.014%, 0.015%, 0.016%, 0.017%, 0.018%, 0.019%, 0.02%, 0.021%, 0.022%, 0.023%, 0.024%, 0.0245% or 0.0249% atropine. In particular, the composition comprises about 0.01%

atropine. More in particular, the composition comprises 0.01%. The composition may further comprise at least one pharmaceutically acceptable excipient.

The composition according to any aspect of the invention may be for use in reducing and/or preventing myopia progression and/or treating myopia. Accordingly, the
5 invention includes a method of reducing and/or preventing myopia progression comprising administering to a subject a composition according to any aspect of the invention. The composition is for administration to the eye. In particular, the composition is for topical administration to the eye. More in particular, the composition is an eye-drop composition

10 After onset, myopia typically progresses during childhood and may only stabilise in adulthood. Accordingly, the composition is suitable for reducing and/or preventing myopia progression in subjects where myopia is still progressing and/or has not stabilised, even in late adulthood. For example, the composition is suitable for reducing and/or preventing myopia progression in subjects from 3 to 30 years old, where myopia
15 is still progressing and/or has not stabilised. In particular, the composition is suitable for reducing and/or preventing myopia in children from 6 to 12 years old.

Accordingly, the invention also provides a method for reducing and/or preventing myopia progression comprising administering to a subject a composition according to any aspect of the invention.

20 In a study (Example 2), 400 children were administered either 0.01%, 0.05% or 0.1% atropine nightly to both eyes and myopia progression was monitored over a period of 2 years. The results of this study showed that 0.01% atropine was found to induce negligible side-effects (for example: loss of accommodation, mydriasis, allergic conjunctivitis, dermatitis) compared to atropine at 0.1% and 0.05% and retains
25 comparable efficacy in controlling myopia progression.

Having now generally described the invention, the same will be more readily understood through reference to the following examples which are provided by way of illustration, and are not intended to be limiting of the present invention.

EXAMPLES

Example 1 First atropine in the treatment of myopia study (ATOM1)

In ATOM1, 400 children aged 6-12 years with spherical equivalents of -1.00 D and -6.00 D were randomly assigned to having 1% atropine or placebo medication in one eye (Chua *et al.*, 2006). The design of the study is illustrated in Figure 1 and summarised below. The results from ATOM1 are compared and also used in Example 2.

Summary of ATOM 1

Purpose: To evaluate the efficacy and safety of topical atropine, a nonselective muscarinic antagonist, in slowing the progression of myopia and ocular axial elongation in Asian children.

Design: Parallel-group, placebo-controlled, randomized, double-masked study.

Subjects: 400 children aged 6 to 12 years with refractive error of spherical equivalent -1.00 to -6.00 D and astigmatism of -1.50 D or less.

Intervention: Subjects (the children) were assigned with equal probability to receive either 1 % atropine or vehicle eye-drops once nightly for 2 years. Only 1 eye of each subject was chosen through randomization for treatment.

Main Outcome Measures: The main efficacy outcome measures were change in spherical equivalent refraction as measured by cycloplegic autorefraction and change in ocular axial length as measured by ultrasonography. The primary safety outcome measure was the occurrence of adverse events.

Results: 346 (86.5%) subjects completed the 2-year study. After 2 years, the mean progression of myopia and of axial elongation in the placebo-treated control eyes was -1.20 ± 0.69 D (Figure 2) and 0.38 ± 0.38 mm (Figure 3), respectively. In the atropine-treated eyes, myopia progression was -0.28 ± 0.92 D (Figure 2), whereas the axial length remained essentially unchanged compared with baseline (-0.02 ± 0.35 mm, Figure 3). The changes in refractive error and axial length in the non-treated eyes of

subjects in both the atropine group and placebo-control group paralleled that of the placebo-treated eyes (Figures 2 and 3). The differences in myopia progression and axial elongation between the 2 groups were -0.92 D (95% confidence interval, -1.10 to -0.77 D; $P < 0.001$) and 0.40 mm (95% confidence interval, 0.35-0.45 mm; $P < 0.001$),
5 respectively. No serious adverse events related to atropine were reported. In this study, glare and photophobia were minimized with the use of photochromatic lenses. 54 subjects withdrew from the study. Reasons for withdrawal were: allergic or hypersensitivity reactions or discomfort (4.5%), glare (1.5%), blurred near vision (1%), logistical difficulties (3.5%), and others (0.5%).

10 **Conclusions:** Topical 1% atropine was effective in slowing the progression of low and moderate myopia and ocular axial elongation in Asian children.

Example 2: Second atropine in the treatment of myopia study (ATOM2)

In ATOM2, the effect of lower doses of atropine in preventing myopia progression and the visual side effects (pupil dilation, loss of accommodation and near-vision blur) were
15 assessed.

(i) Summary of ATOM 2

Purpose: To compare efficacy and visual side-effects of 3 lower doses of atropine: 0.5%, 0.1% and 0.01%.

Design: Single-center, double-masked, randomized study. The design of ATOM2 is
20 illustrated in Figure 4.

Subjects: 400 children aged 6-12 years with myopia of at least -2.0 D and astigmatism of -1.50 D or less.

Intervention: Subjects (the children) were randomly assigned in a 2:2:1 ratio to 0.5%, 0.1% and 0.01% atropine, to be administered once nightly to both eyes for 2 years.
25 Cycloplegic refraction, axial length, accommodation amplitude, pupil diameter and visual acuity were noted at baseline, 2 weeks and then every 4 months for 2 years.

Main outcome measure: Myopia progression at 2 years. Changes were noted and differences between groups were compared using the Huber-White robust standard error to allow for data clustering of two eyes per subject.

Results: The mean myopia progression at 2 years was -0.30 ± 0.60 D, -0.38 ± 0.60 D and -0.49 ± 0.63 D in the 0.5%, 0.1% and 0.01% atropine groups respectively ($p=0.02$ between 0.01 and 0.5% groups; other $p>0.05$). In comparison, myopia progression in ATOM1 was -1.20 ± 0.69 D in the placebo group and -0.28 ± 0.92 in the 1% atropine group. The mean increase in axial length was 0.27 ± 0.25 mm, 0.28 ± 0.28 mm and 0.41 ± 0.32 mm in the 0.5%, 0.1% and 0.01% groups ($p<0.01$ between the 0.01% and 0.1% groups and between the 0.01% and 0.5% groups). Differences in myopia progression (0.19 D) and axial length change (0.14 mm) between groups, however, were small and may be considered clinically insignificant. 0.01% atropine had negligible effect on accommodation and pupil size and no effect on near visual acuity. Allergic conjunctivitis and dermatitis were the most common adverse effect noted; with 16 cases in 0.1% and 0.5% atropine groups, none in the 0.01% group.

Conclusion: 0.01% atropine has negligible side-effects compared to atropine at 0.1% and 0.5% and retains comparable efficacy in controlling myopia progression.

(ii) ATOM2 in detail

Methods

Children aged between 6-12 years with myopic refraction of at least 2.0 D in both eyes, astigmatism of less than 1.5 D and a documented myopic progression of at least 0.5 D in the past year were enrolled in a double-masked single-centre clinical trial. Excluded were those with ocular pathology (eg. amblyopia, strabismus), previous use of atropine or pirenzepine, an allergy to atropine, or systemic ill health (eg. cardiac or respiratory illness). Written informed consent was obtained from parents or guardians and verbal assent was obtained from children. The study was conducted according to the tenets of the Declaration of Helsinki, with ethics approval from the Singapore Eye Research Institute Review Board.

Subjects (the children) were randomized to receive 0.5%, 0.1% or 0.01% atropine once nightly in both eyes at an allocation ratio of 2:2:1 in six strata defined by gender and age-groups of 6-7, 8-10 and 11-12 years to ensure gender and age balance across the three treatment arms. Trial medications were pre-packaged so that bottles were pre-labelled with subject number and of similar appearance. Trial medication consisted of
5 the appropriate dose of atropine sulfate with 0.02% of 50% benzalkonium chloride as preservative (Ashwood Laboratories Ltd, Macau).

After assessment at the time of enrolment (baseline), the subjects were re-assessed 2 weeks after starting atropine (baseline 2), and then at 4, 8, 12, 16, 20 and 24 months.
10 At each visit, best-corrected distance logMar visual acuity (BCVA) was assessed by an optometrist using the Early Treatment Diabetic Retinopathy study chart. Near visual acuity was assessed using best-corrected distance spectacle correction with a reduced LogMar reading chart placed at 40cm under well-lit conditions. The near point of accommodation (NPA) was measured using a RAF rule using best-corrected distance
15 spectacle correction. Subjects were instructed to move the target inwards till the N5 print became slightly blurred, and then outwards till it just became clear. Accommodation amplitude was calculated as the inverse of NPA. Mesopic pupil size was measured with the Procyon 3000 pupillometer (Lion House, Red Lion Street, London, UK), using the Meso-Hi (4 lux) setting. Photopic pupil size was measured
20 using the Neuroptics pupillometer (Neuroptics Inc, Irvine, CA, USA) while the subjects were viewing a target placed at 3m, after at least 10second of exposure to lamps providing 300 lux of luminance. In both cases, at least 5 pupil size readings (with range <0.5 mm) were recorded and averaged.

Cycloplegic autorefraction was determined 30 minutes after 3 drops of cyclopentolate
25 1% (Cyclogyl, Alcon-Convreur) were administered at 5 minutes apart using a Canon RK-F1autorefractor (Canon Inc. Ltd, Tochigiken, Japan). Five readings, all of which had to be less than 0.25 D apart, were obtained and averaged. Spherical equivalent was calculated as sphere plus half cylinder power. The Zeiss IOL Master (Carl Zeiss Meditec Inc, CA, USA), a non-contact partial coherence interferometry, was used to
30 measure the ocular axial length. Five readings, with a maximum-minimum deviation of 0.05 mm or less, were taken and averaged.

Parents or guardians, subjects (the children) and study investigators were kept masked to the assigned dosage of trial medications. Each subject (child) kept a diary of usage of the trial medication. Compliance level of each subject was classified according to mean number of frequency of using atropine per week as reported by subjects over the
5 first 24 months. Subjects with 75% compliance rate (≥ 5.25 days/week) were considered compliant.

The primary end-point was myopia progression over 2 years. Since a hyperopic shift may occur after commencing atropine, myopic progression was calculated from the second baseline, when the subjects had been on trial medication for 2 weeks. Level of
10 myopia progression in each eye was further categorized as being mild (<0.5 D), moderate (0.5 to 0.99 D) or severe (>1.0 D).

Secondary end-points included myopia progression at one year, change in axial length at one and two years, and side-effect parameters such as changes in accommodation amplitude, mesopic and photopic pupil size and best-corrected distance and near
15 visual acuity. Myopia and axial changes were noted from second baseline, while accommodation, pupil size and visual acuity were monitored from first baseline. Any adverse events, regardless of whether they appeared relevant to atropine use, were documented.

Statistical analysis

20 All analyses were based on intention to treat principle and performed in statistical software Stata (version 10.1, Stata Corp., College Station, TX). For demographic and other person-level data such as compliance and ever experiencing adverse events, Fisher's exact test was used to test for difference in proportion of subjects between treatment groups and ANOVA for difference in means between treatment groups.
25 Endpoints from both eyes were pooled in a combined analysis using the Huber-White robust standard errors to allow for the correlation between eyes within person 25. Results on left and right eyes were very similar. For example, mean difference (95% CI) in 2-year myopia progression between left and right eyes were -0.01 (-0.06, 0.03). For brevity and better precision, this report shows analyses pooling both eyes with
30 robust standard errors for clustered data. The global null hypothesis of no difference

between 3 treatment groups was tested first, followed by pair-wise comparisons. Nominal level of statistical significance (p-value) was reported, i.e. no adjustment for multiple comparison. Interpretation will begin with considering the global null hypothesis between 3 groups in order to prevent inflated type I error rate. Placebo and
5 atropine treated eyes in ATOM1 were used for reference in secondary analyses.

Results

A total of 400 children were recruited into the study, with 161, 155 and 84 children in the 0.5%, 0.1% and 0.01% atropine treatment arms respectively (Figure 4). There were almost equal numbers of males and females and 91% of children were of ethnic
10 Chinese origin (Table 1). No differences were noted in demographics, baseline refractive error, accommodation, pupil diameter or best corrected visual acuity between groups (Table 1). Correlation between change in spherical equivalent and axial length over 2 years was high (correlation coefficient=0.82, $p<0.001$), and suggests good measurement validity.

Table 1: Characteristics at baseline and second baseline (ie. 2 weeks after starting trial medication)

Variables	Atropine(A) dose			p-value ^a
	A 0.01% (n 84)	A 0.1% (n 155)	A 0.5% (n 161)	
Age (yr), mean (sd)	9.5 (1.5)	9.7 (1.6)	9.7 (1.5)	0.95
Female, %	48.8	46.5	47.2	0.95
Chinese %	90.5	92.3	90.0	0.99
Spherical equivalent (D)				
- baseline	-4.5 (1.5)	-4.8 (1.5)	-4.7 (1.8)	0.40
- second baseline	-4.5 (1.5)	-4.5 (1.4)	-4.3 (1.8)	0.67
Axial length (mm)				
- baseline	25.1 (1.0)	25.2 (0.8)	25.2 (0.9)	0.94
- second baseline	25.2 (1.0)	25.1 (0.8)	25.1 (0.9)	0.93
Accommodation (D)				
- baseline	16.2 (3.4)	16.7 (3.0)	15.8 (3.4)	0.01
- second baseline	11.3 (4.3)	3.8 (2.5)	2.2 (1.2)	<0.001
Mesopic pupil diameter (mm)				
- baseline	3.9 (0.6)	3.9 (0.6)	4.0 (0.7)	0.21
- second baseline	5.2 (0.8)	7.2 (0.7)	7.8 (0.5)	<0.001
Photopic pupil diameter (mm)				
- baseline	4.7 (0.7)	4.6 (0.7)	4.6 (0.7)	0.63
- second baseline	5.8 (0.8)	7.4 (0.7)	7.9 (0.6)	<0.001
BCVA distant (logMar)				
- baseline	0.01 (0.05)	0.01 (0.06)	0.02 (0.06)	0.56
- second baseline	0.01 (0.05)	0.01 (0.05)	0.01 (0.06)	0.86
Near vision (logMar)				
- baseline	0.04 (0.09)	0.04 (0.08)	0.04 (0.07)	0.38
- second baseline	0.06 (0.08)	0.29 (0.18)	0.48 (0.16)	<0.001

a. Fisher's exact test for binary demographic variables; ANOVA for age; Huber-White robust standard error for clustered data (both eyes pooled) on ocular parameters

- 5 Two-year primary endpoint data were available for 355 of 400 (88.8%) subjects. 44 subjects withdrew participation on their own accord; 9 (10.7%), 14 (9.0%) and 21 (13.0%) from the 0.01%, 0.1% and 0.5% treatment group respectively (p=0.43); 1 subject did not turn up for the second year assessment. Compliance, defined as >75% expected usage was 98.7%, 96.8% and 98.8% in the 0.5%, 0.1% and 0.01% arms
- 10 (p=0.53) in the 2 year period.

Change in myopic progression and axial length

A clinically small, dose related response on myopic progression was noted between the 3 treatment arms (Figure 5). An initial hyperopia shift of 0.3 to 0.4 D was noted in the 0.1% and 0.5% groups but not in the 0.01% group (Table 1). At the end of 1 year, there

was a significant difference in myopia progression between the 0.5% atropine group and the 0.01% ($p < 0.001$) and 0.1% ($p = 0.01$) groups, but no statistical significant difference between 0.01% and 0.1% groups. The final myopia progression over 2 years was -0.49 ± 0.60 D, -0.38 ± 0.60 D and -0.30 ± 0.63 D in the atropine 0.01%, 0.1% and 5 0.5% groups respectively ($p = 0.07$), with significant difference only between the 0.01% and 0.5% groups (Table 2). There was no significant difference in spherical equivalent levels between groups ($p = 0.20$). Fifty percent of the 0.01% group had progressed by less than 0.5 D, compared to 58% and 63% in the 0.1 and 0.5% group respectively, with approximately 18% progressing by > 1.0 D in all 3 groups (Figure 6).

Table 2: Ophthalmology parameters at 2nd annual visit

	Atropine (A) dose (mean (SD))			p-value
	A 0.01%	A 0.1%	A 0.5%	
Spherical equivalent (D)				
- at 1 year	-4.9 (1.5)	-4.8 (1.4)	-4.6 (1.9)	0.26
at 2 years	-5.1 (1.5)	-4.9 (1.3)	-4.7 (1.7)	0.20
- mean change over 1 year	-0.43 (0.52)	-0.31 (0.50)	-0.17 (0.47)	<0.001 ^{A,C}
mean change over 2 years	-0.49 (0.63)	-0.38 (0.60)	-0.30 (0.60)	0.07 ^A
Axial length (mm)				
- at 1 year	25.4 (1.0)	25.3 (0.8)	25.3 (0.9)	0.36
at 2 years	25.7 (1.0)	25.4 (0.8)	25.4 (1.0)	0.08 ^B
- mean change over 1 year	0.24 (0.19)	0.13 (0.18)	0.11 (0.17)	<0.001 ^{A,B}
mean change over 2 years	0.41 (0.32)	0.28 (0.27)	0.27 (0.25)	0.002 ^{A,B}
Accommodation (D)				
- at 1 year	11.7 (4.3)	6.0 (3.4)	3.6 (3.2)	<0.001 ^{A,B,C}
at 2 years	11.8 (3.2)	6.8 (3.4)	4.0 (2.6)	<0.001 ^{A,B,C}
- mean change over 1 year	-4.4 (4.9)	-10.9 (4.0)	-12.4 (3.3)	<0.001 ^{A,B,C}
mean change over 2 years	-4.6 (4.2)	-10.1 (4.3)	-11.8 (4.4)	<0.001 ^{A,B,C}
Mesopic pupil size (mm)				
- at 1 year	5.1 (0.9)	6.7 (1.0)	7.5 (1.1)	<0.001 ^{A,B,C}
at 2 years	5.1 (0.9)	6.7 (1.1)	7.5 (1.2)	<0.001 ^{A,B,C}
- mean change over 1 year	1.15 (0.78)	2.77 (1.03)	3.50 (1.05)	<0.001 ^{A,B,C}
mean change over 2 years	1.15 (0.71)	2.71 (1.12)	3.56 (1.14)	<0.001 ^{A,B,C}
Photopic pupil size (mm)				
- at 1 year	5.6 (0.8)	7.0 (1.0)	7.7 (1.0)	<0.001 ^{A,B,C}
at 2 years	5.5 (0.8)	6.9 (1.0)	7.8 (1.1)	<0.001 ^{A,B,C}
- mean change over 1 year	0.91 (0.78)	2.42 (0.91)	3.11 (1.08)	<0.001 ^{A,B,C}
mean change over 2 years	0.74 (0.75)	2.25 (1.01)	3.11 (1.10)	<0.001 ^{A,B,C}
BCVA distant (logMar)				
- at 1 year	-0.005 (0.042)	-0.003 (0.054)	-0.003 (0.054)	0.99
at 2 years	-0.001 (0.057)	0.005 (0.054)	0.011 (0.057)	0.25
- mean change over 1 year	-0.02 (0.05)	-0.02 (0.06)	-0.03 (0.05)	0.21
mean change over 2 years	-0.02 (0.06)	0.01 (0.06)	-0.01 (0.06)	0.44
Near vision (logMar)				
- at 1 year	0.03 (-0.06)	0.15 (0.15)	0.35 (0.18)	<0.001 ^{A,B,C}
at 2 years	0.01 (0.07)	0.10 (0.13)	0.29 (0.18)	<0.001 ^{A,B,C}
- mean change over 1 year	-0.01 (0.10)	0.10 (0.16)	0.32 (0.19)	<0.001 ^{A,B,C}
mean change over 2 years	-0.02 (0.08)	0.06 (0.13)	0.25 (0.19)	<0.001 ^{A,B,C}

BCVA: best-corrected visual acuity

Myopia progression and axial length: change from second baseline; other parameters: change from initial baseline

- 5 P-values for test of global null hypotheses of all groups being the same are shown. Pairwise comparison P-values are represented by A: significant ($P < 0.05$) difference between 0.01% and 0.5% atropine, B: significant difference between 0.01% and 0.1% atropine, and C: significant difference between 0.1% and 0.5% atropine.

With respect to axial length, change at 1 year was larger in the 0.01% group (0.24 ± 0.19 mm) than in the 0.1% (0.13 ± 0.18 mm) and 0.5% (0.11 ± 0.17 mm) groups ($p < 0.001$) (Figure 7). Pair-wise comparison showed statistically significant difference

between 0.01% and the other two groups ($p < 0.001$). This difference persisted till the end of the 24 month period (Table 2).

Changes in accommodation, pupil diameter and visual acuity

There was no difference in accommodation, mesopic and photopic pupil diameter between groups at baseline (Table 1). However, significant dose-related differences quickly became evident by second baseline visit (Table 1). Changes within the 0.01% group were significantly less than in the 2 other groups. Accommodation amplitude in the 0.01% group was only reduced to 11.3 D compared to 3.8 D and 2.2 D in the 0.1% and 0.5% groups (Table 1). In functional terms, this meant that near visual acuity was not significantly impaired in the 0.01% group, while deficiencies were noted in the 2 other groups. Mean best-corrected distant visual acuity was not affected by atropine use (Table 2), although 10% of subjects did encounter mild distance blur (Table 3).

Table 3. Adverse event and serious adverse events

	Atropine (A) dose			Exact test p-value ^a
	A 0.01% (n=84)	A 0.1% (n=155)	A 0.5% (n=161)	
	Number of episode /number of children (% children)			
Adverse Events				
Allergic conjunctivitis	0/0 (0)	7/6 (4)	7/7 (4)	0.16
Dermatitis involving eyelids	0/0 (0)	2/1 (1)	4/3 (2)	0.54
Stye/chalazion	2/2 (2)	16/12 (8)	16/12 (7)	0.22
Loss of distant BCVA > 1 line	11/11 (13)	20/20 (13)	13/13 (8)	0.38
Others, eye-related	2/1 (1)	2/2 (2)	3/3 (2)	1.00
Others, non eye-related	306/69 (82)	470/122 (78)	477/132 (82)	0.73
Severe Adverse Events				
Events requiring hospitalisation	1/1 (1)	3/3 (2)	3/3 (2)	1.00

a. Fisher's exact test for proportion of children with adverse events

Pupil size, under both photopic and mesopic conditions, in the 0.01% group increased by only 1 mm, while pupils in the 0.1% and 0.5% groups were about 3 mm larger (Table 2). While the atropine effect on pupil diameter remained unchanged over time,

the accommodation appeared to improve in the 0.1% and 0.5% groups over time (Table 2). The mean accommodation amplitude in the 0.5% group, for example, fell from 15.8 D at baseline to 2.2 D at the second baseline visit but rose to 3.6 D and 4.1 D by the end of the first and second years. Changes in 0.01% group were less, varying
5 from 16.2 D to 11.3 D, 11.7 D and 11.8 D over the same time-period.

Changes in spherical equivalent (myopia) and axial length after stopping atropine for 1 year (between 24 and 36 months)

356 children (89%) entered into the wash-out phase of the ATOM2 study. On cessation of atropine, there was a rebound increase in myopia was noted in all 3 groups which
10 was greater in 0.5% atropine eyes (-0.87 ± 0.52 D) than in 0.1% atropine (-0.68 ± 0.45 D) and 0.01% atropine (-0.28 ± 0.33 D) eyes ($p < 0.001$). This resulted in overall progression over the 36 month period being significantly less in the 0.01% atropine eyes (-0.72 ± 0.72 D) than in the 0.1% atropine (-1.04 ± 0.83 D) and 0.5% atropine eyes (-1.15 ± 0.81 D) (Figure 8).

15 During the same period, there was a significantly greater increase in axial length in the 0.1% atropine and 0.5% atropine eyes compared to the 0.01% atropine eyes (Figure 9). Overall change in axial length, however, was not significantly different between groups.

Adverse events

20 Majority of the adverse events were deemed to be unrelated to study treatment (eg. flu-like illness) (Table 3). Adverse reactions directly attributable to atropine included allergic conjunctivitis, which occurred in 13 subjects (4.1%) in 0.1% atropine and 0.5% atropine groups. In 3 (1.2%) subjects, symptoms were severe enough to warrant ceasing trial medication. Four subjects in the 0.1% and 0.5% groups (1.3%) had allergy
25 related dermatitis of the eyelids. Six subjects had other eye symptoms, 5 of which could be attributed to atropine including 1 case of irritation and another of blur in the 0.01% atropine group, and 2 cases of ocular irritation and 1 with intolerable glare in the 0.5% atropine group.

- Seven subjects had a severe adverse event requiring hospitalization. In the 0.01% group, one subject had acute gastric pain. In the 0.1% atropine group, there was 1 case each of appendicitis, respiratory infection and Ewing's sarcoma. In the 0.5% atropine group, there was 1 case each of tachycardia, dengue fever and gastroenteritis.
- 5 None of these events are thought to be associated with atropine.

Discussion

- At the end of 2 years, the mean myopia and axial length progression in the ATOM1 study was -0.28 ± 0.92 D and -0.02 ± 0.35 mm in the 1% atropine eyes compared to -1.20 ± 0.69 D and 0.38 ± 0.38 mm in the placebo eyes. The progression of myopia in
- 10 the ATOM2 subjects lie in a dose-related manner between these two extremes (Figure 5).

- In ATOM2, the progression of myopia in subjects on 0.5% atropine was -0.17 ± 0.47 D over 1 year, and -0.30 ± 0.60 D over 2 years. This was similar to the progression noted in subjects on 1% atropine in the ATOM1 study (Figure 5).
- 15 Changes in myopia and axial lengths outcome in the 0.1% atropine group were very similar to the 0.5% atropine group. The myopia progression was initially larger in the 0.1% atropine at 1 year (-0.31 D vs -0.17 D, $p=0.01$) but this gap had closed by the second year (-0.38 D vs -0.30 D, $p=0.25$). In terms of effect on other ocular parameters, accommodation (-10.9 D vs -12.4 D), mesopic pupil diameter (2.7mm vs
- 20 3.5mm) and photopic pupil diameter (2.2 D vs 3.1 D) were also less in the 0.1% atropine compared to the 0.5% atropine group, making the overall efficacy-side-effect profile of 0.1% atropine better than 0.5% atropine.

- The changes in spherical equivalent and axial lengths upon stopping atropine is interesting. There was a rebound increase in myopia and axial length which was
- 25 greater in higher dose atropine. The change in the 0.01% group, however, was more gradual with overall change in spherical equivalent being less in the 0.01% group compared to all other groups.

The subjects from ATOM1 were slightly younger (mean age: 9.2 versus 9.6 years), had lower spherical equivalents (mean spherical equivalent -3.4 versus -4.7 D) and smaller

axial lengths (mean axial length 24.8 versus 25.2 mm) than those in the ATOM2 group. Nevertheless, the reduction in myopia progression with atropine eyedrops observed in both studies with otherwise similar study profiles and methodologies was consistent and should be regarded as definitive outcomes in these studies. Axial lengths were
5 measured differently between the two studies with A-scan ultrasonography used in ATOM1 (Chua *et al.*, 2006) and IOLmaster in ATOM2. Thus, the axial lengths of ATOM1 and ATOM2 have not been compared in Figure 7.

In designing ATOM2, 0.01% atropine was initially assumed to have minimal effect, and thus act as a potential control; hence the lower allocation of subjects to this group.
10 However, contrary to expectations, 0.01% atropine also had significant clinical efficacy on reducing myopia progression not dissimilar to the higher concentrations, but unlike the other concentrations, had negligible effect on accommodation and pupil size. The myopia progression rate in this group ($-0.49 \text{ D} \pm 0.63 \text{ D}$ at 2 years) was much less than the $-1.20 \pm 0.69 \text{ D}$ at 2 years in the ATOM1 placebo groups. Compared with the 2
15 higher doses, the difference in myopia progression at 2 years in the 0.01% group was statistically significant compared to the 0.5% group and similarly, the difference in axial length increase was statistically larger than both the 0.1% and 0.5% group. However, absolute differences between groups were clinically small with differences in myopic progression and axial length increase of only 0.19 D and 0.13 mm over 2 years (Table
20 2, Figures 5 and 7). Most importantly, the ocular side-effect profile was significantly better with accommodation remaining at 11.8 D, mean pupil size of 5 mm and a mean near logMar vision of 0.01. In other words, 0.01% atropine was still clinically effective in reducing myopia progression, but did not cause side-effects normally associated with higher concentrations of atropine.

25 Overall, atropine-related adverse effects were uncommon at the 0.01% dose. Allergic reactions were most frequent; with 3.2% experiencing allergic conjunctivitis and 0.8% experiencing an allergy-associated dermatitis, all of which were in the 0.1% or 0.5% groups. It should be noted that the benzalkonium preservative in the 0.01% atropine eyedrop formulation may be at least partly responsible for these allergies. A number of
30 subjects (11%) also noted at least 1 line loss in distance best-corrected vision (Table 3). These effects are reversible on stopping medication (Tong *et al.*, 2009). There are
~~no long-term studies on the effect of atropine on the eye and continued vigilance is~~

necessary, but so far there are no known long-term adverse effects associated with its use (North and Kelly, 1987).

The strength of ATOM2 was its randomised double-blind design and low drop out rate. Instead of a placebo group, the comparison was based on external (historical and
5 population) controls. The non-inclusion of a placebo group was a decision based on findings from the ATOM1 study, which clearly showed the efficacy of atropine treatment compared to placebo, rendering a placebo arm unethical. The more important aspect of this trial remained the comparison of low dose versus high dose not only in terms of efficacy, but also in terms of the visual side effects of atropine. ATOM2 was otherwise
10 designed to have largely similar study parameters so that direct comparison with ATOM1 was deemed appropriate.

In conclusion, the results of ATOM2 suggest that 0.5%, 0.1% and 0.01% atropine remain effective in reducing myopia progression, as compared to placebo treatment, and that the clinical differences in myopia progression between these 3 groups are
15 small. In terms of side-effects, 0.5% and 0.1% atropine formulations were still noted to cause visual side-effects of accommodation loss and pupil dilation, but the 0.01% atropine formulation had no or negligible effect on accommodation or pupil dilation. The lowest concentration of 0.01% atropine appears to retain efficacy and is thus a viable concentration for reducing myopia progression in children, whilst attaining a
20 clinically significant improved safety profile in terms of accommodation, pupil size and near visual acuity, and subsequently much reduced adverse impact on visual function. Moreover, the 0.01% formulation exhibited fewer adverse events, and exhibited much less myopic rebound after it was stopped. These findings collectively suggest that 0.01% atropine nightly appears to be a safe and effective regime for slowing myopia
25 progression in children, with minimal impact on visual function in children.

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Claims

1. A composition for reducing and/or preventing myopia progression comprising less than 0.025% atropine.
2. The composition according to claim 1; comprising 0.001% to 0.0249% atropine.
- 5 3. The composition according to any one of the preceding claims; comprising 0.005% to 0.02% atropine.
4. The composition according to any one of the preceding claims, comprising 0.005% to 0.015 % atropine.
- 10 5. The composition according to claim 1, wherein the composition comprises 0.001%, 0.002%, 0.003%, 0.004%, 0.005%, 0.006%, 0.007%, 0.008%, 0.009%, 0.01%, 0.011%, 0.012%, 0.013%, 0.014%, 0.015%, 0.016%, 0.017%, 0.018%, 0.019%, 0.02%, 0.021%, 0.022%, 0.023%, 0.024%, 0.0245% or 0.0249% atropine.
- 15 6. The composition according to any one of the preceding claims, wherein the composition comprises about 0.01% atropine.
7. The composition according to any one of the preceding claims, wherein the composition comprises 0.01% atropine.
8. The composition according to any one of the preceding claims, further comprising at least one pharmaceutically acceptable excipient.
- 20 9. The composition according to any one of the preceding claims, wherein the composition is for administration to the eye.
10. The composition according to any one of the preceding claims, wherein the composition is an eye-drop composition.
- 25 11. The composition according to any one of claims 1 to 10, for use in reducing and/or preventing myopia progression and/or treating myopia.

12. A method for reducing and/or preventing myopia progression comprising administering to a subject a composition according to any one of claims 1 to 10.
13. Use of atropine in the preparation of a composition for reducing and/or preventing myopia progression, wherein the composition comprises less than
5 0.5% atropine.
14. Use according to claim 13, wherein the composition comprises 0.001% to 0.0249% atropine.
15. Use according to claim 13 or 14, wherein the composition comprises 0.005 to 0.02% atropine.
- 10 16. Use according to any one of claims 13 to 15, wherein the composition comprises 0.005 to 0.015% atropine.
17. Use according to any one of claims 13 to 16, wherein the composition comprises 0.008 to 0.012% atropine.
18. Use according to claim 13, wherein the composition comprises 0.001%,
15 0.002%, 0.003%, 0.004%, 0.005%, 0.006%, 0.007%, 0.008%, 0.009%, 0.01%, 0.011%, 0.012%, 0.013%, 0.014%, 0.015%, 0.016%, 0.017%, 0.018%, 0.019%, 0.02%, 0.021%, 0.022%, 0.023%, 0.024%, 0.0245% or 0.0249% atropine.
19. Use according to any one of claims 13 to 18, wherein the composition comprises about 0.01% atropine.
- 20 20. Use according to any one of claims 13 to 19, wherein the composition comprises 0.01% atropine.
21. Use according to any one of claims 10 to 15, wherein the composition further comprises at least one pharmaceutically acceptable excipient.
22. Use according to any one of claims 10 to 16, wherein the composition is for
25 administration to the eye.

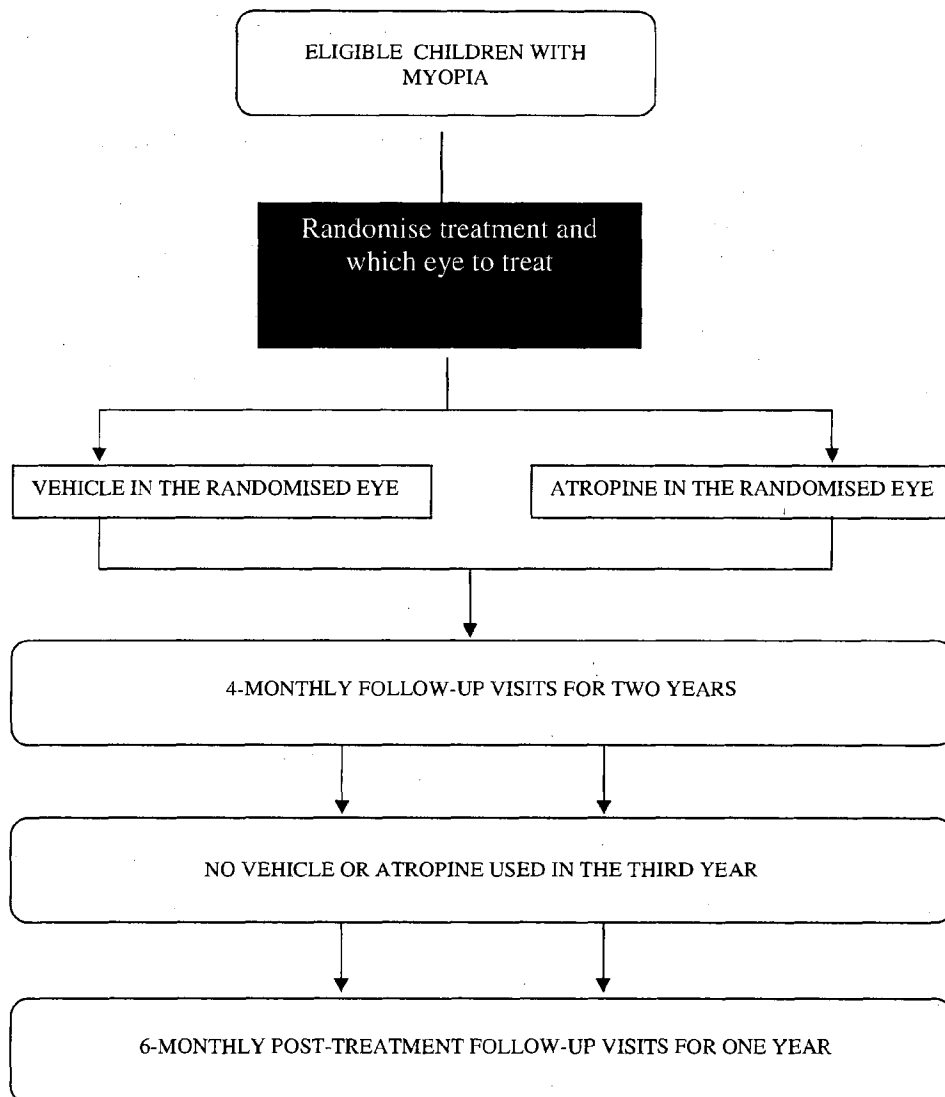


Figure 1

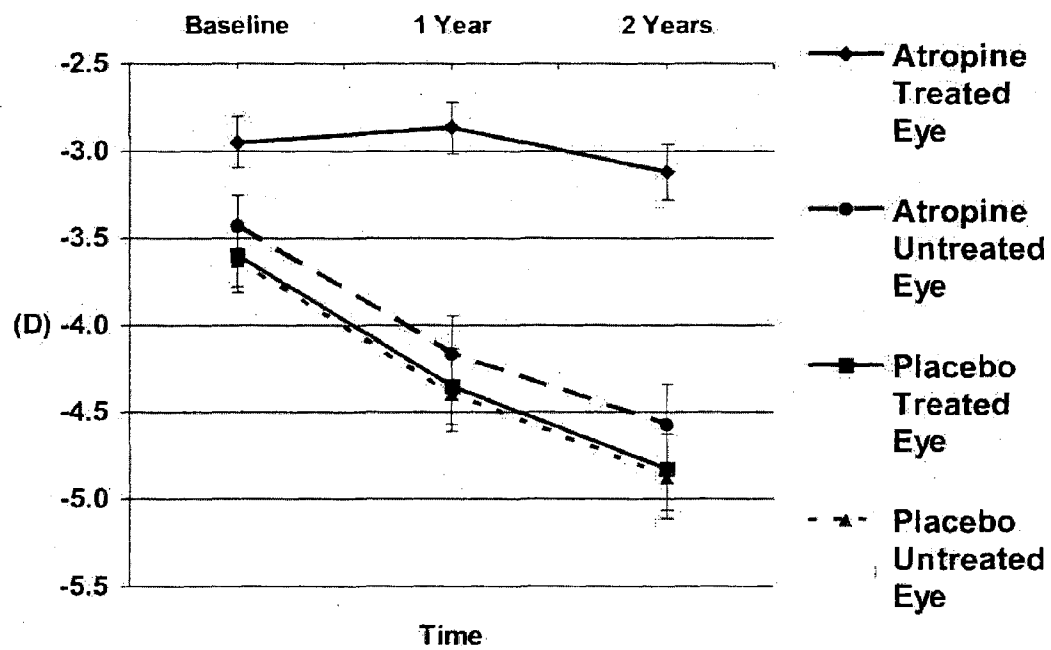


Figure 2

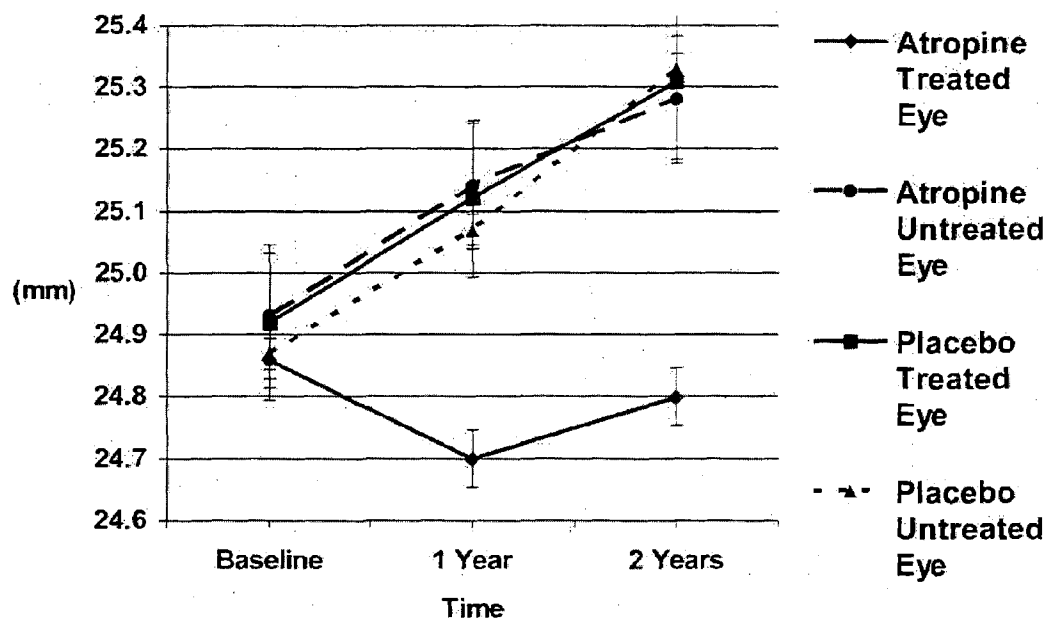


Figure 3

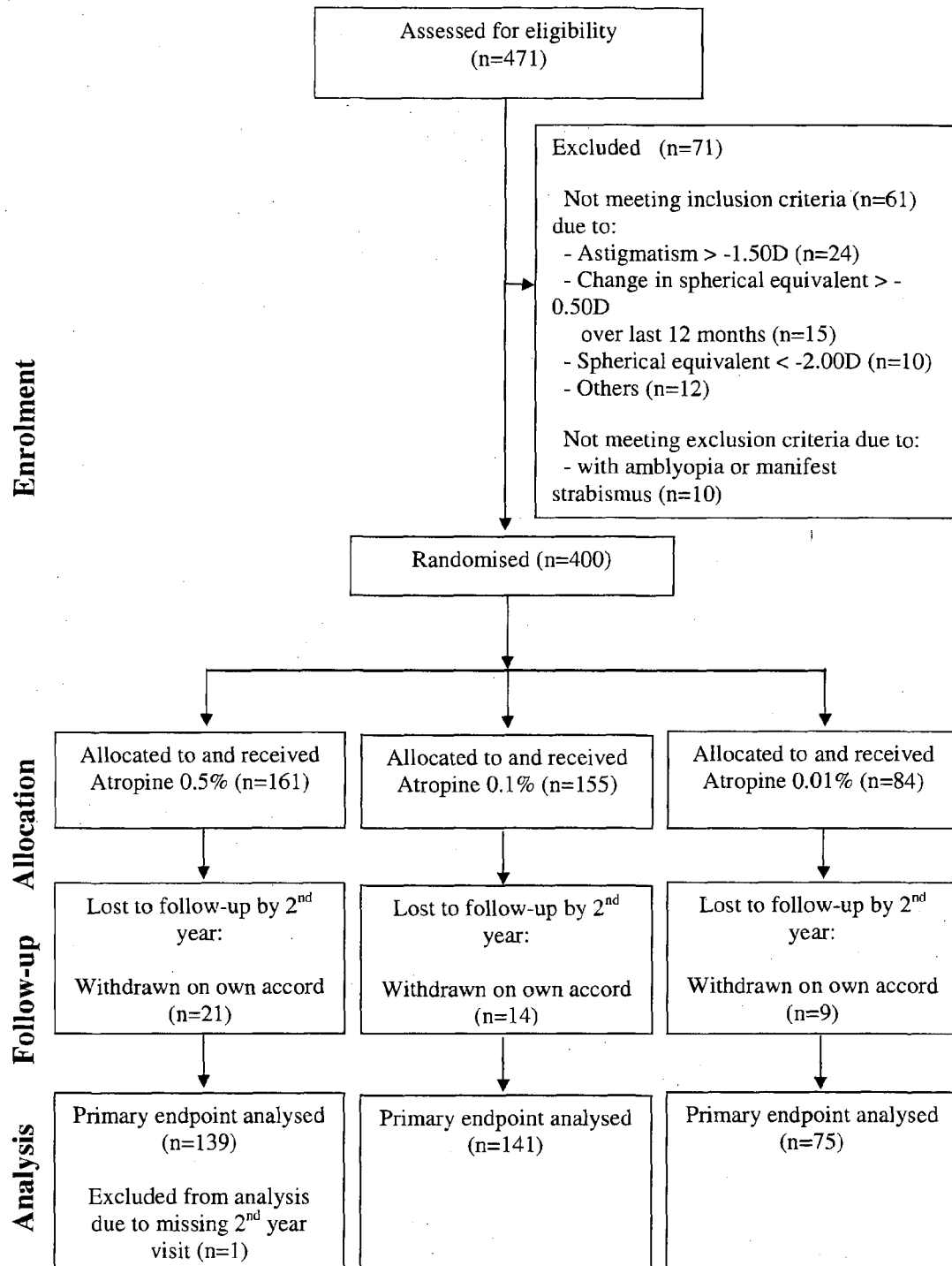


Figure 4

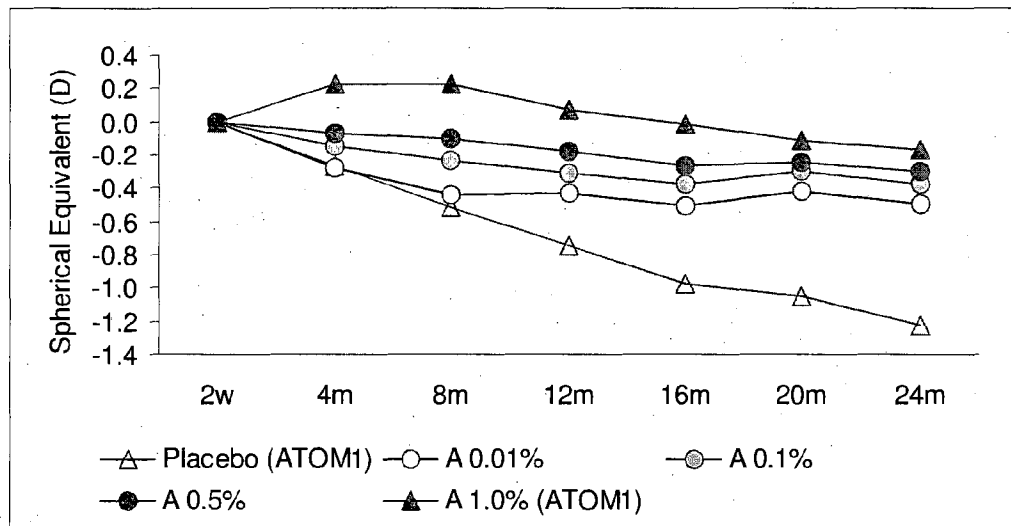


Figure 5

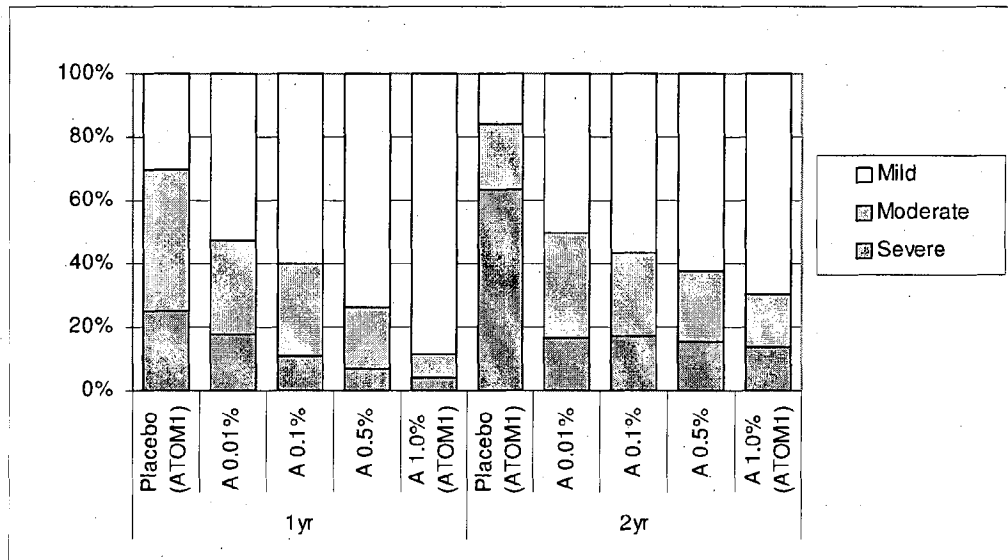


Figure 6

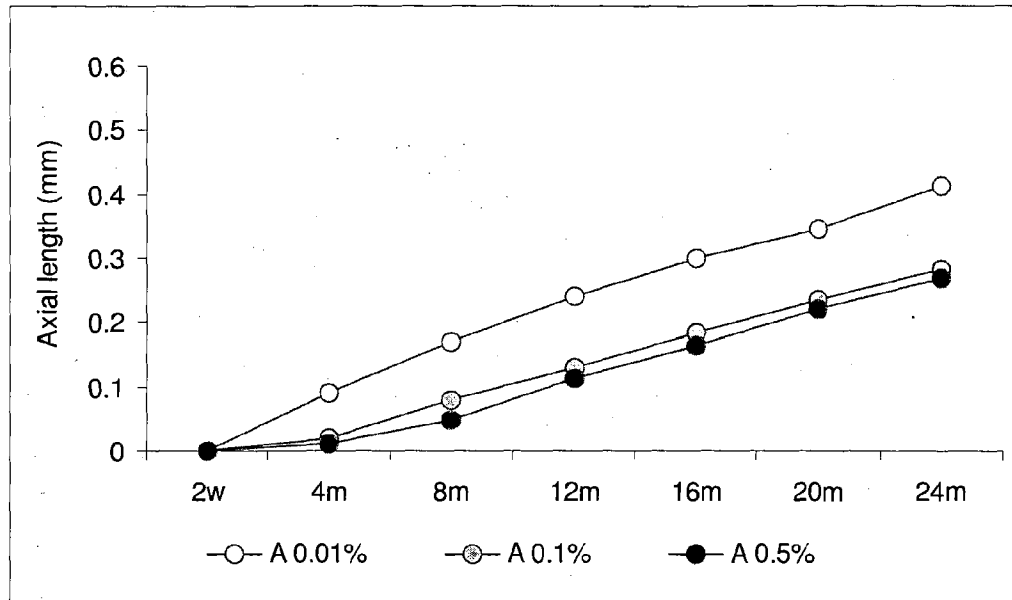


Figure 7

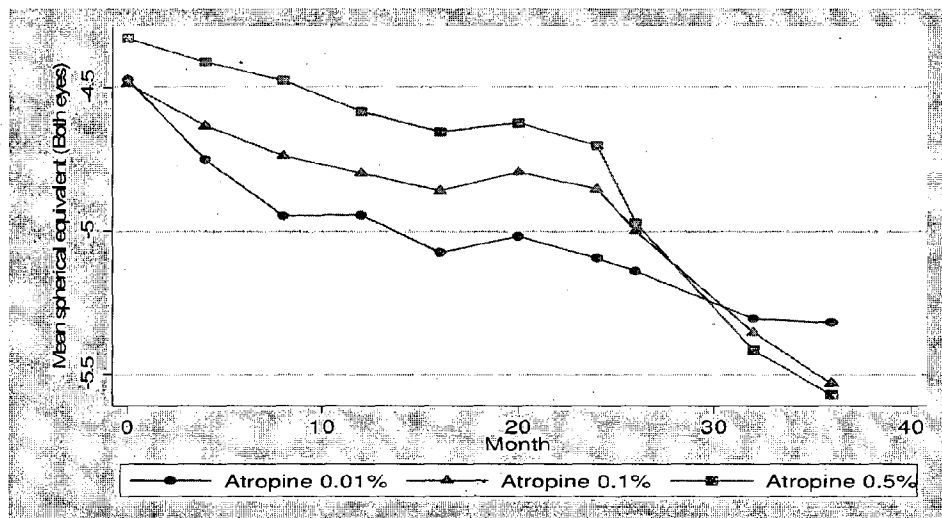


Figure 8

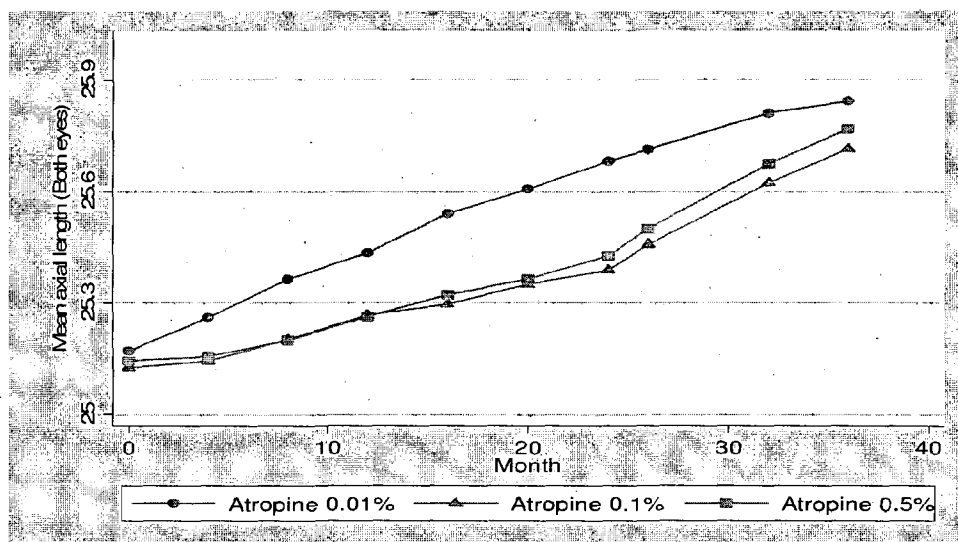


Figure 9

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SG2012/000174

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/46 (OCT 2005) A61P 27/10 (OCT 2005)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Medline, WPI, EPODOC: atropine, atropen, hyoscyamine, cytopaz, anaspaz, myopia, short sightedness, near sightedness; Clinical trials.gov website: myopia, atropine

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

☒ Further documents are listed in the continuation of Box C☒ See patent family annex

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search
09 July 2012Date of mailing of the international search report
12 July 2012

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INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		PCT/SG2012/000174
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	'Safety and Efficacy Study of 0.5%, 0.1% & 0.01% Atropine Treatment to Both Eyes in Treatment of Myopia in Children.' [retrieved 28 June 2012] Retrieved from the internet, URL: http://clinicaltrials.gov/ct2/show/NCT00371124?term=ATROPINE&rank=18 > published 30 August 2010. whole document	1-22
X	US 2007/0254914 A1 (WU, P-C. et al.) 01 November 2007 paragraphs 0015, 0017	1-22
X	SHIH. Y-F. et al. 'Effects of Different Concentrations of Atropine on Controlling Myopia in Myopic Children.' Journal of Ocular Pharmacology and Therapeutics. 1999. 15(1):85-90 page 86, 2nd paragraph	13, 21-22
X	FANG, P-C. et al. 'Prevention of Myopia Onset with 0.025% Atropine in Premyopic Children'. 'Journal of Ocular Pharmacology and Therapeutics. 2010 Aug; 26(4):341-5. page 342	13, 21-22
P,X	CHIA. A. et al. 'Atropine for the Treatment of Childhood Myopia: Safety and Efficacy of 0.5%, 0.1%, and 0.01% Doses (Atropine for the Treatment of Myopia 2).' Ophthalmology. Feb 2012. 119(2):347-54. whole document	1-22

INTERNATIONAL SEARCH REPORT Information on patent family members		International application No. PCT/SG2012/000174	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
US 2007/0254914 A1	01 Nov 2007	US 2007254914 A1	01 Nov 2007
End of Annex			
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001. Form PCT/ISA/210 (Family Annex)(July 2009)			



(51) International Patent Classification:

A61K 31/46 (2006.01) *A61K 47/12* (2006.01)
A61K 9/08 (2006.01) *A61K 47/18* (2006.01)
A61K 47/02 (2006.01) *A61K 47/26* (2006.01)
A61K 47/10 (2006.01) *A61K 47/38* (2006.01)

(21) International Application Number:

PCT/JP2017/019423

(22) International Filing Date:

24 May 2017 (24.05.2017)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

10201604200P 25 May 2016 (25.05.2016) SG

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(81) **Designated States** (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR,

KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) **Title:** ATROPINE-CONTAINING AQUEOUS COMPOSITION

(57) **Abstract:** Disclosed herein is an aqueous composition comprising 0.001 - 0.1 % (w/v) atropine or a salt thereof, a water-soluble polymer, and buffer (I), which is at a pH range of 6 or lower, wherein the buffer (I) is at least one selected from the group consisting of a phosphate buffer, an aminocarboxylate buffer, a carbonate buffer, an acetate buffer, a tartrate buffer, a borate buffer, and trometamol.

Description

Title of Invention: ATROPINE-CONTAINING AQUEOUS COMPOSITION

Technical Field

[0001] The present invention mainly relates to an aqueous composition that comprises atropine or a salt thereof (hereinafter also referred to simply as "atropine").

Background Art

[0002] Myopia, a type of refractive error, is a condition of eyes where light coming into an eye from a distance is not focused on retina, but focused before retina, which causes the image of an object to appear blurred. It is known that myopia is caused by an ocular axial length (length from the cornea to the retina) that is longer than normal (axial myopia) or by excessively high refractive powers of the cornea or the crystalline lens (refractive myopia).

[0003] Atropine is known to have the property of preventing the elongation of an ocular axial length. For example, Patent Literature 1 discloses that a composition comprising less than 0.025% atropine inhibits or prevents myopia progression.

[0004] On the other hand, an atropine ophthalmic solution is used as a mydriatic, and also reduces accommodation. An atropine ophthalmic solution, when instilled into the eye, relaxes the pupillary sphincter muscle of the iris and thus induces mydriasis that causes glare, which persists for a period during which the action of the atropine ophthalmic solution is maintained, and also reduces accommodation of the crystalline lens to result in poor near-acuity. This can be a hindrance in performing daily activities. It would therefore be highly desirable that a medication for inhibiting or preventing myopia progression, should induce a lesser degree of mydriasis and a lesser loss of accommodation so as to enhance the quality of life (QOL).

Citation List

Patent Literature

[0005] [PTL 1] WO 2012/161655

Summary of Invention

Technical Problem

[0006] A purpose of the present invention is to find an aqueous composition comprising atropine which has a potent action for inhibiting the elongation of eye axial length and improving the refractive error. The important goal is to find an atropine-containing aqueous composition that induces a lesser degree of mydriasis and also a lesser loss of accommodation. And, another purpose of the present invention is to find an aqueous

composition comprising atropine whose viscosity does not decrease with time and wherein atropine or a salt thereof is stable.

Solution to Problem

[0007] The present inventors have intensively studied to solve the aforementioned problem and consequently have found that an aqueous composition comprising 0.001 - 0.1 % (w/v) atropine or a salt thereof, a water-soluble polymer, and buffer (I), which is at a pH range of 6 or lower, wherein the buffer (I) is at least one selected from the group consisting of a phosphate buffer, an aminocarboxylate buffer, a carbonate buffer, an acetate buffer, a tartrate buffer, a borate buffer, and trometamol, surprisingly has a potent action for inhibiting the elongation of eye axial length and improving the refractive error without exacerbating the mydriatic action of atropine. Additionally, the present inventors have also found that the above aqueous composition, but which comprises no benzalkonium chloride or a limited amount of benzalkonium chloride, has a lower mydriatic action. Furthermore, the present inventors have also found that, in an aqueous composition comprising atropine or a salt thereof and a water-soluble polymer which is at a pH range of 6 or lower, the addition of a nonionic tonicity agent can make it possible to inhibit the debasement over time of the viscosity given by the water-soluble polymer and additionally maintain the stability of atropine or a salt thereof. The aqueous composition of the present invention is expected to inhibit or prevent the progression of myopia and lead to a lesser degree of mydriasis, and lesser loss of accommodation so as to be optimal in terms of quality of life.

[0008] That is, the present invention relates to the following.

[0009] (Term 1)

An aqueous composition comprising 0.001 - 0.1 % (w/v) atropine or a salt thereof, a water-soluble polymer, and buffer (I), which is at a pH range of 6 or lower, wherein the buffer (I) is at least one selected from the group consisting of a phosphate buffer, an aminocarboxylate buffer, a carbonate buffer, an acetate buffer, a tartrate buffer, a borate buffer, and trometamol.

[0010] (Term 2)

The aqueous composition of Term 1, wherein the buffer (I) is at least one selected from the group consisting of a phosphate buffer, an aminocarboxylate buffer, a carbonate buffer, and an acetate buffer.

[0011] (Term 3)

The aqueous composition of Term 1 or 2, wherein the buffer (I) is a phosphate buffer.

[0012] (Term 4)

The aqueous composition of Term 1 or 2, wherein the aminocarboxylate buffer is at

least one selected from the group consisting of epsilon-aminocaproic acid, a glutamate buffer, and an aspartate buffer.

[0013] (Term 5)

The aqueous composition according to any one of Terms 1 to 4, wherein the phosphate buffer is derived from at least one selected from the group consisting of dibasic sodium phosphate hydrate, sodium dihydrogen phosphate, sodium dihydrogen phosphate monohydrate, sodium dihydrogen phosphate dihydrate, potassium dihydrogen phosphate, sodium monohydrogen phosphate heptahydrate, trisodium phosphate, and dipotassium phosphate,

the carbonate buffer is derived from at least one selected from the group consisting of carbonic acid, sodium bicarbonate, sodium carbonate, ammonium carbonate, potassium carbonate, calcium carbonate, potassium bicarbonate, and magnesium carbonate,

the acetate buffer is derived from at least one selected from the group consisting of acetic acid, ammonium acetate, potassium acetate, calcium acetate, and sodium acetate,

the tartrate buffer is derived from at least one selected from the group consisting of sodium tartrate and potassium tartrate,

the borate buffer is derived from at least one selected from the group consisting of boric acid, sodium borate, potassium borate, potassium tetraborate, potassium metaborate, ammonium borate, and borax,

the glutamate buffer is derived from at least one selected from the group consisting of glutamic acid, sodium glutamate and potassium glutamate, and/or

the aspartate buffer is derived from at least one selected from the group consisting of aspartic acid, sodium aspartate and magnesium aspartate.

[0014] (Term 6)

The aqueous composition according to any one of Terms 1 to 5, further comprising a citrate buffer as buffer (II).

[0015] (Term 7)

The aqueous composition of Term 6 wherein the citrate buffer is derived from at least one selected from the group consisting of citric acid hydrate, sodium citrate, sodium citrate hydrate, potassium citrate, calcium citrate, sodium dihydrogen citrate, and disodium citrate.

[0016] (Term 8)

The aqueous composition according to any one of Terms 1 to 7, wherein the water-soluble polymer is at least one selected from the group consisting of a cellulose derivative, carboxyvinyl polymer and sodium alginate.

[0017] (Term 9)

The aqueous composition of Term 8, wherein the cellulose derivative is at least one selected from the group consisting of hydroxyethyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, ethyl cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxyethyl methyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, hypromellose acetate succinate, hypromellose phthalate, carboxymethylethyl cellulose, and cellulose acetate phthalate.

[0018] (Term 10)

The aqueous composition of Term 8 or 9, wherein the cellulose derivative is at least one selected from the group consisting of hydroxyethyl cellulose and hydroxypropyl methylcellulose.

[0019] (Term 11)

The aqueous composition according to any one of Terms 8 to 10, wherein the cellulose derivative is hydroxyethyl cellulose.

[0020] (Term 12)

An aqueous composition comprising 0.001 - 0.1 % (w/v) atropine or a salt thereof, hydroxyethyl cellulose, and buffer (I), which is at a pH range of 6 or lower, wherein the buffer (I) is a phosphate buffer.

[0021] (Term 13)

The aqueous composition of Term 12, further comprising a citrate buffer as buffer (II).

[0022] (Term 14)

The aqueous composition according to any one of Terms 1 to 13, which comprises less than 50 ppm benzalkonium chloride.

[0023] (Term 15)

The aqueous composition according to any one of Terms 1 to 14, which does not substantially comprise benzalkonium chloride.

[0024] (Term 16)

The aqueous composition according to any one of Terms 1 to 15, further comprising a nonionic tonicity agent.

[0025] (Term 17)

The aqueous composition of Term 16, wherein the nonionic tonicity agent is at least one selected from the group consisting of glycerin, mannitol, propylene glycol, polyethylene glycol, glucose, sorbitol, xylitol and trehalose.

[0026] (Term 18)

The aqueous composition of Term 16 or 17, wherein the nonionic tonicity agent is at least one compound selected from the group consisting of glycerin and mannitol.

[0027] (Term 19)

The aqueous composition according to any one of Terms 16 to 18, wherein the

nonionic tonicity agent is glycerin.

[0028] (Term 20)

The aqueous composition according to any one of Terms 1 to 19, wherein the concentration of the buffer is 0.001 - 10 % (w/v).

[0029] (Term 21)

The aqueous composition according to any one of Terms 6 to 11 and 13 to 20, wherein the concentration of citrate buffer is 0.001 - 1.0 % (w/v).

[0030] (Term 22)

The aqueous composition of Term 21, wherein the concentration of citrate buffer is 0.01 - 0.05 % (w/v).

[0031] (Term 23)

The aqueous composition according to any one of Terms 1 to 22, wherein the concentration of the water-soluble polymer is 0.01 - 5 % (w/v).

[0032] (Term 24)

The aqueous composition according to any one of Terms 16 to 23, wherein the concentration of the nonionic tonicity agent is 0.01 to 10 % (w/v).

[0033] (Term 25)

An aqueous composition comprising 0.001 - 0.1 % (w/v) atropine or a salt thereof, a water-soluble polymer, and a buffer, which is at a pH range of less than 5.

[0034] (Term 26)

The aqueous composition of Term 25, wherein the buffer is at least one selected from the group consisting of a phosphate buffer, a citrate buffer, an aminocarboxylate buffer, a carbonate buffer, an acetate buffer, a tartrate buffer, a borate buffer, and trometamol.

[0035] (Term 27)

The aqueous composition of Term 25 or 26, wherein the buffer is a citrate buffer.

[0036] (Term 28)

An aqueous composition comprising 0.001 - 0.1 % (w/v) atropine or a salt thereof, and a phosphate buffer, which is at pH range of 6 or lower.

[0037] (Term 29)

The aqueous composition of Term 28, further comprising a water-soluble polymer.

[0038] (Term 30)

The aqueous composition of Term 29, wherein the water-soluble polymer is at least one selected from the group consisting of hydroxyethyl cellulose, carboxyvinyl polymer, hydroxypropyl methylcellulose, and sodium alginate.

[0039] (Term 31)

The aqueous composition according to Term 29 or 30, wherein the water-soluble polymer is hydroxyethyl cellulose.

