

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NEVAKAR, INC.,
Petitioner,

v.

SYDNEXIS, INC.,
Patent Owner.

IPR2021-00439 (Patent 9,421,199 B2)
IPR2021-00440 (Patent 9,770,447 B2)
IPR2021-00441 (Patent 10,076,515 B2)
IPR2021-00442 (Patent 10,201,534 B2)¹

Before ERICA A. FRANKLIN, SUSAN L. C. MITCHELL, and
JAMIE T. WISZ, *Administrative Patent Judges*.

FRANKLIN, *Administrative Patent Judge*.

ORDER

Granting Joint Motion to Terminate the Proceedings Before Institution
37 C.F.R. §§ 42.71; 42.74

¹ This order addresses issues common to each of the captioned cases. Thus, we issue a single order for entry in each case.

IPR2021-00439 (Patent 9,421,199 B2)
IPR2021-00440 (Patent 9,770,447 B2)
IPR2021-00441 (Patent 10,076,515 B2)
IPR2021-00442 (Patent 10,201,534 B2)

On April 22, 2021, in each of the above-captioned cases, with authorization of the Board, the parties filed a joint motion to terminate the proceeding. Paper 7.² The parties also filed a true copy of their written settlement agreement. Ex. 1090. Additionally, citing to 35 U.S.C § 317 (b) and 37 C.F.R. § 42.74 (c), the parties filed a joint request that the settlement agreement be treated as business confidential information, maintained separate from the publicly available files of the involved patent, and made available only to Federal Government agencies on written request, or to persons showing good cause on written request. Paper 8, 2.

In each joint motion, the parties explain that termination of the proceeding is appropriate because they have reached an agreement settling their dispute with respect to the involved patents. Paper 7, 1.

These cases are in the preliminary proceeding stage; a decision whether to institute trial in each case has not been entered. Under these circumstances, we determine that it is appropriate to enter judgment terminating the proceedings. Additionally, the parties' request for the settlement agreement to be treated as business confidential information and kept separate from the file of the involved patents is *granted*.

² Citations to paper and exhibit numbers in this Order refer to filings in IPR2021-00439. Similar documents were filed in each of the above-captioned cases.

IPR2021-00439 (Patent 9,421,199 B2)
IPR2021-00440 (Patent 9,770,447 B2)
IPR2021-00441 (Patent 10,076,515 B2)
IPR2021-00442 (Patent 10,201,534 B2)

Accordingly, it is hereby

ORDERED that, in each of the above-captioned cases, the joint motion to terminate the captioned proceeding is *granted*;

FURTHER ORDERED that, in each of the above-captioned cases, the joint request for the settlement agreement to be treated as business confidential information and kept separate from the file of the involved patent under the provisions of 35 U.S.C. § 317(b) and 37 C.F.R. § 42.74(c) is *granted*; and

FURTHER ORDERED that the proceeding in each of the above-captioned cases is *terminated*.

IPR2021-00439 (Patent 9,421,199 B2)
IPR2021-00440 (Patent 9,770,447 B2)
IPR2021-00441 (Patent 10,076,515 B2)
IPR2021-00442 (Patent 10,201,534 B2)

PETITIONER:

James R. Barney
Mark J. Feldstein
Joshua L. Goldberg
Yieyie Yang
Drew D. Christie
Lin Chen
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PATENT OWNER:

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WILSON SONSINI GOODRICH & ROSATI
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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.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/208,537	Filing Date 07/12/2016	☐ 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), (l), 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	07/09/2018	CLAIMS REMAINING AFTER AMENDMENT	Minus	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)
	Total (37 CFR 1.16(i))	* 8	Minus	** 20	= 0	x \$100 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	x \$460 =	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.

LIE
DENISE T. LILES

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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 9,770,447 B2
APPLICATION NO. : 15/208537
DATED : September 26, 2017
INVENTOR(S) : Gregory I. Ostrow et al.

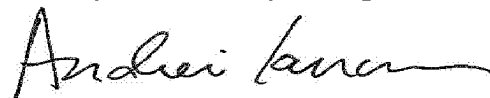
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

Column 87, Line 10, Claim 3, “muscarinic agent” should read --ophthalmic agent--.

Signed and Sealed this
Twenty-fourth Day of April, 2018



Andrei Iancu
Director of the United States Patent and Trademark Office

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: Gregory I. Ostrow, et al.

CONFIRMATION NO: 1009

Serial Number: 15/208,537

Filing Date: July 12, 2016

Issued Patent No.: 9,770,447

Issued: September 26, 2017

Title: OPTHALMIC COMPOSITION

FILED ELECTRONICALLY ON NOVEMBER 1, 2017

**REQUEST FOR CERTIFICATE OF CORRECTION OF THE ISSUED PATENT
FOR**

☒ **PATENT OFFICE MISTAKE (37 C.F.R. §1.322)**

☒ **APPLICANT MISTAKE (37 C.F.R. §1.323)**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
ATTN: Certificate of Correction Branch

Commissioner:

It is noted that errors of a minor nature or character appears in this patent due to mistakes on the part of the Office and/or on the part of the Applicant, as more fully described below. The Patentee believes that correction thereof does not involve such changes in the patent as would constitute new matter or would require re-examination of the patent. A certificate of correction is therefore requested.

Attached hereto is Form PTO/SB/44 which is suitable for printing.

☒ **MISTAKES ON THE PART OF THE OFFICE:**

In reviewing the issued Patent, Applicant noted the following errors, which Applicant believes are attributable to the Patent Office. These errors are located in the issued Patent at:

Requested Correction:

Support for Correction found in the
Prosecution File History at:

Column 88, Lines 36-38:

In claim 18, “the ophthalmic composition is stored at between about 2° C. to about 10° C. prior”

should read:

--the ophthalmic composition is stored at between about 2°C to about 10°C prior--

Claim 49, as filed in Amendment After

Final dated April 21, 2017 and initialed by the Examiner on May 30, 2017.

Column 88, Lines 39-41:

In claim 19, “the ophthalmic composition is stored at between about 16° C. to about 26° C. after”

should read:

--the ophthalmic composition is stored at between about 16°C to about 26°C after--

Claim 50, as filed in Amendment After

Final dated April 21, 2017 and initialed by the Examiner on May 30, 2017.

☒ **MISTAKES ON THE PART OF APPLICANT:**

Applicant respectfully requests correction to the language in the issued Patent in order to correct an error in antecedent basis. The changes requested are:

In claim 3, Column 87, Line 10, please replace “muscarinic antagonist” with --ophthalmic agent--

FEE AUTHORIZATION

Please charge the processing fee under 37 CFR 1.20(a) to Deposit Account No. 23-2415 (Docket No. 46682-701.301). The Commissioner is authorized to charge any additional fees which may be required, including petition fees, or credit any overpayment to Deposit Account No. 23-2415 (Docket No. 46682-701.301).

Respectfully submitted,

Dated: October 31, 2017

By: Xiaofan Yang/
Xiaofan Yang, Ph.D., Esq.
Registration No. 61,459

WILSON SONSINI GOODRICH & ROSATI
650 Page Mill Road
Palo Alto, California 94304
Telephone: 858-350-2300
Customer No. 21971

**UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION**

PATENT NO. : 9,770,447

Page 1 of 1

APPLICATION NO. : 15/208,537

ISSUE DATE : September 26, 2017

INVENTOR(S) : Gegroy I. Ostrow, et al.

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below.

Column 87, Line 10, Claim 3, "muscarinic agent" should read --ophthalmic agent--.

Column 88, Lines 36-38, Claim 18, "the ophthalmic composition is stored at between about 2° C. to about 10° C. prior" should read -- the ophthalmic composition is stored at between about 2°C to about 10°C prior --.

Column 88, Lines 39-41, Claim 19, "the ophthalmic composition is stored at between about 16° C. to about 26° C. after" should read -- the ophthalmic composition is stored at between about 16°C to about 26°C after --.

MAILING ADDRESS OF SENDER: (Please do not use customer number below)

Wilson Sonsini Goodrich & Rosati
650 Page Mill Road
Palo Alto, California 94304-1050

This collection of information is required by 37 CFR 1.322, 1.323, and 1.324. 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 1.0 hour 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. 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Attention Certificate of Corrections Branch, 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.

Electronic Patent Application Fee Transmittal				
Application Number:		15208537		
Filing Date:		12-Jul-2016		
Title of Invention:		OPHTHALMIC COMPOSITION		
First Named Inventor/Applicant Name:		Gregory I. OSTROW		
Filer:		Xiaofan Yang/Lori Ford		
Attorney Docket Number:		46682-701.301		
Filed as Large 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:				
Certificate of correction	1811	1	100	100

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				100

Electronic Acknowledgement Receipt

EFS ID:	30831210
Application Number:	15208537
International Application Number:	
Confirmation Number:	1009
Title of Invention:	OPHTHALMIC COMPOSITION
First Named Inventor/Applicant Name:	Gregory I. OSTROW
Customer Number:	21971
Filer:	Xiaofan Yang/Lori Ford
Filer Authorized By:	Xiaofan Yang
Attorney Docket Number:	46682-701.301
Receipt Date:	01-NOV-2017
Filing Date:	12-JUL-2016
Time Stamp:	18:41:56
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	\$ 100
RAM confirmation Number	110217INTEFSW00005070232415
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	Request for Certificate of Correction	46682_701_301_Request_for_COC.pdf	25278	no	2
			3b0b83c9616c11739428e1b9d74aa01406438074		
Warnings:					
Information:					
2	Request for Certificate of Correction	46682_701_301_COC.pdf	22256	no	1
			76a47f1fb5e5be4db9bffa8135931f53d30495b0		
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30120	no	2
			6143b9b109a4cbf99955b35547c0095ec411ec27		
Warnings:					
Information:					
Total Files Size (in bytes):			77654		
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.					



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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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	REQUEST ID
15/208,537	07/12/2016	Sydnexis, Inc.	46682-701.301	50379

Acknowledgement of Loss of Entitlement to Entity Status Discount

The entity status change request below filed through Private PAIR on 11/01/2017 has been accepted.

CERTIFICATIONS:

Change of Entity Status:

× Applicant changing to regular undiscounted fee status.

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

This portion must be completed by the signatory or signatories making the entity status change in accordance with 37 CFR 1.4(d)(4).

Signature:	/Xiaofan Yanhg/
Name:	Xiaofan Yang
Registration Number:	61459



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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.
15/208,537	09/26/2017	9770447	46682-701.301	1009

21971 7590 09/06/2017
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

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):

Sydnexis, Inc., San Diego, CA;
Gregory I. OSTROW, San Diego, CA;
Kenneth J. WIDDER, Rancho Santa Fe, CA;
David S. BAKER, Carlsbad, CA;

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.



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/208,537	07/12/2016	Gregory I. OSTROW	46682-701.301	1009

21971 7590 08/30/2017
WILSON, SONSINI, GOODRICH & ROSATI
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EXAMINER

FAY, ZOHREH A

ART UNIT	PAPER NUMBER

1621

NOTIFICATION DATE	DELIVERY MODE

08/30/2017

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):

patentdocket@wsgr.com

Response to Rule 312 Communication	Application No. 15/208,537	Applicant(s) OSTROW ET AL.
	Examiner ZOHREH FAY	Art Unit 1621

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

1. ☒ The amendment filed on 31 July 2017 under 37 CFR 1.312 has been considered, and has been:

a) ☒ entered.

b) ☐ entered as directed to matters of form not affecting the scope of the invention.

c) ☐ disapproved because the amendment was filed after the payment of the issue fee.

Any amendment filed after the date the issue fee is paid must be accompanied by a petition under 37 CFR 1.313(c)(1) and the required fee to withdraw the application from issue.

d) ☐ disapproved. See explanation below.

e) ☐ entered in part. See explanation below.

/ZOHREH FAY/
Primary Examiner, Art Unit 1621

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: **Mail** Mail Stop ISSUE FEE
 Commissioner for Patents
 P.O. Box 1450
 Alexandria, Virginia 22313-1450
 or **Fax** (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)

21971 7590 05/30/2017
WILSON, SONSINI, GOODRICH & ROSATI
 650 PAGE MILL ROAD
 PALO ALTO, CA 94304-1050

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.

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 facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/208,537	07/12/2016	Gregory I. OSTROW	46682-701.301	1009

TITLE OF INVENTION: OPHTHALMIC COMPOSITION

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$480	\$0	\$0	\$480	08/30/2017

EXAMINER	ART UNIT	CLASS-SUBCLASS
FAY, ZOHREH A	1621	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 (03-02 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. <u>Wilson Sonsini Goodrich & Rosati</u> 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 has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

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

SYDNEXIS, INC.

San Diego, California

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

4a. The following fee(s) are submitted:

- ☒ Issue Fee
☐ Publication Fee (No small entity discount permitted)
☐ Advance Order - # of Copies _____

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

- ☐ A check is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☒ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 23-2451 (enclose an extra copy of this form).

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 undi-counted 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 _____

Date 08/03/2017

Typed or printed name Xiaofan Yang

Registration No. 61459

Electronic Patent Application Fee Transmittal

Application Number:	15208537			
Filing Date:	12-Jul-2016			
Title of Invention:	OPHTHALMIC COMPOSITION			
First Named Inventor/Applicant Name:	Gregory I. OSTROW			
Filer:	Michael J. Hostetler/F. Yang/Jennifer Vail			
Attorney Docket Number:	46682-701.301			
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	480	480

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				480

Electronic Acknowledgement Receipt

EFS ID:	29980586
Application Number:	15208537
International Application Number:	
Confirmation Number:	1009
Title of Invention:	OPHTHALMIC COMPOSITION
First Named Inventor/Applicant Name:	Gregory I. OSTROW
Customer Number:	21971
Filer:	Michael J. Hostetler/F. Yang/Jennifer Vail
Filer Authorized By:	Michael J. Hostetler
Attorney Docket Number:	46682-701.301
Receipt Date:	03-AUG-2017
Filing Date:	12-JUL-2016
Time Stamp:	18:19:15
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	\$ 480
RAM confirmation Number	080417INTEFSW00005074232415
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)	46682-701-301_IssueFeeTrans mittal.pdf	160587	no	1
			caf0c06822cd75ebf5fbb3b6ea3325dfc896a644		
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30546	no	2
			b3cc014acec230ecec0fa4e3f85f605ca1dcba200		
Warnings:					
Information:					
Total Files Size (in bytes):			191133		
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.					

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application:

Inventor: Gregory I. Ostrow et al.

Application No.: 15/208,537

Filed: July 12, 2016

Title: **OPHTHALMIC COMPOSITION**

Confirmation No.: 1009

Examiner: Zohreh A. Fay

Group Art Unit: 1621

Certificate of Electronic Filing

I hereby certify that the attached Preliminary Amendment is being deposited by Electronic Filing on **July 31, 2017** by using the EFS – Web patent filing system and addressed to:

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

By: /Lori Ford/

Lori Ford

Mail Stop Issue Fee

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

AMENDMENT UNDER 37 CFR § 1.132

Commissioner:

An amendment under 37 C.F.R. § 1.312 is filed herein after the Notice of Allowance mailed May 30, 2017. Entry of the following amendment under 37 C.F.R. § 1.312 is respectfully requested. No new matter is being added by the amendment made herein.

Amendment to the Specification is on page **2** of this paper.

Remarks and Conclusion are on page **3** of this paper.

AMENDMENTS TO THE SPECIFICATION

Please insert the below headin and paragraph before paragraph [0001] on page 1.

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. Application Serial No. 14/726,139, filed May 29, 2015, now U.S. Patent No. 9,421,199, issued August 23, 2016, which claims the benefit of U.S. Provisional Application Serial No. 62/151,926, filed April 23 2015, U.S. Provisional Application Serial No. 62/096,433, filed December 23, 2014, and U.S. Provisional Application Serial No. 62/016,502, filed June 24, 2014, each of which are incorporated herein in their entirety.

REMARKS

The Specification has been amended to set forth the priority claim in this application. No new matter is added by this amendment

CONCLUSION

Applicant believes no fee is required. If this is incorrect, the Commissioner is authorized to charge any additional fees to Deposit Account No. 23-2415 (Attorney Docket No. 46682-701.301).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI
Professional Corporation

Date: July 31, 2017

By: /Xiaofan Yang/
Xiaofan Yang, Ph.D., Esq.
Reg. No. 61,459

650 Page Mill Road
Palo Alto, CA 94304
Direct Dial: (858) 350-2339
Customer No. 021971

Electronic Acknowledgement Receipt

EFS ID:	29941847
Application Number:	15208537
International Application Number:	
Confirmation Number:	1009
Title of Invention:	OPHTHALMIC COMPOSITION
First Named Inventor/Applicant Name:	Gregory I. OSTROW
Customer Number:	21971
Filer:	Xiaofan Yang/Lori Ford
Filer Authorized By:	Xiaofan Yang
Attorney Docket Number:	46682-701.301
Receipt Date:	31-JUL-2017
Filing Date:	12-JUL-2016
Time Stamp:	20:57:23
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		46682_701_301_312_Amendment.pdf	32194	yes	3
			2e23ecec83cc5b6f962bb6ee587614943b005d6ac		

Multipart Description/PDF files in .zip description			
Document Description	Start	End	
Amendment after Notice of Allowance (Rule 312)	1	1	
Specification	2	2	
Applicant Arguments/Remarks Made in an Amendment	3	3	

Warnings:

Information:

Total Files Size (in bytes):	32194

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
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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
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Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	15208537
				Filing Date	07-12-2016
				First Named Inventor	OSTROW, Gregory I.
				Art Unit	1621
				Examiner Name	Zohreh A Fay
Sheet	1	of	2	Attorney Docket Number	46682-701.301

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			
		None			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T ⁶
		Country Code ³ Number ⁴ Kind Code ⁵ (if known)				
		None				

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No. ¹	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
	001	U.S. Serial No. 14/859,042 Office Action dated May 18, 2017.	☐

Examiner Signature	/ZOHREH A FAY/	Date Considered	06/21/2017

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.97 and 1.98. 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 2 hours 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, 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 (1-800-786-9199) and select option 2.

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)		Complete if Known			
		Application Number	15208537		
		Filing Date	07-12-2016		
		First Named Inventor	OSTROW, Gregory I.		
		Art Unit	1621		
		Examiner Name	Zohreh A Fay		
Sheet	2	of	2	Attorney Docket Number	46682-701.301

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.

- ☒ 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	/Xiaofan Yang/	Date (YYYY-MM-DD)	2017-05-30
Name/Print	Xiaofan Yang	Registration Number	61459

This collection of information is required by 37 CFR 1.97 and 1.98. 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 1 hour 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.**



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/208,537	07/12/2016	Gregory I. OSTROW	46682-701.301	1009

21971 7590 06/27/2017
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER

FAY, ZOHREH A

ART UNIT	PAPER NUMBER

1621

NOTIFICATION DATE	DELIVERY MODE

06/27/2017

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):

patentdocket@wsgr.com

**UNITED STATES DEPARTMENT OF COMMERCE****U.S. Patent and Trademark Office**

Address : COMMISSIONER FOR PATENTS

P.O. Box 1450

Alexandria, Virginia 22313-1450

APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
15/208,537	12 July, 2016	OSTROW ET AL.	46682-701.301

WILSON, SONSINI, GOODRICH & ROSATI 650 PAGE MILL ROAD PALO ALTO, CA 94304-1050		EXAMINER	
		ZOHREH FAY	
		ART UNIT	PAPER
		1621	20170621

DATE MAILED:

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

Commissioner for Patents

The Information Disclosure Statement filed on 5/31/2017 has been considered by the examiner.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZOHREH FAY whose telephone number is (571)272-0573. The examiner can normally be reached on Monday to Friday 9:30-6:00. Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Winston Shen can be reached on (571) 272-3157. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. 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). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ZOHREH FAY/
Primary Examiner, Art Unit 1621

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.

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	15208537
				Filing Date	07-12-2016
				First Named Inventor	OSTROW; Gregory I.
				Art Unit	1621
				Examiner Name	Zohreh A Fay
Sheet	1	of	2	Attorney Docket Number	46682-701.301

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			
		None			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T ⁶
		Country Code ³ Number ⁴ Kind Code ⁵ (if known)				
		None				

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No. ¹	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
	001	U.S. Serial No. 14/859,042 Office Action dated May 18, 2017.	☐

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.97 and 1.98. 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 2 hours 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, 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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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)		Complete if Known			
		Application Number	15208537		
		Filing Date	07-12-2016		
		First Named Inventor	OSTROW, Gregory I.		
		Art Unit	1621		
		Examiner Name	Zohreh A Fay		
Sheet	2	of	2	Attorney Docket Number	46682-701.301

CERTIFICATION STATEMENT

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- ☒ See attached certification statement.

- ☒ 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	/Xiaofan Yang/	Date (YYYY-MM-DD)	2017-05-30
Name/Print	Xiaofan Yang	Registration Number	61459

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Electronic Patent Application Fee Transmittal

Application Number:	15208537			
Filing Date:	12-Jul-2016			
Title of Invention:	OPHTHALMIC COMPOSITION			
First Named Inventor/Applicant Name:	Gregory I. OSTROW			
Filer:	Michael J. Hostetler/F. Yang/Jennifer Vail			
Attorney Docket Number:	46682-701.301			
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:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	2806	1	90	90
Total in USD (\$)				90

Electronic Acknowledgement Receipt

EFS ID:	29360886
Application Number:	15208537
International Application Number:	
Confirmation Number:	1009
Title of Invention:	OPHTHALMIC COMPOSITION
First Named Inventor/Applicant Name:	Gregory I. OSTROW
Customer Number:	21971
Filer:	Michael J. Hostetler/F. Yang/Jennifer Vail
Filer Authorized By:	Michael J. Hostetler
Attorney Docket Number:	46682-701.301
Receipt Date:	31-MAY-2017
Filing Date:	12-JUL-2016
Time Stamp:	18:16:17
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	\$90
RAM confirmation Number	060117INTEFSW00006161232415
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		46682-701-301_IDS.pdf	262965	yes	6
			e6699f6a9bc98e4b67aa4e3192ba12931b35af41		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Transmittal Letter		1	4	
	Information Disclosure Statement (IDS) Form (SB08)		5	6	
Warnings:					
Information:					
2	Non Patent Literature	US14859042_OA_18May2017.pdf	306469	no	8
			89bedeaaaa290f31edd7ee75e7a7c96482faa7f42		
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30781	no	2
			ea6ebd7a53f88e864db0eb6e901622048ea455c1		
Warnings:					
Information:					
Total Files Size (in bytes):			600215		

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New International Application Filed with the USPTO as a Receiving Office

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	OSTROW; Gregory I. et al.
Serial Number:	15/208,537
Filing or 371 (c) Date:	2016-07-12
Title:	OPHTHALMIC COMPOSITION

Group Art Unit:	1621
Examiner:	Zohreh A Fay
CONFIRMATION NO:	1009

FILED ELECTRONICALLY ON: May 31, 2017

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

INFORMATION DISCLOSURE STATEMENT
UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

- A. ☐ 37 CFR § 1.97 (b). This Information Disclosure Statement should be considered by the Office because:
- ☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);
-- OR --
 - ☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;
-- OR --
 - ☐ (3) It is being filed before the mailing of a first Office action on the merits;
-- OR --
 - ☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.
- B. ☐ 37 CFR § 1.97(c). Although this Information Disclosure Statement is being filed after the period specified in 37 CFR § 1.97(b), above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:
- ☐ a statement as specified in §1.97 (e) provided concurrently herewith;
-- OR --
 - ☐ a fee of \$180.00 as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.
- C. ☒ 37 CFR § 1.97 (d). Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:
- i. a statement as specified in § 1.97 (e);
-- AND --
 - ii. a fee of \$90.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.
- D. ☒ 37 CFR §1.97 (e). Statement.
- ☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);
-- AND/OR --
 - ☒ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);
-- AND/OR --
 - ☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

- E. ☒ *Statement Under 37 C.F.R. §1.704(d)*. Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.
- F. ☒ *37 CFR §1.98 (a) (2)*. The content of the Information Disclosure Statement is as follows:
- ☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.
- OR --
- ☐ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.
- AND/OR --
- ☒ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).
- AND/OR --
- ☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).
- G. ☐ *37 CFR §1.98(a)(3)*. The Information Disclosure Statement includes non-English patents and/or references.
- ☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.
- ☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.
- OR --
- ☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____
- ☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.
- H. ☐ *37 CFR §1.98(d)*. Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:
- ☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.
- Application in which the information was submitted: _____
- Information Disclosure Statement(s) filed on: _____
- AND
- ☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

- I. ☒ *Fee Authorization.* The Commissioner is hereby authorized to charge the above-referenced fees of \$90.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No.46682-701.301).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: May 30, 2017

By: /Xiaofan Yang/

Xiaofan Yang, Reg. No. 64159

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 21971



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

21971 7590 05/30/2017
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER

FAY, ZOHREH A

ART UNIT

PAPER NUMBER

1621

DATE MAILED: 05/30/2017

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.

15/208,537

07/12/2016

Gregory I. OSTROW

46682-701.301

1009

TITLE OF INVENTION: OPHTHALMIC COMPOSITION

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$480	\$0	\$0	\$480	08/30/2017

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: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (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.

21971 7590 05/30/2017
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

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 facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/208,537	07/12/2016	Gregory I. OSTROW	46682-701.301	1009

TITLE OF INVENTION: OPTHALMIC COMPOSITION

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$480	\$0	\$0	\$480	08/30/2017

EXAMINER	ART UNIT	CLASS-SUBCLASS
FAY, ZOHREH A	1621	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 03-02 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 has been filed for recordation as set forth in 37 CFR 3.11. 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. The following fee(s) are submitted:

- ☐ Issue Fee
☐ Publication Fee (No small entity discount permitted)
☐ Advance Order - # of Copies _____

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

- ☐ A check is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☐ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

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 _____ Date _____
Typed or printed name _____ Registration No. _____



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/208,537	07/12/2016	Gregory I. OSTROW	46682-701.301	1009

21971 7590 05/30/2017
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER

FAY, ZOHREH A

ART UNIT	PAPER NUMBER

1621

DATE MAILED: 05/30/2017

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 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, 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. 15/208,537	Applicant(s) OSTROW ET AL.	
	Examiner ZOHREH FAY	Art Unit 1621	AIA (First Inventor to File) 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 the amendments and remarks filed on 4/21/2017.
☐ 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 31-39 and 41-50. 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 a reply 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)	5. ☐ Examiner's Amendment/Comment
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____	6. ☒ Examiner's Statement of Reasons for Allowance
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material	7. ☐ Other _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____.	

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

Reasons for Allowance:

Applicant's amendments of April 21, 2017, amending the claims to atropine as the only active ingredient and the arguments that in the examples of EP 0332826 atropine is not dissolved in deuterated water, but it is dissolved in ordinary water placed the application in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZOHREH FAY whose telephone number is (571)272-0573. The examiner can normally be reached on Monday to Friday 9:30-6:00.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Winston Shen can be reached on (571) 272-3157. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1621

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). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ZF
/ZOHREH FAY/
Primary Examiner, Art Unit 1621

Search Notes 	Application/Control No. 15208537	Applicant(s)/Patent Under Reexamination OSTROW ET AL.
	Examiner ZOHREH FAY	Art Unit 1621

CPC- SEARCHED		
Symbol	Date	Examiner
A61K 31/46	5/17/2017	ZF

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
West	9/15/2016	ZF
inventor search	9/15/2016	ZF
Updated	1/19/2017	ZF
Updated	5/17/2017	ZF

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
A61K	31/46	5/17/2017	ZF

Issue Classification 	Application/Control No. 15208537	Applicant(s)/Patent Under Reexamination OSTROW ET AL.
	Examiner ZOHREH FAY	Art Unit 1621

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

CPC Combination Sets				
Symbol	Type	Set	Ranking	Version

NONE (Assistant Examiner) _____ (Date) _____		Total Claims Allowed: 19	
/ZOHREH FAY/ Primary Examiner.Art Unit 1621 5/17/2017 (Primary Examiner) _____ (Date) _____		O.G. Print Claim(s) 1	O.G. Print Figure none

Issue Classification 	Application/Control No. 15208537	Applicant(s)/Patent Under Reexamination OSTROW ET AL.
	Examiner ZOHREH FAY	Art Unit 1621

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47															
Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	31	17	48												
2	32	18	49												
3	33	19	50												
4	34														
5	35														
6	36														
7	37														
8	38														
9	39														
10	41														
11	42														
12	43														
13	44														
14	45														
15	46														
16	47														

NONE (Assistant Examiner) _____ (Date) _____		Total Claims Allowed: 19	
/ZOHREH FAY/ Primary Examiner.Art Unit 1621 5/17/2017 (Primary Examiner) _____ (Date) _____		O.G. Print Claim(s) 1	O.G. Print Figure none

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application:

Inventor: Gregory I. Ostrow et al.

Application No.: 15/208,537

Filed: July 12, 2016

Title: **OPHTHALMIC COMPOSITION**

Confirmation No.: 1009

Examiner: Zohreh A. Fay

Group Art Unit: 1621

ELECTRONICALLY FILED ON APRIL 21, 2017

M/S AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**AFCP2.0 RESPONSE TO FINAL OFFICE ACTION DATED JANUARY 25, 2017 AND
ADVISORY ACTION DATED APRIL 13, 2017**

Commissioner:

This paper is filed under the After Final Consideration Pilot 2.0 in response to the Final Office Action dated January 25, 2017, and the Advisory Action dated April 13, 2017. Applicant respectfully requests reconsideration and withdrawal of the obviousness rejections based on the remarks submitted herein. If any additional fee is due, please charge it to Deposit Account No. 23-2415, referencing Docket No. 46682-701.301.

Listing of the Claims begins on page 2 of this paper.

Remarks begin on page 6 of this paper.

Conclusion is at page 15

OK TO ENTER: /Z.A.F/

PATENT
Attorney Docket No. 46682-701.301

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application:

Inventor: Gregory I. Ostrow et al.

Application No.: 15/208,537

Filed: July 12, 2016

Title: **OPHTHALMIC COMPOSITION**

Confirmation No.: 1009

Examiner: Zohreh A. Fay

Group Art Unit: 1621

**ELECTRONICALLY FILED
ON MARCH 21, 2017**

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

RESPONSE TO FINAL OFFICE ACTION DATED JANUARY 25, 2017

Commissioner:

This paper responds to the Final Office Action dated January 25, 2017, setting forth a two-month response due date of March 25, 2017, for Advisory Action. Accordingly, this response is timely submitted.

Listing of the Claims begins on page 2 of this paper.

Remarks begin on page 5 of this paper.

Conclusion is on page 14 of this paper.

PATENT
Attorney Docket No. 46682-701.301

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Alexandria, VA 22313-1450

**AFCP2.0 RESPONSE TO FINAL OFFICE ACTION DATED JANUARY 25, 2017 AND
ADVISORY ACTION DATED APRIL 13, 2017**

Commissioner:

This paper is filed under the After Final Consideration Pilot 2.0 in response to the Final Office Action dated January 25, 2017, and the Advisory Action dated April 13, 2017. Applicant respectfully requests reconsideration and withdrawal of the obviousness rejections based on the remarks submitted herein. If any additional fee is due, please charge it to Deposit Account No. 23-2415, referencing Docket No. 46682-701.301.

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/208,537	Filing Date 07/12/2016	☐ 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	04/21/2017	CLAIMS REMAINING AFTER AMENDMENT	Minus	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)
	Total (37 CFR 1.16(i))	* 19	Minus	** 20	= 0	X \$40 =	0
	Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X \$210 =	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.

SLIE
HELENA PAYTON

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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CERTIFICATION AND REQUEST FOR CONSIDERATION UNDER THE AFTER FINAL CONSIDERATION PILOT PROGRAM 2.0		
Practitioner Docket No.: 46682-701.301	Application No.: 15/208,537	Filing Date: July 12, 2016
First Named Inventor: Gregory I. Ostrow	Title: OPHTHALMIC COMPOSITION	
APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS CONSIDERATION UNDER THE AFTER FINAL CONSIDERATION PILOT PROGRAM 2.0 (AFCP 2.0) OF THE ACCOMPANYING RESPONSE UNDER 37 CFR 1.116. 1. The above-identified application is (i) an original utility, plant, or design nonprovisional application filed under 35 U.S.C. 111(a) [a continuing application (<i>e.g.</i>, a continuation or divisional application) is filed under 35 U.S.C. 111(a) and is eligible under (i)], or (ii) an international application that has entered the national stage in compliance with 35 U.S.C. 371(c). 2. The above-identified application contains an outstanding final rejection. 3. Submitted herewith is a response under 37 CFR 1.116 to the outstanding final rejection. The response includes an amendment to at least one independent claim, and the amendment does not broaden the scope of the independent claim in any aspect. 4. This certification and request for consideration under AFCP 2.0 is the only AFCP 2.0 certification and request filed in response to the outstanding final rejection. 5. Applicant is willing and available to participate in any interview requested by the examiner concerning the present response. 6. This certification and request is being filed electronically using the Office's electronic filing system (EFS-Web). 7. Any fees that would be necessary consistent with current practice concerning responses after final rejection under 37 CFR 1.116, <i>e.g.</i>, extension of time fees, are being concurrently filed herewith. [There is no additional fee required to request consideration under AFCP 2.0.] 8. By filing this certification and request, applicant acknowledges the following: • Reissue applications and reexamination proceedings are not eligible to participate in AFCP 2.0. • The examiner will verify that the AFCP 2.0 submission is compliant, <i>i.e.</i>, that the requirements of the program have been met (see items 1 to 7 above). For compliant submissions: ○ The examiner will review the response under 37 CFR 1.116 to determine if additional search and/or consideration (i) is necessitated by the amendment and (ii) could be completed within the time allotted under AFCP 2.0. If additional search and/or consideration is required but cannot be completed within the allotted time, the examiner will process the submission consistent with current practice concerning responses after final rejection under 37 CFR 1.116, <i>e.g.</i>, by mailing an advisory action. ○ If the examiner determines that the amendment does not necessitate additional search and/or consideration, or if the examiner determines that additional search and/or consideration is required and could be completed within the allotted time, then the examiner will consider whether the amendment places the application in condition for allowance (after completing the additional search and/or consideration, if required). If the examiner determines that the amendment does not place the application in condition for allowance, then the examiner will contact the applicant and request an interview. ▪ The interview will be conducted by the examiner, and if the examiner does not have negotiation authority, a primary examiner and/or supervisory patent examiner will also participate. ▪ If the applicant declines the interview, or if the interview cannot be scheduled within ten (10) calendar days from the date that the examiner first contacts the applicant, then the examiner will proceed consistent with current practice concerning responses after final rejection under 37 CFR 1.116.		
Signature /Xiaofan Yang/	Date April 21, 2017	
Name (Print/Typed) Xiaofan Yang	Practitioner Registration No. 61459	
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, see below*.		
☒ * Total of <u>1</u> 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:

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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.
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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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ELECTRONICALLY FILED ON APRIL 21, 2017

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Listing of the Claims begins on page 2 of this paper.

Remarks begin on page 6 of this paper.

Conclusion is at page 15

LISTING OF THE CLAIMS

The following listing of claims replaces all prior listings of claims in this application.

CLAIM LISTING:

1-30. (Cancelled).