- [0040] (Term 32)
The aqueous composition according to any one of Terms 1 to 24 and 28 to 31, which is at a pH range of 4 - 6.
- [0041] (Term 33)
The aqueous composition according to any one of Terms 1 to 32, wherein the concentration of phosphate buffer is 0.01 - 1.0 % (w/v).
- [0042] (Term 34)
The aqueous composition according to any one of Terms 1 to 33, wherein the concentration of the atropine or a salt thereof is 0.001 to 0.025% (w/v).
- [0043] (Term 35)
The aqueous composition according to any one of Terms 1 to 34, wherein the concentration of the atropine or a salt thereof is 0.001 to 0.01% (w/v).
- [0044] (Term 36)
The aqueous composition according to any one of Terms 1 to 35, wherein the atropine or a salt thereof is atropine sulfate or a hydrate thereof.
- [0045] (Term 37)
The aqueous composition according to any one of Terms 1 to 36, which is enclosed in a unit-dose container.
- [0046] (Term 38)
The aqueous composition according to any one of Terms 1 to 37, wherein the aqueous composition is an eyedrop.
- [0047] (Term 39)
The aqueous composition according to any one of Terms 1 to 38, for inhibiting and/or preventing progression of myopia.
- [0048] (Term 40)
Use of an aqueous composition according to any one of Terms 1 to 38 in the preparation of a medicament to inhibit and/or preventing the progression of myopia.
- [0049] (Term 41)
A method for inhibiting and/or preventing progression of myopia comprising administering to a subject a composition according to any one of Terms 1 to 38.
- [0050] (Term 42)
The aqueous composition according to any one of Terms 1 to 38 for use in inhibiting and/or preventing progression of myopia.
- [0051] (Term 43)
A method for inhibiting the viscosity reduction of an aqueous composition comprising 0.001 - 0.1 % (w/v) atropine or a salt thereof and a water-soluble polymer which is at a pH range of 6 or lower, by adding a nonionic tonicity agent thereto.
- [0052] (Term 44)

A method for stabilizing atropine or a salt thereof in an aqueous composition comprising 0.001 - 0.1 % (w/v) atropine or a salt thereof and a water-soluble polymer which is at a pH range of 6 or lower, by adding a nonionic tonicity agent thereto.

Advantageous Effect of Invention

[0053] As is apparent from the test results which will be described later, it has been shown that an aqueous composition comprising 0.001 - 0.1 % (w/v) atropine or a salt thereof, a water-soluble polymer, and a buffer (I), which is at a pH range of 6 or lower, wherein the buffer (I) is at least one selected from the group consisting of a phosphate buffer, an aminocarboxylate buffer, a carbonate buffer, an acetate buffer, a tartrate buffer, a borate buffer, and trometamol, has a potent action for inhibiting the elongation of eye axial length and improving the refractive error without exacerbating the mydriatic action of atropine. Additionally, it has been also shown that the above aqueous composition, but which comprises no benzalkonium chloride or a limited amount of benzalkonium chloride, has a lower mydriatic action. Furthermore, it has been also shown that, in an aqueous composition comprising atropine or a salt thereof and a water-soluble polymer which is at a pH range of 6 or lower, the addition of a nonionic tonicity agent can make it possible to inhibit the debasement over time of the viscosity given by the water-soluble polymer and additionally maintain the stability of atropine or a salt thereof. The present aqueous composition is therefore expected to inhibit or prevent the progression of myopia and lead to a lesser degree of mydriasis, and lesser loss of accommodation so as to be optimal in terms of quality of life. A further advantage associated with the compositions of the present invention, such as compositions that further comprise a tonicity agent, is that the compositions may retain their initial viscosity (or a substantial proportion thereof) over an extended period of time.

Brief Description of Drawings

[0054] [fig.1]Fig. 1 shows the results of the viscosity determination test in Test 5.
 [fig.2]Fig. 2 shows the results of the stability test in Test 5.
 [fig.3]Fig. 3 shows the results of Examples 23 to 25 in the viscosity determination test in Test 6.
 [fig.4]Fig. 4 shows the results of Examples 26 to 28 in the viscosity determination test in Test 6.

Description of Embodiments

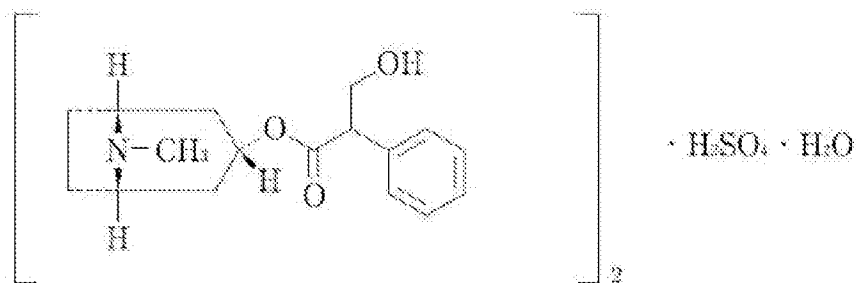
[0055] The present aqueous composition comprises "atropine or a salt thereof," which serves as an active ingredient.

[0056] In the present invention, the term "atropine or a salt thereof" also includes (i) a hydrate of atropine or a salt thereof, (ii) an organic solvate of atropine or a salt thereof,

and (iii) a combination of the hydrate and the organic solvate.

[0057] The salt of atropine includes atropine sulfate or a hydrate thereof, and is preferably an atropine sulfate hydrate.

[0058] Atropine sulfate hydrate is a compound represented by the following structural formula:



[0059] In a case where the atropine or the salt thereof includes a crystal polymorph and a group of crystal polymorphs (crystal polymorph system), those crystal polymorph and group of crystal polymorphs (crystal polymorph system) are also encompassed by the scope of the present invention. Here, the group of crystal polymorphs (crystal polymorph system) means not only individual crystal forms obtained at respective stages where crystals transform into various forms depending on conditions and states during the manufacture, crystallization, storage, and the like of the crystals, but also a mixture of the crystal forms obtained at two or more of the stages.

[0060] Atropine or a salt thereof can be manufactured in accordance with a method commonly employed in the field of organic synthetic chemistry or can alternatively be a commercially available product. For example, atropine sulfate hydrate can be a commercially available product from Tokyo Chemical Industry Co., Ltd. (product code: A0550).

[0061] In the present invention, the concentration of atropine or a salt thereof is preferably 0.001 to 0.1 % (w/v), more preferably 0.001 to 0.05 % (w/v), still more preferably 0.001 to 0.025 % (w/v), and particularly preferably 0.001 to 0.01 % (w/v). More specifically, the concentration is preferably 0.0010 % (w/v), 0.0015 % (w/v), 0.0020 % (w/v), 0.0025 % (w/v), 0.0030 % (w/v), 0.0035 % (w/v), 0.0040 % (w/v), 0.0045 % (w/v), 0.0050 % (w/v), 0.0055 % (w/v), 0.0060 % (w/v), 0.0065 % (w/v), 0.0070 % (w/v), 0.0075 % (w/v), 0.0080 % (w/v), 0.0085 % (w/v), 0.0090 % (w/v), 0.0095 % (w/v), or 0.010 % (w/v).

[0062] In the present invention, the term "aqueous composition" means a composition containing water that serves as a solvent.

[0063] In the present invention, the "water-soluble polymer" can be any pharmaceutically acceptable polymer capable of dissolving in water. Non-limiting examples of such a

polymer include celluloses and their derivatives (e.g., methyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, carboxymethylethyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, hydroxyethyl cellulose, cellulose acetate phthalate, ethyl cellulose, hydroxymethyl cellulose, hydroxyethylmethyl cellulose, hypromellose acetate succinate and hypromellose phthalate); synthetic polymers (e.g., polyethylene glycol, polyvinyl alcohol, polyvinyl pyrrolidone, polyvinylacetal diethylamino acetate, aminoalkyl methacrylate copolymer E, aminoalkyl methacrylate copolymer RS, methacrylic acid copolymer L, methacrylic acid copolymer LD, methacrylic acid copolymer S, and carboxyvinyl polymer); and naturally-occurring polymers and saccharides (e.g., gum arabic, sodium alginate, alginic acid propylene glycol ester, agar, gelatin, tragacanth, and xanthan gum). Among them, preferably used in the present invention as the water-soluble polymer are cellulose and its derivative, carboxyvinyl polymer and sodium alginate. Among them, more preferably used in the present invention as the water-soluble polymer are hydroxyethyl cellulose, carboxyvinyl polymer and hydroxypropyl methylcellulose.

- [0064] The present aqueous composition can comprise one or more types of water-soluble polymers.
- [0065] In the present invention, the concentration of the water-soluble polymer in the present aqueous composition is set to a value by adjusting the content of a water-soluble polymer as appropriate to reflect the influence of the water-soluble polymer on a medicinal substance (active ingredient), other additive(s), pH, osmotic pressure, and/or viscosity. However, the concentration of the water-soluble polymer in the present aqueous composition is preferably 0.01 to 5 % (w/v), and more preferably 0.1 to 2 % (w/v).
- [0066] In the present invention, in a case where the water-soluble polymer is cellulose and its derivative, the concentration of the cellulose and its derivative is preferably 0.01 to 5 % (w/v), more preferably 0.1 to 2 % (w/v), still more preferably 0.1 to 1 % (w/v), particularly preferably 0.1 to 0.6 %.
- [0067] In the present invention, in a case where the water-soluble polymer is hydroxyethyl cellulose, the concentration of the hydroxyethyl cellulose is preferably 0.1 to 1.0 % (w/v), and more preferably 0.1 to 0.6 % (w/v).
- [0068] In the present invention, in a case where the water-soluble polymer is carboxyvinyl polymer, the concentration of the carboxyvinyl polymer is preferably 0.04 to 0.4 % (w/v), and more preferably 0.08 to 0.4 % (w/v).
- [0069] In the present invention, in a case where the water-soluble polymer is hydroxypropyl methylcellulose, the concentration of the hydroxypropyl methylcellulose is preferably 0.1 to 1.0 % (w/v), and more preferably 0.1 to 0.6 % (w/v).

- [0070] In the present invention, in a case where the water-soluble polymer is sodium alginate, the concentration of the sodium alginate is preferably 0.1 to 2% (w/v), and more preferably 0.5 to 2% (w/v).
- [0071] In the present invention, the term "buffer" should not be limited as long as it is pharmaceutically acceptable ones, which includes, for example, a phosphate buffer, a citrate buffer, a borate buffer, a carbonate buffer, an acetate buffer, a tartrate buffer, an aminocarboxylate buffer, and trometamol. The aminocarboxylate buffer includes, for example, an aspartate buffer, a glutamate buffer, and epsilon-aminocaproic acid. These buffers may be used as a single ingredient or as a combination of any two or more ingredients. Among these buffers, a phosphate buffer, a citrate buffer, a carbonate buffer, an acetate buffer, and an aminocarboxylate buffer are preferable; a phosphate buffer, a citrate buffer, an acetate buffer, and an aminocarboxylate buffer are more preferable; a phosphate buffer and/or a citrate buffer are still more preferable; and a phosphate buffer and a citrate buffer are particularly preferable.
- [0072] In the present invention, the concentration of the buffer in the present aqueous composition is set to a value by adjusting the content of the buffer as appropriate to reflect the influence of the buffer on a medicinal substance (active ingredient), other additive(s), pH, osmotic pressure, and/or viscosity. However, the concentration of the buffer in the present aqueous composition is preferably 0.001 to 10 % (w/v), more preferably 0.01 to 5 % (w/v), still more preferably 0.01 to 3 % (w/v), still much more preferably 0.01 to 1 % (w/v), particularly preferably 0.01 to 0.5 % (w/v), more particularly preferably 0.01 to 0.1 % (w/v), wherein the weight of the buffer is that of a buffering agent as its material.
- [0073] In the present invention, the phosphate buffer can be derived from any pharmaceutically acceptable phosphate buffering agent. Non-limiting examples of such a phosphate buffering agent include: phosphoric acid; phosphates such as alkali metal phosphates and alkaline earth metal phosphates; and hydrates thereof. More specifically, the phosphate buffering agent includes dibasic sodium phosphate hydrate (referred to as "dibasic sodium phosphate" or "sodium phosphate"), sodium dihydrogen phosphate (referred to as "monosodium phosphate"), sodium dihydrogen phosphate monohydrate (referred to as "monosodium phosphate"), sodium dihydrogen phosphate dihydrate (referred to as "monosodium phosphate"), potassium dihydrogen phosphate (referred to as "monopotassium phosphate"), sodium monohydrogen phosphate heptahydrate, trisodium phosphate, dipotassium phosphate, and the like.
- [0074] In the present invention, the concentration of the phosphate buffer in the present aqueous composition is set to a value by adjusting the content of the phosphate buffer as appropriate to reflect the influence of the phosphate buffer on a medicinal substance (active ingredient), other additive(s), pH, osmotic pressure, and/or viscosity. However,

the concentration of the phosphate buffer in the present aqueous composition is preferably 0.01 to 1.0 % (w/v), more preferably 0.05 to 1.0 % (w/v), and still more preferably 0.05 to 0.5 % (w/v), wherein the weight of the phosphate buffer is that of a phosphate buffering agent as its material.

[0075] In the present invention, the "citrate buffer" can be derived from a citrate buffering agent which should not be limited as long as it is pharmaceutically acceptable ones, which includes, for example, citric acid; citrates such as alkali metal citrates and alkaline earth metal citrates; and hydrates thereof. More specifically, the citrate buffer includes citric acid hydrate, sodium citrate, sodium citrate hydrate, potassium citrate, calcium citrate, sodium dihydrogen citrate, and disodium citrate.

[0076] In the present invention, the concentration of the citrate buffer in the present aqueous composition is set to a value by adjusting the content of citrate buffer as appropriate to reflect the influence of the citrate buffer on a medicinal substance (active ingredient), other additive(s), pH, osmotic pressure, and/or viscosity. However, the concentration of the citrate buffer in the present aqueous composition is preferably 0.001 to 1.0 % (w/v), more preferably 0.005 to 0.5 % (w/v), still more preferably 0.01 to 0.1 % (w/v), still much more preferably 0.01 to 0.05 % (w/v) and particularly preferably 0.02 to 0.04 % (w/v), wherein the weight of the citrate buffer is that of a citrate buffering agent as its material.

[0077] In the present invention, the "borate buffer" can be derived from a borate buffering agent which includes, for example, boric acid or a salt thereof, and borax. More specifically, the borate buffering agent includes boric acid, sodium borate, potassium borate, potassium tetraborate, potassium metaborate, ammonium borate, and borax. The "carbonate buffer" can be derived from a carbonate buffering agent which includes, for example, carbonic acid or a salt thereof. More specifically, the carbonate buffering agent includes carbonic acid, sodium bicarbonate, sodium carbonate, ammonium carbonate, potassium carbonate, calcium carbonate, potassium bicarbonate, and magnesium carbonate. The "acetate buffer" can be derived from an acetate buffering agent which includes, for example, acetic acid or a salt thereof. More specifically, the acetate buffering agent includes acetic acid, ammonium acetate, potassium acetate, calcium acetate, and sodium acetate. The "tartrate buffer" can be derived from a tartrate buffering agent which includes, for example, tartaric acid or a salt thereof. More specifically, the tartrate buffering agent includes sodium tartrate and potassium tartrate. The "aspartate buffer" can be derived from an aspartate buffering agent which includes, for example, aspartic acid or a salt thereof. More specifically, the aspartate buffering agent includes sodium aspartate and magnesium aspartate. The "glutamate buffer" can be derived from a glutamate buffering agent which includes, for example, glutamic acid or a salt thereof. More specifically, the glutamate buffering

agent includes sodium glutamate and potassium glutamate.

- [0078] The aqueous composition of the present invention may comprise buffer (I) as sole buffers, or buffer (I) and buffer (II) as sole buffers. And, the aqueous composition of the present invention may also comprise further different buffers besides buffer (I) and buffer (II).
- [0079] In the present invention, the term "buffer (I)" is at least one selected from the group consisting of a phosphate buffer, an aminocarboxylate buffer, a carbonate buffer, an acetate buffer, a tartrate buffer, a borate buffer, and trometamol. The definition of each buffer and the preferred range of each concentration are as explained in the above section of "buffer".
- [0080] In the present invention, the term "buffer (II)" is a citrate buffer. The definition of the citrate buffer and the preferred range of the concentration are as explained in the above section of "buffer".
- [0081] The viscosity of the present aqueous composition is adjusted to fall within preferably a range of 3 to 500 mPa · s, and more preferably a range of 6 to 70 mPa · s, when measured by an E-type viscometer (25°C; shear rate of 50 s⁻¹).
- [0082] The present aqueous composition may further comprise a tonicity agent. The tonicity agent used in the present invention can be any pharmaceutically acceptable tonicity agent. Non-limiting examples of such a tonicity agent include nonionic tonicity agents such as glycerin, mannitol, propylene glycol, polyethylene glycol, glucose, sorbitol, xylitol, and trehalose. In the present invention, a nonionic tonicity agent is preferable as the tonicity agent. As the nonionic tonicity agent, glycerin, mannitol, propylene glycol, polyethylene glycol, glucose, sorbitol, xylitol, and trehalose are preferable, glycerin and mannitol are more preferable, and glycerin is particularly preferable.
- [0083] As the tonicity agent used in the present invention, the tonicity agents listed above may be used singly or in combination of two or more.
- [0084] In the present invention, the concentration of the tonicity agent in the present aqueous composition is set to a value by adjusting the content of a tonicity agent as appropriate to reflect the influence of the tonicity agent on a medicinal substance (active ingredient), other additive(s), pH, osmotic pressure, and/or viscosity. However, the concentration of the tonicity agent in the present aqueous composition is preferably 0.01 to 10 % (w/v), more preferably 0.05 to 5 % (w/v), still more preferably 0.1 to 5 % (w/v), still much more preferably 0.5 to 5 % (w/v), and particularly preferably 1 to 5 % (w/v).
- [0085] In the present invention, in a case where the tonicity agent is glycerin, the concentration of glycerin is preferably 0.1 to 5.0 % (w/v), more preferably 0.1 to 3.0 % (w/v), still more preferably 0.5 to 3.0 % (w/v) and particularly preferably 1.0 to 3.0 % (w/v).

- [0086] The present aqueous composition can comprise a pharmaceutically acceptable additive(s) as needed. The additive(s) can be mixed with other ingredients of the present aqueous composition by a widely used technique. The additive(s) can be selected from, for example, surfactants such as polyoxyethylene sorbitan monooleate, polyoxyl 40 stearate, and polyoxyethylene hydrogenated castor oil; stabilizers such as disodium edetate; preservatives such as benzalkonium chloride and boric acid; pH adjusting agents such as hydrochloric acid and sodium hydroxide; and the like as needed.
- [0087] In general, benzalkonium chloride is used as a preservative. In the present invention, it suggests that an aqueous composition of atropine which comprises no benzalkonium chloride has lower mydriatic action than another aqueous composition of atropine which comprises benzalkonium chloride, as shown later. Thus, it is preferable that the present aqueous composition comprises no benzalkonium chloride or a limited amount of benzalkonium chloride. The "limited amount" used herein means an amount of benzalkonium chloride used in the present aqueous composition of atropine which does not exacerbate the mydriatic action. Specifically, the concentration of benzalkonium chloride is preferably less than 100 ppm, more preferably less than 50 ppm, and even more preferably the present aqueous composition comprises substantially no benzalkonium chloride.
- [0088] The term "unit-dose container" used herein means an eyedrop container in which a cap is tightly attached to the bottle mouth with fusion, which is opened by breaking the fused part between the cap and the bottle mouth when it is used. The unit-dose container may contain just one dose of the aqueous composition for one shot, or more doses thereof used several times in one day.
- [0089] The term "multiple-dose container" used herein means an eyedrop container equipped with a bottle body and a cap which can be fixed to the bottle body, said cap can be freely opened and closed. The multiple-dose container generally contains plural doses of the eyedrop liquid for using for a certain period.
- [0090] The aqueous composition of the present invention can be contained in a unit-dose container or a multiple-dose container. Unless the present aqueous composition substantially comprises a preservative such as benzalkonium chloride, a unit-dose container is preferable.
- [0091] The pH of the present aqueous composition is not limited to a specific value, provided that it falls within a medically acceptable range. However, the pH of the present aqueous composition is preferably in a range of 6 or less, more preferably 4 to 6, still more preferably in a range of 4 to 5, and particularly preferably in the neighborhood of 4 or 5. More specifically, for example, pH 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, and

6.0 are preferable, and pH 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, and 5.4 are more preferable.

[0092] Further, the osmotic pressure of the aqueous composition in the present invention is not limited to a specific value, provided that it falls within a range acceptable to a living body. The osmotic pressure of the aqueous composition in the present invention is, for example, 100 to 1000 mOsm, preferably 200 to 500 mOsm, and more preferably 250 to 350 mOsm. In general, the osmotic pressure of an aqueous composition is more than a little affected by the amounts of medicinal substance and additive in the aqueous composition. In the present invention, the osmotic pressure can be adjusted to fall within the above-described ranges by appropriately adjusting the amounts of those substances that can affect the osmotic pressure. It should be noted that the osmotic pressure of the aqueous composition in the present invention can be measured by a common method. For example, the osmotic pressure of the aqueous composition in the present invention can be measured in accordance with the method described in the "Osmometry (Osmolarity Determination)" section of the Japanese Pharmacopoeia, 15th Revised Edition.

[0093] Examples of a dosage form of the present aqueous composition include an eyedrop or an ophthalmic aqueous solution.

[0094] The dosage and administration of the aqueous composition administered in the present invention are not limited as long as it can sufficiently provide a desired efficacy, which can be administered in eyedrops, preferably at a frequency of 1 - 5 times a day in an amount of 1 - 3 drops each time, more preferably at a frequency of 2 - 4 times a day in an amount of 1 - 2 drops each time, and the most preferably once a day, before bedtime in an amount of 1 drop.

[0095] The present aqueous composition is preferably used to inhibit or prevent the progression of myopia, to prevent myopia, and/or to treat myopia, and is more preferably used to inhibit or prevent the progression of childhood myopia.

[0096] The term "inhibit or prevent the progression of myopia" used herein may mean slowing myopia progression or reducing myopia progression. The term "prevent myopia" used herein may mean preventing the onset of myopia or delaying the onset of myopia.

Examples

[0097] The test results and preparation examples shown below are given for better understanding of the present invention, but the scope of the present invention should not be limited thereto.

[0098] The meanings of abbreviates are as follows.

BAK: Benzalkonium chloride

CVP: Carboxyvinyl polymer

HEC: Hydroxyethyl cellulose

HPMC: Hydroxypropyl methylcellulose

[0099] Test 1

Some aqueous compositions were evaluated in terms of their mydriatic action.

[0100] (Sample Preparation Method)

(Example 1)

An aqueous composition in Example 1 was prepared in accordance with the formulation shown in Table 1. Specifically, 0.01 g of atropine sulfate hydrate, 0.32 g of hydroxyethyl cellulose, 0.1 g of sodium dihydrogen phosphate, and 2.4 g of concentrated glycerin were dissolved in purified water. To the solution thus obtained were added hydrochloric acid and sodium hydroxide as appropriate, so that the solution was adjusted to pH 5 and brought to a total volume of 100 ml.

[0101] (Examples 2 and 3 and Comparative Examples 1 to 3)

Aqueous compositions in Examples 2 and 3 and in Comparative Examples 1 to 3 were prepared as in Example 1 in accordance with the formulation shown in Table 1.

Table 1. (Unit: g/100 ml)						
	Com. Ex. 1	Com. Ex. 2	Com. Ex. 3	Ex. 1	Ex. 2	Ex. 3
Atropine sulfate hydrate	0.01	0.01	0.01	0.01	0.004	0.01
Hydroxyethyl cellulose	0.32	0.32	—	0.32	0.32	—
Sodium dihydrogen phosphate	0.1	—	—	0.1	0.1	0.1
Sodium citrate hydrate	—	0.1	—	—	—	—
Concentrated glycerin	2.4	2.4	2.4	2.4	2.4	2.4
pH adjusting agent	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
pH	7	5	5	5	5	5
Viscosity (mPa·s)	31.77	30.42	*	31.30	33.94	*
*: unmeasured						

[0102] (Test Method)

A single dose of each aqueous composition (50 μ l in volume) was instilled into one eye of a rabbit (four eyes from four rabbits or six eyes from six rabbits for each aqueous composition). Images of pupils of the rabbits before the instillation and 1 hour after the instillation were captured by optical coherence tomography (OCT) and were then analyzed by image analysis software to calculate pupil areas of the rabbits and a mydriasis rate. The mydriasis rate was calculated by the following equation:

$$\text{Mydriasis rate (\%)} = ((b - a)/a) \times 100,$$

where a is a mean value (mm²) of the pupil area before the instillation in each of Comparative Examples 1 to 3 and Examples 1 to 3, a is 16.8 (mm²) and b is a value of the pupil area 1 hour after the instillation.

[0103] (Test Results)

The results in Examples 1 to 3 and in Comparative Examples 1 to 3 are shown in Table 2. In Table 2, each value is a mean value of data from the four or six cases.

The mydriatic action of each aqueous composition was evaluated under the following criteria.

A: in case that the pupil area is less than 30.0 mm² one hour after the instillation.

B: in case that the pupil area is 30.0 mm² to less than 35.0 mm² one hour after the instillation.

C: in case that the pupil area is 35.0 mm² to less than 40.0 mm² one hour after the instillation.

D: in case that the pupil area is 40.0 mm² or more one hour after the instillation.

Table 2			
	Value of pupil area 1 hour after the instillation (mm ²)	Mydriasis rate (%)	Evaluation
Comparative Example 1	40.8	143	D
Comparative Example 2	40.1	139	D
Comparative Example 3	43.4	158	D
Example 1	35.3	110	C
Example 2	31.9	90	B
Example 3	35.1	109	C

[0104] (Discussion)

As is apparent from Table 2, it has been shown that an aqueous composition (i) comprising atropine or a salt thereof, (ii) having pH in a range of 6 or less, and (iii) further comprising a phosphate buffer, induces lesser degree of mydriasis than a composition comprising no phosphate buffer.

[0105] Test 2 Some aqueous compositions of the present invention were evaluated in terms of their mydriatic action.

[0106] (Sample Preparation Method)

(Examples 4 to 11) Aqueous compositions in Examples 4 to 11 were prepared as in Example 1 in accordance with the formulation shown in Table 3.

[0107] (Test Method)

A single dose of each aqueous composition (50 μ l in volume) was instilled into one eye of a rabbit (four eyes from four rabbits or six eyes from six rabbits for each aqueous composition). Images of pupils of the rabbits 1 hour after the instillation were captured by optical coherence tomography (OCT) and were then analyzed by image analysis software to calculate pupil areas of the rabbits.

[0108] (Test Results)

The results in Examples 4 to 11 are shown in Table 3. In Table 3, each value is a mean value of data from the four or six cases.

The mydriatic action of each aqueous composition was evaluated under the following criteria.

A: in case that the pupil area is less than 30.0 mm² one hour after the instillation.

B: in case that the pupil area is 30.0 mm² to less than 35.0 mm² one hour after the instillation.

C: in case that the pupil area is 35.0 mm² to less than 40.0 mm² one hour after the instillation.

D: in case that the pupil area is 40.0 mm² or more one hour after the instillation.

Table 3 (Unit: g/100 ml)								
Example	4	5	6	7	8	9	10	11
Atropine sulfate hydrate	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Hydroxyethyl cellulose	0.32	0.32	0.32	0.45	0.45	0.32	0.32	0.32
Sodium dihydrogen phosphate	0.1	-	0.1	0.1	0.1	-	-	-
Sodium citrate hydrate	-	0.02	0.02	0.02	0.04	0.04	-	-
Epsilon-Aminocaproic acid	-	-	-	-	-	-	0.04	-
Acetic acid	-	-	-	-	-	-	-	0.04
Concentrated glycerin	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
pH adjusting agent	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
pH	4.3	4.3	4.3	4.3	4.3	4.3	4.3	4.3
Value of pupil area 1 hour after the instillation (mm ²)	30.8	35.4	24.1	27.1	28.0	33.4	30.4	39.0
Evaluation	B	C	A	A	A	B	B	C

[0109] (Discussion)

When the aqueous composition comprised a phosphate buffer as buffer (I), the mydriatic action was low (Example 4). In addition, when the aqueous composition further comprised a citrate buffer as buffer (II) besides a phosphate buffer, the mydriatic action was lower (Examples 6 to 8).

[0110] Test 3

Some aqueous compositions of the present invention were evaluated in terms of their mydriatic action.

[0111] (Sample Preparation Method)

(Examples 12 to 14)

Aqueous compositions in Examples 12 to 14 were prepared as in Example 1 in accordance with the formulation shown in Table 4.

[0112] (Test Method)

A single dose of each aqueous composition (50 μ l in volume) was instilled into one eye of a rabbit (four eyes from four rabbits for each aqueous composition). Images of pupils of the rabbits 1 hour after the instillation were captured by optical coherence tomography (OCT) and were then analyzed by image analysis software to calculate pupil areas of the rabbits.

[0113] (Test Results)

The results in Examples 12 to 14 are shown in Table 4. In Table 4, each value is a mean value of data from the four cases.

The mydriatic action of each aqueous composition was evaluated under the following criteria.

A: in case that the pupillary area one hour after eyedropping is less than 30.0 mm².

B: in case that the pupillary area one hour after eyedropping is 30.0 mm² to less than 35.0 mm².

C: in case that the pupillary area one hour after eyedropping is 35.0 mm² to less than 40.0 mm².

D: in case that the pupillary area one hour after eyedropping is 40.0 mm² or more.

Table 4 (Unit: g/100 ml)			
Example	12	13	14
Atropine sulfate hydrate	0.005	0.005	0.005
Hydroxyethyl cellulose	0.45	0.45	0.45
Sodium dihydrogen phosphate	0.1	0.1	0.1
Sodium citrate hydrate	-	0.03	0.04
Concentrated glycerin	2.4	2.4	2.4
pH adjusting agent	q.s.	q.s.	q.s.
pH	4.3	4.3	4.3
Value of pupil area 1 hour after the instillation (mm ²)	25.0	24.2	20.8
Evaluation	A	A	A

[0114] (Discussion)

Even though the aqueous composition comprised 0.005 % (w/v) atropine, the

mydriatic action was low when the aqueous composition comprised a phosphate buffer as buffer (I) (Example 12). In addition, when the aqueous composition further comprised a citrate buffer as buffer (II) besides a phosphate buffer, the mydriatic action was lower (Examples 13 and 14).

[0115] Test 4

The effect of benzalkonium chloride which is generally used as a preservative to the mydriatic action of the present aqueous composition was studied.

[0116] (Sample Preparation Method)

(Examples 15 to 17)

Aqueous compositions in Examples 15 to 17 were prepared as in Example 1 in accordance with the formulation shown in Table 5.

[0117] (Test Method)

A single dose of each aqueous composition (50 μ l in volume) was instilled into one eye of a rabbit (four eyes from four rabbits for each aqueous composition). Images of pupils of the rabbits 1 hour after the instillation were captured by optical coherence tomography (OCT) and were then analyzed by image analysis software to calculate pupil areas of the rabbits.

[0118] (Test Results)

The results in Examples 15 to 17 are shown in Table 5. In Table 5, each value is a mean value of data from the four cases.

The mydriatic action of each aqueous composition was evaluated under the following criteria.

A: in case that the pupil area is less than 30.0 mm² one hour after the instillation.

B: in case that the pupil area is 30.0 mm² to less than 35.0 mm² one hour after the instillation.

C: in case that the pupil area is 35.0 mm² to less than 40.0 mm² one hour after the instillation.

D: in case that the pupil area is 40.0 mm² to less than 45.0 mm² one hour after the instillation.

E: in case that the pupil area is 45.0 mm² or more one hour after the instillation.

Table 5 (Unit: g/100 ml)			
Example	15	16	17
Atropine sulfate hydrate	0.01	0.01	0.01
Hydroxyethyl cellulose	0.53	0.53	0.53
Sodium dihydrogen phosphate	0.1	0.1	0.1
Concentrated glycerin	2.4	2.4	2.4
BAK (Unit: ppm)	—	50	100
pH adjusting agent	q.s.	q.s.	q.s.
pH	5	5	5
Value of pupil area 1 hour after the instillation (mm ²)	35.1	44.8	45.1
Evaluation	C	D	E

[0119] (Discussion)

As is clear from Table 5, the aqueous composition comprising no benzalkonium chloride (Example 15) exhibited lower mydriatic action than the aqueous composition comprising benzalkonium chloride (Examples 16 and 17).

[0120] Test 5

(Viscosity Determination Test 1 and Stability Test 1)

The effects of a tonicity agent to the viscosity of an aqueous composition comprising atropine and a water-soluble polymer and the stability of atropine therein were studied.

[0121] (Sample Preparation Method)

(Examples 18 to 22)

Aqueous compositions in Examples 18 to 22 were prepared as in Example 1 in accordance with the formulation shown in Table 6. Each prepared sample (5 mL) was put into a polyethylene eyedrop container, an inside plug was attached to the bottle mouth, and the container was sealed-up with a cap. The containers were stored under dark at 60°C for 4 weeks.

Table 6 (Unit: g/100 ml)					
Example	18	19	20	21	22
Atropine sulfate hydrate	0.01	0.01	0.01	0.01	0.01
Hydroxyethyl cellulose	0.45	0.45	0.45	0.45	0.45
Sodium dihydrogen phosphate	0.1	0.1	0.1	0.1	0.1
Sodium chloride	-	0.9	-	-	-
Boric acid	-	-	1.9	-	-
Concentrated glycerin	-	-	-	2.4	-
Mannitol	-	-	-	-	5
pH adjusting agent	q.s.	q.s.	q.s.	q.s.	q.s.
pH	5	5	5	5	5

[0122] (Test Method)

(1) Viscosity Determination Test 1

According to "Method II, Viscosity measurement by rotational viscometer" in the Japanese Pharmacopoeia 16th edition, each viscosity of the freshly-prepared aqueous compositions and the aqueous compositions stored for 1, 2 and 4 weeks after the productions was measured with a cone-flat plate-type rotational viscometer. The measuring conditions are shown below.

- Instrument: Rotary rheometer (Kinexus pro+)
- Rotating speed (S-1): 50/sec
- Measurement temperature: 25°C

[0123] (2) Stability Test 1

Tropic acid can be formed in the decomposition of atropine. In order to evaluate the stability of atropine in the present test, the content of tropic acid in the freshly-prepared aqueous compositions and the aqueous compositions stored for 1, 2 and 4 weeks after the productions was determined by high-performance liquid chromatography.

[0124] (Test Results)

The results of Viscosity Determination Test 1 are shown in Figure 1. The results of Stability Test 1 are shown in Figure 2.

[0125] (Discussion)

(1) Viscosity Determination Test 1

As shown in Figure 1, each viscosity of the aqueous composition comprising atropine and hydroxyethyl cellulose, but no tonicity agent (Example 18 which corresponds to "without" in Figure 1), the aqueous composition further comprising sodium chloride as a tonicity agent (Example 19 which corresponds to "NaCl" in Figure 1), and the aqueous composition further comprising boric acid as a tonicity

agent (Example 20 which corresponds to "Boric acid" in Figure 1), decreased over time. On the other hand, each viscosity of the aqueous composition comprising atropine and hydroxyethyl cellulose, and further comprising glycerin as a tonicity agent (Example 21 which corresponds to "Glycerin" in Figure 1) and the aqueous composition further comprising mannitol as a tonicity agent (Example 22 which corresponds to "Mannitol" in Figure 1) was maintained, i.e., the decrease of viscosity over time was inhibited.

[0126] (2) Stability Test 1

As shown in Figure 2, more tropic acid was produced from the aqueous composition comprising atropine and hydroxyethyl cellulose, and further comprising mannitol or boric acid as a tonicity agent than from the other aqueous compositions. The result suggested that it is not preferable to add mannitol or boric acid as a tonicity agent to an aqueous composition comprising atropine and hydroxyethyl cellulose from the viewpoint of the stability of atropine.

In addition, the above results of Viscosity Determination Test 1 and Stability Test 1 suggested that it is preferable to add glycerin as a tonicity agent to an aqueous composition comprising atropine and hydroxyethyl cellulose to inhibit the decrease of viscosity over time and maintain the stability of atropine.

[0127] Test 6

(Viscosity Determination Test 2)

The effect of a tonicity agent to the viscosity of an aqueous composition comprising atropine and a water-soluble polymer was studied.

[0128] (Sample Preparation Method)

(Examples 23 to 28)

Aqueous compositions in Examples 23 to 28 were prepared as in Example 1 in accordance with the formulation shown in Table 7. Each prepared sample (5 mL) was put into a polyethylene eyedrop container, an inside plug was attached to the bottle mouth, and the container was sealed-up with a cap. The containers were stored under dark at 60°C for 4 weeks.

Table 7 (Unit: g/100 ml)						
Example	23	24	25	26	27	28
Atropine sulfate hydrate	0.01	0.01	0.01	0.01	0.01	0.01
HPMC	0.6	0.6	0.6	-	-	-
CVP	-	-	-	0.14	0.14	0.14
Sodium dihydrogen phosphate	0.1	0.1	0.1	0.1	0.1	0.1
Concentrated glycerin	-	2.4	-	-	2.4	-
Mannitol	-	-	5	-	-	5
pH adjusting agent	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
pH	5	5	5	5	5	5

[0129] (Test Method)

(Viscosity Determination Test 2)

According to "Method II, Viscosity measurement by rotational viscometer" in the Japanese Pharmacopoeia 16th edition, each viscosity of the freshly-prepared aqueous compositions and the aqueous compositions stored for 1, 2 and 4 weeks after the productions was measured with a cone-flat plate-type rotational viscometer. The measuring conditions are shown below.

- Instrument: Rotary rheometer (Kinexus pro+)
- Rotating speed (S-1): 50/sec
- Measurement temperature: 25°C

[0130] (Test Results)

The results of Examples 23 to 25 in the viscosity determination test are shown in Figure 3. The results of Examples 26 to 28 in the viscosity determination test are shown in Figure 4.

[0131] (Discussion)

(Viscosity Determination Test 2)

As shown in Figure 3, the viscosity of the aqueous composition comprising atropine and hydroxypropyl methylcellulose, but no tonicity agent (Example 23 which corresponds to "without" in Figure 3) decreased over time. On the other hand, the viscosity of the aqueous composition further comprising glycerin or mannitol as a tonicity agent (Example 24 or 25 which corresponds to "Glycerin" or "Mannitol" in Figure 3) was maintained, i.e., the decrease of viscosity over time was inhibited.

In addition, as shown in Figure 4, the viscosity of the aqueous composition comprising atropine and carboxyvinyl polymer, but no tonicity agent (Example 26 which corresponds to "without" in Figure 4) decreased over time. On the other hand, the viscosity of the aqueous composition further comprising glycerin or mannitol as a tonicity agent (Example 27 or 28 which corresponds to "Glycerin" or "Mannitol" in

Figure 4) was maintained, i.e., the decrease of viscosity over time was inhibited.

[0132] Test 7

The effects of a water-soluble polymer to the actions for inhibiting the elongation of eye axial length and improving the refractive error were studied with myopia mouse models.

[0133] (Sample Preparation Method)

(Examples A to D)

Aqueous compositions in Examples A to D were prepared as in Example 1 in accordance with the formulation shown in Table 8.

Table 8 (Unit: g/100 ml)				
Example	A	B	C	D
Atropine sulfate hydrate	-	-	0.01	0.01
Hydroxyethyl cellulose	-	0.45	-	0.45
Sodium dihydrogen phosphate	0.1	0.1	0.1	0.1
Concentrated glycerin	2.4	2.4	2.4	2.4
pH adjusting agent	q.s.	q.s.	q.s.	q.s.
pH	4.5	4.5	4.5	4.5

[0134] (Test Method)

Murine model of experimental myopia: Spectacle lens-induced myopia model was established by placing -10D lens on the right eye of the mice (C57BL/6J), which served as the experimental eye, at post-natal day 24. Briefly, a -10D lens (PMMA spectacle lens in blue tint, radius of outer curvature 8.5 mm, inner curvature 8 mm, lens thickness 0.5 mm) was glued to an annulus (with 8 mm base curve) of Velcro. This mating piece was then attached to the Velcro that had been glued to the hair around the right experimental eye using a cyanoacrylate. Through this set up, we made sure that an air gap of 1.5 mm existed between the back part of the lens and the anterior surface of the cornea.

[0135] Ocular biometry methods: Ocular biometry such as axial length and refractive error measurements were done using in vivo Optical Low Coherence Interferometry (OLCI-AcMaster) and automated eccentric photorefractor respectively. The axial length was measured at post-natal days 38 and 66, whereas the animal eyes were refracted at days 52 and 66.

Drug treatment: Atropine sulphate (at 0.01 % concentration) with and without hydroxyethyl cellulose were administered once a day at post-natal day 39 until day 66 in the spectacle lens-induced myopia model. 7 μ L of each drug was administered topically to the right eye in dim red light each day.

[0136] (Test Results)

(1) Action for inhibiting the elongation of eye axial length

The results in Examples B to D are shown in Table 9.

The ratio for inhibiting the elongation of eye axial length with each Example was calculated by the following equation:

Difference of eye axial lengths (mm) = [eye axial length on day 66] - [eye axial length on day 38]

Ratio (%) for inhibiting the elongation of eye axial length with Example B =

$$\left(1 - \frac{[\text{Difference of eye axial lengths in Example B administration group}]}{[\text{Difference of eye axial lengths in Example A administration group}]}\right) \times 100$$

Ratio (%) for inhibiting the elongation of eye axial length with Example C =

$$\left(1 - \frac{[\text{Difference of eye axial lengths in Example C administration group}]}{[\text{Difference of eye axial lengths in Example A administration group}]}\right) \times 100$$

Ratio (%) for inhibiting the elongation of eye axial length with Example D =

$$\left(1 - \frac{[\text{Difference of eye axial lengths in Example D administration group}]}{[\text{Difference of eye axial lengths in Example A administration group}]}\right) \times 100$$

Table 9	
Example	Ratio (%) for inhibiting the elongation of eye axial length
B	0
C	5.81
D	24.65

[0137] (2) Action for improving the refractive error

The results in Examples A to D are shown in Table 10.

Change in refractive error (diopters) = [degree of refraction (diopters) on day 66] - [degree of refraction (diopters) on day 52]

Table 10	
Example	Change in refractive error (diopters)
A	-1.9
B	-2.7
C	-0.6
D	+0.7

[0138] (Discussion)

The aqueous composition comprising the water-soluble polymer, but no atropine (Example B) had no action for inhibiting the elongation of eye axial length. On the other hand, it has been found that the aqueous composition comprising atropine and further the water-soluble polymer (Example D) has more potent action for inhibiting the elongation of eye axial length than the aqueous composition comprising atropine,

but no water-soluble polymer (Example C).

In addition, as is the case with the action for inhibiting the elongation of eye axial length, it has been found that the aqueous composition comprising atropine and further the water-soluble polymer (Example D) has more potent action for improving the refractive error than the aqueous composition comprising atropine, but no water-soluble polymer (Example C).

As is apparent from the results of Examples 1 and 3 in Tables 1 and 2, it is shown that the addition of a water-soluble polymer cannot create an adverse impact on the mydriatic action of atropine. Thus, an aqueous composition comprising atropine and a water-soluble polymer is expected to become an agent for inhibiting myopia progression which has a lower mydriatic action.

[0139] Preparation Examples

Medications of the present invention will be more specifically described by way of preparation examples; however, it should be noted that the present invention will not be limited only to those preparation examples.

[0140] Formulation Example 1: Eye Drop (0.01% (w/v))

In 100 ml,	
Atropine sulfate hydrate	0.01 g
Hydroxyethyl cellulose	0.32 g
Sodium dihydrogen phosphate	0.1 g
Concentrated glycerin	2.4 g
pH adjusting agent	q.s.
Sterile purified water	q.s.

To sterile purified water are added atropine sulfate hydrate and the other ingredients as listed above. These ingredients are mixed well to prepare the above-described eye drop.

[0141] Formulation Example 2: Eye Drop (0.004% (w/v))

In 100 ml,	
Atropine sulfate hydrate	0.004 g
Hydroxyethyl cellulose	0.32 g
Sodium dihydrogen phosphate	0.1 g
Concentrated glycerin	2.4 g
pH adjusting agent	q.s.
Sterile purified water	q.s.

To sterile purified water are added atropine sulfate hydrate and the other ingredients

as listed above. These ingredients are mixed well to prepare the above-described eye drop.

Industrial Applicability

[0142] It has been shown that an aqueous composition comprising 0.001 - 0.1 % (w/v) atropine or a salt thereof, a water-soluble polymer, and buffer (I), which is at a pH range of 6 or lower, wherein the buffer (I) is at least one selected from the group consisting of a phosphate buffer, an aminocarboxylate buffer, a carbonate buffer, an acetate buffer, a tartrate buffer, a borate buffer, and trometamol, has a potent action for inhibiting the elongation of eye axial length and improving the refractive error without exacerbating the mydriatic action of atropine. Additionally, it has been also shown that the above aqueous composition, but which comprises no benzalkonium chloride or a limited amount of benzalkonium chloride, has a lower mydriatic action. Furthermore, it has been also shown that, in an aqueous composition comprising atropine or a salt thereof and a water-soluble polymer which is at a pH range of 6 or lower, the addition of a nonionic tonicity agent can make it possible to inhibit the debasement over time of the viscosity given by the water-soluble polymer and additionally maintain the stability of atropine or a salt thereof. The present aqueous composition is expected to inhibit or prevent the progression of myopia and lead to a lesser degree of mydriasis, and lesser loss of accommodation so as to be optimal in terms of quality of life.

Claims

- [Claim 1] An aqueous composition comprising 0.001 - 0.1 % (w/v) atropine or a salt thereof, a water-soluble polymer, and buffer (I), which is at a pH range of 6 or lower, wherein the buffer (I) is at least one selected from the group consisting of a phosphate buffer, an aminocarboxylate buffer, a carbonate buffer, an acetate buffer, a tartrate buffer, a borate buffer, and trometamol.
- [Claim 2] The aqueous composition of claim 1, wherein the buffer (I) is at least one selected from the group consisting of a phosphate buffer, an aminocarboxylate buffer, a carbonate buffer, and an acetate buffer.
- [Claim 3] The aqueous composition of claim 1 or 2, wherein the buffer (I) is a phosphate buffer.
- [Claim 4] The aqueous composition of claim 1 or 2, wherein the aminocarboxylate buffer is at least one selected from the group consisting of epsilon-aminocaproic acid, a glutamate buffer, and an aspartate buffer.
- [Claim 5] The aqueous composition according to any one of claims 1 to 4, wherein
- the phosphate buffer is derived from at least one selected from the group consisting of dibasic sodium phosphate hydrate, sodium dihydrogen phosphate, sodium dihydrogen phosphate monohydrate, sodium dihydrogen phosphate dihydrate, potassium dihydrogen phosphate, sodium monohydrogen phosphate heptahydrate, trisodium phosphate, and dipotassium phosphate,
- the carbonate buffer is derived from at least one selected from the group consisting of carbonic acid, sodium bicarbonate, sodium carbonate, ammonium carbonate, potassium carbonate, calcium carbonate, potassium bicarbonate, and magnesium carbonate,
- the acetate buffer is derived from at least one selected from the group consisting of acetic acid, ammonium acetate, potassium acetate, calcium acetate, and sodium acetate,
- the tartrate buffer is derived from at least one selected from the group consisting of sodium tartrate and potassium tartrate,
- the borate buffer is derived from at least one selected from the group consisting of boric acid, sodium borate, potassium borate, potassium tetraborate, potassium metaborate, ammonium borate, and borax,
- the glutamate buffer is derived from at least one selected from the group consisting of glutamic acid, sodium glutamate and potassium

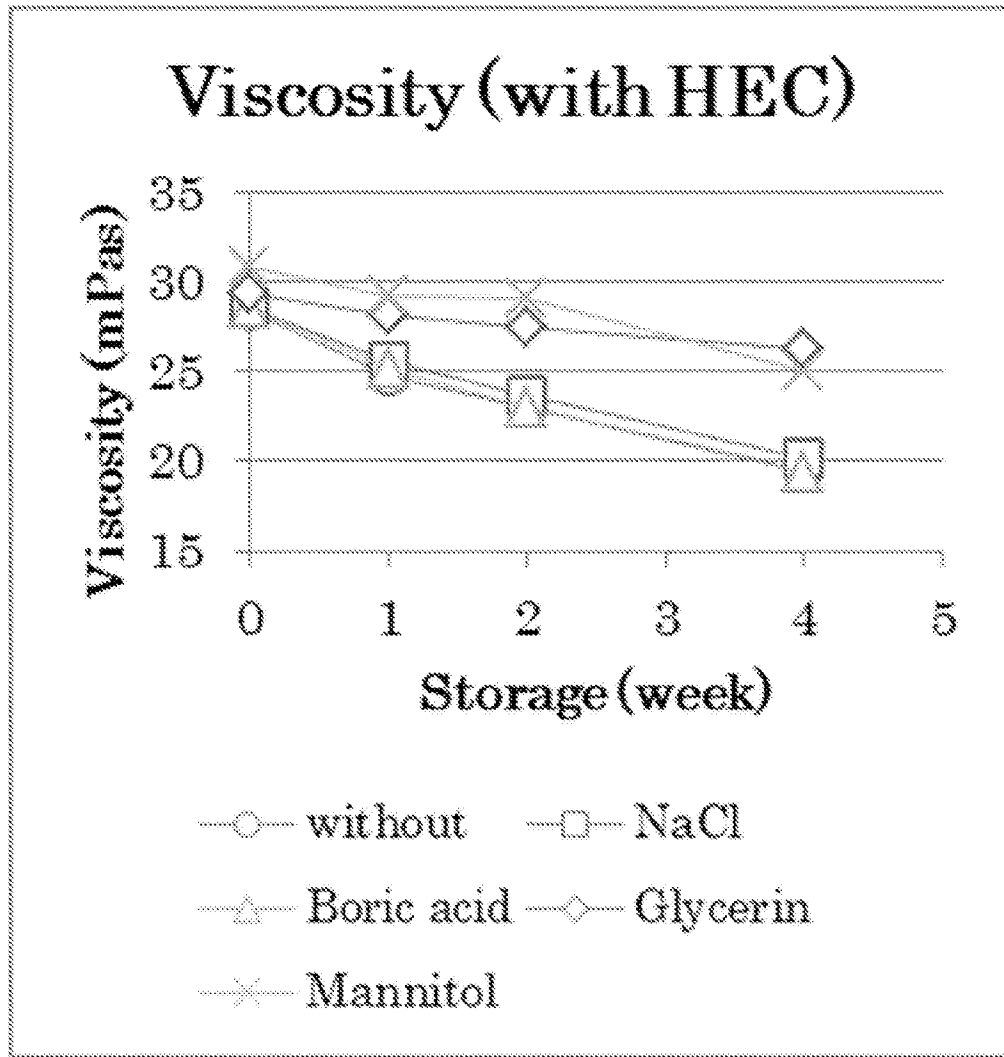
- glutamate, and/or
the aspartate buffer is derived from at least one selected from the group consisting of aspartic acid, sodium aspartate and magnesium aspartate.
- [Claim 6] The aqueous composition according to any one of claims 1 to 5, further comprising a citrate buffer as buffer (II).
- [Claim 7] The aqueous composition of claim 6 wherein the citrate buffer is derived from at least one selected from the group consisting of citric acid hydrate, sodium citrate, sodium citrate hydrate, potassium citrate, calcium citrate, sodium dihydrogen citrate, and disodium citrate.
- [Claim 8] The aqueous composition according to any one of claims 1 to 7, wherein the water-soluble polymer is at least one selected from the group consisting of a cellulose derivative, carboxyvinyl polymer and sodium alginate.
- [Claim 9] The aqueous composition of claim 8, wherein the cellulose derivative is at least one selected from the group consisting of hydroxyethyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, ethyl cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxyethyl methyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, hypromellose acetate succinate, hypromellose phthalate, carboxymethylethyl cellulose, and cellulose acetate phthalate.
- [Claim 10] The aqueous composition of claim 8 or 9, wherein the cellulose derivative is at least one selected from the group consisting of hydroxyethyl cellulose and hydroxypropyl methylcellulose.
- [Claim 11] The aqueous composition according to any one of claims 8 to 10, wherein the cellulose derivative is hydroxyethyl cellulose.
- [Claim 12] An aqueous composition comprising 0.001 - 0.1 % (w/v) atropine or a salt thereof, hydroxyethyl cellulose, and buffer (I), which is at a pH range of 6 or lower, wherein the buffer (I) is a phosphate buffer.
- [Claim 13] The aqueous composition of claim 12, further comprising a citrate buffer as buffer (II).
- [Claim 14] The aqueous composition according to any one of claims 1 to 13, which comprises less than 50 ppm benzalkonium chloride.
- [Claim 15] The aqueous composition according to any one of claims 1 to 14, which does not substantially comprise benzalkonium chloride.
- [Claim 16] The aqueous composition according to any one of claims 1 to 15, further comprising a nonionic tonicity agent.
- [Claim 17] The aqueous composition of claim 16, wherein the nonionic tonicity

- agent is at least one selected from the group consisting of glycerin, mannitol, propylene glycol, polyethylene glycol, glucose, sorbitol, xylitol and trehalose.
- [Claim 18] The aqueous composition of claim 16 or 17, wherein the nonionic tonicity agent is at least one compound selected from the group consisting of glycerin and mannitol.
- [Claim 19] The aqueous composition according to any one of claims 16 to 18, wherein the nonionic tonicity agent is glycerin.
- [Claim 20] The aqueous composition according to any one of claims 1 to 19, wherein the concentration of the buffer is 0.001 - 10 % (w/v).
- [Claim 21] The aqueous composition according to any one of claims 6 to 11 and 13 to 20, wherein the concentration of citrate buffer is 0.001 - 1.0 % (w/v).
- [Claim 22] The aqueous composition of claim 21, wherein the concentration of citrate buffer is 0.01 - 0.05 % (w/v).
- [Claim 23] The aqueous composition according to any one of claims 1 to 22, wherein the concentration of the water-soluble polymer is 0.01 - 5 % (w/v).
- [Claim 24] The aqueous composition according to any one of claims 16 to 23, wherein the concentration of the nonionic tonicity agent is 0.01 to 10 % (w/v).
- [Claim 25] An aqueous composition comprising 0.001 - 0.1 % (w/v) atropine or a salt thereof, a water-soluble polymer, and a buffer, which is at a pH range of less than 5.
- [Claim 26] The aqueous composition of claim 25, wherein the buffer is at least one selected from the group consisting of a phosphate buffer, a citrate buffer, an aminocarboxylate buffer, a carbonate buffer, an acetate buffer, a tartrate buffer, a borate buffer, and trometamol.
- [Claim 27] The aqueous composition of claim 25 or 26, wherein the buffer is a citrate buffer.
- [Claim 28] An aqueous composition comprising 0.001 - 0.1 % (w/v) atropine or a salt thereof, and a phosphate buffer, which is at pH range of 6 or lower.
- [Claim 29] The aqueous composition of claim 28, further comprising a water-soluble polymer.
- [Claim 30] The aqueous composition of claim 29, wherein the water-soluble polymer is at least one selected from the group consisting of hydroxyethyl cellulose, carboxyvinyl polymer, hydroxypropyl methylcellulose, and sodium alginate.
- [Claim 31] The aqueous composition according to claim 29 or 30, wherein the

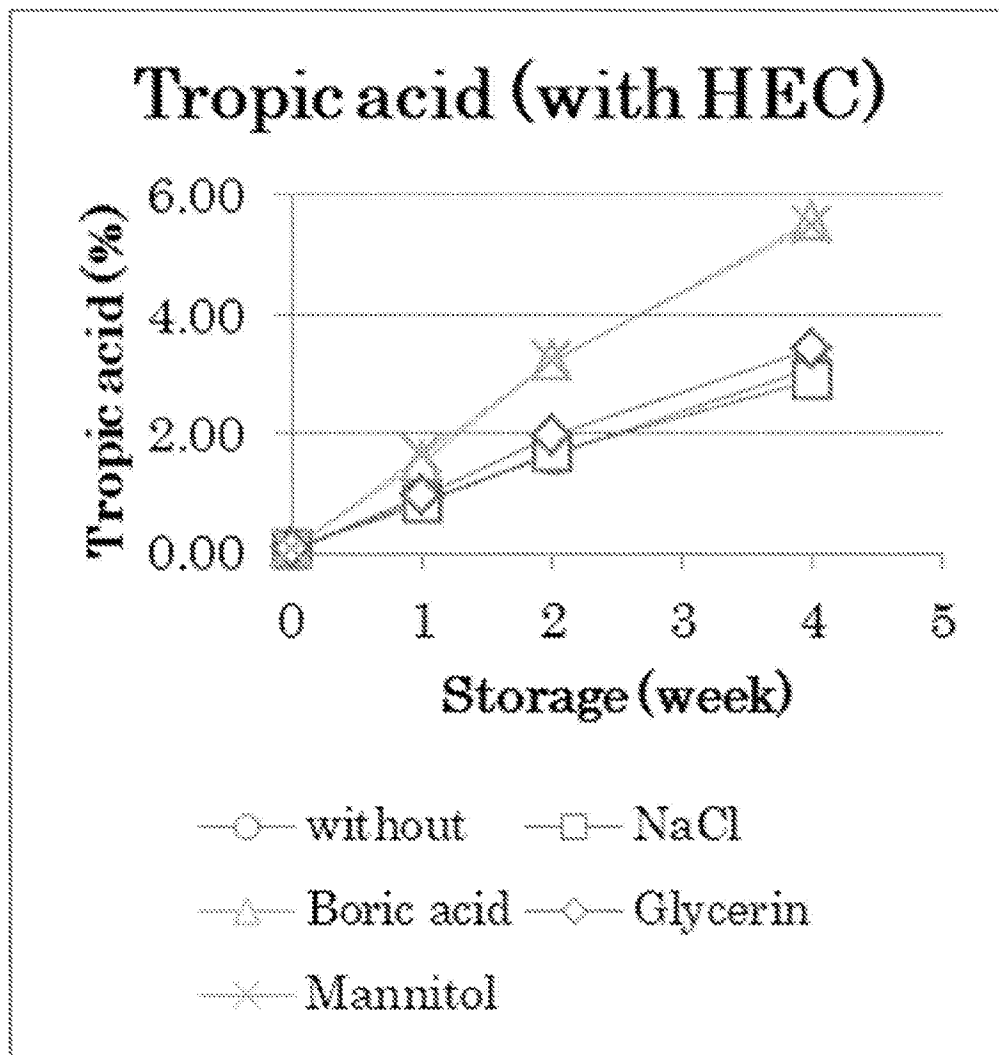
water-soluble polymer is hydroxyethyl cellulose.

- [Claim 32] The aqueous composition according to any one of claims 1 to 24 and 28 to 31, which is at a pH range of 4 - 6.
- [Claim 33] The aqueous composition according to any one of claims 1 to 32, wherein the concentration of phosphate buffer is 0.01 - 1.0 % (w/v).
- [Claim 34] The aqueous composition according to any one of claims 1 to 33, wherein the concentration of the atropine or a salt thereof is 0.001 to 0.025% (w/v).
- [Claim 35] The aqueous composition according to any one of claims 1 to 34, wherein the concentration of the atropine or a salt thereof is 0.001 to 0.01% (w/v).
- [Claim 36] The aqueous composition according to any one of claims 1 to 35, wherein the atropine or a salt thereof is atropine sulfate or a hydrate thereof.
- [Claim 37] The aqueous composition according to any one of claims 1 to 36, which is enclosed in a unit-dose container.
- [Claim 38] The aqueous composition according to any one of claims 1 to 37, wherein the aqueous composition is an eyedrop.
- [Claim 39] The aqueous composition according to any one of claims 1 to 38, for inhibiting and/or preventing progression of myopia.
- [Claim 40] Use of an aqueous composition according to any one of claims 1 to 38 in the preparation of a medicament to inhibit and/or preventing the progression of myopia.
- [Claim 41] A method for inhibiting and/or preventing progression of myopia comprising administering to a subject a composition according to any one of claims 1 to 38.
- [Claim 42] The aqueous composition according to any one of claims 1 to 38 for use in inhibiting and/or preventing progression of myopia.
- [Claim 43] A method for inhibiting the viscosity reduction of an aqueous composition comprising 0.001 - 0.1 % (w/v) atropine or a salt thereof and a water-soluble polymer which is at a pH range of 6 or lower, by adding a nonionic tonicity agent thereto.
- [Claim 44] A method for stabilizing atropine or a salt thereof in an aqueous composition comprising 0.001 - 0.1 % (w/v) atropine or a salt thereof and a water-soluble polymer which is at a pH range of 6 or lower, by adding a nonionic tonicity agent thereto.

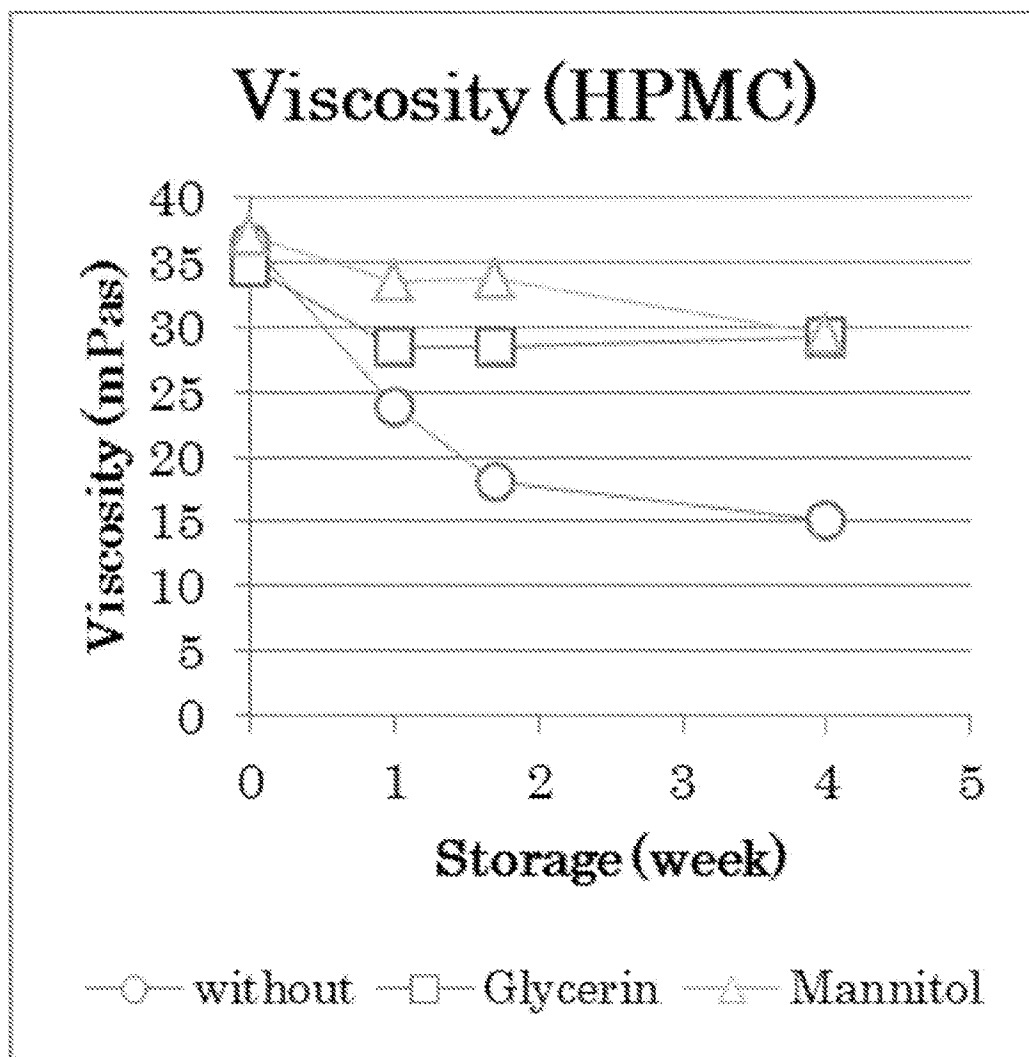
[Fig. 1]



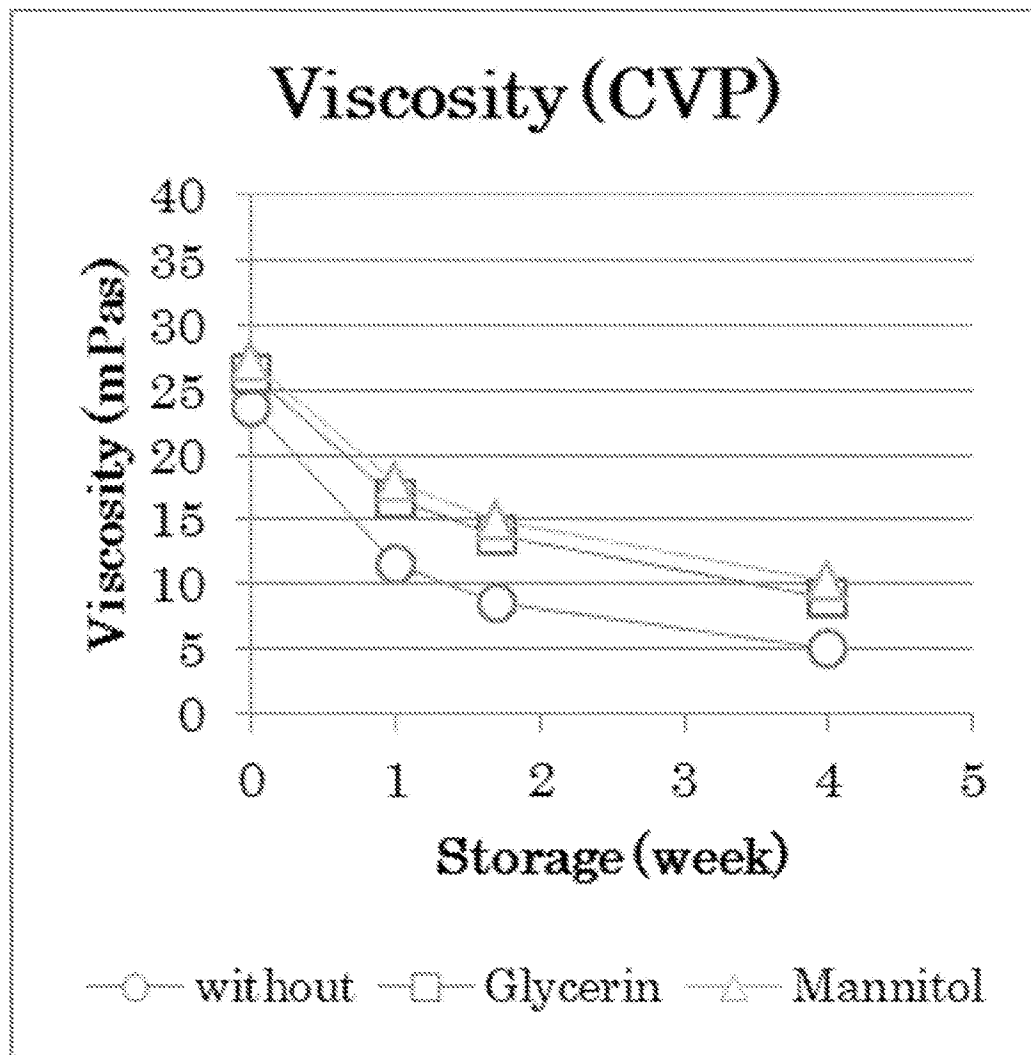
[Fig. 2]



[Fig. 3]



[Fig. 4]



INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2017/019423

A. CLASSIFICATION OF SUBJECT MATTER			
Int.Cl. See extra sheet			
According to International Patent Classification (IPC) or to both national classification and IPC			
B. FIELDS SEARCHED			
Minimum documentation searched (classification system followed by classification symbols)			
Int.Cl. A61K31/46, A61K9/08, A61K47/02, A61K47/10, A61K47/12, A61K47/18, A61K47/26, A61K47/38			
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched			
Published examined utility model applications of Japan 1922-1996 Published unexamined utility model applications of Japan 1971-2017 Registered utility model specifications of Japan 1996-2017 Published registered utility model applications of Japan 1994-2017			
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)			
JSTPlus/JMEDPlus/JST/580 (JDreamIII), CAPLUS/MEDLINE/EMBASE/BIOSIS (STN)			
C. DOCUMENTS CONSIDERED TO BE RELEVANT			
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	
X Y A	JP 1-203320 A (EISAI Co.Ltd.) 1989.08.16, Claims, page 3, upper left column, lines 14-20, page3, upper right column, lines 1-14, Example 2 (No Family)	1-5, 14-20, 23-29, 32-38, 43-44 39-42 6-13, 21-22, 30-31	
X Y A	WO 2015/200361 A1 (SYDNEXIS, INC.) 2015.12.30, Claims, [0018], [00118], [00236]-[00238], [00303], Table 6 & US 2015/0366854 A1 & EP 3160471 A1	1-12, 14-44 39-42 13	
Y	JP 2007-308398 A (Taiwan Chang-Gung Memorial Hospital) 2007.11.29, Claims, Examples (No Family)	39-42	
☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.			
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Date of the actual completion of the international search		Date of mailing of the international search report	
04.07.2017		11.07.2017	
Name and mailing address of the ISA/JP		Authorized officer	4C 3402
Japan Patent Office 3-4-3, Kasumigaseki, Chiyoda-ku, Tokyo 100-8915, Japan		Yumiko ISHII	Telephone No. +81-3-3581-1101 Ext. 3452

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP2017/019423

CLASSIFICATION OF SUBJECT MATTER

A61K31/46(2006.01)i, A61K9/08(2006.01)i, A61K47/02(2006.01)i,
A61K47/10(2006.01)i, A61K47/12(2006.01)i, A61K47/18(2006.01)i,
A61K47/26(2006.01)i, A61K47/38(2006.01)i



(51) International Patent Classification:

A61K 31/46 (2006.01) A61P 27/02 (2006.01)
A61K 9/08 (2006.01)

(21) International Application Number:

PCT/US2016/029222

(22) International Filing Date:

25 April 2016 (25.04.2016)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/151,926 23 April 2015 (23.04.2015) US
14/726,139 29 May 2015 (29.05.2015) US
PCT/US2015/037249 23 June 2015 (23.06.2015) US

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(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY,
BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM,
DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR,
KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG,
MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM,
PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC,
SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

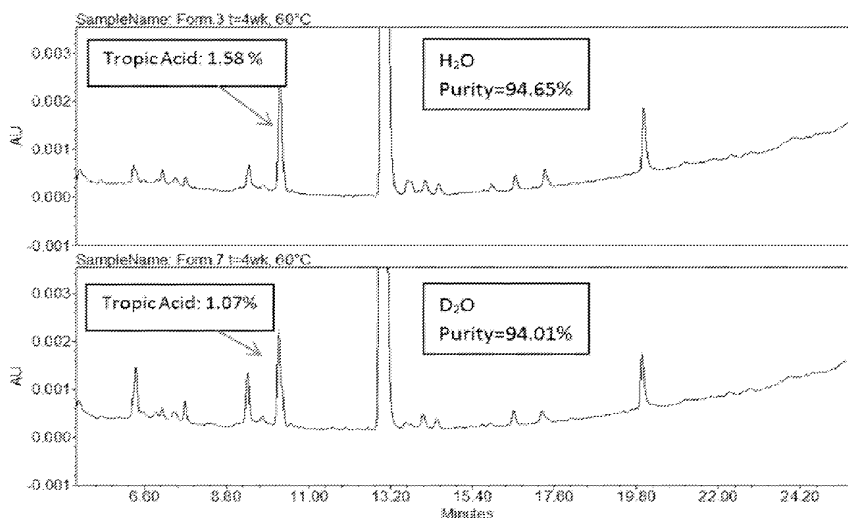
(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ,
TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU,
TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE,
DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU,
LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK,
SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished
upon receipt of that report (Rule 48.2(g))

(54) Title: OPHTHALMIC COMPOSITION

Fig. 4



(57) Abstract: Provided herein is an ophthalmic composition. In some embodiments, the ophthalmic composition includes a low concentration of an ophthalmic agent for treatment of an ophthalmic disorder or condition; and an ophthalmically acceptable carrier, wherein the ophthalmic agent is distributed with substantial uniformity throughout the ophthalmically acceptable carrier. Further disclosed herein include an ophthalmic composition including a low concentration of an ophthalmic agent and deuterated water. Also disclosed herein are methods of arresting or preventing myopia development by administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition as described herein.