31. (Currently Amended) An ophthalmic composition, ~~consisting essentially of from about 0.001 wt% to about 0.03 wt% of a muscarinic antagonist~~ comprising one and no more than one ophthalmic agent, and deuterated water, at a pD of from about 4.2 to about 7.9, wherein the ~~muscarinic antagonist is~~ ophthalmic agent consists of atropine, ~~or~~ atropine sulfate, or a combination thereof, at a concentration of from about 0.001 wt% to about 0.03 wt%.
32. (Previously Presented) The ophthalmic composition of claim 31, 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.
33. (Previously Presented) The ophthalmic composition of claim 31, wherein the muscarinic antagonist is present in the composition at a concentration of one of: 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%.
34. (Previously Presented) The ophthalmic composition of claim 31, wherein the ophthalmic composition further comprises an osmolarity adjusting agent.

35. (Previously Presented) The ophthalmic composition of claim 34, wherein the osmolarity adjusting agent is sodium chloride.
36. (Previously Presented) The ophthalmic composition of claim 31, wherein the ophthalmic composition further comprises a preservative.
37. (Previously Presented) The ophthalmic composition of claim 36, wherein the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof.
38. (Previously Presented) The ophthalmic composition of claim 31, wherein the ophthalmic composition further comprises a buffer agent.
39. (Previously Presented) The ophthalmic composition of claim 38, wherein 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.
40. (Cancelled).
41. (Previously Presented) The ophthalmic composition of claim 31, wherein the ophthalmic composition further comprises a pD adjusting agent.
42. (Previously Presented) The ophthalmic composition of claim 41, wherein the pD adjusting agent comprises deuterated hydrochloric acid, deuterated sodium hydroxide, deuterated acetic acid, or deuterated citric acid.
43. (Previously Presented) The ophthalmic composition of claim 31, 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.

44. (Previously Presented) The ophthalmic composition of claim 31, wherein the ophthalmic composition is not formulated as an injectable formulation.
45. (Currently Amended) An ophthalmic solution, ~~consisting essentially of from about 0.001 wt% to about 0.03 wt% of a muscarinic antagonist comprising one and no more than one~~ ophthalmic agent, and deuterated water, at a pD of from about 4.2 to about 7.9, wherein the ~~muscarinic antagonist is~~ ophthalmic agent consists of atropine, ~~or atropine sulfate, or a combination thereof, at a concentration of from about 0.001 wt% to about 0.03 wt%.~~
46. (Previously Presented) The ophthalmic solution of claim 45, wherein 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.
47. (Previously Presented) The ophthalmic solution of claim 45, wherein 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.
48. (Currently Amended) A method of arresting myopia progression, comprising administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition ~~consisting essentially of from about 0.001 wt% to about 0.03 wt% of a muscarinic antagonist comprising one and no more than one~~ ophthalmic agent, and deuterated water, at a pD of from about 4.2 to about 7.9, wherein the ~~muscarinic antagonist is~~ ophthalmic agent consists of atropine, ~~or atropine sulfate, or a combination thereof, at a concentration of from about 0.001 wt% to about 0.03 wt%.~~
49. (Previously Presented) The method of claim 48, wherein the ophthalmic composition is stored at between about 2 °C to about 10 °C prior to first use.

50. (Previously Presented) The method of claim 48, wherein the ophthalmic composition is stored at between about 16 °C to about 26 °C after first use.

REMARKS

This paper is filed in response to the Final Office Action dated January 25, 2017 and the Advisory Action dated April 13, 2017. In the Office Action, claims 31-50 are rejected as allegedly obvious over EP0332826 (“Teva”) in view of US5,716,952 (“WoldeMussie”) and US2012/0015035 (“Widsoet”). For the sole purpose of expediting prosecution of the present application, Applicant has amended claims 31, 45, and 48 to recite an ophthalmic composition comprising one and no more than one ophthalmic agent, and deuterated water, at a pD of from about 4.2 to about 7.9, wherein the ophthalmic agent consists of atropine, ~~or~~ atropine sulfate, or a combination thereof, at a concentration of from about 0.001 wt% to about 0.03 wt%. Claim 40 is cancelled without prejudice. Support for the claim amendment can be found throughout the specification. No new matter is added. In light of the claim amendment and remarks submitted herewith, reconsideration and withdrawal of the obviousness rejections are respectfully requested.

To support an obviousness rejection, MPEP §2143.03 requires “all words of a claim to be considered” and MPEP § 2141.02 requires consideration of the “[claimed] invention and prior art as a whole.” Further, the Board of Patent Appeal and Interferences recently confirmed that a proper, post-KSR obviousness determination still requires the Office make “a searching comparison of the claimed invention – including all its limitations – with the teaching of the prior art.” See, *In re Wada and Murphy*, Appeal 2007-3733, citing *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis in original). In sum, it remains well-settled law that an obviousness rejection requires at least a suggestion of *all* of the claim elements. Applicant submits that the cited references, whether taken alone or in combination, do not teach or suggest an ophthalmic composition, comprising one and no more than one ophthalmic agent, and deuterated water at a pD of from about 4.2 to about 7.9, wherein the ophthalmic agent consists of atropine, atropine sulfate, or a combination thereof, at a concentration of from about 0.001 wt% to about 0.03 wt%, much less recognizing the technical effects thereof, as discussed in greater detail below.

WoldeMussie and Widsoet Are Irrelevant to D₂O-Based Atropine Formulations

In the Office Action, the Patent Office cites WoldeMussie for allegedly teaching ophthalmic formulations containing a muscarinic antagonist; and Widsoet for allegedly

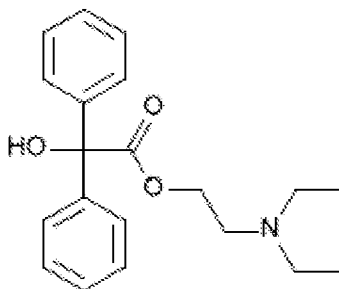
teaching atropine being used as a muscarinic antagonist in ophthalmic formulations (page 6 of the Office Action). Applicant notes that neither reference teaches or suggests D₂O-based atropine formulations, much less recognizing the technical effects thereof.

Teva Cannot Be Properly Combined with WoldeMussie and Widsoet to Teach D2O-Based Atropine Formulations Containing Atropine and/or Atropine Sulfate as Sole Ophthalmic Agents

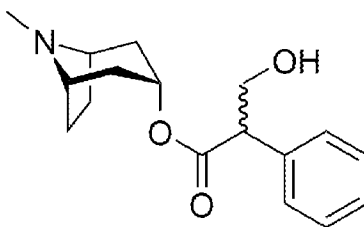
The Office Action cites Teva for allegedly teaching the following:

The EP 0332826 teaches an injectable pharmaceutical formulation having a long shelf life comprising a solvent, such as deuterium oxide and atropine. See claims 1 and 13-15. The EP differs from the claimed invention in the ophthalmic use of atropine and the concentrations used. WoldeMussie et al. Teach the use of the claimed muscarinic

Applicant notes that Teva does not teach the use of deuterium oxide to stabilize pharmaceutical formulations in general regardless of the active agents it contains. Instead, Teva purportedly relates to D₂O-based injectable formulations containing a very specific active agent – α -amino or α -hydroxy carboxylic acid derivatives (esters or amides). See Abstract and Summary of Teva. The preferred example of α -amino or α -hydroxy carboxylic acid derivatives is benactyzine (chemical structure below).



In comparison, Atropine (chemical structure above) is a **β -hydroxy** carboxylic ester.



Teva purportedly describes that formulations containing benactyzine can have additional active agent, including atropine sulfate. See col. 5 of Teva. However, in Teva's Example 1, the benactyzine injectable formulation, purportedly stabilized in D₂O, is used separately (*i.e.* in multistage automatic injector) with an atropine formulation **dissolved in ordinary water**. See below.

EXAMPLE I

Benactyzine hydrochloride (80 mg) is dissolved in 18 ml of deuterium oxide, the pH is adjusted by known methods (see e.g. A.K. Covington, *Analytical Chemistry*, 40: 700 (1968)) to 2.7 with strong acid, and the volume is brought to 20 ml with more deuterium oxide. The resulting solution is sterilized by passing through a pharmaceutically acceptable and antimicrobial filtering device, and then divided into 1 ml portions. The resultant composition is suitable for use in a single stage automatic injector, where benactyzine is the only active ingredient to be administered, or in a multistage automatic injector together with relatively more stable active ingredients (such as atropine and trimedoxime) dissolved in ordinary water in one or more further separate compartment(s).

Thus, not only does Teva fail to recognize the stability problem for ultra-diluted atropine formulations or to contemplate solution for such problems, Teva actively teaches that atropine **is stable in ordinary water**. In other words, one of ordinary skill in the art would understand that there is no reason to substitute ordinary water, in which the atropine is "stable" as explicit taught by Teva in its Example 1, with the more expensive D₂O for the purpose of stabilizing atropine therein. See MPEP 2143A (Example 3), stating that

Office personnel should note that in this case the modification of the prior art that had been presented as an argument for obviousness was an extra process step that added an additional component to a known, successfully marketed formulation. The proposed modification thus amounted to extra work and greater expense for no apparent reason. . . In the *Omeprazole* case, in view of the expectations of those of ordinary skill in the art, adding the subcoating would not have been expected to confer any particular desirable property on the final product. Rather, the final product obtained according to

the proposed modifications would merely have been expected to have the same functional properties as the prior art product.

On the other hand, it is Applicant, through unexpected results discovered in stability studies, recognized the stability problem for ultra-diluted atropine formulations, and developed its solution through the use of D2O solvent, and did so against Teva's explicit teaching that atropine is stable in ordinary water. See also, MPEP 2143A (Example 3), where the Office discusses *In re Omeprazole Patent Litigation*, 536 F.3d 1361 (Fed. Cir. 2008), and states:

The Omeprazole case can also be analyzed in view of the discovery of a previously unknown problem by the patentee. If the adverse interaction between active agent and coating had been known, it might well have been obvious to use a subcoating. However, since the problem had not been previously known, there would have been no reason to incur additional time and expense to add another layer, even though the addition would have been technologically possible. This is true because the prior art of record failed to mention any stability problem, despite the acknowledgment during testimony at trial that there was a known theoretical reason that omeprazole might be subject to degradation in the presence of the known coating material.

Applicant further notes that Teva also purportedly describe another example as follows:

EXAMPLE II

Benactyzine hydrochloride (40 mg), atropine sulfate (10 mg) and trimedoxime bromide (400 mg) are dissolved in 18 ml of deuterium oxide. The pH is adjusted by known methods to 2.7 with strong acid, and the volume is brought to 20 ml with more deuterium oxide. The resulting solution is sterilized by passing through a pharmaceutically acceptable and antimicrobial filtering device, and then divided into 2 ml portions. The resultant composition is suitable for use in a single stage automatic injector. – *Concentration of atropine in this example is 0.05 wt%.*

However, understanding that Teve does not recognize the stability problem for ultra-diluted atropine formulations, one of ordinary skill in the art would consider the inclusion of atropine in the D2O formulation in Example II as a result of mere convenience, *i.e.* so that the formulation can be used in "a single stage automatic injector". In other words, one of ordinary skill in the art would not consider Teva's Example II as teaching the using of D2O to stabilize atropine formulations in which α -amino or α -hydroxy carboxylic acid derivatives (*e.g.* benactyzine) is not present.

To the extent the Patent Office holds that Teva's Example II describes use of D₂O to stabilize α -amino or α -hydroxy carboxylic acid derivatives (e.g. benactyzine) in a combination formulation that also contains atropine for convenience of co-administration, the amended claims of the present application has been amended to recite "an ophthalmic composition, comprising one and no more than one ophthalmic agent, and deuterated water at a pD of from about 4.2 to about 7.9, wherein the ophthalmic agent consists of atropine, atropine sulfate, or a combination thereof, at a concentration of from about 0.001 wt% to about 0.03 wt%." As a result, Teva's Example II directed to a combination formulation of benactyzine and atropine is **specifically excluded** from the amended claims.

In summary, Applicant notes that there is insufficient rationale to combine Teva and other references to produce a D₂O-based formulation in which atropine is the monotherapeutic agent because atropine and its derivatives are specifically recognized as stable in ordinary water. In other words, any modification or combination of Teva and other references to arrive at a D₂O-based formulation in which atropine is the monotherapeutic agent as featured in the amended claims would lack the requisite rationale because "the final product obtained according to the proposed modifications would merely have been expected to have the same functional properties as the prior art product."

Unexpected Technical Effects of D₂O-Based Atropine Formulation

Finally, Applicant draws the Patent Office's attention to the surprising data presented in the application. In particular, the D₂O formulations disclosed in the present application yield the following unexpected properties:

- Better stability
- Lower main degradant
- Longer shelf-life

Better stability

Tables 24A and 24B under paragraph [00329] (Example 11) and Table 15 under paragraph [00300] (Example 9) show atropine sulfate purity data of different formulations. Table 24A shows atropine sulfate formulations in water. Table 24B shows similar atropine sulfate formulations in deuterated water. The pair-wise formulations can be viewed as:

- Formulation 3 and Formulation 7
- Formulation 5 and Formulation 8
- Formulations 10/11 and Formulation 9
- Formulation 13 and Formulation 12

Formulation 8 shows a pD of 6.2 (with effective pH of 5.8; Table 24B). It is formulated similarly as Formulation 5 (Table 24A), with the exception of deuterated water. At week 0, both formulations (5 and 8) contain similar percentage of atropine sulfate (98.16% for Formulation 5 and 98.93% for Formulation 8). However, at week 2, a higher degradation is observed for Formulation 5 across all three temperature ranges while a much lower degradation is observed for Formulation 8. Similarly, at week 4, only 66.83% of atropine sulfate remains at 60°C in Formulation 5. In contrast, 92.72% of atropine sulfate remains at 60°C in Formulation 8.

Similarly, Formulation 9 shows a higher purity percentage at week 4 across all 3 temperatures than either Formulation 10 or 11. Formulation 12 (pD 7.2; effective pH of 6.8) shows about 46% atropine sulfate at week 4 and 60°C while Formulation 13 only retained about 28% atropine sulfate at week 4 and 60°C.

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

Lower Main Degradant

With respect to the main degradant—tropic acid, Tables 25A and 25B (under paragraph [00330]) further show the percentage of tropic acid are present with each individual formulations. For example, only 4.03% of tropic acid was observed at 60°C in Formulation 8 while about 29% of tropic acid was observed at 60°C at week 4 in Formulation 5. Formulation 9 contains about 29% of tropic acid at 60°C at week 4 while Formulations 10 and 11 each contains about 54% or 62% tropic acid at 60°C, respectively. Similarly, Formulation 12 contains about 48% tropic acid at 60°C while Formulation 13 contains 69%. As such, the deuterated water stabilizes the atropine sulfate.

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

Longer Shelf-life

Table 30 under Example 12 (paragraph [00334]) shows the predicted shelf life at temperatures of 40°C, 30°C, 25°C, and 2-8°C for Formulations 2-8 for total Related Substance and for the main degradant tropic acid, respectively. As shown from the table, Formulation 8 has longer shelf life across all 4 temperature ranges when compared with Formulation 5. In particular, at 2-8 degree C, Formulation 8 has a shelf life of about 158 months while Formulation 5 only has a shelf life of about 37 months.

Table 30

Formulation	Stability Prediction		RS		Tropic Acid	
	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

For reasons stated above, the cited references do not teach or suggest the use of deuterated water in an ophthalmic formulation in which atropine, atrophine sulfate, or combination thereof is the monotherapeutic agent, much less recognizing the technical effect thereof, as summarized above. Accordingly, the obviousness rejections should be withdrawn.

CONCLUSION

Applicant submits that this response fully addresses the Final Office Action dated January 25, 2017 and respectfully request consideration and allowance of the claims.

Should the Examiner have any questions, the Examiner is encouraged to contact the undersigned attorney at (858) 350-2339. If additional fees are believed to be required, the Commissioner is authorized to charge any additional fees to Deposit Account No. 23-2415 (Attorney Docket No. 46682-701.301).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI
Professional Corporation

Date: April 21, 2017

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Electronic Acknowledgement Receipt

EFS ID:	28997939
Application Number:	15208537
International Application Number:	
Confirmation Number:	1009
Title of Invention:	OPHTHALMIC COMPOSITION
First Named Inventor/Applicant Name:	Gregory I. OSTROW
Customer Number:	21971
Filer:	Xiaofan Yang/Lori Ford
Filer Authorized By:	Xiaofan Yang
Attorney Docket Number:	46682-701.301
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	After Final Consideration Program Request	46682_701_301_AFCP_Request.PDF	226619	no	2
			8bc1b0e4dcb0914073da924e96db9a5e55961ff9		

Warnings:

Information:					
2		46682_701_301_Response.pdf	218918	yes	15
			583ce15f3ae6179a9cf66d5a80f34dd524ccc394		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Response After Final Action		1	1	
	Claims		2	5	
	Applicant Arguments/Remarks Made in an Amendment		6	15	
Warnings:					
Information:					
Total Files Size (in bytes):			445537		
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.
15/208,537	07/12/2016	Gregory I. OSTROW	46682-701.301	1009

21971 7590 04/13/2017
WILSON, SONSINI, GOODRICH & ROSATI
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EXAMINER

FAY, ZOHREH A

ART UNIT	PAPER NUMBER

1621

NOTIFICATION DATE	DELIVERY MODE

04/13/2017

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):

patentdocket@wsgr.com

Advisory Action Before the Filing of an Appeal Brief	Application No. 15/208,537	Applicant(s) OSTROW ET AL.	
	Examiner ZOHREH FAY	Art Unit 1621	AIA (First Inventor to File) Status Yes

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

THE REPLY FILED 21 March 2017 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

NO NOTICE OF APPEAL FILED

1. ☒ The reply was filed after a final rejection. No Notice of Appeal has been filed. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance;
(2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114 if this is a utility or plant application. Note that RCEs are not permitted in design applications. The reply must be filed within one of the following time periods:

a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.

b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action; or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

c) ☐ A prior Advisory Action was mailed more than 3 months after the mailing date of the final rejection in response to a first after-final reply filed within 2 months of the mailing date of the final rejection. The current period for reply expires _____ months from the mailing date of the prior Advisory Action or SIX MONTHS from the mailing date of the final rejection, whichever is earlier.

Examiner Note: If box 1 is checked, check either box (a), (b) or (c). ONLY CHECK BOX (b) WHEN THIS ADVISORY ACTION IS THE FIRST RESPONSE TO APPLICANT'S FIRST AFTER-FINAL REPLY WHICH WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. ONLY CHECK BOX (c) IN THE LIMITED SITUATION SET FORTH UNDER BOX (c). See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) or (c) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendments filed after a final rejection, but prior to the date of filing a brief, will not be entered because

a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);

b) ☐ They raise the issue of new matter (see NOTE below);

c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. ☐ Applicant's reply has overcome the following rejection(s): _____.

6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. ☒ For purposes of appeal, the proposed amendment(s): (a) ☐ will not be entered, or (b) ☒ will be entered, and an explanation of how the new or amended claims would be rejected is provided below or appended.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

9. ☐ The affidavit or other evidence filed after final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

10. ☐ The affidavit or other evidence filed after the date of filing the Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

11. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

12. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:
See Continuation Sheet.

13. ☐ Note the attached Information *Disclosure Statement(s)*. (PTO/SB/08) Paper No(s). _____

14. ☐ Other: _____.

STATUS OF CLAIMS

15. The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: none.
Claim(s) objected to: none.
Claim(s) rejected: 31-50.
Claim(s) withdrawn from consideration: none.

/ZOHREH FAY/
Primary Examiner, Art Unit 1621

Applicant's arguments have been noted. Applicant alleges criticality to the phrase "consisting essentially". It is the examiner's position that such phrase is the same as "comprising" in the absence of showing that the addition of other ingredients would materially effect the nature of the claimed invention. Applicant in his remarks also argues that Teva does not teach that the addition of D2O would increase the stability of atropine. It is the examiner's position that the claims of the instant application are composition claims. The increased stability is the expected property of such components being used together. Applicant's arguments regarding the example I of Teva have been noted. Applicant argues that Teva teaches the use of atropine in regular water. Applicant's attention is drawn to example II of Teva, which teaches the addition of D2O to atropine. The arguments regarding the unexpected results have been noted. It is the examiner's position that such results are obtained by combination of atropine and D2O, which is the expected property of Teva's composition as well.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application:

Inventor: Gregory I. Ostrow et al.

Application No.: 15/208,537

Filed: July 12, 2016

Title: **OPHTHALMIC COMPOSITION**

Confirmation No.: 1009

Examiner: Zohreh A. Fay

Group Art Unit: 1621

**ELECTRONICALLY FILED
ON MARCH 21, 2017**

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RESPONSE TO FINAL OFFICE ACTION DATED JANUARY 25, 2017

Commissioner:

This paper responds to the Final Office Action dated January 25, 2017, setting forth a two-month response due date of March 25, 2017, for Advisory Action. Accordingly, this response is timely submitted.

Listing of the Claims begins on page 2 of this paper.

Remarks begin on page 5 of this paper.

Conclusion is on page 14 of this paper.

LISTING OF THE CLAIMS

The following listing of claims replaces all prior listings of claims in this application.

CLAIM LISTING:

1-30. (Cancelled).

31. (Previously Presented) An ophthalmic composition, consisting essentially of from about 0.001 wt% to about 0.03 wt% of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9, wherein the muscarinic antagonist is atropine, or atropine sulfate.
32. (Previously Presented) The ophthalmic composition of claim 31, 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.
33. (Previously Presented) The ophthalmic composition of claim 31, wherein the muscarinic antagonist is present in the composition at a concentration of one of: 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%.
34. (Previously Presented) The ophthalmic composition of claim 31, wherein the ophthalmic composition further comprises an osmolarity adjusting agent.
35. (Previously Presented) The ophthalmic composition of claim 34, wherein the osmolarity adjusting agent is sodium chloride.

36. (Previously Presented) The ophthalmic composition of claim 31, wherein the ophthalmic composition further comprises a preservative.
37. (Previously Presented) The ophthalmic composition of claim 36, wherein the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof.
38. (Previously Presented) The ophthalmic composition of claim 31, wherein the ophthalmic composition further comprises a buffer agent.
39. (Previously Presented) The ophthalmic composition of claim 38, wherein 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.
40. (Previously Presented) The ophthalmic composition of claim 31, wherein the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof.
41. (Previously Presented) The ophthalmic composition of claim 31, wherein the ophthalmic composition further comprises a pD adjusting agent.
42. (Previously Presented) The ophthalmic composition of claim 41, wherein the pD adjusting agent comprises deuterated hydrochloric acid, deuterated sodium hydroxide, deuterated acetic acid, or deuterated citric acid.
43. (Previously Presented) The ophthalmic composition of claim 31, 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.

44. (Previously Presented) The ophthalmic composition of claim 31, wherein the ophthalmic composition is not formulated as an injectable formulation.
45. (Previously Presented) An ophthalmic solution, consisting essentially of from about 0.001 wt% to about 0.03 wt% of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9, wherein the muscarinic antagonist is atropine, or atropine sulfate.
46. (Previously Presented) The ophthalmic solution of claim 45, wherein 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.
47. (Previously Presented) The ophthalmic solution of claim 45, wherein 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.
48. (Previously Presented) A method of arresting myopia progression, comprising administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition consisting essentially of from about 0.001 wt% to about 0.03 wt% of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9, wherein the muscarinic antagonist is atropine, or atropine sulfate.
49. (Previously Presented) The method of claim 48, wherein the ophthalmic composition is stored at between about 2 °C to about 10 °C prior to first use.
50. (Previously Presented) The method of claim 48, wherein the ophthalmic composition is stored at between about 16 °C to about 26 °C after first use.

REMARKS

This paper is filed in response to the Final Office Action dated January 25, 2017. In the Office Action, claims 31-50 are rejected as allegedly obvious over EP0332826 (“Teva”) in view of US5,716,952 (“WoldeMussie”) and US2012/0015035 (“Wildsoet”).

To support an obviousness rejection, MPEP §2143.03 require Tevas “all words of a claim to be considered” and MPEP § 2141.02 requires consideration of the “[claimed] invention and prior art as a whole.” Further, the Board of Patent Appeal and Interferences recently confirmed that a proper, post-KSR obviousness determination still requires the Office make “a searching comparison of the claimed invention – including all its limitations – with the teaching of the prior art.” See, *In re Wada and Murphy*, Appeal 2007-3733, citing *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis in original). In sum, it remains well-settled law that an obviousness rejection requires at least a suggestion of *all* of the claim elements. Applicant submits that the cited references, whether taken alone or in combination, do not teach or suggest D₂O-based ophthalmic composition, **consisting essentially of** from about 0.001 wt% to about 0.03 wt% of atropine or atropine sulfate, much less recognizing the technical effects thereof, as discussed in greater detail below.

WoldeMussie and Wildsoet Are Irrelevant to D₂O-Based Atropine Formulations

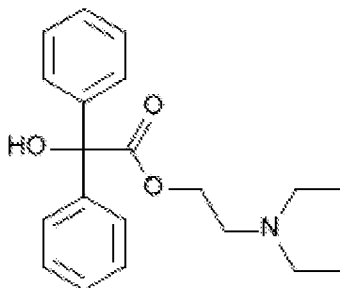
In the Office Action, the Patent Office cites WoldeMussie for allegedly teaching ophthalmic formulations containing a muscarinic antagonist; and Wildsoet for allegedly teaching atropine being used as a muscarinic antagonist in ophthalmic formulations (page 6 of the Office Action). Applicant notes that neither reference teaches or suggests D₂O-based atropine formulations, much less recognizing the technical effects thereof.

Teva Cannot Be Properly Combined with WoldeMussie and Wildsoet to Teach D₂O-Based Atropine Formulations Consisting Essentially of from about 0.001 wt% to about 0.03 wt% of Atropine or Atropine Sulfate

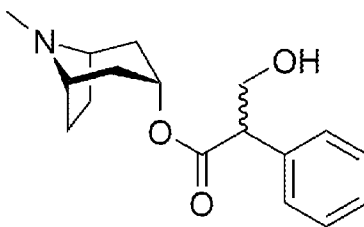
The Office Action cites Teva for allegedly teaching the following:

The EP 0332826 teaches an injectable pharmaceutical formulation having a long shelf life comprising a solvent, such as deuterium oxide and atropine. See claims 1 and 13-15. The EP differs from the claimed invention in the ophthalmic use of atropine and the concentrations used. WoldeMussie et al. Teach the use of the claimed muscarinic

Applicant notes that Teva does not teach the use of deuterium oxide to stabilize pharmaceutical formulations in general regardless of the active agents it contains. Instead, Teva purportedly relates to D₂O-based injectable formulations containing a very specific active agent – α -amino or α -hydroxy carboxylic acid derivatives (esters or amides). See Abstract and Summary of Teva. The preferred example of α -amino or α -hydroxy carboxylic acid derivatives is benactyzine (chemical structure below).



In comparison, Atropine (chemical structure above) is a **β -hydroxy** carboxylic ester.



Teva purportedly describes that formulations containing benactyzine can have additional active agent, including atropine sulfate. See col. 5 of Teva. However, in Teva's Example 1, the benactyzine injectable formulation, purportedly stabilized in D₂O, is used separately (*i.e.* in

multistage automatic injector) with an atropine formulation **dissolved in ordinary water**. See below.

EXAMPLE I

Benactyzine hydrochloride (80 mg) is dissolved in 18 ml of deuterium oxide, the pH is adjusted by known methods (see e.g. A.K. Covington, *Analytical Chemistry*, 40: 700 (1968)) to 2.7 with strong acid, and the volume is brought to 20 ml with more deuterium oxide. The resulting solution is sterilized by passing through a pharmaceutically acceptable and antimicrobial filtering device, and then divided into 1 ml portions. The resultant composition is suitable for use in a single stage automatic injector, where benactyzine is the only active ingredient to be administered, or in a multistage automatic injector together with relatively more stable active ingredients (such as atropine and trimedoxime) dissolved in ordinary water in one or more further separate compartment(s).

Thus, not only does Teva fail to recognize the stability problem for ultra-diluted atropine formulations or to contemplate solution for such problems, Teva actively teaches that atropine **is stable in ordinary water**. In other words, one of ordinary skill in the art would understand that there is no reason to substitute ordinary water, in which the atropine is “stable” as explicit taught by Teva in its Example 1, with the more expensive D2O for the purpose of stabilizing atropine therein. See MPEP 2143A (Example 3), stating that

Office personnel should note that in this case the modification of the prior art that had been presented as an argument for obviousness was an extra process step that added an additional component to a known, successfully marketed formulation. The proposed modification thus amounted to extra work and greater expense for no apparent reason. . . . In the *Omeprazole* case, in view of the expectations of those of ordinary skill in the art, adding the subcoating would not have been expected to confer any particular desirable property on the final product. Rather, the final product obtained according to the proposed modifications would merely have been expected to have the same functional properties as the prior art product.

On the other hand, it is Applicant, through unexpected results discovered in stability studies, recognized the stability problem for ultra-diluted atropine formulations, and developed its solution through the use of D2O solvent, and did so against Teva’s explicit teaching that atropine is stable in ordinary water. See also, MPEP 2143A (Example 3), where the Office discusses *In re Omeprazole Patent Litigation*, 536 F.3d 1361 (Fed. Cir. 2008), and states:

The *Omeprazole* case can also be analyzed in view of the discovery of a previously unknown problem by the patentee. If the adverse interaction between active agent and

coating had been known, it might well have been obvious to use a subcoating. However, since the problem had not been previously known, there would have been no reason to incur additional time and expense to add another layer, even though the addition would have been technologically possible. This is true because the prior art of record failed to mention any stability problem, despite the acknowledgment during testimony at trial that there was a known theoretical reason that omeprazole might be subject to degradation in the presence of the known coating material.

Applicant further notes that Teva also purportedly describe another example as follows:

EXAMPLE II

Benactyzine hydrochloride (40 mg), atropine sulfate (10 mg) and trimedoxime bromide (400 mg) are dissolved in 18 ml of deuterium oxide. The pH is adjusted by known methods to 2.7 with strong acid, and the volume is brought to 20 ml with more deuterium oxide. The resulting solution is sterilized by passing through a pharmaceutically acceptable and antimicrobial filtering device, and then divided into 2 ml portions. The resultant composition is suitable for use in a single stage automatic injector. – *Concentration of atropine in this example is 0.05 wt%.*

However, understanding that Teva does not recognize the stability problem for ultra-diluted atropine formulations, one of ordinary skill in the art would consider the inclusion of atropine in the D2O formulation in Example II as a result of mere convenience, *i.e.* so that the formulation can be used in “a single stage automatic injector”. In other words, one of ordinary skill in the art would not consider Teva’s Example II as teaching the using of D2O to stabilize atropine formulations in which α -amino or α -hydroxy carboxylic acid derivatives (*e.g.* benactyzine) is not present.

To the extent the Patent Office holds that Teva’s Example II describes use of D2O to stabilize α -amino or α -hydroxy carboxylic acid derivatives (*e.g.* benactyzine) in a combination formulation that also contains atropine for convenience of co-administration, the pending claims of the present application has been amended to recite “An ophthalmic composition, **consisting essentially of** from about 0.001 wt% to about 0.03 wt% of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9, wherein the muscarinic antagonist is atropine, or atropine sulfate.” As a result, Teva’s Example II directed to a combination formulation of benactyzine and atropine is excluded from the amended claims.

In summary, Applicant notes that there is insufficient rationale to combine Teva and other references to produce a D₂O-based formulation in which atropine is the **monotherapeutic agent**

because atropine and its derivatives are specifically recognized as stable in ordinary water. In other words, any modification or combination of Teva and other references to arrive at a D₂O-based formulation in which atropine is the monotherapeutic agent as featured in the amended claims would lack the requisite rationale because “the final product obtained according to the proposed modifications would merely have been expected to have the same functional properties as the prior art product.”

Unexpected Technical Effects of D₂O-Based Atropine Formulation

Finally, Applicant draws the Patent Office’s attention to the surprising data presented in the application. In particular, the D₂O formulations disclosed in the present application yield the following unexpected properties:

- Better stability
- Lower main degradant
- Longer shelf-life

Better stability

Tables 24A and 24B under paragraph [00329] (Example 11) and Table 15 under paragraph [00300] (Example 9) show atropine sulfate purity data of different formulations. Table 24A shows atropine sulfate formulations in water. Table 24B shows similar atropine sulfate formulations in deuterated water. The pair-wise formulations can be viewed as:

- Formulation 3 and Formulation 7
- Formulation 5 and Formulation 8
- Formulations 10/11 and Formulation 9
- Formulation 13 and Formulation 12

Formulation 8 shows a pD of 6.2 (with effective pH of 5.8; Table 24B). It is formulated similarly as Formulation 5 (Table 24A), with the exception of deuterated water. At week 0, both formulations (5 and 8) contain similar percentage of atropine sulfate (98.16% for Formulation 5 and 98.93% for Formulation 8). However, at week 2, a higher degradation is observed for Formulation 5 across all three temperature ranges while a much lower degradation is observed for

Formulation 8. Similarly, at week 4, only 66.83% of atropine sulfate remains at 60 degree C in Formulation 5. In contrast, 92.72% of atropine sulfate remains at 60 degree C in Formulation 8.

Similarly, Formulation 9 shows a higher purity percentage at week 4 across all 3 temperatures than either Formulation 10 or 11. Formulation 12 (pD 7.2; effective pH of 6.8) shows about 46% atropine sulfate at week 4 and 60 degree C while Formulation 13 only retained about 28% atropine sulfate at week 4 and 60 degree C.

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

Lower Main Degradant

With respect to the main degradant—tropic acid, Tables 25A and 25B (under paragraph [00330]) further show the percentage of tropic acid are present with each individual formulations. For example, only 4.03% of tropic acid was observed at 60 degree C in Formulation 8 while about 29% of tropic acid was observed at 60 degree C at week 4 in Formulation 5. Formulation 9 contains about 29% of tropic acid at 60 degree C at week 4 while Formulations 10 and 11 each contains about 54% or 62% tropic acid at 60 degree C, respectively. Similarly, Formulation 12 contains about 48% tropic acid at 60 degree C while Formulation 13 contains 69%. As such, the deuterated water stabilizes the atropine sulfate.

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

Longer Shelf-life

Table 30 under Example 12 (paragraph [00334]) shows the predicted shelf life at temperatures of 40°C, 30°C, 25°C, and 2-8°C for Formulations 2-8 for total Related Substance and for the main degradant tropic acid, respectively. As shown from the table, Formulation 8 has longer shelf life across all 4 temperature ranges when compared with Formulation 5. In particular, at 2-8 degree C, Formulation 8 has a shelf life of about 158 months while Formulation 5 only has a shelf life of about 37 months.

Table 30

Formulation	Stability Prediction		RS		Tropic Acid	
	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

For reasons stated above, the cited references do not teach or suggest the use of deuterated water in an ophthalmic formulation in which atropine is the monotherapeutic agent,

much less recognizing the technical effect thereof, as summarized above. Accordingly, the obviousness rejections should be withdrawn.

CONCLUSION

Applicant submits that this response fully addresses the Office Action dated January 27, 2017, and respectfully requests consideration and allowance of the claims.

Should the Examiner have any questions, the Examiner is encouraged to contact the undersigned attorney at (858) 350-2339. If additional fees are believed to be required, the Commissioner is authorized to charge any additional fees to Deposit Account No. 23-2415 (Attorney Docket No. 46682-701.301).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI
Professional Corporation

Date: March 21, 2017

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Electronic Acknowledgement Receipt

EFS ID:	28695502
Application Number:	15208537
International Application Number:	
Confirmation Number:	1009
Title of Invention:	OPHTHALMIC COMPOSITION
First Named Inventor/Applicant Name:	Gregory I. OSTROW
Customer Number:	21971
Filer:	Xiaofan Yang/Lori Ford
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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		46682_701_301_Response.pdf	211876	yes	14
			282e9d6bb3de7660d4f7e4542ff7f3eedd866f0f		

	Multipart Description/PDF files in .zip description		
	Document Description	Start	End
	Response After Final Action	1	1
	Claims	2	4
	Applicant Arguments/Remarks Made in an Amendment	5	14
Warnings:			
Information:			
Total Files Size (in bytes):		211876	
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.			

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/208,537	Filing Date 07/12/2016	☐ 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), (l), 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	03/21/2017	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 \$40 =	0
	Independent (37 CFR 1.16(h))	* 3	Minus	*** 3	= 0	X \$210 =	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.

LIE
ROZENIA HARMON

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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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/208,537	07/12/2016	Gregory I. OSTROW	46682-701.301	1009

21971 7590 01/25/2017
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER

FAY, ZOHREH A

ART UNIT	PAPER NUMBER

1621

NOTIFICATION DATE	DELIVERY MODE

01/25/2017

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):

patentdocket@wsgr.com

Office Action Summary	Application No. 15/208,537	Applicant(s) OSTROW ET AL.	
	Examiner ZOHREH FAY	Art Unit 1621	AIA (First Inventor to File) Status Yes

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 8/30/2016.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on ____.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ 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.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

- 5) ☒ Claim(s) 31-50 is/are pending in the application.
5a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 6) ☐ Claim(s) ____ is/are allowed.
- 7) ☒ Claim(s) 31-50 is/are rejected.
- 8) ☐ Claim(s) ____ is/are objected to.
- 9) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, 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.

Application Papers

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

- 12) ☐ 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)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)	3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. ____.
2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date <u>10/19/2016, 11/7/2016</u> .	4) ☐ Other: ____.

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Claims 31-50 are presented for examination.

The amendments and remarks filed on October 18, 2016 have been received and entered.

Claim Rejections - 35 USC § 103

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, 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.

This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to

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consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

Claims 31-51 is/are rejected under 35 U.S.C. 103 as being unpatentable over EP 0332826 in view of WoldeMussie et al. (US 5,716,952) and Wildsoet et al. (US 2012/0015035).

The EP 0332826 teaches an injectable pharmaceutical formulation having a long shelf life comprising a solvent, such as deuterium oxide and atropine. See claims 1 and 13-15. The EP differs from the claimed invention in the ophthalmic use of atropine and the concentrations used. WoldeMussie et al. Teach the use of the claimed muscarinic antagonists in an ophthalmic formulation in combination with purified water. See the abstract, column 2, lines 46-67 and column 3, lines 1-20 and column 4, lines 23-32. The use of sodium chloride is taught in column 5, lines 18-22. The use of the buffering agents, such as phosphate, borate and citrate is taught in column 2, lines 23-29. The use of preservatives is taught in column 5, lines 9-14. The concentration of 0.0001-0.01% of muscarinic antagonist is taught in claim 1. WooldeMussie differs from the claimed invention in using deuterated water and the use of atropine. Wildsoet et al. teach the use of atropine as a muscarinic antagonist, being used in ophthalmic formulations. It would have been obvious to a person skilled in the art to use atropine in combination with deuterated water for ophthalmic use, motivated by the teachings of WoldeMussie and Wildsoet, which teach the use of muscarinic antagonists and atropine as one muscarinic antagonists by ophthalmic application. The EP 0332826 makes clear that the use of deuterated water instead of water as a solvent is advantages in

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dissolving atropine. The secondary references make clear that atropine has been previously used by ophthalmic administration.

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on November 7, 2016 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZOHREH FAY whose telephone number is (571)272-0573. The examiner can normally be reached on Monday to Friday 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Winston Shen can be reached on (571) 272-3157. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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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). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ZF
/ZOHREH FAY/
Primary Examiner, Art Unit 1621

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	15208537
				Filing Date	07-12-2016
				First Named Inventor	OSTROW; Gregory I.
				Art Unit	1621
				Examiner Name	Zohreh A Fay
				Attorney Docket Number	46682-701.301
Sheet	1	of	1		

U. S. PATENT DOCUMENTS					
Examiner Initials*	Cite No.	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			
	001	US-20120028910	02-02-2012	COMBAL; Jean-Philippe et al.	

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T ⁶
		Country Code ³ Number ⁴ Kind Code ⁵ (if known)				
	001	WO-2011019940-A2	02-17-2011	SEROS MEDICAL LLC [US], et al.		☐
	002	WO-2016172712-A2	10-27-2016	SYDNEXIS INC [US]		☐

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
	001	PCT/US2016/029222 International Search Report and Written Opinion dated October 21, 2016.	☐
	002	U.S. Serial No. 14/859,042 Office Action dated October 25, 2016.	☐

Examiner Signature	/ZOHREH A FAY/	Date Considered	01/19/2017

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.97 and 1.98. 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 2 hours 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, 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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				First Named Inventor	OSTROW; Gregory I.
				Art Unit	1621
				Examiner Name	Zohreh A Fay
				Attorney Docket Number	46682-701.301
Sheet	1	of	2		

U. S. PATENT DOCUMENTS					
Examiner Initials*	Cite No.	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			
	001	US-8980839	03-17-2015	MITRA; Ashim K. et al.	

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No.	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T ⁶
		Country Code ³ -Number ⁴ -Kind Code ⁵ (if known)				
		None				

NON-PATENT LITERATURE DOCUMENTS			
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	001	Guidance for Industry: Q1A (R2) Stability Testing of New Drug Substances and Products. U.S. Department of Health and Human Services, Food and Drug Administration. Retrieved from the internet http://fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073369.pdf (25 pgs.) (November 2013/retrieved 7/27/2016).	☐
	002	PCT/US2016/34823 International Search Report and Written Opinion dated August 23, 2016.	☐

Examiner Signature	/ZOHREH A FAY/	Date Considered	01/19/2017

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Substitute for form 1449/PTO

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**

(Use as many sheets as necessary)

Complete if Known

Application Number	15208537
Filing Date	07-12-2016
First Named Inventor	OSTROW; Gregory I.
Art Unit	1621
Examiner Name	Zohreh A Fay
Attorney Docket Number	46682-701.301

Sheet	2	of	2

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.
- ☐ 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	/Xiaofan Yang/	Date (YYYY-MM-DD)	2016-10-18
Name/Print	Xiaofan Yang	Registration Number	61459

This collection of information is required by 37 CFR 1.97 and 1.98. 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 1 hour 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.**

Search Notes 	Application/Control No. 15208537	Applicant(s)/Patent Under Reexamination OSTROW ET AL.
	Examiner ZOHREH FAY	Art Unit 1621

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
West	9/15/2016	ZF
inventor search	9/15/2016	ZF
Updated	1/19/2017	ZF

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner



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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/208,537	07/12/2016	Gregory I. OSTROW	46682-701.301

CONFIRMATION NO. 1009

PUBLICATION NOTICE



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21971
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

Title:OPHTHALMIC COMPOSITION

Publication No.US-2016-0339007-A1

Publication Date:11/24/2016

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/>.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

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Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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		Number-Kind Code ² (if known)			
	001	US-20120028910	02-02-2012	COMBAL; Jean-Philippe et al.	

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		Country Code ³ Number ⁴ Kind Code ⁵ (if known)				
	001	WO-2011019940-A2	02-17-2011	SEROS MEDICAL LLC [US], et al.		☐
	002	WO-2016172712-A2	10-27-2016	SYDNEXIS INC [US]		☐

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	001	PCT/US2016/029222 International Search Report and Written Opinion dated October 21, 2016.	☐
	002	U.S. Serial No. 14/859,042 Office Action dated October 25, 2016.	☐

Examiner Signature		Date Considered	

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(43) International Publication Date
17 February 2011 (17.02.2011)

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(51) International Patent Classification:

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A61K 47/42 (2006.01) *A61K 9/08* (2006.01)
A61K 31/14 (2006.01) *A61P 27/02* (2006.01)

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12 August 2010 (12.08.2010)

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(26) Publication Language:

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(30) Priority Data:

61/233,315 12 August 2009 (12.08.2009) US

(71) Applicant (for all designated States except US): **SEROS MEDICAL, LLC** [US/US]; 226 W. Edith Avenue, Unit #23, Los Altos, California 94022 (US).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **HEREKAR, Satish V.** [US/US]; 820 La Para Avenue, Palo Alto, California 94306 (US).

(74) Agents: **LUPKOWSKI, Mark** et al.; Squire, Sanders & Dempsey L.L.P., 275 Battery Street, Suite 2600, San Francisco, California 94111 (US).

(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, RO, RS, RU, 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.

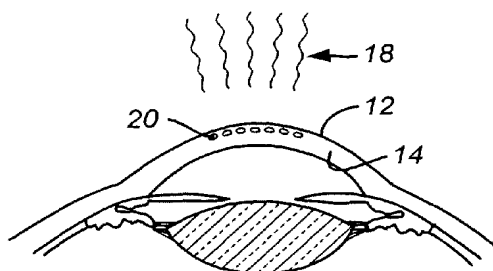
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, 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: DEUTERATED WATER AND RIBOFLAVIN SOLUTION FOR EXTENDING SINGLET OXYGEN LIFETIMES IN TREATMENT OF OCULAR TISSUE AND METHOD FOR USE

FIG. 1C



(57) Abstract: A solution of deuterated water containing a riboflavin-based photosensitizer is provided in order to extend lifetimes of UVA/Rf photo-generated intra-stromal singlet oxygen, in combination with UVA delivery profiles of pulsing, fractionation, and optionally auxiliary stromal/Rf hyper-oxygenation in order to accelerate protein cross-linking density rates in ocular tissue. A 100% deuterated water solution with 0.1% riboflavin in solution increases singlet oxygen lifetimes by at least an order of magnitude without inducing endothelial cell apoptosis, thereby also permitting use of some combination of lower percentages of deuterated water, lower concentrations of riboflavin or lower dosages of UVA on intact (un-debrided) epithelium for equivalent cross-link densities compared to current acceptable corneal cross-linking procedures. Lower concentrations of deuterated water with regular water, for example, yields shorter singlet oxygen lifetimes in approximately linear proportion to concentration, which are considered acceptable in therapies known or being developed in the art of corneal cross-linking.

**DEUTERATED WATER AND RIBOFLAVIN SOLUTION FOR
EXTENDING SINGLET OXYGEN LIFETIMES IN TREATMENT OF
OCULAR TISSUE AND METHOD FOR USE**

5 This application claims benefit of U.S. Patent Application No. 61/233,315
which was filed on August 12, 2009.

BACKGROUND OF THE INVENTION

10 **[0001]** This invention relates to compositions, methods and delivery systems for promoting
cross-linking of proteins in tissue using ultraviolet irradiation of a solution of water
containing riboflavin or its analogues, particularly in ocular tissue (such as tissue in the
sclera, cornea, prepapillary region, etc.).

15 **[0002]** Therapies are known or are under laboratory investigation for promoting structural
enhancement of stromal and scleral tissues by application of ultraviolet A radiation to
riboflavin in a water solution on ocular tissue in the presence of oxygen-containing
atmosphere. The present inventor has determined that singlet oxygen lifetimes have an
evident impact on degree of cross-linking densities of protein such as collagen, a main
structural component of stromal and scleral tissues.

20 **[0003]** Literature reports that deuterated water can increase singlet oxygen lifetimes in
various methods for generating singlet oxygen. This invention takes advantage of this
discovery in a new context. A search of the literature has found no reports or suggestions of
the present methodology and compositions. Reference is made to the collection of references
supplied by the inventor to the Patent and Trademark Office for consideration.

25 **[0004]** Collagen cross-linking (CXL) in ophthalmology, as it currently exists in Europe
(where it is approved), provides a biomechanical basis of increased corneal strength (i.e.,
stability & stiffness) as a result of the formation of covalent bonding between collagen
strands. This occurs when a photo-sensitizer, riboflavin (Vitamin B-2) is applied to the de-
epithelialized surface of the cornea. This epithelial protective tissue over the cornea is
surgically debrided (i.e., surgically removed) so the riboflavin can pass (i.e., be absorbed)
30 into the stroma (collagen layers) of the cornea. After the riboflavin saturates the stroma, it is
exposed to UVA light (approximately 365 nm). This excitation of the riboflavin by the UVA
results in the creation of free radicals that interact with amino acids and carbonyl groups in

neighboring collagen molecules to form the strong covalent chemical bonds. Debride refers to removal of dead, contaminated or adherent tissue or foreign material.

[0005] The primary emphasis in the application of CXL for ophthalmology has been in the treatment of keratoconus, which is prevalent in about one in 2,000 people in the US and Europe, with a slightly higher percentage in Asian countries. This condition is manifested by a weak cornea which becomes too elastic and stretches, causing it to bulge forward. This changes the curvature of the cornea which almost always leads to poor visual acuity (not correctable with glasses and/or soft contact lenses) that requires the use of rigid gas permeable lens. Thus, when the cornea begins losing its shape (i.e., becomes cone shaped instead of spherical) the person typically becomes nearsighted and will develop irregular astigmatism, which causes the blurring of vision. As this condition progresses, this person may develop scarring and a very irregular corneal curvature. If the person cannot be helped with the rigid contact lens, then he/she will require a corneal transplantation.

[0006] There are other conditions/corneal diseases where the cornea can become stretched and distorted. One of these, where CXL is currently being utilized, is in corneal ectasia. This condition involves stretching of the cornea (collagen tissue) that occurs after refractive surgeries, such as laser in situ keratomileusis (LASIK) or photorefractive keratectomy (PRK). Other corneal diseases in which CXL has been tried successfully include corneal ulceration (possible sequelae to bacterial, viral or fungal infections) and bullous keratopathy (excess fluid accumulation causing corneal edema).

[0007] The existing procedure of CXL has been clinically proven (in Europe) to be safe. However, in its current form, the procedure is very rudimentary with a number of significant limitations including but not limited to: the procedure takes too long (approximately one hour in total); removal of the corneal epithelium (i.e., debridement) is required, making the procedure invasive and uncomfortable for the patient intra-operatively and for 3-4 days following surgery; and, it is not fully measurable for accuracy. These limitations clearly preclude the use of CXL for many corneal treatments that would require a fast and highly accurate process for stiffening and stabilizing the cornea.

SUMMARY OF THE INVENTION

[0008] According to the invention, a solution of deuterated water containing a riboflavin-based photosensitizer (Rf aka Vitamin B2) is provided in order to extend lifetimes of UVA/Rf photo-generated intra-stromal singlet oxygen, in combination with UVA delivery

profiles of pulsing, fractionation, and optionally auxiliary stromal/Rf hyper-oxygenation in order to accelerate protein cross-linking density rates in ocular tissue.

5 [0009] This invention is based upon the discovery that there is a correlation between the concentration of dissolved [singlet] oxygen in irradiated ocular tissue and the efficiency of cross-linking with the photo-sensitizer riboflavin. Our studies have demonstrated that a 100% deuterated water (D2O) solution with 0.1% riboflavin in solution increases singlet oxygen lifetimes by about an order of magnitude (10X or more). Further studies have shown that the such application of deuterated water does not induce endothelial cell apoptosis.

10 [0010] Our studies have also shown that by delivering optimized combinations of deuterated water, riboflavin, and UVA dosage on an intact (undebrided) epithelium, equivalent cross-link densities are rapidly achieved with reduced adverse effects as compared to current treatments. Lower concentrations of deuterated water with regular water, for example, yields shorter singlet oxygen lifetimes. These lifetimes have approximately a linear relationship to the concentration of deuterated water. These lower concentrations are
15 considered acceptable in therapies known or being developed in the art of corneal cross-linking.

[0011] Our experiments have shown various correlations such as between the following: the concentration of D2O and reactive oxygen species (ROS) lifetimes; the UVA fluence and ROS concentration; and, the dissolved oxygen consumption and UVA fluence.

20 [0012] Deuterated water refers to water containing a higher-than-normal proportion of the hydrogen isotope deuterium, either as deuterium oxide, D2O or ²H2O, or as deuterium protium oxide, HDO or ¹H²HO. Conventional water is water that has a normal proportion of deuterium isotope, such as in tap water to distilled water.

25 [0013] The invention will be better understood by reference to the following detailed description in connection with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] Figures 1A-1C are illustrations of a first method according to the invention.

[0015] Figures 2A-2D are illustrations of a second method according to the invention.

[0016] Figure 3 is a schematic diagram of a delivery system according to the invention.

30 [0017] Figure 4 is a graph showing the relationship between D2O and ROS lifetimes.

[0018] Figure 5 is a graph showing the relationship between ROS concentration and UVA irradiation (fluence).

[0019] Figure 6 is a graph showing the relationship between rate of oxygen consumption and UVA irradiation.

5

DETAILED DESCRIPTION OF THE INVENTION

[0020] The invention is embodied in methods, compositions and delivery systems, particularly in relation to therapies for strengthening and re-shaping ocular tissue. The formulation invention includes a composition or substance comprising a solution of deuterated water (between 100 wt% D₂O and 10 wt% D₂O in water) containing a riboflavin based photo-sensitizer, carboximethylcellulose (CMC), and benzalkonium chloride (BAC). In one embodiment, the riboflavin based photo-sensitizer is Rf aka Vitamin B2. It should be noted that all concentrations are, unless otherwise specified, wt/vol (for example, 0.1% Rf refers to ~0.1 gm in 100mL). The molecular weight of Rf is: ~378 gm/L. In some embodiments, the concentration of the riboflavin based photo-sensitizer, such as Rf aka Vitamin B2, is between X and Y, or more narrowly, V and W. In some embodiments, the concentration of carboximethylcellulose, is 0.2% or about 0.2%. In some embodiments, the concentration of carboximethylcellulose is between X and Y, or more narrowly, V and W. In some embodiments, the concentration of BAC, is 0.2% or about 0.2%. In some embodiments, the concentration of BAC is between X and Y, or more narrowly, V and W. In certain embodiments, the formulation invention includes deuterated water between 100% D₂O and 10% D₂O in water containing, the riboflavin based photo-sensitizer Rf aka Vitamin B2 of about 0.1% Molar concentration, carboximethylcellulose (CMC) of about 0.2%, and benzalkonium chloride (BAC) of about 0.02%. Embodiments of the invention include any value or range of D₂O between 10% and 100% in the formulation.

[0021] Referring to Figures 1A-1C, a method according to the invention is illustrated. Figure 1A depicts an intact cornea 11 comprising an epithelium 12 with underlying stromal tissue 14. As shown in Figure 1B, the formulation 16 according to the invention is applied as a spray or droplets to the epithelium 12 in the presence of ambient oxygen (in the air) to an undebrided corneal surface. The period of exposure of formulation is several minutes. In some embodiments, the period of exposure can be between 1 to 2, 2 to 3, 3 to 5, 5 to 7, 7 to 10, or greater than 10 minutes. Bursts of spray or droplets are applied over the affected area for the duration of the soaking cycle.

[0022] Then the solution-soaked stromal region 14 is irradiated with ultraviolet A 18, as shown in Figure 1C. The UVA irradiation treatment may be continuous (i.e., irradiation without interruption) for a period ranging from 1 to 15 minutes or fractionated (turned on and off for a few seconds to a minute) or pulsed (brief bursts of high irradiance with ON times in the 1 microsecond to millisecond range, and frequencies in the 1 kilohertz to 500 kilohertz range. The irradiation creates reactive oxygen species (ROS) that cause the desired crosslinking of proteins 20. In one preferred embodiment, which maximizes benefits efficiently, the irradiation is pulsed and fractionated, to promote the production of singlet oxygen, or reactive oxygen species (ROS) in the intrastromal region to thereby promote the desired cross-linking of proteins 20 during the lifetimes of the reactive oxygen.

[0023] In embodiments of the invention, there may be various compounds which can function as both preservative and penetration enhancers. These compounds include, but are not limited to benzalkonium chloride (BAC) and sodium ethylenediaminetetraacetate (EDTA), as well as viscosity agents such as carboxymethylcellulose (CMC) or dextran. BAC (~0.02%) and EDTA (~0.1%) enhance penetration of the riboflavin and D₂O water formulation. CMC (~0.2%) or dextran (~20%) enhance the lubricity and the formation of a persistent, broader, and more uniform corneal tear film before and during the procedure. This allows greater absorption of the active ingredients of the formulation into the cornea.

[0024] Significantly, the riboflavin formulation can also be manufactured with a high concentration of dissolved oxygen. This oxygen enrichment enables the production of greater ROS concentration in a shorter period of time, and, in turn, this makes higher UVA irradiance practical. However, it should be noted that there may be other means to diffuse oxygen gas into the stroma, which might include, among others, the use of a device that would deliver such oxygen gas to the corneal surface. This oxygen gas then diffuses (albeit slowly) into the stroma, thereby increasing dissolved oxygen. In summary, the ability to increase dissolved oxygen in the stroma enables the use of a higher UVA irradiance exposure to the collagen tissue. This concept of embedding dissolved oxygen in the stroma means that optimum cross-linking (i.e., adequate stiffness of the cornea with minimal side effects) can be achieved in a shorter period of time. A means to manufacture the enriched oxygen deuterated Rf formulation, that will provide up to and over 1 year of extended shelf life, is contemplated by this invention. The components of the formulation invention, which are set forth hereinabove, may be optimized for penetration rate, pH, hypotonicity, and lubricity by the proportions that each component is used within the formulation.

[0025] Referring to Figures 2A-2D, a further method according to the invention is illustrated. The intact cornea 11 (Figure 1A) comprises an epithelium 12 with underlying stromal tissue 14. The corneal surface is debrided to remove the surface layer and expose the underlying tissue (Figure 2B) in a debrided region 13. A solution 16 according to the invention is applied as a spray or droplets to the debrided region 13 in the presence of ambient oxygen (in the air) to the (Figure 1B). The period of exposure is several minutes. The same ranges of exposure disclosed in the embodiments of Figures 1A-C apply to Figures 2A-D. Bursts of spray or droplets are applied over the affected area for the duration of the soaking cycle. Due to the debriding, the stromal tissue 14 is soaked to a greater depth than the embodiments of Figures 1A-C. Then the solution-soaked stromal region 14 is irradiated with ultraviolet A 18 (Figure 2D). As described above, the UVA irradiation treatment may be continuous or fractionated (turned on and off for extended periods) or pulsed (brief bursts of high illumination for an extended period), or most preferably pulsed and fractionated, to promote the production of singlet oxygen, or reactive oxygen species (ROS) in the deep intrastromal region to thereby promote the desired cross-linking of proteins 20 during the lifetimes of the reactive oxygen.

[0026] The process of soaking the formulation, on either a debrided or undebrided surface, results in diffusing oxygen into the stroma. For a undebrided surface, the penetration is to a depth of up to about 0.5 mm. The penetration into debrided surfaces is greater than 0.5 mm. The UVA irradiation in the presence of oxygen promotes singlet oxygen species generation. The deuterated water with riboflavin extends lifetimes of UVA/Rf photo-generated intrastromal singlet oxygen. This in combination with UVA delivery profiles of pulsing, fractionation, and optionally auxiliary stromal/Rf hyper-oxygenation accelerates protein cross-linking density rates in the ocular tissue. Our studies have shown that the use of a 100% deuterated water solution with 0.1% riboflavin in solution increases singlet oxygen lifetimes by at least an order of magnitude (10X or more) without inducing endothelial cell apoptosis. It is well known in the arts that the current cross-linking procedure may induce the following side effects: (1) stromal haze due to keratocyte apoptosis; (2) endothelial cell density loss.

[0027] In another embodiment, the formulation includes a combination of lower percentages of deuterated water, lower concentrations of riboflavin or lower dosages of UVA on intact (un-debrided) epithelium may be employed for equivalent cross-link densities as compared to current acceptable corneal cross-linking standards for CXL procedures. In various embodiments, the ranges of components and delivery parameters of the formulation

are as follows: 100% D₂O to 1%; 0.1% Rf to 0.01%; 0.02% BAC to .01%; 0.2% CMC to 0.1%; 5.4 J/cm² UVA to 2.5J/cm²; 30 minutes or less UVA exposure.

[0028] Figure 4 shows the singlet oxygen lifetime in deuterated water as a function of concentration of D₂O. Figure 4 demonstrates the correlation of ROS lifetimes to varying D₂O solvent (0% to 100%) in the 0.1% Rf solution under normoxic (i.e., ambient oxygen dissolved into the test sample at room temperature by natural diffusion conditions in collagen and 0.1% Rf matrices. As shown in Figure 4, lower concentrations of deuterated water with regular water, for example, yield shorter singlet oxygen lifetimes. The relationship between singlet oxygen lifetime and D₂O concentration in regular water is approximately linear, as shown in Figure 5. This data was generated by a custom built photon counter and dissolved oxygen probe, which was excited by a frequency tripled Nd:Yag laser for time-resolved measurements.

[0029] The inventor has measured reactive oxygen species (ROS) in vitro in aerated collagen and riboflavin under UVA illumination and has found an increase in the ROS duration of about 4.5 μSecs for H₂O with no D₂O to a duration of over 45 μSecs for a 100% deuterated solvent D₂O (See Figure 5). Figure 5 shows a strong linear correlation of ROS concentration in a normoxic collagen and Rf matrix as UVA irradiance is varied from about 3 mW/cm² to about 50 mW/cm².

[0030] Figure 6 shows the inverse correlation of dissolved oxygen concentration (due to consumption from varying ROS generation) with varying UVA irradiance in a normoxic collagen+0.1% Rf matrix. A 500% factor is shown in the example below.

[0031] A system using dual UVA/Blue sources is able to provide pulsed irradiances up to 150 mW/cm², with pulsing frequencies at up to 200 kHz and is, for example, set to deliver pulses at a 20 kHz (50 μSecs) pulse repetition frequency, and a duty cycle of about 20% (intermittency). This is a 40 μSec UVA OFF period and a 10 μSec high intensity UVA ON period applied cyclically. It is believed that the 10 μSec UVA ON pulse rapidly generates a maximal new population of ROS molecules in the targeted stroma just as the previously stimulated ROS population is about to be depleted or otherwise be consumed through quenching mechanisms in the local microenvironment. It is believed that the 40 μSec UVA OFF period provides sufficient time for chemical interactions in the microenvironment to effect cross-linking of proteins, specifically collagen, in the target region. The singlet oxygen population in the presence of the aerated deuterated solvent survives for an extended duration of about 40 μSecs, while the UVA is OFF.

[0032] In a specific embodiment, during the extended reactive lifetime of singlet oxygen, rapid cross-linking reactions are induced in the carbonyl (aldehyde) groups of collagen while dissolved oxygen O₂, riboflavin, and singlet oxygen species (ROS) are consumed (as long as present in sufficient concentrations) by Type II (energy transfer) mechanisms. (From photo-chemistry competitive mechanisms of radicals formation are known: electron transfer or Type I; and, energy transfer, Type II.) This on-off cycle repeats every 50 uSecs (at 20 kHz). Analogues of riboflavin may also be employed, such as 3-methyl-riboflavin tetraacetate.

[0033] As riboflavin molecules degrade and transform through such singlet oxygen regenerative timing cycles, they generate reduced fluorescence intensity in the 530nm-570nm band in response to UVA which may thereby signal a riboflavin “reinstillation” cycle.

[0034] In addition to increased endothelial safety due to reduced riboflavin concentration requirements, the use of viscous carboxy-methyl-cellulose (CMC) in the present formulation forms a corneal film of thickness ~ 50μM-200μM, which provides added UVA protection to the endothelium. Pulsed UVA applied as herein described (instead of CW UVA) provides for a reduced apoptotic effect on both keratocytes and endothelial cells.

[0035] The formulation (D₂O + CMC + BAC) provides for faster penetration and clearance, reducing pre-treat soak times and end-product clearance periods. The use of BAC as a penetration enhancer has been previously reported in the literature.

[0036] The rate of diffusion of dissolved oxygen through the stroma depend on corneal thickness, epithelialization state (whether or not debrided), sensitizer pre-oxygenation, viscosity and ambient oxygen environment of the stroma. Some amount of dissolved oxygen will continue to migrate into the stroma and sclera. However, during UVA irradiation a much larger consumption of local dissolved oxygen occurs than can be supplied through ambient diffusion. The formulation, and the use of UVA pulsation and fractionation is able to overcome the dissolved oxygen limitations inherent in ambient diffusion. Depending on the depth of cross-linking desired, a pause in the UVA irradiation (of the order of seconds to minutes) cycle may permit dissolved oxygen to permeate deeper in the stroma before localized consumption due to ROS generation.

[0037] Total cross-linking treatment times and singlet oxygen/riboflavin molecular efficiencies are significantly enhanced due to this timed UVA/oxygen modulation sequencing with minimized UVA dosage but with minimal or no loss in effectivity and little or no increase in toxicity.

[0038] Singlet oxygen concentration as generated according to this method is highly linearly correlated to UVA irradiance. Figure 6 shows the rate of dissolved oxygen consumption in the collagen at 15 mW/cm² in two test samples. Each test sample included collagen and 0.1% Rf solution. Figure 6 shows the inverse correlation of dissolved oxygen concentration (due to consumption from varying ROS generation) with varying UVA irradiance in a normoxic collagen+0.1% Rf matrix. A 500% modulation factor is shown in the graph below. Here we show that a 500% increase in UVA irradiance increases the rate of dissolved oxygen consumption by 500%. Increased UVA (See Figure 6) irradiance also generates correspondingly increased cross-link densities with correspondingly greater dissolved oxygen consumption during exposure.

[0039] While the main focus persistent in prior art publications is on collagen cross-linking in the stroma, the inventor has concluded that extra-cellular matrix (ECM)/proteoglycans may play a role in the stromal cross-linking process and may form inter-molecular and intra-molecular collagen/proteoglycan cross-links. The object of this proposed method includes such cross-linking as well.

[0040] D₂O is non-toxic and is readily available. One supplier is Sigma Aldrich, from which a 10 gram vial costs about \$40.

[0041] A generalized formulation for cross-linking according to the invention may be characterized as: a) an effective amount of a penetration enhancing agent; b) an effective amount of a viscosity agent which maintains film thickness and extends UV protection c) an effective amount of an agent imparting a hypotonic solution (i.e., a solution which has an osmolarity less than ~ 295mOsm, and is adjusted by the salt NaCl); d) an effective amount of an agent for extending singlet oxygen lifetimes, e) an effective amount of a photosensitizing agent, and, f) an effective amount of deuterated water forming a solution. The formulation is configured upon delivery to ocular tissue (through its delivery mechanism and the like) for reaction with UVA irradiation directed (via a lamp or fiber) at the ocular tissue in the presence of oxygen (such as ambient air). The lifetimes of singlet oxygen released by the UVA radiation for promoting protein cross-linking in the ocular tissue are extended by the formulation. The viscosity agent imparting viscosity control may be or contain CMC at a concentration between [1%] and [90%]. The penetrating enhancing agent may be or contain 0.02% or less BAC, and the photosensitizing agent may be or contain riboflavin or its analogues.

[0042] Referring to Figure 3, an appropriate delivery system 100 may be the content of a substance in a single use dose container 102 and an appropriate applicator subsystem

comprising one or more medical grade peristaltic pumps 104, 106 in a housing 108 having outlets 110, 112, coupled via tubes 114, 116 to a pair of spray dispensing devices 118, 120 each to be mounted on frame 122, 124 over an eye 126, 128 of a patient to provide sterile delivery of the substance to the affected area of each eye, a region about 8 mm in diameter.

- 5 Irradiation ports 130, 132 mounted to the frame 122, 124 provide directed radiation, which is controlled by a UVA source and controller 134 that delivers the prescribed irradiation dosage (e.g., fractionated pulsed UVA for a period of a few minutes) via fiber optic cables 136, 138. The same controller 134 may be coupled to and control the pumps 104, 106 to meter the delivery of the solution according to the invention. The delivery system provides for dual
10 delivery of the formulation, i.e., delivery simultaneously to both eyes. The system further provides for dual irradiation of UVA to each eye simultaneously. Although delivery and irradiation to one eye or sequentially is also an embodiment of this invention.

- [0043] Features of the invention are advantageous when exciting the sensitizer, since one can select the duty cycle with an OFF time of about 50 μ secs (ROS lifetime). The peak
15 amplitudes can be dynamically set from $3\text{mW}/\text{cm}^2$ to $>100\text{mW}/\text{cm}^2$ and at up to 100kHz frequency. A simple nomogram might be: 10 kHz Pulsing Frequency with 50% duty cycle (50 μ secs ON/50 μ secs OFF).

- [0044] This invention has been explained with respect to specific embodiments. Other embodiments will be evident to those of ordinary skill in the art. For example, cross-linking
20 may be employed for treatment of maladies or used in procedures including keratoconus, myopia, presbyopia, LASIK, cataract, and corneal transplantation. Therefore, it is not intended that the invention be limited, except as indicated by the amended claims.

WHAT IS CLAIMED IS:

1 1. A substance for ocular treatment comprising:
2 carboxy-methyl-cellulose for providing viscosity control and protection against
3 incident ultraviolet radiation;
4 an effective amount of benzalkonium chloride (BAC) as a penetration enhancer of
5 the substance into ocular tissue;
6 an effective amount of deuterated water for extending singlet oxygen lifetimes;
7 and
8 an effective amount of a riboflavin-based photosensitizer in solution with the
9 deuterated water and carboxy-methyl-cellulose,
10 said solution being configured for reaction with ultraviolet A radiation directed at
11 ocular tissue in the presence of oxygen, such that the lifetimes of singlet oxygen released by the
12 ultraviolet A radiation are extended for promoting protein cross-linking in the ocular tissue.

1 2. The substance according to claim 1 further including conventional water
2 in mixture with the deuterated water, the deuterated water exceeding one percent of the total
3 solution.

4 3. The substance according to claim 1 wherein the concentration of D2O in
5 the solution is between 10% and 100%.

1 4. A substance for ocular treatment comprising:
2 a) an effective amount of a viscosity agent for film thickness control and UV
3 protection;
4 b) an effective amount of an agent imparting a hypotonic solution; [what does
5 hypotonic solution mean]
6 c) an effective amount of an agent for extending singlet oxygen lifetimes;
7 d) an effective amount of a photosensitizing agent that absorbs UV radiation;
8 e) an effective amount of deuterated water forming a solution;
9 said solution being configured for reaction with ultraviolet A radiation directed at
10 ocular tissue in the presence of oxygen, such that the lifetimes of singlet oxygen released by the
11 ultraviolet A radiation are extended for promoting protein cross-linking in the ocular tissue.
12

1 5. The substance according to claim 4 wherein the viscosity agent imparting
2 viscosity control comprise CMC at a concentration between [1%] and [90%].