OPHTHALMIC COMPOSITION**CROSS-REFERENCE**

[0001] This application claims the benefit of U.S. Provisional Application No. 62/151,926, filed April 23, 2015; is a continuation in part of U.S. Application No. 14/726,139, filed May 29, 2015; and is a continuation in part of PCT Application No. PCT/US2015/037249, which are incorporated herein by reference in their entirety.

BACKGROUND OF THE DISCLOSURE

[0002] Pharmaceutical formulations have an expiration date which is based on the degradation of the active ingredient.

SUMMARY OF THE DISCLOSURE

[0003] Provided herein are ophthalmic compositions. In some embodiments, disclosed herein is an ophthalmic composition, comprising from about 0.001 wt% to about 0.05 wt% of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9.

[0004] In some embodiments, provided herein is an ophthalmic composition, comprising from about 0.001 wt% to about 0.05 wt% of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9, wherein the muscarinic antagonist does not extend singlet oxygen lifetime.

[0005] In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the the muscarinic antagonist comprises atropine, atropine sulfate, scopolomine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine. In some embodiments, the muscarinic antagonist is atropine sulfate.

[0006] In some embodiments, the muscarinic antagonist quenches photogenerated singlet oxygen species in the composition. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the the muscarinic antagonist comprises atropine, atropine sulfate, scopolomine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine. In some embodiments, the muscarinic antagonist is atropine sulfate.

[0007] In some embodiments, the ophthalmic composition has a pD of one of: less than about 7.9, less than about 7.3, less than about 7.2, less than about 7.1, less than about 7, less than about 6.8, less than about 6.5, less than about 6.4, less than about 6.3, less than about 6.2, less than about 6.1, less than about 6, less than about 5.9, less than about 5.8, less than about 5.2, or less than about 4.8 after extended period of time under storage condition.

[0008] In some embodiments, the ophthalmic composition has a pD of one of: less than about 7.9, less than about 7.8, less than about 7.7, less than about 7.6, less than about 7.5, less than about 7.4, less than about 7.3, less than about 7.2, less than about 7.1, less than about 7, less than about 6.9, less than about 6.8, less than about 6.7, less than about 6.6, less than about 6.5, less than about 6.4, less than about 6.3, less than about 6.2, less than about 6.1, less than about 6.

[0009] In some embodiments, the ophthalmic composition comprises one of: at least about 80%, at least about 85%, at least about 90%, at least about 93%, at least about 95%, at least about 97%, at least about 98%, or at least about 99% of the muscarinic antagonist based on initial concentration after extended period of time under storage condition. As described in this disclosure, the percentage of the ophthalmic agent in the composition after storage is based on the amount of ophthalmic agent that is initially present in the composition (i.e. prior to the storage condition).

[0010] In some embodiments, the ophthalmic composition further has a potency of one of: at least 80%, at least 85%, at least 90%, at least 93%, at least 95%, at least 97%, at least 98%, or at least 99% after extended period of time under storage condition. As described in this disclosure, the potency of the ophthalmic agent in the composition after storage is based on the potency of ophthalmic agent that is initially present in the composition (i.e. prior to the storage condition).

[0011] In some embodiments, the extended period of time is one of: about 1 week, about 2 weeks, about 3 weeks, about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 8 months, about 10 months, about 12 months, about 18 months, about 24 months, about 36 months, about 4 years, or about 5 years.

[0012] In some embodiments, the storage condition has a storage temperature of from about 2°C to about 10°C or from about 16°C to about 26°C. In some embodiments, the storage condition has a storage temperature of about 25°C. In some embodiments, the storage condition has a storage temperature of about 40°C. In some embodiments, the storage condition has a storage temperature of about 60°C.

[0013] In some embodiments, the storage condition has a relative humidity of about 60%. In some embodiments, the storage condition has a relative humidity of about 75%.

[0014] In some embodiments, the muscarinic antagonist is present in the composition at a concentration of one of: from about 0.001 wt% to about 0.04 wt%, from about 0.001 wt% to about 0.03 wt%, from about 0.001 wt% to about 0.025 wt%, from about 0.001 wt% to about 0.02 wt%, from about 0.001 wt% to about 0.01 wt%, from about 0.001 wt% to about 0.008 wt%, or from about 0.001 wt% to about 0.005 wt%.

[0015] In some embodiments, the composition comprises less than 20% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 15% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition.

[0016] In some embodiments, the composition comprises less than 10% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 5% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 2.5% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 2.0% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 1.5% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 1.0% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.5% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.4% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.3% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.2% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.1% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the major degradant is tropic acid. As described in this disclosure, the percentage of the primary degradant in the composition after storage is based on the amount of ophthalmic agent that is initially present in the composition (i.e. prior to the storage condition).

[0017] In some embodiments, the composition is in a form of an aqueous solution.

[0018] In some embodiments, the composition further comprises an osmolarity adjusting agent. In some embodiments, the osmolarity adjusting agent is sodium chloride.

[0019] In some embodiments, the ophthalmic composition further comprises a preservative. In some embodiments, the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof.

[0020] In some embodiments, the ophthalmic composition further comprises a buffer agent. In some embodiments, the buffer agent is selected from borates, borate-polyol complexes, succinate, phosphate buffering agents, citrate buffering agents, acetate buffering agents, carbonate buffering agents, organic buffering agents, amino acid buffering agents, or combinations thereof.

[0021] In some embodiments, the ophthalmic composition further comprises a tonicity adjusting agent. In some embodiments, the tonicity adjusting agent is selected from sodium chloride, sodium

nitrate, sodium sulfate, sodium bisulfate, potassium chloride, calcium chloride, magnesium chloride, zinc chloride, potassium acetate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium thiosulfate, magnesium sulfate, disodium hydrogen phosphate, sodium dihydrogen phosphate, potassium dihydrogen phosphate, dextrose, mannitol, sorbitol, dextrose, sucrose, urea, propylene glycol, glycerin, trehalose, or a combination thereof.

[0022] In some embodiments, the composition is stored in a plastic container. In some embodiments, the material of the plastic container comprises low-density polyethylene (LDPE). In some cases, the material of the plastic container comprises polypropylene.

[0023] In some embodiments, the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof.

[0024] In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 50%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 40%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 30%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 20%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 10%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 5%. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 10 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 8 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 5 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 3 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 2 consecutive doses.

[0025] In some embodiments, the composition further comprises a pH adjusting agent. In some embodiments, the pH adjusting agent comprises HCl, NaOH, CH₃COOH, or C₆D₈O₇.

[0026] In some embodiments, the composition further comprises a pharmaceutically acceptable carrier. In some embodiments, the ophthalmically acceptable carrier further comprises at least one viscosity-enhancing agent. In some embodiments, the viscosity-enhancing agent is selected from cellulose-based polymers, polyoxyethylene-polyoxypropylene triblock copolymers, dextran-based polymers, polyvinyl alcohol, dextrin, polyvinylpyrrolidone, polyalkylene glycols, chitosan, collagen, gelatin, hyaluronic acid, or combinations thereof.

[0027] In some embodiments, the ophthalmic composition comprises one of: less than 60% of H₂O, less than 55% of H₂O, less than 50% of H₂O, less than 45% of H₂O, less than 40% of H₂O, less than 35% of H₂O, less than 30% of H₂O, less than 25% of H₂O, less than 20% of H₂O, less than 15% of H₂O, or less than 10% of H₂O.

[0028] In some embodiments, the ophthalmic composition comprises one of: less than 5% of H₂O, less than 4% of H₂O, less than 3% of H₂O, less than 2% of H₂O, less than 1% of H₂O, less than 0.5% of H₂O, less than 0.1% of H₂O, or 0% of H₂O.

[0029] In some embodiments, the ophthalmic composition is stored below room temperature prior to first use. In some embodiments, the ophthalmic composition is stored at between about 2 °C to about 10 °C prior to first use. In some embodiments, the ophthalmic composition is stored at between about 4 °C to about 8 °C prior to first use.

[0030] In some embodiments, the ophthalmic composition is stored at room temperature after first use. In some embodiments, the ophthalmic composition is stored at between about 16 °C to about 26 °C after first use.

[0031] In some embodiments, the ophthalmic composition is not formulated as an injectable formulation.

[0032] In some embodiments, the ophthalmic composition does not comprise water-hydrolyzable derivatives of α -amino or α -hydroxy- carboxylic acids.

[0033] In some embodiments, the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof.

[0034] In some embodiments, the ophthalmic composition is formulated as an ophthalmic solution for the treatment of an ophthalmic disorder. In some embodiments, the ophthalmic disorder or condition is pre-myopia, myopia, or progression of myopia. In some embodiments, the ophthalmic composition is formulated as an ophthalmic solution for the treatment of pre-myopia, myopia, or progression of myopia.

[0035] In some embodiments, the ophthalmic composition is a solution.

[0036] In some embodiments, disclosed herein is a method of treating an ophthalmic disorder comprising administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition described herein. In some embodiments, described herein is a method of treating an ophthalmic disorder, comprising administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition comprising from about 0.001 wt% to about 0.05 wt% of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9. In some embodiments, the ophthalmic composition is administered at predetermined time intervals over an extended period of time. In some embodiments, the ophthalmic composition is administered once every day. In some embodiments, the ophthalmic composition is administered every other day. In some embodiments, the ophthalmic composition is administered over 1 week, 2 weeks, 1 month, 2 months, 3 months, 6 months, 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 11 years, or 12-15 years. In some embodiments, the ophthalmic composition is stored below room temperature prior to first use. In some embodiments, the ophthalmic composition is stored at between about 2 °C to about 10 °C prior to first use. In some embodiments, the ophthalmic composition is stored at between about 4 °C to about 8 °C prior to first use. In some embodiments, the ophthalmic composition

is stored at room temperature after first use. In some embodiments, the ophthalmic composition is stored at between about 16 °C to about 26 °C after first use.

[0037] In some embodiments, disclosed herein is a method of arresting myopia development that comprises administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition described herein. Also described herein is a method of preventing myopia development that comprises administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition described herein. In some embodiments, described herein is a method of arresting or preventing myopia development, comprising administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition comprising from about 0.001 wt% to about 0.05 wt% of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9. In some embodiments, the ophthalmic composition is administered at predetermined time intervals over an extended period of time. In some embodiments, the ophthalmic composition is administered once every day. In some embodiments, the ophthalmic composition is administered every other day. In some embodiments, the ophthalmic composition is administered over 1 week, 2 weeks, 1 month, 2 months, 3 months, 6 months, 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 11 years, or 12-15 years. In some embodiments, the ophthalmic composition is stored below room temperature prior to first use. In some embodiments, the ophthalmic composition is stored at between about 2 °C to about 10 °C prior to first use. In some embodiments, the ophthalmic composition is stored at between about 4 °C to about 8 °C prior to first use. In some embodiments, the ophthalmic composition is stored at room temperature after first use. In some embodiments, the ophthalmic composition is stored at between about 16 °C to about 26 °C after first use.

[0038] In some embodiments, disclosed herein is an ophthalmic solution that comprises from about 0.001 wt% to about 0.05 wt% of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9. In some embodiments, the ophthalmic solution has a pD of one of: less than about 7.3, less than about 7.2, less than about 7.1, less than about 7, less than about 6.8, less than about 6.5, less than about 6.4, less than about 6.3, less than about 6.2, less than about 6.1, less than about 6, less than about 5.9, less than about 5.8, less than about 5.2, or less than about 4.8 after extended period of time under storage condition. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the ophthalmic solution comprises one of: less than 5% of H₂O, less than 4% of H₂O, less than 3% of H₂O, less than 2% of H₂O, less than 1% of H₂O, less than 0.5% of H₂O, less than 0.1% of H₂O, or 0% of H₂O. In some embodiments, the ophthalmic composition comprises one of: at least about 80%, at least about 85%, at least about 90%, at least about 93%, at least about 95%, at least about 97%, at least about 98%, or at least about 99% of the muscarinic antagonist based on initial concentration after extended period of time under storage condition. In some embodiments, the ophthalmic composition further has a potency of one of: at least 80%, at least 85%, at least 90%, at least 93%, at least 95%, at least 97%, at least 98%, or

at least 99% after extended period of time under storage condition. In some embodiments, the extended period of time is one of: about 1 week, about 2 weeks, about 3 weeks, about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 8 months, about 10 months, about 12 months, about 18 months, about 24 months, about 36 months, about 4 years, or about 5 years. In some embodiments, the muscarinic antagonist is present in the composition at a concentration of one of: from about 0.001 wt% to about 0.04 wt%, from about 0.001 wt% to about 0.03 wt%, from about 0.001 wt% to about 0.025 wt%, from about 0.001 wt% to about 0.02 wt%, from about 0.001 wt% to about 0.01 wt%, from about 0.001 wt% to about 0.008 wt%, or from about 0.001 wt% to about 0.005 wt%. In some embodiments, the storage condition has a storage temperature of from about 2°C to about 10°C or from about 16°C to about 26°C. In some embodiments, the ophthalmic composition has a dose-to-dose muscarinic antagonist concentration variation of one of: less than 50%, less than 40%, less than 30%, less than 20%, less than 10%, or less than 5%. In some embodiments, the dose-to-dose muscarinic antagonist concentration variation is based on one of: 10 consecutive doses, 8 consecutive doses, 5 consecutive doses, 3 consecutive doses, or 2 consecutive doses.

[0039] In some embodiments, disclosed herein is an ophthalmic composition, comprising from about 0.001 wt% to about 0.05 wt% of a muscarinic antagonist and water, at a pH of from about 3.8 to about 7.5.

[0040] In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine or atropine sulfate.

[0041] In some embodiments, the ophthalmic composition comprises one of: at least about 80%, at least about 85%, at least about 90%, at least about 93%, at least about 95%, at least about 97%, at least about 98%, or at least about 99% of the muscarinic antagonist based on initial concentration after extended period of time under storage condition.

[0042] In some embodiments, the ophthalmic composition has a pH of one of: less than about 7.3, less than about 7.2, less than about 7.1, less than about 7, less than about 6.8, less than about 6.5, less than about 6.4, less than about 6.3, less than about 6.2, less than about 6.1, less than about 6, less than about 5.9, less than about 5.8, less than about 5.2, less than about 4.8, or less than about 4.2 after extended period of time under storage condition.

[0043] In some embodiments, the ophthalmic composition further has a potency of one of: at least 80%, at least 85%, at least 90%, at least 93%, at least 95%, at least 97%, at least 98%, or at least 99% after extended period of time under storage condition.

[0044] In some embodiments, the extended period of time is one of: about 1 week, about 2 weeks, about 3 weeks, about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 8 months, about 10 months, about 12 months, about 18 months, about 24 months, about 36 months, about 4 years, or about 5 years.

[0045] In some embodiments, the storage condition has a storage temperature of one of: about 25°C, about 40°C, or about 60°C. In some embodiments, the storage condition has a storage temperature of from about 2°C to about 10°C or from about 16°C to about 26°C.

[0046] In some embodiments, the storage condition has a relative humidity of about 60% or about 75%.

[0047] In some embodiments, the muscarinic antagonist is present in the composition at a concentration of one of: from about 0.001 wt% to about 0.04 wt%, from about 0.001 wt% to about 0.03 wt%, from about 0.001 wt% to about 0.025 wt%, from about 0.001 wt% to about 0.02 wt%, from about 0.001 wt% to about 0.01 wt%, from about 0.001 wt% to about 0.008 wt%, or from about 0.001 wt% to about 0.005 wt%.

[0048] In some embodiments, the ophthalmic composition further comprises an osmolarity adjusting agent. In some embodiments, the osmolarity adjusting agent is sodium chloride.

[0049] In some embodiments, the ophthalmic composition further comprises a preservative. In some embodiments, the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof.

[0050] In some embodiments, the ophthalmic composition further comprises a buffer agent. In some embodiments, the buffer agent is selected from borates, borate-polyol complexes, succinate, phosphate buffering agents, citrate buffering agents, acetate buffering agents, carbonate buffering agents, organic buffering agents, amino acid buffering agents, or combinations thereof.

[0051] In some embodiments, the ophthalmic composition further comprises a tonicity adjusting agent. In some embodiments, the tonicity adjusting agent is selected from sodium chloride, sodium nitrate, sodium sulfate, sodium bisulfate, potassium chloride, calcium chloride, magnesium chloride, zinc chloride, potassium acetate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium thiosulfate, magnesium sulfate, disodium hydrogen phosphate, sodium dihydrogen phosphate, potassium dihydrogen phosphate, dextrose, mannitol, sorbitol, dextrose, sucrose, urea, propylene glycol, glycerin, trehalose, or a combination thereof.

[0052] In some embodiments, the ophthalmic composition is stored in a plastic container. In some embodiments, the material of the plastic container comprises low-density polyethylene (LDPE).

[0053] In some embodiments, the ophthalmic composition has a dose-to-dose muscarinic antagonist concentration variation of one of: less than 50%, less than 40%, less than 30%, less than 20%, less than 10%, or less than 5%.

[0054] In some embodiments, the dose-to-dose muscarinic antagonist concentration variation is based on one of: 10 consecutive doses, 8 consecutive doses, 5 consecutive doses, 3 consecutive doses, or 2 consecutive doses.

[0055] In some embodiments, the ophthalmic composition has a pH of one of: from about 3.8 to about 7.5, from about 4.2 to about 7.5, from about 4.8 to about 7.3, from about 5.2 to about 7.2, from about 5.8 to about 7.1, from about 6.0 to about 7.0, or from about 6.2 to about 6.8.

[0056] In some embodiments, the ophthalmic composition further comprises a pH adjusting agent. In some embodiments, the pH adjusting agent comprises HCl, NaOH, CH₃COOH, or C₆H₈O₇.

[0057] In some embodiments, the ophthalmic composition comprises one of: less than 60% of D₂O, less than 55% of D₂O, less than 50% of D₂O, less than 45% of D₂O, less than 40% of D₂O, less than 35% of D₂O, less than 30% of D₂O, less than 25% of D₂O, less than 20% of D₂O, less than 15% of D₂O, or less than 10% of D₂O.

[0058] In some embodiments, the ophthalmic composition comprises one of: less than 5% of D₂O, less than 4% of D₂O, less than 3% of D₂O, less than 2% of D₂O, less than 1% of D₂O, less than 0.5% of D₂O, less than 0.1% of D₂O, or 0% of D₂O. In some embodiments, ophthalmic composition is essentially free of D₂O.

[0059] In some embodiments, the composition further comprises a pharmaceutically acceptable carrier.

[0060] In some embodiments, the ophthalmic composition is formulated as an ophthalmic solution for the treatment of an ophthalmic disorder. In some embodiments, the ophthalmic disorder or condition is pre-myopia, myopia, or progression of myopia.

[0061] In some embodiments, the ophthalmic composition is not formulated as an injectable formulation.

[0062] Other features and technical effects of the methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only.

BRIEF DESCRIPTION OF THE DRAWINGS

[0063] The novel features of the disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the disclosure are utilized, and the accompanying drawings of which:

[0064] Fig. 1A-Fig. 1C show the shelf life prediction of 0.01% atropine sulfate solution with a primary degradant RRT 0.87-0.89, and a n.m.t. of 0.5% area, based on data obtained from samples stored at 25°C and 40°C. The pH range of the atropine sulfate solution is from 5.9-6.2.

[0065] Fig. 2A-Fig. 2C show the shelf life prediction of 0.01% atropine sulfate solution with a primary degradant RRT 0.87-0.89, and a n.m.t. of 0.5% area, based on data obtained from samples stored at 25°C and 60°C. The pH range of the atropine sulfate solution is from 5.9-6.2.

[0066] Fig. 3 illustrates mass balance at 4 weeks and at 60°C condition for atropine sulfate formulations disclosed in Example 9.

[0067] Fig. 4 illustrates atropine sulfate (0.010%) formulation stability in acetic acid. The atropine sulfate formulation is formulated with acetic acid and either with H₂O (top panel, Formulation 3) or D₂O (bottom panel, Formulation 7). Formulation 3 has a pH of 4.8 and Formulation 7 has a pD of 5.2. Both formulations are stored at 60 °C for 4 weeks prior to analysis.

[0068] Fig. 5 illustrates atropine sulfate (0.01%) formulation stability in citric acid. The atropine sulfate formulation is formulated with citric acid and either with H₂O (top panel, Formulation 5) or D₂O (bottom panel, Formulation 8). Formulation 5 has a pH of 5.8 and Formulation 8 has a pD of 6.2. Both formulations are stored at 60 °C for 4 weeks prior to analysis.

[0069] Fig. 6 illustrates comparison of total RS and tropic acid for atropine sulfate (0.025%) formulation (Formulation 4) at pH 4.8 in H₂O.

[0070] Fig. 7 illustrates comparison of total RS and tropic acid for atropine sulfate (0.01%) formulation (Formulation 7) at pD 5.2 in D₂O.

[0071] Fig. 8 illustrates comparison of total RS and tropic acid for atropine sulfate (0.01%) formulation (Formulation 5) at pH 5.8 in H₂O.

[0072] Fig. 9 illustrates comparison of total RS and tropic acid for atropine sulfate (0.025%) formulation (Formulation 6) at pH 5.8 in H₂O.

[0073] Fig. 10 illustrates estimated shelf lifes for D₂O and H₂O formulations disclosed in Examples 11 and 12.

[0074] Fig. 11A-Fig. 11C illustrate stability of atropine sulfate formulation 8 in H₂O and D₂O under three storage conditions.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0075] The present disclosure recognizes that there is a need for a stabilized ophthalmic composition with extended shelf life upon storage. The present disclosure also recognizes that there is a need for stabilizing an ophthalmic composition through arresting or reducing hydrolysis of at least some of its active agents. The present disclosure further recognizes that there is a need for an ophthalmic composition that provides convenient and effective delivery of a muscarinic antagonist such as atropine in the eye of a patient.

[0076] The present disclosure recognizes that muscarinic antagonist (e.g. atropine or its pharmaceutically acceptable salts) prevents or arrests the development of myopia in humans, for example as evidenced by reduction of the rate of increase of myopia in young people. The present disclosure also recognizes the effects of muscarinic antagonist (e.g. atropine or its pharmaceutically acceptable salts) on reduction of axial elongation and myopia in visually impaired chick eyes, and on ocular growth and muscarinic cholinergic receptors in young rhesus monkeys.

[0077] In addition, the present disclosure recognizes that systemic absorption of muscarinic antagonist (e.g. atropine) sometimes leads to undesirable side effect, and that localized delivery of muscarinic antagonist (e.g. atropine or its pharmaceutically acceptable salts) reduces or prevents the aforementioned systemic exposure.

[0078] Further, the present disclosure recognizes that some liquid muscarinic antagonist (e.g. atropine) compositions are formulated at a relatively lower pH range (e.g. less than 4.5) for stability of muscarinic antagonist (e.g. atropine or its pharmaceutically acceptable salts). For some individuals, the lower pH range in some instances causes discomfort or other side effects such as pain or burning sensation in the eye, which is prevented or alleviated by formulating muscarinic antagonist (e.g. atropine) compositions at higher pH ranges. For some individuals, the lower pH in some instances elicits a tear response which reduces the absorption of the drug in the eye and therefore the effectiveness.

[0079] Still further, the present disclosure recognizes that some muscarinic antagonist (e.g. atropine) liquid compositions formulated at lower concentrations (e.g. 0.001% to 0.05%) present stability challenges that are less so in higher concentrations (e.g. 0.1-1%). Without wishing to be bound by any particular theory, it is contemplated that the some muscarinic antagonist (e.g. atropine) contributes to the stability of an ophthalmic composition, such as an aqueous solution. For example, the concentration of the muscarinic antagonist (e.g. atropine) in some embodiments affects the pH or pD of the ophthalmic composition, such as with the muscarinic antagonist acting as a buffering agent. Furthermore, the concentration of the muscarinic antagonist (e.g. atropine) in some embodiments affects the interaction between the muscarinic antagonist and other ingredients of the ophthalmic composition, which in turn affects the stability of the ophthalmic composition.

[0080] Finally, the present disclosure recognizes that deuterated water stabilizes ophthalmic compositions. In some cases, the deuterated water is a weak acid as compared to H₂O, as such deuterated water comprises a lower concentration of the reactive species (e.g., -OD) which in some instances leads to base catalyzed hydrolysis of an active agent in the ophthalmic composition. As such, in some instances compositions comprising deuterated water leads to reduced base catalyzed hydrolysis when compared to compositions comprising H₂O. In some instances, deuterated water further lowers the buffering capacity of an ophthalmic composition, leading to less tear reflex in the eye.

[0081] Myopia, axial elongation of the eye, affects a large proportion of the population. The onset of myopia is generally during the grade school years and progresses until growth of the eye is completed. The present disclosure recognizes the importance of compositions and treatments for preventing or arresting the development of myopia, especially compositions and treatments that allow convenient administration, reduce potential side effects, has suitable stability, and/or provide relatively consistent therapeutic effects.

[0082] Ophthalmic Muscarinic Antagonist Composition

[0083] Provided herein is an ophthalmic composition containing low concentrations of an ophthalmic agent. In some embodiments, the ophthalmic composition includes from about 0.001 wt% to

about 0.05 wt% of an ophthalmic agent for treatment of an ophthalmic disorder or condition; and an ophthalmically acceptable carrier, wherein the ophthalmic agent is distributed with substantial uniformity throughout the ophthalmically acceptable carrier. In some instances, the ophthalmic agent is a muscarinic antagonist.

[0084] Provided herein is an ophthalmic composition containing low concentrations of a muscarinic antagonist. In some embodiments, the ophthalmic composition includes from about 0.001 wt% to about 0.05 wt% of a muscarinic antagonist for treatment of an ophthalmic disorder or condition; and an ophthalmically acceptable carrier, wherein the muscarinic antagonist is distributed with substantial uniformity throughout the ophthalmically acceptable carrier.

[0085] In some instances, the muscarinic antagonist includes atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, atropine methonitrate, diphenhydramine, dimenhydrinate, dicyclomine, flavoxate, oxybutynin, tiotropium, hyoscine, scopolomine (L-hyoscine), hydroxyzine, ipratropium, tropicamide, cyclopentolate, pirenzapine, homatropine, solifenacin, darifenacin, benztropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, tolterodine, or a combination thereof. In some instances, the muscarinic antagonist includes atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt or prodrug thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

[0086] In some embodiments, the ophthalmic composition comprise a muscarinic antagonist selected from atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, atropine methonitrate, diphenhydramine, dimenhydrinate, dicyclomine, flavoxate, oxybutynin, tiotropium, hyoscine, scopolomine (L-hyoscine), hydroxyzine, ipratropium, tropicamide, cyclopentolate, pirenzapine, homatropine, solifenacin, darifenacin, benztropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, tolterodine, or a combination thereof. In some instances, the muscarinic antagonist includes atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, or homatropine.

[0087] In some embodiments, the ophthalmic composition comprise two or more muscarinic antagonists in which the two or more muscarinic antagonists comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, atropine methonitrate, diphenhydramine, dimenhydrinate, dicyclomine, flavoxate, oxybutynin, tiotropium, hyoscine, scopolomine (L-hyoscine), hydroxyzine, ipratropium, tropicamide, cyclopentolate, pirenzapine, homatropine, solifenacin, darifenacin, benztropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, tolterodine, or a combination thereof. In some instances, the muscarinic antagonist includes atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or any combination thereof.

[0088] In some embodiments, the ophthalmic composition comprises one or more muscarinic antagonist in combination with one or more sympathetic agonists. In some embodiments, the sympathetic agonist is selected from phenylephrine or hydroxyamphetamine. In some embodiments, the ophthalmic composition comprises one or more of muscarinic antagonist: atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, atropine methonitrate, diphenhydramine, dimenhydrinate, dicyclomine, flavoxate, oxybutynin, tiotropium, hyoscine, scopolomine (L-hyoscine), hydroxyzine, ipratropium, tropicamide, cyclopentolate, pirenzapine, homatropine, solifenacin, darifenacin, benztropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, or tolterodine; in combination with one or more of sympathetic agonists: phenylephrine or hydroxyamphetamine.

[0089] Provided herein is an ophthalmic composition containing low concentrations of atropine or its pharmaceutically acceptable salts. In some embodiments, the ophthalmic composition includes from about 0.001 wt% to about 0.05 wt% of atropine or its pharmaceutically acceptable salts for treatment of an ophthalmic disorder or condition; and an ophthalmically acceptable carrier, wherein the ophthalmic agent is distributed with substantial uniformity throughout the ophthalmically acceptable carrier.

[0090] Provided herein is an ophthalmic composition containing low concentrations of atropine sulfate. In some embodiments, the ophthalmic composition includes from about 0.001 wt% to about 0.05 wt% of atropine sulfate for treatment of an ophthalmic disorder or condition; and an ophthalmically acceptable carrier, wherein the ophthalmic agent is distributed with substantial uniformity throughout the ophthalmically acceptable carrier.

[0091] In some embodiments, the ophthalmic disorder or condition is pre-myopia, myopia or progression of myopia.

[0092] The present disclosure further recognizes that the clinical use of atropine as a therapy has been limited due to its ocular side effects including glare from pupillary dilation and blurred vision due to loss of accommodation. Without wishing to be bound by any particular theory, it is contemplated that the limited use of atropine against myopia development, include its ocular side effects, is attributable to the concentration of atropine used in known ophthalmic formulations (e.g. 1wt% or higher).

[0093] The present disclosure further recognizes the challenges present in formulation of compositions that contain low concentrations, especially very low concentrations (e.g. from about 0.001 wt% to about 0.5 wt%), of ophthalmic agents, such as muscarinic antagonist (e.g. atropine or its pharmaceutically acceptable salts). In particular, pharmaceutical compositions with ophthalmic agent at such low concentrations are difficult to maintain dose-to-dose uniformity in term of ophthalmic agent content and/or distribution.

[0094] In some aspects, described herein are formulations or solutions of muscarinic antagonist (e.g., atropine) formulated in deuterated water. In some aspects, formulations or solutions of muscarinic antagonist (e.g., atropine) formulated in deuterated water are stable at different temperatures, at different relative humidity, with an acidic pD, and with a potency of at least 80% relative to the ophthalmic agent.

In additional aspects, formulations or solutions of muscarinic antagonist (e.g., atropine) formulated in deuterated water has a lowered buffering capacity. In such instances, the lowered buffering capacity of the ophthalmic formulations or solutions when administered into the eye allows the ophthalmic formulation or solution to reach physiological pH at a faster rate than compared to an equivalent ophthalmic formulation or solution formulated in H₂O.

[0095] In some aspects, described herein are formulations of muscarinic antagonist (e.g. atropine) at low concentrations that does not have a dose-to-dose variation. In some aspects, described herein are formulations of muscarinic antagonist (e.g. atropine) at low concentrations that are stable at different temperatures, at different relative humidity, with an acidic pD, and with a potency of at least 80% relative to the ophthalmic agent.

[0096] In other aspects, described herein include formulating the ophthalmic composition as an ophthalmic gel or an ophthalmic ointment. For example, some ophthalmic gel or an ophthalmic ointment described herein allows desirable dose-to-dose uniformity, reduced or limited systemic exposure, or combinations thereof.

[0097] Ophthalmic Solution Muscarinic Antagonist Composition

[0098] Disclosed herein, in certain embodiments, is an ophthalmic composition formulated as an aqueous solution. In some embodiments, the ophthalmic composition comprises from about 0.001 wt% to about 0.05 wt% of a muscarinic antagonist and deuterated water. As used herein, deuterated water refers to D₂O, DHO, heavy water, and/or deuterium oxide.

[0099] In some embodiments, the composition comprises at least about 70% of the ophthalmic agent (e.g. muscarinic antagonist) for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 75% of the ophthalmic agent (e.g. muscarinic antagonist) for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 80% of the ophthalmic agent (e.g. muscarinic antagonist) for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 81% of the ophthalmic agent (e.g. muscarinic antagonist) for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 82% of the ophthalmic agent (e.g. muscarinic antagonist) for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 83% of the ophthalmic agent (e.g. muscarinic antagonist) for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 84% of the ophthalmic agent (e.g. muscarinic antagonist) for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 85% of the ophthalmic agent (e.g. muscarinic antagonist) for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 86% of the ophthalmic agent (e.g. muscarinic antagonist) for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 87% of the ophthalmic agent (e.g. muscarinic antagonist) for an extended period of time under storage condition. In some embodiments, the

92% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least 93% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least 94% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least 95% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least 96% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least 97% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least 98% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least 99% after extended period of time under storage condition.

[00101] In some embodiments, the extended period of time is at least 1 week. In some embodiments, the extended period of time is at least 2 weeks. In some embodiments, the extended period of time is at least 3 weeks. In some embodiments, the extended period of time is at least 1 month. In some embodiments, the extended period of time is at least 2 months. In some embodiments, the extended period of time is at least 3 months. In some embodiments, the extended period of time is at least 4 months. In some embodiments, the extended period of time is at least 5 months. In some embodiments, the extended period of time is at least 6 months. In some embodiments, the extended period of time is at least 7 months. In some embodiments, the extended period of time is at least 8 months. In some embodiments, the extended period of time is at least 9 months. In some embodiments, the extended period of time is at least 10 months. In some embodiments, the extended period of time is at least 11 months. In some embodiments, the extended period of time is at least 12 months (i.e. 1 year). In some embodiments, the extended period of time is at least 18 months (i.e. 1.5 years). In some embodiments, the extended period of time is at least 24 months (i.e. 2 years). In some embodiments, the extended period of time is at least 36 months (i.e. 3 years). In some embodiments, the extended period of time is at least 3 years. In some embodiments, the extended period of time is at least 5 years, or more.

[00102] In some embodiments, the temperature of the storage condition is between about 20°C and about 70°C. In some embodiments, the temperature of the storage condition is between about 25°C and about 65°C, about 30°C and about 60°C, about 35°C and about 55°C, or about 40°C and about 50°C. In some embodiments, the temperature of the storage condition is about 25°C. In some embodiments, the temperature of the storage condition is about 40°C. In some embodiments, the temperature of the storage condition is about 60°C.

[00103] In some embodiments, the relative humidity of the storage condition is between about 50% and about 80%, or between about 60% and about 75%. In some embodiments, the relative humidity of the storage condition is about 60%. In some embodiments, the relative humidity of the storage condition is about 75%.

[00104] In some embodiments, the composition comprises less than 60% of H₂O. In some embodiments, the composition comprises less than 55% of H₂O. In some embodiments, the composition comprises less than 50% of H₂O. In some embodiments, the composition comprises less than 45% of

H₂O. In some embodiments, the composition comprises less than 40% of H₂O. In some embodiments, the composition comprises less than 35% of H₂O. In some embodiments, the composition comprises less than 30% of H₂O. In some embodiments, the composition comprises less than 25% of H₂O. In some embodiments, the composition comprises less than 20% of H₂O. In some embodiments, the composition comprises less than 15% of H₂O. In some embodiments, the composition comprises less than 10% of H₂O.

[00105] In some embodiments, the composition comprises from less than 5% of H₂O to 0% of H₂O. In some embodiments, the composition comprises less than 5% of H₂O. In some embodiments, the composition comprises less than 4.5% of H₂O. In some embodiments, the composition comprises less than 4% of H₂O. In some embodiments, the composition comprises less than 3.5% of H₂O. In some embodiments, the composition comprises less than 3% of H₂O. In some embodiments, the composition comprises less than 2.5% of H₂O. In some embodiments, the composition comprises less than 2% of H₂O. In some embodiments, the composition comprises less than 1.5% of H₂O. In some embodiments, the composition comprises less than 1% of H₂O. In some embodiments, the composition comprises less than 0.5% of H₂O. In some embodiments, the composition comprises less than 0.4% of H₂O. In some embodiments, the composition comprises less than 0.3% of H₂O. In some embodiments, the composition comprises less than 0.2% of H₂O. In some embodiments, the composition comprises less than 0.1% of H₂O. In some embodiments, the composition comprises 0% of H₂O.

[00106] In some embodiments, the composition has a pD of between about 4 and about 8, about 4.5 and about 7.8, about 5 and about 7.5, or about 5.5 and about 7. In some embodiments, the composition has a pD of less than about 7.5. In some embodiments, the composition has a pD of less than about 7.4. In some embodiments, the composition has a pD of less than about 7.3. In some embodiments, the composition has a pD of less than about 7.2. In some embodiments, the composition has a pD of less than about 7.1. In some embodiments, the composition has a pD of less than about 7. In some embodiments, the composition has a pD of less than about 6.9. In some embodiments, the composition has a pD of less than about 6.8. In some embodiments, the composition has a pD of less than about 6.7. In some embodiments, the composition has a pD of less than about 6.6. In some embodiments, the composition has a pD of less than about 6.5. In some embodiments, the composition has a pD of less than about 6.4. In some embodiments, the composition has a pD of less than about 6.3. In some embodiments, the composition has a pD of less than about 6.2. In some embodiments, the composition has a pD of less than about 6.1. In some embodiments, the composition has a pD of less than about 6. In some embodiments, the composition has a pD of less than about 5.9. In some embodiments, the composition has a pD of less than about 5.8. In some embodiments, the composition has a pD of less than about 5.7. In some embodiments, the composition has a pD of less than about 5.6. In some embodiments, the composition has a pD of less than about 5.5. In some embodiments, the composition has a pD of less than about 5.4. In some embodiments, the composition has a pD of less than about 5.3. In some embodiments, the composition has a pD of less than about 5.2. In some embodiments,

the composition has a pD of less than about 5.1. In some embodiments, the composition has a pD of less than about 5. In some embodiments, the composition has a pD of less than about 4.9. In some embodiments, the composition has a pD of less than about 4.8. In some embodiments, the composition has a pD of less than about 4.7. In some embodiments, the composition has a pD of less than about 4.6. In some embodiments, the composition has a pD of less than about 4.5. In some embodiments, the composition has a pD of less than about 4.4. In some embodiments, the composition has a pD of less than about 4.3. In some embodiments, the composition has a pD of less than about 4.2. In some embodiments, the composition has a pD of less than about 4.1. In some embodiments, the composition has a pD of less than about 4.

[00107] In some embodiments, the composition comprising deuterated water has a lowered buffering capacity than an equivalent composition comprising H₂O. As described elsewhere herein, in some embodiments, the lowered buffering capacity allows the composition comprising deuterated water to normalize to physiological pH at a faster rate than a composition comprising H₂O. In some embodiments, the lowered buffering capacity allows the composition to induce less tear reflex than an equivalent composition comprising H₂O.

[00108] In some instances, the composition comprising deuterated water stabilizes muscarinic antagonist (e.g., atropine). In some embodiments, this is due to a lower concentration of the reactive species (e.g., -OD) in the D₂O aqueous system compared to the concentration of the reactive species (e.g., -OH) in an equivalent H₂O aqueous system. In some cases, base catalyzed hydrolysis leads to the presence of tropine degradant from atropine. In some cases, with a lower concentration of the reactive species that causes tropine degradant formation, atropine solution is more stable in a D₂O aqueous system than compared to an equivalent H₂O aqueous system. In some embodiments, the ophthalmic composition formulated with deuterated water allows for a more stable ophthalmic composition relative to the ophthalmic composition formulated with H₂O.

[00109] In some embodiments, the composition comprises less than 20% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 15% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition.

[00110] In some embodiments, the composition comprises less than 10% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 5% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 2.0% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 1.5% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 1.0% of major degradant based on the concentration of the ophthalmic agent after

extended period of time under storage condition. In some embodiments, the composition comprises less than 0.5% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.4% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.3% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.2% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.1% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the major degradant is tropic acid.

[00111] In some embodiments, the primary degradant is an early eluting related substance at RRT of 0.87-0.89 according to the UPLC method described herein (Table 10). In some instances, the early eluting related substance is referred to as RRT 0.87-0.89. In some embodiments, the primary degradant is RRT 0.87-0.89.

[00112] In some embodiments, the composition does not stabilize singlet oxygen upon irradiation with UV. In some cases, one or more of muscarinic antagonists described herein does not extend singlet oxygen lifetime. In some cases, one or more of muscarinic antagonists described herein is a radical scavenger, which quenches photogenerated singlet oxygen species within the composition. In some instances, the one or more muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolamine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some instances, the one or more muscarinic antagonist comprises atropine, atropine sulfate, homatropine, scopolamine or a combination thereof. In some instances, the one or more muscarinic antagonist comprises atropine or atropine sulfate. In some instances, a composition comprising atropine or atropine sulfate does not stabilize singlet oxygen upon irradiation with UV. In some instances, a composition comprising atropine or atropine sulfate quenches photogenerated singlet oxygen species present in the composition.

[00113] Ophthalmic Muscarinic Antagonist Concentration

[00114] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.050%, between about 0.005% to about 0.050%, between about 0.010% to about 0.050%, between about 0.015% to about 0.050%, between about 0.020% to about 0.050%, between about 0.025% to about 0.050%, between about 0.030% to about 0.050%, between about 0.035% to about 0.050%, between about 0.040% to about 0.050%, or between about 0.045% to about 0.050% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some instances, the prodrug of the ophthalmic agent (e.g. muscarinic antagonist) is chemically converted into the ophthalmic agent (e.g. muscarinic antagonist) after the administration of the ophthalmic composition. In a non-limiting example, the muscarinic antagonist

prodrug has a chemical bond that is cleavable by one or more enzymes in tears. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate. As described herein, the ophthalmic agent includes optically pure stereoisomers, optically enriched stereoisomers, and a racemic mixture of stereoisomers. For example, some ophthalmic compositions disclosed herein includes atropine or atropine sulfate in which the atropine is a racemic mixture of D- and L-isomers; and some ophthalmic compositions disclosed herein includes atropine or atropine sulfate in which the atropine is a optically enriched in favor of the more ophthalmically active L-isomer.

[00115] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.045%, between about 0.005% to about 0.045%, between about 0.010% to about 0.045%, between about 0.015% to about 0.045%, between about 0.020% to about 0.045%, between about 0.025% to about 0.045%, between about 0.030% to about 0.045%, between about 0.035% to about 0.045%, or between about 0.040% to about 0.045% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

[00116] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.040%, between about 0.005% to about 0.040%, between about 0.010% to about 0.040%, between about 0.015% to about 0.040%, between about 0.020% to about 0.040%, between about 0.025% to about 0.040%, between about 0.030% to about 0.040%, between about 0.035% to about 0.040% of the active ingredient, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

[00117] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.035%, between about 0.005% to about 0.035%, between about 0.010% to about 0.035%, between about 0.015% to about 0.035%, between about 0.020% to about 0.035%, between about 0.025% to about 0.035%, or between about 0.030% to about 0.035% of

the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

[00118] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.030%, between about 0.005% to about 0.030%, between about 0.010% to about 0.030%, between about 0.015% to about 0.030%, between about 0.020% to about 0.030%, or between about 0.025% to about 0.030% of the active ingredient, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

[00119] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.025%, between about 0.005% to about 0.025%, between about 0.010% to about 0.025%, between about 0.015% to about 0.025%, or between about 0.020% to about 0.025% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

[00120] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.020%, between about 0.005% to about 0.020%, between about 0.010% to about 0.020%, or between about 0.015% to about 0.020% of the active ingredient, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

[00121] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.015%, between about 0.005% to about 0.015%, or between about 0.010% to about 0.015% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

[00122] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.010%, between about 0.005% to about 0.010%, or between about 0.008% to about 0.010% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

[00123] In some embodiments, the compositions described herein have a concentration of ophthalmic agent about 0.001%, 0.005%, 0.010%, 0.015%, 0.020%, 0.025%, 0.030%, 0.035%, 0.040%, 0.045%, or 0.050% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine, or a pharmaceutically acceptable salt thereof. In some embodiments, the muscarinic antagonist is atropine sulfate.

[00124] Without wishing to be bound by any particular theory, it is contemplated herein that the low concentration of the ophthalmic agent (e.g. muscarinic antagonist such as atropine or atropine sulfate) in the disclosed ophthalmic composition provides sufficient and consistent therapeutic benefits to an individual in need thereof, while reducing or avoiding the ocular side effects including glare from pupillary dilation and blurred vision due to loss of accommodation that are associated with ophthalmic formulations containing higher concentrations of the ophthalmic agent (e.g. muscarinic antagonist such as atropine or atropine sulfate).

[00125] **Aqueous Solution Stability**

[00126] In some embodiments, the composition described herein comprises a buffer. In some embodiments, a buffer is selected from borates, borate-polyol complexes, succinate, phosphate buffering

agents, citrate buffering agents, acetate buffering agents, carbonate buffering agents, organic buffering agents, amino acid buffering agents, or combinations thereof. In some embodiments, the composition described herein comprises buffer comprising deuterated water. In some embodiments, a deuterated buffer is selected from borates, borate-polyol complexes, succinate, phosphate buffering agents, citrate buffering agents, acetate buffering agents, carbonate buffering agents, organic buffering agents, amino acid buffering agents, or combinations thereof, formulated in deuterated water.

[00127] In some instances, borates include boric acid, salts of boric acid, other pharmaceutically acceptable borates, and combinations thereof. In some cases, borates include boric acid, sodium borate, potassium borate, calcium borate, magnesium borate, manganese borate, and other such borate salts.

[00128] As used herein, the term polyol includes any compound having at least one hydroxyl group on each of two adjacent carbon atoms that are not in trans configuration relative to each other. In some embodiments, the polyols is linear or cyclic, substituted or unsubstituted, or mixtures thereof, so long as the resultant complex is water soluble and pharmaceutically acceptable. In some instances, examples of polyol include: sugars, sugar alcohols, sugar acids and uronic acids. In some cases, polyols include, but are not limited to: mannitol, glycerin, xylitol and sorbitol.

[00129] In some embodiments, phosphate buffering agents include phosphoric acid; alkali metal phosphates such as disodium hydrogen phosphate, sodium dihydrogen phosphate, trisodium phosphate, dipotassium hydrogen phosphate, potassium dihydrogen phosphate, and tripotassium phosphate; alkaline earth metal phosphates such as calcium phosphate, calcium hydrogen phosphate, calcium dihydrogen phosphate, monomagnesium phosphate, dimagnesium phosphate (magnesium hydrogen phosphate), and trimagnesium phosphate; ammonium phosphates such as diammonium hydrogen phosphate and ammonium dihydrogen phosphate; or a combination thereof. In some instances, the phosphate buffering agent is an anhydride. In some instances, the phosphate buffering agent is a hydrate.

[00130] In some embodiments, borate-polyol complexes include those described in U.S. Pat. No. 6,503,497. In some instances, the borate-polyol complexes comprise borates in an amount of from about 0.01 to about 2.0% w/v, and one or more polyols in an amount of from about 0.01% to about 5.0% w/v.

[00131] In some cases, citrate buffering agents include citric acid and sodium citrate.

[00132] In some instances, acetate buffering agents include acetic acid, potassium acetate, and sodium acetate.

[00133] In some instances, carbonate buffering agents include sodium bicarbonate and sodium carbonate.

[00134] In some cases, organic buffering agents include Good's Buffer, such as for example 2-(N-morpholino)ethanesulfonic acid (MES), *N*-(2-Acetamido)iminodiacetic acid, *N*-(Carbamoylmethyl)iminodiacetic acid (ADA), piperazine-N,N'-bis(2-ethanesulfonic acid (PIPES), *N*-(2-acetamido)-2-aminoethanesulfonic acid (ACES), β -Hydroxy-4-morpholinepropanesulfonic acid, 3-Morpholino-2-hydroxypropanesulfonic acid (MOPSO), cholamine chloride, 3-(N-morpholino)propanesulfonic acid (MOPS), N,N-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid (BES),

2-[(2-Hydroxy-1,1-bis(hydroxymethyl)ethyl)amino]ethanesulfonic acid (TES), 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES), 3-(N,N-Bis[2-hydroxyethyl]amino)-2-hydroxypropanesulfonic acid (DIPSO), acetamidoglycine, 3-[[1,3-Dihydroxy-2-(hydroxymethyl)-2-propanyl]amino]-2-hydroxy-1-propanesulfonic acid (TAPSO), piperazine-1,4-bis (2-hydroxypropanesulphonic acid) (POPSO), 4-(2-hydroxyethyl)piperazine-1-(2-hydroxypropanesulfonic acid) hydrate (HEPPSO), 3-[4-(2-hydroxyethyl)-1-piperazinyl]propanesulfonic acid (HEPPS), tricine, glycine, bicine or N-tris(hydroxymethyl)methyl-3-aminopropanesulfonic acid sodium (TAPS); glycine; and diethanolamine (DEA).

[00135] In some cases, amino acid buffering agents include taurine, aspartic acid and its salts (e.g., potassium salts, etc), E-aminocaproic acid, and the like.

[00136] In some instances, the composition described herein further comprises a tonicity adjusting agent. Tonicity adjusting agent is an agent introduced into a preparation such as an ophthalmic composition to reduce local irritation by preventing osmotic shock at the site of application. In some instances, buffer solution and/or a pD adjusting agent that broadly maintains the ophthalmic solution at a particular ion concentration and pD are considered as tonicity adjusting agents. In some cases, tonicity adjusting agents include various salts, such as halide salts of a monovalent cation. In some cases, tonicity adjusting agents include mannitol, sorbitol, dextrose, sucrose, urea, and glycerin. In some instances, suitable tonicity adjustors comprise sodium chloride, sodium nitrate, sodium sulfate, sodium bisulfate, potassium chloride, calcium chloride, magnesium chloride, zinc chloride, potassium acetate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium thiosulfate, magnesium sulfate, disodium hydrogen phosphate, sodium dihydrogen phosphate, potassium dihydrogen phosphate, dextrose, mannitol, sorbitol, dextrose, sucrose, urea, propylene glycol, glycerin, trehalose, or a combination thereof.

[00137] In some instances, the concentration of the tonicity adjusting agent in a composition described herein is between about 0.5% and about 2.0%. In some instances, the concentration of the tonicity adjusting agent in a composition described herein is between about 0.7% and about 1.8%, about 0.8% and about 1.5%, or about 1% and about 1.3%. In some instances, the concentration of the tonicity adjusting agent is about 0.6%, 0.7%, 0.8%, 0.9%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, or 1.9%. In some cases, the percentage is a weight percentage.

[00138] In some cases, the composition described herein further comprises a pD adjusting agent. In some embodiments, the pD adjusting agent used is an acid or a base. In some embodiments, the base is oxides, hydroxides, carbonates, bicarbonates and the likes. In some instances, the oxides are metal oxides such as calcium oxide, magnesium oxide and the likes; hydroxides are of alkali metals and alkaline earth metals such as sodium hydroxide, potassium hydroxide, calcium hydroxide and the likes or their deuterated equivalents, and carbonates are sodium carbonate, sodium bicarbonates, potassium bicarbonates and the likes. In some instances, the acid is mineral acid and organic acids such as hydrochloric acid, nitric acid, phosphoric acid, acetic acid, citric acid, fumaric acid, malic acid tartaric

acid and the likes or their deuterated equivalents. In some instances, the pD adjusting agent includes, but is not limited to, acetate, bicarbonate, ammonium chloride, citrate, phosphate, pharmaceutically acceptable salts thereof and combinations or mixtures thereof. In some embodiments, the pD adjusting agent comprises DCl and NaOD.

[00139] In some instances, the composition has a pD of between about 4 and about 8, about 4.5 and about 7.8, about 5 and about 7.5, or about 5.5 and about 7. In some embodiments, the composition has a pD of less than about 7.5. In some embodiments, the composition has a pD of less than about 7.4. In some embodiments, the composition has a pD of less than about 7.3. In some embodiments, the composition has a pD of less than about 7.2. In some embodiments, the composition has a pD of less than about 7.1. In some embodiments, the composition has a pD of less than about 7. In some embodiments, the composition has a pD of less than about 6.9. In some embodiments, the composition has a pD of less than about 6.8. In some embodiments, the composition has a pD of less than about 6.7. In some embodiments, the composition has a pD of less than about 6.6. In some embodiments, the composition has a pD of less than about 6.5. In some embodiments, the composition has a pD of less than about 6.4. In some embodiments, the composition has a pD of less than about 6.3. In some embodiments, the composition has a pD of less than about 6.2. In some embodiments, the composition has a pD of less than about 6.1. In some embodiments, the composition has a pD of less than about 6. In some embodiments, the composition has a pD of less than about 5.9. In some embodiments, the composition has a pD of less than about 5.8. In some embodiments, the composition has a pD of less than about 5.7. In some embodiments, the composition has a pD of less than about 5.6. In some embodiments, the composition has a pD of less than about 5.5. In some embodiments, the composition has a pD of less than about 5.4. In some embodiments, the composition has a pD of less than about 5.3. In some embodiments, the composition has a pD of less than about 5.2. In some embodiments, the composition has a pD of less than about 5.1. In some embodiments, the composition has a pD of less than about 5. In some embodiments, the composition has a pD of less than about 4.9. In some embodiments, the composition has a pD of less than about 4.8. In some embodiments, the composition has a pD of less than about 4.7. In some embodiments, the composition has a pD of less than about 4.6. In some embodiments, the composition has a pD of less than about 4.5. In some embodiments, the composition has a pD of less than about 4.4. In some embodiments, the composition has a pD of less than about 4.3. In some embodiments, the composition has a pD of less than about 4.2. In some embodiments, the composition has a pD of less than about 4.1. In some embodiments, the composition has a pD of less than about 4. In some embodiments, the pD is the pD of the composition after extended period of time under storage condition.

[00140] In some instances, the composition has an initial pD of between about 4 and about 8, about 4.5 and about 7.8, about 5 and about 7.5, or about 5.5 and about 7. In some embodiments, the composition has an initial pD of about 7.5. In some embodiments, the composition has an initial pD of about 7.4. In some embodiments, the composition has an initial pD of about 7.3. In some embodiments, the composition has an initial pD of about 7.2. In some embodiments, the composition has an initial pD

of about 7.1. In some embodiments, the composition has an initial pD of about 7. In some embodiments, the composition has an initial pD of about 6.9. In some embodiments, the composition has an initial pD of about 6.8. In some embodiments, the composition has an initial pD of about 6.7. In some embodiments, the composition has an initial pD of about 6.6. In some embodiments, the composition has an initial pD of about 6.5. In some embodiments, the composition has an initial pD of about 6.4. In some embodiments, the composition has an initial pD of about 6.3. In some embodiments, the composition has an initial pD of about 6.2. In some embodiments, the composition has an initial pD of about 6.1. In some embodiments, the composition has an initial pD of about 6. In some embodiments, the composition has an initial pD of about 5.9. In some embodiments, the composition has an initial pD of about 5.8. In some embodiments, the composition has an initial pD of about 5.7. In some embodiments, the composition has an initial pD of about 5.6. In some embodiments, the composition has an initial pD of about 5.5. In some embodiments, the composition has an initial pD of about 5.4. In some embodiments, the composition has an initial pD of about 5.3. In some embodiments, the composition has an initial pD of about 5.2. In some embodiments, the composition has an initial pD of about 5.1. In some embodiments, the composition has an initial pD of about 5. In some embodiments, the composition has an initial pD of about 4.9. In some embodiments, the composition has an initial pD of about 4.8. In some embodiments, the composition has an initial pD of about 4.7. In some embodiments, the composition has an initial pD of about 4.6. In some embodiments, the composition has an initial pD of about 4.5. In some embodiments, the composition has an initial pD of about 4.4. In some embodiments, the composition has an initial pD of about 4.3. In some embodiments, the composition has an initial pD of about 4.2. In some embodiments, the composition has an initial pD of about 4.1. In some embodiments, the composition has an initial pD of about 4.

[00141] In some embodiments, the pD of the composition described herein is associated with the stability of the composition. In some embodiments, a stable composition comprises a pD of between about 4 and about 8, about 4.5 and about 7.8, about 5 and about 7.5, or about 5.5 and about 7. In some embodiments, a stable composition comprises a pD of less than about 7.5. In some embodiments, a stable composition comprises a pD of less than about 7.4. In some embodiments, a stable composition comprises a pD of less than about 7.3. In some embodiments, a stable composition comprises a pD of less than about 7.2. In some embodiments, a stable composition comprises a pD of less than about 7.1. In some embodiments, a stable composition comprises a pD of less than about 7. In some embodiments, a stable composition comprises a pD of less than about 6.9. In some embodiments, a stable composition comprises a pD of less than about 6.8. In some embodiments, a stable composition comprises a pD of less than about 6.7. In some embodiments, a stable composition comprises a pD of less than about 6.6. In some embodiments, a stable composition comprises a pD of less than about 6.5. In some embodiments, a stable composition comprises a pD of less than about 6.4. In some embodiments, a stable composition comprises a pD of less than about 6.3. In some embodiments, a stable composition comprises a pD of less than about 6.2. In some embodiments, a stable composition comprises a pD of

less than about 6.1. In some embodiments, a stable composition comprises a pD of less than about 6. In some embodiments, a stable composition comprises a pD of less than about 5.9. In some embodiments, a stable composition comprises a pD of less than about 5.8. In some embodiments, a stable composition comprises a pD of less than about 5.7. In some embodiments, a stable composition comprises a pD of less than about 5.6. In some embodiments, a stable composition comprises a pD of less than about 5.5. In some embodiments, a stable composition comprises a pD of less than about 5.4. In some embodiments, a stable composition comprises a pD of less than about 5.3. In some embodiments, a stable composition comprises a pD of less than about 5.2. In some embodiments, a stable composition comprises a pD of less than about 5.1. In some embodiments, a stable composition comprises a pD of less than about 5. In some embodiments, a stable composition comprises a pD of less than about 4.9. In some embodiments, a stable composition comprises a pD of less than about 4.8. In some embodiments, a stable composition comprises a pD of less than about 4.7. In some embodiments, a stable composition comprises a pD of less than about 4.6. In some embodiments, a stable composition comprises a pD of less than about 4.5. In some embodiments, a stable composition comprises a pD of less than about 4.4. In some embodiments, a stable composition comprises a pD of less than about 4.3. In some embodiments, a stable composition comprises a pD of less than about 4.2. In some embodiments, a stable composition comprises a pD of less than about 4.1. In some embodiments, a stable composition comprises a pD of less than about 4.

[00142] As described elsewhere herein, in some instances, the D₂O aqueous system stabilizes a muscarinic antagonist (e.g., atropine). In some embodiments, this is due to a lower concentration of the reactive species (e.g., -OD) in the D₂O aqueous system compared to the concentration of the reactive species (e.g., -OH) in an equivalent H₂O aqueous system. In some instances, the concentration of the reactive species (e.g., -OD) in the D₂O aqueous system is about one third less than the concentration of the reactive species (e.g., -OH) in the equivalent H₂O aqueous system. In some cases, this is due to a lower or smaller dissociation constant of D₂O than H₂O. For example, the K_a(H₂O) is 1×10^{-14} , whereas the K_a(D₂O) is 1×10^{-15} . As such, D₂O is a weaker acid than H₂O. In some cases, base catalyzed hydrolysis leads to the presence of tropine degradant from atropine. In some cases, with a lower concentration of the reactive species that causes tropine degradant formation, atropine solution is more stable in a D₂O aqueous system than compared to an equivalent H₂O aqueous system. In some embodiments, the ophthalmic composition formulated with deuterated water allows for a more stable ophthalmic composition relative to the ophthalmic composition formulated with H₂O.

[00143] In some embodiments, the presence of deuterated water shifts the pK_a of the buffer. In some embodiments, the presence of deuterated water allows for the ophthalmic composition to simulate the stability of a lower pH system. In some instances, the buffer capacity of the ophthalmic composition is lowered, thereby allowing a faster shift in pH. In some instances, the lowered buffering capacity of the ophthalmic composition when administered into the eye allows the ophthalmic composition to reach physiological pH at a faster rate than compared to an ophthalmic composition formulated in H₂O. In some instances, the ophthalmic composition formulated with deuterated water allows for a lower tear

production, or less tear reflex in the eye, in comparison with an ophthalmic composition formulated with H₂O.

[00144] In some instances, the composition described herein further comprises a disinfecting agent. In some cases, disinfecting agents include polymeric biguanides, polymeric quarternary ammonium compounds, chlorites, bisbiguanides, chlorite compounds (e.g. potassium chlorite, sodium chlorite, calcium chlorite, magnesium chlorite, or mixtures thereof), and a combination thereof.

[00145] In some instances, the composition described herein further comprises a preservative. In some cases, a preservative is added at a concentration to a composition described herein to prevent the growth of or to destroy a microorganism introduced into the composition. In some instances, microorganisms refer to bacteria (e.g. *Proteus mirabilis*, *Serratia marcesens*), virus (e.g. Herpes simplex virus, herpes zoster virus), fungus (e.g. fungi from the genus *Fusarium*), yeast (e.g. *Candida albicans*), parasites (e.g. *Plasmodium* spp., *Gnathostoma* spp.), protozoan (e.g. *Giardia lamblia*), nematodes (e.g. *Onchocercus volvulus*), worm (e.g. *Dirofilaria immitis*), and/or amoeba (e.g. *Acanthameoba*).

[00146] In some instances, the concentration of the preservative is between about 0.0001% and about 1%, about 0.001% and about 0.8%, about 0.004% and about 0.5%, about 0.008 % and about 0.1%, and about 0.01% and about 0.08%. In some cases, the concentration of the preservatives is about 0.001%, 0.002%, 0.003%, 0.004%, 0.005%, 0.006%, 0.008%, 0.009%, 0.009%, 0.01%, 0.015%, 0.02%, 0.025%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9% or 1.0%.

[00147] In some embodiments, the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia (Alcon), polyquaternium-1, chlorobutanol, edetate disodium, and polyhexamethylene biguanide.

[00148] In some embodiments, the composition described herein is stored in a plastic container. In some embodiments, the material of the plastic container comprises high density polyethylene (HDPE), low density polyethylene (LDPE), polyethylene terephthalate (PET), polyvinyl chloride (PVC), polypropylene (PP), polystyrene (PS), fluorine treated HDPE, post-consumer resin (PCR), K-resine (SBC), or bioplastic. In some embodiments, the material of the plastic container comprises LDPE.

[00149] In some embodiments, the composition described herein is stored in a plastic container. In some embodiments, the composition stored in a plastic container has a pD of between about 4 and about 8, about 4.5 and about 7.9, or about 4.9 and about 7.5. In some embodiments, the composition stored in a plastic container has a pD of less than about 7.4. In some embodiments, the composition stored in a plastic container has a pD of less than about 7.3. In some embodiments, the composition stored in a plastic container has a pD of less than about 7.2. In some embodiments, the composition stored in a plastic container has a pD of less than about 7.1. In some embodiments, the composition stored in a plastic container has a pD of less than about 7. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.9. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.8. In some embodiments, the composition stored in a

[illegible]

[00150] In some embodiments, the composition stored in a plastic container has a potency of at least 70% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 75% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 80% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 85% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 90% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 93% after extended period of time under storage condition. In

some embodiments, the composition stored in a plastic container has a potency of at least 95% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 97% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 98% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 99% after extended period of time under storage condition. In some instances, the storage condition comprises a temperature of about 25°C, about 40°C, or about 60°C. In some instances, the extended period of time is at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months.

[00151] In some embodiments, the composition stored in a plastic container has a potency of at least 80% at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container has a potency of at least 85% at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container has a potency of at least 90% at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container has a potency of at least 93% at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container has a potency of at least 95% at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container has a potency of at least 97% at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container has a potency of at least 98% at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container has a potency of at least 99% at a temperature of about 25°C, about 40°C, or about 60°C.

[00152] In some embodiments, the composition stored in a plastic container has a potency of at least 80% for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container has a potency of at least 85% for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container has a potency of at least 90% for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container has a potency of at least 93% for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12

months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container has a potency of at least 95% for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container has a potency of at least 97% for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container has a potency of at least 98% for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container has a potency of at least 99% for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months.

[00153] In some embodiments, the composition stored in a plastic container comprises less than 20% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container comprises less than 15% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container comprises less than 10% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container comprises less than 5% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition.

[00154] In some embodiments, the composition stored in a plastic container comprises from less than 2.5% of primary degradant to less than 0.1% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container comprises less than 2.5% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container comprises less than 2.0% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container comprises less than 1.5% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container comprises less than 1.0% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container comprises less than 0.5% of primary degradant based on the concentration of the ophthalmic

agent after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container comprises less than 0.4% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container comprises less than 0.3% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container comprises less than 0.2% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container comprises less than 0.1% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some instances, the storage condition comprises a temperature of about 25°C, about 40°C, or about 60°C. In some instances, the extended period of time is at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months.

[00155] In some embodiments, the composition stored in a plastic container comprises less than 20% of primary degradant based on the concentration of the ophthalmic agent at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container comprises less than 15% of primary degradant based on the concentration of the ophthalmic agent at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container comprises less than 10% of primary degradant based on the concentration of the ophthalmic agent at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container comprises less than 5% of primary degradant based on the concentration of the ophthalmic agent at a temperature of about 25°C, about 40°C, or about 60°C.

[00156] In some embodiments, the composition stored in a plastic container comprises from less than 2.5% of primary degradant to less than 0.1% of primary degradant based on the concentration of the ophthalmic agent at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container comprises less than 2.5% of primary degradant based on the concentration of the ophthalmic agent at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container comprises less than 2.0% of primary degradant based on the concentration of the ophthalmic agent at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container comprises less than 1.5% of primary degradant based on the concentration of the ophthalmic agent at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container comprises less than 1.0% of primary degradant based on the concentration of the ophthalmic agent at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container comprises less than 0.5% of primary degradant based on the concentration of the ophthalmic agent at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the

composition stored in a plastic container comprises less than 0.4% of primary degradant based on the concentration of the ophthalmic agent at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container comprises less than 0.3% of primary degradant based on the concentration of the ophthalmic agent at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container comprises less than 0.2% of primary degradant based on the concentration of the ophthalmic agent at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container comprises less than 0.1% of primary degradant based on the concentration of the ophthalmic agent at a temperature of about 25°C, about 40°C, or about 60°C.

[00157] In some embodiments, the composition stored in a plastic container comprises less than 20% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 15% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 10% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 5% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months.

[00158] In some embodiments, the composition stored in a plastic container comprises from less than 2.5% of primary degradant to less than 0.1% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 2.5% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 2.0% of primary

degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 1.5% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 1.0% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 0.5% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 0.4% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 0.3% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 0.2% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 0.1% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months.

[00159] In some embodiments, the composition described herein is stored in a glass container. In some embodiments, the glass container is a glass vial, such as for example, a type I, type II or type III glass vial. In some embodiments, the glass container is a type I glass vial. In some embodiments, the type I glass vial is a borasilicate glass vial.

[00160] In some embodiments, the composition stored in a glass container has a pD of higher than about 7. In some embodiments, the composition stored in a glass container has a pD of higher than about 7.5. In some embodiments, the composition stored in a glass container has a pD of higher than about 8. In some embodiments, the composition stored in a glass container has a pD of higher than about 8.5. In some embodiments, the composition stored in a glass container has a pD of higher than about 9.

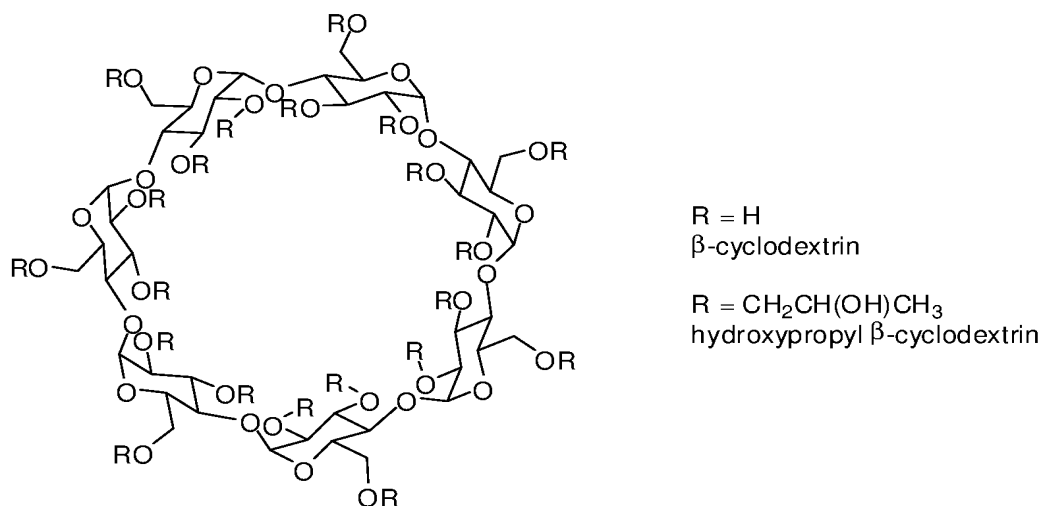
[00161] In some embodiments, the composition stored in a glass container has a potency of less than 60% at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a glass container has a potency of less than 60% for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months.

[00162] In some embodiments, the composition stored in a glass container is less stable than a composition stored in a plastic container.

[00163] In some embodiments, the composition is stored under in the dark. In some instances, the composition is stored in the presence of light. In some instances, the light is indoor light, room light, or sun light. In some instances, the composition is stable while stored in the presence of light.

[00164] In some embodiments, the composition described herein is formulated as an aqueous solution. In some embodiments, the aqueous solution is a stable aqueous solution. In some instances, the aqueous solution is stored in a plastic container as described above. In some instances, the aqueous solution is not stored in a glass container. In some instances, the aqueous solution is stored in the dark. In some instances, the aqueous solution is stored in the presence of light. In some instances, the aqueous solution is stable in the presence of light.

[00165] In a specific embodiment, the ophthalmically acceptable formulations alternatively comprise a cyclodextrin. Cyclodextrins are cyclic oligosaccharides containing 6, 7, or 8 glucopyranose units, referred to as α -cyclodextrin, β -cyclodextrin, or γ -cyclodextrin respectively. Cyclodextrins have a hydrophilic exterior, which enhances water-soluble, and a hydrophobic interior which forms a cavity. In an aqueous environment, hydrophobic portions of other molecules often enter the hydrophobic cavity of cyclodextrin to form inclusion compounds. Additionally, cyclodextrins are also capable of other types of nonbonding interactions with molecules that are not inside the hydrophobic cavity. Cyclodextrins have three free hydroxyl groups for each glucopyranose unit, or 18 hydroxyl groups on α -cyclodextrin, 21 hydroxyl groups on β -cyclodextrin, and 24 hydroxyl groups on γ -cyclodextrin. In some embodiments, one or more of these hydroxyl groups are reacted with any of a number of reagents to form a large variety of cyclodextrin derivatives, including hydroxypropyl ethers, sulfonates, and sulfoalkylethers. Shown below is the structure of β -cyclodextrin and the hydroxypropyl- β -cyclodextrin (HP β CD).



[00166] In some embodiments, the use of cyclodextrins in the pharmaceutical compositions described herein improves the solubility of the drug. Inclusion compounds are involved in many cases of enhanced solubility; however other interactions between cyclodextrins and insoluble compounds also improves solubility. Hydroxypropyl- β -cyclodextrin (HP β CD) is commercially available as a pyrogen free product. It is a nonhygroscopic white powder that readily dissolves in water. HP β CD is thermally stable and does not degrade at neutral pH. Thus, cyclodextrins improve the solubility of a therapeutic agent in a composition or formulation. Accordingly, in some embodiments, cyclodextrins are included to increase the solubility of the ophthalmically acceptable ophthalmic agents within the formulations described herein. In other embodiments, cyclodextrins in addition serve as controlled release excipients within the formulations described herein.

[00167] By way of example only, cyclodextrin derivatives for use include α -cyclodextrin, β -cyclodextrin, γ -cyclodextrin, hydroxyethyl- β -cyclodextrin, hydroxypropyl- γ -cyclodextrin, sulfated β -cyclodextrin, sulfated α -cyclodextrin, sulfobutyl ether β -cyclodextrin.

[00168] The concentration of the cyclodextrin used in the compositions and methods disclosed herein varies according to the physiochemical properties, pharmacokinetic properties, side effect or adverse events, formulation considerations, or other factors associated with the therapeutically ophthalmic agent, or a salt or prodrug thereof, or with the properties of other excipients in the composition. Thus, in certain circumstances, the concentration or amount of cyclodextrin used in accordance with the compositions and methods disclosed herein will vary, depending on the need. When used, the amount of cyclodextrins needed to increase solubility of the ophthalmic agent and/or function as a controlled release excipient in any of the formulations described herein is selected using the principles, examples, and teachings described herein.

[00169] Other stabilizers that are useful in the ophthalmically acceptable formulations disclosed herein include, for example, fatty acids, fatty alcohols, alcohols, long chain fatty acid esters, long chain ethers, hydrophilic derivatives of fatty acids, polyvinyl pyrrolidones, polyvinyl ethers, polyvinyl alcohols, hydrocarbons, hydrophobic polymers, moisture-absorbing polymers, and combinations thereof.

In some embodiments, amide analogues of stabilizers are also used. In further embodiments, the chosen stabilizer changes the hydrophobicity of the formulation, improves the mixing of various components in the formulation, controls the moisture level in the formula, or controls the mobility of the phase.

[00170] In other embodiments, stabilizers are present in sufficient amounts to inhibit the degradation of the ophthalmic agent. Examples of such stabilizing agents, include, but are not limited to: glycerol, methionine, monothioglycerol, EDTA, ascorbic acid, polysorbate 80, polysorbate 20, arginine, heparin, dextran sulfate, cyclodextrins, pentosan polysulfate and other heparinoids, divalent cations such as magnesium and zinc, or combinations thereof.

[00171] Additional useful stabilization agents for ophthalmically acceptable formulations include one or more anti-aggregation additives to enhance stability of ophthalmic formulations by reducing the rate of protein aggregation. The anti-aggregation additive selected depends upon the nature of the conditions to which the ophthalmic agents, for example a muscarinic antagonist (e.g. atropine or its pharmaceutically acceptable salts), are exposed. For example, certain formulations undergoing agitation and thermal stress require a different anti-aggregation additive than a formulation undergoing lyophilization and reconstitution. Useful anti-aggregation additives include, by way of example only, urea, guanidinium chloride, simple amino acids such as glycine or arginine, sugars, polyalcohols, polysorbates, polymers such as polyethylene glycol and dextrans, alkyl saccharides, such as alkyl glycoside, and surfactants.

[00172] Other useful formulations optionally include one or more ophthalmically acceptable antioxidants to enhance chemical stability where required. Suitable antioxidants include, by way of example only, ascorbic acid, methionine, sodium thiosulfate and sodium metabisulfite. In one embodiment, antioxidants are selected from metal chelating agents, thiol containing compounds and other general stabilizing agents.

[00173] Still other useful compositions include one or more ophthalmically acceptable surfactants to enhance physical stability or for other purposes. Suitable nonionic surfactants include, but are not limited to, polyoxyethylene fatty acid glycerides and vegetable oils, e.g., polyoxyethylene (60) hydrogenated castor oil; and polyoxyethylene alkylethers and alkylphenyl ethers, e.g., octoxynol 10, octoxynol 40.

[00174] In some embodiments, the ophthalmically acceptable pharmaceutical formulations described herein are stable with respect to compound degradation (e.g. less than 30% degradation, less than 25% degradation, less than 20% degradation, less than 15% degradation, less than 10% degradation, less than 8% degradation, less than 5% degradation, less than 3% degradation, less than 2% degradation, or less than 5% degradation) over a period of any of at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 4 weeks, at least about 5 weeks, at least about 6 weeks, at least about 7 weeks, at least about 8 weeks, at least about 3 months, at least about 4 months, at least about 5 months, or at least about 6 months under storage conditions (e.g.

room temperature). In other embodiments, the formulations described herein are stable with respect to compound degradation over a period of at least about 1 week. Also described herein are formulations that are stable with respect to compound degradation over a period of at least about 1 month.

[00175] In other embodiments, an additional surfactant (co-surfactant) and/or buffering agent is combined with one or more of the pharmaceutically acceptable vehicles previously described herein so that the surfactant and/or buffering agent maintains the product at an optimal pD for stability. Suitable co-surfactants include, but are not limited to: a) natural and synthetic lipophilic agents, e.g., phospholipids, cholesterol, and cholesterol fatty acid esters and derivatives thereof; b) nonionic surfactants, which include for example, polyoxyethylene fatty alcohol esters, sorbitan fatty acid esters (Spans), polyoxyethylene sorbitan fatty acid esters (e.g., polyoxyethylene (20) sorbitan monooleate (Tween 80), polyoxyethylene (20) sorbitan monostearate (Tween 60), polyoxyethylene (20) sorbitan monolaurate (Tween 20) and other Tweens, sorbitan esters, glycerol esters, e.g., Myrj and glycerol triacetate (triacetin), polyethylene glycols, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, polysorbate 80, poloxamers, poloxamines, polyoxyethylene castor oil derivatives (e.g., Cremophor[®] RH40, Cremphor A25, Cremphor A20, Cremophor[®] EL) and other Cremophors, sulfosuccinates, alkyl sulphates (SLS); PEG glyceryl fatty acid esters such as PEG-8 glyceryl caprylate/caprate (Labrasol), PEG-4 glyceryl caprylate/caprate (Labrafac Hydro WL 1219), PEG-32 glyceryl laurate (Gelucire 444/14), PEG-6 glyceryl mono oleate (Labrafil M 1944 CS), PEG-6 glyceryl linoleate (Labrafil M 2125 CS); propylene glycol mono- and di-fatty acid esters, such as propylene glycol laurate, propylene glycol caprylate/caprate; Brij[®] 700, ascorbyl-6-palmitate, stearylamine, sodium lauryl sulfate, polyoxethyleneglycerol triiricinoleate, and any combinations or mixtures thereof; c) anionic surfactants include, but are not limited to, calcium carboxymethylcellulose, sodium carboxymethylcellulose, sodium sulfosuccinate, dioctyl, sodium alginate, alkyl polyoxyethylene sulfates, sodium lauryl sulfate, triethanolamine stearate, potassium laurate, bile salts, and any combinations or mixtures thereof; and d) cationic surfactants such as cetyltrimethylammonium bromide, and lauryldimethylbenzyl-ammonium chloride.

[00176] In a further embodiment, when one or more co-surfactants are utilized in the ophthalmically acceptable formulations of the present disclosure, they are combined, e.g., with a pharmaceutically acceptable vehicle and is present in the final formulation, e.g., in an amount ranging from about 0.1% to about 20%, from about 0.5% to about 10%.

[00177] In one embodiment, the surfactant has an HLB value of 0 to 20. In additional embodiments, the surfactant has an HLB value of 0 to 3, of 4 to 6, of 7 to 9, of 8 to 18, of 13 to 15, of 10 to 18.

[00178] pD

[00179] In some embodiments, the pD of a composition described herein is adjusted (e.g., by use of a buffer and/or a pD adjusting agent) to an ophthalmically compatible pD range of from about 4 to about 8, about 4.5 to about 7.5, or about 5 to about 7. In some embodiments, the ophthalmic composition

has a pD of from about 5.0 to about 7.0. In some embodiments, the ophthalmic composition has a pD of from about 5.5 to about 7.0. In some embodiments, the ophthalmic composition has a pD of from about 6.0 to about 7.0.

[00180] In some embodiments, useful formulations include one or more pD adjusting agents or buffering agents. Suitable pD adjusting agents or buffers include, but are not limited to acetate, bicarbonate, ammonium chloride, citrate, phosphate, deuterated forms of acetate, bicarbonate, ammonium chloride, citrate, phosphate, pharmaceutically acceptable salts thereof and combinations or mixtures thereof. In some embodiments, the pD adjusting agents or buffers include deuterated hydrochloric acid (DCI), deuterated sodium hydroxide (NaOD), deuterated acetic acid (CD_3COOD), or deuterated citric acid ($\text{C}_6\text{D}_8\text{O}_7$).

[00181] In one embodiment, when one or more buffers are utilized in the formulations of the present disclosure, they are combined, e.g., with a pharmaceutically acceptable vehicle and are present in the final formulation, e.g., in an amount ranging from about 0.1% to about 20%, from about 0.5% to about 10%. In certain embodiments of the present disclosure, the amount of buffer included in the gel formulations are an amount such that the pD of the gel formulation does not interfere with the body's natural buffering system.

[00182] In one embodiment, diluents are also used to stabilize compounds because they provide a more stable environment. In some instances, salts dissolved in buffered solutions (which also provides pD control or maintenance) are utilized as diluents in the art, including, but not limited to a phosphate buffered saline solution.

[00183] In some embodiments, the pD is calculated according to the formula disclosed in Glasoe *et al.*, "Use of glass electrodes to measure acidities in deuterium oxide," J. Physical Chem. 64(1): 188-190 (1960). In some embodiment, the pD is calculated as $\text{pD} = \text{pH}^* + 0.4$, in which pH^* is the measured or observed pH of the ophthalmic composition formulated in a solution comprising deuterated water (e.g., D_2O).

[00184] In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4 and about 8, between about 4.5 and about 8, between about 4.9 and about 7.9, between about 5.4 and about 7.9, between about 5.9 and about 7.9, between about 6.4 and about 7.9, or between about 7.4 and about 7.9. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4.5-7.5, between about 5.0 and about 7.5, between about 5.5 and about 7.5, between about 6.0 and about 7.5, or between about 7.0 and about 7.5. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4.5-7.0, between about 5.0 and about 7.0, between about 5.5 and about 7.0, between about 6.0 and about 7.0, or between about 6.5 and about 7.0. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4.9-7.4, between about 5.4 and about 7.4, between about 5.9 and about 7.4, between about 6.4 and about 7.4, or between about 6.9 and about 7.4. In some embodiments, the ophthalmic aqueous, gel, or ointment

composition described herein has a pD of between about 4.5-6.5, between about 5.0 and about 6.5, between about 5.5 and about 6.5, or between about 6.0 and about 6.5. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4.9-6.9, between about 5.4 and about 6.9, between about 5.9 and about 6.9, or between about 6.4 and about 6.9. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4.5-6.0, between about 5.0 and about 6.0, or between about 5.5 and about 6.0. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4.9-6.4, between about 5.4 and about 6.4, or between about 5.9 and about 6.4. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4.5-5.5, or between about 5.0 and about 5.5. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4.9-5.9, or between about 5.4 and about 5.9. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4.5-5.0. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4.9-5.4.

[00185] In some embodiments, the ophthalmic composition is an ophthalmic aqueous composition. In some instances, the ophthalmic aqueous composition has a pD of between about 4 and about 8, about 4.5 and about 7.8, about 5 and about 7.5, or about 5.5 and about 7. In some embodiments, the ophthalmic aqueous composition has a pD of about 7.5. In some embodiments, the ophthalmic aqueous composition has a pD of about 7.4. In some embodiments, the ophthalmic aqueous composition has a pD of about 7.3. In some embodiments, the ophthalmic aqueous composition has a pD of about 7.2. In some embodiments, the ophthalmic aqueous composition has a pD of about 7.1. In some embodiments, the ophthalmic aqueous composition has a pD of about 7. In some embodiments, the ophthalmic aqueous composition has a pD of about 6.9. In some embodiments, the ophthalmic aqueous composition has a pD of about 6.8. In some embodiments, the ophthalmic aqueous composition has a pD of about 6.7. In some embodiments, the ophthalmic aqueous composition has a pD of about 6.6. In some embodiments, the ophthalmic aqueous composition has a pD of about 6.5. In some embodiments, the ophthalmic aqueous composition has a pD of about 6.4. In some embodiments, the ophthalmic aqueous composition has a pD of about 6.3. In some embodiments, the ophthalmic aqueous composition has a pD of about 6.2. In some embodiments, the ophthalmic aqueous composition has a pD of about 6.1. In some embodiments, the ophthalmic aqueous composition has a pD of about 6. In some embodiments, the ophthalmic aqueous composition has a pD of about 5.9. In some embodiments, the ophthalmic aqueous composition has a pD of about 5.8. In some embodiments, the ophthalmic aqueous composition has a pD of about 5.7. In some embodiments, the ophthalmic aqueous composition has a pD of about 5.6. In some embodiments, the ophthalmic aqueous composition has a pD of about 5.5. In some embodiments, the ophthalmic aqueous composition has a pD of about 5.4. In some embodiments, the ophthalmic aqueous composition has a pD of about 5.3. In some embodiments, the ophthalmic aqueous composition has a pD of about 5.2. In some embodiments, the ophthalmic aqueous composition has a pD of about 5.1. In some

embodiments, the ophthalmic aqueous composition has a pD of about 5. In some embodiments, the ophthalmic aqueous composition has a pD of about 4.9. In some embodiments, the ophthalmic aqueous composition has a pD of about 4.8. In some embodiments, the ophthalmic aqueous composition has a pD of about 4.7. In some embodiments, the ophthalmic aqueous composition has a pD of about 4.6. In some embodiments, the ophthalmic aqueous composition has a pD of about 4.5. In some embodiments, the ophthalmic aqueous composition has a pD of about 4.4. In some embodiments, the ophthalmic aqueous composition has a pD of about 4.3. In some embodiments, the ophthalmic aqueous composition has a pD of about 4.2. In some embodiments, the ophthalmic aqueous composition has a pD of about 4.1. In some embodiments, the ophthalmic aqueous composition has a pD of about 4. In some embodiments, the pD is an initial pD of the ophthalmic aqueous composition. In some embodiments, the pD is the pD of the ophthalmic aqueous composition after extended period of time under storage condition.

[00186] In some instances, the ophthalmic aqueous composition has an initial pD of between about 4 and about 8, about 4.5 and about 7.8, about 5 and about 7.5, or about 5.5 and about 7. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7.5. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7.4. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7.3. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7.2. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7.1. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.9. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.8. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.7. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.6. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.5. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.4. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.3. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.2. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.1. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.9. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.8. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.7. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.6. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.5. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.4. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.3. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.2. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.1. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 4.9. In some

embodiments, the ophthalmic aqueous composition has an initial pD of about 4.8. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 4.7. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 4.6. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 4.5. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 4.4. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 4.3. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 4.2. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 4.1. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 4.

[illegible]

composition has a pD of less than about 4.6. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 4.5. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 4.4. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 4.3. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 4.2. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 4.1. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 4. In some embodiments, the pD is the pD of the ophthalmic aqueous composition after extended period of time under storage condition.

[00188] In some embodiments, the pD of the ophthalmic aqueous composition described herein is associated with the stability of the ophthalmic aqueous composition. In some embodiments, a stable composition comprises a pD of between about 4 and about 8, about 4.5 and about 7.8, about 5 and about 7.5, or about 5.5 and about 7. In some embodiments, a stable composition comprises a pD of less than about 7.5. In some embodiments, a stable composition comprises a pD of less than about 7.4. In some embodiments, a stable composition comprises a pD of less than about 7.3. In some embodiments, a stable composition comprises a pD of less than about 7.2. In some embodiments, a stable composition comprises a pD of less than about 7.1. In some embodiments, a stable composition comprises a pD of less than about 7. In some embodiments, a stable composition comprises a pD of less than about 6.9. In some embodiments, a stable composition comprises a pD of less than about 6.8. In some embodiments, a stable composition comprises a pD of less than about 6.7. In some embodiments, a stable composition comprises a pD of less than about 6.6. In some embodiments, a stable composition comprises a pD of less than about 6.5. In some embodiments, a stable composition comprises a pD of less than about 6.4. In some embodiments, a stable composition comprises a pD of less than about 6.3. In some embodiments, a stable composition comprises a pD of less than about 6.2. In some embodiments, a stable composition comprises a pD of less than about 6.1. In some embodiments, a stable composition comprises a pD of less than about 6. In some embodiments, a stable composition comprises a pD of less than about 5.9. In some embodiments, a stable composition comprises a pD of less than about 5.8. In some embodiments, a stable composition comprises a pD of less than about 5.7. In some embodiments, a stable composition comprises a pD of less than about 5.6. In some embodiments, a stable composition comprises a pD of less than about 5.5. In some embodiments, a stable composition comprises a pD of less than about 5.4. In some embodiments, a stable composition comprises a pD of less than about 5.3. In some embodiments, a stable composition comprises a pD of less than about 5.2. In some embodiments, a stable composition comprises a pD of less than about 5.1. In some embodiments, a stable composition comprises a pD of less than about 5. In some embodiments, a stable composition comprises a pD of less than about 4.9. In some embodiments, a stable composition comprises a pD of less than about 4.8. In some embodiments, a stable composition comprises a pD of less than about 4.7. In some embodiments, a stable composition comprises a pD of less than about 4.6. In some embodiments, a stable composition comprises a pD of less than about 4.5. In some embodiments, a stable composition comprises a pD of

less than about 4.4. In some embodiments, a stable composition comprises a pD of less than about 4.3. In some embodiments, a stable composition comprises a pD of less than about 4.2. In some embodiments, a stable composition comprises a pD of less than about 4.1. In some embodiments, a stable composition comprises a pD of less than about 4.

[00189] In some embodiments, the D₂O aqueous system stabilizes a muscarinic antagonist (e.g., atropine). In some embodiments, this is due to a lower concentration of the reactive species (e.g., -OD) in the D₂O aqueous system compared to the concentration of the reactive species (e.g., -OH) in an equivalent H₂O aqueous system. In some instances, the concentration of the reactive species (e.g., -OD) in the D₂O aqueous system is about one third less than the concentration of the reactive species (e.g., -OH) in the equivalent H₂O aqueous system. In some cases, this is due to a lower or smaller dissociation constant of D₂O than H₂O. For example, the K_a(H₂O) is 1×10^{-14} , whereas the K_a(D₂O) is 1×10^{-15} . As such, D₂O is a weaker acid than H₂O. In some cases, base catalyzed hydrolysis leads to the presence of tropine degradant from atropine. In some cases, with a lower concentration of the reactive species that causes tropine degradant formation, atropine solution is more stable in a D₂O aqueous system than compared to an equivalent H₂O aqueous system. In some embodiments, the ophthalmic composition formulated with deuterated water allows for a more stable ophthalmic composition relative to the ophthalmic composition formulated with H₂O.

[00190] In some embodiments, the presence of deuterated water shifts the pK_a of the buffer. In some embodiments, the presence of deuterated water allows for the ophthalmic composition to simulate the stability of a lower pH system. In some instances, the buffer capacity of the ophthalmic composition is lowered, thereby allowing a faster shift in pH. In some instances, the lowered buffering capacity of the ophthalmic composition when administered into the eye allows the ophthalmic composition to reach physiological pH at a faster rate than compared to an ophthalmic composition formulated in H₂O. In some instances, the ophthalmic composition formulated with deuterated water allows for a lower tear production, or less tear reflex in the eye, in comparison with an ophthalmic composition formulated with H₂O.

[00191] In some embodiment, the ophthalmic gel or ointment composition described herein has a pD of about 4, about 4.1, about 4.2, about 4.3, about 4.4, about 4.5, about 4.6, about 4.7, about 4.8, about 4.9, about 5.0, about 5.1, about 5.2, about 5.3, about 5.4, about 5.5, about 5.6, about 5.7, about 5.8, about 5.9, about 6.0, about 6.1, about 6.2, about 6.3, about 6.4, about 6.5, about 6.6, about 6.7, about 6.8, about 6.9, about 7.0, about 7.1, about 7.2, about 7.3, about 7.4, about 7.5, about 7.6, about 7.7, about 7.8, or about 7.9.

[00192] In some embodiment, the pD of the ophthalmic aqueous, gel, or ointment composition described herein is suitable for sterilization (e.g., by filtration or aseptic mixing or heat treatment and/or autoclaving (e.g., terminal sterilization)) of ophthalmic formulations described herein. As used in the present disclosure, the term “aqueous composition” includes compositions that are based on D₂O.

[00193] In some embodiments, the pharmaceutical formulations described herein are stable with respect to pD over a period of any of at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 4 weeks, at least about 5 weeks, at least about 6 weeks, at least about 7 weeks, at least about 8 weeks, at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about 18 months, at least about 24 months, at least about 3 years, at least about 4 years, at least about 5 years, at least about 6 years, at least about 7 years, at least about 8 years, at least about 9 years, at least about 10 years, or more. In other embodiments, the formulations described herein are stable with respect to pD over a period of at least about 1 week. In other embodiments, the formulations described herein are stable with respect to pD over a period of at least about 2 weeks. In other embodiments, the formulations described herein are stable with respect to pD over a period of at least about 3 weeks. In other embodiments, the formulations described herein are stable with respect to pD over a period of at least about 1 month. Also described herein are formulations that are stable with respect to pD over a period of at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 12 months, at least about 18 months, at least about 2 years, or more.

[00194] Aqueous Solution Dose-To-Dose Uniformity

[00195] Typical ophthalmic aqueous solutions are packaged in eye drop bottles and administered as drops. For example, a single administration (i.e. a single dose) of an ophthalmic aqueous solution includes a single drop, two drops, three drops or more into the eyes of the patient. In some embodiments, one dose of the ophthalmic aqueous solution described herein is one drop of the aqueous solution composition from the eye drop bottle.

[00196] In some cases, described herein include ophthalmic aqueous compositions which provide a dose-to-dose uniform concentrations. In some instances, the dose-to-dose uniform concentration does not present significant variations of drug content from one dose to another. In some instances, the dose-to-dose uniform concentration does provide consistent drug content from one dose to another.

[00197] In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 50%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 40%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 30%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 20%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 10%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 5%.

[00198] In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 10 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 8 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 5 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 3 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 2 consecutive doses.

[00199] A nonsettling formulation should not require shaking to disperse drug uniformly. A “no-shake” formulation is potentially advantageous over formulations that require shaking for the simple reason that patients’ shaking behavior is a major source of variability in the amount of drug dosed. It has been reported that patients often times do not or forget to shake their ophthalmic compositions that requires shaking before administering a dose, despite the instructions to shake that were clearly marked on the label. On the other hand, even for those patients who do shake the product, it is normally not possible to determine whether the shaking is adequate in intensity and/or duration to render the product uniform. In some embodiments, the ophthalmic gel compositions and ophthalmic ointment compositions described herein are “no-shake” formulations that maintained the dose-to-dose uniformity described herein.

[00200] To evaluate the dose-to-dose uniformity, drop bottles or tubes containing the ophthalmic aqueous compositions, the ophthalmic gel compositions, or ophthalmic ointment compositions are stored upright for a minimum of 12 hours prior to the start of the test. To simulate the recommended dosing of these products, predetermined number of drops or strips are dispensed from each commercial bottles or tubes at predetermined time intervals for an extended period of time or until no product was left in the bottle or tube. All drops and strips are dispensed into tared glass vials, capped, and stored at room temperature until analysis. Concentrations of a muscarinic antagonist such as atropine in the expressed drops were determined using a reverse-phase HPLC method.

[00201] **Aqueous Solution Viscosity**

[00202] In some embodiments, the composition has a Brookfield RVDV viscosity of from about 10 to about 50,000 cps at about 20°C and sheer rate of 1s^{-1} . In some embodiments, the composition has a Brookfield RVDV viscosity of from about 100 to about 40,000 cps at about 20°C and sheer rate of 1s^{-1} . In some embodiments, the composition has a Brookfield RVDV viscosity of from about 500 to about 30,000 cps at about 20°C and sheer rate of 1s^{-1} . In some embodiments, the composition has a Brookfield RVDV viscosity of from about 1000 to about 20,000 cps at about 20°C and sheer rate of 1s^{-1} . In some embodiments, the composition has a Brookfield RVDV viscosity of from about 2000 to about 10,000 cps at about 20°C and sheer rate of 1s^{-1} . In some embodiments, the composition has a Brookfield RVDV viscosity of from about 4000 to about 8000 cps at about 20°C and sheer rate of 1s^{-1} .

[00203] In some embodiments, the ophthalmic aqueous formulation contains a viscosity enhancing agent sufficient to provide a viscosity of between about 500 and 50,000 centipoise, between about 750 and 50,000 centipoise; between about 1000 and 50,000 centipoise; between about 1000 and

40,000 centipoise; between about 2000 and 30,000 centipoise; between about 3000 and 20,000 centipoise; between about 4000 and 10,000 centipoise, or between about 5000 and 8000 centipoise.

[00204] In some embodiments, the compositions described herein are low viscosity compositions at body temperature. In some embodiments, low viscosity compositions contain from about 1% to about 10% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, low viscosity compositions contain from about 2% to about 10% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, low viscosity compositions contain from about 5% to about 10% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, low viscosity compositions are substantially free of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, a low viscosity ophthalmic agent composition described herein provides an apparent viscosity of from about 100 cP to about 10,000 cP. In some embodiments, a low viscosity ophthalmic agent composition described herein provides an apparent viscosity of from about 500 cP to about 10,000 cP. In some embodiments, a low viscosity ophthalmic agent composition described herein provides an apparent viscosity of from about 1000 cP to about 10,000 cP.

[00205] **Osmolarity**

[00206] In some embodiments, a composition disclosed herein is formulated in order to not disrupt the ionic balance of the eye. In some embodiments, a composition disclosed herein has an ionic balance that is the same as or substantially the same as the eye. In some embodiments, a composition disclosed herein does not does not disrupt the ionic balance of the eye.

[00207] As used herein, “practical osmolarity/osmolality” or “deliverable osmolarity/osmolality” means the osmolarity/osmolality of a composition as determined by measuring the osmolarity/osmolality of the ophthalmic agent and all excipients except the gelling and/or the thickening agent (e.g., polyoxyethylene-polyoxypropylene copolymers, carboxymethylcellulose or the like). The practical osmolarity of a composition disclosed herein is measured by a suitable method, e.g., a freezing point depression method as described in Viegas et. al., Int. J. Pharm., 1998, 160, 157-162. In some instances, the practical osmolarity of a composition disclosed herein is measured by vapor pressure osmometry (e.g., vapor pressure depression method) that allows for determination of the osmolarity of a composition at higher temperatures. In some instances, vapor pressure depression method allows for determination of the osmolarity of a composition comprising a gelling agent (e.g., a thermoreversible polymer) at a higher temperature wherein the gelling agent is in the form of a gel.

[00208] In some embodiments, the osmolarity at a target site of action (e.g., the eye) is about the same as the delivered osmolarity of a composition described herein. In some embodiments, a composition described herein has a deliverable osmolarity of about 150 mOsm/L to about 500 mOsm/L, about 250 mOsm/L to about 500 mOsm/L, about 250 mOsm/L to about 350 mOsm/L, about 280 mOsm/L to about 370 mOsm/L or about 250 mOsm/L to about 320 mOsm/L.

[00209] The practical osmolality of an ophthalmic composition disclosed herein is from about 100 mOsm/kg to about 1000 mOsm/kg, from about 200 mOsm/kg to about 800 mOsm/kg, from about 250 mOsm/kg to about 500 mOsm/kg, or from about 250 mOsm/kg to about 320 mOsm/kg, or from about 250 mOsm/kg to about 350 mOsm/kg or from about 280 mOsm/kg to about 320 mOsm/kg. In some embodiments, a composition described herein has a practical osmolality of about 100 mOsm/L to about 1000 mOsm/L, about 200 mOsm/L to about 800 mOsm/L, about 250 mOsm/L to about 500 mOsm/L, about 250 mOsm/L to about 350 mOsm/L, about 250 mOsm/L to about 320 mOsm/L, or about 280 mOsm/L to about 320 mOsm/L.

[00210] In some embodiments, suitable tonicity adjusting agents include, but are not limited to any pharmaceutically acceptable sugar, salt or any combinations or mixtures thereof, such as, but not limited to dextrose, glycerin, mannitol, sorbitol, sodium chloride, and other electrolytes. In some instances, the tonicity adjusting agent is selected from sodium chloride, sodium nitrate, sodium sulfate, sodium bisulfate, potassium chloride, calcium chloride, magnesium chloride, zinc chloride, potassium acetate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium thiosulfate, magnesium sulfate, disodium hydrogen phosphate, sodium dihydrogen phosphate, potassium dihydrogen phosphate, dextrose, mannitol, sorbitol, dextrose, sucrose, urea, propylene glycol, glycerin, trehalose, or a combination thereof.

[00211] In some embodiment, the ophthalmic compositions described herein include one or more salts in an amount required to bring osmolality of the composition into an acceptable range. Such salts include those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or bisulfite anions; suitable salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfite and ammonium sulfate.

[00212] **Sterility**

[00213] In some embodiments, the compositions are sterilized. Included within the embodiments disclosed herein are means and processes for sterilization of a pharmaceutical composition disclosed herein for use in humans. The goal is to provide a safe pharmaceutical product, relatively free of infection causing micro-organisms. The U. S. Food and Drug Administration has provided regulatory guidance in the publication "Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing" available at: <http://www.fda.gov/cder/guidance/5882fnl.htm>, which is incorporated herein by reference in its entirety.

[00214] As used herein, sterilization means a process used to destroy or remove microorganisms that are present in a product or packaging. Any suitable method available for sterilization of objects and compositions is used. Available methods for the inactivation of microorganisms include, but are not limited to, the application of extreme heat, lethal chemicals, or gamma radiation. In some embodiments, a process for the preparation of an ophthalmic formulation comprises subjecting the formulation to a sterilization method selected from heat sterilization, chemical sterilization, radiation sterilization or filtration sterilization. The method used depends largely upon the nature of the device or composition to

be sterilized. Detailed descriptions of many methods of sterilization are given in Chapter 40 of Remington: The Science and Practice of Pharmacy published by Lippincott, Williams & Wilkins, and is incorporated by reference with respect to this subject matter.

Filtration

[00215] Filtration sterilization is a method used to remove but not destroy microorganisms from solutions. Membrane filters are used to filter heat-sensitive solutions. Such filters are thin, strong, homogenous polymers of mixed cellulosic esters (MCE), polyvinylidene fluoride (PVF; also known as PVDF), or polytetrafluoroethylene (PTFE) and have pore sizes ranging from 0.1 to 0.22 μm . Solutions of various characteristics are optionally filtered using different filter membranes. For example, PVF and PTFE membranes are well suited to filtering organic solvents while aqueous solutions are filtered through PVF or MCE membranes. Filter apparatus are available for use on many scales ranging from the single point-of-use disposable filter attached to a syringe up to commercial scale filters for use in manufacturing plants. The membrane filters are sterilized by autoclave or chemical sterilization. Validation of membrane filtration systems is performed following standardized protocols (Microbiological Evaluation of Filters for Sterilizing Liquids, Vol 4, No. 3. Washington, D.C: Health Industry Manufacturers Association, 1981) and involve challenging the membrane filter with a known quantity (ca. $10^7/\text{cm}^2$) of unusually small microorganisms, such as *Brevundimonas diminuta* (ATCC 19146).

[00216] Pharmaceutical compositions are optionally sterilized by passing through membrane filters. Formulations comprising nanoparticles (U.S. Pat No. 6,139,870) or multilamellar vesicles (Richard et al., International Journal of Pharmaceutics (2006), 312(1-2):144-50) are amenable to sterilization by filtration through 0.22 μm filters without destroying their organized structure.

[00217] In some embodiments, the methods disclosed herein comprise sterilizing the formulation (or components thereof) by means of filtration sterilization. In ophthalmic gel compositions that includes thermosetting polymers, filtration is carried out below (e.g. about 5°C) the gel temperature (T_{gel}) of a formulation described herein and with viscosity that allows for filtration in a reasonable time using a peristaltic pump (e.g. below a theoretical value of 100cP).

[00218] Accordingly, provided herein are methods for sterilization of ophthalmic formulations that prevent degradation of polymeric components (e.g., thermosetting and/or other viscosity enhancing agents) and/or the ophthalmic agent during the process of sterilization. In some embodiments, degradation of the ophthalmic agent (e.g., a muscarinic antagonist such as atropine or atropine sulfate) is reduced or eliminated through the use of specific pD ranges for buffer components and specific proportions of viscosity enhancing agents in the formulations. In some embodiments, the choice of an appropriate viscosity enhancing agents or thermosetting polymer allows for sterilization of formulations described herein by filtration. In some embodiments, the use of an appropriate thermosetting polymer or other viscosity enhancing agents in combination with a specific pD range for the formulation allows for high temperature sterilization of formulations described with substantially no degradation of the

therapeutic agent or the polymeric excipients. An advantage of the methods of sterilization provided herein is that, in certain instances, the formulations are subjected to terminal sterilization via autoclaving without any loss of the ophthalmic agent and/or excipients and/or viscosity enhancing agents during the sterilization step and are rendered substantially free of microbes and/or pyrogens.

Radiation Sterilization

[00219] One advantage of radiation sterilization is the ability to sterilize many types of products without heat degradation or other damage. The radiation commonly employed is beta radiation or alternatively, gamma radiation from a ^{60}Co source. The penetrating ability of gamma radiation allows its use in the sterilization of many product types, including solutions, compositions and heterogeneous mixtures. The germicidal effects of irradiation arise from the interaction of gamma radiation with biological macromolecules. This interaction generates charged species and free-radicals. Subsequent chemical reactions, such as rearrangements and cross-linking processes, result in the loss of normal function for these biological macromolecules. The formulations described herein are also optionally sterilized using beta irradiation.

Sterilization by Heat

[00220] Many methods are available for sterilization by the application of high heat. One method is through the use of a saturated steam autoclave. In this method, saturated steam at a temperature of at least 121 °C is allowed to contact the object to be sterilized. The transfer of heat is either directly to the microorganism, in the case of an object to be sterilized, or indirectly to the microorganism by heating the bulk of an aqueous solution to be sterilized. This method is widely practiced as it allows flexibility, safety and economy in the sterilization process.

Microorganisms

[00221] In some embodiments, the compositions are substantially free of microorganisms. Acceptable bioburden or sterility levels are based on applicable standards that define therapeutically acceptable compositions, including but not limited to United States Pharmacopeia Chapters <1111> et seq. For example, acceptable sterility (e.g., bioburden) levels include about 10 colony forming units (cfu) per gram of formulation, about 50 cfu per gram of formulation, about 100 cfu per gram of formulation, about 500 cfu per gram of formulation or about 1000 cfu per gram of formulation. In some embodiments, acceptable bioburden levels or sterility for formulations include less than 10 cfu/mL, less than 50 cfu/mL, less than 500 cfu/mL or less than 1000 cfu/mL microbial agents. In addition, acceptable bioburden levels or sterility include the exclusion of specified objectionable microbiological agents. By way of example, specified objectionable microbiological agents include but are not limited to *Escherichia coli* (*E. coli*), *Salmonella* sp., *Pseudomonas aeruginosa* (*P. aeruginosa*) and/or other specific microbial agents.

[00222] An important component of the sterility assurance quality control, quality assurance and validation process is the method of sterility testing. Sterility testing, by way of example only, is performed by two methods. The first is direct inoculation wherein a sample of the composition to be tested is added to growth medium and incubated for a period of time up to 21 days. Turbidity of the

growth medium indicates contamination. Drawbacks to this method include the small sampling size of bulk materials which reduces sensitivity, and detection of microorganism growth based on a visual observation. An alternative method is membrane filtration sterility testing. In this method, a volume of product is passed through a small membrane filter paper. The filter paper is then placed into media to promote the growth of microorganisms. This method has the advantage of greater sensitivity as the entire bulk product is sampled. The commercially available Millipore Steritest sterility testing system is optionally used for determinations by membrane filtration sterility testing. For the filtration testing of creams or ointments Steritest filter system No. TLHVSL210 are used. For the filtration testing of emulsions or viscous products Steritest filter system No. TLAREM210 or TDAREM210 are used. For the filtration testing of pre-filled syringes Steritest filter system No. TTHASY210 are used. For the filtration testing of material dispensed as an aerosol or foam Steritest filter system No. TTHVA210 are used. For the filtration testing of soluble powders in ampoules or vials Steritest filter system No. TTHADA210 or TTHADV210 are used.

[00223] Testing for *E. coli* and *Salmonella* includes the use of lactose broths incubated at 30 – 35 °C for 24-72 hours, incubation in MacConkey and/or EMB agars for 18-24 hours, and/or the use of Rappaport medium. Testing for the detection of *P. aeruginosa* includes the use of NAC agar. United States Pharmacopeia Chapter <62> further enumerates testing procedures for specified objectionable microorganisms.

[00224] In certain embodiments, the ophthalmic formulation described herein has less than about 60 colony forming units (CFU), less than about 50 colony forming units, less than about 40 colony forming units, or less than about 30 colony forming units of microbial agents per gram of formulation. In certain embodiments, the ophthalmic formulations described herein are formulated to be isotonic with the eye.

Endotoxins

[00225] An additional aspect of the sterilization process is the removal of by-products from the killing of microorganisms (hereinafter, “Product”). The process of depyrogenation removes pyrogens from the sample. Pyrogens are endotoxins or exotoxins which induce an immune response. An example of an endotoxin is the lipopolysaccharide (LPS) molecule found in the cell wall of gram-negative bacteria. While sterilization procedures such as autoclaving or treatment with ethylene oxide kill the bacteria, the LPS residue induces a proinflammatory immune response, such as septic shock. Because the molecular size of endotoxins varies widely, the presence of endotoxins is expressed in “endotoxin units” (EU). One EU is equivalent to 100 picograms of *E. coli* LPS. In some cases, humans develop a response to as little as 5 EU/kg of body weight. The bioburden (e.g., microbial limit) and/or sterility (e.g., endotoxin level) is expressed in any units as recognized in the art. In certain embodiments, ophthalmic compositions described herein contain lower endotoxin levels (e.g. < 4 EU/kg of body weight of a subject) when compared to conventionally acceptable endotoxin levels (e.g., 5 EU/kg of body weight of a subject). In some embodiments, the ophthalmic formulation has less than about 5 EU/kg of body weight

of a subject. In other embodiments, the ophthalmic formulation has less than about 4 EU/kg of body weight of a subject. In additional embodiments, the ophthalmic formulation has less than about 3 EU/kg of body weight of a subject. In additional embodiments, the ophthalmic formulation has less than about 2 EU/kg of body weight of a subject.

[00226] In some embodiments, the ophthalmic formulation has less than about 5 EU/kg of formulation. In other embodiments, the ophthalmic formulation has less than about 4 EU/kg of formulation. In additional embodiments, the ophthalmic formulation has less than about 3 EU/kg of formulation. In some embodiments, the ophthalmic formulation has less than about 5 EU/kg Product. In other embodiments, the ophthalmic formulation has less than about 1 EU/kg Product. In additional embodiments, the ophthalmic formulation has less than about 0.2 EU/kg Product. In some embodiments, the ophthalmic formulation has less than about 5 EU/g of unit or Product. In other embodiments, the ophthalmic formulation has less than about 4 EU/g of unit or Product. In additional embodiments, the ophthalmic formulation has less than about 3 EU/g of unit or Product. In some embodiments, the ophthalmic formulation has less than about 5 EU/mg of unit or Product. In other embodiments, the ophthalmic formulation has less than about 4 EU/mg of unit or Product. In additional embodiments, the ophthalmic formulation has less than about 3 EU/mg of unit or Product. In certain embodiments, ophthalmic formulations described herein contain from about 1 to about 5 EU/mL of formulation. In certain embodiments, ophthalmic formulations described herein contain from about 2 to about 5 EU/mL of formulation, from about 3 to about 5 EU/mL of formulation, or from about 4 to about 5 EU/mL of formulation.

[00227] In certain embodiments, ophthalmic compositions described herein contain lower endotoxin levels (e.g. < 0.5 EU/mL of formulation) when compared to conventionally acceptable endotoxin levels (e.g., 0.5 EU/mL of formulation). In some embodiments, the ophthalmic formulation has less than about 0.5 EU/mL of formulation. In other embodiments, the ophthalmic formulation has less than about 0.4 EU/mL of formulation. In additional embodiments, the ophthalmic formulation has less than about 0.2 EU/mL of formulation.

[00228] Pyrogen detection, by way of example only, is performed by several methods. Suitable tests for sterility include tests described in United States Pharmacopoeia (USP) <71> Sterility Tests (23rd edition, 1995). The rabbit pyrogen test and the Limulus amoebocyte lysate test are both specified in the United States Pharmacopoeia Chapters <85> and <151> (USP23/NF 18, Biological Tests, The United States Pharmacopoeial Convention, Rockville, MD, 1995). Alternative pyrogen assays have been developed based upon the monocyte activation-cytokine assay. Uniform cell lines suitable for quality control applications have been developed and have demonstrated the ability to detect pyrogenicity in samples that have passed the rabbit pyrogen test and the Limulus amoebocyte lysate test (Taktak et al, J. Pharm. Pharmacol. (1990), 43:578-82). In an additional embodiment, the ophthalmic formulation is subject to depyrogenation. In a further embodiment, the process for the manufacture of the ophthalmic

formulation comprises testing the formulation for pyrogenicity. In certain embodiments, the formulations described herein are substantially free of pyrogens.

[00229] Ophthalmic Muscarinic Antagonist-Mucus Penetrating Particle (MPP)

Composition

[00230] Mucus-penetrating particles (MPPs) are particles that rapidly traverse mucus (e.g. human mucus). In some cases, MPPs comprise of a nanoparticle with a particle size of between about 200nm and 500nm. In some instances, the nanoparticle is further coated with a mucus penetrating agent. In some instances, a composition described herein is formulated with MPPs for mucus penetration. In some instances, an ophthalmic agent composition described herein is formulated with MPPs for mucus penetration. In some instances, the ophthalmic agent is a muscarinic antagonist. In some instances, a muscarinic antagonist composition described herein is formulated with MPPs for mucus penetration. In some instances, a muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, atropine methonitrate, diphenhydramine, dimenhydrinate, dicyclomine, flavoxate, oxybutynin, tiotropium, hyoscine, scopolomine (L-hyoscine), hydroxyzine, ipratropium, tropicamide, cyclopentolate, pirenzapine, homatropine, solifenacin, darifenacin, benzatropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, or tolterodine. In some instances, a muscarinic antagonist is atropine or its pharmaceutically acceptable salt thereof. In some instances, a muscarinic antagonist is atropine sulfate. In some instances, an atropine composition described herein is formulated with MPPs for mucus penetration. In some instances, an atropine sulfate composition described herein is formulated with MPPs for mucus penetration. In a non-limiting example, the MPPs for use in the disclosed composition is obtained from Kala Pharmaceuticals, Inc. (100 Beaver Street #201, Waltham, MA 02453).

[00231] In some embodiments, the nanoparticle comprises of any suitable material, such as an organic material, an inorganic material, a polymer, or combinations thereof. In some instances, the nanoparticle comprises of inorganic material, such as for example, a metal (e.g., Ag, Au, Pt, Fe, Cr, Co, Ni, Cu, Zn, and other transition metals), a semiconductor (e.g., silicon, silicon compounds and alloys, cadmium selenide, cadmium sulfide, indium arsenide, and indium phosphide), or an insulator (e.g., ceramics such as silicon oxide). In some instances, the nanoparticle comprises organic materials such as a synthetic polymer and/or a natural polymer. Examples of synthetic polymers include non-degradable polymers such as polymethacrylate and degradable polymers such as polylactic acid, polyglycolic acid and copolymers thereof. Examples of natural polymers include hyaluronic acid, chitosan, and collagen.

[00232] In some embodiments, the nanoparticle is coated with a mucus penetrating agent. In some instances, the mucus penetrating agent comprises any suitable material, such as a hydrophobic material, a hydrophilic material, and/or an amphiphilic material. In some instances, the mucus penetrating agent is a polymer. In some instances, the polymer is a synthetic polymer (i.e., a polymer not produced in nature). In other embodiments, the polymer is a natural polymer (e.g., a protein, polysaccharide, rubber). In certain embodiments, the polymer is a surface active polymer. In certain

embodiments, the polymer is a non-ionic polymer. In certain embodiments, the polymer is a non-ionic block copolymer. In some embodiments, the polymer is a diblock copolymer, a triblock copolymer, e.g., e.g., where one block is a hydrophobic polymer and another block is a hydrophilic polymer. In some embodiments, the polymer is charged or uncharged.

[00233] Additional examples of suitable polymers include, but are not limited to, polyamines, polyethers, polyamides, polyesters, polycarbamates, polyureas, polycarbonates, polystyrenes, polyimides, polysulfones, polyurethanes, polyacetylenes, polyethylenes, polyethyleneimines, polyisocyanates, polyacrylates, polymethacrylates, polyacrylonitriles, and polyarylates. Non-limiting examples of specific polymers include poly(caprolactone) (PCL), ethylene vinyl acetate polymer (EVA), poly(lactic acid) (PLA), poly(L-lactic acid) (PLLA), poly(glycolic acid) (PGA), poly(lactic acid-co-glycolic acid) (PLGA), poly(L-lactic acid-co-glycolic acid) (PLLGA), poly(D,L-lactide) (PDLA), poly(L-lactide) (PLLA), poly(D,L-lactide-co-caprolactone), poly(D,L-lactide-co-caprolactone-co-glycolide), poly(D,L-lactide-co-PEO-co-D,L-lactide), poly(D,L-lactide-co-PPO-co-D,L-lactide), polyalkyl cyanoacrylate, polyurethane, poly-L-lysine (PLL), hydroxypropyl methacrylate (HPMA), poly(ethylene glycol), poly-L-glutamic acid, poly(hydroxy acids), polyanhydrides, polyorthoesters, poly(ester amides), polyamides, poly(ester ethers), polycarbonates, polyalkylenes such as polyethylene and polypropylene, polyalkylene glycols such as poly(ethylene glycol) (PEG), polyalkylene oxides (PEO), polyalkylene terephthalates such as poly(ethylene terephthalate), polyvinyl alcohols (PVA), polyvinyl ethers, polyvinyl esters such as poly(vinyl acetate), polyvinyl halides such as poly(vinyl chloride) (PVC), polyvinylpyrrolidone, polysiloxanes, polystyrene (PS), polyurethanes, derivatized celluloses such as alkyl celluloses, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitro celluloses, hydroxypropylcellulose, carboxymethylcellulose, polymers of acrylic acids, such as poly(methyl(meth)acrylate) (PMMA), poly(ethyl(meth)acrylate), poly(butyl(meth)acrylate), poly(isobutyl(meth)acrylate), poly(hexyl(meth)acrylate), poly(isodecyl(meth)acrylate), poly(lauryl(meth)acrylate), poly(phenyl(meth)acrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate) (jointly referred to herein as "polyacrylic acids"), and copolymers and mixtures thereof, polydioxanone and its copolymers, polyhydroxyalkanoates, polypropylene fumarate), polyoxymethylene, poloxamers, poly(ortho)esters, poly(butyric acid), poly(valeric acid), poly(lactide-co-caprolactone), and trimethylene carbonate, polyvinylpyrrolidone.

[00234] In some cases, an ophthalmic agent (e.g. a muscarinic antagonist such as atropine or atropine sulfate) is present in the MPP formulation at a concentration of between about 0.001 wt% and about 0.05 wt%, between about 0.005% to about 0.050%, between about 0.010% to about 0.050%, between about 0.015% to about 0.050%, between about 0.020% to about 0.050%, between about 0.025% to about 0.050%, between about 0.030% to about 0.050%, between about 0.035% to about 0.050%, between about 0.040% to about 0.050%, or between about 0.045% to about 0.050% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some

instances, additional agents such as buffers, pH adjusting agents, and/or preservatives are formulated in the MPP formulation.

[00235] In some instances, ophthalmic agent-MPP composition is formulated using any suitable method. In some embodiments, a milling process is used to reduce the size of a solid material to form particles in the micrometer to nanometer size range. In some cases, dry and wet milling processes such as jet milling, cryo-milling, ball milling, media milling, and homogenization are known and are used in methods described herein. Generally, in a wet milling process, a suspension of the material to be used as the nanoparticle is mixed with milling media with or without excipients to reduce particle size. Dry milling is a process wherein the material to be used as the nanoparticle is mixed with milling media with or without excipients to reduce particle size. In a cryo-milling process, a suspension of the material to be used as the nanoparticle is mixed with milling media with or without excipients under cooled temperatures.

[00236] In some embodiments, any suitable grinding medium is used for milling. In some embodiments, a ceramic and/or polymeric material and/or a metal is used. Examples of suitable materials include zirconium oxide, silicon carbide, silicon oxide, silicon nitride, zirconium silicate, yttrium oxide, glass, alumina, alpha- alumina, aluminum oxide, polystyrene, poly(methyl methacrylate), titanium, steel. In some cases, a grinding medium has any suitable size. For example, the grinding medium has an average diameter of at least about 0.1 mm, at least about 0.2 mm, at least about 0.5 mm, at least about 0.8 mm, at least about 1 mm, at least about 2 mm, or at least about 5 mm. In some cases, the grinding medium has an average diameter of less than or equal to about 5 mm, less than or equal to about 2 mm, less than or equal to about 1 mm, less than or equal to about 0.8, less than or equal to about 0.5 mm, or less than or equal to about 0.2 mm. Combinations of the above-referenced ranges are also possible (e.g., an average diameter of at least about 0.5 millimeters and less than or equal to about 1 mm). Other ranges are also possible.

[00237] In some embodiments, any suitable solvent are used for milling. In some cases, the choice of solvent is depend on factors such as the solid material (e.g., a muscarinic antagonist such as atropine) being milled, the particular type of stabilizer/mucus penetrating agent being used (e.g., one that renders the particle mucus penetrating), the grinding material be used, among other factors. In some cases, suitable solvents are ones that do not substantially dissolve the solid material or the grinding material, but dissolve the stabilizer/mucus penetrating agent to a suitable degree. Non-limiting examples of solvents include, but are not limited to, water, buffered solutions, other aqueous solutions, alcohols (e.g., ethanol, methanol, butanol), and mixtures thereof that optionally include other components such as pharmaceutical excipients, polymers, pharmaceutical agents, salts, preservative agents, viscosity modifiers, tonicity modifier, taste masking agents, antioxidants, pH modifier, and other pharmaceutical excipients. In other embodiments, an organic solvent is used. In some cases, a pharmaceutical agent (e.g. a muscarinic antagonist such as atropine) has any suitable solubility in these or other solvents, such as a

solubility in one or more of the ranges described above for aqueous solubility or for solubility in a coating solution.

[00238] In some instances, a MPP is a MPP as described in WO2013/166385. In some instances, a MPP is a MPP as described in Lai *et al.*, “Rapid transport of large polymeric nanoparticles in fresh undiluted human mucus,” *PNAS* 104(5):1482-1487 (2007). In some instances, an ophthalmic agent-MPP composition is formulated using a method as described in WO2013/166385. In some instances, an ophthalmic agent-MPP composition is formulated using a method as described in Lai *et al.*, “Rapid transport of large polymeric nanoparticles in fresh undiluted human mucus,” *PNAS* 104(5):1482-1487 (2007). In some instances, the ophthalmic agent is a muscarinic antagonist such as atropine or atropine sulfate.

[00239] Muscarinic Antagonist-Ophthalmic Delivery Devices and Delivery System

[00240] In some embodiments, a muscarinic antagonist described herein is delivered to a target site by an ophthalmic delivery device. In some cases, the ophthalmic delivery device is configured for controlled sustained release of a muscarinic antagonist. In some instances, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some cases, the muscarinic antagonist comprises atropine or atropine sulfate.

[00241] In some embodiments, an ophthalmic delivery device comprises a punctal plug, a scleral patch, a scleral ring, a Cul-de sac insert, a subconjunctival/episcleral implant, an intravitreal implant, or a non-invasive delivery device. In some instances, a non-invasive delivery device comprises topical ophthalmic drug delivery device (TODD) or a contact lens. In some instances, the ophthalmic delivery device is a biodegradable ophthalmic delivery device. In other instances, the ophthalmic delivery device is a non-biodegradable ophthalmic delivery device. In some cases, the biodegradable ophthalmic delivery device is configured for controlled sustained release of a muscarinic antagonist. In other cases, the non-biodegradable ophthalmic delivery device is configured for controlled sustained release of a muscarinic antagonist.

[00242] In some instances, an ophthalmic delivery device comprises a core or reservoir which comprises a muscarinic antagonist (e.g., atropine or atropine sulfate) and is configured for a controlled sustained release of the muscarinic antagonist. In some cases, the muscarinic antagonist is formulated within the core or reservoir as a solution, a gel, or in a solid form. In other embodiments, a muscarinic antagonist (e.g., atropine or atropine sulfate) is dispersed (e.g., uniformly) within the material of the ophthalmic delivery device, and is configured for a controlled sustained release of the muscarinic antagonist. In some instances, the ophthalmic delivery device is a punctal plug, a scleral patch, a scleral ring, a Cul-de sac insert, a subconjunctival/episcleral implant, an intravitreal implant, or a non-invasive delivery device.

[00243] *Punctal Plug*

[00244] A punctal plug or tear duct plug is an ocular device that in some cases is inserted into the tear duct (or puncta) of an eye. In some instances, a punctal plug is used for the delivery of an ophthalmic composition, for example, an ophthalmic composition described herein. In some cases, a punctal plug is used for the delivery of a muscarinic antagonist formulated in deuterated water. In additional cases, a punctal plug is used for the delivery of atropine or atropine sulfate formulated in deuterated water.

[00245] In some instances, a punctal plug is used for controlled sustained release of a muscarinic antagonist (e.g., atropine or atropine sulfate). In some cases, the period of controlled sustained release is, for example, up to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 30, 45, 60 days or longer. In some instances, the period of controlled sustained release is, for example, up to 7 days. In some cases, the period of controlled sustained release is, for example, up to 14 days. In some cases, the period of controlled sustained release is, for example, up to 1 month.

[00246] In some embodiments, a punctal plug comprises a core or reservoir which comprises a muscarinic antagonist (e.g., atropine or atropine sulfate) and is configured for a controlled sustained release of the muscarinic antagonist. In other embodiments, a muscarinic antagonist (e.g., atropine or atropine sulfate) is dispersed within the punctal plug material, and is configured for a controlled sustained release of the muscarinic antagonist.

[00247] In some embodiments, a punctal plug described herein utilizes a diffusion mechanism for the delivery of a muscarinic antagonist (e.g., atropine or atropine sulfate). In some instances, the configuration of the punctal plug is tubular with its cylindrical wall closed by transverse end walls to define a reservoir for the muscarinic antagonist (either in liquid or gel form). In some cases, at least the cylindrical wall is a membrane permeable by diffusion so that the muscarinic antagonist is released continuously at a controlled rate through the membrane into the tear fluid.

[00248] Exemplary materials for a permeable membrane for the diffusion mechanism include insoluble microporous materials of polycarbonates, polyvinyl chlorides, polyamides, copolymers of polyvinyl chloride and acrylonitrile, polysulphones, polyvinylidene fluorides, polyvinyl fluorides, polychloroethers, polyformaldehydes, acrylic resins, polyurethanes, polyimides, polybenzimidazoles, polyvinyl acetates, polyethers, cellulose esters, porous rubbers, cross-linked poly(ethylene oxide), cross-linked polyvinyl pyrrolidone, cross-linked poly(vinyl alcohol) and polystyrenes.

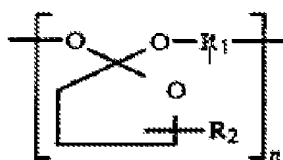
[00249] In some embodiments, a punctal plug described herein utilizes an osmosis mechanism for the delivery of a muscarinic antagonist (e.g., atropine or atropine sulfate). In some cases, the configuration of the punctal plug is tubular with domed end walls, and the device comprises a transverse impermeable elastic membrane dividing the tubular interior of the device into a first compartment and a second compartment; the first compartment is bounded by a semi-permeable membrane and the impermeable elastic membrane, and the second compartment is bounded by an impermeable material and the elastic membrane. In some cases, a drug release aperture is included in the impermeable end wall of the device. When the device is placed in the aqueous environment of the eye water diffuses into the first

compartment and stretches the elastic membrane to expand the first compartment and contract the second compartment so that the drug is forced through the drug release aperture.

[00250] Examples of materials for an osmotic semi-permeable membrane include cellulose acetate and its derivatives, partial and completely hydrolyzed ethylene-vinyl acetate copolymers, highly plasticized polyvinyl chloride, homo- and copolymers of polyvinyl acetate, polyesters of acrylic acid and methacrylic acid, polyvinyl alkyl ethers, polyvinyl fluoride; silicone polycarbonates, aromatic nitrogen-containing polymeric membranes, polymeric epoxides, copolymers of an alkylene oxide and alkyl glycidyl ether, polyurethanes, polyglycolic or polyacetic acid and derivatives thereof, derivatives of polystyrene such as poly(sodium styrenesulfonate) and poly(vinyl benzyltrimethyl-ammonium chloride), ethylene-vinyl acetate copolymers.

[00251] In some embodiments, a punctal plug described herein utilizes a bioerosion mechanism for the delivery of a muscarinic antagonist (e.g., atropine or atropine sulfate). In some cases, the configuration of the punctal plug is rod-like being constituted from a matrix of bioerodible material in which the drug is dispersed. Contact of the device with tear fluid results in controlled sustained release of the drug by bioerosion of the matrix. In such cases, the drug is dispersed uniformly throughout the matrix but it is believed a more controlled release is obtained if the drug is superficially concentrated in the matrix.

[00252] Examples of bioerodible matrix materials include polyesters of the general formula --O--(W)--CO-- and mixture thereof, wherein W is a lower alkylene of 1 to 7 carbons and may include a member selected from the group of alkylenes of the formula --CH₂--, or --CH--CH₂--, and Y has a value such that the molecular weight of the polymer is from about 4,000 to 100,000. The polymers are polymerization-condensation products of monobasic hydroxy acid of the formula C_n H_{2n} (OH)COOH wherein n has a value of 1 to 7, preferably 1 or 2 and the acid is especially lactic acid or glycolic acid. Also included are copolymers derived from mixtures of these acids. Bioerodible materials also include poly(orthoesters). These materials have the following general formula:



wherein R₁ is an alkylene of 4 to 12 carbons, a cycloalkylene of 5 to 6 carbons substituted with an alkylene of 1 to 7 carbons and an alkyleneoxy of 1 to 7 carbons, and R₂ is a lower alkyl of 1 to 7 carbons.

[00253] Additional bioerodible matrix materials include: (1) Polyanhydrides such as poly(p-carboxyphenoxy) alkyl (e.g. p-carboxyphenoxypropane) or polymeric fatty acid dimer (e.g. poly-dodecanedioic acid) compounds and further co-polymers with sebacic acid, or phthalic acid such as disclosed in Chasin *et al.*, Polyanhydrides for Controlled Drug Delivery, *Biopharm.*, Feb. 1988, 33-46; and Lee *et al.* (1988), The Use of Bioerodible Polymers and 5 fluorouracil in Glaucoma Filtration Surgery, *Invest. Ophthalmol. Vis. Sci.*, **29**, 1692-1697; (2) Poly (alkyl-2-cyanoacrylates) such as poly (hexyl-2-

cyanoacrylate) as described by Douglas *et al.* (1987), Nanoparticles in Drug Delivery, CRC Crit. Rev. Therap. Drug Carr. System., 3, 233-261; and (3) Polyamino acids such as copolymers of leucine and methyl glutamate.