1 6. The substance according to claim 4 wherein the photosensitizing agent
2 comprises riboflavin.

1 7. The substance according to claim 4 further including conventional water
2 in mixture with the deuterated water, the deuterated water exceeding one percent of the total
3 solution.

1 8. A delivery system comprising:
2 the substance of claim 4;
3 a single use dose container containing the substance; and
4 an applicator for sterile delivery of the substance,
5 wherein the applicator comprises tubes fluidly connecting the container to a pair
6 of spray dispensing devices,
7 wherein each pair of spray dispensing devices is mounted on a frame,
8 wherein each of the frames is configured to be disposed over an eye of a patient to
9 provide sterile delivery of the substance to an affected area of each eye, and
10 wherein irradiation ports are mounted to each of the frames to provide directed
11 radiation controlled by a UVA source.

1 9. A method for promoting cross-linking of proteins in ocular tissue
2 comprising:
3 applying a solution comprising an effective amount of deuterated water and an
4 effective amount of riboflavin as a photosensitizer in solution with the deuterated water to ocular
5 tissue in the present of oxygen; and
6 irradiating the ocular tissue with ultraviolet A radiation to effect creation of
7 singlet oxygen for reaction with protein forming the ocular tissue in order to effect protein cross-
8 linking in the ocular tissue.

1 10. The method according to claim 9, wherein the protein being collagen.

1 11. The method according to claim 10, wherein the solution being externally
2 applied to the ocular tissue.

1 12. The method according to claim 9, wherein the irradiation being pulsed.

1 13. The method according to claim 12, wherein the pulsed irradiation being
2 intermittent.

1 14. The method according to claim 9, further including a preparatory step, the
2 preparatory step comprising debriding the ocular tissue in a treatment region to promote deeper
3 infiltration of stromal tissue by the solution.
4

5 15. The method according to claim 9, wherein the solution further comprises
6 carboxy-methyl-cellulose (CMC), wherein the CMC provides viscosity control and protection
7 against damage to the ocular issue from the ultraviolet radiation radiation.
8

9 16. The method according to claim 9, wherein the solution further comprises
10 benzalkonium chloride (BAC) which enhances penetration of the solution into ocular tissue.

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FIG. 1A

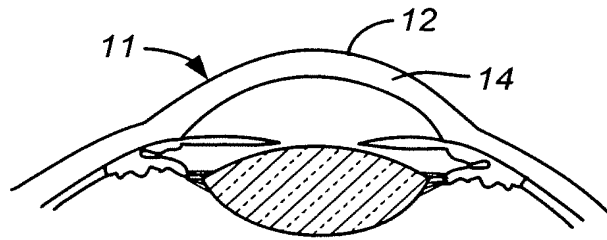


FIG. 1B

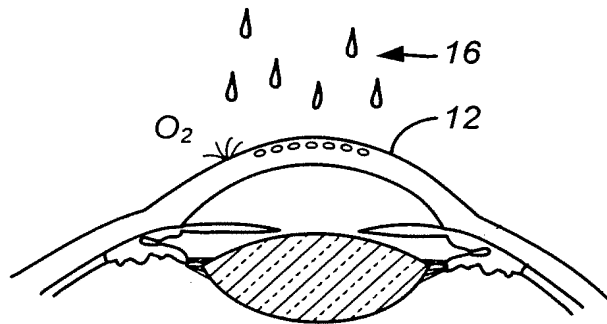
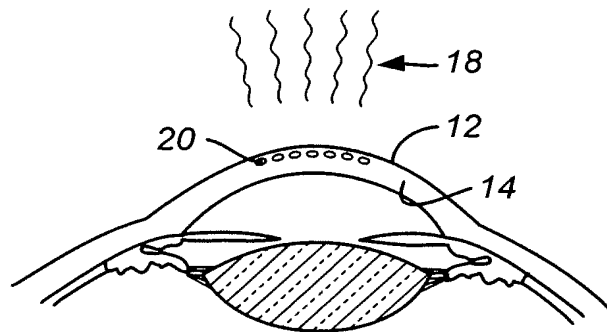


FIG. 1C



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FIG. 2A

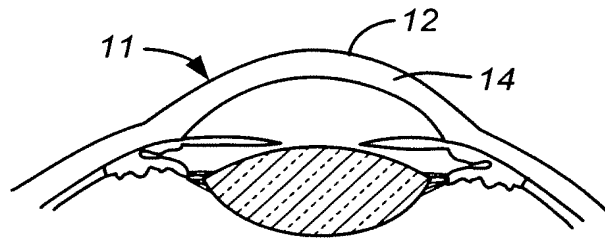


FIG. 2B

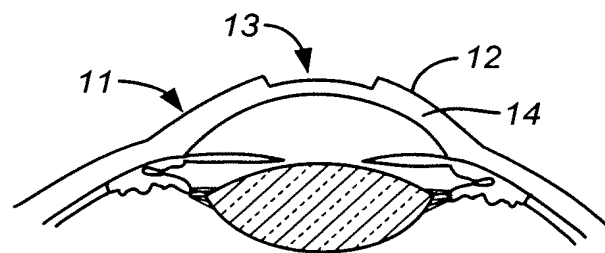


FIG. 2C

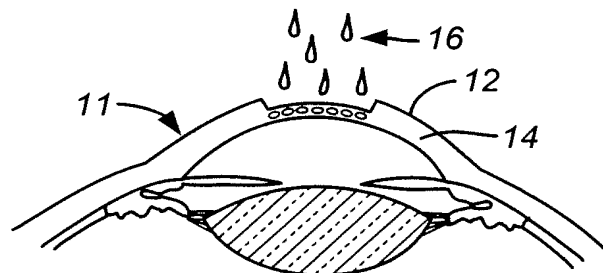
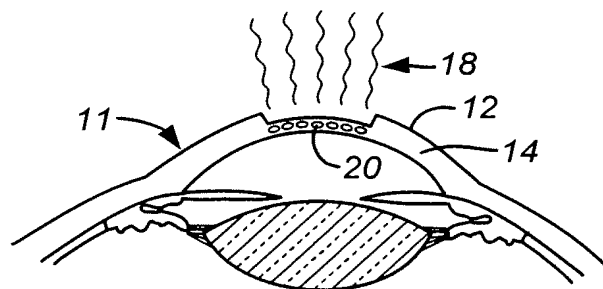


FIG. 2D



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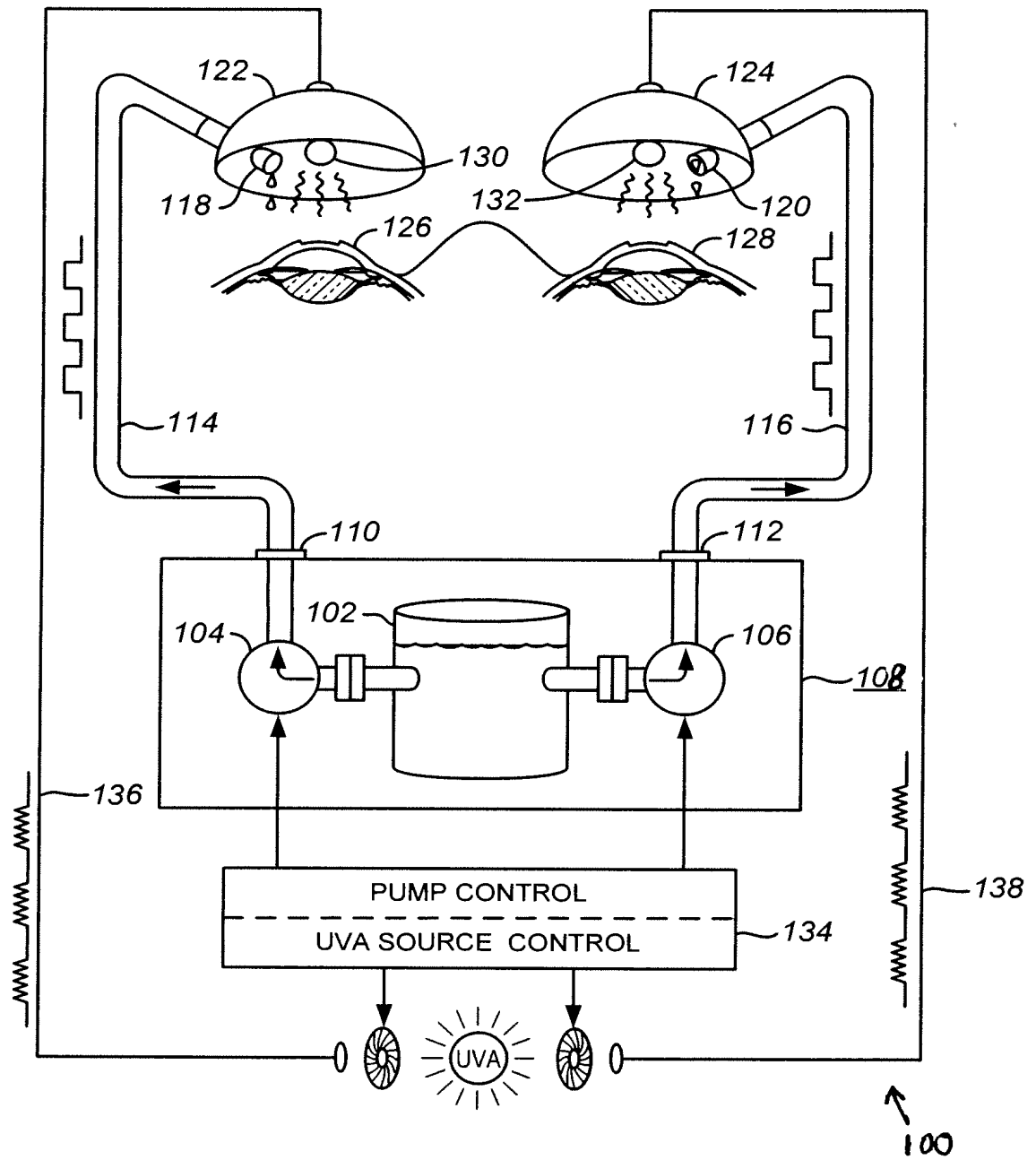


FIG. 3

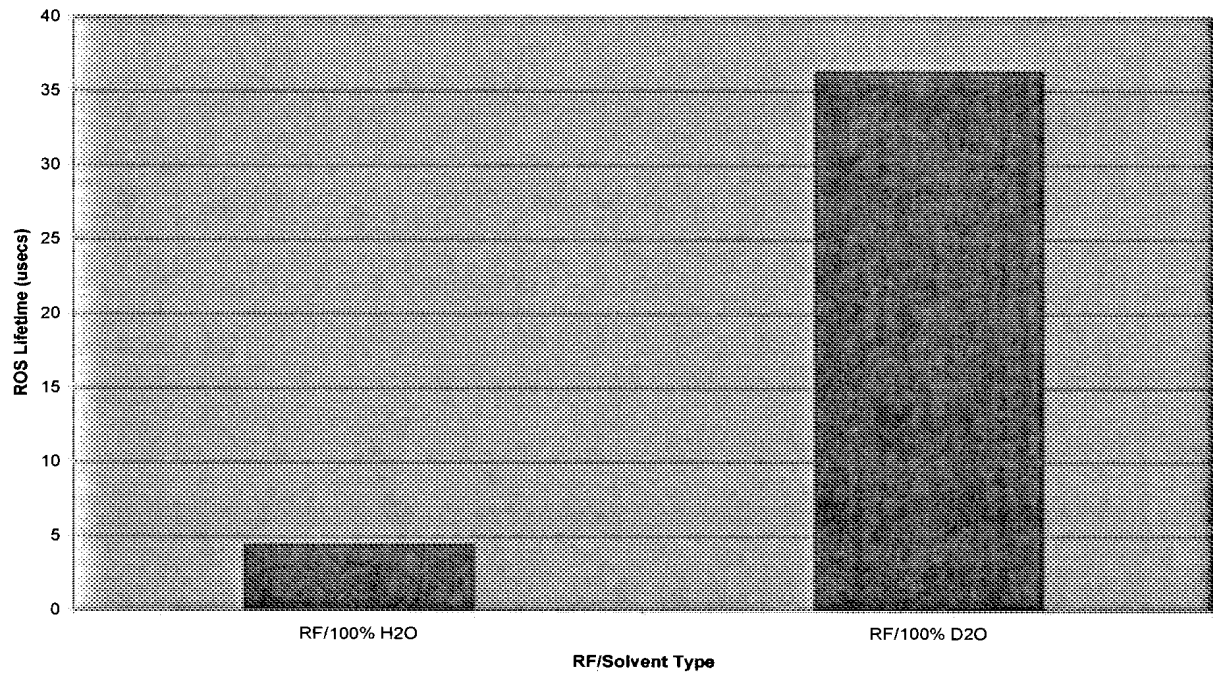


FIG. 4

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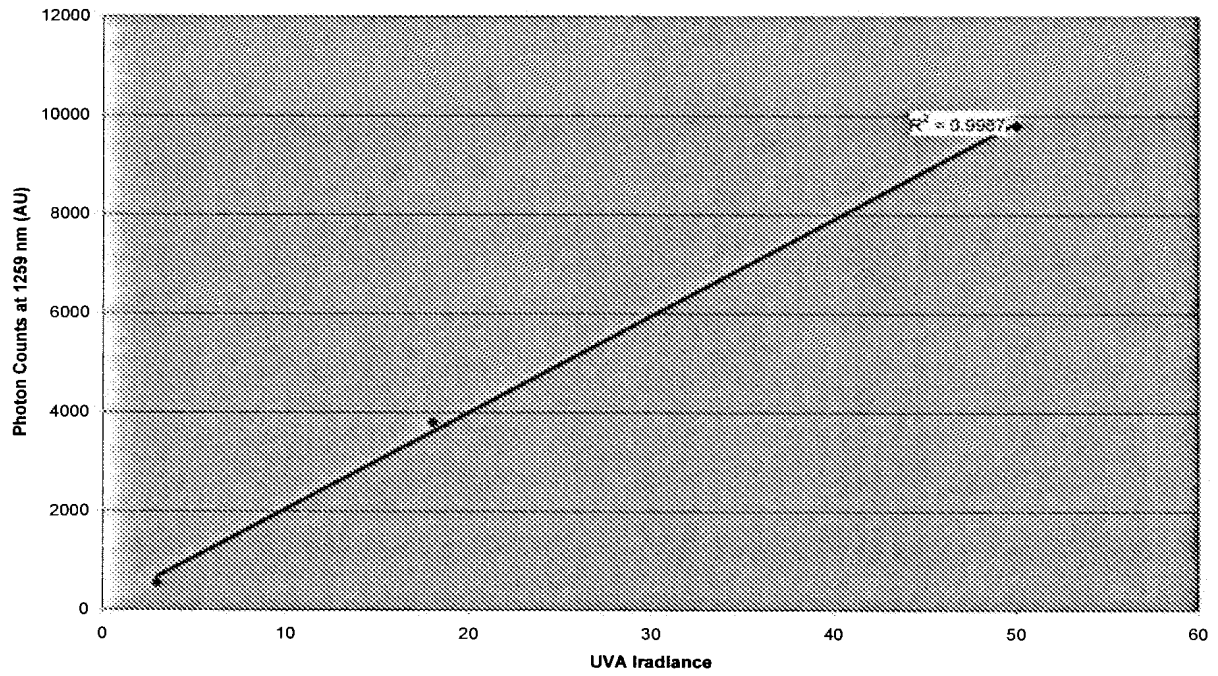


FIG. 5

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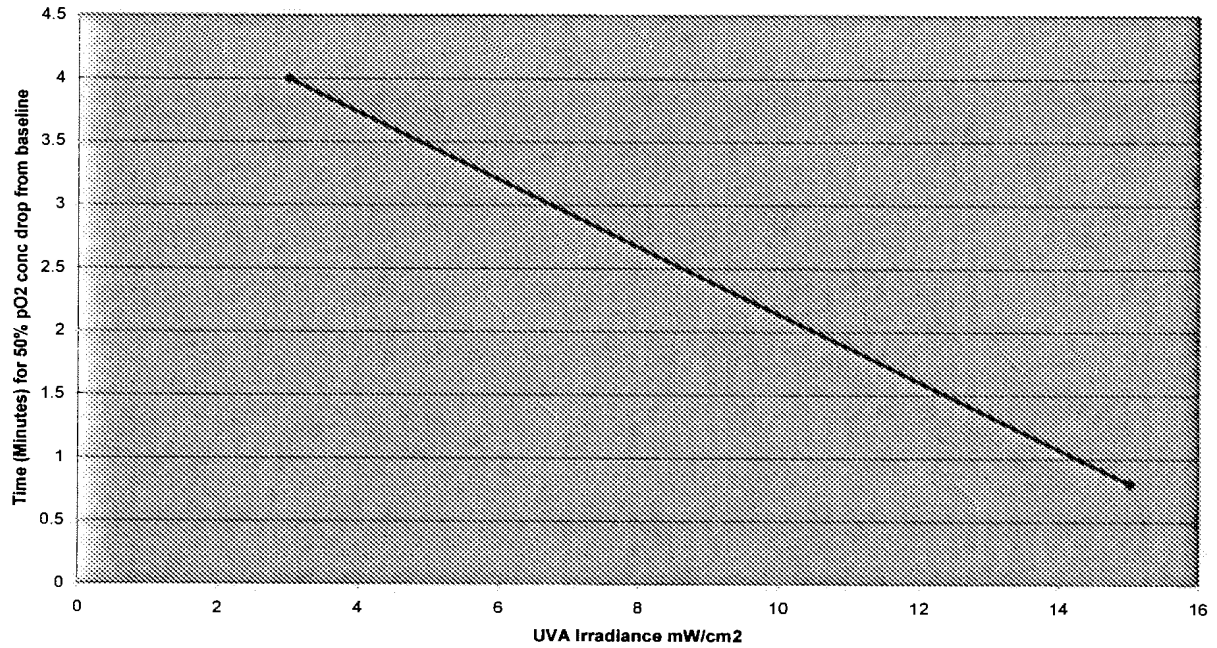


FIG. 6



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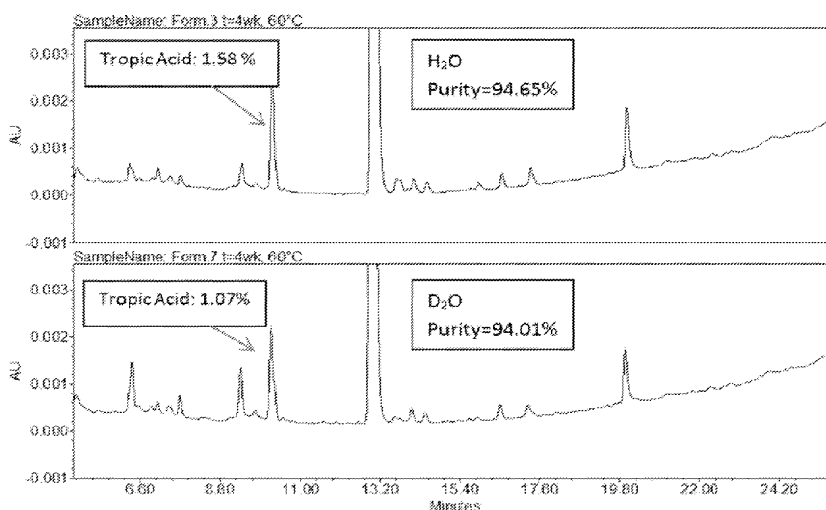
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(54) Title: OPHTHALMIC COMPOSITION

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, hyoscyne, 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, hyoscyne, 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 pD adjusting agent. In some embodiments, the pD adjusting agent comprises DCl, NaOD, CD_3COOD , or $\text{C}_6\text{D}_8\text{O}_7$.

[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 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 .

[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 lives 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, benzatropine, 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 pH, 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, 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. 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, 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.

[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, 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.

[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, 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.

[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, 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.

[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, 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.

[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), 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-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 pH adjusting agent that broadly maintains the ophthalmic solution at a particular ion concentration and pH 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 adjusters 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 pH adjusting agent. In some embodiments, the pH 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.

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.

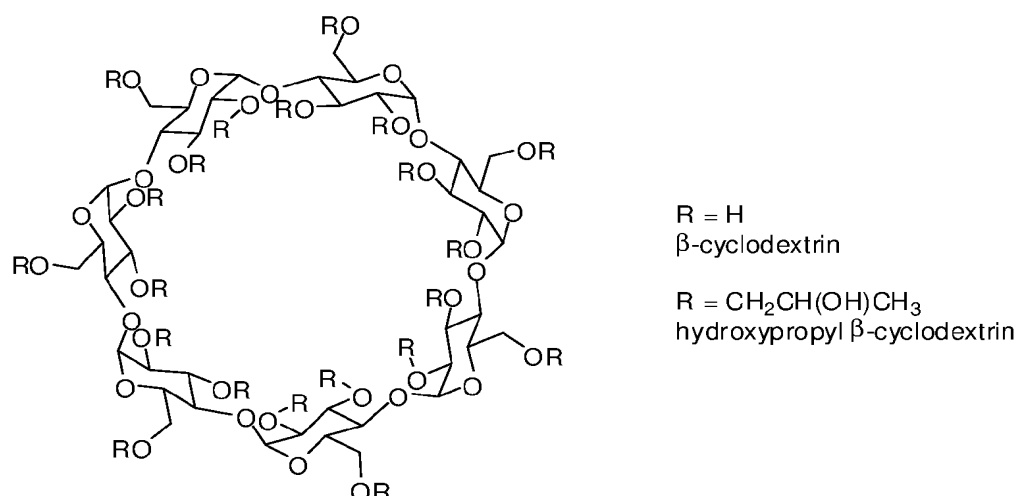
[00161] In some embodiments, the composition stored in a glass container has a potency of less than 60% at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a glass container has a potency of less than 60% for a period of at least 1 week, at least 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/caprates (Labrasol), PEG-4 glyceryl caprylate/caprates (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/caprates; 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 (DCl), deuterated sodium hydroxide (NaOD), deuterated acetic acid (CD₃COOD), or deuterated citric acid (C₆D₈O₇).

[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 $pD = pH^* + 0.4$, in which pH* is the measured or observed pH of the ophthalmic composition formulated in a solution comprising deuterated water (e.g., D₂O).

[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 $K_a(\text{H}_2\text{O})$ 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.

[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, benztatropine, 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 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., c.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, scopolamine, 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.

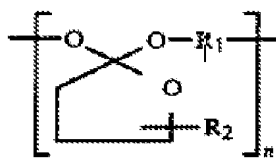
[00249] In some embodiments, a punctal plug described herein utilizes an osmosis mechanism for the delivery of a muscarinic antagonist (e.g., atropine or atropine sulfate). In some cases, the configuration of the punctal plug is tubular with domed end walls, and the device comprises a transverse impermeable 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-trimethylopropane 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, methyl di(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, carboxyvinyl polymers, 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 ($C_{18}H_{37}OH$), cetyl alcohol ($C_{16}H_{33}OH$) 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 n_D^{25} =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 $H-(OCH_2-CH_2)_nOH$, 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 1 s^{-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 1 s^{-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 1 s^{-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 1 s^{-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 1 s^{-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	55.0	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 doses 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 (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 +/- 3* 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 cyc 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 Purity ¹	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 Purity ¹	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 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.

[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 benactyzinc, 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

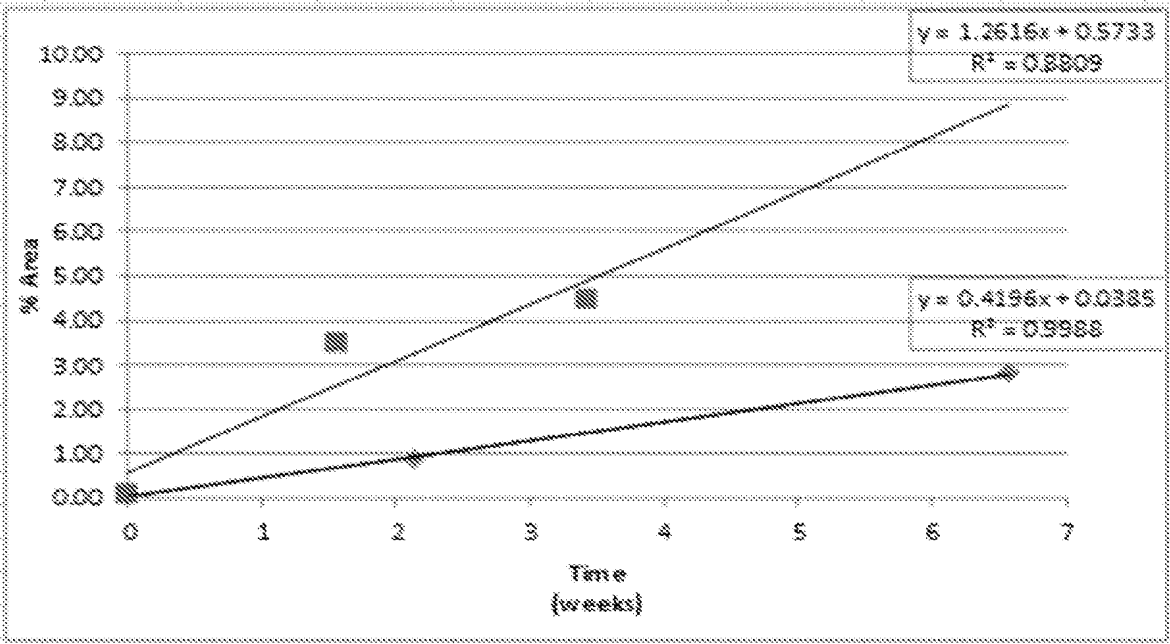


Fig. 1C

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

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

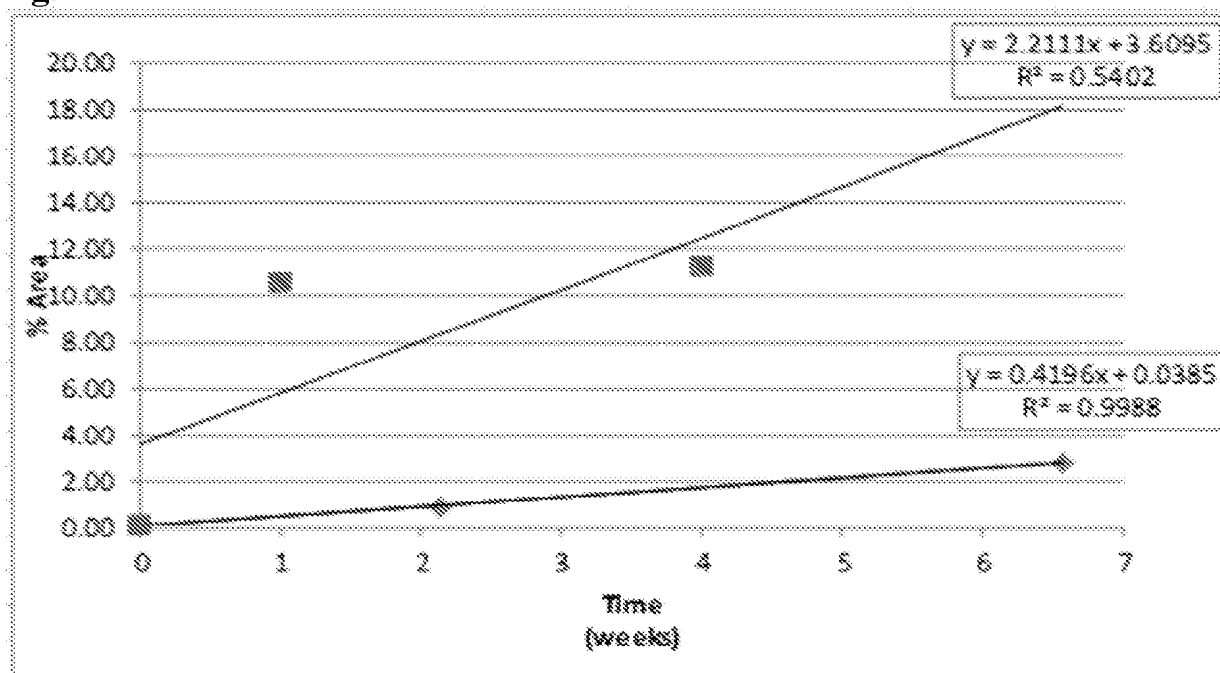


Fig. 2C

Formulation:		Average of Analysts		
Stability Prediction:		RRT 0.87		
	spec limit:	0.50	% (not more than)	
			shelf life	
			weeks	months
rate	0.88878 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/ 13