[00254] In some cases, a punctal plug described herein comprises a solid non-erodible rod with pores. In some instances, the release of a muscarinic antagonist takes place via diffusion through the pores. In such instances, controlled release is further regulated by gradual dissolution of solid dispersed drug within this matrix as a result of inward diffusion of aqueous solutions.

[00255] Examples of materials for use as non-erodible rods include polymers such as hydroxyethylmethacrylate and co-polymers with methacrylic acid, methylmethacrylate, N-vinyl 2-pyrrolidone, allyl methacrylate, ethylene glycol dimethacrylate, ethylene dimethacrylate, or 1,1,1-trimethylpropane trimethacrylate, and dimethyl diphenyl methylvinyl polysiloxane.

[00256] In some instances, the body of the plug is wholly or partially transparent or opaque. Optionally, the body includes a tint or pigment that makes the plug easier to see when it is placed in a punctum.

[00257] In some cases, the surface of the plug body is wholly or partially coated. In some cases, the coating provides one or more of lubriciousness to aid insertion, muco-adhesiveness to improve tissue compatibility, and texture to aid in anchoring the plug within the punctum. Examples of suitable coatings include, without limitation, gelatin, collagen, hydroxyethyl methacrylate, PVP, PEG, heparin, chondroitin sulphate, hyaluronic acid, synthetic and natural proteins, and polysaccharides, thiomers, thiolated derivatives of polyacrylic acid and chitosan, polyacrylic acid, carboxymethyl cellulose and the like and combinations thereof.

[00258] In some embodiments, a punctal plug described herein is a punctal plug described in U.S. Patent No. 5147647; U.S. Publication No. 2012/0277694; or 2010/0256557.

[00259] In some instances, the size of the opening of the punctal plug is from about 0.05 mm to about 2.5 mm. In some instances, it is from about 0.1 mm to about 2.0 mm, or from about 0.15 mm to about 1 mm.

[00260] In some embodiments, the amount of a muscarinic antagonist (e.g., atropine or atropine sulfate) used in the plugs depends upon the muscarinic antagonist selected, the desired doses to be delivered via the punctal plug, the desired release rate, and the melting points of the muscarinic antagonist and muscarinic antagonist-containing material.

[00261] *Scleral Patch or Scleral Ring*

[00262] In some embodiments, a muscarinic antagonist described herein is delivered to an eye through a scleral patch or a scleral ring. In some instances, a scleral patch or a scleral ring is a biodegradable scleral patch or scleral ring. In other instances, a scleral patch or a scleral ring is a non-biodegradable scleral patch or scleral ring. In additional instances, a scleral patch or a scleral ring is formulated for controlled sustained release of one or more of a muscarinic antagonist described herein. In some cases, a scleral patch comprises a multi-layered patch in which one or more layer within the

patch comprises a muscarinic antagonist described herein. In some cases, a scleral ring comprises a core or reservoir which comprises a muscarinic antagonist (e.g., atropine or atropine sulfate), and the muscarinic antagonist is formulated within the core or reservoir as a solution, a gel, or in a solid form. In other embodiments, a muscarinic antagonist (e.g., atropine or atropine sulfate) is dispersed (e.g., uniformly) within the material of the scleral patch or the scleral ring.

[00263] *Cul-de sac Inserts*

[00264] In some embodiments, a muscarinic antagonist described herein is delivered to an eye through a Cul-de sac insert. In some instances, the Cul-de sac insert comprises a single-layered device comprising muscarinic antagonist dispersed within the insert material, or multilayered, solid or semisolid consistency insert. In some instances, the Cul-de sac insert is a biodegradable insert. In other instances, the Cul-de sac insert is a non-biodegradable insert. In additional instances, a Cul-de sac insert is formulated for controlled sustained release of one or more of a muscarinic antagonist described herein. In some instances, a Cul-de sac insert comprises a membrane-bound ocular insert, which comprises of two outer layers of a copolymer such as ethylene-vinyl acetate copolymer (EVA) and an inner layer comprising a muscarinic antagonist. In some instances, the muscarinic antagonist within the inner layer is formulated as a gel or as a solution. An exemplary membrane-bound ocular insert is Ocuserts from Alza Corp.

[00265] In some cases, a Cul-de sac insert comprises an ocular film or sheath (mucoadhesive film or sheath or collagen shields), a coil, a polymer rod, HEMA hydrogel, or polysulfone capillary fiber. In some instances, a Cul-de sac insert comprises rod-shaped water soluble insert comprising of hydroxypropyl cellulose, a muscarinic antagonist, and one or more additional excipients. In some instances, the Cul-de sac insert comprising a rod-shaped water soluble insert is a biodegradable insert. An example comprises Lacrisert (Merck).

[00266] *Subconjunctival/Episcleral Implant*

[00267] In some embodiments, a muscarinic antagonist described herein is delivered to an eye through a subconjunctival/episcleral implant. In some instances, a subconjunctival/episcleral implant is a biodegradable implant. In other instances, a subconjunctival/episcleral implant is a non-biodegradable implant. In additional instances, a subconjunctival/episcleral implant is formulated for controlled sustained release of one or more of a muscarinic antagonist described herein. In some cases, a subconjunctival/episcleral implant comprises a core or reservoir which comprises a muscarinic antagonist (e.g., atropine or atropine sulfate), and the muscarinic antagonist is formulated within the core or reservoir as a solution, a gel, or in a solid form. In other embodiments, a muscarinic antagonist (e.g., atropine or atropine sulfate) is dispersed (e.g., uniformly) within the material of the subconjunctival/episcleral implant. Exemplary subconjunctival/episcleral implants include LX201 (Lux Biosciences Inc.), an episcleral implant from 3T Ophthalmics, or a subconjunctival insert from Pfizer.

[00268] *Intravitreal Implants*

[00269] In some embodiments, a muscarinic antagonist described herein is delivered to an eye through an intravitreal implant. In some instances, an intravitreal implant is a biodegradable implant. In other instances, an intravitreal implant is a non-biodegradable implant. In additional instances, an intravitreal implant is formulated for controlled sustained release of one or more of a muscarinic antagonist described herein. In some cases, an intravitreal implant comprises a core or reservoir which comprises a muscarinic antagonist (e.g., atropine or atropine sulfate), and the muscarinic antagonist is formulated within the core or reservoir as a solution, a gel, or in a solid form. In other embodiments, a muscarinic antagonist (e.g., atropine or atropine sulfate) is dispersed (e.g., uniformly) within the material of the intravitreal implant. Exemplary intravitreal implant comprises Durasert™ technology system (pSivida Corp.) (such as Vitrasert® and Retisert® from Bausch & Lomb Inc, and Iluvien® from Alimera sciences), Novadur™ technology system (such as Ozurdex® from Allergan), I-vation™ technology system (such as a delivery system developed from SurModics, Inc.), and NT-501 from Neurotech Pharmaceuticals.

[00270] *Non-invasive Delivery System*

[00271] In some embodiments, a non-invasive delivery system comprises a topical ophthalmic agent delivery device. In some embodiments, a muscarinic antagonist described herein is delivered to an eye through a topical ophthalmic agent delivery device. In some instances, the topical ophthalmic agent delivery device comprises a soft elastomer drug depot that floats atop the sclera under the eyelid. In some instances, the topical ophthalmic agent delivery device is a biodegradable delivery device. In other instances, the topical ophthalmic agent delivery device is a non-biodegradable delivery device. In some cases, the topical ophthalmic agent delivery device is impregnated with a muscarinic antagonist described herein. In other cases, a muscarinic antagonist is dispersed (e.g., uniformly) in the topical ophthalmic agent delivery device. In some instances, the topical ophthalmic agent delivery device is formulated for controlled sustained release of the muscarinic antagonist. In some instances, an exemplary delivery device is a topical ophthalmic drug delivery device (TODD) from Amorphex Therapeutics.

[00272] In some embodiments, a non-invasive delivery system comprises a contact lens. In some embodiments, a muscarinic antagonist described herein is delivered to an eye through a contact lens. In some instances, the contact lens is impregnated with a muscarinic antagonist, for example, in which the muscarinic antagonist is dispersed, e.g., as colloidal structure, within the lens. In other instances, the contact lens is further combined with a muscarinic antagonist layer, and is configured for controlled sustained release to the eye. Exemplary polymers, e.g., hydrogel copolymers, for making a contact lens include at least one hydrophilic monomer and a crosslinking agent (a crosslinker being defined as a monomer having multiple polymerizable functionalities). Representative, hydrophilic monomers include: unsaturated carboxylic acids, such as methacrylic acid and acrylic acid; (meth)acrylic substituted alcohols, such as 2-hydroxyethylmethacrylate and 2-hydroxyethylacrylate; vinyl lactams, such as N-vinyl pyrrolidone; and (meth)acrylamides, such as methacrylamide and N,N-dimethylacrylamide. Typical crosslinking agents include polyvinyl, typically di- or tri-vinyl monomers, such as di- or

tri(meth)acrylates of diethyleneglycol, triethyleneglycol, butyleneglycol and hexane-1,6-diol; and divinylbenzene. A specific example of a hydrogel-forming monomer mixture is polymacon, composed primarily of 2-hydroxyethylmethacrylate with a small amount of diethyleneglycol dimethacrylate as a crosslinking monomer. Optionally, the monomer mixture may include a silicone-containing monomer in order to form a silicone hydrogel copolymer. Examples of silicone-containing monomers include: monomers including a single activated unsaturated radical, such as methacryloxypropyl tris(trimethylsiloxy)silane, pentamethyldisiloxanyl methylmethacrylate, tris(trimethylsiloxy)methacryloxy propylsilane, methyldi(trimethylsiloxy)methacryloxymethyl silane, 3-[tris(trimethylsiloxy)silyl]propyl vinyl carbamate, and 3-[tris(trimethylsiloxy)silyl]propyl vinyl carbonate; and multifunctional ethylenically “end-capped” siloxane-containing monomers, especially difunctional monomers having two activated unsaturated radicals. A specific example of a silicone hydrogel-forming monomer mixture is balafilcon, based on N-vinyl pyrrolidone and the aforementioned vinyl carbonate and carbamate monomers, disclosed in U.S. Patent No. 5,260,000.

[00273] Ophthalmic Gel Muscarinic Antagonist Composition

[00274] Gels have been defined in various ways. For example, the United States Pharmacopoeia defines gels as semisolid systems consisting of either suspensions made up of small inorganic particles or large organic molecules interpenetrated by a liquid. Gels include a single-phase or a two-phase system. A single-phase gel consists of organic macromolecules distributed uniformly throughout a liquid in such a manner that no apparent boundaries exist between the dispersed macromolecules and the liquid. Some single-phase gels are prepared from synthetic macromolecules (e.g., carbomer) or from natural gums, (e.g., tragacanth). In some embodiments, single-phase gels are generally aqueous, but will also be made using alcohols and oils. Two-phase gels consist of a network of small discrete particles.

[00275] In some embodiments, gels are also classified as being hydrophobic or hydrophilic. In certain embodiments, the base of a non-limiting example of a hydrophobic gel includes a liquid paraffin with polyethylene or fatty oils gelled with colloidal silica, or aluminum or zinc soaps. In contrast, the base of a non-limiting example of a hydrophilic gel includes water, glycerol, or propylene glycol gelled with a suitable gelling agent (e.g., tragacanth, starch, cellulose derivatives, carboxyvinylpolymers, and magnesium-aluminum silicates). In certain embodiments, the rheology of the compositions disclosed herein is pseudo plastic, plastic, thixotropic, or dilatant.

[00276] In some embodiments, the ophthalmic composition is an ophthalmic gel, and wherein the ophthalmically acceptable carrier comprises water and at least one viscosity-enhancing agent. In some embodiments, the viscosity-enhancing agent is selected from cellulose-based polymers, polyoxyethylene-polyoxypropylene triblock copolymers, dextran-based polymers, polyvinyl alcohol, dextrin, polyvinylpyrrolidone, polyalkylene glycols, chitosan, collagen, gelatin, hyaluronic acid, or combinations thereof.

[00277] In some embodiment, the ophthalmic gel composition described herein is a semi-solid or id in a gelled state before it is topically administered (e.g. at room temperature). For example, suitable

viscosity-enhancing agents for such gels include by way of example only, gelling agents and suspending agents. In one embodiment, the enhanced viscosity formulation does not include a buffer. In other embodiments, the enhanced viscosity formulation includes a pharmaceutically acceptable buffer. Sodium chloride or other tonicity agents are optionally used to adjust tonicity, if necessary.

[00278] By way of example only, the ophthalmically acceptable viscosity agent includes hydroxypropyl methylcellulose, hydroxyethyl cellulose, polyvinylpyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium chondroitin sulfate, sodium hyaluronate. Other viscosity enhancing agents compatible with the targeted ocular site include, but are not limited to, acacia (gum arabic), agar, aluminum magnesium silicate, sodium alginate, sodium stearate, bladderwrack, bentonite, carbomer, carrageenan, Carbopol, xanthan, cellulose, microcrystalline cellulose (MCC), ceratonia, chitin, carboxymethylated chitosan, chondrus, dextrose, furcellaran, gelatin, Ghatti gum, guar gum, hectorite, lactose, sucrose, maltodextrin, mannitol, sorbitol, honey, maize starch, wheat starch, rice starch, potato starch, gelatin, sterculia gum, xanthum gum, gum tragacanth, ethyl cellulose, ethylhydroxyethyl cellulose, ethylmethyl cellulose, methyl cellulose, hydroxyethyl cellulose, hydroxyethylmethyl cellulose, hydroxypropyl cellulose, poly(hydroxyethyl methacrylate), oxypolygelatin, pectin, polygeline, povidone, propylene carbonate, methyl vinyl ether/maleic anhydride copolymer (PVM/MA), poly(methoxyethyl methacrylate), poly(methoxyethoxyethyl methacrylate), hydroxypropyl cellulose, hydroxypropylmethyl-cellulose (HPMC), sodium carboxymethyl-cellulose (CMC), silicon dioxide, polyvinylpyrrolidone (PVP: povidone), Splenda® (dextrose, maltodextrin and sucralose) or combinations thereof. In specific embodiments, the viscosity-enhancing excipient is a combination of MCC and CMC. In another embodiment, the viscosity-enhancing agent is a combination of carboxymethylated chitosan, or chitin, and alginate. The combination of chitin and alginate with the ophthalmic agents disclosed herein acts as a controlled release formulation, restricting the diffusion of the ophthalmic agents from the formulation. Moreover, the combination of carboxymethylated chitosan and alginate is optionally used to assist in increasing the permeability of the ophthalmic agents in the eye.

[00279] In some embodiments is an enhanced viscosity formulation, comprising from about 0.1 mM and about 100 mM of an ophthalmic agent, a pharmaceutically acceptable viscosity agent, and water for injection, the concentration of the viscosity agent in the water being sufficient to provide an enhanced viscosity formulation with a final viscosity from about 100 to about 100,000 cP. In certain embodiments, the viscosity of the gel is in the range from about 100 to about 50,000 cP, about 100 cP to about 1,000 cP, about 500 cP to about 1500 cP, about 1000 cP to about 3000 cP, about 2000 cP to about 8,000 cP, about 4,000 cP to about 50,000 cP, about 10,000 cP to about 500,000 cP, about 15,000 cP to about 1,000,000 cP. In other embodiments, when an even more viscous medium is desired, the biocompatible gel comprises at least about 35%, at least about 45%, at least about 55%, at least about 65%, at least about 70%, at least about 75%, or even at least about 80% or so by weight of the ophthalmic agent. In highly concentrated samples, the biocompatible enhanced viscosity formulation comprises at least about 25%, at

least about 35%, at least about 45%, at least about 55%, at least about 65%, at least about 75%, at least about 85%, at least about 90% or at least about 95% or more by weight of the ophthalmic agent.

[00280] In one embodiment, the pharmaceutically acceptable enhanced viscosity ophthalmically acceptable formulation comprises at least one ophthalmic agent and at least one gelling agent. Suitable gelling agents for use in preparation of the gel formulation include, but are not limited to, celluloses, cellulose derivatives, cellulose ethers (e.g., carboxymethylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxymethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, methylcellulose), guar gum, xanthan gum, locust bean gum, alginates (e.g., alginic acid), silicates, starch, tragacanth, carboxyvinyl polymers, carrageenan, paraffin, petrolatum and any combinations or mixtures thereof. In some other embodiments, hydroxypropylmethylcellulose (Methocel®) is utilized as the gelling agent. In certain embodiments, the viscosity enhancing agents described herein are also utilized as the gelling agent for the gel formulations presented herein.

[00281] In some embodiments, the ophthalmic gel composition described herein is an in situ gel formulation. In some instances, the in situ gel formation is based on increased pre-corneal residence time of the ophthalmic composition which improves ocular bioavailability, corneal mucoadhesion, lysosomal interaction and ionic gelation, improved corneal absorption, thermal gelation, or a combination thereof. In some instances, the in situ gel formulation is activated by pH, temperature, ion, UV, or solvent exchange.

[00282] In some instances, the ophthalmic gel composition comprises a muscarinic antagonist and one or more gelling agents. In some instances, the gelling agent includes, but is not limited to, poloxamer (e.g. Poloxamer 407), tetronics, ethyl (hydroxyethyl) cellulose, cellulose acetate phthalate (CAP), carbopol (e.g. Carbopol 1342P NF, Carbopol 980 NF), alginates (e.g. low acetyl gellan gum (Gelrite®)), gellan, hyaluronic acid, pluronics (e.g. Pluronic F-127), chitosan, polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), dextran, hydroxy propyl methyl cellulose (HPMC), hydroxyethylcellulose (HEC), methylcellulose (MC), thiolated xyloglucan, polymethacrylic acid (PMMA), polyethylene glycol (PEG), pseudolatexes, xyloglucans, or combinations thereof.

[00283] In some instances, the in situ gel formation further comprises a permeation enhancer. In some instances, the permeation enhancer includes surfactants (e.g. non-ionic surfactants), benzalkonium chloride, EDTA, surface-active heteroglycosides, calcium chelators, hydroxyl propyl beta cyclodextrin (HP beta CD), bile salts, and the like.

[00284] In some embodiments, other gel formulations are useful depending upon the particular ophthalmic agent, other pharmaceutical agent or excipients/additives used, and as such are considered to fall within the scope of the present disclosure. For example, other commercially-available glycerin-based gels, glycerin-derived compounds, conjugated, or crosslinked gels, matrices, hydrogels, and polymers, as well as gelatins and their derivatives, alginates, and alginate-based gels, and even various native and synthetic hydrogel and hydrogel-derived compounds are all expected to be useful in the ophthalmic agent formulations described herein. In some embodiments, ophthalmically acceptable gels include, but are not

limited to, alginate hydrogels SAF®-Gel (ConvaTec, Princeton, N.J.), Duoderm® Hydroactive Gel (ConvaTec), Nu-gel® (Johnson & Johnson Medical, Arlington, Tex.); Carrasyn® (V) Acemannan Hydrogel (Carrington Laboratories, Inc., Irving, Tex.); glycerin gels Elta® Hydrogel (Swiss-American Products, Inc., Dallas, Tex.) and K-Y® Sterile (Johnson & Johnson). In further embodiments, biodegradable biocompatible gels also represent compounds present in ophthalmically acceptable formulations disclosed and described herein.

[00285] In some embodiments, the viscosity-enhancing agent is a cellulose-based polymer selected from cellulose gum, alkylcellulose, hydroxyl-alkyl cellulose, hydroxyl-alkyl alkylcellulose, carboxy-alkyl cellulose, or combinations thereof. In some embodiments, the viscosity-enhancing agent is hydroxyl-alkyl alkylcellulose. In some embodiment, the viscosity-enhancing agent is hydroxypropyl methylcellulose.

[00286] In certain embodiments, the enhanced viscosity formulation is characterized by a phase transition between room temperature and body temperature (including an individual with a serious fever, e.g., up to about 42 °C). In some embodiments, the phase transition occurs at 1 °C below body temperature, at 2 °C below body temperature, at 3 °C below body temperature, at 4 °C below body temperature, at 6 °C below body temperature, at 8 °C below body temperature, or at 10 °C below body temperature. In some embodiments, the phase transition occurs at about 15 °C below body temperature, at about 20 °C below body temperature or at about 25 °C below body temperature. In specific embodiments, the gelation temperature (T_{gel}) of a formulation described herein is about 20 °C, about 25 °C, or about 30 °C. In certain embodiments, the gelation temperature (T_{gel}) of a formulation described herein is about 35 °C, or about 40 °C. Included within the definition of body temperature is the body temperature of a healthy individual, or an unhealthy individual, including an individual with a fever (up to ~42 °C). In some embodiments, the pharmaceutical compositions described herein are liquids at about room temperature and are administered at or about room temperature.

[00287] Copolymers polyoxypropylene and polyoxyethylene (e.g. polyoxyethylene-polyoxypropylene triblock copolymers) form thermosetting gels when incorporated into aqueous solutions. These polymers have the ability to change from the liquid state to the gel state at temperatures close to body temperature, therefore allowing useful formulations that are applied to the targeted ocular site. The liquid state-to-gel state phase transition is dependent on the polymer concentration and the ingredients in the solution.

[00288] In some embodiments, the amount of thermosetting polymer in any formulation described herein is about 10%, about 15%, about 20%, about 25%, about 30%, about 35% or about 40% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer in any formulation described herein is about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24% or about 25% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 7.5% of the

total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 10% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 11% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 12% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 13% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 14% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 15% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 16% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 17% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 18% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 19% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 20% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 21% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 23% of the total weight of the formulation. In some embodiments, the amount of thermosetting polymer (e.g., Poloxamer 407) in any formulation described herein is about 25% of the total weight of the formulation. In some embodiments, the amount of thickening agent (e.g., a gelling agent) in any formulation described herein is about 1%, about 5%, about 10%, or about 15% of the total weight of the formulation. In some embodiments, the amount of thickening agent (e.g., a gelling agent) in any formulation described herein is about 0.5%, about 1%, about 1.5%, about 2%, about 2.5%, about 3%, about 3.5%, about 4%, about 4.5%, or about 5% of the total weight of the formulation.

[00289] In an alternative embodiment, the thermogel is a PEG-PLGA-PEG triblock copolymer (Jeong et al, Nature (1997), 388:860-2; Jeong et al, J. Control. Release (2000), 63:155-63; Jeong et al, Adv. Drug Delivery Rev. (2002), 54:37-51). The polymer exhibits sol-gel behavior over a concentration of about 5% w/w to about 40% w/w. Depending on the properties desired, the lactide/glycolide molar ratio in the PLGA copolymer ranges from about 1:1 to about 20:1. The resulting copolymers are soluble in water and form a free-flowing liquid at room temperature, but form a hydrogel at body temperature. A commercially available PEG-PLGA-PEG triblock copolymer is RESOMER RGP t50106 manufactured

by Boehringer Ingelheim. This material is composed of a PLGA copolymer of 50:50 poly(DL-lactide-co-glycolide) and is 10% w/w of PEG and has a molecular weight of about 6000.

[00290] Additional biodegradable thermoplastic polyesters include AtriGel® (provided by Atrix Laboratories, Inc.) and/or those disclosed, e.g., in U.S. Patent Nos. 5,324,519; 4,938,763; 5,702,716; 5,744,153; and 5,990,194; wherein the suitable biodegradable thermoplastic polyester is disclosed as a thermoplastic polymer. Examples of suitable biodegradable thermoplastic polyesters include polylactides, polyglycolides, polycaprolactones, copolymers thereof, terpolymers thereof, and any combinations thereof. In some such embodiments, the suitable biodegradable thermoplastic polyester is a polylactide, a polyglycolide, a copolymer thereof, a terpolymer thereof, or a combination thereof. In one embodiment, the biodegradable thermoplastic polyester is 50/50 poly(DL-lactide-co-glycolide) having a carboxy terminal group; is present in about 30 wt. % to about 40 wt. % of the composition; and has an average molecular weight of about 23,000 to about 45,000. Alternatively, in another embodiment, the biodegradable thermoplastic polyester is 75/25 poly (DL-lactide-co-glycolide) without a carboxy terminal group; is present in about 40 wt. % to about 50 wt. % of the composition; and has an average molecular weight of about 15,000 to about 24,000. In further or alternative embodiments, the terminal groups of the poly(DL-lactide-co-glycolide) are either hydroxyl, carboxyl, or ester depending upon the method of polymerization. Polycondensation of lactic or glycolic acid provides a polymer with terminal hydroxyl and carboxyl groups. Ring-opening polymerization of the cyclic lactide or glycolide monomers with water, lactic acid, or glycolic acid provides polymers with the same terminal groups. However, ring-opening of the cyclic monomers with a monofunctional alcohol such as methanol, ethanol, or 1-dodecanol provides a polymer with one hydroxyl group and one ester terminal groups. Ring-opening polymerization of the cyclic monomers with a diol such as 1,6-hexanediol or polyethylene glycol provides a polymer with only hydroxyl terminal groups.

[00291] Since the polymer systems of thermosetting gels dissolve more completely at reduced temperatures, methods of solubilization include adding the required amount of polymer to the amount of water to be used at reduced temperatures. Generally after wetting the polymer by shaking, the mixture is capped and placed in a cold chamber or in a thermostatic container at about 0-10 °C in order to dissolve the polymer. The mixture is stirred or shaken to bring about a more rapid dissolution of the thermosetting gel polymer. The ophthalmic agent and various additives such as buffers, salts, and preservatives are subsequently added and dissolved. In some instances the pharmaceutically agent is suspended if it is insoluble in water. The pD is modulated by the addition of appropriate buffering agents.

[00292] Ophthalmic Ointment Muscarinic Antagonist Composition

[00293] An ointment is a homogeneous, viscous, semi-solid preparation, most commonly a greasy, thick oil (e.g. oil 80% - water 20%) with a high viscosity, intended for external application to the skin or mucous membranes. Ointments have a water number that defines the maximum amount of water that it contains. They are used as emollients or for the application of active ingredients to the skin for protective, therapeutic, or prophylactic purposes and where a degree of occlusion is desired. Ointments

are used topically on a variety of body surfaces. These include the skin and the mucous membranes of the eye (an eye ointment), vulva, anus, and nose

[00294] The vehicle of an ointment is known as the ointment base. The choice of a base depends upon the clinical indication for the ointment. The different types of ointment bases are: hydrocarbon bases, e.g. hard paraffin, soft paraffin, microcrystalline wax and ceresine; absorption bases, e.g. wool fat, beeswax; water soluble bases, e.g. macrogols 200, 300, 400; emulsifying bases, e.g. emulsifying wax, cetrimide; vegetable oils, e.g. olive oil, coconut oil, sesame oil, almond oil and peanut oil.

[00295] Ointments are formulated using hydrophobic, hydrophilic, or water-emulsifying bases to provide preparations that are immiscible, miscible, or emulsifiable with skin secretions. In some embodiments, they are also derived from hydrocarbon (fatty), absorption, water-removable, or water-soluble bases. The active agents are dispersed in the base, and later they get divided after the drug penetration into the target sites (e.g. membranes, skins, etc.).

[00296] The present disclosure recognizes that it is sometimes difficult to incorporate into the ointment a drug of low concentration with sufficient dose-to-dose uniformity for effectively treating a disorder or disease. In some embodiments, poly(ethylene-glycols), polyethoxylated castor oils (Cremophor®EL), alcohols having 12 to 20 carbon atoms or a mixture of two or more of said components are effective excipients for dispersing and/or dissolving effective amounts of ophthalmic drugs, in particular of ascomycins and staurosporine derivatives, in an ointment base, in particular in an ointment base substantially comprising oleaginous and hydrocarbon components, and that the resulting ointments are excellently tolerated by the skin and by ocular tissue.

[00297] The present disclosure further recognizes that ophthalmic drugs, such as a muscarinic antagonist (e.g. atropine or its pharmaceutically acceptable salts), incorporated in the ointment compositions describes herein target the choroid and/or retina in a patient when the compositions are topically administered to the ocular surface, in particular to the sclera of said patient. In some embodiments, an ophthalmic ointment composition includes an ophthalmic drug, an ointment base and an agent for dispersing and/or dissolving said drug in the ointment base, selected from a poly(ethylene-glycol), a polyethoxylated castor oil, an alcohol having 12 to 20 carbon atoms and a mixture of two or more of said components.

[00298] In some embodiments, the ointment bases include ophthalmically acceptable oil and fat bases, such as natural wax e.g. white and yellow bees wax, carnauba wax, wool wax (wool fat), purified lanolin, anhydrous lanolin; petroleum wax e.g. hard paraffin, microcrystalline wax; hydrocarbons e.g. liquid paraffin, white and yellow soft paraffin, white petrolatum, yellow petrolatum; or combinations thereof.

[00299] The above mentioned oil and fat bases are described in more detail, for instance, in the British Pharmacopoeia, Edition 2001, or the European Pharmacopoeia, 3rd Edition.

[00300] In some embodiments, the ointment base is present in amounts of about 50 to about 95, preferably of 70 to 90% by weight based on the total weight of the composition.

[00301] A preferred ointment base comprises a combination of one or more of one or more natural waxes like those indicated above, preferably wool wax (wool fat), and one or more hydrocarbons like those indicated above, preferably a soft paraffin or a petrolatum, more preferably in combination with liquid paraffin.

[00302] A special embodiment of the aforementioned ointment base comprises e.g. 5 to 17 parts by weight of wool fat, and 50 to 65 parts by weight of white petrolatum as well as 20 to 30 parts by weight of liquid paraffin.

[00303] In some embodiments, the agent for dispersing and/or dissolving the ophthalmic drug in the ointment base is selected from a poly(ethylene-glycol), a polyethoxylated castor oil, an alcohol having 12 to 20 carbon atoms and a mixture of two or more of said components. The agent is preferably used in amounts of 1 to 20 percent, more preferably 1 to 10 percent by weight of the entire semisolid ophthalmic composition.

[00304] Alcohols having 12 to 20 carbon atoms include particularly stearyl alcohol (C₁₈H₃₇OH), cetyl alcohol (C₁₆H₃₃OH) and mixtures thereof. Preferred are so-called cetostearyl alcohols, mixtures of solid alcohols substantially consisting of stearyl and cetyl alcohol and preferably comprising not less than 40 percent by weight of stearyl alcohol and a sum of stearyl alcohol and cetyl alcohol amounting to at least 90 percent by weight, and compositions comprising not less than 80 percent by weight of cetylstearyl alcohol and an emulsifier, in particular sodium cetostearyl sulfate and/or sodium lauryl sulfate, preferably in amounts not less than 7 percent by weight of emulsifier.

[00305] Polyethoxylated castor oils are reaction products of natural or hydrogenated castor oils and ethylene glycol. In some instances, such products are obtained in known manner, e.g. by reaction of a natural or hydrogenated castor oil or fractions thereof with ethylene oxide, e.g. in a molar ratio of from about 1:30 to about 1:60, with optional removal of free polyethylene glycol components from the product, e.g. in accordance with the methods disclosed in German Auslegeschriften 1,182,388 and 1,518,819. Especially suitable and preferred is a product commercially available under the trade name Cremophor®EL having a molecular weight (by steam osmometry)=ca. 1630, a saponification no.=ca. 65-70, an acid no.=ca. 2, an iodine no.=ca. 28-32 and an nD₂₅=ca. 1.471. Also suitable for use in this category is, for instance, Nikkol®HCO-60, a reaction product of hydrogenated castor oil and ethylene oxide exhibiting the following characteristics: acid no.=ca. 0.3; saponification no.=ca. 47.4; hydroxy value=ca. 42.5. pH (5%)=ca. 4.6; Color APHA=ca. 40; m.p.=ca. 36.0° C.; Freezing point=ca. 32.4° C.; H₂O content (% , KF)=ca. 0.03.

[00306] Poly(ethylene-glycols) are used in some embodiments as the agent for dispersing and/or dissolving the ophthalmic drug in the ointment base according to the present disclosure. Suitable poly(ethylene-glycol)s are typically mixtures of polymeric compounds of the general formula H—(OCH₂—CH₂)_nOH, wherein the index n typically range from 4 to 230 and the mean molecular weight from about 200 to about 10000. Preferably n is a number from about 6 to about 22 and the mean molecular weight between about 300 and about 1000, more preferably n ranges from about 6 to about 13

and the mean molecular weight from about 300 to about 600, most preferably n has a value of about 8.5 to about 9 and the relative molecular weight is about 400. Suitable poly(ethylene-glycols) are readily available commercially, for example poly(ethylene-glycols) having a mean molecular weight of about 200, 300, 400, 600, 1000, 1500, 2000, 3000, 4000, 6000, 8000 and 10000.

[00307] The poly(ethylene-glycols), in particular the preferred types described in the foregoing paragraph, are preferably used in amounts of 1 to 10, more preferably 1 to 5 percent by weight of the entire semisolid ophthalmic composition.

[00308] An especially preferred embodiment of the compositions according to the instant disclosure comprises an agent for dispersing and/or dissolving of the drug in the ointment base which is selected from a poly(ethylene-glycol), a polyethoxylated castor oil and preferably a mixture of said components.

[00309] **Gel/Ointment Viscosity**

[00310] In some embodiments, the composition has a Brookfield RVDV viscosity of from about 10,000 to about 300,000 cps at about 20°C and sheer rate of $1s^{-1}$. In some embodiments, the composition has a Brookfield RVDV viscosity of from about 15,000 to about 200,000 cps at about 20°C and sheer rate of $1s^{-1}$. In some embodiments, the composition has a Brookfield RVDV viscosity of from about 50,000 to about 150,000 cps at about 20°C and sheer rate of $1s^{-1}$. In some embodiments, the composition has a Brookfield RVDV viscosity of from about 70,000 to about 130,000 cps at about 20°C and sheer rate of $1s^{-1}$. In some embodiments, the composition has a Brookfield RVDV viscosity of from about 90,000 to about 110,000 cps at about 20°C and sheer rate of $1s^{-1}$.

[00311] In some embodiments, the ophthalmic gel formulation contains a viscosity enhancing agent sufficient to provide a viscosity of between about 500 and 1,000,000 centipoise, between about 750 and 1,000,000 centipoise; between about 1000 and 1,000,000 centipoise; between about 1000 and 400,000 centipoise; between about 2000 and 100,000 centipoise; between about 3000 and 50,000 centipoise; between about 4000 and 25,000 centipoise; between about 5000 and 20,000 centipoise; or between about 6000 and 15,000 centipoise. In some embodiments, the ophthalmic gel formulation contains a viscosity enhancing agent sufficient to provide a viscosity of between about 50,000 and 1,000,000 centipoise.

[00312] In some embodiments, the compositions described herein are low viscosity compositions at body temperature. In some embodiments, low viscosity compositions contain from about 1% to about 10% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, low viscosity compositions contain from about 2% to about 10% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, low viscosity compositions contain from about 5% to about 10% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, low viscosity compositions are substantially free of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In

some embodiments, a low viscosity ophthalmic agent composition described herein provides an apparent viscosity of from about 100 cP to about 10,000 cP. In some embodiments, a low viscosity ophthalmic agent composition described herein provides an apparent viscosity of from about 500 cP to about 10,000 cP. In some embodiments, a low viscosity ophthalmic agent composition described herein provides an apparent viscosity of from about 1000 cP to about 10,000 cP.

[00313] In some embodiments, the compositions described herein are viscous compositions at body temperature. In some embodiments, viscous compositions contain from about 10% to about 25% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, the viscous compositions contain from about 14% to about 22% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, the viscous compositions contain from about 15% to about 21% of a viscosity enhancing agent (e.g., gelling components such as polyoxyethylene-polyoxypropylene copolymers). In some embodiments, a viscous ophthalmic composition described herein provides an apparent viscosity of from about 100,000 cP to about 1,000,000 cP. In some embodiments, a viscous ophthalmic composition described herein provides an apparent viscosity of from about 150,000 cP to about 500,000 cP. In some embodiments, a viscous ophthalmic composition described herein provides an apparent viscosity of from about 250,000 cP to about 500,000 cP. In some of such embodiments, a viscous ophthalmic composition is a liquid at room temperature and gels at about between room temperature and body temperature (including an individual with a serious fever, e.g., up to about 42 °C). In some embodiments, a viscous ophthalmic composition is administered as monotherapy for treatment of an ophthalmic disease or condition described herein.

[00314] In some embodiments, the viscosity of the gel formulations presented herein is measured by any means described. For example, in some embodiments, an LVDV-II+CP Cone Plate Viscometer and a Cone Spindle CPE-40 is used to calculate the viscosity of the gel formulation described herein. In other embodiments, a Brookfield (spindle and cup) viscometer is used to calculate the viscosity of the gel formulation described herein. In some embodiments, the viscosity ranges referred to herein are measured at room temperature. In other embodiments, the viscosity ranges referred to herein are measured at body temperature (e.g., at the average body temperature of a healthy human).

[00315] Gel/Ointment Dose-To-Dose Uniformity

[00316] Typical ophthalmic gels are packaged in eye drop bottles and administered as drops. For example, a single administration (i.e. a single dose) of an ophthalmic gel includes a single drop, two drops, three drops or more into the eyes of the patient. Furthermore, typical ophthalmic ointments are packaged in tubes or other squeezable containers with a dispensing nozzle through which strips of the ointment are delivered. For example, a single administration (i.e. a single dose) of an ophthalmic ointment includes a single strip, or multiple strips into the eyes of the patient. In some embodiments, one dose of the ophthalmic gel described herein is one drop of the gel composition from the eye drop bottle.

In some embodiments, one dose of the ophthalmic ointment is one strip of the ointment composition dispensed through the nozzle of a dispersing tube.

[00317] In some cases, described herein include ophthalmic gel compositions which provide a dose-to-dose uniform concentrations. In some instances, the dose-to-dose uniform concentration does not present significant variations of drug content from one dose to another. In some instances, the dose-to-dose uniform concentration does provide consistent drug content from one dose to another.

[00318] In some cases, described herein include ophthalmic ointment compositions which provide a dose-to-dose uniform concentrations. In some instances, the dose-to-dose uniform concentration does not present significant variations of drug content from one dose to another. In some instances, the dose-to-dose uniform concentration does provide consistent drug content from one dose to another.

[00319] In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 50%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 40%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 30%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 20%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 10%. In some embodiments, the composition has a dose-to-dose ophthalmic agent concentration variation of less than 5%.

[00320] In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 10 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 8 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 5 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 3 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 2 consecutive doses.

[00321] A nonsettling formulation should not require shaking to disperse drug uniformly. A “no-shake” formulation is potentially advantageous over formulations that require shaking for the simple reason that patients’ shaking behavior is a major source of variability in the amount of drug dosed. It has been reported that patients often times do not or forget to shake their ophthalmic compositions that requires shaking before administering a dose, despite the instructions to shake that were clearly marked on the label. On the other hand, even for those patients who do shake the product, it is normally not possible to determine whether the shaking is adequate in intensity and/or duration to render the product uniform. In some embodiments, the ophthalmic gel compositions and ophthalmic ointment compositions described herein are “no-shake” formulations that maintained the dose-to-dose uniformity described herein.

[00322] To evaluate the dose-to-dose uniformity, drop bottles or tubes containing the ophthalmic aqueous compositions, the ophthalmic gel compositions, or ophthalmic ointment compositions are stored

upright for a minimum of 12 hours prior to the start of the test. To simulate the recommended dosing of these products, predetermined number of drops or strips are dispensed from each commercial bottles or tubes at predetermined time intervals for an extended period of time or until no product was left in the bottle or tube. All drops and strips are dispensed into tared glass vials, capped, and stored at room temperature until analysis. Concentrations of a muscarinic antagonist such as atropine in the expressed drops were determined using a reverse-phase HPLC method.

[00323] Methods of Treatment

[00324] Disclosed herein are methods of arresting myopia development by administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition as described above. Also disclosed herein are methods of preventing myopia development by administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition as described above.

[00325] In some embodiments, the ophthalmic aqueous formulations described herein are packaged in eye drop bottles and administered as drops. For example, a single administration (i.e. a single dose) of an ophthalmic aqueous formulation includes a single drop, two drops, three drops or more into the eyes of the patient. In some embodiments, the ophthalmic gel formulations described herein are packaged in eye drop bottles and administered as drops. For example, a single administration (i.e. a single dose) of an ophthalmic gel includes a single drop, two drops, three drops or more into the eyes of the patient. In some embodiments, the ophthalmic ointment formulations described herein are packaged in tubes or other squeezable containers with a dispensing nozzle through which strips of the ointment are delivered. For example, a single administration (i.e. a single dose) of an ophthalmic ointment includes a single strip, or multiple strips into the eyes of the patient. In some embodiments, one dose of the ophthalmic aqueous formulation described herein is one drop of the aqueous composition from the eye drop bottle. In some embodiments, one dose of the ophthalmic gel described herein is one drop of the gel composition from the eye drop bottle. In some embodiments, one dose of the ophthalmic ointment is one strip of the ointment composition dispensed through the nozzle of a dispersing tube.

[00326] In some embodiments of the disclosed method, the ophthalmic composition is stored below room temperature prior to first use. In some embodiments of the disclosed method, the ophthalmic composition is stored at between about 2 °C to about 10 °C prior to first use. In some embodiments of the disclosed method, the ophthalmic composition is stored at about 2 °C, about 3 °C, about 4 °C, about 5 °C, about 6 °C, about 7 °C, about 8 °C, about 9 °C, or about 10 °C prior to first use. In some embodiments of the disclosed method, the ophthalmic composition is stored at between about 4 °C to about 8 °C prior to first use.

[00327] In some embodiments of the disclosed method, the ophthalmic composition is stored at room temperature after first use. In some embodiments of the disclosed method, the ophthalmic composition is stored at between about 16 °C to about 26 °C after to first use. In some embodiments of the disclosed method, the ophthalmic composition is stored at about 16 °C, about 17 °C, about 18 °C,

about 19 °C, about 20 °C, about 21 °C, about 22 °C, about 23 °C, about 24 °C, about 25 °C, or about 26 °C after to first use.

[00328] In some embodiments, the ophthalmic aqueous formulations are administered as follows: the lower lid of the eye to be administered was pulled down and a predetermined amount of the aqueous formulation (e.g. 1-3 drops) is applied to the inside of the eyelid. The ophthalmic tip of the dispensing mechanism does not touch any surface to avoid contamination and/or injury.

[00329] In some embodiments, the ophthalmic gel formulations are administered as follows: the lower lid of the eye to be administered was pulled down and a predetermined amount of gel (e.g. 1-3 drops) is applied to the inside of the eyelid. The ophthalmic tip of the dispensing mechanism does not touch any surface to avoid contamination and/or injury.

[00330] In some embodiments, the ophthalmic ointment formulations are administered as follows: the lower lid of the eye to be administered was pulled down and a small amount of ointment (approximately 0.25 inches) was applied to the inside of the eyelid. The ophthalmic tip of the dispensing mechanism does not touch any surface to avoid contamination and/or injury.

[00331] In some embodiments, the ophthalmic composition is administered at predetermined time intervals over an extended period of time. In some embodiments, the ophthalmic composition is administered once every day. In some embodiments, the ophthalmic composition is administered every other day. In some embodiments, the ophthalmic composition is administered over 1 week, 2 weeks, 1 month, 2 months, 3 months, 6 months, 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 11 years, or 12-15 years.

[00332] In some embodiments, the ophthalmic composition is administered in doses having a dose-to-dose ophthalmic agent concentration variation of less than 50%, less than 40%, less than 30%, less than 20%, less than 10%, or less than 5%.

[00333] The number of times a composition is administered to an individual in need thereof depends on the discretion of a medical professional, the disorder, the severity of the disorder, and the individual's response to the formulation. In some embodiments, a composition disclosed herein is administered once to an individual in need thereof with a mild acute condition. In some embodiments, a composition disclosed herein is administered more than once to an individual in need thereof with a moderate or severe acute condition. In the case wherein the patient's condition does not improve, upon the doctor's discretion the administration of an ophthalmic agent is administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

[00334] In the case wherein the patient's condition does not improve, upon the doctor's discretion the administration of the ophthalmic agent is administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

[00335] In the case wherein the patient's status does improve, upon the doctor's discretion the administration of the ophthalmic agent is given continuously; alternatively, the dose of drug being administered is temporarily reduced or temporarily suspended for a certain length of time (*i.e.*, a "drug holiday"). The length of the drug holiday varies between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, and 365 days. The dose reduction during a drug holiday is from 10%-100%, including by way of example only 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 100%.

[00336] Once improvement of the patient's ophthalmic conditions has occurred, a maintenance ophthalmic agent dose is administered if necessary. Subsequently, the dosage or the frequency of administration, or both, is optionally reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained. In certain embodiments, patients require intermittent treatment on a long-term basis upon any recurrence of symptoms.

[00337] The amount of ophthalmic agent that will correspond to such an amount will vary depending upon factors such as the particular compound, disease condition and its severity, according to the particular circumstances surrounding the case, including, *e.g.*, the specific ophthalmic agent being administered, the route of administration, the condition being treated, the target area being treated, and the subject or host being treated. The desired dose is presented in a single dose or as divided doses administered simultaneously (or over a short period of time) or at appropriate intervals.

[00338] In some embodiments, the initial administration is a particular ophthalmic agent and the subsequent administration a different formulation or ophthalmic agent.

[00339] **Kits/Articles of Manufacture**

[00340] The disclosure also provides kits for preventing or arresting myopia development. Such kits generally will comprise one or more of the ophthalmic compositions disclosed herein, and instructions for using the kit. The disclosure also contemplates the use of one or more of the ophthalmic compositions, in the manufacture of medicaments for treating, abating, reducing, or ameliorating the symptoms of a disease, dysfunction, or disorder in a mammal, such as a human that has, is suspected of having, or at risk for developing myopia.

[00341] In some embodiments, kits include a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) including one of the separate elements to be used in a method described herein. Suitable containers include, for example, bottles, vials, syringes, and test tubes. In other embodiments, the containers are formed from a variety of materials such as glass or plastic.

[00342] The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products are also presented herein. See, *e.g.*, U.S. Patent Nos. 5,323,907, 5,052,558 and 5,033,252. Examples of pharmaceutical packaging materials include, but

are not limited to, drop bottles, tubes, pumps, bags, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment. A wide array of ophthalmic compositions provided herein are contemplated as are a variety of treatments for any disease, disorder, or condition that benefits by controlled release administration of an ophthalmic agent to the eye.

[00343] In some embodiments, a kit includes one or more additional containers, each with one or more of various materials (such as rinses, wipes, and/or devices) desirable from a commercial and user standpoint for use of a formulation described herein. Such materials also include labels listing contents and/or instructions for use and package inserts with instructions for use. A set of instructions is optionally included. In a further embodiment, a label is on or associated with the container. In yet a further embodiment, a label is on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label is associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. In other embodiments a label is used to indicate that the contents are to be used for a specific therapeutic application. In yet another embodiment, a label also indicates directions for use of the contents, such as in the methods described herein.

[00344] In certain embodiments, the ophthalmic compositions are presented in a dispenser device which contains one or more unit dosage forms containing a compound provided herein. In a further embodiment, the dispenser device is accompanied by instructions for administration. In yet a further embodiment, the dispenser is also accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. In another embodiment, such notice, for example, is the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. In yet another embodiment, compositions containing a compound provided herein formulated in a compatible pharmaceutical carrier are also prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

EXAMPLES

Example 1 – Ophthalmic Formulations

[00345] Exemplary compositions for preparation of ophthalmic formulations are described in Tables 1-8.

Table 1 —Aqueous Solution Formulation (Atropine)

Ingredient	Quantity (mg/g)	Concentration (wt%)
Atropine	0.01-0.5	0.001-0.05 (wt%)
Buffer agent and/or pD adjusting agent (e.g.	-	q.s. for pD=4.2-7.9

, borates and/or DCl)		
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	-	q.s. to prevent the growth of or to destroy microorganism introduced into the solution
Tonicity and/or Osmolarity adjustor (e.g. NaCl, mannitol, etc)	-	q.s. to 0.5-2.0 wt%
Deuterated Water	-	q.s. to 100 wt%

Table 2 —Aqueous Solution Formulation (Atropine Sulfate)

Ingredient	Quantity (mg/g)	Concentration (wt%)
Atropine sulfate	0.01-0.5	0.001-0.05 (wt%)
Buffer agent and/or pD adjusting agent (e.g. , borates and/or DCl)	-	q.s. for pD=4.2-7.9
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	-	q.s. to prevent the growth of or to destroy microorganism introduced into the solution
Tonicity and/or Osmolarity adjustor (e.g. NaCl, mannitol, etc)	-	q.s. to 0.5-2.0 wt%
Deuterated Water	-	q.s. to 100 wt%

Table 3 —Aqueous Solution Formulation (Atropine Sulfate)

Ingredient	Quantity (mg/g)	Concentration (wt%)
Atropine sulfate	0.05-0.15	0.005-0.015 (wt%)
Buffer agent and/or pD adjusting agent (e.g. , borates and/or DCl)	-	q.s. for pD=4.2-7.9
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	-	q.s. to prevent the growth of or to destroy microorganism introduced into the solution
Tonicity and/or Osmolarity adjustor (e.g. NaCl, mannitol, etc)	-	q.s. to 0.5-2.0 wt%
Deuterated Water	-	q.s. to 100 wt%

Table 4 —Mucus Penetrating Particle Formulation (Atropine)

Ingredient	Quantity (mg/g)	Concentration (wt%)
Atropine	0.01-0.5	0.001-0.05 (wt%)
Buffer agent and/or pD adjusting agent (e.g. , borates and/or DCl)	-	q.s. for pD=4.2-7.9
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	-	q.s. to prevent the growth of or to destroy microorganism introduced into the solution
Mucus penetrating particles	-	q.s. to formulate atropine at 0.001-0.05 wt%
Deuterated Water	-	q.s. to 100 wt%

Table 5 —Mucus Penetrating Particle Formulation (Atropine Sulfate)

Ingredient	Quantity (mg/g)	Concentration (wt%)
Atropine sulfate	0.01-0.5	0.001-0.05 (wt%)
Buffer agent and/or pD adjusting agent (e.g. , borates and/or DCl)	-	q.s. for pD=4.2-7.9
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	-	q.s. to prevent the growth of or to destroy microorganism introduced into the solution
Mucus penetrating particles	-	q.s. to formulate atropine at 0.001-0.05 wt%
Deuterated Water	-	q.s. to 100 wt%

Table 6 —Cellulose Gel Formulation (Atropine Sulfate)

Ingredient	Quantity (mg/g)	Concentration (wt%)
Atropine Sulfate	0.01-0.5	0.001-0.05 (wt%)
Viscosity enhancing agent (e.g. hydroxypropyl methylcellulose)	10-50	1-5 (wt%)
Buffer agent and/or pD adjusting agent (e.g. , sodium acetate and/or DCl)	-	q.s. for pD=4.2-7.9

Stabilizer (e.g. EDTA, cyclodextrin, etc.)	-	q.s. for low degradation of atropine sulfate (e.g. less than 10%, 5% or 1% degradation)
Osmolarity modifier (e.g. NaCl)	-	q.s. 150-500 mOsm/L
Deuterated Water	-	q.s. to 100 wt%

Table 7 —Thermosetting Gel Formulation (Atropine Sulfate)

Ingredient	Quantity (mg/g)	Concentration (wt%)
Atropine sulfate	0.01-0.5	0.001-0.05 (wt%)
Viscosity enhancing agent (e.g. poloxamer 407)	100-250	10-25 (wt%)
Buffer agent and/or pD adjusting agent (e.g. , sodium acetate and/or DCl)	-	q.s. for pH=4.2-7.9
Stabilizer (e.g. EDTA, cyclodextrin, etc.)	-	q.s. for low degradation of atropine sulfate (e.g. less than 10%, 5% or 1% degradation)
Osmolarity modifier (e.g. NaCl)	-	q.s. 150-500 mOsm/L
Deuterated Water	-	q.s. to 100 wt%

Table 8 — Ointment Formulation (Atropine Sulfate)

Ingredient	Quantity (g) for 1000 mL solution	Concentration in 1000 mL aqueous solution
Atropine sulfate	0.01-0.5	0.001-0.05 (wt%)
Dispersing agent (e.g. polyethyleneglycol, and/or polyethoxylated castor oil and/or C12-C20 alcohol	10-200	1-20 (wt%)
Buffering agent pD adjusting agent (e.g. DCl)	-	q.s. for pD=4.2-7.9
Stabilizer (e.g. EDTA, cyclodextrin, etc.)	-	q.s. for low degradation of atropine sulfate (e.g. less than 10%, 5% or 1% degradation)
Osmolarity modifier (e.g. NaCl)	-	q.s. 150-500 mOsm/L

Ointment base (e.g. wool wax and/or petrolatum and/or liquid paraffin)		q.s. to 100 wt%

Example 2 - Preparation of an Aqueous Solution Formulation Containing 0.01% Atropine in D₂O

[00346] Stock 1% Solution

[00347] In a 100mL solution, 1 gram of atropine, and 0.77 g of NaCl (and other ingredients/components preferably in their dry state) are added along with a quantity sufficient to equal 100mL sterile deuterated water for injection. The solution is mixed in an appropriately sized beaker with a stir bar on a hot plate until all of the solid powders have dissolved and the solution has become clear with no visible particles. Next, the stir bar is removed, and the solution is poured into a filter bottle and vacuum filtered through a 0.22 micron pothyethersulfone membrane filter into a sterile bottle. The filter top is removed from the sterile stock bottle and the stock bottle is capped for storage with a sterile bottle cap.

[00348] Diluted 0.01% Solution

[00349] 0.3mL of the 1% solution was combined with a quantity sufficient to achieve 30mL total of sterile 0.9% Sodium Chloride For Injection USP. The solution was thoroughly mixed. The pH of the solution was recorded. A 0.22 micron filter was placed on the tip of the syringe and the solution was aliquotted into separate sterile containers.

Example 3 - Preparation of an Aqueous Solution Formulation Containing 0.01% Atropine Sulfate

[00350] Stock 1% Solution

[00351] In a 100mL solution, 1 gram of atropine sulfate, and 0.77 g of NaCl (and other ingredients/components preferably in their dry state) were added along with a quantity sufficient to equal 100mL sterile water for injection. The solution was mixed in an appropriately sized beaker with a stir bar on a hot plate until all of the solid powders had dissolved and the solution became clear with no visible particles. Next, the stir bar was removed, and the solution was poured into a filter bottle and vacuum filtered through a 0.22 micron pothyethersulfone membrane filter into a sterile bottle. The filter top was removed from the sterile stock bottle and the stock bottle was capped for storage with a sterile bottle cap.

[00352] Diluted 0.01% Solution

[00353] 0.3mL of the 1% solution was combined with a quantity sufficient to achieve 30mL total of sterile 0.9% Sodium Chloride For Injection USP. The solution was thoroughly mixed. The pH of the solution was recorded. A 0.22 micron filter was placed on the tip of the syringe and the solution was aliquotted into separate sterile containers.

Example 4 – Stability Analysis

[00354] Five 0.01% atropine sulfate solutions were prepared from the 1% atropine sulfate stock solution (preparation as described in Example 2). The pH of the five solutions was 5.87, 5.97, 5.90, 6.24,

and 6.16 for solutions 1-5, respectively. Each solution was thoroughly mixed. A 0.22 micron filter was placed on the tip of the syringe and the solution was aliquotted into separate sterile containers according to Table 9.

Table 9. Container Filling Outline

Type of Container	Volume of 0.01 % Atropine Sulfate Drug Product in Container	Total Containers Filled
Sterile Eyedroppers	5-mL	12
Sterile Glass Vials	5-mL	12

[00355] The samples were then stored at different conditions for stability analysis. The samples were analyzed at different time points up to 2 months. The storage conditions include: 40°C with 75% relative humidity (RH) (samples were transferred from 2-8°C condition after 3 days), 25°C with 60% RH, and 60°C. The time points were 1 week, 2 weeks, 1 month, and 2 months. At each of the time point, one plastic eyedropper (LDPE plastic) and one glass vial from each of the stored condition were removed and allowed to equilibrate to ambient conditions. Once equilibrated, both the plastic eyedropper and the glass vials were inverted 3 times. The solution in the eyedroppers was transferred to an HPLC vial in a drop wise fashion through the dropper. The solution in the glass vial was aliquotted into an HPLC vial using a glass Pasteur pipette. The samples were then tested for purity and potency using the UPLC method listed in Table 10.

Table 10. UPLC Method Parameters

Parameter	Condition
Column	EMD, Hiber HR PurospherSTAR C-18, 100 x 2.1 mm, 2 μ m
Mobile Phase/Diluent	87:13, 50 mM Potassium Phosphate: Acetonitrile, pH 3.5
Flow	Isocratic
Flow Rate	0.5 mL/min
Detection Wavelength	210 nm
Column Temperature	30 $\pm$ 3 °C
Autosampler Temperature	5 $\pm$ 3 °C
Run Time	6.0 minutes
Injection Volume	10 μ L*
Needle Wash Solution	90/10 Water: Acetonitrile

* Modified from original method to maintain sensitivity at 100 μ g/mL nominal.

[00356] Table 11 lists the stability data for the 0.01% atropine sulfate solutions.

Table 11. Stability Data for 0.01% Atropine Sulfate Solutions

Analyst	Container Type	Storage Condition	t=0			t=1 week		t=2 week ¹		t=1 month ²			t=2 month ³		
			Purity	Potency	pH	Purity	Potency	Purity	Potency	Purity	Potency	pH	Purity	Potency	pH
1	Eyedropper, LDPE (Plastic)	25 °C/60% RH	99.5	99.8	5.9	ND	ND	99.1	99.9	ND	ND	ND	95.4	97.4	6.3
		40 °C/75% RH				ND	ND	96.2	97.3	95.1	95.6	5.2	ND	ND	ND
		60 °C				80.8	83.3	86.2	88.6	88.3	91.5	4.2	ND	ND	ND
	Glass Vial	25 °C/60% RH	99.8	100.4	ND	ND	ND	92.2	93.1	80.7	80.5	7.8	73.0	74.5	7.3
		40 °C/75% RH				ND	ND	73.6	74.1	50.1	50.2	7.4	ND	ND	ND
		60 °C				43.1	43.9	28.3	28.4	ND	ND	ND	ND	ND	ND
2	Eyedropper, LDPE (Plastic)	25 °C/60% RH	99.7	99.9	6.0	ND	ND	99.1	99.6	ND	ND	ND	97.0	99.1	6.1
		40 °C/75% RH				ND	ND	96.6	97.2	95.5	95.8	5.6	ND	ND	ND
		60 °C				89.4	92.2	92.2	94.0	90.6	94.4	4.1	ND	ND	ND
	Glass Vial	25 °C/60% RH	99.8	100.2	ND	ND	ND	92.6	92.9	82.5	82.2	7.6	80.2	81.6	7.3
		40 °C/75% RH				ND	ND	74.7	75.1	59.1	59.0	7.2	ND	ND	ND
		60 °C				54.2	55.2	37.3	37.4	ND	ND	ND	ND	ND	ND
3	Eyedropper, LDPE (Plastic)	25 °C/60% RH	99.3	96.3	5.9	ND	ND	98.7	96.1	ND	ND	ND	95.8	94.8	6.3
		40 °C/75% RH				ND	ND	96.7	93.1	94.8	91.8	5.5	ND	ND	ND
		60 °C				88.8	89.0	88.0	86.8	88.6	87.7	4.1	ND	ND	ND
	Glass Vial	25 °C/60% RH	99.4	98.4	ND	ND	ND	94.1	91.2	85.0	81.9	7.5	79.3	78.3	7.3
		40 °C/75% RH				ND	ND	72.2	74.6	61.3	63.0	7.2	ND	ND	ND
		60 °C				48.6	51.1	34.1	34.9	ND	ND	ND	ND	ND	ND
4	Eyedropper, LDPE (Plastic)	25 °C/60% RH	99.8	99.6	6.2	ND	ND	99.1	98.8	ND	ND	ND	96.4	97.6	6.3
		40 °C/75% RH				ND	ND	96.3	97.0	94.5	94.2	5.6	ND	ND	ND
		60 °C				90.5	93.0	89.3	90.6	84.2	85.8	4.2	ND	ND	ND
	Glass Vial	25 °C/60% RH	99.8	98.8	ND	ND	ND	90.7	90.0	76.9	75.1	7.6	72.5	71.6	7.4
		40 °C/75% RH				ND	ND	71.0	68.7	57.0	56.7	7.2	ND	ND	ND
		60 °C				52.4	52.1	29.7	28.6	ND	ND	ND	ND	ND	ND
5	Eyedropper, LDPE (Plastic)	25 °C/60% RH	99.6	100.5	6.2	ND	ND	99.3	100.4	ND	ND	ND	97.8	100.5	6.2
		40 °C/75% RH				ND	ND	95.9	96.7	96.8	97.6	5.5	ND	ND	ND
		60 °C				91.2	94.6	91.4	93.6	90.3	92.8	4.2	ND	ND	ND
	Glass Vial	25 °C/60% RH	99.8	100.7	ND	ND	ND	90.5	91.3	79.3	79.7	7.8	72.8	74.6	7.3
		40 °C/75% RH				ND	ND	71.3	71.9	56.0	56.4	7.3	ND	ND	ND
		60 °C				46.3	47.4	29.5	29.6	ND	ND	ND	ND	ND	ND

¹ The 25 °C and the 60 °C samples were pulled at 15 days, the 40 °C samples were pulled at 11 days.

² The 25 °C and the 60 °C samples were pulled at 28 days, the 40 °C samples were pulled at 24 days.

³ The 25 °C and the 60 °C samples were pulled at 46 days.

[00357] A change in the pH of the 0.01% Atropine Sulfate solutions was observed over the course of the stability study. The plastic (LDPE) eyedroppers maintained pH around 6.2 when stored at 25 °C for 2 months. However at the same time point, the pH of the 0.01% atropine has increased to 7.2 when stored in glass vials. Additionally, when stored at elevated temperatures (e.g. 40°C and 60°C), the pH in the plastic (LDPE) eyedroppers dropped to approximately 4-5, while the pH maintained around 7.2 when stored in the glass vials.

[00358] There was also a significant difference in the rate of degradation for Atropine Sulfate (0.01%) when stored in plastic (LDPE) eyedroppers versus Type I glass vials. However, in both containers there was an increase of an early eluting related substance at relative retention time (RRT) =0.87-0.89. In some cases, this early eluting related substance is referred to as primary degradant. In some instances, the primary degradant is referred to as RRT 0.87-0.89. This related substance is likely to be the first parameter to fail specification regardless of the container. The amount of this related substance was tracked at each time point and is listed in Table 12.

Table 12. Area (%) of the Main Degradation Species for 0.01% Atropine Sulfate (RRT 0.87-0.89)

Analyst	Temperature °C	t=0	t=1 week	t=2 week	t=1 month	t=2 months
1	25	0.08	NA	0.92	NA	3.98
	40	NA	NA	3.74	4.78	NA
	60	NA	17.78	13.49	11.51	NA
2	25	0.07	NA	0.88	NA	2.46
	40	NA	NA	3.26	4.37	NA
	60	NA	9.38	7.67	9.13	NA
3	25	0.07	NA	1.05	NA	2.88
	40	NA	NA	2.98	4.85	NA
	60	NA	9.59	11.57	10.55	NA
4	25	0.08	NA	0.92	NA	3.09
	40	NA	NA	3.43	5.32	NA
	60	NA	8.30	10.46	15.49	NA
5	25	0.08	NA	0.64	NA	1.66
	40	NA	NA	3.96	3.07	NA
	60	NA	7.61	8.35	9.7	NA
Average 25 °C		0.08	NA	0.88	NA	2.81
Average 40 °C		NA	NA	3.47	4.48	NA
Average 60 °C		NA	10.53	10.31	11.28	NA

[00359] Arrhenius based shelf life predictions were calculated using the related substance data from Table 12. These predictions are based on an assumption that the degradation is first order (linear). These predictions are illustrated in Figs. 1 and 2. Fig. 1 shows the shelf life prediction of 0.01% atropine sulfate solution with a primary degradant RRT 0.87-0.89, and a n.m.t. of 0.5% area, based on data obtained from samples stored at 25°C and 40°C. The pH range of the atropine sulfate solution is from 5.9-6.2. Fig. 2 shows the shelf life prediction of 0.01% atropine sulfate solution with a primary degradant RRT 0.87-0.89, and a n.m.t. of 0.5% area, based on data obtained from samples stored at 25°C and 60°C. The pH range of the atropine sulfate solution is from 5.9-6.2.

Example 5 – 1% Atropine Sulfate (Bausch + Lomb) Sample Analysis

[00360] The 1% atropine sulfate sample was obtained from Bausch + Lomb (Lot 198421). For comparison the pH of the 1% Atropine Sulfate drug product was determined in the neat solution as well as a sample that was diluted to the current nominal concentration (0.01% Atropine Sulfate) using the vehicle. Additionally a sample was diluted to the nominal concentration with method diluent. Both samples diluted to the nominal concentration were analyzed using the RP-UPLC method (Table 10). The results are listed in Table 13.

Table 13. pH and Purity of the Bausch + Lomb Atropine Sulfate Sample

Sample	pH	Purity (% area)
1% Atropine Sulfate	4.89	ND
0.01% Atropine Sulfate, diluted with Vehicle	6.16	99.6%
0.01% Atropine Sulfate,	ND	99.6%

<i>diluted with Diluent</i>		
Vehicle	7.94	ND

ND= not determined

Example 6 – Dose Uniformity (10-Dose)

[00361] To evaluate the dose-to-dose uniformity, drop bottles containing the ophthalmic aqueous composition are stored upright for a predetermined period of time (e.g. 12 hours) prior to the start of the test. To simulate the recommended dosing of the product, 10 drops of the aqueous composition are dispensed from each bottle at predetermined time intervals (e.g. consecutively, every 1 minute, every 10 minutes, every hour or every 24 hours). All drops are dispensed into tared glass vials, capped, and stored at room temperature until analysis. Concentrations of atropine in the expressed drops are determined using a reverse-phase HPLC method.

Example 7 – Dose Uniformity (5-Dose)

[00362] To evaluate the dose-to-dose uniformity, drop bottles containing the ophthalmic aqueous composition are stored upright for a predetermined period of time (e.g. 12 hours) prior to the start of the test. To simulate the recommended dosing of the product, 5 drops of the aqueous composition are dispensed from each bottle at predetermined time intervals (e.g. consecutively, every 1 minute, every 10 minutes, every hour or every 24 hours). All drops are dispensed into tared glass vials, capped, and stored at room temperature until analysis. Concentrations of atropine in the expressed drops are determined using a reverse-phase HPLC method.

Example 8 – Dose Uniformity (2-Dose)

[00363] To evaluate the dose-to-dose uniformity, drop bottles containing the ophthalmic aqueous composition are stored upright for a predetermined period of time (e.g. 12 hours) prior to the start of the test. To simulate the recommended dosing of the product, 2 drops of the aqueous composition are dispensed from each bottle at predetermined time intervals (e.g. consecutively, every 1 minute, every 10 minutes, every hour or every 24 hours). All drops are dispensed into tared glass vials, capped, and stored at room temperature until analysis. Concentrations of atropine in the expressed drops are determined using a reverse-phase HPLC method.

Example 9 – Formulation Stability Comparison

[00364] Atropine sulfate monohydrate (MP Bio; Lot Number 7825K) and tropic acid (Sigma Aldrich; Lot Number STBD6457V) were used for this experiment. Eight formulations illustrated in Table 14A were analyzed at t=0, 2 weeks, and 4 weeks. A RP-HPLC method was used to carry out the analysis.