Fig. 3

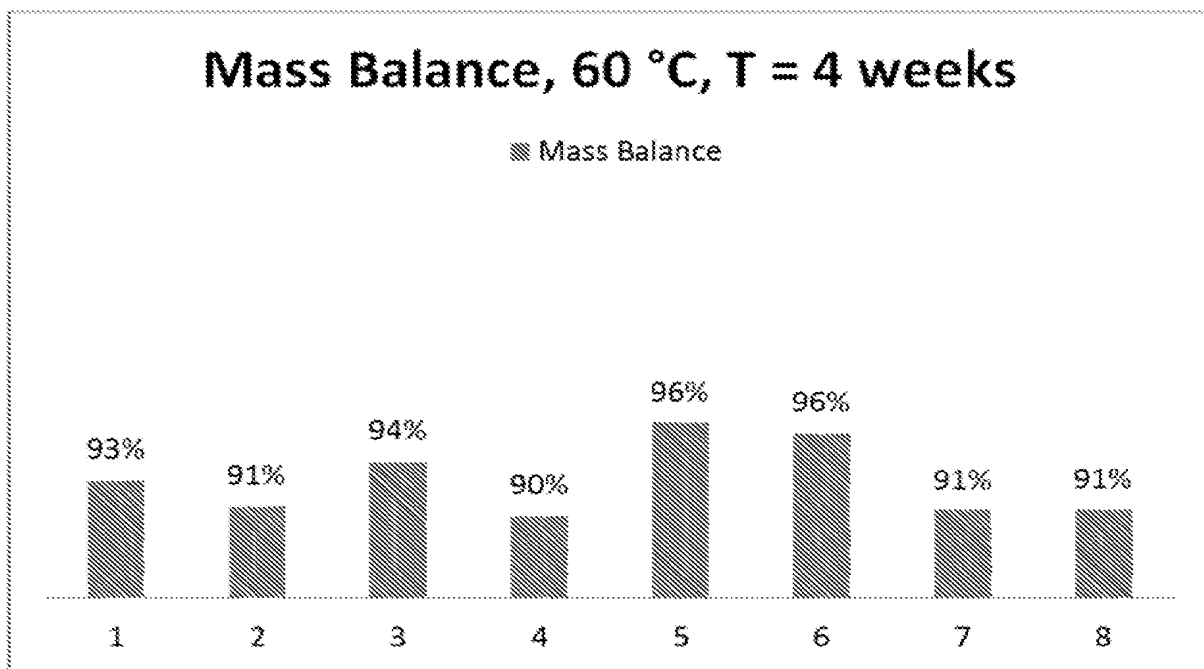


Fig. 4

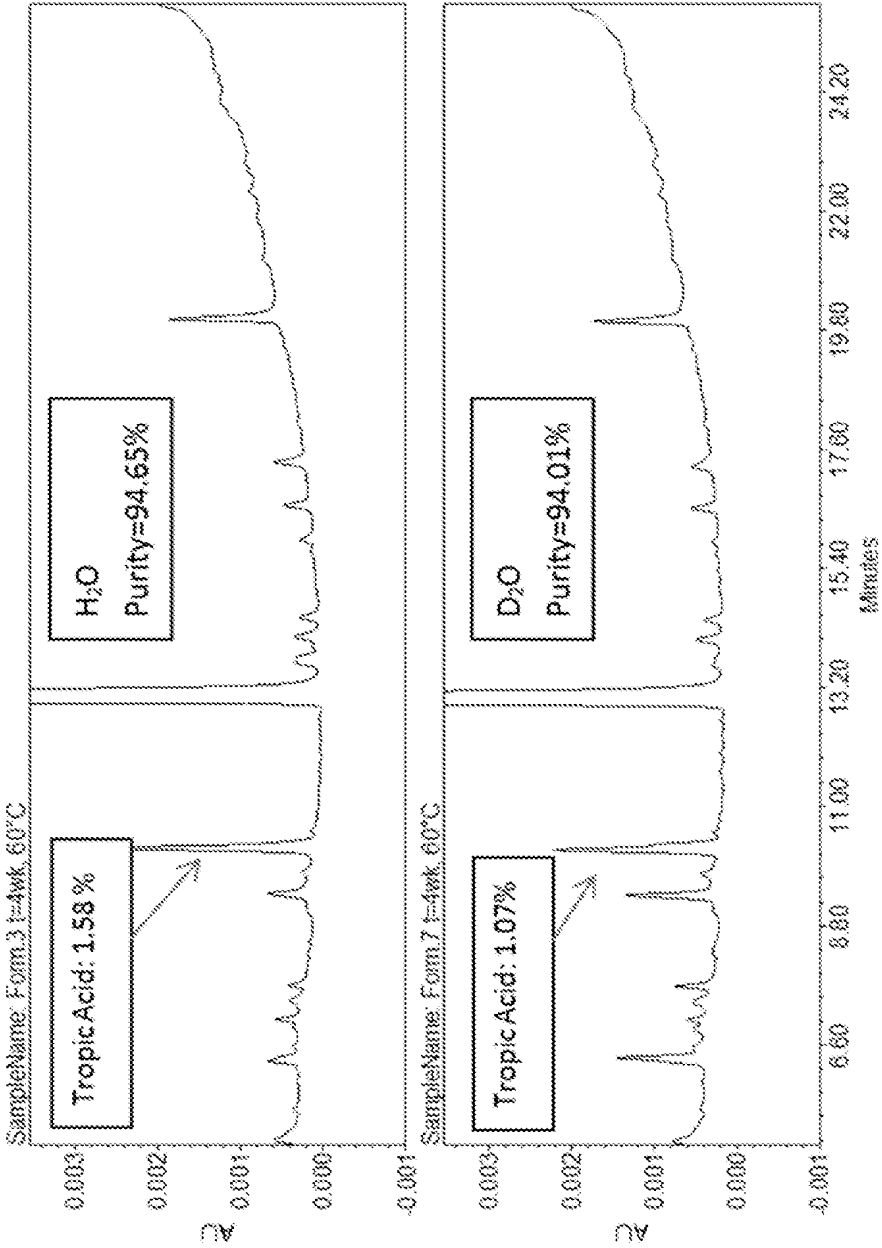


Fig. 5

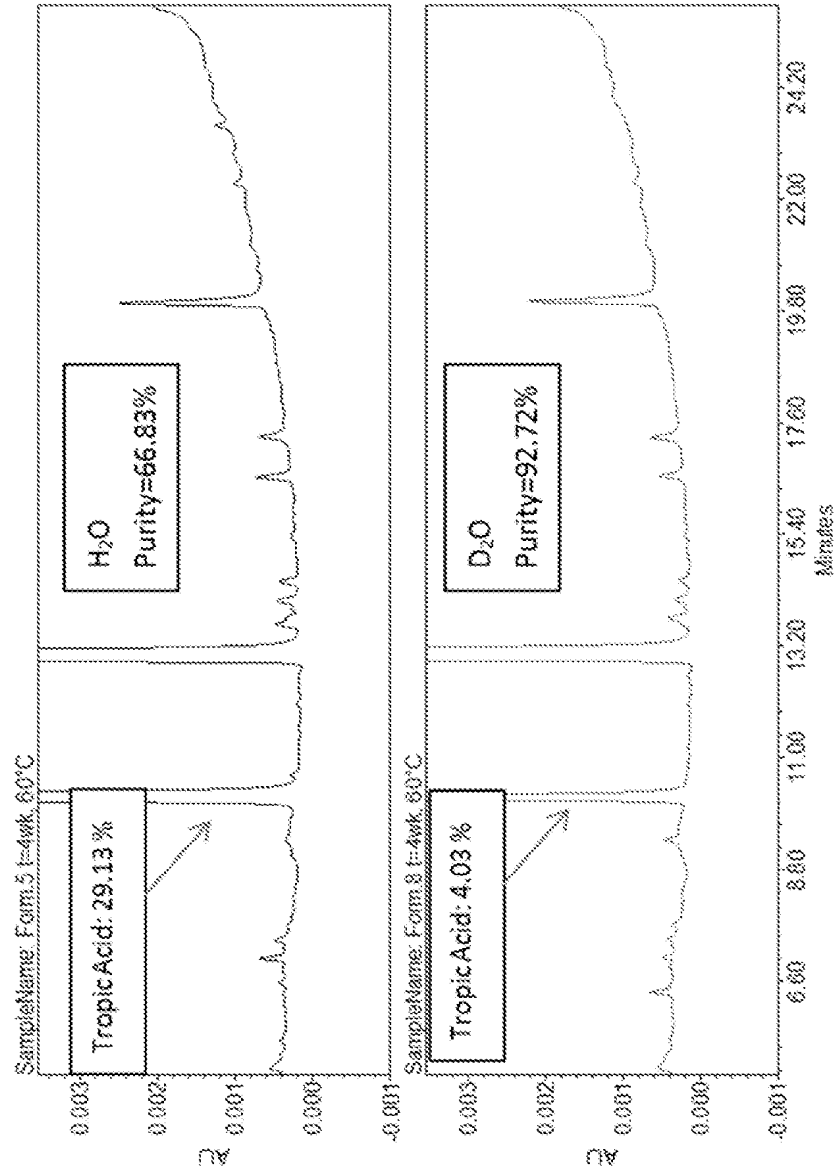


Fig. 6

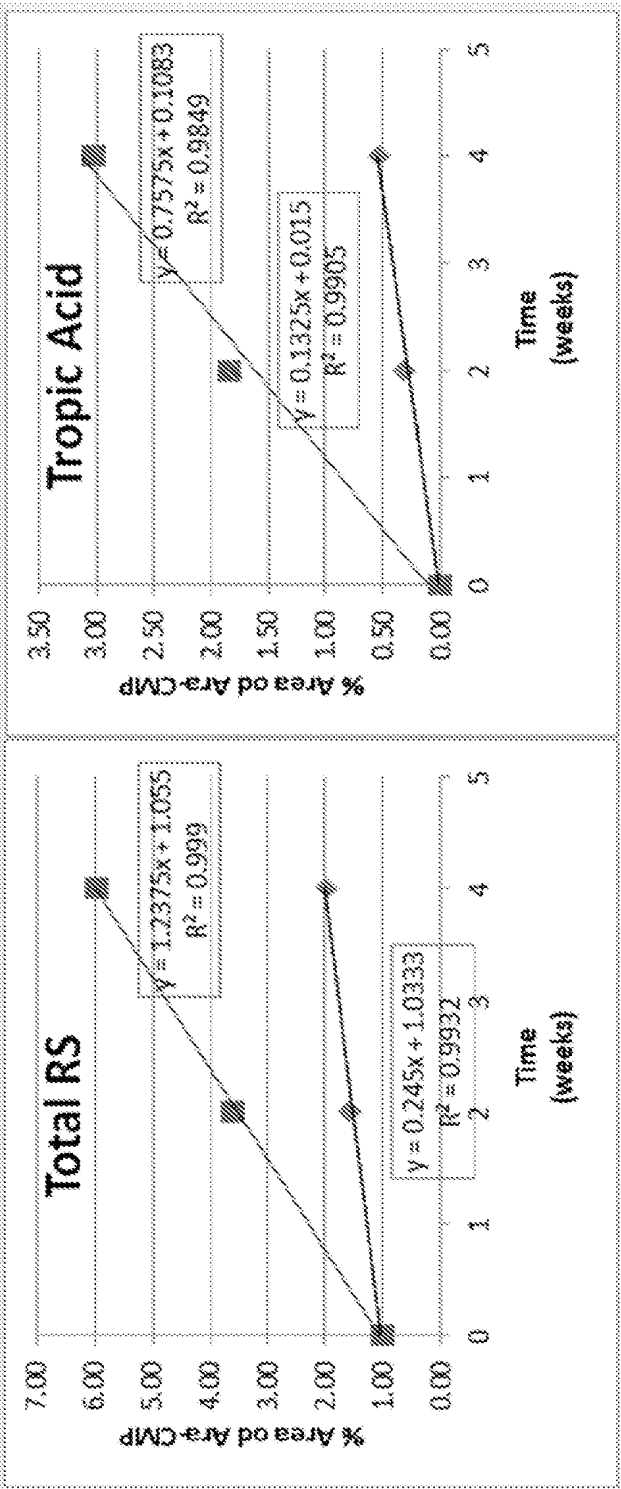


Fig. 7

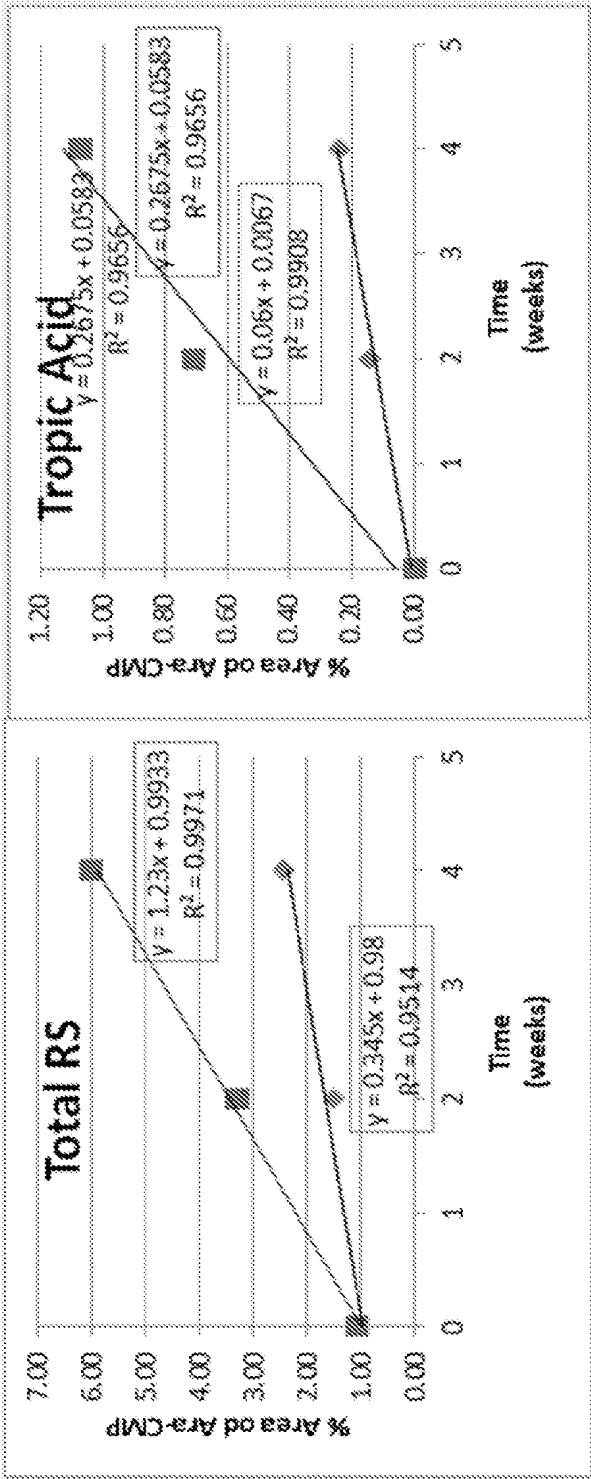


Fig. 8

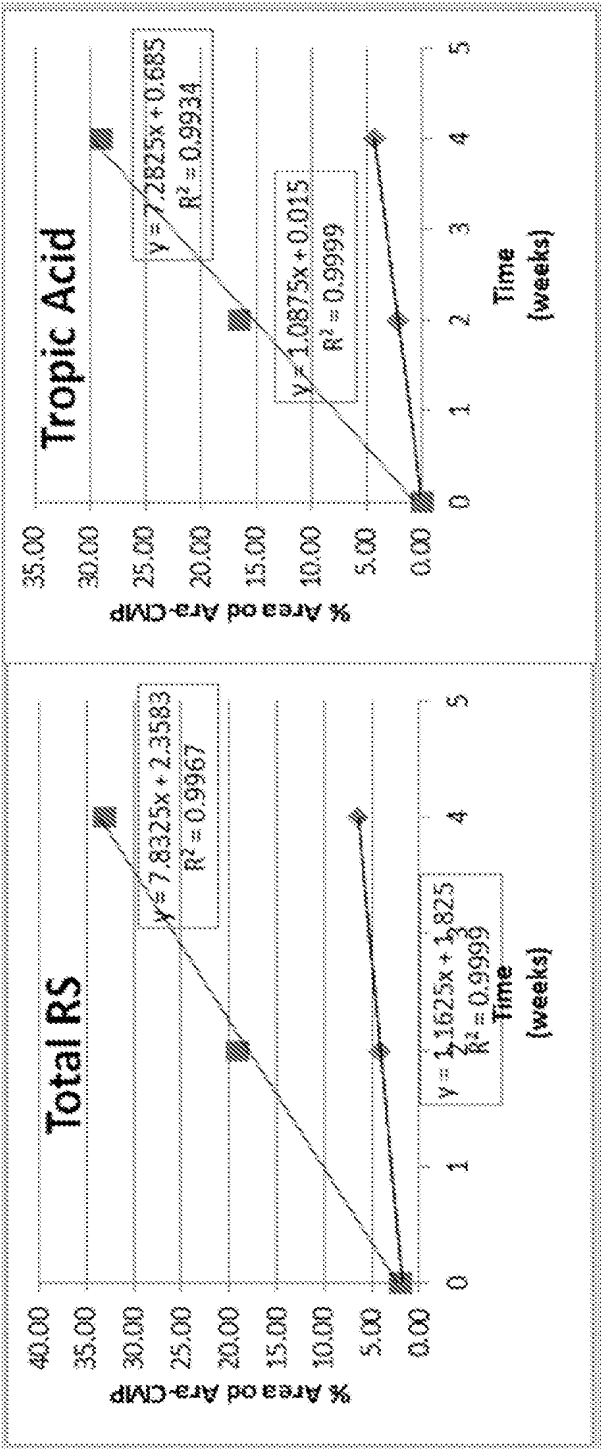


Fig. 9

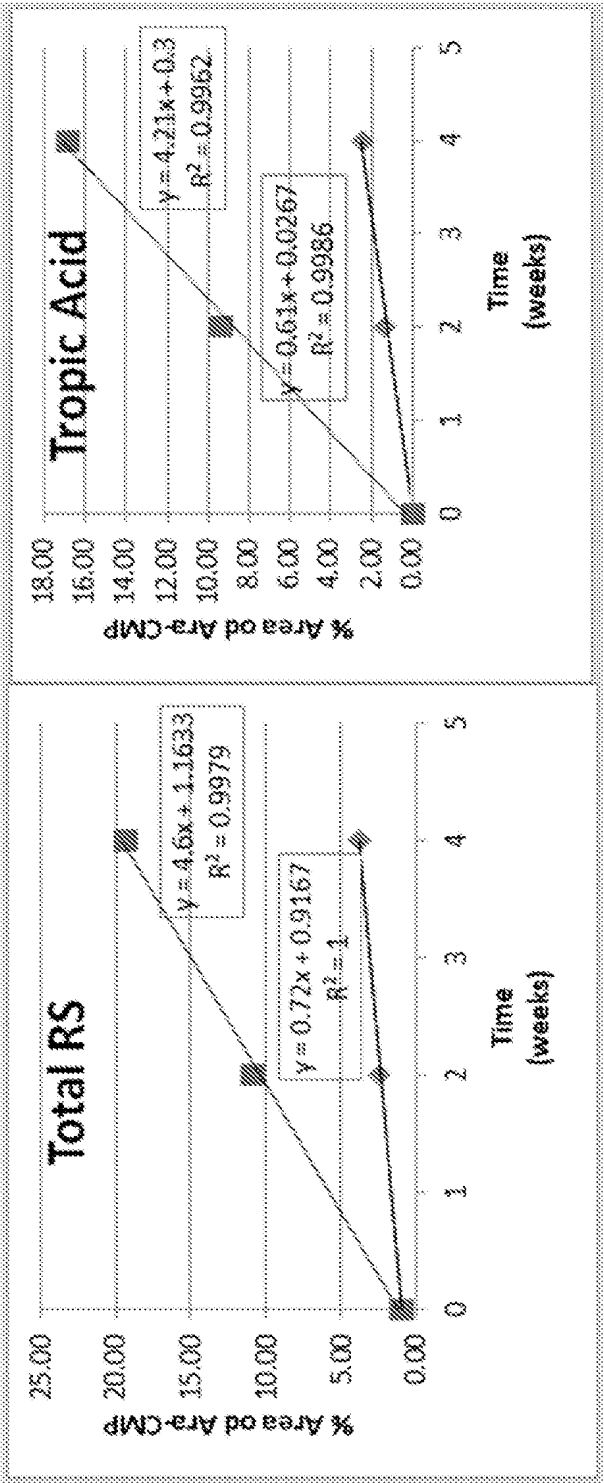


Fig. 10

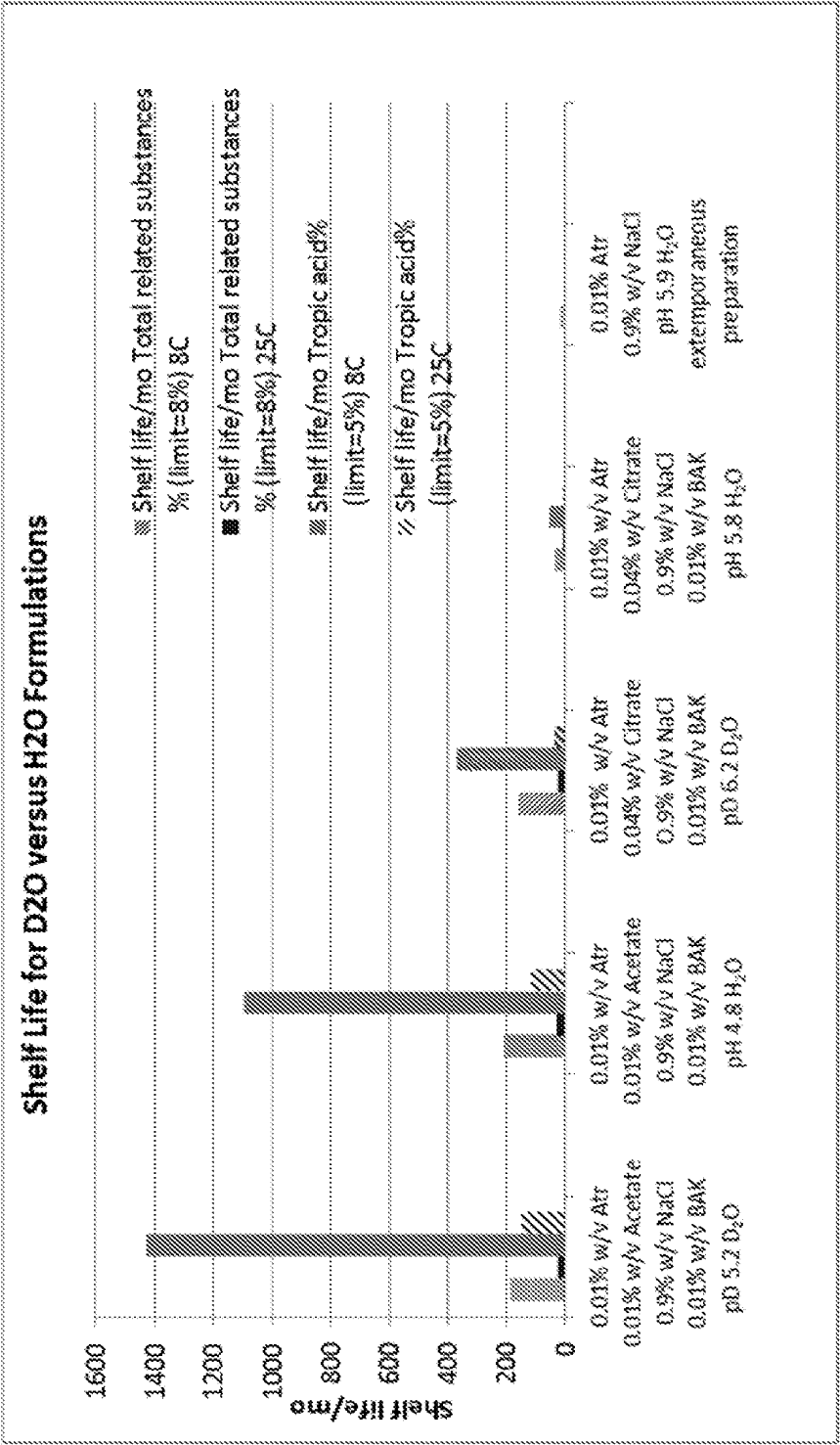


Fig. 11A

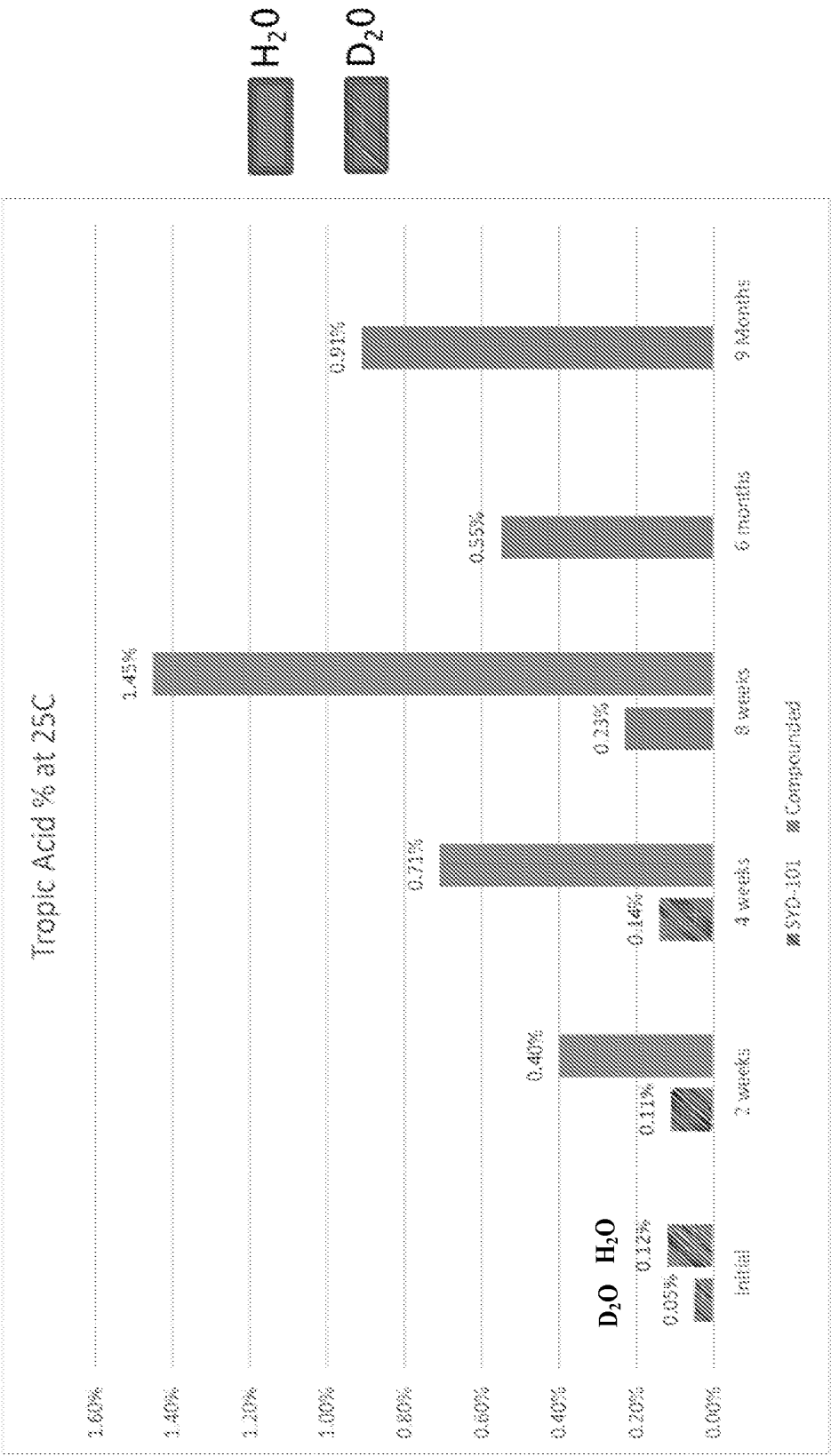


Fig. 11B

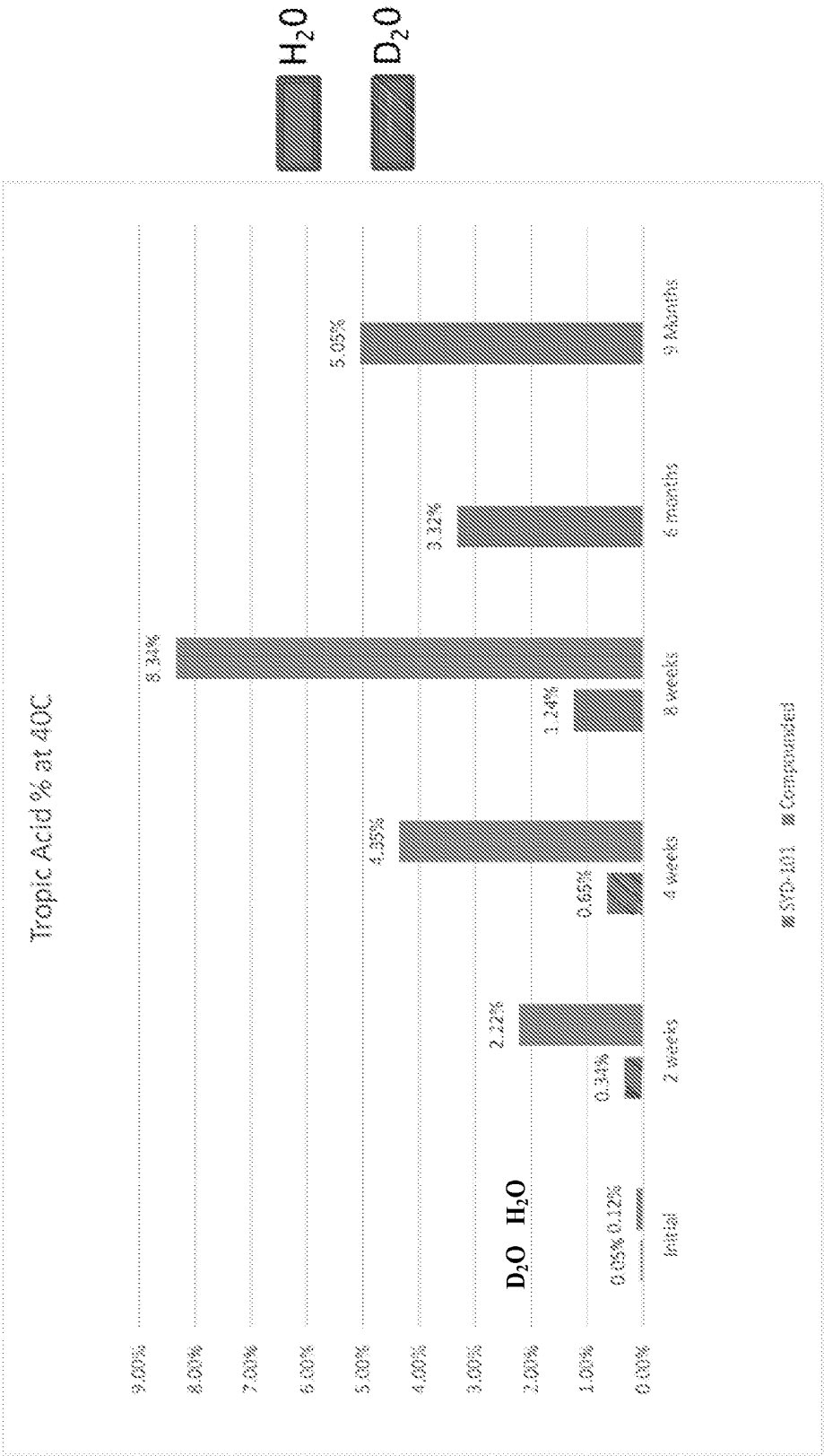
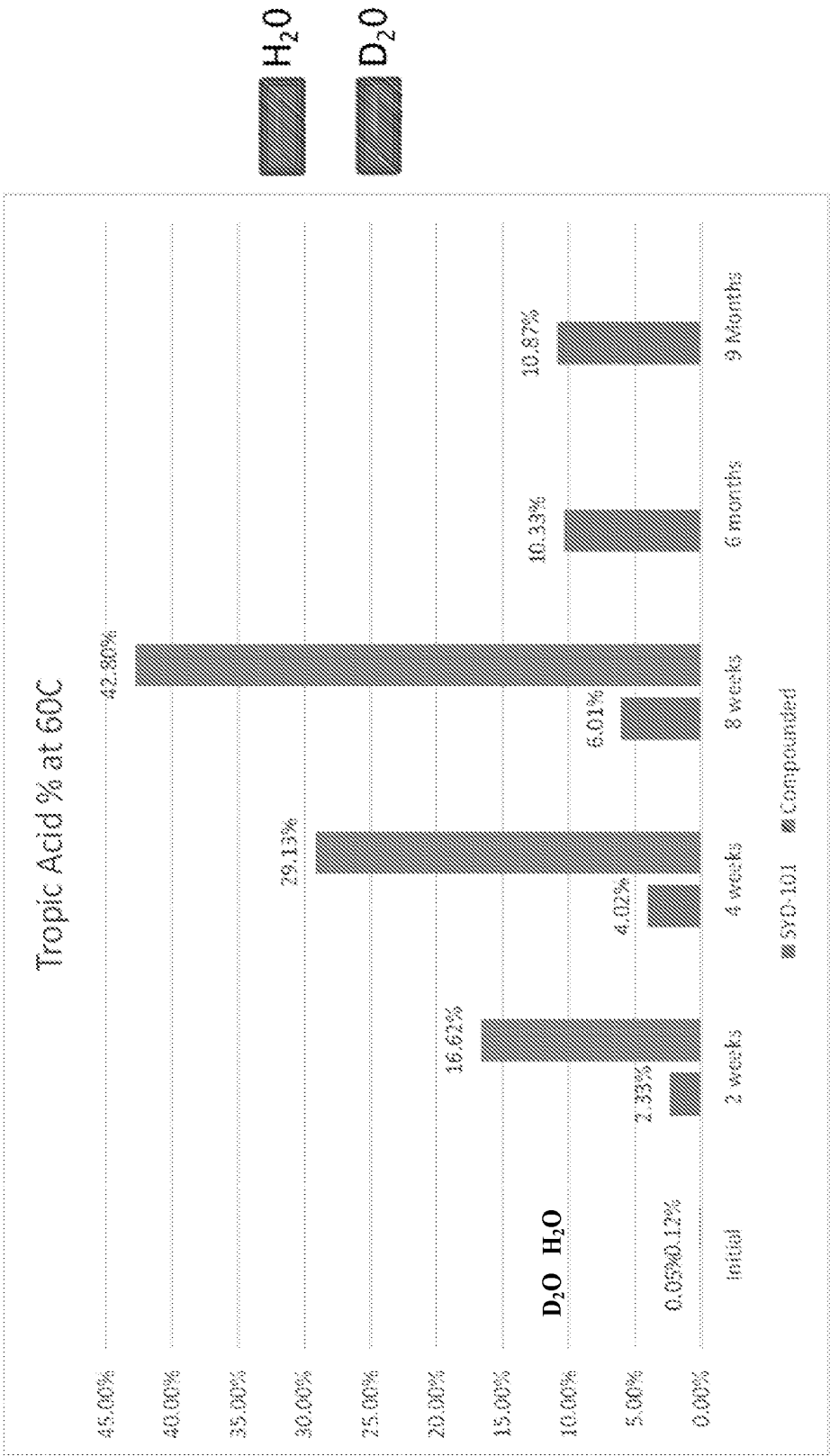


Fig. 11C



PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:

YANG, XIAOFAN

WILSON SONSINI GOODRICH & ROS 650 PAGE MILL
ROAD PALO ALTO CA 94304 USA**PCT****NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION**

(PCT Rule 44.1)

Date of mailing
(day/month/year) 21 October 2016 (21.10.2016)Applicant's or agent's file reference
46682-701602**FOR FURTHER ACTION** See paragraphs 1 and 4 belowInternational application No.
PCT/US2016/029222International filing date
(day/month/year) **25 April 2016 (25.04.2016)**

Applicant

SYDNEXIS, INC.

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.**How?** Directly to the International Bureau of WIPO preferably through ePCT or on paper to, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70**For more detailed instructions,** see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 - 9-011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90bis.1 and 90bis.3).

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Within **19 months** from the priority date, the applicant may request that a supplementary international search be carried out by an International Searching Authority, that offers this service (Rule 45bis.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the ISA/KR

International Application Division
Korean Intellectual Property Office
189 Cheongsu-ro, Seo-gu, Daejeon, 35208, Republic of Korea

Facsimile No. 82-42-481-8578

Authorized officer

COMMISSIONER

Telephone No. 82-42-481-5875



* Attention

Copies of the documents cited in the international search report can be searched in the following Korean Intellectual Property Office English website for six months(expire date : **2017.04.21**) from the date of mailing of the international search report.

<http://www.kipo.go.kr/en/> => PCT Services => PCT Services

ID : PCT international application number

PW : **VD73HPDY**

Inquiries related to PCT International Search Report or Written Opinion prepared by KIPO as an International Searching Authority can be answered not only by KIPO but also through IPKC (Intellectual Property Korea Center), located in Vienna, VA, which functions as a PCT Help Desk for PCT applicants.

Homepage: <http://www.ipkcenter.com>

Email: ipkc@ipkcenter.com

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 46682-701602	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2016/029222	International filing date (<i>day/month/year</i>) 25 April 2016 (25.04.2016)	(Earliest) Priority Date (<i>day/month/year</i>) 23 April 2015 (23.04.2015)
Applicant SYDNEXIS, INC.		

This International search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of :

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (See Box No. II)

3. ☐ **Unity of invention is lacking** (See Box No. III)

4. With regard to the **title**,

- ☒ the text is approved as submitted by the applicant.
☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant.
☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. 4
☒ as suggested by the applicant.
☐ as selected by this Authority, because the applicant failed to suggest a figure.
☐ as selected by this Authority, because this figure better characterizes the invention.
- b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/029222

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, 20
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 19 and 20 pertain to methods for treatment of the human body by surgery or 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.: 14
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:
Claim 14 is unclear since it refers to multiple dependent claim 13 which does not comply with PCT Rule 6.4(a).
3. ☒ Claims Nos.: 4-13, 15-20
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

International application No.
PCT/US2016/029222**A. CLASSIFICATION OF SUBJECT MATTER****A61K 31/46(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; A61K 31/55; A61K 31/505; A61K 9/50; A61K 47/32; A61K 47/38; A61K 47/42; A61K 47/00; A61K 9/08; C07D 401/14; 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, muscarinic antagonist, deuterated water

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0332826 A1 (TEVA PHARMACEUTICAL INDUSTRIES LIMITED) 20 September 1989 See abstract; column 2, lines 10-26; column 4, lines 1-7; column 5, lines 44-55; column 6, lines 35-40; column 7, lines 29-31; and claims 1, 13-15.	1-3
A	US 5716952 A (WOLDEMUSSE, E. et al.) 10 February 1998 See abstract; and claims 1, 8.	1-3
A	WO 97-16192 A1 (MERCK & CO., INC.) 9 May 1997 See abstract; and claims 5-9, 17.	1-3
A	US 2012-0015035 A1 (WILDSOET, C. F. et al.) 19 January 2012 See abstract; paragraphs [0030], [0031]; and claim 1.	1-3
A	WO 2011-019940 A2 (SEROS MEDICAL, LLC) 17 February 2011 See abstract; paragraph [0020]; and claims 1, 3.	1-3



Further documents are listed in the continuation of Box C.



See patent family amex.

* 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

21 October 2016 (21.10.2016)

Date of mailing of the international search report

21 October 2016 (21.10.2016)

Name and mailing address of the ISA/KR

International Application Division

Korean Intellectual Property Office

189 Cheongsa-ro, Seo-gu, Daejeon, 35208, Republic of Korea

Facsimile No. +82-42-481-8578

Authorized officer

CHO, KI YUN

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2016/029222

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0332826 A1	20/09/1989	AU 1989-51489 A IL 85312 A JP 02-022220 A KR 10-1989-0012634 A	03/08/1989 16/08/1991 25/01/1990 18/09/1989
US 5716952 A	10/02/1998	AU 1993-10993 A AU 666536 B2 CA 2132007 C DE 69332048 T2 EP 0634932 A1 EP 0634932 B1 ES 2177543 T3 JP 07-504915 A WO 93-18772 A1	21/10/1993 15/02/1996 18/07/2006 23/01/2003 25/01/1995 19/06/2002 16/12/2002 01/06/1995 30/09/1993
WO 97-16192 A1	09/05/1997	AU 1997-28696 A	22/05/1997
US 2012-0015035 A1	19/01/2012	US 8883214 B2 WO 2010-083129 A2 WO 2010-083129 A9	11/11/2014 22/07/2010 09/12/2010
WO 2011-019940 A2	17/02/2011	EP 2464387 A2 EP 2464387 A4 US 2012-0203161 A1 WO 2011-019940 A3	20/06/2012 15/05/2013 09/08/2012 16/06/2011

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

To:
YANG, XIAOFAN

WILSON SONSINI GOODRICH & ROS 650 PAGE MILL
ROAD PALO ALTO CA 94304 USA

Date of mailing
(day/month/year) **21 October 2016 (21.10.2016)**

Applicant's or agent's file reference
46682-701602

FOR FURTHER ACTION

See paragraph 2 below

International application No.
PCT/US2016/029222

International filing date (day/month/year)
25 April 2016 (25.04.2016)

Priority date(day/month/year)
23 April 2015 (23.04.2015)

International Patent Classification (IPC) or both national classification and IPC
A61K 31/46(2006.01)i, A61K 9/08(2006.01)i, A61P 27/02(2006.01)i

Applicant
SYDNEXIS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/KR
International Application Division
Korean Intellectual Property Office
189 Cheongsu-ro, Seo-gu, Daejeon,
35208, Republic of Korea
Facsimile No. +82-42-481-8578



Date of completion of this opinion

21 October 2016 (21.10.2016)

Authorized officer

CHO, KI YUN

Telephone No. +82-42-481-5655



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2016/029222

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of :
- ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))
3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
- a. ☐ forming part of the international application as filed:
 - ☐ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2016/029222

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 4-20

because:

☒ the said international application, or the said claims Nos. 19, 20

relate to the following subject matter which does not require an international search (*specify*):

Claims 19 and 20 pertain to a method for treatment of the human body by therapy (PCT Rule 43bis2.1(b) and Rule 67.1(iv)).