Table 14A. Atropine sulfate formulations

Formulation	Atropine Sulfate Monohydrate	Benzalkonium Chloride (BAK)	Sodium Chloride	Acetic Acid	Citric Acid	pH/pD	Aqueous
1	0.010	0.01	0.90	0.01	-	4.2	SWFI
2	0.025	0.01	0.90	0.01	-	4.2	SWFI
3	0.010	0.01	0.90	0.01	-	4.8	SWFI
4	0.025	0.01	0.90	0.01	-	4.8	SWFI
5	0.010	0.01	0.90	-	0.04	5.8	SWFI
6	0.025	0.01	0.90	-	0.04	5.8	SWFI
7	0.010	0.01	0.90	0.01	-	5.2 (pD)	D ₂ O
8	0.010	0.01	0.90	-	0.04	6.2 (pD)	D ₂ O

[00365] The values are % w/v. The formulations were prepared at 100mL scale in volumetric glassware. The pD of Formulation 7 and Formulation 8 are 5.2 and 6.2, respectively. In some instances, the pD is calculated as $pD = 0.4 + pH^*$, in which pH^* is the measured or observed pH of the solution formulated in a solution containing deuterated water.

[00366] Table 14B illustrates analysis time points for the formulations listed in Table 14A. Table 14B. Schedule for atropine sulfate formulation testing

Storage Condition (Horizontal)	Time Point		
	Initial (t=0)	2 Week	4 Week
25 °C/60%RH	X	X	X
40 °C/75%RH		X	X
60 °C		X	X

[00367] Table 15 illustrates the atropine sulfate purity data associated with each of the eight formulations. Purity is indicated as percentage of area under the curve.

Table 15. Atropine sulfate purity as Area-%

Solvent	Condition	t=0	t=2 weeks	t=4 weeks ¹
Formulation 1 pH 4.2	25/60	97.39	97.76	98.20
	40/75		97.25	97.04
	60 °C		94.98	93.87
Formulation 2 pH 4.2	25/60	98.85	99.03	99.08
	40/75		98.50	98.32

	60 °C		97.47	96.65
Formulation 3 pH 4.8	25/60	98.16	98.16	98.45
	40/75		97.98	97.35
	60 °C		95.94	94.65
Formulation 4 pH 4.8	25/60	98.81	98.75	98.46
	40/75		98.26	98.01
	60 °C		96.22	94.04
Formulation 5 pH 5.8	25/60	98.16	97.92	97.54
	40/75		95.88	93.51
	60 °C		80.94	66.83
Formulation 6 pH 5.8	25/60	99.08	98.91	98.46
	40/75		97.65	96.20
	60 °C		89.15	80.68
Formulation 7 pD 5.2	25/60	98.93	99.07	98.39
	40/75		98.51	97.55
	60 °C		96.70	94.01
Formulation 8 pD 6.2	25/60	98.93	98.95	98.51
	40/75		98.53	97.44
	60 °C		95.97	92.72

¹Some chromatographic interference were observed to occur late in the run (~27-32 minutes) for many of the t=4 week stability samples and in some instances is proposed to be system related.

[00368] After four weeks of storage at 60 °C, in some instances the atropine sulfate concentration have an impact on the stability for the formulations containing acetic acid at pH 4.2. For example, atropine sulfate concentration at 0.025 % w/v (Formulation 2) showed a 2.8% increase in % purity at pH 4.2 compared to the atropine sulfate concentration at 0.010 % w/v (Formulation 1). This trend was not observed for the acetic acid formulations at pH 4.8 (Formulations 3 and 4); rather a 0.6% decrease in % purity was observed for the higher doses.

[00369] The dose dependent stability trend that was observed at pH=4.2 was also seen in the formulations containing citric acid at pH 5.8 (Formulations 5 and 6). After four weeks of storage at 60 °C there is approximately 14% less degradation in the higher does than observed in the lower dose.

[00370] At both the high and the low doses, more degradation is observed in the formulations that start at a higher pH. This degradation is predominantly the growth of tropic acid. In some instances, buffer species plays a role in the observed degradation between the different pH values.

[00371] The percentage of tropic acid observed for each of the formulations at t=4 weeks and at 60°C are as follow:

[00372] Formulation 1- Tropic acid observed is 0.54%.

[00373] Formulation 2-Tropic acid observed is 0.93%.

[00374] Formulation 3-Tropic acid observed is 1.58%.

[00375] Formulation 4-Tropic acid observed is 3.03%.

[00376] Formulation 5-Tropic acid observed is 29.13%.

[00377] Formulation 6-Tropic acid observed is 16.84%.

[00378] Formulation 7-Tropic acid observed is 1.07%.

[00379] Formulation 8-Tropic acid observed is 4.03%.

[00380] In some embodiments, switching the water source to deuterated water (D₂O) has an impact on stabilizing the growth of the tropic acid peak for the formulation containing acetic acid at pD 5.2 (Formulation 7), see Fig. 4. In addition, in the formulation containing citric acid at pD 6.2 (Formulation 8), the deuterated water also stabilizes atropine sulfate, see Fig. 5.

[00381] Table 16 illustrates tropic acid as area under the curve for each of the eight formulations. Tropic acid is a degradant of atropine sulfate. In some instances, LOQ was previously found to be 0.05% for the RP-HPLC method.

Table 16. Tropic acid as area-%

Solvent	Condition	t=0	t=2 weeks	t=4 weeks
Formulation 1 pH 4.2	25/60	<LOQ	0.08	<LOQ
	40/75		0.10	0.10
	60 °C		0.37	0.51
Formulation 2 pH 4.2	25/60	<LOQ	0.05	<LOQ
	40/75		0.11	0.12
	60 °C		0.46	0.93
Formulation 3 pH 4.8	25/60	<LOQ	0.12	0.05
	40/75		0.19	0.27
	60 °C		0.90	1.58
Formulation 4 pH 4.8	25/60	<LOQ	0.10	0.13
	40/75		0.31	0.53
	60 °C		1.84	3.03
Formulation 5 pH 5.8	25/60	<LOQ	0.40	0.71
	40/75		2.22	4.35
	60 °C		16.62	29.13
Formulation 6 pH 5.8	25/60	<LOQ	0.24	0.42
	40/75		1.30	2.44
	60 °C		9.32	16.84
Formulation 7 pD 5.2	25/60	<LOQ	0.07	0.08
	40/75		0.14	0.24
	60 °C		0.71	1.07
Formulation 8 pD 6.2	25/60	<LOQ	0.11	0.14
	40/75		0.33	0.65
	60 °C		2.32	4.03

[00382] Table 17 illustrates percentage of potency of atropine in the eight formulations.

Table 17. % Potency

Solvent	Condition	t=0	t=2 weeks	t=4 weeks
Formulation 1 pH 4.2	25/60	109.4	110.3	112.8
	40/75		111.0	112.4
	60 °C		112.8	114.8
Formulation 2 pH 4.2	25/60	102.9	107.1	109.7
	40/75		108.4	109.6
	60 °C		109.4	111.0
Formulation 3 pH 4.8	25/60	106.3	108.0	109.6
	40/75		108.1	110.0
	60 °C		108.0	109.9
Formulation 4 pH 4.8	25/60	102.5	107.9	109.2
	40/75		107.4	108.9
	60 °C		107.9	108.8
Formulation 5 pH 5.8	25/60	105.0	105.9	107.1
	40/75		103.8	103.5
	60 °C		90.2	77.7
Formulation 6 pH 5.8	25/60	107.2	107.1	109.1
	40/75		106.8	107.1
	60 °C		99.0	93.7
Formulation 7 pD 5.2	25/60	107.3	111.3	112.9
	40/75		111.6	113.5
	60 °C		111.8	113.5
Formulation 8 pD 6.2	25/60	99.0	103.0	105.0
	40/75		104.9	104.7
	60 °C		101.6	103.0

[00383] After 4 weeks of storage, the observed potency values were elevated from the t=0 and 2 week time points, with the exception of Formulations 5 and 6 at 60 °C where the potencies dropped due to degradation. In some instances, these potency values are within the error of the HPLC method, but appear to be trending upward. Mass balance was calculated for the 60 °C data and results were consistent across the formulations and levels of degradation, although skewed lower due to the higher than anticipated potency values at 4 weeks, see Figure 3.

[00384] Table 18 illustrates pH or pD stability of the eight formulations.

Table 18. pH/pD Stability

Solvent	Condition	t=0	t=2 weeks	t=4 weeks
Formulation 1 (pH)	25/60	4.21	3.93	4.02
	40/75		3.86	3.96
	60 °C		3.71	3.86
Formulation 2 (pH)	25/60	4.26	4.11	4.25
	40/75		4.04	4.17

	60 °C		3.93	4.10
Formulation 3 (pH)	25/60	4.85	4.44	4.61
	40/75		4.41	4.54
	60 °C		4.32	4.40
Formulation 4 (pH)	25/60	4.98	4.93	5.05
	40/75		4.89	4.98
	60 °C		4.77	4.77
Formulation 5 (pH)	25/60	5.87	5.93	6.03
	40/75		5.96	5.96
	60 °C		5.82	5.78
Formulation 6 (pH)	25/60	5.80	5.69	5.77
	40/75		5.65	5.67
	60 °C		5.54	5.50
Formulation 7 (pD)	25/60	5.31	5.10	5.24
	40/75		5.08	5.15
	60 °C		5.00	4.93
Formulation 8 (pD)	25/60	6.25	5.72	5.88
	40/75		5.74	5.78
	60 °C		5.58	5.50

[00385] The italicized values are pD values for a deuterated sample. In some embodiments, the pD of the deuterated samples are $pD = pH_{\text{reading}} + 0.4$ (Glasoe, *et al.* “Use of glass electrodes to measure acidities in deuterium oxide” J. Physical Chem. 64(1): 188-190 (1960)).

[00386] At the two lower temperatures, the pH values at t=4 week are slightly elevated from the t=2 week time point. These data were generated using a new glass pH probe. In some instances, the observed differences are due to the probe differences or additional variables such as for example, the age of the standard buffers or temperature gradients within the laboratory environment. The downward pH trend for each formulation with increasing temperatures at t=4 week is consistent with previous data and is consistent with the increase in the amount of tropic acid present in the stability sample.

Example 10-Determination of Shelf Life and Activation Energy

[00387] Activation energy was calculated for the eight formulations disclosed in Example 9 and comparison with a reference standard was made with Formulations 4-7.

[00388] Table 19 illustrates the activation energy (E_a) calculation. The E_a minimum is 17.8 Kcal/mol, the E_a maximum is 21.3 Kcal/mol, and the E_a mean is 19.5 Kcal/mol. Mean is $\pm 3 \times \text{stdev}$. Figs. 6 and 7 illustrate the poor correlation between RS and tropic acid with Formulation 4 and Formulation 7, respectively. Figs. 8 and 9 illustrate improved correlation between RS and tropic acid with Formulation 5 and Formulation 6, respectively. At a lower pH (e.g. pH 4.8 or lower), there was a poor correlation observed (Formulation 4 and Formulation 7). This was due to a slowed hydrolysis and

increased alternative degradation pathways. At a higher pH (e.g., pH 5.8 or higher), an improved or better correlation was observed (Formulation 5 and Formulation 6). This was due to the hydrolysis of atropine as the primary degradant. It is noted that the activation energy is for the specific acid catalyzed degradation to tropic acid- the predominant degradation product and degradation mechanism operating at pH 5.8 or higher.

Table 19. Activation energy for total related substance (RS) and tropic acid.

	Total RS	Tropic Acid	
1	Poor Corr	Poor Corr	
2	12.2	Poor Corr	
3	Poor Corr	18.3	
4	16.8	18.1	
5	19.8	19.7	
6	19.2	20.0	
7	13.2	15.5	
8	Poor Corr	18.9	
Mean	16.2	18.4	Kcal/mole
Stdev	3.4	1.6	
RSD	21%	9%	

[00389] Table 20 illustrates the rate of RS or tropic acid formation per week at 40°C.

Table 20.

	Formulation	Rate 40°C (total RS %/wk)	Rate 40°C (Tropic acid %/wk)
Formulation 5	0.01% Atr Citrate pH5.8	1.16	1.09
Formulation 6	0.025% Atr Citrate pH5.8	0.72	0.61
Formulation 8	0.01% Atr Citrate pD 6.2 D ₂ O		0.163

[00390] Table 21 illustrates the activation energy and predicted shelf life at 30°C calculated based on Table 20. It is assumed for the calculation that tropic acid and total RS is 5% (self-life).

Table 21A.

	Rate @30°C (Total RS %/wk)			Estimated Shelf life @30°C (mo)		
Formulation	Ea min	Ea mean	Ea max	Ea min	Ea mean	Ea max
5	0.45	0.41	0.38	2.78	3.04	3.33

6	0.28	0.26	0.23	4.47	4.90	5.37
8	--	--	--	--	--	--

Table 21B.

	Rate @30°C (Tropic acid %/wk)			Estimated Shelf life @30°C (mo)		
Formulation	Ea min	Ea mean	Ea max	Ea min	Ea mean	Ea max
5	0.42	0.39	0.35	2.95	3.24	3.54
6	0.24	0.22	0.20	5.28	5.78	6.33
8	0.06	0.06	0.05	19.75	21.64	23.70

[00391] At pD 6.2, the deuterated formulation (Formulation 8) has a predicted shelf life of close to 2 years at 30°C.

[00392] Table 22 illustrate the predicted shelf life at temperatures of 40°C, 30°C, 25°C, and 2-8°C for Formulations 4-8 for total RS and tropic acid, respectively.

Table 22

Formulation	Stability Prediction		RS		Tropic Acid	
	Temperature (°C)	weeks	months	Temperature (°C)	weeks	months
4	40	16.5	4.1	40	7.7	1.9
	30	40.2	10.1	30	20.0	5.0
	25	64.2	16.0	25	33.0	8.3
	2-8	493.4	123.4	2-8	296.8	74.2
5	40	2.8	0.7	40	0.9	0.2
	30	7.9	2.0	30	2.7	0.7
	25	13.7	3.4	25	4.6	1.2
	2-8	151.1	37.8	2-8	50.5	12.6
6	40	5.8	1.4	40	1.7	0.4
	30	15.9	4.0	30	4.8	1.2
	25	27.3	6.8	25	8.4	2.1
	2-8	281.6	70.4	2-8	95.9	24.0
7	40	11.5	2.9	40	16.9	4.2
	30	23.2	5.8	30	38.4	9.6
	25	33.4	8.4	25	59.1	14.8
	2-8	165.7	41.4	2-8	388.2	97.1
8	40	-	-	40	6.2	1.6
	30	-	-	30	17.0	4.3
	25	-	-	25	28.9	7.2

2-8	-	-	2-8	287.1	71.8

Example 11-Additional Formulation Stability Comparison

[00393] Atropine sulfate monohydrate (MP Bio; Lot Number 7825K) and tropic acid (Sigma Aldrich; Lot Number STBD6457V) were used for this experiment. Thirteen formulations illustrated in Table 23A were analyzed. Formulations 1-8 had been analyzed at t=0, 2 weeks, 4 weeks, and 8 weeks. Formulations 9-13 had been analyzed at t=0, 2 weeks, and 4 weeks. The pH values reported herein are the measured pH values obtained using the Thermo Scientific, Orion Dual Star pH/ISE benchtop pH meter and the Orion Double Junction Micro pH probe S/N S01-18520 calibrated with H₂O based standards.

Table 23A. Atropine sulfate Formulations

Formulation	Atropine Sulfate Monohydrate	Benzalkonium Chloride (BAK)	Sodium Chloride	Acetic Acid	Citric Acid	pH/pD	Aqueous
1	0.010	0.01	0.90	0.01	-	4.2	SWFI
2	0.025	0.01	0.90	0.01	-	4.2	SWFI
3	0.010	0.01	0.90	0.01	-	4.8	SWFI
4	0.025	0.01	0.90	0.01	-	4.8	SWFI
5	0.010	0.01	0.90	-	0.04	5.8	SWFI
6	0.025	0.01	0.90	-	0.04	5.8	SWFI
7	0.010	0.01	0.90	0.01	-	5.2 (pD)	D ₂ O
8	0.010	0.01	0.90	-	0.04	6.2 (pD)	D ₂ O
9	0.010	-	0.90	-	0.04	6.8 (pD)	D ₂ O
10	0.010	-	0.90	-	0.04	6.4	H ₂ O (control)
11	0.010	-	0.90	-	0.08	6.4	H ₂ O (control)
12	0.010	-	0.90	-	0.04	7.2 (pD)	D ₂ O
13	0.010	-	0.90	-	0.04	6.8	H ₂ O (control)

[00394] The values are % w/v. The formulations were prepared at 100 mL scale in volumetric glassware and filled into LDPE eye droppers. In some instances, the pD is calculated as $pD = 0.4 + pH^*$, in which pH* is the measured or observed pH of the solution formulated in a solution containing deuterated water.

[00395] Table 23B illustrates analysis time points for the formulations listed in Table 23A.

Table 23B. Schedule for atropine sulfate formulation testing

Storage Condition (Horizontal)	Time Point		
	Initial (t=0)	2 Week	4 Week
25 °C/60%RH	X	X	X
40 °C/75%RH		X	X
60 °C		X	X

[00396] Table 24A and Table 24B illustrate atropine sulfate purity data associated with the atropine sulfate formulations. Purity is indicated as percentage of area under the curve. The ↑ & ↓ indicate the high or low concentration of atropine sulfate monohydrate (0.01% and 0.025%). The A & C indicate the buffer species used, acetic acid and citric acid respectively.

Table 24A. Atropine Sulfate Purity as Area-% for H₂O Formulations

Solvent	Condition	t=0	t=2 weeks	t=4 weeks
Formulation 3 ↓A H ₂ O pH 4.8	25/60	98.16	98.16	98.45
	40/75		97.98	97.35
	60 °C		95.94	94.65
Formulation 5 ↓C H ₂ O pH 5.8	25/60	98.16	97.92	97.54
	40/75		95.88	93.51
	60 °C		80.94	66.83
Formulation 10 ↓C H ₂ O pH 6.4	25/60	98.66	96.67	95.81
	40/75		91.07	85.27
	60 °C		59.77	42.87
Formulation 11 ↓C(2x) H ₂ O pH 6.4	25/60	99.47	97.87	96.69
	40/75		90.97	84.26
	60 °C		54.96	34.40
Formulation 13 ↓C H ₂ O pH 6.8	25/60	97.21	95.42	93.24
	40/75		83.05	73.00
	60 °C		43.99	27.50

Table 24B. Atropine Sulfate Purity as Area-% for D₂O Formulations

Solvent	Condition	t=0	t=2 weeks	t=4 weeks
Formulation 7 ↓A D ₂ O pD 5.2	25/60	98.93	99.07	98.39
	40/75		98.51	97.55
	60 °C		96.70	94.01
Formulation 8 ↓C D ₂ O pD 6.2	25/60	98.93	98.95	98.51
	40/75		98.53	97.44
	60 °C		95.97	92.72
Formulation 9 ↓C D ₂ O pD 6.8	25/60	99.29	98.42	98.07
	40/75		95.20	93.22
	60 °C		75.17	65.97
Formulation 12 ↓C D ₂ O pD 7.2	25/60	98.53	97.17	95.99
	40/75		90.75	84.64

	60 °C		56.78	46.05

[00397] Table 25A and Table 25B illustrate tropic acid formation associated with the atropine sulfate formulations. Tropic acid is a degradant of atropine sulfate, and is indicated as percentage of area under the curve. LOQ was found to be 0.05% for the RP-HPLC method. The ↑ & ↓ indicate the high or low concentration of atropine sulfate monohydrate (0.01% and 0.025%). The A & C indicate the buffer species used, acetic acid and citric acid, respectively.

Table 25A. Tropic Acid as Area-% for H₂O Formulations

Solvent	Condition	t=0	t=2 weeks	t=4 weeks
Formulation 3 ↓A H ₂ O pH 4.8	25/60	<LOQ	0.12	0.05
	40/75		0.19	0.27
	60 °C		0.90	1.58
Formulation 5 ↓C H ₂ O pH 5.8	25/60	<LOQ	0.40	0.71
	40/75		2.22	4.35
	60 °C		16.62	29.13
Formulation 10 ↓C H ₂ O pH 6.4	25/60	0.74	1.90	3.21
	40/75		7.61	13.49
	60 °C		37.44	54.06
Formulation 11 ↓C(2x) H ₂ O pH 6.4	25/60	0.09	1.31	2.64
	40/75		7.61	14.68
	60 °C		42.43	62.23
Formulation 13 ↓C H ₂ O pH 6.8	25/60	2.21	3.66	6.11
	40/75		15.47	25.80
	60 °C		53.24	69.34

Table 25B. Tropic Acid as Area-% for D₂O Formulations

Solvent	Condition	t=0	t=2 weeks	t=4 weeks
Formulation 7 ↓A D ₂ O pD 5.2	25/60	<LOQ	0.07	0.08
	40/75		0.14	0.24
	60 °C		0.71	1.07
Formulation 8 ↓C D ₂ O pD 6.2	25/60	<LOQ	0.11	0.14
	40/75		0.33	0.65
	60 °C		2.32	4.03
Formulation 9 ↓C D ₂ O pD 6.8	25/60	0.06	0.55	1.06
	40/75		3.16	6.29
	60 °C		21.09	29.25
Formulation 12 ↓C D ₂ O pD 7.2	25/60	0.42	1.35	2.62
	40/75		7.27	13.53
	60 °C		38.58	48.15

[00398] Table 26A and Table 26B illustrate the percentage of potency of atropine in the formulations. The ↑ & ↓ indicate the high or low concentration of atropine sulfate monohydrate (0.01% and 0.025%). The A & C indicate the buffer species used, acetic acid and citric acid respectively.

Table 26A. Percentage of potency for H₂O Formulations

Solvent	Condition	t=0	t=2 weeks	t=4 weeks
Formulation 3 ↓A H ₂ O pH 4.8	25/60	106.3	108.0	109.6
	40/75		108.1	110.0
	60 °C		108.0	109.9
Formulation 5 ↓C H ₂ O pH 5.8	25/60	105.0	105.9	107.1
	40/75		103.8	103.5
	60 °C		90.2	77.7
Formulation 10 ↓C H ₂ O pH 6.4	25/60	101.7	100.0	98.0
	40/75		89.4	87.0
	60 °C		63.7	45.7
Formulation 11 ↓C(2x) H ₂ O pH 6.4	25/60	97.5	96.1	94.3
	40/75		89.4	82.0
	60 °C		55.7	35.20
Formulation 13 ↓C H ₂ O pH 6.8	25/60	99.4	96.9	94.1
	40/75		85.0	74.0
	60 °C		46.4	29.8

Table 26B. Percentage of potency for D₂O Formulations

Solvent	Condition	t=0	t=2 weeks	t=4 weeks
Formulation 7 ↓A D ₂ O pD 5.2	25/60	107.3	111.3	112.9
	40/75		111.6	113.5
	60 °C		111.8	113.5
Formulation 8 ↓C D ₂ O pD 6.2	25/60	99.0	103.0	105.0
	40/75		104.9	104.7
	60 °C		101.6	103.0
Formulation 9 ↓C D ₂ O pD 6.8	25/60	101.4	99.9	100.1
	40/75		97.4	93.2
	60 °C		78.7	68.9
Formulation 12 ↓C D ₂ O pD 7.2	25/60	104.9	103.5	101.6
	40/75		96.9	89.1
	60 °C		62.5	50.9

[00399] Table 27A and Table 27B illustrate the stability of pH or pD for the atropine sulfate formulations. The ↑ & ↓ indicate the high or low concentration of atropine sulfate monohydrate (0.01% and 0.025%). The A & C indicate the buffer species used, acetic acid and citric acid respectively.

Table 27A. Stability of pH for H₂O Formulations

Solvent	Condition	t=0	t=2 weeks	t=4 weeks
Formulation 3 ↓A H ₂ O pH 4.8	25/60	4.85	4.44	4.61
	40/75		4.41	4.54
	60 °C		4.32	4.40
Formulation 5 ↓C H ₂ O pH 5.8	25/60	5.87	5.93	6.03
	40/75		5.96	5.96
	60 °C		5.82	5.78
Formulation 10 ↓C H ₂ O pH 6.4	25/60	6.43	6.41	6.46
	40/75		6.62	6.67
	60 °C		6.01	5.92
Formulation 11 ↓C(2x) H ₂ O pH 6.4	25/60	6.44	6.47	6.72
	40/75		6.66	6.61

	60 °C		6.27	6.23
Formulation 13 ↓C H ₂ O pH 6.8	25/60	6.77	6.91	6.91
	40/75		6.65	6.62
	60 °C		6.30	6.19

Table 27B. Stability of pD for D₂O Formulations

Solvent	Condition	t=0	t=2 weeks	t=4 weeks
Formulation 7 ↓A D ₂ O pD 5.2	25/60	5.31	5.10	5.24
	40/75		5.08	5.15
	60 °C		5.00	4.93
Formulation 8 ↓C D ₂ O pD 6.2	25/60	6.25	5.72	5.88
	40/75		5.74	5.78
	60 °C		5.58	5.50
Formulation 9 ↓C D ₂ O pD 6.8	25/60	6.76	6.80	6.81
	40/75		6.78	6.86
	60 °C		6.45	6.24
Formulation 12 ↓C D ₂ O pD 7.2	25/60	7.25	7.18	7.26
	40/75		7.14	7.15
	60 °C		6.52	6.36

Example 12. Determination of shelf life and activation energy for atropine sulfate formulations of Example 11

[00400] Activation energy was calculated for the atropine sulfate formulations disclosed in Example 11. Specifically, activation energies were calculated from the total % of related substances (RS) at 40°C and 60°C (2 point calculations) and from tropic acid formation at 40°C and 60°C (2 point calculations). These values were then averaged. Table 28 illustrates the activation energy calculation. Table 29 illustrates estimated shelf-lives from the 40°C rate of formation of %RS and tropic acid, respectively. Figure 10 illustrates estimated shelf lives for D₂O and H₂O formulations.

Table 28. Activation Energy

Atropine Formulations	Total RS	Tropic Acid
7	14	19
3	16	17
8	20	21
5	14	Poor Corr
6	15	16
Mean	16.3	18.7
Stdev	2.68	1.90
RSD	16%	10%
Poor Corr:	One or more curve had R ² < 0.95	

Table 29. Estimated Shelf Life

	Estimated Shelf life/mo			
	Total related substances % (limit=8%)		Tropic acid % (limit=5%)	
Formulation	8°C	25°C	8°C	25°C
0.01% w/v Atr 0.01% w/v Acetate 0.9% w/v NaCl 0.01% w/v BAK pD 5.2 D₂O (Formulation 7)	189	26	1427	147
0.01% w/v Atr 0.01% w/v Acetate 0.9% w/v NaCl 0.01% w/v BAK pH4.8 H₂O (Formulation 3)	211	29	1095	113
0.01% w/v Atr 0.04% w/v Citrate 0.9% w/v NaCl 0.01% w/v BAK pD 6.2 D₂O (Formulation 8)	158	22	369.8	38
0.01% w/v Atr 0.04% w/v Citrate 0.9% w/v NaCl 0.01% w/v BAK pH5.8 H₂O (Formulation 5)	37	5.2	54	5.5
0.01% Atr 0.9% w/v NaCl pH5.9 H₂O extemporaneous preparation	13.6	2.6		

[00401] Tables 30 illustrate the predicted shelf life at temperatures of 40°C, 30°C, 25°C, and 2-8°C for Formulations 2-8 for total RS and tropic acid, respectively.

Table 30

Stability Prediction		RS				Tropic Acid	
Formulation	Temperature (°C)	weeks	months		Temperature (°C)	weeks	months
2	40	64.5	16.1		40	-	-
	30	153.2	38.3		30	-	-
	25	241.2	60.3		25	-	-
	2-8	1747.9	437.0		2-8	-	-
3	40	31.1	7.8		40	99.5	24.9
	30	73.9	18.5		30	268.3	67.1
	25	116.3	29.1		25	451.8	113.0
	2-8	842.9	210.7		2-8	4382.0	1095.5
4	40	30.7	7.7		40	42.1	10.5
	30	73.0	18.2		30	113.7	28.4
	25	114.9	28.7		25	191.5	47.9
	2-8	832.6	208.1		2-8	1857.0	464.2
5	40	5.5	1.4		40	4.9	1.2
	30	13.1	3.3		30	13.2	3.3
	25	20.6	5.2		25	22.2	5.5
	2-8	149.3	37.3		2-8	215.0	53.8
6	40	10.7	2.7		40	8.8	2.2
	30	25.5	6.4		30	23.7	5.9
	25	40.1	10.0		25	39.8	10.0
	2-8	290.5	72.6		2-8	386.5	96.6
7	40	27.9	7.0		40	129.6	32.4
	30	66.4	16.6		30	349.6	87.4
	25	104.5	26.1		25	588.7	147.2
	2-8	757.3	189.3		2-8	5709.4	1427.4
8	40	23.3	5.8		40	33.6	8.4
	30	55.3	13.8		30	90.6	22.6
	25	87.2	21.8		25	152.5	38.1
	2-8	631.6	157.9		2-8	1479.2	369.8

Example 13 – Forced Degradation Study of Atropine Formulation 8 in D₂O and H₂O Conditions

[00402] Atropine sulfate monohydrate (MP Bio; Lot Number 7825K) was used for this experiment. A correction factor of 83.3% is used to quantitate amount of free Atropine. Table 31 shows the D₂O and H₂O formulation compositions.

Table 31. Formulation 8 Compositions

Formulation	[Free Atropine] (µg/mL)	Composition
8 – D ₂ O	83.3	0.01% (w/v) Benzalkonium Chloride, 0.9% (w/v) NaCl, 0.208 mM Citric Acid in D ₂ O, pD 6.2
8 – H ₂ O	83.3	0.01% (w/v) Benzalkonium Chloride, 0.9% (w/v) NaCl, 0.208 mM Citric Acid in H ₂ O, pH 5.8

[00403] D₂O-based Formulation 8 and H₂O-based Formulation 8 were subjected to acid, base, light, heat and oxidative stress. Approximately 5-20% degradation was targeted for all stress conditions to produce sufficient degradation while avoiding secondary degradation. At each condition, Formulation 8 samples were incubated alongside a vehicle control containing BAK. For the light condition, a foil wrapped Formulation 8 control and foil wrapped vehicle control were prepared to understand if extraneous degradation, such as heat in the light box, were to occur. A RP-HPLC method was used to carry out the analysis. Mass balance (the correlation of potency and purity by area-%) was also evaluated using Equation I.

$$\text{Mass Balance} = \frac{(\text{Potency}_{\text{initial}} + (100 - \text{Purity}_{\text{initial}}))}{(\text{Potency}_{\text{final}} + (100 - \text{Purity}_{\text{final}}))}$$

[00404] The forced degradation results were processed at 210 nm, and are presented in Tables 32A and 32B for H₂O and D₂O formulations, respectively.

Table 32A. Forced Degradation Results for Formulation 8—H₂O

Stress Condition		Duration	% Recovery (vs. Control)	% Purity (vs. Control)	Peak Purity Angle	Peak Purity Threshold	Main Peak Spectrally Pure?	Mass Balance
Control	2-8 °C, foil wrapped	3 day	100.9	100.0	0.412	0.657	Y	
Acid (1.0N HCl)	Ambient, foil wrapped	23 day	-7.9	-5.9	0.301	0.513	Y	101.8%

Base (0.001N NaOH)	Ambient, foil wrapped	4 hr	-5.2	-6.6	0.417	0.725	Y	98.7%
		6 hr	-7.3	-7.9	0.462	0.741	Y	99.5%
Heat	60 °C, foil wrapped	7 day	-12.1	-11.9	0.428	0.478	Y	100.3%
		10 day	-18.4	-18.4	0.476	0.752	Y	100.0%
Light	Ambient, clear glass vial	1.1 million lux hours (10 day)	-10.1	-7.6	0.478	0.831	Y	102.5%
		1.5 million lux hours (14 day)	-19.1	-12.2	0.597	0.911	Y	107.1%
Light Control	Ambient, foil wrapped	1.1 million lux hours (10 day)	-0.4	-0.5	0.411	0.665	Y	99.9%
		1.5 million lux hours (14 day)	-3.0	-0.3	0.388	0.592	Y	102.8%
Oxidation (3% H ₂ O ₂)	Ambient, foil wrapped	3 day	-16.0	-7.9	0.532	0.791	Y	108.8%
		4 day	-28.0	-13.9	0.473	0.777	Y	115.7%
		7 day	-29.4	-13.5	0.705	0.967	Y	118.9%

Table 32B. Forced Degradation Results for Formulation 8—D₂O

Stress Condition		Duration	% Recovery (vs. Control)	% Purity (vs. Control)	Peak Purity Angle	Peak Purity Threshold	Main Peak Spectrally Pure?	Mass Balance
Control	2-8 °C, foil wrapped	4 day	106.7	98.3	0.361	0.659	Y	
Acid (1.0N HCl)	Ambient, foil wrapped	17 day	-6.9	-5.5	0.250	0.469	Y	97.9%
Base (0.001N NaOH)	Ambient, foil wrapped	5 day	-2.3	-2.2	0.495	0.849	Y	100.0%
Base (0.005N NaOH)	Ambient, foil wrapped	30 min	-9.7	-9.6	0.601	0.894	Y	100.2%
Heat	60 °C,	17 day	-18.1	-16.9	0.281	0.550	Y	101.1%

	foil wrapped							
Light	Ambient, clear glass vial	0.44 million lux hours (4 day)	-14.1	-4.5	0.463	0.733	Y	109.6%
		0.87 million lux hours (8 day)	-24.2	-11.3	0.528	0.846	Y	113.8%
Light Control (foil covered)	Ambient, foil wrapped	0.44 million lux hours (4 day)	-0.2	1.7	0.354	0.640	Y	101.8%
		0.87 million lux hours (8 day)	0.0	1.4	0.330	0.599	Y	101.3%
Oxidation (3% H ₂ O ₂)	Ambient, foil wrapped	4 day	-10.6	-3.0	0.439	0.720	Y	107.5%
		8 day	-17.9	-8.3	0.385	0.672	Y	109.9%

Example 14 - Formulation 8 Stability Comparison

[00405] The long-term stability of atropine sulfate formulation 8 in D₂O (see Table 31 for formulation composition) was analyzed at three different storage conditions. Table 33 illustrates the stability criteria: appearance, potency, tropic acid level, total purity, and pD at storage conditions of 25°C with 60% humidity, 40°C with 75% humidity, and 60°C. As discussed above, $pD = pH_{\text{reading}} + 0.4$ (Glasoe, *et al.* "Use of glass electrodes to measure acidities in deuterium oxide" J. Physical Chem. 64(1): 188-190 (1960)).

Table 33. Formulation 8 Stability

Parameter	Initial	2 weeks	4 weeks	8 weeks	6 months	9 months ²	12 months ³
Storage Condition: 25°C/60% RH							
Appearance	Clear Colorless Solution Free of Particulates						
Potency (Assay)	99.2%	103.0%	105.0%	96.0%	99.7%	97.7%	101.7%
Tropic Acid Level	0.05%	0.11%	0.14%	0.23%	0.55%	0.91%	1.24%
Total Purity¹	98.9%	98.9%	98.5%	98.1%	99.2%	98.4%	97.8%
pD	6.3 (pH 5.9)	5.7 (pH 5.3)	5.9 (pH 5.5)	5.7 (pH 5.3)	5.8 (pH 5.4)	5.7 (pH 5.3)	5.8 (pH 5.4)
Storage Condition: 40°C/75% RH							
Appearance	Clear Colorless Solution Free of Particulates						
Potency (Assay)	99.2%	104.8%	104.7%	94.9%	96.6%	94.2%	95.6%
Tropic Acid Level	0.05%	0.34%	0.65%	1.24%	3.32%	5.05%	6.71%
Total Purity¹	98.9%	98.5%	97.5%	96.6%	96.3%	92.5%	90.5%
pD	6.3	5.7	5.8	5.6	5.7	5.5	5.7

	(pH 5.9)	(pH 5.3)	(pH 5.4)	(pH 5.2)	(pH 5.3)	(pH 5.1)	(pH 5.3)
Storage Condition: 60 °C							
Appearance	Clear Colorless Solution Free of Particulates						
Potency (Assay)⁴	99.2%	101.6%	103.0%	92.9%	100.6%	104.0%	115.9%
Tropic Acid Level	0.05%	2.33%	4.02%	6.01%	10.33%	10.87%	12.97%
Total Purity¹	98.9%	96.0%	92.8%	88.8%	85.5%	78.0%	72.4%
pD	6.3 (pH 5.9)	5.6 (pH 5.2)	5.5 (pH 5.1)	5.2 (pH 4.8)	5.1 (pH 4.7)	4.9 (pH 4.5)	5.0 (pH 4.6)

¹Slight variability is observed in the total purity results due to sensitivity differences from one HPLC system to the next.

²Results reported are from a second aliquot taken from the original assay eyedropper.

³Results reported are from an aliquot taken from the original assay eyedropper.

⁴A growing unknown related substance peak is observed to co-elute with the main peak and is included in the Atropine Sulfate potency result due to a lack of a clear inflection point between the two species upon integration.

[00406] A comparison of Formula 8 in H₂O and D₂O under three storage conditions is further illustrated in Fig. 11. Fig. 11A shows the presence of tropic acid degradant at 25°C with 60% humidity. By week 8, about 1.45% of tropic acid was observed in the H₂O formulation while only 0.23% of tropic acid was observed in the D₂O formulation. Similarly, at 40°C with 75% humidity storage condition (Fig. 11B), 8.34% of tropic acid was observed in the H₂O formulation while only 1.24% of tropic acid was observed in the D₂O formulation by week 8. At 60°C storage condition (Fig. 11C), 42.8% of tropic acid was observed in the H₂O formulation while only 6.01% of tropic acid was observed in the D₂O formulation by week 8.

Example 15 - Effect of pH on Ophthalmic Acceptance in Guinea Pigs

[00407] A cohort of guinea pigs is administered 50 µL of ophthalmic formulations having different pH values described herein. For example, ophthalmic formulations comprising H₂O or deuterated water (e.g., D₂O) are administered to the animals. Animal behavior is recorded at predetermined time intervals to evaluate the acceptance of the ophthalmic formulations

Example 16 – In vivo Rabbit Eye Irritation Test

[00408] The exemplary compositions disclosed herein are subjected to rabbit eye irritation test to evaluate their safety profile. The test composition are tested for eye irritation test in New Zealand Rabbits (see for example Abraham M H, et al., *Draize rabbit eye test compatibility with eye irritation thresholds in humans: a quantitative structure-activity relationship analysis*. Toxicol Sci. 2003 December; 76(2):384-91. Epub 2003 Sep. 26; see also Gettings S D et al., *A comparison of low volume, Draize and in vitro eye irritation test data. III. Surfactant-based formulations*. Food Chem Toxicol. 1998 March; 36(3):209-31). The study involves single ocular administration into the right eye and the same volume of its placebo in the left eye of each of the three rabbits. Rabbits are examined immediately and after instillation of the compositions for 4, 24, 48 and 72 hours post instillation to note the signs/symptoms of

eye irritation, if any. The test compositions show no sign of irritancy in cornea, iris and conjunctivae of the rabbit eyes.

Example 17 – In vivo Testing of Ophthalmic Aqueous Formulation in Guinea Pigs

[00409] Focus deprivation myopia (FDM) is achieved using a latex shield to cover one eye. For defocus-induced myopia, a latex-made facemask was held in place by a rubber-band around the head of animals, leaving both eyes, the nose, mouth and ears freely exposed. A - 4.00 D lens is glued onto a plastic lens frame. The lens frame is then attached to the facemask around one eye by a fabric hook-and-loop fastener after the optical center of the lens was aligned with the pupil center. The lens is detached and cleaned on both sides with a water-wetted gauze at least once daily followed by re-attachment to the facemask. All the animals are maintained on a cycle of 12-h illumination (500 Lux) and 12-h darkness during the experimental period

[00410] A cohort of guinea pigs at age of 3 weeks are randomly assigned to FDM (a facemask worn monocularly) or defocus-induced myopia (a -4.00 D lens worn monocularly) and control groups. The FDM groups were treated with the ophthalmic aqueous formulation, the ophthalmic carrier (without the ophthalmic agent), or FDM-only. The defocus-induced myopia groups were treated with the ophthalmic aqueous formulation, the ophthalmic carrier (without the ophthalmic agent), or defocus-only. The control groups were treated with the ophthalmic aqueous formulation, the ophthalmic carrier (without the ophthalmic agent), or no treatment. Ocular biometric parameters are measured in both eyes of individual animals before and at 11 days of treatment

[00411] Biometric parameters (e.g. refraction, corneal curvature, and axial components of the eye) are measured by an optometrist, orthoptist, or ophthalmologist with help from an animal care assistant during the light cycle (daytime) after removal of the facemask or lens. The optometrist, orthoptist, or ophthalmologist is masked in regard to the treatment conditions for each animal.

[00412] Refraction is measured by retinoscopy after the pupil is completely dilated by topical administration of 1% cyclopentolate hydrochloride. The results of retinoscopy are recorded as the mean value of the horizontal and vertical meridians.

[00413] Corneal curvature is measured with a keratometer modified by attachment of an +8 D lens onto the anterior surface of the keratometer. A group of stainless steel balls with diameters from 5.5 to 11.0 mm are measured by the modified keratometer. Three readings are recorded for each measurement to provide a mean result. The radius of corneal curvature is then deduced from the readings on the balls with known radii.

[00414] A-scan ultrasonograph is used to measure axial components of the eye (lens thickness and vitreous length and axial length). The conducting velocity was 1,723.3 m/s for measurement of the lens thickness and 1,540 m/s for measurement of the vitreous length as described previously. Each of the axial components is calculated as the mean of 10 repeated measurements.

Example 18 – Safety and Efficacy Studies of Ophthalmic Aqueous Formulation

[00415] A clinical trial is performed to investigate the efficacy and safety of ophthalmic aqueous formulations described herein in patents with myopia. In some instances, the study is open-label, single blind, or double blind study. Patient selection criteria include myopic refraction of at least 1.0D in both eyes, and additional factors such as astigmatism, a documented myopic progression, age, sex, and/or health conditions.

[00416] The patients are randomized to receive 0.05%, 0.01%, or 0.001 atropine aqueous formulation formulated in either H₂O or deuterated water (e.g., D₂O) once nightly in both eyes. Allocation ratio in some instances is defined based the patient population.

[00417] The patients are evaluated on day 0 (baseline), day 14, day 30, and then at 2, 3, 4, 5, 6, 8, 10, 12, 18, 20, 24, and 36 months. At each visit, best-coorrected distance logMar visual acuity (BCVA) is assessed by an optometrist, orthoptist, or ophthalmologist using the Early Treatment Diabetic Retinopathy study chart. Near visual acuity is assessed using best-corrected distance spectacle correction with a reduced logMar reading chart placed at 40cm under well-lit conditions. The near point of accommodation (NPA) is measured using a RAF rule using best-corrected distance spectacle correction. Patients are instructed to move the target inwards till the N5 print becomes slightly blurred and then outwards till it just becomes clear. Accommodation amplitude is calculated as the inverse of NPA. Mesopic pupil size is measured with Procyon 3000 pupillometer. Photopic pupil size is measured using the Neuroptics pupillometer.

[00418] Cycloplegic autorefraction is determined 30 minutes after 3 drops of cyclopentolate 1% are administered at 5 minutes apart using a Canon RK-F1 autorefractor. A Zeiss IOL Master, a non-contact partial coherence interferometry, is used to measure the ocular axial length.

[00419] The primary outcome is myopia progression over the time period of the study. Safety is assessed by adverse events including allergic reactions, irritation, or development of blurring of vision in one or both eyes.

Example 19 – Preparation of an Ointment Formulation Containing Atropine Sulfate

[00420] Atropine sulfate is mixed with the dispersing agent (e.g. polyethyleneglycol) under heating and sonication and this mixture is further thoroughly mixed with a molten ointment base (e.g. a mixture of wool wax, white petrolatum, and liquid paraffin). The mixture is placed in a pressure vessel, and sterilized at 125 °C for 30-45 minutes and cooled to room temperature. In another embodiment, autoclaving is conducted under nitrogen. The resulting ophthalmic ointment is aseptically filled into pre-sterilized containers (e.g. tubes).

Example 20 – Atropine-Mucus Penetrating Particle Composition

[00421] A 0.01% atropine-mucus penetrating particle composition was prepared utilizing a milling procedure. An aqueous dispersion containing atropine particles and an MPP-enabling mucus

penetrating agent was milled with grinding medium until particle size was reduced to approximately 200nm with a polydispersity index less than 0.15 as measured by dynamic light scattering. Additional agents such as preservatives are also added during the milling procedure. Subsequently, the atropine-MPP composition are be stored at temperatures of between about 15°C and about 25°C.

Example 21 – Atropine Sulfate-Mucus Penetrating Particle Composition

[00422] A 0.01% atropine sulfate-mucus penetrating particle composition was prepared utilizing a milling procedure. An aqueous dispersion containing atropine particles and an MPP-enabling mucus penetrating agent was milled with grinding medium until particle size was reduced to approximately 200nm with a polydispersity index less than 0.15 as measured by dynamic light scattering. Additional agents such as preservatives are also be added during the milling procedure. Subsequently, the atropine-MPP composition are be stored at temperatures of between about 15°C and about 25°C.

[00423] According to another aspect of the disclosure, described herein is an ophthalmic composition that comprises from about 0.001 wt% to about 0.05 wt% of a muscarinic antagonist and water, at a pH of from about 3.8 to about 7.5.

[00424] In some instances, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof. In some cases, the muscarinic antagonist is atropine. In some cases, the muscarinic antagonist is atropine sulfate.

[00425] In some instances, the ophthalmic composition comprises one of: at least about 80%, at least about 85%, at least about 90%, at least about 93%, at least about 95%, at least about 97%, at least about 98%, or at least about 99% of the muscarinic antagonist based on initial concentration after extended period of time under storage condition.

[00426] In some instances, the ophthalmic composition has a pH of one of: less than about 7.3, less than about 7.2, less than about 7.1, less than about 7, less than about 6.8, less than about 6.5, less than about 6.4, less than about 6.3, less than about 6.2, less than about 6.1, less than about 6, less than about 5.9, less than about 5.8, less than about 5.2, less than about 4.8, or less than about 4.2 after extended period of time under storage condition.

[00427] In some instances, the ophthalmic composition further has a potency of one of: at least 80%, at least 85%, at least 90%, at least 93%, at least 95%, at least 97%, at least 98%, or at least 99% after extended period of time under storage condition.

[00428] In some instances, the extended period of time is one of: about 1 week, about 2 weeks, about 3 weeks, about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 8 months, about 10 months, about 12 months, about 18 months, about 24 months, about 36 months, about 4 years, or about 5 years.

[00429] In some instances, the storage condition has a storage temperature of one of: about 25°C, about 40°C, or about 60°C. In some cases, the storage condition has a storage temperature of from about 2°C to about 10°C or from about 16°C to about 26°C. In some cases, the storage condition has a relative humidity of about 60% or about 75%.

[00430] In some instances, the ophthalmic composition is in the form of an aqueous solution. In some cases, the muscarinic antagonist is present in the composition at a concentration of one of: from about 0.001 wt% to about 0.04 wt%, from about 0.001 wt% to about 0.03 wt%, from about 0.001 wt% to about 0.025 wt%, from about 0.001 wt% to about 0.02 wt%, from about 0.001 wt% to about 0.01 wt%, from about 0.001 wt% to about 0.008 wt%, or from about 0.001 wt% to about 0.005 wt%.

[00431] In some instances, the ophthalmic composition further comprises an osmolarity adjusting agent. In some cases, the osmolarity adjusting agent is sodium chloride.

[00432] In some instances, the ophthalmic composition further comprises a preservative. In some cases, the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof.

[00433] In some instances, the ophthalmic composition further comprises a buffer agent. In some cases, the buffer agent is selected from borates, borate-polyol complexes, phosphate buffering agents, citrate buffering agents, acetate buffering agents, carbonate buffering agents, organic buffering agents, amino acid buffering agents, or combinations thereof.

[00434] In some instances, the ophthalmic composition further comprises a tonicity adjusting agent. In some cases, the tonicity adjusting agent is selected from sodium chloride, sodium nitrate, sodium sulfate, sodium bisulfate, potassium chloride, calcium chloride, magnesium chloride, zinc chloride, potassium acetate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium thiosulfate, magnesium sulfate, disodium hydrogen phosphate, sodium dihydrogen phosphate, potassium dihydrogen phosphate, dextrose, mannitol, sorbitol, dextrose, sucrose, urea, propylene glycol, glycerin, or a combination thereof.

[00435] In some instances, the ophthalmic composition is stored in a plastic container. In some cases, the material of the plastic container comprises low-density polyethylene (LDPE).

[00436] In some instances, the ophthalmic composition has a dose-to-dose muscarinic antagonist concentration variation of one of: less than 50%, less than 40%, less than 30%, less than 20%, less than 10%, or less than 5%. In some cases, the dose-to-dose muscarinic antagonist concentration variation is based on one of: 10 consecutive doses, 8 consecutive doses, 5 consecutive doses, 3 consecutive doses, or 2 consecutive doses.

[00437] In some instances, the ophthalmic composition has a pH of one of: from about 3.8 to about 7.5, from about 4.2 to about 7.5, from about 4.8 to about 7.3, from about 5.2 to about 7.2, from about 5.8 to about 7.1, from about 6.0 to about 7.0, or from about 6.2 to about 6.8.

[00438] In some instances, the ophthalmic composition further comprises a pH adjusting agent. In some cases, the pH adjusting agent comprises HCl, NaOH, CH₃COOH, or C₆H₈O₇.

[00439] In some instances, the ophthalmic composition comprises one of: less than 5% of D₂O, less than 4% of D₂O, less than 3% of D₂O, less than 2% of D₂O, less than 1% of D₂O, less than 0.5% of D₂O, less than 0.1% of D₂O, or 0% D₂O. In some cases, the ophthalmic composition is essentially free of D₂O.

[00440] In some instances, the ophthalmic composition further comprises a pharmaceutically acceptable carrier.

[00441] In some instances, the ophthalmic composition is formulated as an ophthalmic solution for the treatment of an ophthalmic disorder. In some cases, the ophthalmic disorder or condition is pre-myopia, myopia, or progression of myopia.

[00442] In some instances, the ophthalmic composition is not formulated as an injectable formulation.

[00443] While preferred embodiments of the present disclosure have been shown and described herein, such embodiments are provided by way of example only. Various alternatives to the embodiments described herein are optionally employed in practicing the disclosure. It is intended that the following claims define the scope of the disclosure and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

WHAT IS CLAIMED IS:

1. An ophthalmic composition, comprising from about 0.001 wt% to about 0.05 wt% of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9, wherein the muscarinic antagonist does not extend singlet oxygen lifetime.
2. The ophthalmic composition of claim 1, wherein the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolomine, tropicamide, cyclopentolate, pirenzapine, homatropine, or a combination thereof.
3. The ophthalmic composition of claim 1 or 2, wherein the muscarinic antagonist quenches photogenerated singlet oxygen species in the composition.
4. The ophthalmic composition of any one of the claims 1-3, wherein the muscarinic antagonist comprises atropine, atropine sulfate, scopolomine, homatropine, or a combination thereof.
5. The ophthalmic composition of any one of the claims 1-4, wherein the muscarinic antagonist is atropine or atropine sulfate.
6. The ophthalmic composition of any one of the claims 1-5, wherein the ophthalmic composition has a pD of one of: less than about 7.9, less than about 7.5, less than about 7.3, less than about 7.2, less than about 7.1, less than about 7, less than about 6.8, less than about 6.5, less than about 6.4, less than about 6.3, less than about 6.2, less than about 6.1, less than about 6, less than about 5.9, less than about 5.8, less than about 5.7, less than about 5.2, or less than about 4.8 after extended period of time under storage condition.
7. The ophthalmic composition of any one of the claims 1-6, wherein the ophthalmic composition has a pD of one of: less than about 7.9, less than about 7.8, less than about 7.7, less than about 7.6, less than about 7.5, less than about 7.4, less than about 7.3, less than about 7.2, less than about 7.1, less than about 7, less than about 6.9, less than about 6.8, less than about 6.7, less than about 6.6, less than about 6.5, less than about 6.4, less than about 6.3, less than about 6.2, less than about 6.1, less than about 6.
8. The ophthalmic composition of any one of the claims 1-7, wherein the ophthalmic composition further has a potency of one of: at least 80%, at least 85%, at least 90%, at least 93%, at least

95%, at least 97%, at least 98%, or at least 99% after extended period of time under storage condition.

9. The ophthalmic composition of any one of the claims 1-8, wherein the extended period of time is one of: about 1 week, about 2 weeks, about 3 weeks, about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 8 months, about 10 months, about 12 months, about 18 months, about 24 months, about 36 months, about 4 years, or about 5 years.
10. The ophthalmic composition of any one of the claims 1-9, wherein the storage condition has a storage temperature of from about 2°C to about 10°C or from about 16°C to about 26°C.
11. The ophthalmic composition of any one of the claims 1-10, wherein the muscarinic antagonist is present in the composition at a concentration of one of: from about 0.001 wt% to about 0.04 wt%, from about 0.001 wt% to about 0.03 wt%, from about 0.001 wt% to about 0.025 wt%, from about 0.001 wt% to about 0.02 wt%, from about 0.001 wt% to about 0.01 wt%, from about 0.001 wt% to about 0.008 wt%, or from about 0.001 wt% to about 0.005 wt%.
12. The ophthalmic composition of any one of the claims 1-11, wherein the ophthalmic composition further comprises an osmolarity adjusting agent, a preservative, a buffer agent, a tonicity adjusting agent, or a combination thereof.
13. The ophthalmic composition of any one of the claims 1-12, wherein the ophthalmic composition further comprises a pD adjusting agent.
14. The ophthalmic composition of claim 13, wherein the pD adjusting agent comprises DCl, NaOD, CD₃COOD, or C₆D₈O₇.
15. The ophthalmic composition of any one of the claims 1-14, wherein the ophthalmic composition comprises one of: less than 5% of H₂O, less than 4% of H₂O, less than 3% of H₂O, less than 2% of H₂O, less than 1% of H₂O, less than 0.5% of H₂O, less than 0.1% of H₂O, or 0% of H₂O.
16. The ophthalmic composition of any one of the claims 1-15, wherein the ophthalmic composition is not formulated as an injectable formulation.
17. The ophthalmic composition of any one of the claims 1-16, wherein the ophthalmic composition does not comprise water-hydrolyzable derivatives of α-amino or α-hydroxy- carboxylic acids.

18. The ophthalmic composition of any one of the claims 1-17, wherein the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof.
19. A method of treating an ophthalmic disorder comprising administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition of claims 1-18.
20. A method of arresting myopia development or preventing myopia development, comprising administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition of claims 1-18.

Fig. 1A

Weeks							
	Temp (°C)	0	1	1.571429	2.142857	3.428571	6.571429
T1	25	0.08			0.88		2.81
T2	40	0.08		3.47		4.48	

Fig. 1B

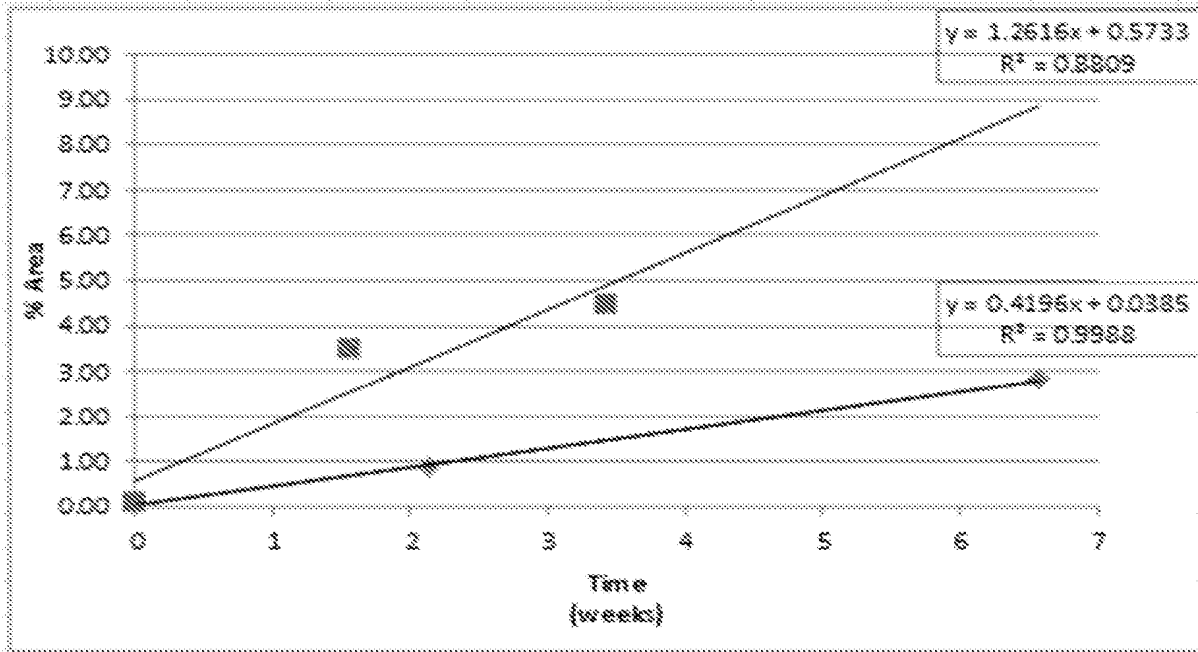


Fig. 1C

Formulation:		Average of Analysts		
Stability Prediction:		RRT 0.87		
	spec limit:	0.50	% (not more than)	
			shelf life	
			weeks	months
rate	1.24844 at 40C		0.4	0.1
rate	0.60617 at 30C		0.8	0.2
rate	0.41477 at 25C		1.2	0.3
rate	0.07932 at 2-8C		6.3	1.6
rate	0.00694 at -20C		N/A	N/A

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Fig. 2A

		Weeks				
	Temp (°C)	0	1	2.142857	4	6.571429
T1	25	0.08		0.9		2.8
T2	60	0.08	10.5		11.3	

Fig. 2B

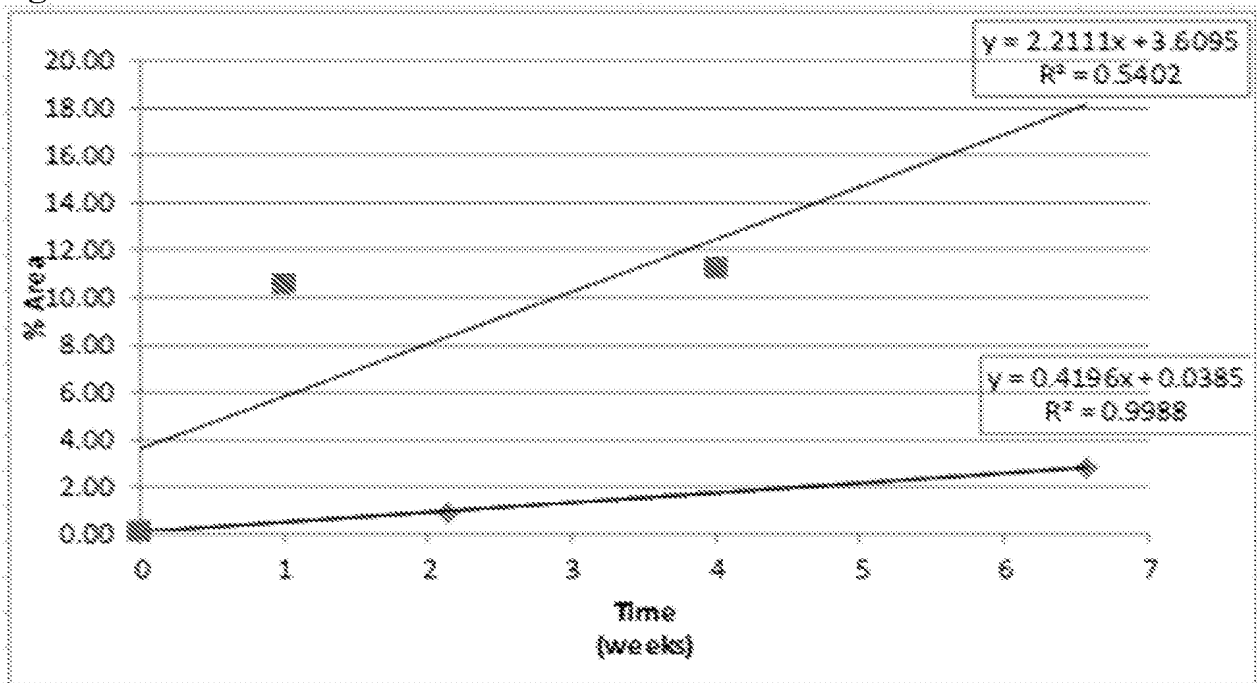


Fig. 2C

Formulation:		Average of Analysts		
Stability Prediction:		RRT 0.87		
	spec limit:	0.50	% (not more than)	
			shelf life	
			weeks	months
rate	0.88876 at 40C		0.6	0.1
rate	0.54051 at 30C		0.9	0.2
rate	0.41627 at 25C		1.2	0.3
rate	0.13331 at 2-8C		3.8	0.9
rate	0.02493 at -20C		N/A	N/A