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 14
are so unclear that no meaningful opinion could be formed (*specify*):

Claim 14 is unclear since it refers to multiple dependent claim 13 which does not comply with PCT Rule 6.4(a).

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed (*specify*):

☒ no international search report has been established for said claims Nos. 4-20

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).

☐ See Supplemental Box for further details.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US2016/029222

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-3	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-3	NO
Industrial applicability (IA)	Claims	1-3	YES
	Claims	NONE	NO

2. Citations and explanations :

Reference is made to the following document:

D1: EP 0332826 A1 (TEVA PHARMACEUTICAL INDUSTRIES LIMITED) 20 September 1989

1. Novelty and Inventive Step

1.1. Claim 1

The subject matter of claim 1 relates to an ophthalmic composition, comprising about 0.001- 0.005 wt% of a muscarinic antagonist and deuterated water, at a pD of about 4.2-7.9, wherein the muscarinic antagonist does not extend singlet oxygen lifetime.

D1, which is considered to be the closest prior art to the subject matter of claim 1, discloses an injectable pharmaceutical composition having a long term shelf life, which composition comprises, at least one pharmacologically active ingredient; a solvent medium containing an aqueous component, said aqueous component comprising at least a major proportion by volume of deuterium oxide; and additionally at least one further pharmacologically active ingredient such as atropine (See claims 1, 13-15). Moreover, D1 discloses that benactyzine hydrochloride (40 mg), atropine sulfate (10 mg) and trimedoxime bromide (400 mg) are dissolved in 18 ml of deuterium oxide (See column 7, lines 29-31).

The subject matter of claim 1 differs from the injectable pharmaceutical composition of D1 in three aspects: (1) the composition used for ophthalmology, (2) a range of the amount of muscarinic antagonist, and (3) a range of pD.

However, the difference (1) comes within the scope of the customary practice followed by persons skilled in the art, especially as the advantages thus achieved can readily be foreseen. Regarding the difference (2), it would have been readily modified or optimized by a person skilled in the art from D1 and no unexpected effects or properties are

Continued on Supplemental Box

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2016/029222

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

Claims 4-13 and 15-20 do not comply with PCT Rule 6.4(a) because multiple dependent claims should not serve as a basis for any other multiple dependent claim.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US2016/029222

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The expression "about" used in claims 1 and 6-11 is technically vague and unclear, thus leaving the reader in doubt as to the scope of the technical feature to which they refer (PCT Article 6).

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of : Box No. V

indicated in the application. Regarding the difference (3), it can be predicted from D1 by a person skilled in the art considering that the pharmaceutical composition comprises atropine in deuterium oxide (See claims 1, 13-15).

Accordingly, claim 1 would have been obvious over D1. Therefore, claim 1 is novel under PCT Article 33(2) but lacks an inventive step under PCT Article 33(3).

1.2. Claims 2, 3

The additional feature of claim 2 dependent on claim 1, relating to a kind of the muscarinic antagonist, is disclosed in D1 in atropine used as the sulfate salt (See column 5, lines 51-52).

The additional feature of claim 3 dependent on claim 1 or 2, relating to the muscarinic antagonist quenching photogenerated singlet oxygen species in the composition, is not disclosed in D1. However, said difference can be predicted from D1 by a person skilled in the art considering that the injectable pharmaceutical composition comprises atropine used as the sulfate salt (See column 5, lines 51-52).

Accordingly, claims 2 and 3 would have been obvious over D1. Therefore, claims 2 and 3 are novel under PCT Article 33(2) but lack an inventive step under PCT Article 33(3).

2. Industrial Applicability

Claims 1-3 are industrially applicable under PCT Article 33(4).

Electronic Patent Application Fee Transmittal

Application Number:	15208537			
Filing Date:	12-Jul-2016			
Title of Invention:	OPHTHALMIC COMPOSITION			
First Named Inventor/Applicant Name:	Gregory I. OSTROW			
Filer:	Michael J. Hostetler/FY/Jennifer Vail			
Attorney Docket Number:	46682-701.301			
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:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	2806	1	90	90
Total in USD (\$)				90

Electronic Acknowledgement Receipt

EFS ID:	27439383
Application Number:	15208537
International Application Number:	
Confirmation Number:	1009
Title of Invention:	OPHTHALMIC COMPOSITION
First Named Inventor/Applicant Name:	Gregory I. OSTROW
Customer Number:	21971
Filer:	Michael J. Hostetler/FY/Jennifer Vail
Filer Authorized By:	Michael J. Hostetler
Attorney Docket Number:	46682-701.301
Receipt Date:	07-NOV-2016
Filing Date:	12-JUL-2016
Time Stamp:	20:36:15
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	\$90
RAM confirmation Number	110816INTEFSW00005280232415
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		46682-701-301_IDS.pdf	230105	yes	5
			b909f0d69b42031755401c46c7b14650ff44ad09		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Transmittal Letter		1	4	
	Information Disclosure Statement (IDS) Form (SB08)		5	5	
Warnings:					
Information:					
2	Foreign Reference	WO2011019940A2_EFS.PDF	573635	no	20
			e78f37661fbfb3c44b31f3ab021411de56f264c8		
Warnings:					
Information:					
3	Foreign Reference	WO2016172712A2.PDF	7532188	no	124
			e7186caa8ffbd49e4b99066ff0431e264a3c04eb		
Warnings:					
Information:					
4	Non Patent Literature	PCTUS2016029222_ISRWO_21 OCT2016.PDF	1766776	no	13
			d352cebf36a6936ec91fb5609aa16ef5e90ce1dd		
Warnings:					
Information:					
5	Non Patent Literature	US14859042_OA_25OCT2016. PDF	395840	no	10
			f0aa92f8868bf460d69e836b38740ec6a959cd5b		
Warnings:					
Information:					

6	Fee Worksheet (SB06)	fee-info.pdf	30777 b35bfe545714bb6b0dd0ae74cb3eff29687a6591	no	2
Warnings:					
Information:					
Total Files Size (in bytes):			10529321		
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.					

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	OSTROW; Gregory I. et al.	Group Art Unit:	1621
Serial Number:	15/208,537	Examiner:	Zohreh A Fay
Filing or 371 (c) Date:	2016-07-12	CONFIRMATION NO:	1009
Title:	OPHTHALMIC COMPOSITION		

FILED ELECTRONICALLY ON: November 7, 2016

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

INFORMATION DISCLOSURE STATEMENT
UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

- A. ☐ *37 CFR § 1.97 (b)*. This Information Disclosure Statement should be considered by the Office because:
- ☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);
 - OR --
 - ☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;
 - OR --
 - ☐ (3) It is being filed before the mailing of a first Office action on the merits;
 - OR --
 - ☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.
- B. ☒ *37 CFR § 1.97(c)*. Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b)*, above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:
- ☐ a statement as specified in §1.97 (e) provided concurrently herewith;
 - OR --
 - ☒ a fee of \$90.00 as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.
- C. ☐ *37 CFR § 1.97 (d)*. Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:
- i. a statement as specified in § 1.97 (e);
 - AND --
 - ii. a fee of \$180.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.
- D. ☐ *37 CFR §1.97 (e)*. Statement.
- ☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);
 - AND/OR --
 - ☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);
 - AND/OR --
 - ☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

- E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.
- F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:
- ☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.
- OR --
- ☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 is NOT enclosed.
- AND/OR --
- ☒ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).
- AND/OR --
- ☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).
- G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.
- ☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.
- ☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.
- OR --
- ☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____
- ☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.
- H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:
- ☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.
- Application in which the information was submitted: _____
- Information Disclosure Statement(s) filed on: _____
- AND
- ☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

- I. ☒ *Fee Authorization.* The Commissioner is hereby authorized to charge the above-referenced fees of \$90.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No. 46682-701.301).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: November 7, 2016

By: /Xiaofan Yang/

Xiaofan Yang, Reg. No. 61459

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 21971

Application Number 	Application/Control No. 15/208,537	Applicant(s)/Patent under Reexamination OSTROW ET AL.	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 10/18/16	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:
Lawana Hixon

RECEIVED

Sydnexis / 46682-702.601
MHOS / FY6 / AHIR / JUY / CMEK

AUG 29 2016

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

To: Frank Yang
Wilson Sonsini Goodrich & Rosati
650 Page Mill Road
Palo Alto, California 94304
United States of AmericaDate of mailing
(day/month/year)

23 AUG 2016

Applicant's or agent's file reference

46682-702.601

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.

PCT/US16/34823

International filing date
(day/month/year)

27 May 2016 (27.05.2016)

Applicant SYDNEXIS, INC.

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

How? Directly to the International Bureau of WIPO preferably through ePCT or on paper to, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 - 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ With regard to any protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90bis.1 and 90bis.3).

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices. In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Within 19 months from the priority date, the applicant may request that a supplementary international search be carried out by a different International Searching Authority that offers this service (Rule 45bis.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

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

Authorized officer

Shane Thomas

PCT Helpdesk: 571-272-4300
Telephone No. PCT OSP: 571-272-7774

Form PCT/ISA/220 (July 2014)

WSGR PATENT DOCKET

U.S. _____ FOREIGN: ☒
DOCKETED: 8/29/16 BY: a
ACTION: Search report 10/26/16
DUE DATES: Written opinion 8/29/17
No related US case
ATTY: C/M #

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 46682-702.601	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US16/34823	International filing date (<i>day/month/year</i>) 27 May 2016 (27.05.2016)	(Earliest) Priority Date (<i>day/month/year</i>) 29 May 2015 (29.05.2015)
Applicant SYDNEXIS, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed.
☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☒ Certain claims were found unsearchable (see Box No. II).

3. ☐ Unity of invention is lacking (see Box No. III).

4. With regard to the title,

- ☒ the text is approved as submitted by the applicant.
☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

- ☒ the text is approved as submitted by the applicant.
☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

- a. the figure of the drawings to be published with the abstract is Figure No. 1
☒ as suggested by the applicant.
☐ as selected by this Authority, because the applicant failed to suggest a figure.
☐ as selected by this Authority, because this figure better characterizes the invention.
- b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US16/34823

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.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
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:
3. ☒ Claims Nos.: 4-8 and 14-30
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 additional fees, this Authority did not invite payment of 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

International application No.
PCT/US16/34823

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A61K 9/00, 31/00, 47/02, 47/30; A61P 27/02 (2016.01) CPC - A61K 9/00, 31/00, 47/02, 47/30 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) - A61F 9/00; A61K 9/00, 9/08, 31/00, 47/02, 47/30; A61P 27/02 (2016.01); CPC - A61K 9/00, 9/08, 9/0048, 31/00, 47/02, 47/30 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) PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, Other Countries (INPADOC), RU, AT, CH, TH, BR, PH); EBSCO; Google/Google Scholar; PubMed; ophthalmic composition, ophthalmic agent, deuterated water, singlet oxygen, aflibercept, ranibizumab, cyclopentolate, tropicamide, tetracaine, azelastine, oxymetazoline, phenylephrine, tetrahydrozoline, osmolarity adjusting agent, pD, tonicity		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 7,691,099 B2 (BERRY, MJ) 6 April 2010; column 2, lines 23-36	1-2, 3/1-2, 9-13
Y	US 8,980,839 B2 (MITRA, AK et al.) 17 March 2015; column 10, lines 57-67; column 11, lines 1-11; column 12, lines 19-33	1-2, 3/1-2, 9-13
Y	(U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION) Guidance for Industry Q1A (R2) Stability Testing of New Drug Substances and Products. November 2003 [retrieved on 27 July 2016]. Retrieved from the internet; URL: < http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073369.pdf >; page 1, third paragraph; page 2, fourth-fifth paragraphs; page 4, sixth-seventh paragraphs; page 11, first-fourth paragraphs	3/1-2
☐ 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 27 July 2016 (27.07.2016)		Date of mailing of the international search report 23 AUG 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300		Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: Frank Yang
Wilson Sonsini Goodrich & Rosati
650 Page Mill Road
Palo Alto, California 94304
United States of America

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing
(day/month/year) **23 AUG 2016**

Applicant's or agent's file reference
46682-702.601

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US16/34823

International filing date (day/month/year)

27 May 2016 (27.05.2016)

Priority date (day/month/year)

29 May 2015 (29.05.2015)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - **A61K 9/00, 31/00, 47/02, 47/30; A61P 27/02 (2016.01)**
CPC - **A61K 9/00, 31/00, 47/02, 47/30**

Applicant **SYDNEXIS, INC.**

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

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

Date of completion of this opinion

27 July 2016 (27.07.2016)

Authorized officer

Shane Thomas

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

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US16/34823

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:
- ☒ the international application in the language in which it was filed.
- ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
2. ☐ This opinion has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a)).
3. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established on the basis of a sequence listing:
- a. ☐ forming part of the international application as filed:
- ☐ in the form of an Annex C/ST.25 text file.
- ☐ on paper or in the form of an image file.
- b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
- c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
- ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).
- ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US16/34823

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 4-8, 14-30

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 4-8, 14-30 are so unclear that no meaningful opinion could be formed (*specify*):

Claims 4-8 and 14-30 are all dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☒ no international search report has been established for said claims Nos. 4-8, 14-30

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).

☐ See Supplemental Box for further details.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US16/34823

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-2, 3/1-2, 9-13	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-2, 3/1-2, 9-13	NO
Industrial applicability (IA)	Claims	1-2, 3/1-2, 9-13	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1-2 and 9-13 lack an inventive step under PCT Article 33(3) as being obvious over US 7,691,099 B2 ('BERRY') in view of US 8,980,839 B2 to Mitra, et al. (hereinafter 'Mitra').

As per claim 1, Berry discloses an ophthalmic composition (ocular solutions; column 2, lines 23-28) comprising an ophthalmic agent (ocular drug; column 2, lines 26-28) and deuterated water (deuterated water; column 2, lines 26-28), wherein the ophthalmic agent is not a muscarinic antagonist (ocular agent is proparacaine which is not a muscarinic antagonist; column 2, lines 35-36), and wherein the ophthalmic agent does not extend singlet oxygen lifetime (ocular agent is proparacaine which is not a photosensitizer and therefore does not extend singlet oxygen lifetime; column 2, lines 35-36), but Berry does not disclose comprising at a pD of from about 4 to about 8. However, Mitra discloses comprising a pD of from about 4 to about 8 (pH, pD measured in deuterated water, of liquid ophthalmic drug compositions range from 5 to 8; column 10, lines 60-64). It would have been obvious to one skilled in the art at the time of the invention to have modified the ophthalmic composition, as disclosed by Berry, to provide the ophthalmic composition comprising at a pD of from about 4 to about 8, as disclosed by Mitra, as pH values (pD values) inside the range of 5 -8 are preferable for formulating ophthalmic preparations for topical applications to the eye (Mitra; column 10, lines 60-64).

As per claim 2, Berry and Mitra, in combination, disclose the ophthalmic composition of claim 1, and Berry further discloses wherein the ophthalmic agent comprises aflibercept, ranibizumab, pegaptanib, cyclopentolate, phenylephrine, homatropine, scopolamine, cyclopentolate/phenylephrine, phenylephrine/scopolamine, tropicamide, ketorolac/phenylephrine, hydroxyamphetamine/tropicamide, cysteamine, ociprasmin, mitomycin, dapiprazole, lidocaine, proparacaine (proparacaine; column 2, lines 35-36), tetracaine, benoxinate, azithromycin, bacitracin, besifloxacin, boric acid, chloramphenicol, ciprofloxacin, erythromycin, ganciclovir, gatifloxacin, gentamicin, idoxuridine, levofloxacin, moxifloxacin, natamycin, norfloxacin, ofloxacin, bacitracin/polymyxin b, tobramycin, polymyxin b/trimethoprim, povidone iodine, trifluridine, gramicidin/neomycin/polymyxin b, sulfacetamide sodium, sulfisoxazole, bacitracin/neomycin/polymyxin b, oxytetracycline/polymyxin b, phenylephrine/sulfacetamide sodium, vidarabine, bromfenac, nepafenac, ketorolac, cyclosporine, flurbiprofen, suprofen, diclofenac, alcaftadine, azelastine, bepotastine, cromolyn, emedastine, epinastine, ketotifen, levocabastine, lodoxamide, nedocromil, naphazoline, naphazoline/pheniramine, naphazoline/zinc sulfate, olopatadine, oxymetazoline, pemirolast, phenylephrine, phenylephrine/zinc sulfate, tetrahydrozoline, tetrahydrozoline/zinc sulfate, fluorescein, fluorescein/proparacaine, benoxinate/fluorescein, indocyanine green, trypan blue, acetylcholine, apraclonidine, betaxolol, bimatoprost, brimonidine, brinzolamide, brimonidine/brinzolamide, carbachol, carteolol, demecarium bromide, dipivefrin, dorzolamide, dorzolamide/timolol, echothiophate iodide, epinephrine, epinephrine/pilocarpine, latanoprost, levobunolol, levobetaxolol, metipranolol, physostigmine, pilocarpine, tafluprost, timolol, travoprost, unoprostone, artificial tear, dexamethasone, difluprednate, fluocinolone, fluorometholone, loteprednol, medrysone, prednisolone, rimexolone, triamcinolone, fluorometholone/sulfacetamide sodium, dexamethasone/neomycin, dexamethasone/tobramycin, dexamethasone/neomycin/polymyxin b, loteprednol/tobramycin, prednisolone/sulfacetamide sodium, bacitracin/hydrocortisone/neomycin/polymyxin b, hydrocortisone/neomycin/polymyxin b, chloramphenicol/hydrocortisone/polymyxin b, neomycin/polymyxin b/prednisolone, gentamicin/prednisolone, ketorolac/phenylephrine, diphenhydramine, dimenhydrinate, dicyclomine, flavoxate, oxybutynin, tiotropium, hyoscine, scopolamine (L-hyoscine), hydroxyzine, ipratropium, pirenzepine, solifenacin, darifenacin, benzatropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, tolterodine, or any combinations thereof.

As per claim 9, Berry and Mitra, in combination, disclose the ophthalmic composition of claim 1, but Berry does not disclose wherein the ophthalmic composition further comprises an osmolarity adjusting agent, a preservative, a buffer agent, a tonicity adjusting agent, a pD adjusting agent, or a combination thereof. However, Mitra discloses wherein the ophthalmic composition further comprises an osmolarity adjusting agent (osmolarity adjusting agents; column 11, lines 2-3), a preservative (a preservative; column 10, lines 57-60), a buffer agent (a buffer agent; column 10, lines 57-60), a tonicity adjusting agent (a tonicity adjusting agent; column 10, lines 57-60), a pD adjusting agent (a pH, pD in deuterated water, adjusting buffer; column 10, lines 57-60; column 11, lines 2-3), or a combination thereof (combinations thereof; column 10, lines 57-60). It would have been obvious to one skilled in the art at the time of the invention to have modified the ophthalmic composition, as disclosed by Berry, to provide the ophthalmic composition wherein the ophthalmic composition further comprises an osmolarity adjusting agent, a preservative, a buffer agent, a tonicity adjusting agent, a pD adjusting agent, or a combination thereof, as disclosed by Mitra, as ophthalmic compositions for topical application to the eye are formulated with a variety of additives to adjust the pH, osmolarity, etc. for the particular treatment need (Mitra; column 10, lines 57-67; column 11; lines 1-3).

----Continued Within the Next Supplemental Box----

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US16/34823

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:

Continued from Box V: Citations and Explanations

As per claim 10, Berry and Mitra, in combination, disclose the ophthalmic composition of claim 9, but Berry does not disclose wherein the osmolarity adjusting agent is sodium chloride. However, Mitra discloses wherein the osmolarity adjusting agent is sodium chloride (osmolarity adjusting agent is sodium chloride; column 11, lines 9-11). It would have been obvious to one skilled in the art at the time of the invention to have modified the ophthalmic composition, as disclosed by Berry, to provide the ophthalmic composition wherein the osmolarity adjusting agent is sodium chloride, as disclosed by Mitra, as sodium chloride is a tonicity agent that is used to adjust the osmolality of ophthalmic compositions to a preferred range (Mitra; column 11, lines 9-15) and sodium chloride is an aprotic agent that would not exchange with deuterium of deuterated water.

As per claim 11, Berry and Mitra, in combination, disclose the ophthalmic composition of claim 9, but Berry does not disclose wherein the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof. However, Mitra discloses wherein the preservative is selected from benzalkonium chloride (benzalkonium chloride; column 12, lines 19-23), and edetate disodium (EDTA; column 12, lines 19-23). It would have been obvious to one skilled in the art at the time of the invention to have modified the ophthalmic composition, as disclosed by Berry, to provide the ophthalmic composition wherein the preservative is selected from benzalkonium chloride and edetate disodium, as disclosed by Mitra, as ophthalmic composition may be preserved by addition of a preservative that is suitable for topical administration to the eye (Mitra; column 12, lines 19-33) and provides added shelf-life stability to the formulation.

As per claim 12, Berry and Mitra, in combination, disclose the ophthalmic composition of claim 9, but Berry does not disclose wherein 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. However, Mitra discloses wherein the buffer agent is selected from borates (borates; column 10, lines 66-67; column 11, line 1), borate-polyol complexes (borate-polyol complexes; column 11, line 2), phosphate buffering agents (phosphate buffer; column 11, line 1), citrate buffering agents (citrate buffer; column 11, line 1), acetate buffering agents (acetate buffer; column 11, line 1), or carbonate buffering agents (carbonate buffer; column 11, line 1). It would have been obvious to one skilled in the art at the time of the invention to have modified the ophthalmic composition, as disclosed by Berry, to provide the ophthalmic composition wherein the buffer agent is selected from borates, borate-polyol complexes, phosphate buffering agents, citrate buffering agents, acetate buffering agents, or carbonate buffering agents, as disclosed by Mitra, as borate, borate-polyol complexes, phosphates, citrate, acetate, and carbonate buffers are commonly used to adjust the pH, pD in the case of deuterated water, of ophthalmic formulation for topical administration to the eye (Mitra; column 10, lines 60-67; column 11, lines 1-4).

As per claim 13, Berry and Mitra, in combination, disclose the ophthalmic composition of claim 9, but Berry does not disclose wherein 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. However, Mitra discloses wherein the tonicity adjusting agent is sodium chloride (sodium chloride; column 11, lines 9-11). It would have been obvious to one skilled in the art at the time of the invention to have modified the ophthalmic composition, as disclosed by Berry, to provide the ophthalmic composition wherein the tonicity adjusting agent is sodium chloride, as disclosed by Mitra, as sodium chloride is a tonicity agent that is used to adjust ophthalmic compositions to a preferred range (Mitra; column 11, lines 9-15) and sodium chloride is an aprotic agent that would not exchange with deuterium of deuterated water.

Claims 3/1-2 lack an inventive step under PCT Article 33(3) as being obvious Berry in view of Mitra and in further view of the publication "Guidance for Industry Q1A (R2) Stability Testing of New Drug Substances and Products" by U.S. Department of Health and Human Services Food and Drug Administration (hereinafter 'FDA').

As per claims 3/1-2, Berry and Mitra, in combination, disclose the ophthalmic composition of claim 1 or 2, but Berry does not disclose wherein the ophthalmic composition comprises at least one of: about 80 percent, about 85 percent, about 90 percent, about 95 percent, about 97 percent, about 98 percent, or about 99 percent of the ophthalmic agent based on initial concentration after extended period of time under storage condition. However, FDA discloses wherein the ophthalmic composition comprises at least one of: about 95 percent, about 97 percent, about 98 percent, or about 99 percent of the ophthalmic agent based on initial concentration after extended period of time under storage condition (extended storage conditions and times must meet standards including having 95 percent of original value of ophthalmic agent and may have other requirements for stability purity; page 1, third paragraph; page 2, fourth paragraph; page 11, first-fourth paragraphs). It would have been obvious to one skilled in the art at the time of the invention to have modified the ophthalmic composition, as disclosed by Berry, to provide the ophthalmic composition comprises at least one of: about 95 percent, about 97 percent, about 98 percent, or about 99 percent of the ophthalmic agent based on initial concentration after extended period of time under storage condition, as disclosed by FDA, as industrial guidance for extended period of time under storage conditions must be met as part of approval of an ophthalmic composition drug product to assure stability covers storage, shipment and subsequent use of the approved drug concentration (FDA; page 2, fourth-fifth paragraphs; page 4, sixth-seventh paragraphs).

Claims 1-2, 3/1-2, and 9-13 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

PCT Recordation of Search History

Case/PCT Application Number: PCT/US16/34823

CLIN Number/Technical Field of PCT Application: 008 Chemical

Date(s) During Which the Search was Conducted: 25-27 July 2016

Date of Completion of Recordation of Search History Form: 27 July 2016

Research Analyst Initials: TFW

Search Approval Official (SAO) Initials: K1K

Field of Search/Classification Information:

IPC(8) Classifications: A61F 9/00; A61K 9/00, 9/08, 31/00, 47/02, 47/30; A61P 27/02 (2016.01)

CPC Classifications: A61K 9/00, 9/08, 9/0048, 31/00, 47/02, 47/30

Databases Searched (Patent and Non-Patent Literature (NPL), Including Sub-Databases and Files Searched) and Search Terms Used:

PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, Other Countries (INPADOC), RU, AT, CH, TH, BR, PH); EBSCO; Google/Google Scholar; PubMed;

ophthalmic composition, ophthalmic agent, deuterated water, singlet oxygen, aflibercept, ranibizumab, cyclopentolate, tropicamide, tetracaine, azelastine, oxymetazoline, phenylephrine, tetrahydrozoline, osmolarity adjusting agent, tonicity adjusting agent, a pH adjusting agent, sodium chloride, preservative, benzalkonium chloride

Database Search String Recordation, Including Dates of Searches:

Patent Database Search Strategy/Results:

PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, Other Countries
(INPADOC), RU, AT, CH, TH, BR, PH)

ID	Search String	Records	Created Date
L21	TAC:("deuterium oxide" or "deuterated water" or ((deuterium or heavy) w3 water) or D2O) AND TACD:(ophthalmic or ocular) AND CPC:("A61K9/00" or "A61K9/08" or "A61K31/00" or "A61K47/02" or "A61K47/30" or "A61K9/0048")	33	27-Jul-16
L20	TAC:("deuterium oxide" or "deuterated water" or ((deuterium or heavy) w3 water) or D2O) AND CPC:("A61K9/00" or "A61K9/08" or "A61K31/00" or "A61K47/02" or "A61K47/30" or "A61K9/0048")	104	27-Jul-16
L19	CPC:("A61K9/00" or "A61K9/08" or "A61K31/00" or "A61K47/02" or "A61K47/30" or "A61K9/0048")	130534	27-Jul-16
L18	TAC:("deuterium oxide" or "deuterated water" or ((deuterium or heavy) w3 water) or D2O) AND TACD:(ophthalmic or ocular) AND IC:("A61F9/00" or "A61K9/00" or "A61K9/08" or "A61K31/00" or "A61K47/02" or "A61K47/30" or "A61P27/02")	45	27-Jul-16
L17	TAC:("deuterium oxide" or "deuterated water" or ((deuterium or heavy) w3 water) or D2O) AND IC:("A61F9/00" or "A61K9/00" or "A61K9/08" or "A61K31/00" or "A61K47/02" or "A61K47/30" or "A61P27/02")	259	27-Jul-16
L16	IC:("A61F9/00" or "A61K9/00" or "A61K9/08" or "A61K31/00" or "A61K47/02" or "A61K47/30" or "A61P27/02")	646026	27-Jul-16
L15	TAC:((("deuterium oxide" or "deuterated water") and ((ophthalmic or ocular) w3 (preparation or composition or formulation))) and TACD: (Vidarabine or bromfenac or nepafenaz or ketorolac or cyclosporine or flurbiprofen or suprofen or diclofenac or alcaftadine or azelastine or bepotastine or cromolyn or emedastine or epinastine or ketotifen or levocabastine or lodoxamide or nedocromil or naphazoline or olopatadine or oxymetazoline or pemirolast)	1	27-Jul-16
L14	TAC:((("deuterium oxide" or "deuterated water") and ((ophthalmic or ocular) w3 (preparation or composition or formulation))) and TACD: (Erythromycin or ganciclovir or gatifloxacin or gentamicin or idoxuridine or levofloxacin or moxifloxacin or natamycin or norfloxacin or ofloxacin or "bacitracin/polymyxin b" or tobramycin or "Polymyxin b/trimethoprim" or "povidone iodine" or trifluridine or "Gramicidin/neomycin" or "sulfacetamide sodium" or sulfisoxazole or "bacitracin/neomycin" or "oxytetracycline/polymyxin b" or "phenylephrine/sulfacetamide")	2	27-Jul-16
L13	TAC:((("deuterium oxide" or "deuterated water") and ((ophthalmic or ocular) w3 (preparation or composition or formulation))) and TACD: (Aflibercept or ranibizumab or pegaptanib or cyclopentolate or phenylephrine or homatropine or scopolamine or "cyclopentolate/phenylephrine" or "hydroxyamphetamine/tropicamide" or cysteamine or ociprasmin or mitomycin or dapiprazole or lidocaine or proparacaine or tetracaine or benoxinate or azithromycin or bacitracin or besifloxacin or "boric acid" or chloramphenicol or ciprofloxacin)	5	27-Jul-16
L12	TAC:((("deuterium oxide" or "deuterated water") and ((ophthalmic or ocular) w3 (preparation or composition or formulation))) and TACD: (((osmolarity or tonicity) w3 (agent or compound)) or preservative or (Buffer or buffering))	6	27-Jul-16
L11	TACD: ("deuterium oxide" or "deuterated water") and ((ophthalmic or ocular)	307	27-Jul-

	w3 (preparation or composition or formulation)) and (((osmolarity or tonicity) w3 (agent or compound)) or preservative or (Buffer or buffering))		16
L10	TACD: ("deuterium oxide" or "deuterated water" or "heavy water" or D2O or (deuterium w5 water)) and ((ophthalmic or ocular) w3 (preparation or composition or formulation)) and (((osmolarity or tonicity) w3 (agent or compound)) or preservative or (Buffer or buffering))	3507	27-Jul-16
L9	TACD: ("deuterium oxide" or "deuterated water" or "heavy water" or D2O or (deuterium w5 water)) and ((ophthalmic or ocular) w3 (preparation or composition or formulation)) and (osmolarity w3 (agent or compound))	5	27-Jul-16
L8	TA: ("deuterium oxide" or "deuterated water" or "heavy water" or D2O or deuterium) and TACD: ((ophthalmic or ocular) w3 (preparation or composition or formulation))	64	26-Jul-16
L7	TACD: ((ophthalmic or ocular) w3 (preparation or composition or formulation)) and ("deuterium oxide" or "deuterated water" or "heavy water" or D2O)	3536	26-Jul-16
L6	TAC: ((ophthalmic or ocular) w3 (preparation or composition or formulation)) and ("deuterium oxide" or "deuterated water" or "heavy water" or D2O)	9	26-Jul-16
L5	TA: ((ophthalmic or ocular) w3 (preparation or composition or formulation)) and ("deuterium oxide" or "deuterated water" or "heavy water" or D2O)	3	26-Jul-16
L4	TAC:((ophthalmic or ocular) w3 (composition or formulation or preparation)) AND INV:((Gregory w3 Ostrow) or (Kenneth W3 Widder) or (David w3 Baker))	50	26-Jul-16
L3	TAC:("deuterium oxide" or "deuterated water" or D2O) AND INV:((Gregory w3 Ostrow) or (Kenneth W3 Widder) or (David w3 Baker))	3	26-Jul-16
L2	INV:((Gregory w3 Ostrow) or (Kenneth W3 Widder) or (David w3 Baker))	2147	26-Jul-16
L1	ASN:(Sydnexis)	3	26-Jul-16

Non-Patent Literature (NPL) Search Strategy/Results:

Google Scholar; 26 July 2016 (26.07.2016)

ophthalmic composition "deuterium oxide"
ophthalmic composition deuterated water osmolarity pD adjusting agent
D2O ophthalmic formulations
deuterium oxide in ocular preparations pD values

PubMed; 26 July 2016 (26.07.2016)

(ophthalmic composition) AND ((deuterium oxide) or (deuterated water))
((deuterium oxide) or D2O or (deuterated water))) AND (ocular or ophthalmic)
((((Ostrow, Gregory[Author]) OR Widder KJ[Author]) OR Baker, David[Author])) AND
((deuterium oxide) or (deuterated water) or (heavy water))
((((Ostrow, Gregory[Author]) OR Widder KJ[Author]) OR Baker, David[Author])) AND
(ocular or ophthalmic)

EBESCO; 27 July 2016 (27.07.2016)

Search ID#	Search Terms	Results
S6	((ophthalmic or ocular) N5 (composition or formulation or preparation)) AND ((deuterium oxide) or (deuterated water)) NOT muscarinic antagonists NOT singlet oxygen	204
S5	((ophthalmic or ocular) N5 (composition or formulation or preparation)) AND ((deuterium oxide) or (deuterated water) or (heavy water) or D2O) NOT muscarinic antagonists NOT singlet oxygen	2,058
S4	((ophthalmic or ocular) N5 (composition or formulation or preparation)) AND ((deuterium oxide) or (deuterated water) or (heavy water) or D2O) NOT muscarinic antagonists	2,321
S3	((ophthalmic or ocular) N5 (composition or formulation or preparation)) AND ((deuterium oxide) or (deuterated water) or (heavy water) or D2O) NOT muscarinic antagonists	2,321
S2	((ophthalmic or ocular) N5 (composition or formulation or preparation)) AND ((deuterium oxide) or (deuterated water) or (heavy water) or D2O)	3,046
S1	(ophthalmic or ocular) N5 (composition or formulation or preparation)	34,543

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	15208537
				Filing Date	07-12-2016
				First Named Inventor	OSTROW; Gregory I.
				Art Unit	1621
				Examiner Name	Zohreh A Fay
				Attorney Docket Number	46682-701.301
Sheet	1	of	2		

U. S. PATENT DOCUMENTS					
Examiner Initials*	Cite No.	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			
	001	US-8980839	03-17-2015	MITRA; Ashim K. et al.	

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No.	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T ⁶
		Country Code ³ -Number ⁴ -Kind Code ⁵ (if known)				
		None				

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
	001	Guidance for Industry: Q1A (R2) Stability Testing of New Drug Substances and Products. U.S. Department of Health and Human Services, Food and Drug Administration. Retrieved from the internet http://fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073369.pdf (25 pgs.) (November 2013/retrieved 7/27/2016).	☐
	002	PCT/US2016/34823 International Search Report and Written Opinion dated August 23, 2016.	☐

Examiner Signature		Date Considered	

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.97 and 1.98. 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 2 hours 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, 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 (1-800-786-9199) and select option 2.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Complete if Known

Application Number	15208537
Filing Date	07-12-2016
First Named Inventor	OSTROW; Gregory I.
Art Unit	1621
Examiner Name	Zohreh A Fay
Attorney Docket Number	46682-701.301

Sheet 2 of 2

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.
- ☐ 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	/Xiaofan Yang/	Date (YYYY-MM-DD)	2016-10-18
Name/Print	Xiaofan Yang	Registration Number	61459

This collection of information is required by 37 CFR 1.97 and 1.98. 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 1 hour 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.**

Electronic Acknowledgement Receipt

EFS ID:	27264907
Application Number:	15208537
International Application Number:	
Confirmation Number:	1009
Title of Invention:	OPHTHALMIC COMPOSITION
First Named Inventor/Applicant Name:	Gregory I. OSTROW
Customer Number:	21971
Filer:	Michael J. Hostetler/FY/Jennifer Vail
Filer Authorized By:	Michael J. Hostetler
Attorney Docket Number:	46682-701.301
Receipt Date:	19-OCT-2016
Filing Date:	12-JUL-2016
Time Stamp:	16:57:34
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		46682-701-301_IDS.pdf	238646	yes	6
			2974544c8dbd1226e51838c597fb00cbe3a9391b		

	Multipart Description/PDF files in .zip description								
	Document Description		Start	End					
	Transmittal Letter		1	4					
	Information Disclosure Statement (IDS) Form (SB08)		5	6					
Warnings:									
Information:									
2	Non Patent Literature	USDEPHEALTH_GUIDANCEFOR RINDUSTRY_Q1A_NOV2003. PDF	1631224	no	25				
			b16d1eea163e9d326b8e2a67e1bdaca605 09fa83						
Warnings:									
Information:									
3	Non Patent Literature	PCTUS201634823_ISRWO_23A UG2016.PDF	1023006	no	13				
			6854febbcd2c94ed687f3ec223bc761a6332 c2e5						
Warnings:									
Information:									
Total Files Size (in bytes):			2892876						
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.									

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	OSTROW; Gregory I. et al.
Serial Number:	15/208,537
Filing or 371 (c) Date:	2016-07-12
Title:	OPHTHALMIC COMPOSITION

Group Art Unit:	1621
Examiner:	Zohreh A Fay
CONFIRMATION NO:	1009

FILED ELECTRONICALLY ON: October 19, 2016

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

INFORMATION DISCLOSURE STATEMENT
UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

- A. ☐ 37 CFR § 1.97 (b). This Information Disclosure Statement should be considered by the Office because:
- ☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);
-- OR --
 - ☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;
-- OR --
 - ☐ (3) It is being filed before the mailing of a first Office action on the merits;
-- OR --
 - ☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.
- B. ☒ 37 CFR § 1.97(c). Although this Information Disclosure Statement is being filed after the period specified in 37 CFR § 1.97(b), above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:
- ☒ a statement as specified in § 1.97 (e) provided concurrently herewith;
-- OR --
 - ☐ a fee of \$180.00 as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.
- C. ☐ 37 CFR § 1.97 (d). Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:
- i. a statement as specified in § 1.97 (e);
-- AND --
 - ii. a fee of \$180.00 as set forth in § 1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.
- D. ☒ 37 CFR § 1.97 (e). Statement.
- ☒ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);
-- AND/OR --
 - ☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);
-- AND/OR --
 - ☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

- E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.
- F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:
- ☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.
- OR --
- ☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 is NOT enclosed.
- AND/OR --
- ☒ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).
- AND/OR --
- ☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).
- G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.
- ☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.
- ☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.
- OR --
- ☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____
- ☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.
- H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:
- ☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.
- Application in which the information was submitted: _____
- Information Disclosure Statement(s) filed on: _____
- AND
- ☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

- I. ☒ *Fee Authorization.* The Commissioner is hereby authorized to charge the above-referenced fees of \$0.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No. 46682-701.301).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: October 18, 2016

By: /Xiaofan Yang/

Xiaofan Yang, Reg. No. 61459

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 21971

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application:

Inventor: Gregory I. Ostrow et al.

Application No.: 15/208,537

Filed: July 12, 2016

Title: **OPHTHALMIC COMPOSITION**

Group Art Unit: 1621

Examiner: Z. A. Fay

Confirmation No.: 1009

M/S Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO OFFICE ACTION DATED SEPTEMBER 30, 2016

Commissioner:

This paper responds to the Office Action dated September 30, 2016, setting forth an initial due date of December 30, 2016. Accordingly, this response is timely submitted.

Listing of the Claims begins on page 2 of this paper.

Remarks begin on page 5 of this paper.

LISTING OF THE CLAIMS

The following listing of claims replaces all prior listings of claims in this application.

CLAIM LISTING:

1-30. (Cancelled).

31. (Previously Presented) An ophthalmic composition, consisting essentially of from about 0.001 wt% to about 0.03 wt% of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9, wherein the muscarinic antagonist is atropine, or atropine sulfate.
32. (Previously Presented) The ophthalmic composition of claim 31, 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.
33. (Previously Presented) The ophthalmic composition of claim 31, wherein the muscarinic antagonist is present in the composition at a concentration of one of: 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%.
34. (Previously Presented) The ophthalmic composition of claim 31, wherein the ophthalmic composition further comprises an osmolarity adjusting agent.
35. (Previously Presented) The ophthalmic composition of claim 34, wherein the osmolarity adjusting agent is sodium chloride.

36. (Previously Presented) The ophthalmic composition of claim 31, wherein the ophthalmic composition further comprises a preservative.
37. (Previously Presented) The ophthalmic composition of claim 36, wherein the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof.
38. (Previously Presented) The ophthalmic composition of claim 31, wherein the ophthalmic composition further comprises a buffer agent.
39. (Previously Presented) The ophthalmic composition of claim 38, wherein 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.
40. (Previously Presented) The ophthalmic composition of claim 31, wherein the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof.
41. (Previously Presented) The ophthalmic composition of claim 31, wherein the ophthalmic composition further comprises a pD adjusting agent.
42. (Previously Presented) The ophthalmic composition of claim 41, wherein the pD adjusting agent comprises deuterated hydrochloric acid, deuterated sodium hydroxide, deuterated acetic acid, or deuterated citric acid.
43. (Previously Presented) The ophthalmic composition of claim 31, 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.

44. (Previously Presented) The ophthalmic composition of claim 31, wherein the ophthalmic composition is not formulated as an injectable formulation.
45. (Previously Presented) An ophthalmic solution, consisting essentially of from about 0.001 wt% to about 0.03 wt% of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9, wherein the muscarinic antagonist is atropine, or atropine sulfate.
46. (Previously Presented) The ophthalmic solution of claim 45, wherein 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.
47. (Previously Presented) The ophthalmic solution of claim 45, wherein 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.
48. (Previously Presented) A method of arresting myopia progression, comprising administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition consisting essentially of from about 0.001 wt% to about 0.03 wt% of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9, wherein the muscarinic antagonist is atropine, or atropine sulfate.
49. (Previously Presented) The method of claim 48, wherein the ophthalmic composition is stored at between about 2 °C to about 10 °C prior to first use.
50. (Previously Presented) The method of claim 48, wherein the ophthalmic composition is stored at between about 16 °C to about 26 °C after first use.

REMARKS

This response is filed in response to the Office Action dated September 30, 2016. In the Office Action, all pending claims are rejected under obviousness-type double patenting over U.S. Patent No. 9,421,199. For the sole purpose of expediting prosecution of the present application, Applicant hereby submit a Terminal Disclaimer to obviate the double patenting rejection raised in the Office Action. Accordingly, allowance of the pending claims are respectfully requested. Should the Examiner have any questions, Applicant encourages the Examiner to contact the undersigned attorney at 858-350-2339.

FEE AUTHORIZATION

The Commissioner is authorized to charge any additional fees which may be required, including petition fees and extension of time fees, to Deposit Account No. **23-2415**, referencing Attorney Docket No. 46682-701.301.

Respectfully submitted,

Date: October 18, 2016

By: /Xiaofan Yang/
Xiaofan Yang
Registration No. 61,459

WILSON SONSINI GOODRICH & ROSATI
650 Page Mill Road
Palo Alto, CA 94304-1050
Direct Dial: (858) 350-2339
Customer No. 21971

**TERMINAL DISCLAIMER TO OBIATE A DOUBLE PATENTING
REJECTION OVER A "PRIOR" PATENT**

Docket Number (Optional)

46682-701.301

In re Application of: Gregory I. OSTROW et al.

Application No.: 15/208,537

Filed: July 12, 2016

For: OPTHALMIC COMPOSITION

The applicant, Sydnexis, Inc., owner of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of **prior patent** No. 9,421,199 as the term of said **prior patent** is presently shortened by any terminal disclaimer. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the applicant does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the **prior patent**, "as the term of said **prior patent** is presently shortened by any terminal disclaimer," in the event that said **prior patent** later:

expires for failure to pay a maintenance fee;

is held unenforceable;

is found invalid by a court of competent jurisdiction;

is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;

has all claims canceled by a reexamination certificate;

is reissued; or

is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☐ The undersigned is the applicant. If the applicant is an assignee, the undersigned is authorized to act on behalf of the assignee.

I hereby acknowledge that any willful false statements made are punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

2. ☒ The undersigned is an attorney or agent of record. Reg. No. 61,459

/Xiaofan Yang/

Signature

October 18, 2016

Date

Xiaofan Yang

Typed or printed name

Attorney for the Applicant

Title

858-350-2339

Telephone Number

- ☒ Terminal disclaimer fee under 37 CFR 1.20(d) included.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

This collection of information is required by 37 CFR 1.321. 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 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.

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.

Electronic Patent Application Fee Transmittal

Application Number:	15208537			
Filing Date:	12-Jul-2016			
Title of Invention:	OPHTHALMIC COMPOSITION			
First Named Inventor/Applicant Name:	Gregory I. OSTROW			
Filer:	Xiaofan Yang/Angie Hirano			
Attorney Docket Number:	46682-701.301			
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:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Miscellaneous:				
STATUTORY OR TERMINAL DISCLAIMER	2814	1	160	160
Total in USD (\$)				160

Electronic Acknowledgement Receipt

EFS ID:	27252699
Application Number:	15208537
International Application Number:	
Confirmation Number:	1009
Title of Invention:	OPHTHALMIC COMPOSITION
First Named Inventor/Applicant Name:	Gregory I. OSTROW
Customer Number:	21971
Filer:	Xiaofan Yang/Angie Hirano
Filer Authorized By:	Xiaofan Yang
Attorney Docket Number:	46682-701.301
Receipt Date:	18-OCT-2016
Filing Date:	12-JUL-2016
Time Stamp:	17:35:52
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	\$ 160
RAM confirmation Number	101916INTEFSW00004624232415
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		46682-701-301_Resp_to_NFOA.pdf	112185	yes	5
			c81025415f432fd782e247482afd725e2992adb9		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Amendment/Req. Reconsideration-After Non-Final Reject		1	1	
	Claims		2	4	
	Applicant Arguments/Remarks Made in an Amendment		5	5	
Warnings:					
Information:					
2	Terminal Disclaimer Filed	46682-701-301_TerminalDisclaimer.pdf	160855	no	2
			a2e75f5fe6bad407bd6aa96696b07aa79e8fd9d		
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30429	no	2
			49cc7863ba11d3af4c11db83dd8282dd29b2216d		
Warnings:					
Information:					
Total Files Size (in bytes):			303469		

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.



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/208,537	07/12/2016	Gregory I. OSTROW	46682-701.301	1009

21971 7590 09/30/2016
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER

FAY, ZOHREH A

ART UNIT	PAPER NUMBER

1621

NOTIFICATION DATE	DELIVERY MODE

09/30/2016

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):

patentdocket@wsgr.com

Office Action Summary	Application No. 15/208,537	Applicant(s) OSTROW ET AL.	
	Examiner ZOHREH FAY	Art Unit 1621	AIA (First Inventor to File) Status Yes

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on _____.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ 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.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

- 5) ☒ Claim(s) 31-50 is/are pending in the application.
5a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 6) ☐ Claim(s) _____ is/are allowed.
- 7) ☒ Claim(s) 31-50 is/are rejected.
- 8) ☐ Claim(s) _____ is/are objected to.
- 9) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, 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.

Application Papers

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

- 12) ☐ 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)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)
Paper No(s)/Mail Date 8/11/2016.
- 3) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 4) ☐ Other: _____.

DETAILED ACTION

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file

provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 31-50 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 9,421,199. Although the claims at issue are not identical, they are not patentably distinct from each other because they overlap. The claims of the instant application are drawn to a composition and method of arresting myopia progression using an ophthalmic composition consisting essentially of from about 0.001 wt% to about 0.03% of a muscarinic antagonist, such as atropine and atropine sulfate and deuterated water. The claims of the U.S. patent are drawn to the same composition and amounts as the claims of the instant application with the exception of using the term “comprising”. The claims of the instant application are within the scope of the claims of the U.S. patent.

Art Unit: 1621

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZOHREH FAY whose telephone number is (571)272-0573. The examiner can normally be reached on Monday to Friday 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Winston Shen can be reached on (571) 272-3157. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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ZF
/ZOHREH FAY/
Primary Examiner, Art Unit 1621

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	15208537
				Filing Date	07-12-2016
				First Named Inventor	OSTROW; Gregory I.
				Art Unit	1629
				Examiner Name	Not yet assigned
				Attorney Docket Number	46682-701.301
Sheet	1	of	7		

U. S. PATENT DOCUMENTS					
Examiner Initials*	Cite No.	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			
	001	US-3863633	02-04-1975	RYDE; Emma Marta et al.	
	002	US-4014335	03-29-1977	ARNOLD; Randall K.	
	003	US-4474751	10-02-1984	HASLAM; John L. et al.	
	004	US-5259998	11-09-1993	REICH; Cary et al.	
	005	US-5716952	02-10-1998	WOLDEMUSSIE; Elizabeth et al.	
	006	US-5858375	01-12-1999	FURMINGER; Ian George Stephen et al.	
	007	US-5900360	05-04-1999	WELCH; William J. et al.	
	008	US-6218428	04-17-2001	CHYNN; Emil	
	009	US-6270954	08-07-2001	WELCH; William J. et al.	
	010	US-6410048	06-25-2002	FOTINOS; Spiros	
	011	US-6720001	04-13-2004	CHEN; Feng-Jing et al.	
	012	US-7691099	04-06-2010	BERRY; Michael J.	
	013	US-7858582	12-28-2010	JIN; Lei et al.	
	014	US-8333985	12-18-2012	KNAACK; David et al.	
	015	US-20030157187	08-21-2003	HUNTER; William L.	
	016	US-20050249770	11-10-2005	HUNTER; William L.	
	017	US-20060159771	07-20-2006	KADRMAS; Eddie F. et al.	
	018	US-20070207192	09-06-2007	HOLL; Richard et al.	

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Examiner Signature	/Zohreh Fay/	Date Considered	09/16/2016

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		Number-Kind Code ² (if known)			
	019	US-20070280992	12-06-2007	MARGARON; Philippe M.C. et al.	
	020	US-20080113035	05-15-2008	HUNTER; William L.	
	021	US-20080153900	06-26-2008	HUNTER; William L.	
	022	US-20100022495	01-28-2010	HOTAMISLIGIL; Gokhan S. et al.	
	023	US-20100196285	08-05-2010	BAYERL; Thomas	
	024	US-20120015035	01-19-2012	WILDSOET; Christine F. et al.	
	025	US-20120135084	05-31-2012	BAYERL; Thomas	
	026	US-20120203161	08-09-2012	HEREKAR; Satish V.	
	027	US-20130302855	11-14-2013	SELBER; Klaus et al.	
	028	US-20140011761	01-09-2014	HOTAMISLIGIL; Gokhan S. et al.	
	029	US-20140088199	03-27-2014	SHARMA; Anant	
	030	US-20140350049	11-27-2014	HOVNANIAN; Alain et al.	
	031	US-20150290125	10-15-2015	HORN; Gerald et al.	
	032	US-20150366854	12-24-2015	OSTROW; Gregory I. et al.	
	033	US-20160009705	01-14-2016	OSTROW; Gregory I. et al.	

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		Country Code ³ -Number ⁴ -Kind Code ⁵ (if known)				
	001	CN-101327216-A	12-24-2008	ZHENGLIAN XIAO [CN]	Abstract:	☒
	002	CN-1456161-A	11-19-2003	LIU JIDONG [CN]	Abstract:	☒
	003	EP-0332826-A1	09-20-1989	TEVA PHARMA [IL]		☐
	004	WO-0049990-A2	08-31-2000	KHAMAR BAKULESH MAFATLAL [IN]		☐
	005	WO-02096418-A1	12-05-2002	VALLEY FORGE PHARMACEUTICALS [US], et al.		☐
	006	WO-2008005053-A1	01-10-2008	CYDEX INC [US], et al.		☐
	007	WO-2011098578-A2	08-18-2011	BIONEER AS [DK], et al.		☐
	008	WO-2012161655-A1	11-29-2012	SINGAPORE HEALTH SERVICES PTE LTD [SG], et al.		☐

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		Country Code ³ -Number ⁴ -Kind Code ⁵ (if known)				
	009	WO-2014140105-A1	09-18-2014	D2 BIOSCIENCE GROUP LTD., et al.		☐
	010	WO-9421298-A1	09-29-1994	PASTEUR INSTITUT [FR], et al.	Abstract:	☒
	011	WO-9624331-A1	08-15-1996	USTAV MAKROMOLEKUL ARNI CHEMIE [CZ], et al.		☐
	012	WO-9716192-A1	05-09-1997	MERCK & CO INC [US], et al.		☐

NON-PATENT LITERATURE DOCUMENTS			
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	001	ABRAHAM et al. Draize rabbit eye test compatibility with eye irritation thresholds in humans: a quantitative structure-activity relationship analysis. Toxicol Sci 76:384-391 (2003).	☐
	002	BADARO et al. Retinal biocompatibility of brilliant Blue G with deuterated water for chromovitrectomy. J. Ophthalmic and Vision Research 9(2): 204-209 (2014).	☐

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	003	CHENG et al. Water movement in the rabbit eye. Exp. Eye Res. 52:337-339 (1991).	☐
	004	CHENG. Fate of water in the soft contact lens immediately after lens placement onto the cornea. Optometry and Vision Science 68(6):414-417 (1991).	☐
	005	CHIRIERI et al. Investigations concerning the changes induced by deuterium for hydrogen substitution in bioelectric activity of the frog retina. Physiologie 14(2):119-123 (1977).	☐
	006	CRIADO et al. Scavenging of photogenerated oxidative species by antimuscarinic drugs: atropine and derivatives. Redoc Rep 7(6):385-394 (2002).	☐
	007	GANEVA. Heavy water effect on certain energetic processes in retina. Physiologie 6(1):59-62 (1979).	☐
	008	GETTINGS et al. A comparison of low volume, Draize and in vitro eye irritation test data. III. Surfactant-based formulations. Food Chem Toxicol 36(3):209-231 (1998).	☐
	009	GLASOE et al. Use of glass electrodes to measure acidities in deuterium oxide. Journal of Physical Chemistry.64:188-190 (1960).	☐
	010	JANUSCHOWSKI et al. Evaluating retinal toxicity of a new heavy intraocular dye, using a model of perfused and isolated retinal cultures of bovine and human origins. Graefes Arch Clin Exp Ophthalmol. 250:1013-1022 (2012).	☐

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	011	JEONG et al. Biodegradable block copolymers as injectable drug-delivery systems. Nature 388(6645):860-862 (1997).	☐
	012	JEONG et al. Drug release from biodegradable injectable thermosensitive hydrogel of PEG-PLGA-PEG triblock copolymers. J Control Release 63(1-2):155-163 (2000).	☐
	013	JEONG et al. Thermosensitive sol-gel reversible hydrogels. Advanced Drug Delivery Reviews 54:37-51 (2002).	☐
	014	KREZEL et al. A formula for correlating pKa values determined in D2O and H2O. Journal of Inorganic Chemistry 98:161-166 (2008).	☐
	015	LAI et al. Rapid transport of large polymeric nanoparticles in fresh undiluted human mucus. PNAS USA 104(5):1482-1487 (2007).	☐
	016	LUND et al. The Kinetics of atropine and apotatropine in aqueous solutions. ACTA Chemica Scandinavica 22:3085-3097 (1968).	☐
	017	MCCALL et al. Mechanisms of corneal tissue cross-linking in response to treatment with topical riboflavin and long-wavelength ultraviolet radiation (UVA). Investigative Ophthalmology & Visual Science 51(1):129-138 (2010).	☐
	018	OBATA et al. Deuterium magnetic resonance imaging of rabbit eye in Vivo. Magnetic Resonance in Medicine.33(4):569-572 (1995).	☐

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	019	OBATA et al. Deuterium MR in vivo imaging of the rat eye using 2H2O. Acta Radiologica,36:552-555 (1995).	☐
	020	PCT/US2015/037249 International Search Report and Written Opinion dated September 30, 2015.	☐
	021	RICHARD et al. Effects of sterilizing-grade filters on the physico-chemical properties of onion-like vesicles. Int J Pharm 312(1-2):144-150 (2006).	☐
	022	SIEGEL et al. Stability of procaine in deuterium oxide. J Pharm Sci 53:978-979 (1964).	☐
	023	TAKTAK et al. Assay of Pyrogens by Interleukin-6 Release from Monocytic Cell Lines. J. Pharm. Pharmacol. 43:578-582 (1991).	☐
	024	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/5882fn1.htm (August 2003).	☐
	025	VIEGAS et al. Osmotic behavior of poloxamer 407 and other non-ionic surfactants in aqueous solutions. Int J Pharm 160:157-162 (1998).	☐

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Search Notes 	Application/Control No. 15208537	Applicant(s)/Patent Under Reexamination OSTROW ET AL.
	Examiner ZOHREH FAY	Art Unit 1621

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
West	9/15/2016	ZF
inventor search	9/15/2016	ZF

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner



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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
15/208,537	07/12/2016	1629	800	46682-701.301	20	3

CONFIRMATION NO. 1009

UPDATED FILING RECEIPT

21971
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050



Date Mailed: 08/16/2016

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)

Gregory I. OSTROW, San Diego, CA;
Kenneth J. WIDDER, Rancho Santa Fe, CA;
David S. BAKER, Carlsbad, CA;

Applicant(s)

Sydnexis, Inc., San Diego, CA;

Power of Attorney: The patent practitioners associated with Customer Number 21971

Domestic Priority data as claimed by applicant

This application is a CON of 14/726,139 05/29/2015 PAT 9421199
which claims benefit of 62/151,926 04/23/2015
and claims benefit of 62/096,433 12/23/2014
and claims benefit of 62/016,502 06/24/2014

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: 07/26/2016

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/208,537**

Projected Publication Date: 11/24/2016

Non-Publication Request: No

Early Publication Request: No

**** SMALL ENTITY ****

Title

OPHTHALMIC COMPOSITION

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.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

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>.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, <http://www.stopfakes.gov>. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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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 15/208,537		
APPLICATION AS FILED - PART I								
(Column 1)		(Column 2)		SMALL ENTITY		OTHER THAN SMALL ENTITY		
FOR	NUMBER FILED	NUMBER EXTRA	RATE(\$)	FEE(\$)		RATE(\$)	FEE(\$)	
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	70		N/A		
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A	300		N/A		
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	360		N/A		
TOTAL CLAIMS (37 CFR 1.16(j))	20	minus 20 = *	x 40 =	0.00	OR			
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3	minus 3 = *	x 210 =	0.00				
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).			0.00				
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0.00				
			TOTAL	730		TOTAL		
* If the difference in column 1 is less than zero, enter "0" in column 2.								
APPLICATION AS AMENDED - PART II								
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY		
AMENDMENT A	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)	ADDITIONAL FEE(\$)
	Total (37 CFR 1.16(i))	*	Minus **	=	x =	OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus ***	=	x =	OR	x =	
	Application Size Fee (37 CFR 1.16(s))					OR		
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					OR		
				TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY		
AMENDMENT B	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)	ADDITIONAL FEE(\$)
	Total (37 CFR 1.16(i))	*	Minus **	=	x =	OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus ***	=	x =	OR	x =	
	Application Size Fee (37 CFR 1.16(s))					OR		
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					OR		
				TOTAL ADD'L FEE		OR	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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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/208,537	07/12/2016	Gregory I. OSTROW	46682-701.301

21971
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

CONFIRMATION NO. 1009
POA ACCEPTANCE LETTER



Date Mailed: 08/16/2016

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 08/04/2016.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at (571) 272-4000 or (571) 272-4200 or 1-888-786-0101.

/nbekele/

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	15208537
				Filing Date	07-12-2016
				First Named Inventor	OSTROW; Gregory I.
				Art Unit	1629
				Examiner Name	Not yet assigned
				Attorney Docket Number	46682-701.301
Sheet	1	of	7		

U. S. PATENT DOCUMENTS					
Examiner Initials*	Cite No.	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			
	001	US-3863633	02-04-1975	RYDE; Emma Marta et al.	
	002	US-4014335	03-29-1977	ARNOLD; Randall K.	
	003	US-4474751	10-02-1984	HASLAM; John L. et al.	
	004	US-5259998	11-09-1993	REICH; Cary et al.	
	005	US-5716952	02-10-1998	WOLDEMUSSIE; Elizabeth et al.	
	006	US-5858375	01-12-1999	FURMINGER; Ian George Stephen et al.	
	007	US-5900360	05-04-1999	WELCH; William J. et al.	
	008	US-6218428	04-17-2001	CHYNN; Emil	
	009	US-6270954	08-07-2001	WELCH; William J. et al.	
	010	US-6410048	06-25-2002	FOTINOS; Spiros	
	011	US-6720001	04-13-2004	CHEN; Feng-Jing et al.	
	012	US-7691099	04-06-2010	BERRY; Michael J.	
	013	US-7858582	12-28-2010	JIN; Lei et al.	
	014	US-8333985	12-18-2012	KNAACK; David et al.	
	015	US-20030157187	08-21-2003	HUNTER; William L.	
	016	US-20050249770	11-10-2005	HUNTER; William L.	
	017	US-20060159771	07-20-2006	KADRMAS; Eddie F. et al.	
	018	US-20070207192	09-06-2007	HOLL; Richard et al.	

Examiner Signature		Date Considered	

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Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	15208537
				Filing Date	07-12-2016
				First Named Inventor	OSTROW; Gregory I.
				Art Unit	1629
				Examiner Name	Not yet assigned
				Attorney Docket Number	46682-701.301
Sheet	2	of	7		

U. S. PATENT DOCUMENTS					
Examiner Initials*	Cite No.	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			
	019	US-20070280992	12-06-2007	MARGARON; Philippe M.C. et al.	
	020	US-20080113035	05-15-2008	HUNTER; William L.	
	021	US-20080153900	06-26-2008	HUNTER; William L.	
	022	US-20100022495	01-28-2010	HOTAMISLIGIL; Gokhan S. et al.	
	023	US-20100196285	08-05-2010	BAYERL; Thomas	
	024	US-20120015035	01-19-2012	WILDSOET; Christine F. et al.	
	025	US-20120135084	05-31-2012	BAYERL; Thomas	
	026	US-20120203161	08-09-2012	HEREKAR; Satish V.	
	027	US-20130302855	11-14-2013	SELBER; Klaus et al.	
	028	US-20140011761	01-09-2014	HOTAMISLIGIL; Gokhan S. et al.	
	029	US-20140088199	03-27-2014	SHARMA; Anant	
	030	US-20140350049	11-27-2014	HOVNANIAN; Alain et al.	
	031	US-20150290125	10-15-2015	HORN; Gerald et al.	
	032	US-20150366854	12-24-2015	OSTROW; Gregory I. et al.	
	033	US-20160009705	01-14-2016	OSTROW; Gregory I. et al.	

Examiner Signature		Date Considered	

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				First Named Inventor	OSTROW; Gregory I.
				Art Unit	1629
				Examiner Name	Not yet assigned
				Attorney Docket Number	46682-701.301
Sheet	3	of	7		

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T ⁶
		Country Code ³ -Number ⁴ -Kind Code ⁵ (if known)				
	001	CN-101327216-A	12-24-2008	ZHENGLIAN XIAO [CN]	Abstract:	☒
	002	CN-1456161-A	11-19-2003	LIU JIDONG [CN]	Abstract:	☒
	003	EP-0332826-A1	09-20-1989	TEVA PHARMA [IL]		☐
	004	WO-0049990-A2	08-31-2000	KHAMAR BAKULESH MAFATLAL [IN]		☐
	005	WO-02096418-A1	12-05-2002	VALLEY FORGE PHARMACEUTICALS [US], et al.		☐
	006	WO-2008005053-A1	01-10-2008	CYDEX INC [US], et al.		☐
	007	WO-2011098578-A2	08-18-2011	BIONEER AS [DK], et al.		☐
	008	WO-2012161655-A1	11-29-2012	SINGAPORE HEALTH SERVICES PTE LTD [SG], et al.		☐

Examiner Signature		Date Considered	

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Sheet	4	of	7		

FOREIGN PATENT DOCUMENTS						
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		Country Code ³ -Number ⁴ -Kind Code ⁵ (if known)				
	009	WO-2014140105-A1	09-18-2014	D2 BIOSCIENCE GROUP LTD., et al.		☐
	010	WO-9421298-A1	09-29-1994	PASTEUR INSTITUT [FR], et al.	Abstract:	☒
	011	WO-9624331-A1	08-15-1996	USTAV MAKROMOLEKUL ARNI CHEMIE [CZ], et al.		☐
	012	WO-9716192-A1	05-09-1997	MERCK & CO INC [US], et al.		☐

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
	001	ABRAHAM et al. Draize rabbit eye test compatibility with eye irritation thresholds in humans: a quantitative structure-activity relationship analysis. Toxicol Sci 76:384-391 (2003).	☐
	002	BADARO et al. Retinal biocompatibility of brilliant Blue G with deuterated water for chromovitrectomy. J. Ophthalmic and Vision Research 9(2): 204-209 (2014).	☐

Examiner Signature		Date Considered	

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				Art Unit	1629
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				Attorney Docket Number	46682-701.301
Sheet	5	of	7		

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
	003	CHENG et al. Water movement in the rabbit eye. Exp. Eye Res. 52:337-339 (1991).	☐
	004	CHENG. Fate of water in the soft contact lens immediately after lens placement onto the cornea. Optometry and Vision Science 68(6):414-417 (1991).	☐
	005	CHIRIERI et al. Investigations concerning the changes induced by deuterium for hydrogen substitution in bioelectric activity of the frog retina. Physiologie 14(2):119-123 (1977).	☐
	006	CRIADO et al. Scavenging of photogenerated oxidative species by antimuscarinic drugs: atropine and derivatives. Redoc Rep 7(6):385-394 (2002).	☐
	007	GANEA. Heavy water effect on certain energetic processes in retina. Physiologie 6(1):59-62 (1979).	☐
	008	GETTINGS et al. A comparison of low volume, Draize and in vitro eye irritation test data. III. Surfactant-based formulations. Food Chem Toxicol 36(3):209-231 (1998).	☐
	009	GLASOE et al. Use of glass electrodes to measure acidities in deuterium oxide. Journal of Physical Chemistry.64:188-190 (1960).	☐
	010	JANUSCHOWSKI et al. Evaluating retinal toxicity of a new heavy intraocular dye, using a model of perfused and isolated retinal cultures of bovine and human origins. Graefes Arch Clin Exp Ophthalmol. 250:1013-1022 (2012).	☐

Examiner Signature		Date Considered	

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.97 and 1.98. 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 2 hours 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, 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 (1-800-786-9199) and select option 2.