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Fig. 3

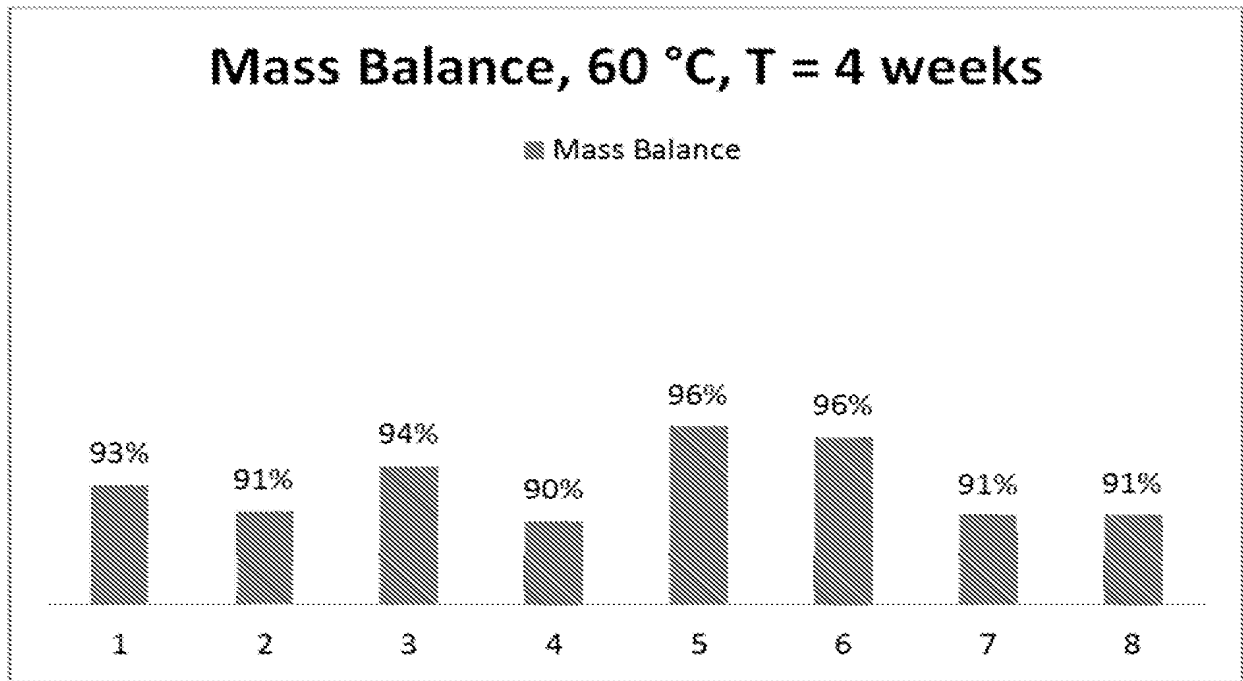


Fig. 4

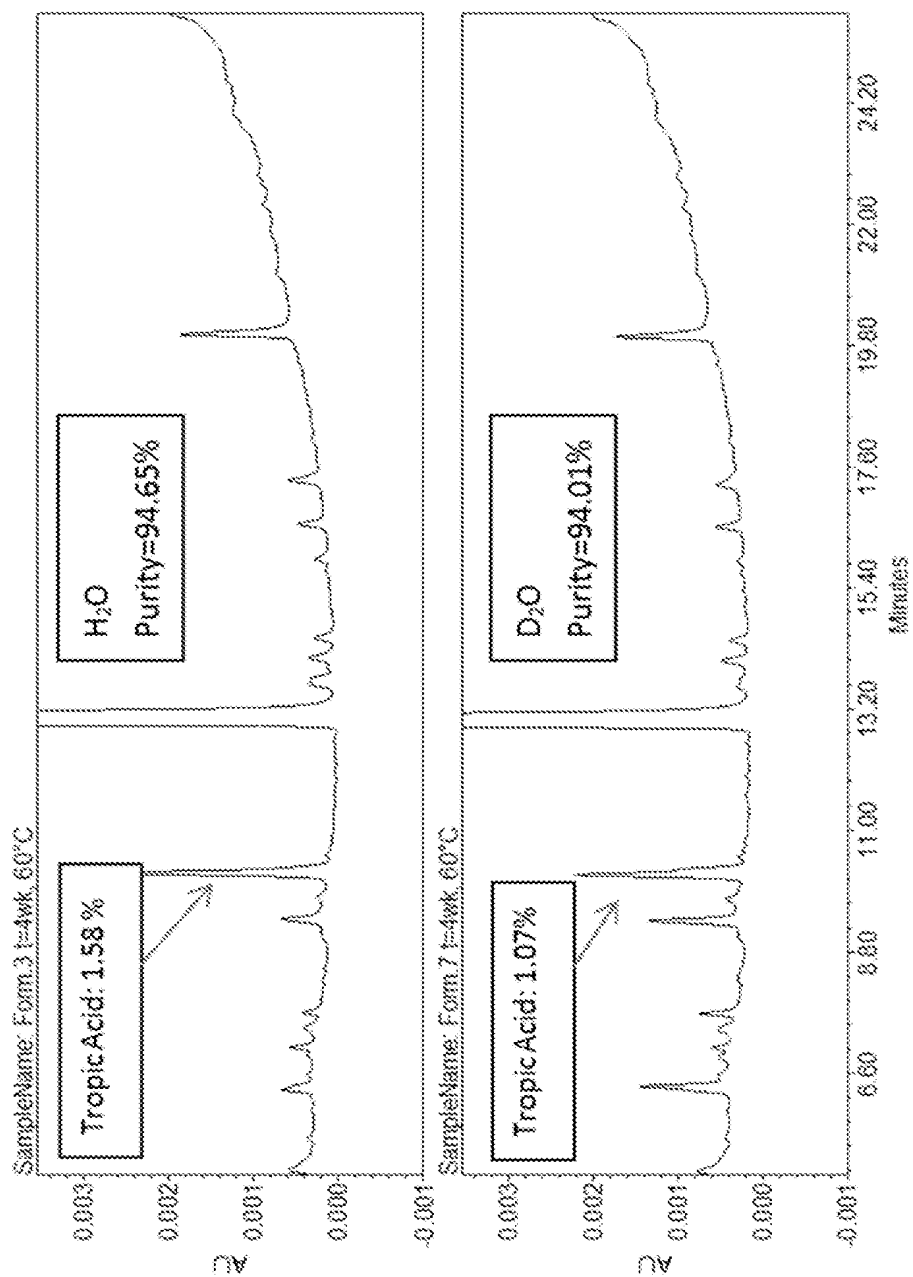


Fig. 5

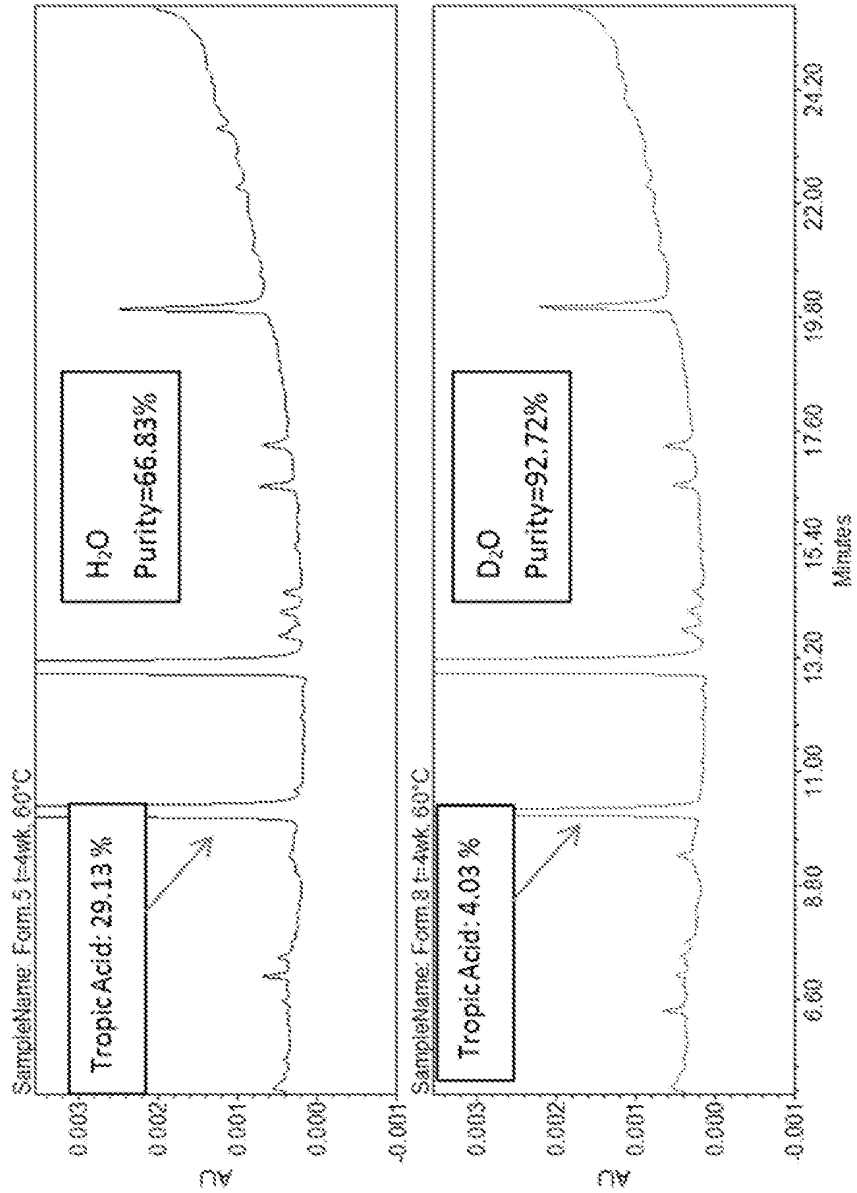


Fig. 6

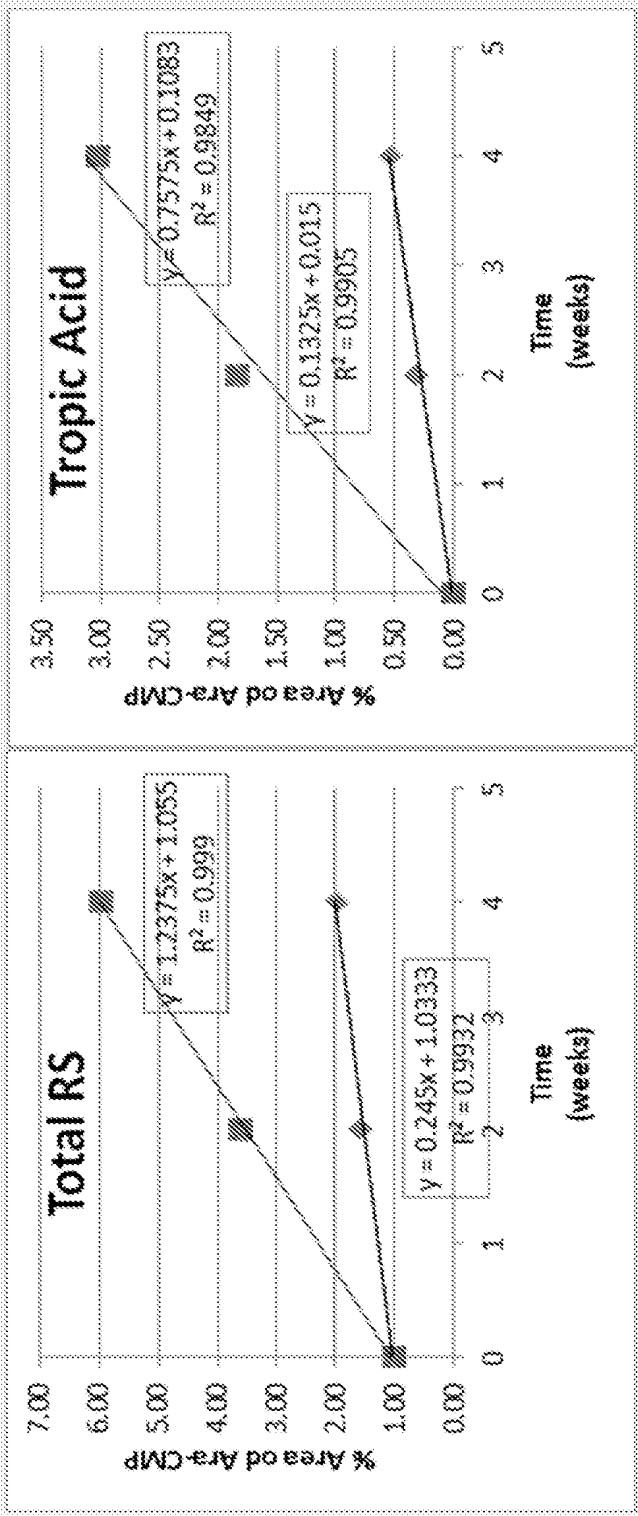


Fig. 7

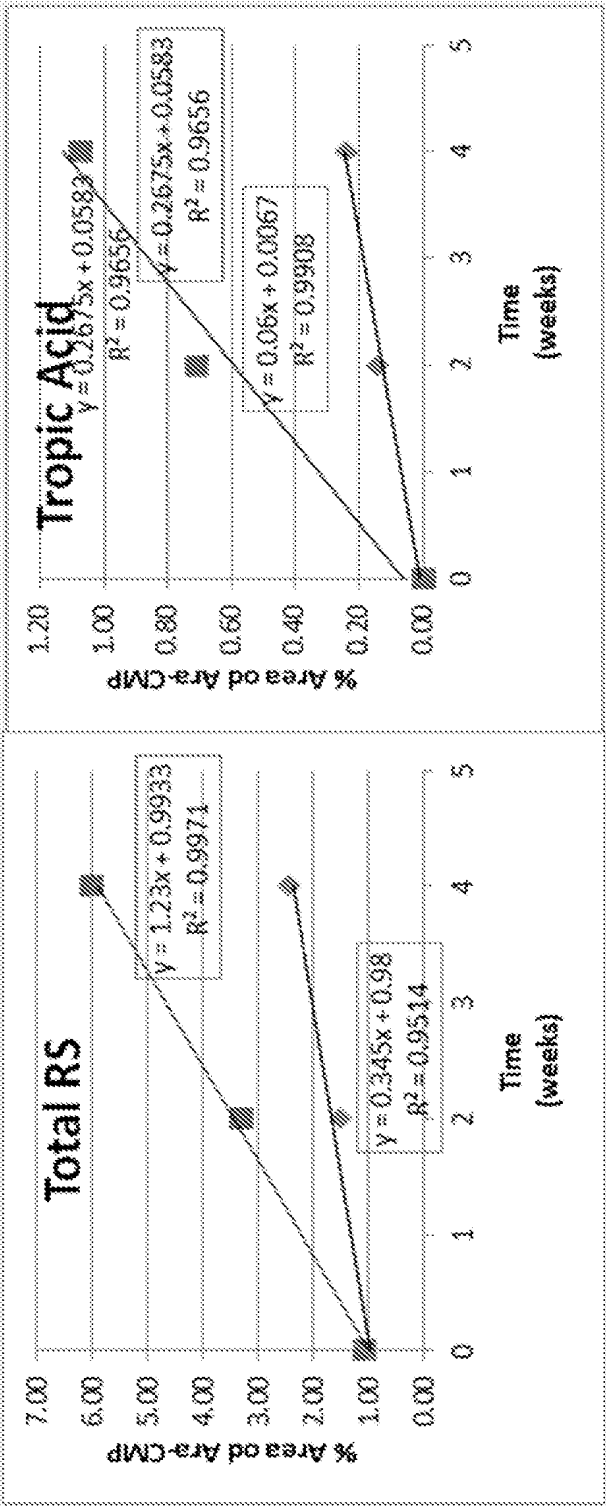


Fig. 8

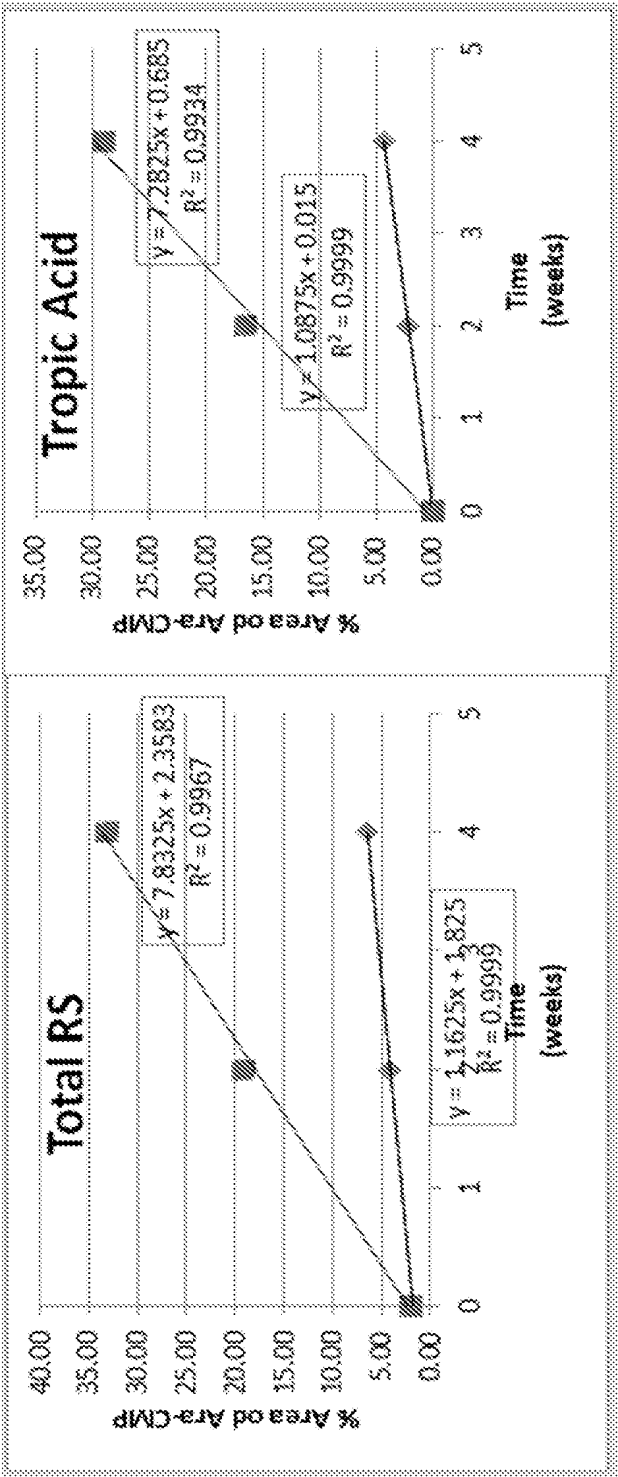


Fig. 9

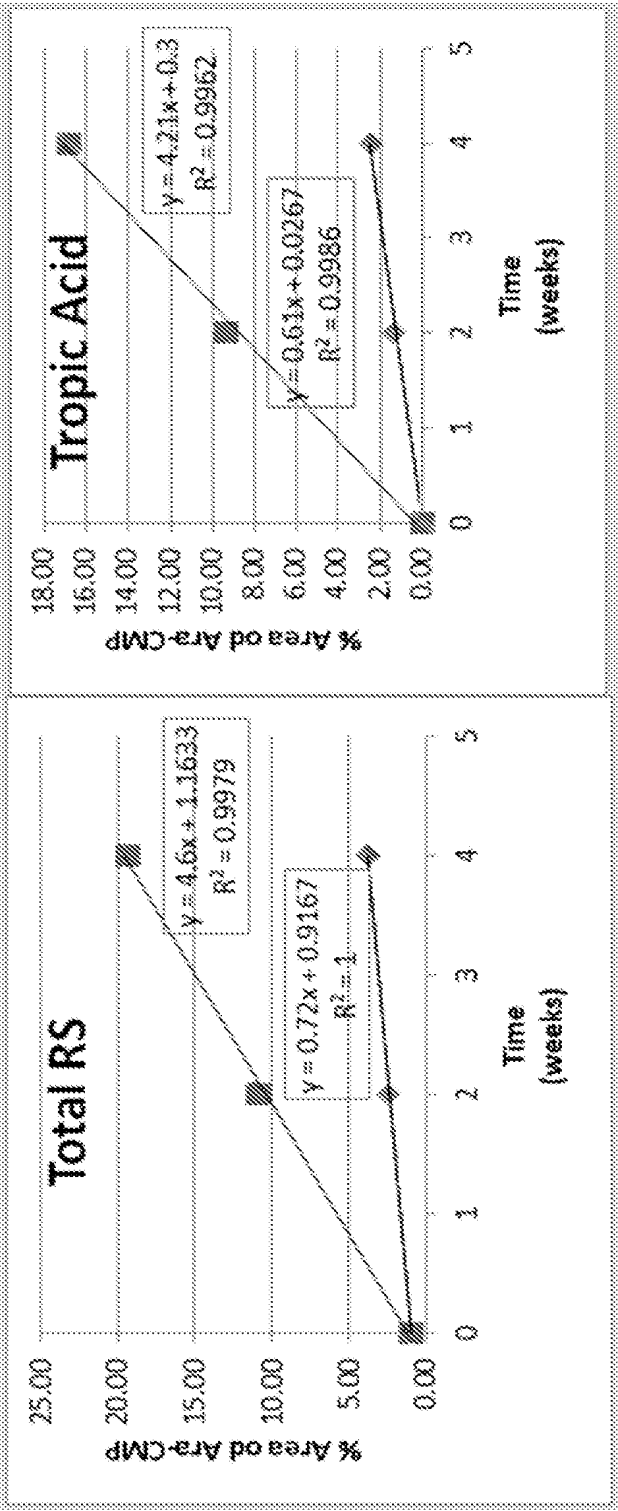


Fig. 10

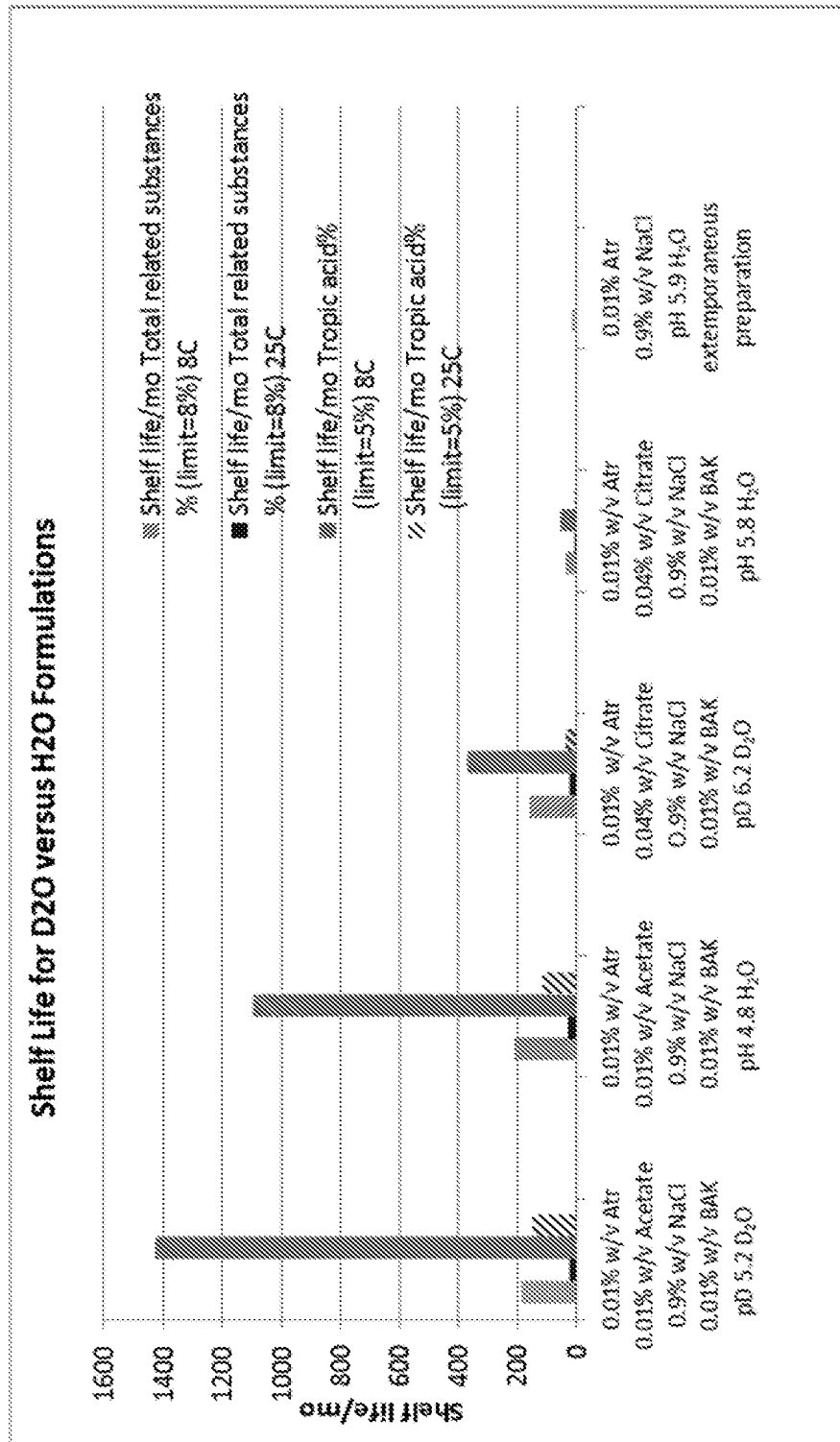


Fig. 11A

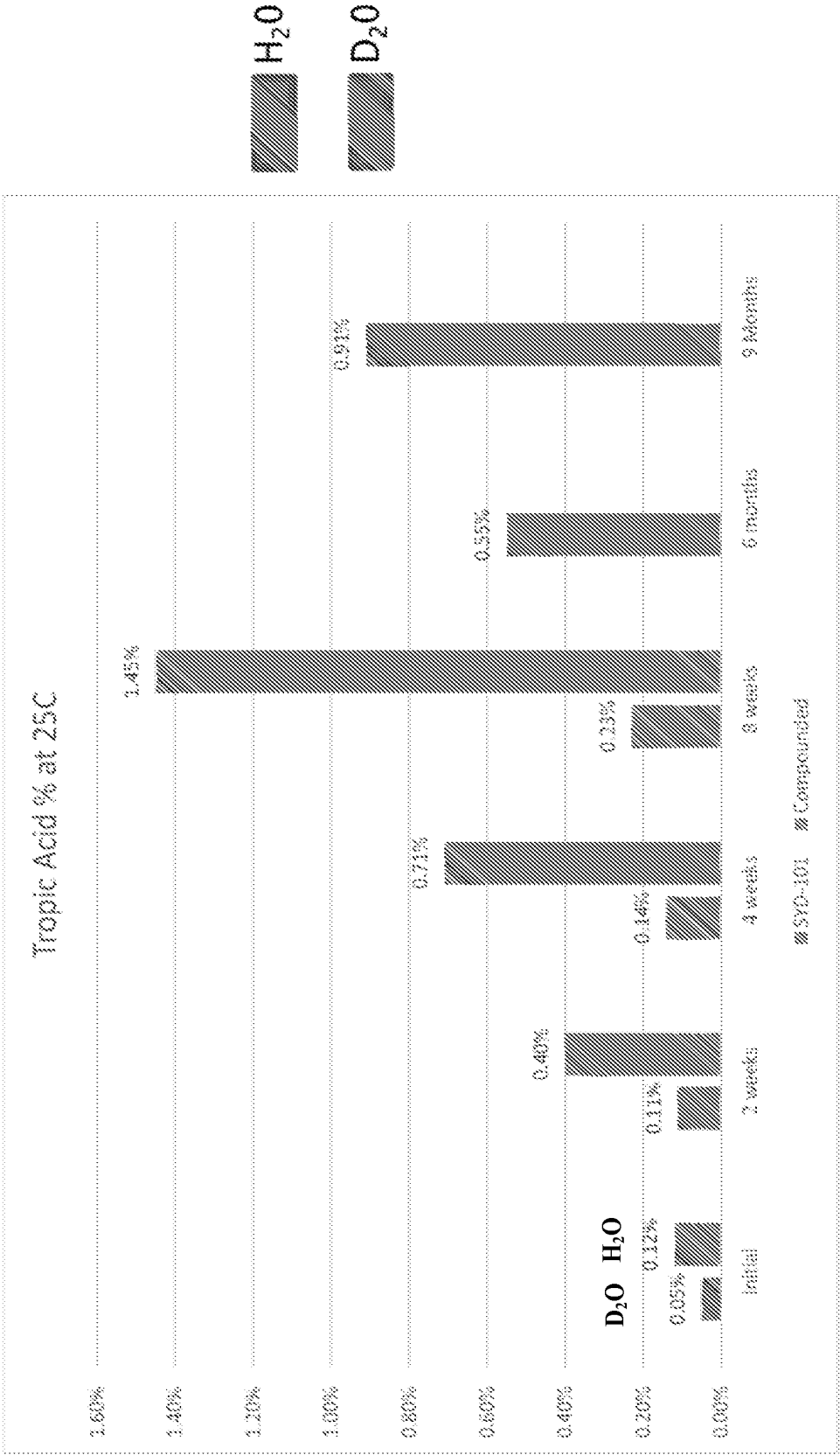


Fig. 11B

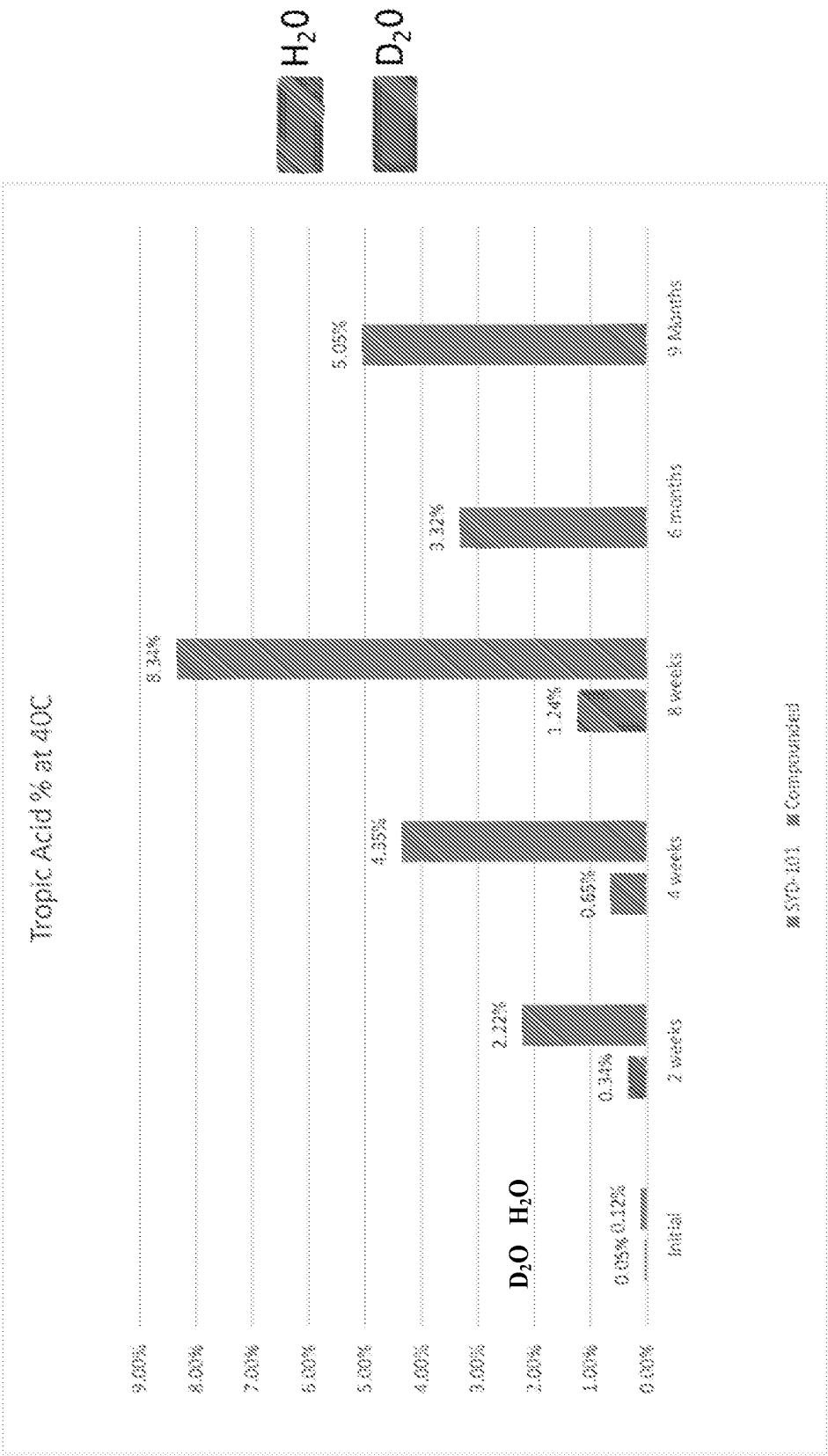
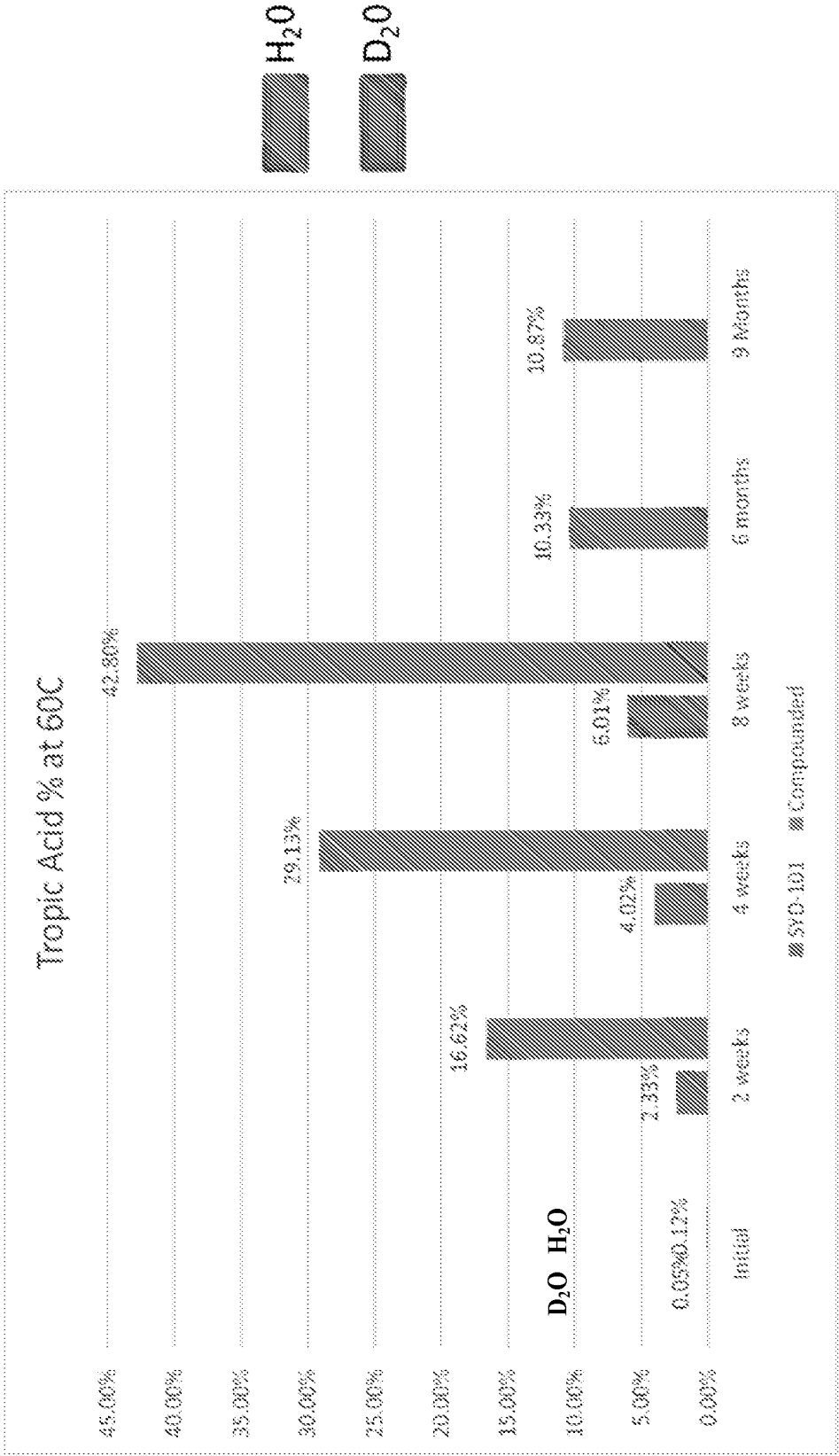


Fig. 11C



Electronic Acknowledgement Receipt

EFS ID:	33428964
Application Number:	15976279
International Application Number:	
Confirmation Number:	1256
Title of Invention:	Atropine Pharmaceutical Compositions
First Named Inventor/Applicant Name:	Navneet Puri
Customer Number:	149344
Filer:	Martin Fessenmaier/Nia Martinez
Filer Authorized By:	Martin Fessenmaier
Attorney Docket Number:	102843.0006US2
Receipt Date:	09-AUG-2018
Filing Date:	10-MAY-2018
Time Stamp:	19:23:46
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	IDS.pdf	613027	no	5
			cdf52fa6ae23d819fb5992e0dccc3d5f5eff08ee		

Warnings:

Information:					
2	Non Patent Literature	Acta_Chem_Scand_1968_1.pdf	1581562	no	13
			44a82690fbd585afa75d7e17aa58b330bee10ac9		
Warnings:					
Information:					
3	Non Patent Literature	December_2016_Clinical_Update_Refractio	3329211	no	3
			78e73b0eb8c67e962c46d48db221e429c20f0624		
Warnings:					
Information:					
4	Non Patent Literature	Schier_et_al-2004-Academic_Emergency_Medicine_1.pdf	532555	no	6
			b739b273474a189e315aad9162a0ce51ac884a3		
Warnings:					
Information:					
5	Foreign Reference	WO2015200361A.pdf	1655382	no	115
			9ec4ce17666a1b651465102901d7aedfd4ca7542		
Warnings:					
Information:					
6	Foreign Reference	WO2012161655A1_.pdf	1690217	no	32
			07a666f337853e0556d4e7a74f1a4be411e130c5		
Warnings:					
Information:					
7	Foreign Reference	WO2017204262A_.pdf	2285541	no	38
			56fce1cac42f249e25e18cb8529d64de1eae4e65		
Warnings:					
Information:					
8	Foreign Reference	WO2016172712A2.pdf	7530952	no	124
			fb0dd2f678c7ee63e6f8cb0f572e960ac2501c6f		
Warnings:					
Information:					
Total Files Size (in bytes):			19218447		

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.



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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
15/976,279	05/10/2018	1629	865	102843.0006US2	20	1

CONFIRMATION NO. 1256

FILING RECEIPT



Date Mailed: 06/05/2018

149344
Umberg Zipser LLP
1920 Main Street Suite 750
Irvine, CA 92614

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Navneet Puri, Lebanon, NJ;
Prem Sagar Akasapu, Edison, NJ;
Irfan A. Mohammed, Cherry Hill, NJ;
Kumaresh Soppimath, Skillman, NJ;
Iouri V. Ilitchev, Hillsborough, NJ;
Tao Zhang, Towaco, NJ;

Applicant(s)

Nevakar Inc., Bridgewater, NJ;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This appln claims benefit of 62/505,027 05/11/2017

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see <http://www.uspto.gov> for more information.) - None.

Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 06/04/2018

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/976,279**

Projected Publication Date: 11/15/2018

Non-Publication Request: No

Early Publication Request: No

**** SMALL ENTITY ****

Title

Atropine Pharmaceutical Compositions

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

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Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at <http://www.uspto.gov/web/offices/pac/doc/general/index.html>.

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Title 37, Code of Federal Regulations, 5.11 & 5.15

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number
15/976,279

APPLICATION AS FILED - PART I

(Column 1)		(Column 2)
FOR	NUMBER FILED	NUMBER EXTRA
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A
TOTAL CLAIMS (37 CFR 1.16(j))	20 minus 20 =	*
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).	
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))		

* If the difference in column 1 is less than zero, enter "0" in column 2.

SMALL ENTITY

RATE(\$)	FEE(\$)
N/A	75
N/A	330
N/A	380
x 50 =	0.00
x 230 =	0.00
	0.00
	0.00
TOTAL	785

OR

OTHER THAN SMALL ENTITY

RATE(\$)	FEE(\$)
N/A	
N/A	
N/A	
TOTAL	

APPLICATION AS AMENDED - PART II

	(Column 1)	(Column 2)	(Column 3)
AMENDMENT A		CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR
	Total (37 CFR 1.16(i))	*	Minus **
	Independent (37 CFR 1.16(h))	*	Minus ***
	Application Size Fee (37 CFR 1.16(s))		
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))		

SMALL ENTITY

RATE(\$)	ADDITIONAL FEE(\$)
x =	
x =	
TOTAL ADD'L FEE	

OR

OTHER THAN SMALL ENTITY

RATE(\$)	ADDITIONAL FEE(\$)
x =	
x =	
TOTAL ADD'L FEE	

	(Column 1)	(Column 2)	(Column 3)
AMENDMENT B		CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR
	Total (37 CFR 1.16(i))	*	Minus **
	Independent (37 CFR 1.16(h))	*	Minus ***
	Application Size Fee (37 CFR 1.16(s))		
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))		

RATE(\$)	ADDITIONAL FEE(\$)
x =	
x =	
TOTAL ADD'L FEE	

OR

RATE(\$)	ADDITIONAL FEE(\$)
x =	
x =	
TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of
Invention

Atropine Pharmaceutical Compositions

As the below named inventor, I hereby declare that:

This declaration
is directed to:

☐

The attached application, or

☒

United States application or PCT international application number 15/976,279

filed on May 10, 2018

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

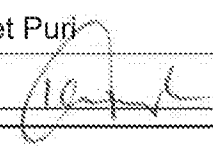
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LEGAL NAME OF INVENTOR

Inventor: Navneet Puri

Date (Optional): 5/11/18

Signature: 

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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LEGAL NAME OF INVENTOR

Inventor: Prem Sagar Akasapu

Date (Optional): 11 May 2018

Signature: *Prem Sagar*

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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LEGAL NAME OF INVENTOR

Inventor: Irfan A. Mohammed

Date (Optional): 11 May 2018

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)**Title of
Invention**

Atropine Pharmaceutical Compositions

As the below named inventor, I hereby declare that:

This declaration
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The attached application, or

United States application or PCT international application number 15/976,279filed on May 10, 2018

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LEGAL NAME OF INVENTORInventor: Kumaresh SoppimathDate (Optional): 11 May 2018Signature: [Signature]

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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Title of Invention	Atropine Pharmaceutical Compositions

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I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

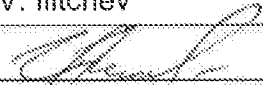
I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Iouri V. Ilitchev Date (Optional): 11 May 2018

Signature: 

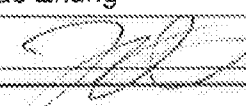
Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/D1 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

**DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN
APPLICATION DATA SHEET (37 CFR 1.76)**

Title of Invention	Atropine Pharmaceutical Compositions	
As the below named inventor, I hereby declare that: This declaration is directed to: ☐ The attached application, or ☒ United States application or PCT international application number <u>15/976,279</u> filed on <u>May 10, 2018</u> The above-identified application was made or authorized to be made by me. I believe that I am the original inventor or an original joint inventor of a claimed invention in the application. I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both. WARNING: Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.		
LEGAL NAME OF INVENTOR		
Inventor:	Tao Zhang	Date (Optional): <u>May 11, 2018</u>
Signature:		
Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.		

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-8199 and select option 2.

Electronic Acknowledgement Receipt

EFS ID:	32633740
Application Number:	15976279
International Application Number:	
Confirmation Number:	1256
Title of Invention:	Atropine Pharmaceutical Compositions
First Named Inventor/Applicant Name:	Navneet Puri
Customer Number:	149344
Filer:	Martin Fessenmaier/Dani Moroz
Filer Authorized By:	Martin Fessenmaier
Attorney Docket Number:	102843.0006US2
Receipt Date:	15-MAY-2018
Filing Date:	
Time Stamp:	19:21:16
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Oath or Declaration filed	Declaration_Puri_signed.pdf	80993	no	1
			ed491b6ef5cc03f33f8d63f02bd0411c0ced867a		

Warnings:

Information:					
2	Oath or Declaration filed	Declaration_Akasapu_signed.pdf	79953	no	1
			3288ad1a145993035da508942d00587a3d5ba319		
Warnings:					
Information:					
3	Oath or Declaration filed	Declaration_Mohammed_signed.pdf	80512	no	1
			a2eac3f9252cdc242000e4499258bdec5ad3d049		
Warnings:					
Information:					
4	Oath or Declaration filed	Declaration-Soppimath_signed.pdf	79582	no	1
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Warnings:					
Information:					
5	Oath or Declaration filed	Declaration_Ilitchev_signed.pdf	89067	no	1
			29699aed23d37784f1171bd801953583d15407b5		
Warnings:					
Information:					
6	Oath or Declaration filed	Declaration_Zhang_signed.pdf	78171	no	1
			bd0255e962f1f4f1eb395c8292d28ab6916f994e		
Warnings:					
Information:					
Total Files Size (in bytes):			488278		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

**CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION
UNDER 37 CFR 1.102(e) (Page 1 of 1)**

First Named Inventor:	Navneet Puri	Nonprovisional Application Number (if known):	
Title of Invention:	Atropine Pharmaceutical Compositions		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently \$0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.
2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.
3. The applicable box is checked below:
 - I. ☒ **Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)**
 - i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.
---OR---
(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.
 - ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, or the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.
 - II. ☐ **Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)**
 - i. A request for continued examination has been filed with, or prior to, this form.
 - ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
 - iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
 - iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
 - v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature <u>/Martin Fessenmaier/</u>	Date <u>May 10, 2018</u>
Name (Print/Typed) <u>Martin Fessenmaier</u>	Practitioner Registration Number <u>46697</u>

Note: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.*

☒ *Total of 1 forms are submitted.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	102843.0006US2
		Application Number	
Title of Invention	Atropine Pharmaceutical Compositions		
The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76. This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.			

Secrecy Order 37 CFR 5.2:

☐	Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor	1				Remove
Legal Name					
Prefix	Given Name	Middle Name	Family Name	Suffix	
	Navneet		Puri		
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service					
City	Lebanon	State/Province	NJ	Country of Residence	US

Mailing Address of Inventor:

Address 1	40 Still Hollow Road				
Address 2					
City	Lebanon	State/Province	NJ		
Postal Code	08833	Country i	US		

Inventor	2				Remove
Legal Name					
Prefix	Given Name	Middle Name	Family Name	Suffix	
	Prem	Sagar	Akasapu		
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service					
City	Edison	State/Province	NJ	Country of Residence	US

Mailing Address of Inventor:

Address 1	906 Rivendell Way				
Address 2					
City	Edison	State/Province	NJ		
Postal Code	08817	Country i	US		

Inventor	3				Remove
Legal Name					
Prefix	Given Name	Middle Name	Family Name	Suffix	
	Irfan	A.	Mohammed		
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service					

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	102843.0006US2
		Application Number	
Title of Invention	Atropine Pharmaceutical Compositions		

City	Cherry Hill	State/Province	NJ	Country of Residence	US

Mailing Address of Inventor:

Address 1	1900 Frontage Road, Apt. 1113				
Address 2					
City	Cherry Hill	State/Province	NJ		
Postal Code	08034	Country	US		
Inventor	4				Remove
Legal Name					

Prefix	Given Name	Middle Name	Family Name	Suffix	
	Kumaresh		Soppimath		
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service					
City	Skillman	State/Province	NJ	Country of Residence	US

Mailing Address of Inventor:

Address 1	97 Autumn Lane				
Address 2					
City	Skillman	State/Province	NJ		
Postal Code	08558	Country	US		
Inventor	5				Remove
Legal Name					

Prefix	Given Name	Middle Name	Family Name	Suffix	
	Jouri	V.	Ilitchev		
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service					
City	Hillsborough	State/Province	NJ	Country of Residence	US

Mailing Address of Inventor:

Address 1	21 Reed Road				
Address 2					
City	Hillsborough	State/Province	NJ		
Postal Code	08844	Country	US		
Inventor	6				Remove
Legal Name					

Prefix	Given Name	Middle Name	Family Name	Suffix	
	Tao		Zhang		
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service					
City	Towaco	State/Province	NJ	Country of Residence	US

Application Data Sheet 37 CFR 1.76		Attorney Docket Number		102843.0006US2	
		Application Number			
Title of Invention		Atropine Pharmaceutical Compositions			
Mailing Address of Inventor:					
Address 1		62 Douglas Drive			
Address 2					
City	Towaco	State/Province	NJ		
Postal Code	07082	Country	US		
All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the Add button.					

Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).			
☐ An Address is being provided for the correspondence Information of this application.			
Customer Number	149344		
Email Address	patents@umbergzipser.com	Add Email	Remove Email

Application Information:

Title of the Invention	Atropine Pharmaceutical Compositions		
Attorney Docket Number	102843.0006US2	Small Entity Status Claimed	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	1	Suggested Figure for Publication (if any)	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)
☐ Request Not to Publish. I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application has not and will not be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	102843.0006US2
		Application Number	
Title of Invention	Atropine Pharmaceutical Compositions		

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	☒ Customer Number	☐ US Patent Practitioner	☐ Limited Recognition (37 CFR 11.9)
Customer Number	149344		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending	Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Claims benefit of provisional	62505027	2017-05-11
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the Add button.			Add

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)ⁱ the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Application Number	Country ⁱ	Filing Date (YYYY-MM-DD)	Remove
			Access Code ⁱ (if applicable)
Additional Foreign Priority Data may be generated within this form by selecting the Add button.			Add

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	102843.0006US2
		Application Number	
Title of Invention	Atropine Pharmaceutical Compositions		

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐	This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013. NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	102843.0006US2
		Application Number	
Title of Invention	Atropine Pharmaceutical Compositions		

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	102843.0006US2
		Application Number	
Title of Invention	Atropine Pharmaceutical Compositions		

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant	1	Remove
If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section. Clear		
☒ Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
Person to whom the inventor is obligated to assign.		Person who shows sufficient proprietary interest
If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:		
Name of the Deceased or Legally Incapacitated Inventor:		
If the Applicant is an Organization check here. ☒		
Organization Name	Nevakar Inc.	
Mailing Address Information For Applicant:		
Address 1	1019 Route 202/206, Bldg. K	
Address 2		
City	Bridgewater	State/Province
Country	US	Postal Code
Phone Number		Fax Number
Email Address		
Additional Applicant Data may be generated within this form by selecting the Add button. Add		

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	102843.0006US2
		Application Number	
Title of Invention	Atropine Pharmaceutical Compositions		

Assignee	1			
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Signature	/Martin Fessenmaier/		Date (YYYY-MM-DD)	2018-05-10
First Name	Martin	Last Name	Fessenmaier	Registration Number
				46697
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Electronic Patent Application Fee Transmittal

Application Number:				
Filing Date:				
Title of Invention:	ATROPINE PHARMACEUTICAL COMPOSITIONS			
First Named Inventor/Applicant Name:	Navneet Puri			
Filer:	Martin Fessenmaier/Dani Moroz			
Attorney Docket Number:	102843.0006US2			
Filed as Small Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
UTILITY FILING FEE (ELECTRONIC FILING)	4011	1	75	75
UTILITY SEARCH FEE	2111	1	330	330
UTILITY EXAMINATION FEE	2311	1	380	380
Pages:				
Claims:				
Miscellaneous-Filing:				
LATE FILING FEE FOR OATH OR DECLARATION	2051	1	80	80
Petition:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				865

Electronic Acknowledgement Receipt

EFS ID:	32590748
Application Number:	15976279
International Application Number:	
Confirmation Number:	1256
Title of Invention:	ATROPINE PHARMACEUTICAL COMPOSITIONS
First Named Inventor/Applicant Name:	Navneet Puri
Customer Number:	149344
Filer:	Martin Fessenmaier/Dani Moroz
Filer Authorized By:	Martin Fessenmaier
Attorney Docket Number:	102843.0006US2
Receipt Date:	10-MAY-2018
Filing Date:	
Time Stamp:	15:11:56
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	\$865
RAM confirmation Number	051118INTEFSW15124700
Deposit Account	
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File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		Application-01b_NVK002_6US2_Rev01.pdf	2322480	yes	40
			91852ddda1a451a2ccbd3a72dcf94cae0d343b8e		
	Multipart Description/PDF files in .zip description				
	Document Description	Start	End		
	Specification	1	35		
	Claims	36	38		
	Abstract	39	39		
	Drawings-only black and white line drawings	40	40		
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			43e342cee3c09870a245fe46b75bab3afd42bdb2		
Warnings:					
Information:					
3	Application Data Sheet	ADS.pdf	1273214	no	10
			99ef1eba8f3a4c600ae0883b477a361c63ca2484		
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	36559	no	2
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New International Application Filed with the USPTO as a Receiving Office

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ATROPINE PHARMACEUTICAL COMPOSITIONS

[0001] This application claims priority to a copending US provisional application with serial number 62/505,027, which was filed May 11, 2017.

Field of the Invention

[0002] The field of the invention is pharmaceutical compositions comprising atropine sulfate, especially as it relates to various storage stable, ready-to-use, preservative free compositions, and method of manufacturing such compositions.

Background

[0003] The background description includes information that may be useful in understanding the present invention. It is not an admission that any of the information provided herein is prior art or relevant to the presently claimed invention, or that any publication specifically or implicitly referenced is prior art.

[0004] All publications and patent applications herein are incorporated by reference to the same extent as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Where a definition or use of a term in an incorporated reference is inconsistent or contrary to the definition of that term provided herein, the definition of that term provided herein applies and the definition of that term in the reference does not apply.

[0005] Atropine is the tropine ester of tropic acid and is generally available as the sulfate salt. Nonenzymatic spontaneous hydrolysis of aqueous atropine yields tropine and tropic acid that are nontoxic but do not have biological activity in ophthalmic use. Stability has been tested, for example, for certain injectable formulations and degradation was observed over time for in-date and out-of-date formulations (*Acad Emerg Med April* 2004, Vol. 11, No. 4:329-334). Notably, atropine loss was significant in most cases, but less than 25% of the starting concentration. However, these formulations included atropine at high concentrations between 0.4 mg/ml and 2 mg/ml and had a very low pH (typically equal or less than pH4), which is in most cases unsuitable for ophthalmic use.

[0006] In ophthalmic use, atropine is marketed as Atropine Care (Akorn) formulated as a 1% drug solution for treatment of amblyopia and further contains 0.01% w/w of the preservative benzalkonium chloride. In another indication, atropine has also been used in several pediatric studies to slow down the progression of myopia. More specifically, children who received topically administered atropine drops had a slower disease progression than a control group in the same study. Advantageously, children receiving eye drops containing low atropine concentrations (e.g., in the range of 0.01-0.05%% w/v (0.01% w/w)) had significantly less photophobia and other side effects (see e.g., *Ophthalmology*, 2015:1-9). Indeed, the use of low-dose (i.e., 0.01%) atropine has become a preferred treatment of choice in slowing the progression of myopia. Unfortunately, the toxic effects of benzalkonium chloride have been demonstrated in the lab and in the clinic, and include tear film instability, loss of goblet cells, conjunctival squamous metaplasia and apoptosis, disruption of the corneal epithelium barrier, and damage to deeper ocular tissues (see e.g., *Prog Retin Eye Res.* 2010 Jul 29(4):312-34).

[0007] In still further known compositions and methods, atropine formulations are described in WO 2017/204262 that include various buffer ingredients and water soluble polymers in which most formulations had a pH of about 4.3, 4.5, or 5.0 at an atropine concentration of 0.01% w/w. While such formulations were shown to reduce progression of myopia without exacerbating mydriatic action of atropine, stability of atropine as measured by an increase in tropic acid was less than desirable within as little as four weeks.

[0008] As normal tears have a pH of about 7.4, an ophthalmic solution should have the same pH as the lacrimal fluid. However, this is a challenge for an ophthalmic solutions containing atropine sulfate, as atropine sulfate is subjected to a greater degree of hydrolysis in solutions that are closer to neutral and basic pH conditions. Thus, atropine is more stable in ophthalmic solutions with a more acidic pH. For example, Atropine Care with a 1% w/w concentration of atropine is maintained at pH 5.5, but the shelf life is still limited to 15 months. Moreover, the degradation of atropine to tropic acid in aqueous solution is notably accelerated with reduced concentrations of atropine (e.g., US 9421199), which still further compounds stability issues, particularly in low-dose atropine formulations.

[0009] To reduce hydrolytic degradation, water in low-dose atropine formulations can be at least in part replaced with deuterated (heavy) water as is described in the US 9421199 patent. While conceptually attractive to use kinetic isotope effects in stability, various disadvantages nevertheless remain. Among other things, at least some of the formulations of the '199 patent still contained a preservative. Moreover, deuterated water is still known to be subject to H/D exchange, and as such delivers deuterium to a subject receiving such formulations.

[0010] Alternatively, atropine may also be delivered at reduced concentrations from a cross-linked non-degradable polymer matrix as is described in US 2016/0338947. Unfortunately, to maintain the polymer away from the cornea, a shaped implant must be worn on the sclera that is typically not well tolerated or may produce discomfort.

[0011] Therefore, there is a need for improved storage stable ready-to-use compositions that contain atropine at low concentrations, have a physiologically desirable pH, and preferably do not contain a preservative.

Summary of the Invention

[0012] The inventive subject matter is directed to ready-to-use atropine compositions having improved stability and a physiologically acceptable pH. Most preferably, such compositions are also substantially preservative free.

[0013] In one aspect of the inventive subject matter, the inventors contemplate a liquid storage-stable low-dose ophthalmic atropine composition that comprises an aqueous solution comprising a buffer, a tonicity agent, a viscosity modifier, and atropine or a pharmaceutically acceptable salt thereof, wherein the atropine or the pharmaceutically acceptable salt thereof is present in the ophthalmic atropine composition in an amount of equal or less than 0.05 wt%, wherein the buffer has a concentration of equal or less than 75mM, and wherein the ophthalmic atropine composition has a pH of between 5.0 and 6.0, and wherein the ophthalmic atropine composition is formulated such that after storage over at least two months at 25 °C and 60% relative humidity equal or less than 0.35% tropic acid is formed from degradation of the atropine.

[0014] Preferably, atropine or the pharmaceutically acceptable salt thereof is atropine sulfate, and is present in the ophthalmic atropine composition in an amount of equal or less than 0.02

wt%, or in an amount of equal or less than 0.01 wt%, or in an amount of between 0.01% and 0.05 wt%, or in an amount of between 0.001 wt% and 0.01 wt%. Most typically, the buffer has a concentration of equal or less than 60mM, or equal or less than 50mM. It is further contemplated that the buffer comprises monobasic and dibasic sodium phosphate. In further embodiments, the composition will further comprise a chelator, typically a bicarboxylic acid, a tricarboxylic acid, or an aminopolycarboxylic acid, and the chelator is present in the ophthalmic atropine composition in an amount of equal or less than 0.01w %.

[0015] Additionally, it is contemplated that the ophthalmic atropine composition has a pH of 5.0 (+/- 0.2), or has a pH of 5.5 (+/- 0.2), or has a pH of 6.0 (+/- 0.2). The tonicity agent is preferably a pharmaceutically acceptable salt that is present in the ophthalmic atropine composition in an amount of between 0.2 wt% and 0.8 wt%. In still further embodiments, the viscosity modifier is a modified cellulose, and preferably a hydroxyethyl cellulose, a hydroxypropyl cellulose, or a hydroxypropyl methylcellulose. Moreover, it is generally preferred that the ophthalmic atropine composition is substantially free of a preservative.

[0016] Therefore, the inventors also contemplate a liquid storage-stable low-dose ophthalmic atropine composition that consists essentially of an aqueous solution comprising a buffer, a tonicity agent, a chelator, a viscosity modifier, and atropine or a pharmaceutically acceptable salt thereof. In such compositions it is preferred that the atropine or the pharmaceutically acceptable salt thereof is present in the ophthalmic atropine composition in an amount of equal or less than 0.05 wt%, that the buffer has a concentration of equal or less than 75mM, and that the ophthalmic atropine composition has a pH of between 5.0 and 6.0. Moreover, such ophthalmic atropine compositions are formulated such that after storage over at least two months at 25 °C and 60% relative humidity equal or less than 0.35% tropic acid is formed from degradation of the atropine.

[0017] Most typically, the atropine or the pharmaceutically acceptable salt thereof is atropine sulfate, and the atropine or a pharmaceutically acceptable salt thereof is present in the ophthalmic atropine composition in an amount of equal or less than 0.02 wt%, or in an amount of equal or less than 0.01 wt%, or in an amount of between 0.001 wt% and 0.01 wt%. In some embodiments, the buffer has a concentration of equal or less than 60mM, or has a concentration

of equal or less than 50mM. it is further contemplated that the buffer comprises monobasic and dibasic sodium phosphate. The chelator is typically a bicarboxylic acid, a tricarboxylic acid, or an aminopolycarboxylic acid. For example, suitable chelators include ethylenediaminetetraacetic acid (EDTA), typically present in the ophthalmic atropine composition in an amount of equal or less than 0.01 wt%.

[0018] In other embodiments, the ophthalmic atropine composition has a pH of between 5.0 (+/- 0.2) and 5.5 (+/- 0.2), or has a pH of between 5.5 (+/- 0.2) and 6.0 (+/- 0.2), and/or the tonicity agent is a pharmaceutically acceptable salt that is present in the ophthalmic atropine composition in an amount of between 0.2 wt% and 0.8 wt%. Suitable viscosity modifiers include a hydroxyethyl cellulose, a hydroxypropyl cellulose, and a hydroxypropyl methylcellulose. Most typically, the ophthalmic atropine composition is substantially free of a preservative.

[0019] For example, contemplated compositions include those in which the atropine or a pharmaceutically acceptable salt thereof is present in the ophthalmic atropine composition in an amount of between 0.001 wt% and 0.01 wt%, wherein the buffer comprises monobasic and dibasic sodium phosphate and has a concentration of equal or less than 50mM, wherein the viscosity modifier is a hydroxyethyl cellulose, a hydroxypropyl cellulose, or a hydroxypropyl methylcellulose, and wherein the ophthalmic atropine composition is substantially free of a preservative. In other examples, contemplated compositions include those in which the atropine or a pharmaceutically acceptable salt thereof is present in the ophthalmic atropine composition in an amount of between 0.01 wt% and 0.05 wt%, wherein the buffer comprises monobasic and dibasic sodium phosphate and has a concentration of equal or less than 50mM, wherein the viscosity modifier is a hydroxyethyl cellulose, a hydroxypropyl cellulose, or a hydroxypropyl methylcellulose, and wherein the ophthalmic atropine composition is substantially free of a preservative.

[0020] Viewed from a different perspective, the inventors also contemplate a storage-stable preservative-free ophthalmic atropine composition that comprises an aqueous solution comprising low-dose atropine or a pharmaceutically acceptable salt thereof, a low-strength buffer, a pharmaceutically acceptable salt, and a cellulosic viscosity modifier, wherein the low-strength buffer has a concentration of equal or less than 50mM, and wherein the low-dose

atropine is present at a concentration of equal or less than 0.05 wt%, and wherein the ophthalmic atropine composition is substantially free of a preservative.

[0021] For example, the low-dose atropine in such compositions is present at a concentration of equal or less than 0.01 wt%, or is present in the ophthalmic atropine composition in an amount of between 0.01% and 0.02 wt%, or is present in the ophthalmic atropine composition in an amount of between 0.001 wt% and 0.01 wt%. Most typically, the atropine or a pharmaceutically acceptable salt thereof is atropine sulfate, and/or the low-strength buffer comprises a first and a second buffer component (*e.g.*, monobasic and dibasic sodium phosphate). Most typically, the ophthalmic atropine composition has a pH of between 5.0 and 6.0, or a pH of between 5.5 (+/- 0.2) and 6.0 (+/- 0.2). Contemplated compositions will typically also include a chelator (*e.g.*, a bicarboxylic acid, a tricarboxylic acid, an aminopolycarboxylic acid) that is preferably present in an amount of 0.01 wt% (+/- 20% abs.). It is further contemplated that the pharmaceutically acceptable salt is present in the ophthalmic atropine composition in an amount of between 0.2 wt% and 0.8 wt%, or in an amount of 0.5 wt% (+/- 0.2 wt%).

[0022] Preferred cellulosic viscosity modifiers include a hydroxyethyl cellulose, a hydroxypropyl cellulose, or a hydroxypropyl methylcellulose, typically present in an amount of 0.5 wt% (+/- 0.1 wt%) of the ophthalmic atropine composition. In preferred embodiments, the ophthalmic atropine composition is formulated such that after storage over at least two months at 25 °C and 60% relative humidity equal or less than 0.35% tropic acid is formed from degradation of the atropine.

[0023] For example, in contemplated compositions the atropine or a pharmaceutically acceptable salt thereof is present in the ophthalmic atropine composition in an amount of between 0.001 wt% and 0.01 wt%, wherein the low-strength buffer comprises monobasic and dibasic sodium phosphate, and wherein the ophthalmic atropine composition has a pH of between 5.5 (+/- 0.2) and 6.0 (+/- 0.2). In another example, the atropine or a pharmaceutically acceptable salt thereof is present in the ophthalmic atropine composition in contemplated compositions is present in an amount of between 0.001 wt% and 0.01 wt%, wherein the ophthalmic atropine composition further comprises a chelator in an amount of 0.01 wt% (+/- 20% abs.) of the ophthalmic atropine composition, and wherein the ophthalmic atropine composition has a pH of between 5.5 (+/- 0.2)

and 6.0 (+/- 0.2). Alternatively, the low-strength buffer in contemplated compositions comprises monobasic and dibasic sodium phosphate, wherein the composition further comprises a chelator in an amount of 0.01 wt% (+/- 20% abs.) of the ophthalmic atropine composition, wherein the ophthalmic atropine composition has a pH of between 5.5 (+/- 0.2) and 6.0 (+/- 0.2), wherein the salt is present in the ophthalmic atropine composition in an amount of 0.5 wt% (+/- 0.2 wt%), and wherein the cellulosic viscosity modifier is present in an amount of 0.5 wt% (+/- 0.1 wt%) of the ophthalmic atropine composition.

[0024] In still another aspect of the inventive subject matter, the inventors also contemplate a method of increasing storage stability of atropine in a liquid low-dose ophthalmic formulation. Typical low-doses are between 0.01 wt% and 0.02 wt%, or between 0.001 wt% and 0.01 wt%, or equal or less than 0.01 wt% of the ophthalmic formulation. Preferred methods will include a step of formulating an aqueous solution with a low-strength buffer system that includes a first and second buffer component, wherein the low-strength buffer system has a concentration of equal or less than 75mM buffer, and a further step of including into the aqueous solution a pharmaceutically acceptable salt, a viscosity modifier, and a chelator. In still another step, atropine or a pharmaceutically acceptable salt thereof is included into the formulation at a low dose (*e.g.*, equal or less than 0.05 wt% of the ophthalmic formulation), and the pH of the ophthalmic formulation is adjusted to a pH between 5 and 6. Preferably, the ophthalmic formulation is formulated such that after storage over at least two months at 25 °C and 60% relative humidity equal or less than 0.35% tropic acid is formed from degradation of the atropine.

[0025] For example, the first and second buffer components are monobasic and dibasic sodium phosphate, respectively, and the low-strength buffer system has a concentration of equal or less than 50mM buffer. Additionally, it is contemplated that the pharmaceutically acceptable salt is sodium chloride, typically present in the ophthalmic atropine composition in an amount of 0.5 wt% (+/- 0.2 wt%) of the ophthalmic formulation. Moreover, it is preferred that the chelator is a bicarboxylic acid, a tricarboxylic acid, or an aminopolycarboxylic acid (*e.g.*, EDTA), preferably in an amount of 0.01 wt% (+/- 20% abs.) of the ophthalmic formulation.

[0026] In other embodiments, the viscosity modifier is a cellulosic viscosity modifier, such as a hydroxyethyl cellulose, a hydroxypropyl cellulose, or a hydroxypropyl methylcellulose. Most

typically the cellulosic viscosity modifier is present in an amount of 0.5 wt% (+/- 0.1 wt%) of the ophthalmic formulation. In still further embodiments, the cellulosic viscosity modifier is prepared as a separate solution, and combined with the aqueous solution containing the buffer system, the pharmaceutically acceptable salt, the viscosity modifier, the chelator, and the atropine or the pharmaceutically acceptable salt thereof. Where desired, the aqueous solution is formulated using deoxygenated water. Most typically, the pH of the formulation is between 5.5 (+/- 0.2) and 6.0 (+/- 0.2), and the atropine or a pharmaceutically acceptable salt thereof is atropine sulfate. Preferably, contemplated methods also include a step of sterilizing the ophthalmic formulation, and especially sterile filtration. As desired, the ophthalmic formulation is then filled into a single-use or multi-dose container.

[0027] Additionally, the inventors also contemplate a method of preparing a storage stable liquid low-dose atropine ophthalmic formulation that includes the steps of formulating in a first container a low-strength buffer low-dose atropine solution, and subjecting the low-strength buffer low-dose atropine solution to sterile filtration to obtain a sterile low-strength buffer low-dose atropine solution, wherein the low-strength buffer has a first and a second buffer component that form a low-strength buffer system having a concentration of equal or less than 75mM in the ophthalmic formulation, wherein the atropine is present in an amount of equal or less than 0.05 wt% of the ophthalmic formulation, and wherein the low-strength buffer low-dose atropine solution further comprises a tonicity agent and a chelator. In another step, a polymer solution is formulated in a second container, and the polymer solution is sterilized in a process other than sterile filtration (*e.g.*, autoclaving) to so obtain a sterile polymer solution. Most typically, the polymer solution comprises a polymer to modify viscosity of the low-strength buffer low-dose atropine solution upon combination. In yet another step, the sterile low-strength buffer low-dose atropine solution and the sterile polymer solution are combined to obtain a sterile liquid low-dose ophthalmic formulation.

[0028] Typically, the first and second buffer components are monobasic and dibasic sodium phosphate, respectively, and/or the low-strength buffer system has a concentration of equal or less than 50mM buffer in the ophthalmic formulation. The atropine is typically present in an amount of between 0.01 wt% and 0.02 wt%, or between 0.001 wt% and 0.01 wt%, or equal or less than 0.01 wt% of the ophthalmic formulation. Most preferably, the tonicity agent is a

pharmaceutically acceptable salt, typically sodium chloride in an amount of 0.5 wt% (+/- 0.2 wt%) of the ophthalmic formulation. Moreover, the chelator is typically a bicarboxylic acid, a tricarboxylic acid, or an aminopolycarboxylic acid (*e.g.*, EDTA), preferably in an amount of 0.01 wt% (+/- 20% abs.) of the ophthalmic formulation.

[0029] It is still further contemplated that the polymer is a cellulosic polymer, and especially a hydroxyethyl cellulose, a hydroxypropyl cellulose, or a hydroxypropyl methylcellulose. Preferably, the cellulosic polymer is present in an amount of 0.5 wt% (+/- 0.1 wt%) of the ophthalmic formulation, and/or the pH of the low-strength buffer low-dose atropine solution is adjusted to a pH between 5 and 6, or between 5.5 (+/- 0.2) and 6.0 (+/- 0.2).

[0030] In further embodiments, the step of combining comprises mixing the sterile low-strength buffer low-dose atropine solution and the sterile polymer solution for at least 30 minutes, and optionally further comprises a step of filling the ophthalmic formulation into a multi-dose container. Preferably, the ophthalmic formulation is formulated such that after storage over at least two months at 25 °C and 60% relative humidity equal or less than 0.35% tropic acid is formed from degradation of the atropine.

[0031] Consequently, the inventors also contemplate a treatment kit for treatment of myopia that includes a first container that contains a liquid storage-stable low-dose atropine ophthalmic formulation, wherein the first container is configured as a disposable single-use container or a multi-dose container, and a second container enclosing the first container, wherein the liquid storage-stable low-dose atropine ophthalmic formulation comprises an aqueous solution comprising a buffer, a tonicity agent, a viscosity modifier, and atropine or a pharmaceutically acceptable salt thereof, wherein the atropine or the pharmaceutically acceptable salt thereof is present in the ophthalmic atropine composition in an amount of equal or less than 0.05 wt%, wherein the buffer has a concentration of equal or less than 75mM, and wherein the ophthalmic atropine composition has a pH of between 5.0 and 6.0, and wherein the ophthalmic atropine composition is formulated such that after storage over at least two months at 25 °C and 60% relative humidity equal or less than 0.35% tropic acid is formed from degradation of the atropine.

[0032] For example, in some embodiments, the first container is a blow-fill-seal (BSF) container and/or the second container is a laminated metallized pouch. In other embodiments, the atropine

or pharmaceutically acceptable salt thereof is present in the ophthalmic atropine composition in an amount of equal or less than 0.01 wt%, or in an amount of between 0.01 wt% and 0.05 wt%, or in an amount of between 0.001 wt% and 0.01 wt%. Most preferably, the buffer has a concentration of equal or less than 75mM, or equal or less than 50mM. For example, preferred buffers comprise monobasic and dibasic sodium phosphate, and may further comprise a chelator (e.g., a bicarboxylic acid, a tricarboxylic acid, or an aminopolycarboxylic acid such as EDTA) that is present in the ophthalmic atropine composition in an amount of equal or less than 0.01 wt%.

[0033] Most typically, the ophthalmic atropine composition has a pH of 5.0 (+/- 0.2), or a pH of 5.5 (+/- 0.2), or a pH of 6.0 (+/- 0.2), and it is further contemplated that the tonicity agent is a pharmaceutically acceptable salt that is present in the ophthalmic atropine composition in an amount of between 0.2 wt% and 0.8 wt%. Preferred viscosity modifiers are modified celluloses such as a hydroxyethyl cellulose, a hydroxypropyl cellulose, or a hydroxypropyl methylcellulose. Still further, it is preferred that the ophthalmic atropine composition is substantially free of a preservative.

[0034] Various objects, features, aspects and advantages of the inventive subject matter will become more apparent from the following detailed description of preferred embodiments.

Brief Description of the Drawing

[0035] Figure 1 depicts an exemplary production process for the storage stable and low-dose atropine ophthalmic formulation.

Detailed Description of the Invention

[0036] The inventive subject matter is directed to stable aqueous ophthalmic compositions of atropine (and pharmaceutically acceptable salts thereof) in a ready-to-use form that are sterile and preferably substantially free of preservatives. The stability of contemplated compositions is characterized by low degradation of atropine to tropic acid at low atropine concentrations, as well as by a physiologically desirable pH. For example, liquid and storage-stable low-dose ophthalmic atropine compositions will typically have stability upon storage over at least two months at 25 °C and 60% relative humidity such that equal or less than 0.35% tropic acid is

formed by the degradation of atropine in the formulation. Most preferably, the compositions are also free of preservatives, and particularly benzalkonium chloride that is commonly used as a preservative. Such stability is particularly unexpected where the atropine concentration in the ophthalmic composition is relatively low (*e.g.*, 0.02 wt%) and where the composition has a relatively high pH (*e.g.*, between 5.0 and 6.0) as it was generally known that atropine stability decreases at decreasing concentrations and increasing pH.

[0037] While not wishing to be bound by any particular theory or hypothesis, the inventors contemplate that low buffer strength using a two-component buffer system at a pH near to a neutral pH (such as pH 5.0-6.0) reduces hydrolysis of atropine to tropic acid where atropine concentrations are relatively low (*e.g.*, equal or less than 0.05 wt%, or equal or less than 0.02 wt%, or equal or less than 0.01 wt%). Unless indicated otherwise, all percentages are weight percentages (wt%) or expressed as weight by volume (w/v). Moreover, it is noted that weight percentages of atropine sulfate provided herein are based on atropine sulfate monohydrate.

[0038] More specifically, and as is described in more detail below, the inventors discovered that low-dose ophthalmic atropine compositions can be prepared with atropine in a ready-to-use concentration (*e.g.*, for treatment of myopia) that have a near-physiological pH, and that preferably lack any preservative in the formulation. Surprisingly, the storage stability at two months at 25 °C and 60% RH of the ophthalmic compositions presented herein is remarkably high, with tropic acid formation from atropine hydrolysis in most cases at or below 0.35%, at or below 0.30%, or at or below 0.28%. Similarly, contemplated formulations at accelerated storage conditions over two months at 40 °C and 75% RH also exhibited an equally favorable profile with tropic acid formation in most cases at or below 1.7%, at or below 1.5%, at or below 1.3%, or at or below 1.2%.

[0039] Therefore, contemplated atropine formulations of the inventive subject matter can be advantageously provided in a ready-to-use format that avoids the inconvenience associated with diluting concentrated atropine formulations into diluents prior to administration. Thus, the ready-to-use formulations also eliminate microbial contamination risks and/or calculation errors associated with dilution. Most typically, contemplated formulations will be available in a range of concentrations commonly required by medical practitioners for treatment of myopia, and

particularly pediatric myopia. Consequently, atropine will typically be present in formulations in an amount of equal or less than 0.05 wt%, or in an amount of equal or less than 0.02 wt%, or in an amount of equal or less than 0.01 wt%. For example, the atropine or a pharmaceutically acceptable salt thereof may be present in the ophthalmic composition in an amount of between 0.01% and 0.05 wt%, between 0.001 wt% and 0.02 wt%, or between 0.001 wt% and 0.01 wt%. As will be readily appreciated, atropine for the preparation of contemplated formulations may be atropine or any suitable pharmaceutically acceptable salt thereof, including mineral salts (*e.g.*, HCl salt) and organic salts (*e.g.*, sulfate). Similarly, where desired, the atropine may also be used in any suitable prodrug form.

[0040] For example, in one exemplary embodiment, the concentration of atropine in contemplated atropine formulations is from about 0.001% to about 0.05% (w/w); or from about 0.005% to about 0.045% (w/w), or from about 0.006% to about 0.035% (w/w), or from about 0.007% to about 0.030% (w/w), or from about 0.008% to about 0.025% (w/w), or from about 0.009% to about 0.022% (w/w), or from about 0.01% to about 0.021% (w/w) or from about 0.01% to about 0.02% (w/w).

[0041] In another exemplary embodiment, the concentration of atropine in contemplated atropine formulations is from about 0.001% to about 0.05% (w/w); or from about 0.005% to about 0.045% (w/w), or from about 0.006% to about 0.035% (w/w), or from about 0.007% to about 0.030% (w/w), or from about 0.008% to about 0.025% (w/w), or from about 0.009% to about 0.022% (w/w), or from about 0.01% to about 0.021% (w/w) or from about 0.01% to about 0.02% (w/w).

[0042] **[0018]** In still an exemplary embodiment, the concentration of atropine in contemplated atropine formulations is about 0.001%, or about 0.002%, or about 0.003%, or about 0.004%, or about 0.005%, or about 0.006%, or about 0.007%, or about 0.008%, or about 0.009%, or about 0.01%, or about 0.011%, or about 0.012%, or about 0.013%, or about 0.014%, or about 0.015%, or about 0.016%, or about 0.017%, or about 0.018%, or about 0.019%, or about 0.02%, or about 0.021%, or about 0.022%, or about 0.023%, or about 0.024%, or about 0.025%, or about 0.026%, or about 0.027%, or about 0.028%, or about 0.029%, or about 0.030%, or about 0.031%, or about 0.032%, or about 0.033%, or about 0.034%, or about 0.035%, or about

0.036%, or about 0.037%, or about 0.038%, or about 0.039%, or about 0.040%, or about 0.041%, or about 0.042%, or about 0.043%, or about 0.044%, or about 0.045%, or about 0.046%, or about 0.047%, or about 0.048%, or about 0.049% or about 0.0499% (w/w).

[0043] In yet an exemplary embodiment, the concentration of atropine in contemplated atropine formulations is about 0.001%, or 0.002%, or 0.003%, or 0.004%, or 0.005%, or 0.006%, or 0.007%, or 0.008%, or 0.009%, or 0.01 %, or 0.011%, or 0.012%, or 0.013%, or 0.014%, or 0.015%, or 0.016%, or 0.017%, or 0.018%, or 0.019%, or 0.02%, or 0.021%, or 0.022%, or 0.023%, or 0.024%, or 0.025%, or 0.026%, or 0.027%, or 0.028%, or 0.029%, or 0.030%, or 0.031%, or 0.032%, or 0.033%, or 0.034%, or 0.035%, or 0.036%, or 0.037%, or 0.038%, or 0.039%, or 0.040%, or 0.041%, or 0.042%, or 0.043%, or 0.044%, or 0.045%, or 0.046%, or 0.047%, or 0.048%, or 0.049% or 0.0499% (w/w).

[0044] In further exemplary embodiments, the concentration of atropine in contemplated atropine formulations is from about 0.005% to about 0.015% (w/w), or from about 0.015% to about 0.025% (w/w), or about 0.01% (w/w), or about 0.02% (w/w), or from 0.005% to 0.015% (w/w), or from 0.015% to 0.025% (w/w), or 0.01% (w/w), or 0.02% (w/w), or from about 0.001% (w/w) to about 0.01% (w/w), or from about 0.005% (w/w) to about 0.02% (w/w), or from about 0.008% (w/w) to about 0.012% (w/w).

[0045] Suitable buffers are generally buffers that stabilize the pH of the contemplated liquid formulations in a near-neutral pH range, for example between pH 4.0 and 7.5, or between pH 4.5 and 6.5, and more preferably between pH 5.0 and 6.0. Therefore, and most typically the pH of contemplated formulations will be equal or less than 6.5 and more typically equal or less than 6.0, and most typically less than 5.8, but higher than 4.5, more typically higher than 5.0, and most typically higher than 5.2. For example, suitable atropine compositions may have a pH of 5.0 (+/- 0.2), or a pH of 5.5 (+/- 0.2), or a pH of 6.0 (+/- 0.2).

[0046] In further aspects of the inventive subject matter, the inventors discovered that the buffer system and/or buffer may have an unexpected influence on atropine stability as is discussed in more detail below. Most notably, once the buffer concentration was adjusted to 75 mM or less at a pH of between 5.0-6.0, the stability of the atropine dramatically increased at normal and accelerated storage conditions as determined by HPLC quantification of tropic acid that is a

byproduct of atropine hydrolysis. While not limiting to the inventive subject matter, the buffer strength is typically relatively low, for example, equal or less than 100 mM, equal or less than 75 mM, equal or less than 60 mM, equal or less than 50 mM, or between 5 mM and 50 mM (*e.g.*, 10 mM, 20mM, 30mM, 40 mM).

[0047] Therefore, in exemplary embodiments, the buffering system is in the pharmaceutical composition in a concentration of from about 10 mM to about 75 mM, or from about 10 mM to about 60 mM, or from about 0.1 mM to about 60 mM, or from about 0.1 mM to about 55 mM, or from about 0.1 mM to about 50 mM, or from about 5 mM to about 60 mM, or from about 0.1 mM to about 10 mM, or from about 1 mM to about 10 mM, or from about 9 mM to about 20 mM, or from about 15 mM to about 25 mM, or from about 19 mM to about 29 mM, or from about 24 mM to about 34 mM, or from about 29 mM to about 39 mM, or from about 34 mM to about 44 mM, or from about 39 mM to about 49 mM, or from about 44 mM to about 54 mM, or from about 19 mM to about 54 mM, or from about 25 mM to about 54 mM.

[0048] Of course, it should be appreciated that there are many types of buffer systems and buffers known in the art, and all of those are deemed suitable for use herein, including buffer systems comprising an acid and a salt of the acid, a first and a second salt (*e.g.*, monobasic and dibasic salt), and amphoteric buffer molecules. For example, suitable buffer systems with an acid and a salt of the acid include citric acid/sodium citrate buffers, ethanoic acid/sodium ethanoate buffers, boric acid/sodium borate, while suitable buffers having a first and a second salt include monobasic sodium phosphate/dibasic sodium phosphate, or monobasic sodium phosphate/sodium citrate, etc. Similarly, suitable amphoteric buffer molecules include HEPES, MOPS, PIPES, MES, etc.

[0049] Moreover, in further contemplated aspects, the formulation will also include one or more chelating agents, and particularly metal ion chelators. For example, suitable chelators include various bicarboxylic acids, tricarboxylic acids, and aminopolycarboxylic acids such as ethylenediaminetetraacetic acid (EDTA), ethylene glycol-bis(β -aminoethyl ether)-N,N,N',N'-tetraacetic acid (EGTA), and penta(carboxymethyl)diethylenetriamine (DTPA), and salts and hydrates thereof. While not limiting to the inventive subject matter, it is contemplated that the metal ion chelators will slow down both the baseline and metal ion-stimulated hydrolysis of

atropine. Remarkably, the inventors unexpectedly observed that the desirable effect of the chelators was observable at relatively low concentrations of the chelators. For example, reduction of the baseline and metal ion-stimulated hydrolysis of atropine was observed at chelator concentrations of between 10 µg/ml and 50 µg/ml, between 50 µg/ml and 250 µg/ml, and between 100 µg/ml and 500 µg/ml. Viewed from a different perspective, chelator concentrations of equal or less than 0.03 wt%, or equal or less than 0.02 wt%, or equal or less than 0.01 wt% are especially advantageous. Interestingly, the chelators, and especially the aminopolycarboxylic acids retained stabilizing effect at low concentrations despite the relatively low pH favoring protonated forms of the chelators.

[0050] Consequently, suitable chelating agents include monomeric polyacids such as EDTA, cyclohexanediamine tetraacetic acid (CDTA), hydroxyethylethylenediamine triacetic acid (HEDTA), diethylenetriamine pentaacetic acid (DTPA), dimercaptopropane sulfonic acid (DMPS), dimercaptosuccinic acid (DMSA), aminotrimethylene phosphonic acid (ATPA), citric acid, ophthalmologically acceptable salts thereof, and combinations of any of the foregoing. Further suitable chelating agents include pyrophosphates, tripolyphosphates, and, hexametaphosphates, chelating antibiotics such as chloroquine and tetracycline, nitrogen-containing chelating agent containing two or more chelating nitrogen atoms within an imino group or in an aromatic ring (e.g., diimines, 2,2'-bipyridines, etc.), and various polyamines such as cyclam (1,4,7,11-tetraazacyclotetradecane), N-(C₁-C₃₀ alkyl)-substituted cyclams (e.g., hexadecyclam, tetramethylhexadecylcyclam), diethylenetriamine (DETA), spermine, diethylnorspermine (DENSPM), diethylhomo-spermine (DEHOP), and deferoxamine (N'-[5-[[4-[[5-(acetylhydroxyamino)pentyl]amino]-1,4-dioxobutyl]hydroxy-amino]pentyl]-N'-(5-aminopentyl)-N-hydroxybutanediamide; also known as desferrioxamine B and DFO).

[0051] With respect to suitable salts it is contemplated that the salt is a pharmaceutically acceptable salt that can be used to increase tonicity. Therefore, pharmaceutically acceptable salts are contemplated, and especially NaCl, at a concentration of at least 0.2 wt%, or at least 0.4 wt%, or at least 0.5 wt%, or at least 0.7 wt%. For example, suitable salt concentrations are between 0.2 wt% and 1.1 wt%, 0.4 wt% and 0.9 wt%, or 0.3 wt% and 0.7 wt%. Depending on the particular salt concentration, additional tonicity agents may be added and suitable tonicity agents include glycerol, thioglycerol, mannitol, lactose, and dextrose. The amount of tonicity adjusting

agent used can be adjusted to obtain osmolality of the formulations in the range of 260 to 340 mOsm/kg. An osmometer can be used to check and adjust the amount of tonicity adjusting agent to be added to obtain the desired osmolality.

[0052] As contemplated formulations are used as an ophthalmic formulation, it is generally preferred that the formulation also includes a viscosity modifier to adjust the viscosity of the formulation to a dynamic viscosity of between 5 and 50 cP (centipoise), and more preferably between 10 and 40 cP, and most preferably between 10 to 30 cP. While there are numerous viscosity modifiers known in the art such as various polymers, glycerol, and polysaccharidic polymers (all of which are contemplated herein), especially preferred viscosity modifiers include cellulosic viscosity modifiers. For example, particularly preferred cellulosic viscosity modifiers include modified and unmodified hydroxyethyl cellulose, hydroxypropyl cellulose, and hydroxypropyl methylcellulose.

[0053] As will be readily appreciated, the exact quantity of the viscosity modifier may vary depending on the type of modifier used and desired final viscosity. For example, where the viscosity modifier is a cellulosic modifier and the final viscosity should be between 1 and 30 cP, suitable quantities of the modifier will typically be in the range of 0.5 wt% (+/- 0.1 wt%) of the ophthalmic atropine composition. The person of ordinary skill will be readily able to adjust the viscosity to a desired measure using viscometers (*e.g.*, rotational, vibration, etc.) well known in the art.

[0054] In exemplary embodiments, suitable concentrations of the viscosity modifier in contemplated ophthalmic formulations may be any value less than 5% (w/w). For example, suitable concentrations of the viscosity modifier include 0.01% to 4.99% (w/w); or 0.05% to 4.50% (w/w), 0.10% to 3.50% (w/w), 0.15% to 3.00% (w/w), 0.20% to 2.50% (w/w), 0.21% to 2.20% (w/w), 0.22% to 2.10% (w/w), 0.23% to 2.00% (w/w), 0.24% to 1.90% (w/w); 0.25% to 1.80% (w/w), 0.26% to 1.70% (w/w), 0.27% to 1.60% (w/w), 0.28% to 1.50% (w/w), 0.29% to 1.40% (w/w), 0.30% to 1.30% (w/w), 0.31% to 1.2% (w/w), 0.32% to 1.10% (w/w), 0.33% to 1.00% (w/w), 0.34% to 0.90% (w/w); 0.35% to 0.80% (w/w), 0.36% to 0.75% (w/w), 0.37% to 0.70% (w/w), 0.38% to 0.69% (w/w), 0.39% to 0.68% (w/w), 0.40% to 0.67% (w/w), 0.41% to 0.66% (w/w), 0.42% to 0.65% (w/w), 0.43% to 0.64% (w/w), 0.44% to 0.63% (w/w), 0.45% to

0.62% (w/w), 0.45% to 0.61% (w/w), 0.45% to 0.60% (w/w), 0.45% to 0.59% (w/w), 0.45% to 0.58% (w/w), 0.45% to 0.57% (w/w), 0.45% to 0.56% (w/w), 0.45% to 0.55% (w/w), 0.46% to 0.54% (w/w), 0.47% to 0.53% (w/w), 0.48% to 0.52% (w/w) or 0.49% to 0.51% (w/w).

[0055] Therefore, appropriate concentrations of the viscosity modifier in contemplated ophthalmic formulations include 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.10%, 0.11%, 0.12%, 0.13%, 0.14%, 0.15%, 0.16%, 0.17%, 0.18%, 0.19%, 0.20%, 0.21%, 0.22%, 0.23%, 0.24%, 0.25%, 0.26%, 0.27%, 0.28%, 0.29%, 0.30%, 0.31%, 0.32%, 0.33%, 0.34%, 0.35%, 0.36%, 0.37%, 0.38%, 0.39%, 0.40%, 0.41%, 0.42%, 0.43%, 0.44%, 0.45%, 0.46%, 0.47%, 0.48%, 0.49%, 0.50%, 0.51 %, 0.52%, 0.53%, 0.54%, 0.55%, 0.56%, 0.57%, 0.58%, 0.59%, 0.60 %, 0.61%, 0.62%, 0.63%, 0.64%, 0.65%, 0.66%, 0.67%, 0.68%, 0.69%, 0.70%, 0.71%, 0.72%, 0.73%, 0.74%, 0.75%, 0.76%, 0.77%, 0.78%, 0.79%, 0.80%, 0.81%, 0.82%, 0.83%, 0.84%, 0.85%, 0.86%, 0.87%, 0.88%, 0.89%, 0.90%, 0.91%, 0.92%, 0.93%, 0.94%, 0.95%, 0.96%, 0.97%, 0.98%, 0.99%, 1.00%, 1.10%, 1.20%, 1.30%, 1.40%, 1.50%, 1.60%, 1.70%, 1.80%, 1.90%, 2.00%, 2.10%, 2.20%, 2.30%, 2.40%, 2.50%, 2.60%, 2.70%, 2.80%, 2.90%, 3.00%, 3.10%, 3.20%, 3.30%, 3.40%, 3.50%, 3.60%, 3.70%, 3.80%, 3.90%, 4.00%, 4.10%, 4.20%, 4.30%, 4.40%, 4.50%, 4.60%, 4.70%, 4.80%, 4.90% and 4.99% (w/w).

[0056] It should further be appreciated that contemplated compositions are substantially free of preservatives (*i.e.*, preservatives not more than 0.01 wt%, and more typically not more than 0.005 wt%). For example, preservatives that are typically not included are benzalkonium chloride, cetrimide or cetrimonium chloride or bromide, benzododecinium bromide, miramine, cetylpyridinium chloride, polidronium chloride or polyquaternium-1, polyquaternium-42 (also known as polixetonium), sepazonium chloride; mercurial derivatives such as the phenylmercury salts (acetate, borate or nitrate), mercuriothiolate sodium (otherwise called thiomersal or thimerosal) and mercurobutol; amidines such as chlorhexidine digluconate or polyhexamethylene biguanide (PHMB); alcohols such as chlorobutanol or phenylethanol or benzyl alcohol or phenol or m-cresol or phenoxyethanol; parabens or esters such as parahydroxybenzoic acid, methylparaben, and propylparaben).

[0057] Indeed, the inventors unexpectedly discovered that the formulations without preservatives had the same stability as with preservatives.

[0058] With respect to the sterilization of contemplated formulations it should be appreciated that contemplated formulations may be sterilized using all known manners of sterilization, including filtration through 0.22 micron filters, heat sterilization, autoclaving, radiation (*e.g.*, gamma, electron beam, microwave). Advantageously, and as is shown in more detail below, the inventors have also discovered that contemplated formulations can be compounded from two batches in which the viscosity agent is separately sterilized using high-pressure saturated steam at 121 °C (for at least 5, or at least 10, or at least 15 minutes) from the atropine, buffer, and salt solution that was independently filter sterilized.

[0059] For example, in one preferred aspect of the inventive subject matter as depicted in the Figure, the production of the ophthalmic solution is performed using two distinct production tracks in which the viscosity modifier solution is separately prepared and sterilized from the drug solution. Most notably, such process allowed for rapid and complete dissolution of the atropine, tonicity, buffer components, and chelator, while also enabling a sterilization process that reduces or even entirely eliminates thermal hydrolysis of atropine. Upon preparation of the sterile atropine solution, that solution can then be combined with the viscosity modifier solution that was also sterilized. While conceptually sterilizable using filter sterilization as was the case with the atropine solution, heat sterilization using an autoclave was found to help fully dissolve the viscosity modifier and render the viscous solution readily mixable with the drug solution. Viewed from a different perspective, it should therefore be appreciated that the separate preparation and sterilization process avoided various difficulties that would be otherwise associated with single batch preparation, including increased mixing time of the component to dissolve buffer, tonicity agent, and chelator at increased agitation, increased sterile filtration time due to higher viscosity, etc.

[0060] Based on the so achieved stability, the combined solutions contemplated herein can be further filtered through a particle filter (*e.g.*, 40 micron polypropylene filter), and filled in to a polyethylene, polypropylene or low-density polyethylene containers using preformed containers in single-use format or multi-dose format, or using a blow-fill-seal (BFS) process. BFS is a form

of advanced aseptic manufacturing wherein the container is formed, filled, and sealed in one continuous, automated system not requiring human intervention. The process begins with the extrusion of plastic granules in the form of a hot hollow pipe of molten plastic called a parison. The next step is the blow molding of the container with an open top through which the container is filled, all while the plastic remains hot and in a molten state. Once filled, the container is hermetically sealed and cooled. The blow-fill seal process can take several seconds, and contemplated ready-to-inject compositions advantageously are formulated to withstand the temperature and pressure requirements without substantial degradation of atropine (*e.g.*, less than 5 wt%, less than 3 wt%, less than 2 wt%, less than 1 wt% degradation).

[0061] Once the atropine formulations are filled in large volume polymeric, semi-permeable infusion containers (*e.g.*, BFS container, typically 1.0mL BFS ampoules), the containers can optionally be layered or covered with a secondary packaging system including an aluminum pouch.

[0062] The following examples are provided for illustrative purposes only and should not be interpreted as limiting the present invention.

Examples

[0063] The following examples illustrate some of the experiments leading to the formulations according to the inventive subject matter, however, should not be construed to limit the scope of the claims in any way.

[0064] Quantitative Analyses:

[0065] A combined test method based on Ultra Performance Liquid Chromatography (UPLC) was developed to perform identification, assay and determination of related compounds in a single run. This was accomplished by using a reversed-phase gradient UPLC with the UV detection including on-line acquisition of UV absorption spectra. Octadecylsilyl-functionalized silica with sub-2 μm particles was used as a stationary phase for chromatographic analysis. The mobile phase is prepared by mixing an aqueous buffer solution with an acidic pH and an acetonitrile-water mixture. Quantification of the active ingredient and related compounds is performed by comparing corresponding peak responses from a Sample Solution to the atropine

peak response from a Standard solution. Relative response factors are used to correct for chemical structure effects on the responses. Two identification methods are incorporated into this test method. Atropine is identified based on the retention time of the major peak in the Sample Solution chromatogram and on the UV absorption spectrum acquired within this peak.

[0066] Exemplary Formulations And Stability Tests:

[0067] Ophthalmic ready-to-use low-dose atropine formulations were prepared using a two-step process substantially as shown in Figure 1.

[0068] Step 1- Preparation of the Polymer Solution Phase: To about 60% of WFI the required quantity of HPMC was added slowly and mixed until a clear solution was observed. The solution was then subjected to autoclaving at 121°C for a period of about 30 min.

[0069] Step 2 – Preparation of the Drug Solution Phase: To about 30% of WFI the required quantities of disodium edetate, monobasic sodium phosphate, dibasic sodium phosphate and sodium chloride were added sequentially upon complete dissolution of each ingredient. The pH of the solution was measured and adjusted to about 5.5 ± 0.1 using hydrochloric acid/ sodium hydroxide. To the above solution atropine sulfate was added and mixed until there was complete dissolution.

[0070] The Drug Solution from Step 2 was then mixed with the Polymer Solution in Step 1. The batch volume was made up using WFI to yield the pharmaceutical composition. Tables 1-3 provide exemplary formulations with and without tonicity agent, with EDTA and low EDTA, and at varying buffer strengths.

No.	Ingredient	100mM Buffer Composition		100mM Buffer Composition (Low EDTA)	
		%w/v	%w/v	%w/v	%w/v
1	Atropine Sulfate	0.01	0.01	0.01	0.01
2	Sodium Dihydrogen Phosphate Anhydrous	0.059	0.06	0.059	0.06
3	Disodium Hydrogen Phosphate Anhydrous	1.15	1.16	1.15	1.16
4	Edetate Sodium	0.10	0.10	0.01	0.01
5	Sodium Chloride	—	—	—	—
6	Hypromellose 2910 (Benecel™ E4M Pharm1)	0.50	0.50	0.50	0.50
7	Hydrochloric Acid	Q.S. for pH adjustment		Q.S. for pH adjustment	

8	Sodium Hydroxide	Q.S. for pH adjustment	Q.S. for pH adjustment
9	Water for Injection	Q.S. to 100%	Q.S. to 100%

Table 1

No.	Ingredient	75mM Buffer Composition with NaCl		No Buffer Composition With NaCl	
		%w/v	%w/v	%w/v	%w/v
1	Atropine Sulfate	0.01	0.01	0.01	0.01
2	Sodium Dihydrogen Phosphate Anhydrous	0.044	0.04	-	-
3	Disodium Hydrogen Phosphate Anhydrous	0.863	0.87	-	-
4	Edetate Sodium	0.1	0.1	0.1	0.1
5	Sodium Chloride	0.15	0.15	0.9	0.91
6	Hypromellose 2910 (Benecel™ E4M Pharm1)	0.5	0.5	0.5	0.5
7	Hydrochloric Acid	Q.S. for pH adjustment		Q.S. for pH adjustment	
8	Sodium Hydroxide	Q.S. for pH adjustment		Q.S. for pH adjustment	
9	Water for Injection	Q.S. to 100%		Q.S. to 100%	

Table 2

No.	Ingredient	50mM Buffer Composition without NaCl		50mM Buffer Composition with NaCl		50mM Buffer Composition with NaCl, low EDTA	
		%w/v	%w/v	%w/v	%w/v	%w/v	%w/v
1	Atropine Sulfate	0.01	0.01	0.01	0.01	0.01	0.01
2	Sodium Dihydrogen Phosphate Anhydrous	0.0295	0.03	0.0295	0.03	0.0295	0.03
3	Disodium Hydrogen Phosphate Anhydrous	0.575	0.58	0.575	0.58	0.575	0.58
4	Edetate Sodium	0.1	0.1	0.1	0.1	0.01	0.01
5	Sodium Chloride	-	-	0.25	0.25	0.25	0.25
6	Hypromellose 2910 (Benecel™ E4M Pharm1)	0.5	0.5	0.5	0.5	0.5	0.5
7	Hydrochloric Acid	Q.S. for pH adjustment		Q.S. for pH adjustment		Q.S. for pH adjustment	
8	Sodium Hydroxide	Q.S. for pH adjustment		Q.S. for pH adjustment		Q.S. for pH adjustment	
9	Water for Injection	Q.S. to 100%		Q.S. to 100%		Q.S. to 100%	

Table 3

[0071] Unless otherwise indicated, pharmaceutical compositions of Table 3 (50mM Buffer Composition with NaCl) were subjected to long term stability studies. Lab scale batches of

atropine sulfate ophthalmic solution were manufactured, (approx. 0.4 mL) filled into 1 mL Blow-Fill-Seal (BFS) ampoules, and were further packaged in aluminum pouches. A number of pouched ampoules were subjected to long term stability studies at $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$ / $60\% \pm 5\%$ RH as per the International Committee on Harmonization stability conditions (see URL: ich.org).

Pouched ampoules subjected to these long term stability studies were collected after 1 week, 2 weeks, 3 weeks, 1 month, 2 months, and 3 months of stability storage, opened, and tested for levels of atropine sulfate, tropic acid, pH (where applicable) and viscosity (where applicable). Atropine and tropic acid levels were measured using the UPLC method, and the results are shown in Tables 4-8.

Sample Information	Test Parameter	100mM buffered compositions						
		Initial	Long term Stability (25°C / 60% RH)					
			1 week	2 weeks	3 weeks	1 month	2 months	3 months
	Assay of Atropine Sulfate	101.0	101.4	102.0	101.6	101.5	101.0	100.6
	Viscosity	23.15	-	-	-	24.00	-	-
	pH	5.52	5.55	5.55	5.51	5.53	5.66	5.58
	Tropic acid (RRT 0.88)	ND	0.1	0.13	0.19	0.22	0.42	0.71
	Assay of Atropine Sulfate	104.2	103.4	103.3	103.2	101.3	102.4	-
	Tropic acid (RRT 0.88)	ND	0.07	0.08	0.12	0.15	0.30	-
	Assay of Atropine Sulfate	98.7	97.7	98	98.1	98	-	-
	pH	5.55	5.40	5.41	5.42	5.43	-	-
	Tropic acid (RRT 0.88)	ND	ND	0.07	0.09	0.12	-	-
Low EDTA	Assay of Atropine Sulfate	98.2	97.3	97.7	97.7	97.1	-	-
	pH	5.55	5.40	5.40	5.41	5.42	-	-
	Tropic acid (RRT 0.88)	ND	ND	0.31	0.1	0.12	-	-

Table 4

Sample Information	Test Parameter	75mM buffered with NaCl Compositions						
		Initial	Long term Stability (25°C / 60% RH)					
			1 week	2 weeks	3 weeks	1 month	2 months	3 months
	Assay of Atropine Sulfate	102.4	101.9	101.7	101.5	101.3	101.0	-
	pH	5.28	-	-	-	-	-	-
	Tropic acid (RRT 0.88)	ND	0.05	0.08	0.1	0.15	0.33	-

Table 5

Sample Information	Test Parameter	50mM buffered Without NaCl Compositions						
		Initial	Long term Stability (25°C / 60% RH)					
			1 week	2 weeks	3 weeks	1 month	2 months	3 months
	Assay of Atropine Sulfate	96.8	96.9	97.2	97.8	97.9	96.9	97.6
	pH	5.38	5.32	5.23	-	-	-	5.38
	Tropic acid (RRT 0.88)	ND	0.1	0.1	0.1	0.12	0.23	0.36
Low EDTA	Assay of Atropine Sulfate	96.1	95.9	95.6	95.6	95.9	-	-
	pH	5.44	5.40	5.32	5.41	5.43	-	-
	Tropic acid (RRT 0.88)	ND	ND	ND	0.07	0.09	-	-

Table 6

Sample Information	Test Parameter	50mM buffered with NaCl Compositions						
		Initial	Long term Stability (25°C / 60% RH)					
			1 week	2 weeks	3 weeks	1 month	2 months	3 months
	Assay of Atropine Sulfate	98.6	98.3	98.4	98.1	98	97.6	-
	pH	5.39	-	-	-	-	5.36	-
	Tropic acid (RRT 0.88)	ND	0.05	0.07	0.08	0.12	0.25	-
Low EDTA	Assay of Atropine Sulfate	98.8	98	98	98	97.9	-	-
	pH	5.41	5.31	5.32	5.35	5.33	-	-
	Tropic acid (RRT 0.88)	ND	ND	0.05	0.06	0.09	-	-

Table 7

Sample Information	Test Parameter	No Buffer Composition						
		Initial	Long term Stability (25°C / 60% RH)					
			1 week	2 weeks	3 weeks	1 month	2 months	3 months
	Assay of Atropine Sulfate	103.7	103.0	103.0	103.0	102.4	101.9	-
	pH	-	-	-	-	-	-	-
	Tropic acid (RRT 0.88)	ND	0.04	0.07	0.09	0.12	0.28	-

Table 8

[0072] As can be readily seen from the above results, atropine solutions with a reduced amount of buffering system concentration (75mM, and particularly 50mM and less) had much lower

levels of tropic acid (atropine degradation product) after already 1 month. Regression analysis was used to extrapolate the degradation levels at the end of 24 months. Based on extrapolation methods commonly used in the art, the 50mM and no buffered concentrations have a shelf life of 18-24 months, which is 3-9 months beyond the 15 month extrapolated shelf life for the 100mM composition.

[0073] The above compositions were also subjected to accelerated stability studies. Lab scale batches of atropine sulfate ophthalmic solution were manufactured, (approx 0.4 mL) filled into 1 mL Blow-Fill-Seal (BFS) ampoules, and were further packaged in aluminum pouches. A number of pouched ampoules were subjected to accelerated stability studies at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ / $75\% \pm 5\%$ RH as per the International Committee on Harmonization stability conditions. Pouched ampoules subjected to these accelerated stability studies were collected after 1 week, 2 weeks, 3 weeks, 1 month, 2 months, and 3 months of stability storage, opened, and tested for levels of atropine sulfate, tropic acid viscosity (where applicable). Atropine and tropic acid levels were measured using the UPLC method, and the results are shown in Tables 9-13.

Sample Information	Test Parameter	100mM buffered compositions						
		Initial	Accelerated Stability (40°C / 75% RH)					
			1 week	2 weeks	3 weeks	1 month	2 months	3 months
	Assay of Atropine Sulfate	101.0	101.6	99.3	101.1	100.0	97.5	95.2
	Viscosity	23.15	-	-	-	19.96	-	-
	pH	5.52	5.55	5.55	5.51	5.48	5.60	5.55
	Tropic acid (RRT 0.88)	ND	0.3	0.76	0.79	0.97	1.98	3.02
	Assay of Atropine Sulfate	104.2	103.1	102.7	102.3	101.7	99.7	-
	Tropic acid (RRT 0.88)	ND	0.19	0.35	0.57	0.67	1.52	-
	Assay of Atropine Sulfate	98.7	97.6	97.4	97.1	95.6	-	-
	pH	5.55	5.41	5.42	5.41	5.43	-	-
	Tropic acid (RRT 0.88)	ND	0.14	0.32	0.46	0.58	-	-
Low EDTA	Assay of Atropine Sulfate	98.2	97	96.9	96.7	96.3	-	-
	pH	5.55	5.40	5.40	5.41	5.42	-	-
	Tropic acid (RRT 0.88)	ND	0.16	0.31	0.45	0.58	-	-

Table 9

		75mM buffered with NaCl compositions

Sample Information	Test Parameter	Initial	Accelerated Stability (40°C / 75% RH)					
			1 week	2 weeks	3 weeks	1 month	2 months	3 months
	Assay of Atropine Sulfate	102.4	101.5	101.0	100.4	99.8	98.0	-
	pH	5.28	-	-	-	-	-	-
	Tropic acid (RRT 0.88)	ND	0.21	0.36	0.63	0.73	1.64	-

Table 10

Sample Information	Test Parameter	50mM buffered Without NaCl compositions						
		Initial	Accelerated Stability (40°C / 75% RH)					
			1 week	2 weeks	3 weeks	1 month	2 months	3 months
	Assay of Atropine Sulfate	96.8	97	97.5	97.6	96.9	108.6	95.1
	pH	5.38	5.31	5.25	-	-	-	5.37
	Tropic acid (RRT 0.88)	ND	0.2	0.3	0.4	0.55	1.16	1.67
Low EDTA	Assay of Atropine Sulfate	96.1	95.1	95.3	94.9	95.2	-	-
	pH	5.44	5.37	5.41	5.36	5.37	-	-
	Tropic acid (RRT 0.88)	ND	0.1	0.21	0.31	0.42	-	-

Table 11

Sample Information	Test Parameter	50mM buffered with NaCl compositions						
		Initial	Accelerated Stability (40°C / 75% RH)					
			1 week	2 weeks	3 weeks	1 month	2 months	3 months
	Assay of Atropine Sulfate	98.6	98.1	97.7	97.2	97.2	95.6	-
	pH	5.39	-	-	-	-	5.42	-
	Tropic acid (RRT 0.88)	ND	0.15	0.26	0.39	0.5	1.12	-
Low EDTA	Assay of Atropine Sulfate	98.8	97.6	97.3	97.1	97.1	-	-
	pH	5.41	5.33	5.35	5.32	5.34	-	-
	Tropic acid (RRT 0.88)	ND	0.09	0.23	0.34	0.45	-	-

Table 12

Sample Information	Test Parameter	No Buffer Composition						
		Initial	Accelerated Stability (40°C / 75% RH)					
			1 week	2 weeks	3 weeks	1 month	2 months	3 months
	Assay of Atropine Sulfate	103.7	102.9	102.4	102.2	101.7	99.9	-
	pH	-	-	-	-	-	-	-

Tropic acid (RRT 0.88)	ND	0.15	0.26	0.4	0.51	1.17	-

Table 13

[0074] Once more, it can be readily taken from the data that atropine solutions with a reduced amount of buffering system concentration (75mM, and particularly 50mM and less) had much lower levels of tropic acid (atropine degradation product) after already 1 month. Regression analysis was utilized to extrapolate the degradation levels at the end of 24 months. Based on extrapolation methods commonly used in the art, the 50mM and no buffered concentrations will have a shelf life of 18-24 months, which is 3-9 months beyond the 15 month extrapolated shelf life for the 100mM composition.

[0075] Additional Stability Studies using further variations in composition again established that lower buffer strength, especially with a two component buffer system provide increased stability of the ophthalmic low-dose atropine formulations having compositions as shown in Tables 14-15 at both normal and accelerated storage conditions below (results shown in Tables 16-19).

No.	Ingredient	Lot: RD-019-020	Lot: RD-019-023	Lot: RD-001-185
		mg/mL	mg/mL	mg/mL
1	Atropine Sulfate Monohydrate	0.1	0.1	0.1
2	Monobasic Sodium Phosphate Anhydrous	0.59	0.59	0.442
3	Dibasic Sodium Phosphate Anhydrous	11.5	11.5	8.63
4	Edetate Disodium Dihydrate	1.0	0.1	1.0
5	Sodium Chloride	-	-	1.5
6	Hypromellose 2910 (Benecel E4M Pharm)	5.0	5.0	5.0
7	Hydrochloric Acid	q.s. for pH adjustment	q.s. for pH adjustment	q.s. for pH adjustment
8	Sodium Hydroxide	q.s. for pH adjustment	q.s. for pH adjustment	q.s. for pH adjustment
9	Water for Injection	q.s. to 100%	q.s. to 100%	q.s. to 100%

Table 14

S. No.	Ingredient	Lot: RD-019-026	Lot: RD-019-029	Lot: RD-001-179
		mg/mL	mg/mL	mg/mL
1	Atropine Sulfate Monohydrate	0.1	0.1	0.1
2	Monobasic Sodium Phosphate Anhydrous	0.295	0.295	-

3	Dibasic Sodium Phosphate Anhydrous	5.75	5.75	
4	Edetate Disodium Dihydrate	1.0	0.1	1.0
5	Sodium Chloride	-	2.5	9.0
6	Hypromellose 2910 (Benecel E4M Pharm)	5.0	5.0	5.0
7	Hydrochloric Acid	q.s. for pH adjustment	q.s. for pH adjustment	q.s. for pH adjustment
8	Sodium Hydroxide	q.s. for pH adjustment	q.s. for pH adjustment	q.s. for pH adjustment
9	Water for Injection	q.s. to 100%	q.s. to 100%	q.s. to 100%

Table 15

Lot Number	Test Parameter		Various formulations						
			Initial	Accelerated Stability (40°C / 75% RH)					
				1 week	2 weeks	3 weeks	1 month	2 months	3 months
Lot: RD-019-020	pH		5.55	5.41	5.42	5.41	5.43	5.37	5.32
	Assay of Atropine Sulfate (%)		98.7	97.6	97.4	97.1	95.6	95.8	94.4
	Related Compounds (%)	Tropic acid	ND	0.14	0.32	0.46	0.58	1.45	2.20
		Unknown (RRT=1.21)	ND	0.19	0.24	0.24	0.25	0.26	0.2
		Apoatropine	ND	ND	0.05	0.06	0.06	0.12	0.17
		Total impurities	ND	0.3	0.6	0.8	0.9	1.8	2.6
Lot: RD-019-023	pH		5.55	5.40	5.40	5.41	5.42	5.36	5.32
	Assay of Atropine Sulfate (%)		98.2	97	96.9	96.7	96.3	95.2	94.3
	Related Compounds (%)	Tropic acid	ND	0.16	0.31	0.45	0.58	1.41	2.14
		Unknown (RRT=1.21)	ND	0.18	0.22	0.23	0.24	0.24	0.23
		Apoatropine	ND	ND	0.04	0.06	0.06	0.13	0.16
		Total impurities	ND	0.3	0.6	0.7	0.9	1.8	2.5
Lot: RD-001-185	pH		5.28	NT	NT	NT	NT	5.46	NT
	Assay of Atropine Sulfate (%)		102.4	101.5	101.0	100.4	99.8	98.0	96.2
	Related Compounds (%)	Tropic acid	ND	0.21	0.36	0.63	0.73	1.64	2.43
		Unknown (RRT=1.21)	ND	0.23	0.25	0.25	0.25	0.25	0.25
		Apoatropine	ND	0.04	0.05	0.06	0.07	0.12	0.17
		Total impurities	ND	0.5	0.7	0.9	1.1	2.0	2.9

Table 16

Lot Number	Test Parameter		Various formulations						
			Initial	Long term Stability (25°C / 60% RH)					
				1 week	2 weeks	3 weeks	1 month	2 months	3 months
Lot: RD-019-020	pH		5.55	5.40	5.41	5.42	5.43	5.37	5.32
	Assay of Atropine Sulfate (%)		98.7	97.7	98	98.1	98	98.1	98.6
	Related Compounds (%)	Tropic acid	ND	ND	0.07	0.09	0.12	0.29	0.44
		Unknown (RRT=1.21)	ND	ND	0.1	0.11	0.14	0.21	0.2
		Apoatropine	ND	ND	ND	ND	ND	ND	0.04
		Total Impurities	ND	ND	0.2	0.2	0.3	0.5	0.7
Lot: RD-019-023	pH		5.55	5.40	5.40	5.41	5.42	5.36	5.31
	Assay of Atropine Sulfate (%)		98.2	97.3	97.7	97.7	97.1	98.0	97.8
	Related Compounds (%)	Tropic acid	ND	ND	0.31	0.1	0.12	0.28	0.43
		Unknown (RRT=1.21)	ND	ND	0.22	0.1	0.12	0.19	0.2
		Apoatropine	ND	ND	ND	ND	ND	ND	0.03
		Total Impurities	ND	ND	0.2	0.2	0.2	0.5	0.7
Lot: RD-001-185	pH		5.28	NT	NT	NT	NT	5.49	NT
	Assay of Atropine Sulfate (%)		102.4	101.9	101.7	101.5	101.3	101.0	100.6
	Related Compounds (%)	Tropic acid	ND	0.05	0.08	0.1	0.15	0.33	0.48
		Unknown (RRT=1.21)	ND	ND	0.1	0.13	0.16	0.21	0.23
		Apoatropine	ND	ND	ND	ND	ND	ND	0.04
		Total Impurities	ND	0.1	0.2	0.2	0.3	0.5	0.7

Table 17

Lot Number	Test Parameter		Various formulations						
			Initial	Accelerated Stability (40°C / 75% RH)					
				1 week	2 weeks	3 weeks	1 month	2 months	3 months
Lot: RD-019-026	pH		5.44	5.37	5.41	5.36	5.37	5.35	5.37
	Assay of Atropine Sulfate (%)		96.1	95.1	95.3	94.9	95.2	94.3	93.8
	Related Compounds (%)	Tropic acid	ND	0.1	0.21	0.31	0.42	1.00	1.53
		Unknown (RRT=1.21)	ND	0.15	0.2	0.21	0.23	0.25	0.24
		Apoatropine	ND	ND	0.04	0.05	0.06	0.10	0.15
		Total Impurities	ND	0.3	0.5	0.6	0.7	1.4	1.9
Lot:	pH		5.41	5.33	5.35	5.32	5.34	5.30	5.24

Lot Number	Test Parameter		Various formulations						
RD-019-029			Initial	Accelerated Stability (40°C / 75% RH)					
				1 week	2 weeks	3 weeks	1 month	2 months	3 months
	Assay of Atropine Sulfate (%)		98.8	97.6	97.3	97.1	97.1	97.5	95.6
	Related Compounds (%)	Tropic acid	ND	0.09	0.23	0.34	0.45	1.08	1.68
		Unknown (RRT=1.21)	ND	0.15	0.19	0.21	0.21	0.22	0.24
		Apoatropine	ND	ND	0.05	0.05	0.06	0.10	0.15
Lot: RD-001-179	pH		5.52	NT	NT	NT	NT	5.58	NT
	Assay of Atropine Sulfate (%)		103.7	102.9	102.4	102.2	101.7	99.9	99.0
	Related Compounds (%)	Tropic acid	ND	0.15	0.26	0.4	0.51	1.17	1.78
		Unknown (RRT=1.21)	ND	0.25	0.28	0.28	0.28	0.29	0.29
		Apoatropine	ND	ND	0	0.05	0.05	0.08	0.11
		Total Impurities	ND	0.4	0.5	0.7	0.8	1.5	2.2

Table 18

Lot Number	Test Parameter		Various formulations						
			Initial	Long term Stability (25°C / 60% RH)					
				1 week	2 weeks	3 weeks	1 month	2 months	3 months
Lot: RD-019-026	pH		5.44	5.40	5.32	5.41	5.43	5.31	5.30
	Assay of Atropine Sulfate (%)		96.1	95.9	95.6	95.6	95.9	96.2	96.5
	Related Compounds (%)	Tropic acid	ND	ND	ND	0.07	0.09	0.21	0.32
		Unknown (RRT=1.21)	ND	ND	ND	ND	0.11	0.18	0.20
		Apoatropine	ND	ND	ND	ND	ND	ND	ND
		Total Impurities	ND	ND	ND	0.1	0.2	0.4	0.5
Lot: RD-019-029	pH		5.41	5.31	5.32	5.35	5.33	5.26	5.25
	Assay of Atropine Sulfate (%)		98.8	98	98	98	97.9	98.0	98.5
	Related Compounds (%)	Tropic acid	ND	ND	0.05	0.06	0.09	0.22	0.32
		Unknown (RRT=1.21)	ND	ND	ND	ND	0.1	0.17	0.2
		Apoatropine	ND	ND	ND	ND	ND	ND	ND
		Total Impurities	ND	ND	0.1	0.1	0.2	0.4	0.5

Lot Number	Test Parameter	Various formulations						
		Initial	Long term Stability (25°C / 60% RH)					
			1 week	2 weeks	3 weeks	1 month	2 months	3 months
Lot: RD-001-179	pH	5.52	NT	NT	NT	NT	5.45	NT
	Assay of Atropine Sulfate (%)	103.7	103.0	103.0	103.0	102.4	101.9	102.2
	Related Compounds (%)	Tropic acid	ND	0.04	0.07	0.09	0.12	0.28
		Unknown (RRT=1.21)	ND	0.09	0.14	0.16	0.2	0.28
		Apoatropine	ND	ND	ND	ND	ND	ND
		Total Impurities	ND	0.1	0.2	0.3	0.3	0.5

Table 19

[0076] The effect of pH and stability of compositions of Table 20 was tested and exemplary test results for pH 3.5 and pH 6.0 are provided in the Tables 21-22 (pH 3.5) and Tables 23-24 (pH 6.0) below.

No.	Ingredient	Qty/mL
1	Atropine Sulfate Monohydrate	0.1 mg
2	Sodium Dihydrogen Phosphate Anhydrous	0.295 mg
3	Disodium Hydrogen Phosphate Anhydrous	5.75 mg
4	Edetate Disodium Dihydrate	0.1 mg
5	Hypromellose 2910, Benecel E4M Pharm	5.0 mg
6	Hydrochloric Acid	pH adjustment to 3.5 or 6.0
7	Sodium Hydroxide	pH adjustment to 3.5 or 6.0
8	Water for Injection	q.s.

Table 20

Test Parameter		Initial	Accelerated Stability (40°C / 75% RH)				
			2 weeks	1 month	2 months	3 months	6 months
Appearance		Clear, colorless solution	Clear, colorless solution	Clear, colorless solution	Clear, colorless solution	Clear, colorless solution	Clear, colorless solution
pH		3.56	3.52	3.54	3.56	3.47	3.70
Assay of Atropine Sulfate (%)		99.5	99.4	98.7	98.2	98.6	97.9
Related Compounds (%)	Tropic acid	ND	ND	ND	0.14	0.20	0.41
	Unknown (RRT=1.21)	ND	ND	ND	0.07	0.07	0.11
	Apoatropine	ND	ND	ND	0.06	0.08	0.13
	Unknown (RRT)	ND	ND	ND	ND	0.10	ND

Test Parameter		Initial	Accelerated Stability (40°C / 75% RH)				
			2 weeks	1 month	2 months	3 months	6 months
	0.508)						
	Unknown (RRT 0.683)	ND	ND	ND	ND	ND	0.20
	Total Impurities	ND	ND	ND	0.3	0.4	0.6

Table 21

Test Parameter		Initial	Accelerated Stability (25°C / 60% RH)				
			2 weeks	1 month	2 months	3 months	6 months
Appearance		Clear, colorless solution	Clear, colorless solution	Clear, colorless solution	Clear, colorless solution	Clear, colorless solution	Clear, colorless solution
pH		3.56	3.52	3.53	3.58	3.46	3.70
Assay of Atropine Sulfate (%)		99.5	99.2	98.9	98.7	98.9	98.9
Related Compounds (%)	Tropic acid	ND	ND	ND	ND	ND	0.09
	Unknown (RRT=1.21)	ND	ND	ND	ND	ND	ND
	Apoatropine	ND	ND	ND	ND	ND	ND
	Unknown (RRT 0.508)	ND	ND	ND	ND	ND	ND
	Unknown (RRT 0.683)	ND	ND	ND	ND	ND	ND
	Total Impurities	ND	ND	ND	ND	ND	0.1

Table 22

Test Parameter		Initial	Accelerated Stability (40°C / 75% RH)				
			2 weeks	1 month	2 months	3 months	6 months
Appearance		Clear, colorless solution	Clear, colorless solution	Clear, colorless solution	Clear, colorless solution	Clear, colorless solution	Clear, colorless solution
pH		5.99	5.87	5.89	5.83	5.83	6.00
Assay of Atropine Sulfate (%)		108.5	106.7	104.1	99.1	95.3	84.2
Related Compounds (%)	Tropic acid	ND	0.90	1.91	4.17	6.07	11.26
	Unknown (RRT=1.21)	ND	0.32	0.32	0.29	0.29	0.27
	Apoatropine	ND	0.06	0.09	0.18	0.25	0.42
	Total Impurities	ND	1.3	2.3	4.6	6.6	12.0

Table 23

Test Parameter	Initial	Accelerated Stability (25°C / 60% RH)				

			2 weeks	1 month	2 months	3 months	6 months
Appearance		Clear, colorless solution	Clear, colorless solution	Clear, colorless solution	Clear, colorless solution	Clear, colorless solution	Clear, colorless solution
pH		5.99	5.87	5.68	5.69	5.82	6.00
Assay of Atropine Sulfate (%)		108.5	108.5	107.1	106.0	105.5	103.1
Related Compounds (%)	Tropic acid	ND	0.19	0.39	0.85	1.21	2.43
	Unknown (RRT=1.21)	ND	0.21	0.25	0.29	0.29	0.29
	Apoatropine	ND	ND	ND	0.05	0.05	0.08
	Total Impurities	ND	0.4	0.6	1.2	1.6	2.8

Table 24

[0077] Atropine sulfate ophthalmic solution is intended to be provided as a single or multi-dose product for topical administration to the eye, which can advantageously be provided as a Blow/Fill/Seal (BFS) ampule as the primary container closure system. For example, suitable ampule materials include Lyondellbasell Purell PE 3020 D resin, which was tested as follows:

[0078] Compositions as shown in Table 3 (50mM Buffer Composition with NaCl, low EDTA), filled in BFS ampoules were tested at concentrations of 0.01% (w/v) and 0.02% (w/v) under accelerated (40°C/75% RH) and long-term (25°C/60% RH) storage conditions. The filled BFS ampoules were then packaged into a secondary packaging (here: laminated pouch) for storage as indicated. The results of this study are presented in Tables 25-28.

Test Parameter		Atropine Concentration 0.01 wt%					
		Initial	Accelerated Storage (40°C / 75% RH)				
			2 weeks	1 month	2 months	3 months	6 months
Appearance		Clear, colorless solution	Clear, colorless solution	Clear, colorless solution	Clear, colorless solution	Clear, colorless solution	Clear, colorless solution
pH		5.49	5.49	5.39	5.42	5.63	5.47
Viscosity (cPs)		19.96	NA	NA	NA	20.48	19.48
Assay of Atropine Sulfate (%)		104.2	104.6	102.0	102.5	99.4	93.0
Related Compounds (%)	Tropic acid	NR	0.41	0.89	1.73	2.66	4.67
	Apoatropine	NR	NR	0.04	0.09	0.14	0.23
	Total impurities	NR	0.41	0.93	1.82	2.80	4.90

Table 25

Test Parameter		Atropine Concentration 0.01 wt%					
		Initial	Long-Term Storage (25°C / 60% RH)				
			2 weeks	1 month	2 months	3 months	6 months
Appearance		Clear, colorless solution	Clear, colorless solution	Clear, colorless solution	Clear, colorless solution	Clear, colorless solution	Clear, colorless solution
pH		5.49	5.50	5.44	5.43	5.67	5.45
Viscosity (cPs)		19.96	NA	NA	NA	20.56	19.42
Assay of Atropine Sulfate (%)		104.2	105.8	103.7	105.9	103.3	105.2
Related Compounds (%)	Tropic acid	NR	0.11	0.20	0.35	0.53	1.06
	Apoatropine	NR	NR	NR	NR	NR	0.05
	Total Impurities	NR	0.11	0.20	0.35	0.53	1.11

Table 26

Test Parameter		Atropine Concentration 0.02 wt%					
		Initial	Accelerated Storage (40°C / 75% RH)				
			2 weeks	1 month	2 months	3 months	6 months
Appearance		Clear, colorless solution	Clear, colorless solution	Clear, colorless solution	Clear, colorless solution	Clear, colorless solution	Clear, colorless solution
pH		5.35	5.43	5.33	5.36	5.57	5.34
Viscosity (cPs)		20.26	NA	NA	NA	21.20	19.82
Assay of Atropine Sulfate (%)		105.5	106.0	104.0	103.1	102.6	95.6
Related Compounds (%)	Tropic acid	NR	0.31	0.70	1.26	1.99	3.73
	Apoatropine	NR	NR	0.13	0.09	0.13	0.24
	Total Impurities	NR	0.31	0.83	1.35	2.12	3.97

Table 27

Test Parameter		Atropine Concentration 0.02 wt%					
		Initial	Long-Term Storage (25°C / 60% RH)				
			2 weeks	1 month	2 months	3 months	6 months
Appearance		Clear, colorless solution	Clear, colorless solution	Clear, colorless solution	Clear, colorless solution	Clear, colorless solution	Clear, colorless solution

Test Parameter		Atropine Concentration 0.02 wt%					
		Initial	Long-Term Storage (25°C / 60% RH)				
			2 weeks	1 month	2 months	3 months	6 months
pH		5.35	5.42	5.33	5.38	5.57	5.34
Viscosity (cPs)		20.26	NA	NA	NA	21.17	20.17
Assay of Atropine Sulfate (%)		105.5	106.2	105.4	105.8	104.9	101.8
Related Compounds (%)	Tropic acid	NR	0.06	0.14	0.24	0.38	0.76
	Apoatropine	NR	NR	NR	NR	NR	NR
	Total Impurities	NR	0.06	0.14	0.24	0.34	0.76

Table 28

[0079] As used in the description herein and throughout the claims that follow, the meaning of “a,” “an,” and “the” includes plural reference unless the context clearly dictates otherwise. Also, as used in the description herein, the meaning of “in” includes “in” and “on” unless the context clearly dictates otherwise.

[0080] In some embodiments, the numbers expressing quantities of ingredients, properties such as concentration, reaction conditions, and so forth, used to describe and claim certain embodiments of the invention are to be understood as being modified in some instances by the term “about.” Accordingly, in some embodiments, the numerical parameters set forth in the written description and attached claims are approximations that can vary depending upon the desired properties sought to be obtained by a particular embodiment. In some embodiments, the numerical parameters should be construed in light of the number of reported significant digits and by applying ordinary rounding techniques. Notwithstanding that the numerical ranges and parameters setting forth the broad scope of some embodiments of the invention are approximations, the numerical values set forth in the specific examples are reported as precisely as practicable. The numerical values presented in some embodiments of the invention may contain certain errors necessarily resulting from the standard deviation found in their respective testing measurements.

[0081] It should be apparent, however, to those skilled in the art that many more modifications besides those already described are possible without departing from the inventive concepts

herein. The inventive subject matter, therefore, is not to be restricted except in the spirit of the disclosure. One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. Indeed, the present invention is in no way limited to the methods and materials described.

[0082] Moreover, in interpreting the disclosure all terms should be interpreted in the broadest possible manner consistent with the context. In particular the terms “comprises” and “comprising” should be interpreted as referring to the elements, components, or steps in a non-exclusive manner, indicating that the referenced elements, components, or steps can be present, or utilized, or combined with other elements, components, or steps that are not expressly referenced.

CLAIMS

What is claimed is:

1. A liquid storage-stable low-dose ophthalmic atropine composition, consisting essentially of:
an aqueous solution comprising a buffer, a tonicity agent, a chelator, a viscosity modifier,
and atropine or a pharmaceutically acceptable salt thereof;
wherein the atropine or the pharmaceutically acceptable salt thereof is present in the
ophthalmic atropine composition in an amount of equal or less than 0.05 wt%;
wherein the buffer has a concentration of equal or less than 75mM, and wherein the
ophthalmic atropine composition has a pH of between 5.0 and 6.0; and
wherein the ophthalmic atropine composition is formulated such that after storage over at
least two months at 25 °C and 60% relative humidity equal or less than 0.35%
tropic acid is formed from degradation of the atropine.
2. The composition of claim 1, wherein the atropine or the pharmaceutically acceptable salt
thereof is atropine sulfate.
3. The composition of claim 1, wherein the atropine or a pharmaceutically acceptable salt
thereof is present in the ophthalmic atropine composition in an amount of equal or less than
0.02 wt%.
4. The composition of claim 1, wherein the atropine or a pharmaceutically acceptable salt
thereof is present in the ophthalmic atropine composition in an amount of equal or less than
0.01 wt%.
5. The composition of claim 1, wherein the atropine or a pharmaceutically acceptable salt
thereof is present in the ophthalmic atropine composition in an amount of between 0.001
wt% and 0.01 wt%.
6. The composition of claim 2, wherein the buffer has a concentration of equal or less than
60mM.
7. The composition of claim 5, wherein the buffer has a concentration of equal or less than
50mM.

8. The composition of claim 6, wherein the buffer comprises monobasic and dibasic sodium phosphate.
9. The composition of claim 7, wherein the buffer comprises monobasic and dibasic sodium phosphate.
10. The composition of claim 1, wherein the chelator is selected from the group consisting of a bicarboxylic acid, a tricarboxylic acid, and an aminopolycarboxylic acid.
11. The composition of claim 8, wherein the chelator is ethylenediaminetetraacetic acid (EDTA).
12. The composition of claim 9, wherein the chelator is ethylenediaminetetraacetic acid (EDTA).
13. The composition of claim 10 wherein the chelator is present in the ophthalmic atropine composition in an amount of equal or less than 0.01 wt%.
14. The composition of claim 1, wherein the ophthalmic atropine composition has a pH of between 5.0 (+/- 0.2) and 5.5 (+/- 0.2).
15. The composition of claim 1, wherein the ophthalmic atropine composition has a pH of between 5.5 (+/- 0.2) and 6.0 (+/- 0.2).
16. The composition of claim 1, wherein the tonicity agent is a pharmaceutically acceptable salt and wherein the salt is present in the ophthalmic atropine composition in an amount of between 0.2 wt% and 0.8 wt%.
17. The composition of claim 1, wherein the viscosity modifier is a hydroxyethyl cellulose, a hydroxypropyl cellulose, or a hydroxypropyl methylcellulose.
18. The composition of claim 1, wherein the ophthalmic atropine composition is substantially free of a preservative.
19. The composition of claim 1, wherein the atropine or a pharmaceutically acceptable salt thereof is present in the ophthalmic atropine composition in an amount of between 0.001 wt% and 0.01 wt%, wherein the buffer comprises monobasic and dibasic sodium phosphate and has a concentration of equal or less than 50mM, wherein the viscosity modifier is a

hydroxyethyl cellulose, a hydroxypropyl cellulose, or a hydroxypropyl methylcellulose, and wherein the ophthalmic atropine composition is substantially free of a preservative.

20. The composition of claim 1, wherein the atropine or a pharmaceutically acceptable salt thereof is present in the ophthalmic atropine composition in an amount of between 0.01 wt% and 0.05 wt%, wherein the buffer comprises monobasic and dibasic sodium phosphate and has a concentration of equal or less than 50mM, wherein the viscosity modifier is a hydroxyethyl cellulose, a hydroxypropyl cellulose, or a hydroxypropyl methylcellulose, and wherein the ophthalmic atropine composition is substantially free of a preservative.

ABSTRACT

The inventive subject matter is directed to compositions and methods for sterile and storage stable low-dose atropine formulations with improved stability. Most preferably, the compositions presented herein are substantially preservative free and exhibit less than 0.35% tropic acid from degradation of atropine. Advantageously, contemplated formulations are also substantially free of preservatives.

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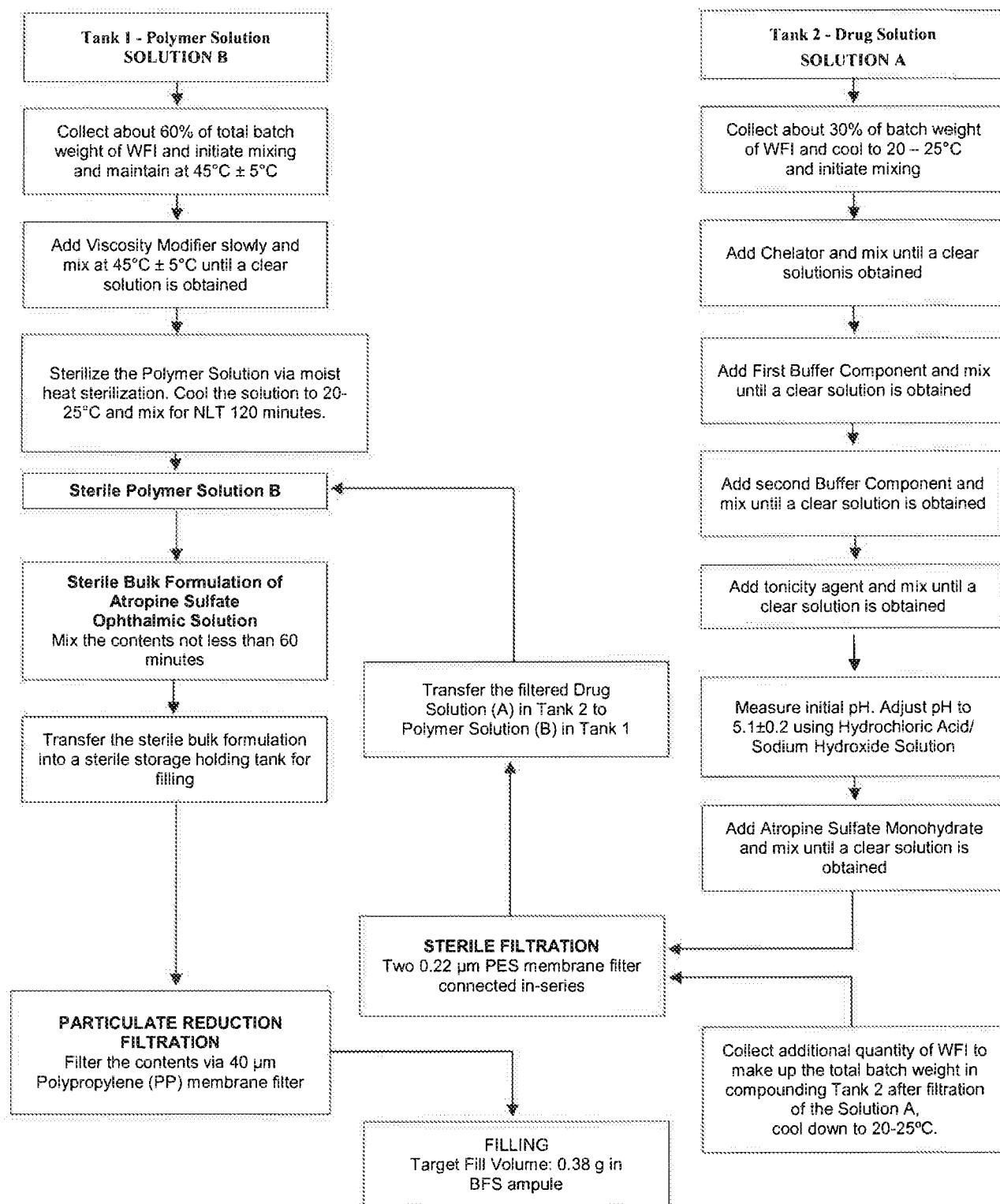


Figure 1

40

Electronic Patent Application Fee Transmittal

Application Number:	15976279			
Filing Date:				
Title of Invention:	Atropine Pharmaceutical Compositions			
First Named Inventor/Applicant Name:	Navneet Puri			
Filer:	Martin Fessenmaier/Dani Moroz			
Attorney Docket Number:	102843.0006US2			
Filed as Small Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
REQUEST FOR PRIORITIZED EXAMINATION	2817	1	2000	2000
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				2000

Electronic Acknowledgement Receipt

EFS ID:	32590959
Application Number:	15976279
International Application Number:	
Confirmation Number:	1256
Title of Invention:	Atropine Pharmaceutical Compositions
First Named Inventor/Applicant Name:	Navneet Puri
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Filer:	Martin Fessenmaier/Dani Moroz
Filer Authorized By:	Martin Fessenmaier
Attorney Docket Number:	102843.0006US2
Receipt Date:	10-MAY-2018
Filing Date:	
Time Stamp:	15:20:35
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	\$ 2000

RAM confirmation Number	051118INTEFSW15205700				
Deposit Account					
Authorized User					
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:					
File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Fee Worksheet (SB06)	fee-info.pdf	30305	no	2
			f07b7a7f5da16a71f8629c85dbda27f47f7c3efc		
Warnings:					
Information:					
Total Files Size (in bytes):			30305		
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