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	15208537
				Filing Date	07-12-2016
				First Named Inventor	OSTROW; Gregory I.
				Art Unit	1629
				Examiner Name	Not yet assigned
				Attorney Docket Number	46682-701.301
Sheet	6	of	7		

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No. ¹	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
	011	JEONG et al. Biodegradable block copolymers as injectable drug-delivery systems. Nature 388(6645):860-862 (1997).	☐
	012	JEONG et al. Drug release from biodegradable injectable thermosensitive hydrogel of PEG-PLGA-PEG triblock copolymers. J Control Release 63(1-2):155-163 (2000).	☐
	013	JEONG et al. Thermosensitive sol-gel reversible hydrogels. Advanced Drug Delivery Reviews 54:37-51 (2002).	☐
	014	KREZEL et al. A formula for correlating pKa values determined in D2O and H2O. Journal of Inorganic Chemistry 98:161-166 (2008).	☐
	015	LAI et al. Rapid transport of large polymeric nanoparticles in fresh undiluted human mucus. PNAS USA 104(5):1482-1487 (2007).	☐
	016	LUND et al. The Kinetics of atropine and apotatropine in aqueous solutions. ACTA Chemica Scandinavica 22:3085-3097 (1968).	☐
	017	MCCALL et al. Mechanisms of corneal tissue cross-linking in response to treatment with topical riboflavin and long-wavelength ultraviolet radiation (UVA). Investigative Ophthalmology & Visual Science 51(1):129-138 (2010).	☐
	018	OBATA et al. Deuterium magnetic resonance imaging of rabbit eye in Vivo. Magnetic Resonance in Medicine.33(4):569-572 (1995).	☐

Examiner Signature		Date Considered	

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.97 and 1.98. 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 2 hours 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, 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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Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	15208537
				Filing Date	07-12-2016
				First Named Inventor	OSTROW; Gregory I.
				Art Unit	1629
				Examiner Name	Not yet assigned
				Attorney Docket Number	46682-701.301
Sheet	7	of	7		

NON-PATENT LITERATURE DOCUMENTS				
Examiner Initials*	Cite No. ¹	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²	
	019	OBATA et al. Deuterium MR in vivo imaging of the rat eye using 2H2O. Acta Radiologica,36:552-555 (1995).	☐	
	020	PCT/US2015/037249 International Search Report and Written Opinion dated September 30, 2015.	☐	
	021	RICHARD et al. Effects of sterilizing-grade filters on the physico-chemical properties of onion-like vesicles. Int J Pharm 312(1-2):144-150 (2006).	☐	
	022	SIEGEL et al. Stability of procaine in deuterium oxide. J Pharm Sci 53:978-979 (1964).	☐	
	023	TAKTAK et al. Assay of Pyrogens by Interleukin-6 Release from Monocytic Cell Lines. J. Pharm. Pharmacol. 43:578-582 (1991).	☐	
	024	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/5882fn1.htm (August 2003).	☐	
	025	VIEGAS et al. Osmotic behavior of poloxamer 407 and other non-ionic surfactants in aqueous solutions. Int J Pharm 160:157-162 (1998).	☐	

Examiner Signature		Date Considered	

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If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

Electronic Acknowledgement Receipt

EFS ID:	26621865
Application Number:	15208537
International Application Number:	
Confirmation Number:	1009
Title of Invention:	OPHTHALMIC COMPOSITION
First Named Inventor/Applicant Name:	Gregory I. OSTROW
Customer Number:	21971
Filer:	Michael J. Hostetler/FY/Jennifer Vail
Filer Authorized By:	Michael J. Hostetler
Attorney Docket Number:	46682-701.301
Receipt Date:	11-AUG-2016
Filing Date:	12-JUL-2016
Time Stamp:	20:24:33
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		46682-701-301_IDS.pdf	302626	yes	11
			ec516c39fd8ef80be2322853a931d913e4a2af60		

	Multipart Description/PDF files in .zip description		
	Document Description	Start	End
	Transmittal Letter	1	4
	Information Disclosure Statement (IDS) Form (SB08)	5	11
Warnings:			
Information:			
Total Files Size (in bytes):		302626	
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	OSTROW; Gregory I. et al.	Group Art Unit:	1629
Serial Number:	15/208,537	Examiner:	Not yet assigned
Filing or 371 (c) Date:	2016-07-12	CONFIRMATION NO:	1009
Title:	OPHTHALMIC COMPOSITION		

FILED ELECTRONICALLY ON: August 11, 2016

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

INFORMATION DISCLOSURE STATEMENT
UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

- A. ☒ *37 CFR § 1.97 (b)*. This Information Disclosure Statement should be considered by the Office because:
- ☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);
 - OR --
 - ☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;
 - OR --
 - ☒ (3) It is being filed before the mailing of a first Office action on the merits;
 - OR --
 - ☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.
- B. ☐ *37 CFR § 1.97(c)*. Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b)*, above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution on the merits, this Information Disclosure Statement should be considered because it is accompanied by one of:
- ☐ a statement as specified in §1.97 (e) provided concurrently herewith;
 - OR --
 - ☐ a fee of \$180.00 as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.
- C. ☐ *37 CFR § 1.97 (d)*. Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113 or (2) a notice of allowance under § 1.311, it is being filed before payment of the issue fee and should be considered because it is accompanied by:
- i. a statement as specified in § 1.97 (e);
 - AND --
 - ii. a fee of \$180.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.
- D. ☐ *37 CFR §1.97 (e)*. Statement.
- ☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);
 - AND/OR --
 - ☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);
 - AND/OR --
 - ☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

- E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.
- F. ☐ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:
- ☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.
- OR --
- ☐ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 is NOT enclosed.
- AND/OR --
- ☐ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).
- AND/OR --
- ☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).
- G. ☒ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.
- ☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.
- ☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.
- OR --
- ☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____
- ☒ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.
- H. ☒ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:
- ☒ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.
- Application in which the information was submitted: 14/726,139
- Information Disclosure Statement(s) filed on: 1/7/2016; 3/7/2016 (892) and 3/29/2016
- AND
- ☒ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

- I. ☒ *Fee Authorization.* The Commissioner is hereby authorized to charge the above-referenced fees of \$0.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No. 46682-701.301).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: August 11, 2016

By: /Xiaofan Yang/
Xiaofan Yang, Reg. No. 61459

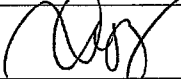
650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
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NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA/82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	15/208,537
Filing Date	July 12, 2016
First Named Inventor	Gregory I. OSTROW
Title	OPHTHALMIC COMPOSITION
Art Unit	1629
Examiner Name	Not Yet Assigned
Attorney Docket Number	46682-701.301

SIGNATURE of Applicant or Patent Practitioner

Signature		Date (Optional)	August 4, 2016
Name	Xiaofan Yang	Registration Number	61,459
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			
NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.			
☒ *Total of <u>1</u> forms are submitted.			

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 3 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: PA..

Document Description: Power of Attorney

PTO/AIA/82B(07-12)

Approved for use through 11/30/2014. OMB 0651-0035

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in the attached transmittal letter.

- ☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A or equivalent):

21971

OR

- ☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A or equivalent):

Name	Registration Number	Name	Registration Number

Please recognize or change the correspondence address for the application identified in the attached transmittal letter to:

- ☐ The address associated with the above-mentioned Customer Number.

OR

- ☐ The address associated with Customer Number:

OR

☐ Firm or
Individual Name

Address

City

State

Zip

Country

Telephone

Email

I am the Applicant:

- ☐ Inventor or Joint Inventor
- ☐ Legal Representative of a Deceased or Legally Incapacitated Inventor
- ☒ Assignee or Person to Whom the Inventor is Under an Obligation to Assign
- ☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document)

SIGNATURE of Applicant for Patent

Signature

Date

Name

Telephone

Title and Company

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms for more than one signature, see below *.

☒ *Total of 2 forms are submitted.

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If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Electronic Acknowledgement Receipt

EFS ID:	26551999
Application Number:	15208537
International Application Number:	
Confirmation Number:	1009
Title of Invention:	OPHTHALMIC COMPOSITION
First Named Inventor/Applicant Name:	Gregory I. OSTROW
Customer Number:	21971
Filer:	Xiaofan Yang/Angie Hirano
Filer Authorized By:	Xiaofan Yang
Attorney Docket Number:	46682-701.301
Receipt Date:	04-AUG-2016
Filing Date:	12-JUL-2016
Time Stamp:	16:38:32
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	Power of Attorney	46682-701-301_PoA.pdf	128018	no	2
			c15d731c8e8de99375c62b925cec14f2db813c35		

Warnings:

Information:	
Total Files Size (in bytes):	128018
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.	

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application:

Inventor: Gregory I. Ostrow et al.

Application No.: 15/208,537

Filed: July 12, 2016

Title: **OPHTHALMIC COMPOSITION**

Confirmation No.: 1009

Examiner: To Be Assigned

Group Art Unit: To Be Assigned

M/S Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT AND
RESPONSE TO NOTICE TO FILE MISSING PARTS DATED JULY 28, 2016

Commissioner:

This paper responds to the Notice to File Missing Parts dated July 28, 2016, setting forth an initial due date of September 28, 2016. Accordingly, this response is timely submitted. Entry of the following Preliminary Amendment is respectfully requested.

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 5 of this paper.

AMENDMENTS TO THE CLAIMS

The following listing of claims replaces all prior listings of claims in this application.

CLAIM LISTING:

- 1-30. (Cancelled).
31. (New) An ophthalmic composition, consisting essentially of from about 0.001 wt% to about 0.03 wt% of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9, wherein the muscarinic antagonist is atropine, or atropine sulfate.
32. (New) The ophthalmic composition of claim 31, 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.
33. (New) The ophthalmic composition of claim 31, wherein the muscarinic antagonist is present in the composition at a concentration of one of: 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%.
34. (New) The ophthalmic composition of claim 31, wherein the ophthalmic composition further comprises an osmolarity adjusting agent.
35. (New) The ophthalmic composition of claim 34, wherein the osmolarity adjusting agent is sodium chloride.
36. (New) The ophthalmic composition of claim 31, wherein the ophthalmic composition further comprises a preservative.

37. (New) The ophthalmic composition of claim 36, wherein the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof.
38. (New) The ophthalmic composition of claim 31, wherein the ophthalmic composition further comprises a buffer agent.
39. (New) The ophthalmic composition of claim 38, wherein 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.
40. (New) The ophthalmic composition of claim 31, wherein the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof.
41. (New) The ophthalmic composition of claim 31, wherein the ophthalmic composition further comprises a pD adjusting agent.
42. (New) The ophthalmic composition of claim 41, wherein the pD adjusting agent comprises deuterated hydrochloric acid, deuterated sodium hydroxide, deuterated acetic acid, or deuterated citric acid.
43. (New) The ophthalmic composition of claim 31, 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.
44. (New) The ophthalmic composition of claim 31, wherein the ophthalmic composition is not formulated as an injectable formulation.

45. (New) An ophthalmic solution, consisting essentially of from about 0.001 wt% to about 0.03 wt% of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9, wherein the muscarinic antagonist is atropine, or atropine sulfate.
46. (New) The ophthalmic solution of claim 45, wherein 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.
47. (New) The ophthalmic solution of claim 45, wherein 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.
48. (New) A method of arresting myopia progression, comprising administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition consisting essentially of from about 0.001 wt% to about 0.03 wt% of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9, wherein the muscarinic antagonist is atropine, or atropine sulfate.
49. (New) The method of claim 48, wherein the ophthalmic composition is stored at between about 2 °C to about 10 °C prior to first use.
50. (New) The method of claim 48, wherein the ophthalmic composition is stored at between about 16 °C to about 26 °C after first use.

REMARKS

This response is filed to preliminarily amend the claims. Examination on their merits is respectfully requested.

Claims

Claims 1-30 are cancelled. Claims 31-50 are submitted herein. Support for the amendment to the claims can be found in the originally filed application. No new matter has been added.

Fees

As amended, the application has not more than three independent claims, and no more than 20 claims in total. As such, no additional claim fee is due. Other missing fees are submitted herewith.

Allowance of Parent Application 14/726,139

Applicant notes that the parent application (US14/726,139) has been examined by the USPTO with issuance of Notice of Allowance on June 13, 2016. As stated in the Notice of Allowance (the paragraph bridging pages 2-3):

The following is an examiner's statement of reasons for allowance: the amendments set forth in the examiner's amendment and the data presented to the advantages of the combination of atropine and deuterated water in comparison to the combination of atropine and water has placed the application in condition for allowance.

The amended claims presented herein are prepared in light of the Examiner's Reasons for Allowance above. Favorable consideration and allowance of the pending claims are respectfully

requested. Should the Examiner have any questions, Applicant encourages the Examiner to contact the undersigned attorney at 858-350-2339.

FEE AUTHORIZATION

The Commissioner is authorized to charge any additional fees which may be required, including petition fees and extension of time fees, to Deposit Account No. **23-2415**, referencing Attorney Docket No. 46682-701.301.

Respectfully submitted,

Date: August 3, 2016

By: /Xiaofan Yang/
Xiaofan Yang
Registration No. 61,459

WILSON SONSINI GOODRICH & ROSATI
650 Page Mill Road
Palo Alto, CA 94304-1050
Direct Dial: (858) 350-2339
Customer No. 21971

Electronic Patent Application Fee Transmittal

Application Number:	15208537			
Filing Date:	12-Jul-2016			
Title of Invention:	OPHTHALMIC COMPOSITION			
First Named Inventor/Applicant Name:	Gregory I. OSTROW			
Filer:	Xiaofan Yang/Angie Hirano			
Attorney Docket Number:	46682-701.301			
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	70	70
Utility Search Fee	2111	1	300	300
Utility Examination Fee	2311	1	360	360
Pages:				
Claims:				
Miscellaneous-Filing:				
Late Filing Fee for Oath or Declaration	2051	1	70	70
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 (\$)				800

Electronic Acknowledgement Receipt

EFS ID:	26539679
Application Number:	15208537
International Application Number:	
Confirmation Number:	1009
Title of Invention:	OPHTHALMIC COMPOSITION
First Named Inventor/Applicant Name:	Gregory I. OSTROW
Customer Number:	21971
Filer:	Xiaofan Yang/Angie Hirano
Filer Authorized By:	Xiaofan Yang
Attorney Docket Number:	46682-701.301
Receipt Date:	03-AUG-2016
Filing Date:	12-JUL-2016
Time Stamp:	17:28:47
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	\$800
RAM confirmation Number	080416INTEFSW00004070232415
Deposit Account	232415
Authorized User	Frank Yang

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		46682-701-301_PA_Resp_to_MP.pdf	166849	yes	6
			4ae31cde5d9fb73f6ec5e739930bcb286242b210		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Applicant Response to Pre-Exam Formalities Notice		1	1	
	Claims		2	4	
	Applicant Arguments/Remarks Made in an Amendment		5	6	
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	37202	no	2
			4c5f54e4473e363c1062c69d39f243619694d5ef		
Warnings:					
Information:					
Total Files Size (in bytes):			204051		

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.



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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
15/208,537	07/12/2016	1629	0.00	46682-701.301	30	3

CONFIRMATION NO. 1009

FILING RECEIPT

21971
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050



Date Mailed: 07/28/2016

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)

Gregory I. OSTROW, San Diego, CA;
Kenneth J. WIDDER, Rancho Santa Fe, CA;
David S. BAKER, Carlsbad, CA;

Applicant(s)

Sydnexis, Inc., San Diego, CA;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 14/726,139 05/29/2015
which claims benefit of 62/151,926 04/23/2015
and claims benefit of 62/096,433 12/23/2014
and claims benefit of 62/016,502 06/24/2014

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: 07/26/2016

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/208,537**

Projected Publication Date: To Be Determined - pending completion of Missing Parts

Non-Publication Request: No

Early Publication Request: No

**** SMALL ENTITY ****

Title

OPHTHALMIC COMPOSITION

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.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

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>.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, <http://www.stopfakes.gov>. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER
Title 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15

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The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875						Application or Docket Number 15/208,537			
APPLICATION AS FILED - PART I									
(Column 1)		(Column 2)		SMALL ENTITY		OTHER THAN SMALL ENTITY			
FOR	NUMBER FILED	NUMBER EXTRA	RATE(\$)	FEE(\$)		RATE(\$)	FEE(\$)		
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	70		N/A			
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A	300		N/A			
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	360		N/A			
TOTAL CLAIMS (37 CFR 1.16(j))	30	minus 20 = *	10	x 40 =					
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3	minus 3 = *		x 210 =					
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).			0.00					
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0.00					
				TOTAL		TOTAL			
				1130					
* If the difference in column 1 is less than zero, enter "0" in column 2.									
APPLICATION AS AMENDED - PART II									
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY		OTHER THAN SMALL ENTITY	
AMENDMENT A		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)	RATE(\$)	ADDITIONAL FEE(\$)
	Total (37 CFR 1.16(i))	*	Minus	**	=	x	=	x	=
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x	=	x	=
	Application Size Fee (37 CFR 1.16(s))								
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))								
						TOTAL ADD'L FEE		TOTAL ADD'L FEE	
AMENDMENT B		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)	RATE(\$)	ADDITIONAL FEE(\$)
	Total (37 CFR 1.16(i))	*	Minus	**	=	x	=	x	=
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x	=	x	=
	Application Size Fee (37 CFR 1.16(s))								
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))								
						TOTAL ADD'L FEE		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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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/208,537	07/12/2016	Gregory I. OSTROW	46682-701.301

CONFIRMATION NO. 1009

FORMALITIES LETTER



OC000000084651812

21971
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

Date Mailed: 07/28/2016

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
- The application search fee must be submitted.
- The application examination fee must be submitted.
- Additional claim fees of \$ 400 as a small entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.
- Surcharge as set forth in 37 CFR 1.16(f) must be submitted.

The surcharge is due for any one of:

- late submission of the basic filing fee, search fee, or examination fee,
- late submission of inventor's oath or declaration,
- filing an application that does not contain at least one claim on filing, or
- submission of an application filed by reference to a previously filed application.

SUMMARY OF FEES DUE:

The fee(s) required within **TWO MONTHS** from the date of this Notice to avoid abandonment is/are itemized below. Small entity discount is in effect. If applicant is qualified for micro entity status, an acceptable Certification of Micro Entity Status must be submitted to establish micro entity status. (See 37 CFR 1.29 and forms PTO/SB/15A and 15B.)

- \$ 70 basic filing fee.
- \$ 70 surcharge.
- \$ 300 search fee.
- \$ 360 examination fee.
- \$ 400 for 10 total claims over 20.

- \$(0) previous unapplied payment amount.
- **\$ 1200** TOTAL FEE BALANCE DUE.

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web, including a copy of this Notice and selecting the document description "Applicant response to Pre-Exam Formalities Notice".
<https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html>

For more information about EFS-Web please call the USPTO Electronic Business Center at 1-866-217-9197 or visit our website at <http://www.uspto.gov/ebc>.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/wtsige/

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UTILITY PATENT APPLICATION TRANSMITTAL <i>(Only for new nonprovisional applications under 37 CFR 1.53(b))</i>		Attorney Docket No. 46682-701.301	
		First Named Inventor Gregory I. Ostrow	
		Title OPHTHALMIC COMPOSITION	
		Express Mail Label No. Electronically Filed 07/12/16	

APPLICATION ELEMENTS <i>See MPEP chapter 600 concerning utility patent application contents.</i>	Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450		
1. ☐ Fee Transmittal Form (PTO/SB/17 or equivalent) 2. ☒ Applicant asserts small entity status. See 37 CFR 1.27 3. ☐ Applicant certifies micro entity status. See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent. 4. ☒ Specification [Total Pages <u>108</u>] Both the claims and abstract must start on a new page. (See MPEP § 608.01(a) for information on the preferred arrangement) 5. ☒ Drawing(s) (35 U.S.C. 113) [Total Sheets <u>10</u>] 6. Inventor's Oath or Declaration [Total Pages <u>3</u>] (including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e)) a. ☐ Newly executed (original or copy) b. ☒ A copy from a prior application (37 CFR 1.63(d)) 7. ☒ Application Data Sheet * See note below. See 37 CFR 1.76 (PTO/AIA/14 or equivalent) 8. CD-ROM or CD-R in duplicate, large table, or Computer Program (Appendix) ☐ Landscape Table on CD 9. Nucleotide and/or Amino Acid Sequence Submission (if applicable, items a. – c. are required) a. ☐ Computer Readable Form (CRF) b. ☐ Specification Sequence Listing on: i. ☐ CD-ROM or CD-R (2 copies); or ii. ☐ Paper c. ☐ Statements verifying identity of above copies	ACCOMPANYING APPLICATION PAPERS 10. ☐ Assignment Papers (cover sheet & document(s)) Name of Assignee _____ 11. ☐ 37 CFR 3.73(c) Statement ☐ Power of Attorney (when there is an assignee) 12. ☐ English Translation Document (if applicable) 13. ☐ Information Disclosure Statement (PTO/SB/08 or PTO-1449) ☐ Copies of citations attached 14. ☐ Preliminary Amendment 15. ☐ Return Receipt Postcard (MPEP § 503) (Should be specifically itemized) 16. ☐ Certified Copy of Priority Document(s) (if foreign priority is claimed) 17. ☐ Nonpublication Request Under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent. 18. ☐ Other: _____ _____ _____ _____		
*Note: (1) Benefit claims under 37 CFR 1.78 and foreign priority claims under 1.55 must be included in an Application Data Sheet (ADS). (2) For applications filed under 35 U.S.C. 111, the application must contain an ADS specifying the applicant if the applicant is an assignee, person to whom the inventor is under an obligation to assign, or person who otherwise shows sufficient proprietary interest in the matter. See 37 CFR 1.46(b).			
19. CORRESPONDENCE ADDRESS			
☒ The address associated with Customer Number: <u>021971</u> OR ☐ Correspondence address below			
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Address			
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Country	Telephone	Email	
Signature	/Xiaofan Yang/		Date
Name (Print/Type)	Xiaofan Yang		Registration No. (Attorney/Agent)
		July 12, 2016	
		61,459	

This collection of information is required by 37 CFR 1.53(b). 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 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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	46682-701.301
		Application Number	
Title of Invention	OPHTHALMIC COMPOSITION		
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		
	Gregory	I.	OSTROW			
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service						
City	San Diego	State/Province	CA	Country of Residence	US	

Mailing Address of Inventor:

Address 1	14051 Caminito Vistana					
Address 2						
City	San Diego	State/Province	CA			
Postal Code	92130	Country	US			

Inventor	2				Remove	
Legal Name						
Prefix	Given Name	Middle Name	Family Name	Suffix		
	Kenneth	J.	WIDDER			
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service						
City	Rancho Santa Fe	State/Province	CA	Country of Residence	US	

Mailing Address of Inventor:

Address 1	P.O. Box 676250					
Address 2						
City	Rancho Santa Fe	State/Province	CA			
Postal Code	92067	Country	US			

Inventor	3				Remove	
Legal Name						
Prefix	Given Name	Middle Name	Family Name	Suffix		
	David	S.	BAKER			
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service						

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		46682-701.301	
		Application Number			
Title of Invention	OPHTHALMIC COMPOSITION				
City	Carlsbad	State/Province	CA	Country of Residence	US
Mailing Address of Inventor:					
Address 1	7205 Aviara Drive				
Address 2					
City	Carlsbad	State/Province	CA		
Postal Code	92011	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	021971		
Email Address	uspatentdocket@wsgr.com	Add Email	Remove Email

Application Information:

Title of the Invention	OPHTHALMIC COMPOSITION		
Attorney Docket Number	46682-701.301	Small Entity Status Claimed	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	10	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	46682-701.301
		Application Number	
Title of Invention	OPHTHALMIC COMPOSITION		

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	021971		

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)
	Continuation of	14726139	2015-05-29
Prior Application Status	Expired	Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
14726139	Claims benefit of provisional	62151926	2015-04-23
Prior Application Status	Expired	Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
14726139	Claims benefit of provisional	62096433	2014-12-23
Prior Application Status	Expired	Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
14726139	Claims benefit of provisional	62016502	2014-06-24
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the Add button.			Add

Foreign Priority Information:

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	46682-701.301
		Application Number	
Title of Invention	OPHTHALMIC COMPOSITION		

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)	Access Code ⁱ (if applicable)	Remove

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

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	46682-701.301
		Application Number	
Title of Invention	OPHTHALMIC COMPOSITION		

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	46682-701.301
		Application Number	
Title of Invention	OPHTHALMIC COMPOSITION		

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	Sydnexis, Inc.	
Mailing Address Information For Applicant:		
Address 1	14051 Caminito Vistana	
Address 2		
City	San Diego	State/Province CA
Country	US	Postal Code 92130
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	46682-701.301
		Application Number	
Title of Invention	OPHTHALMIC COMPOSITION		

Assignee	1			
Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.				
				Remove
If the Assignee or Non-Applicant Assignee is an Organization check here.				☐
Prefix	Given Name	Middle Name	Family Name	Suffix
Mailing Address Information For Assignee including Non-Applicant Assignee:				
Address 1				
Address 2				
City		State/Province		
Country ⁱ		Postal Code		
Phone Number		Fax Number		
Email Address				
Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.				Add

Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). However, if this Application Data Sheet is submitted with the **INITIAL** filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Xiaofan Yang/		Date (YYYY-MM-DD)	2016-07-12
First Name	Xiaofan	Last Name	Yang	Registration Number
				61459
Additional Signature may be generated within this form by selecting the Add button.				Add

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	46682-701.301
		Application Number	
Title of Invention	OPHTHALMIC COMPOSITION		

This collection of information is required by 37 CFR 1.76. 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 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet 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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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 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.

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

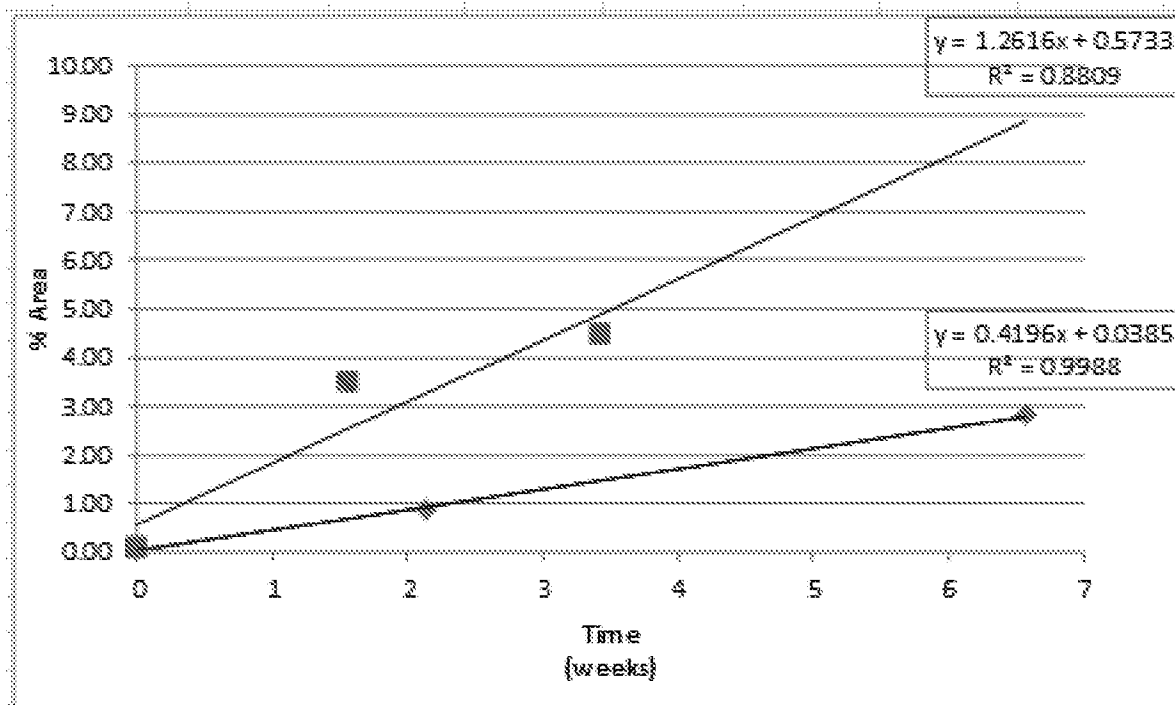


Fig. 1C

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

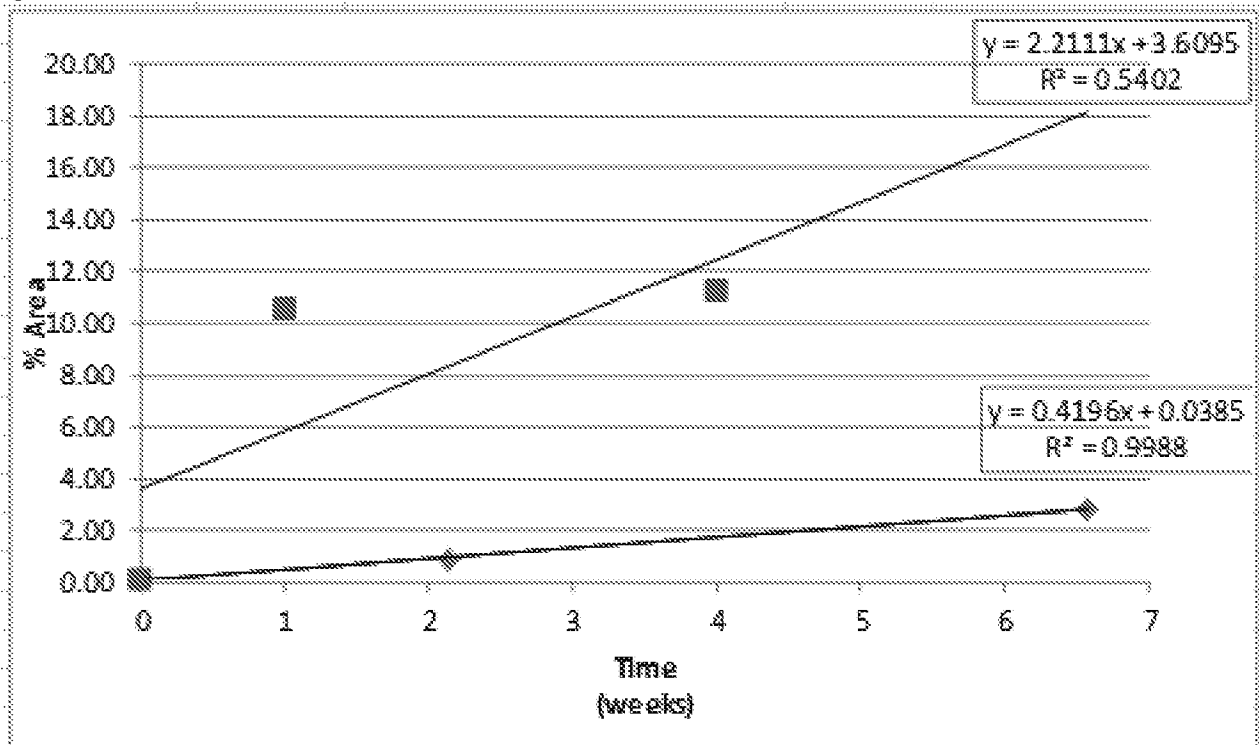


Fig. 2C

Formulation:		Average of Analysts		
Stability Prediction:		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

Fig. 3

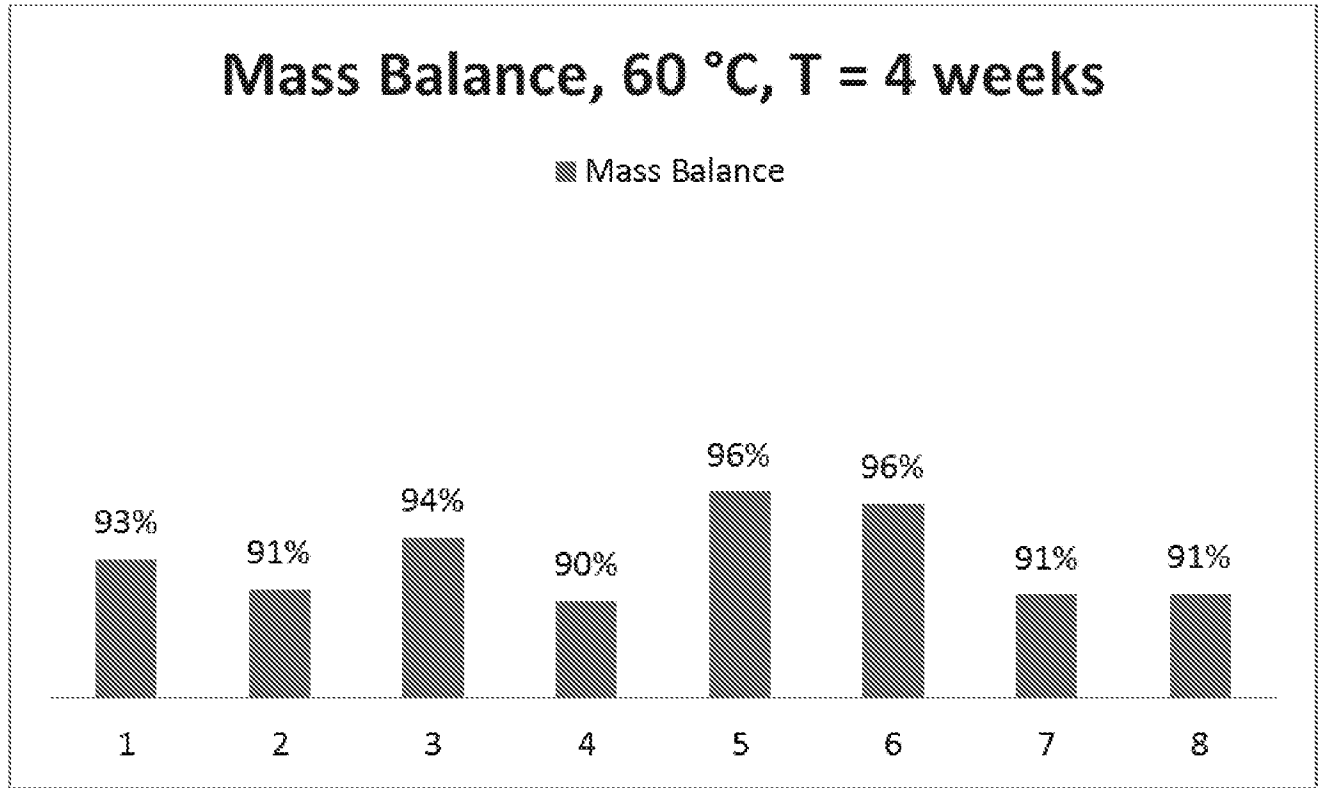


Fig. 4

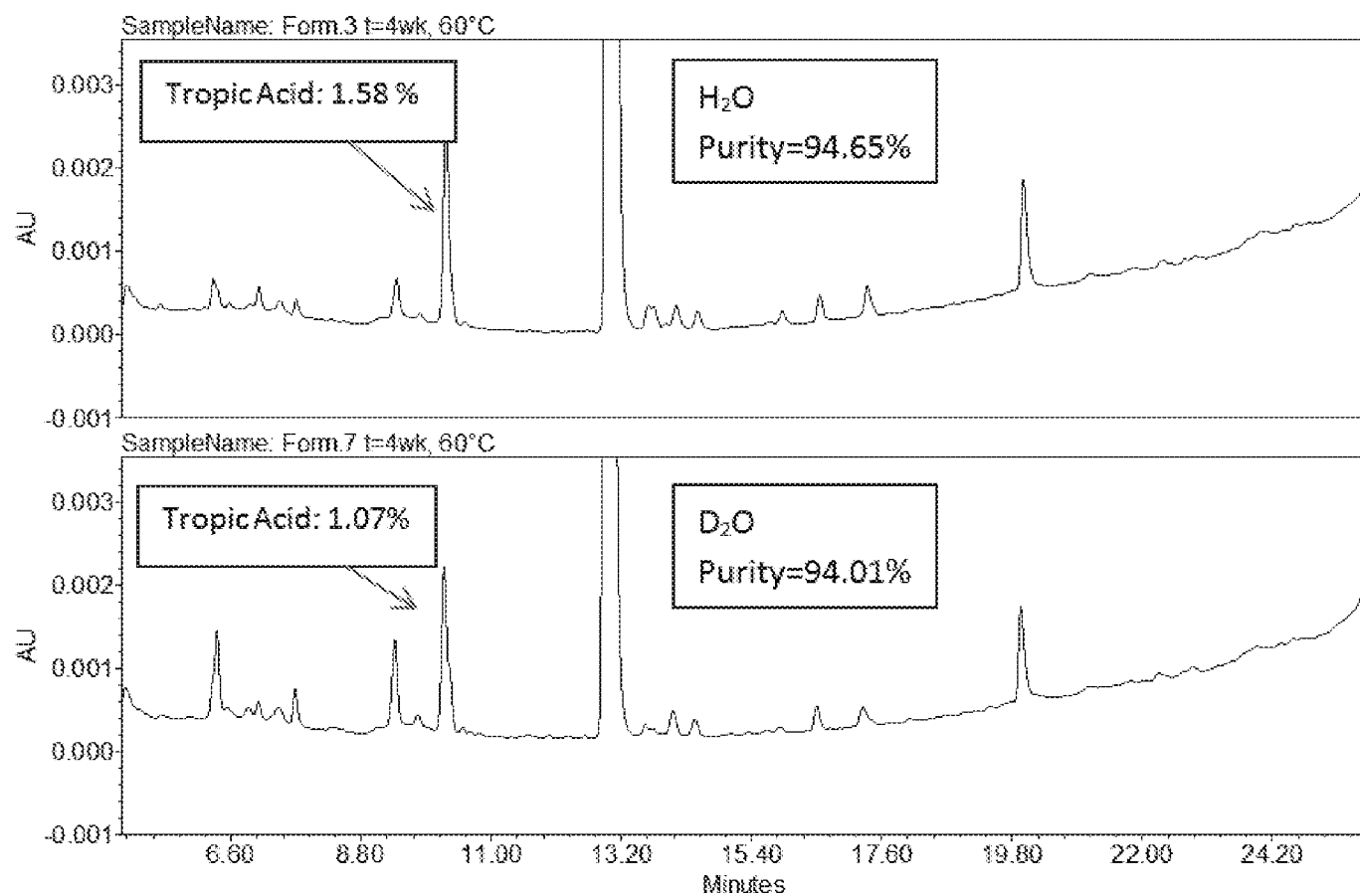


Fig. 5

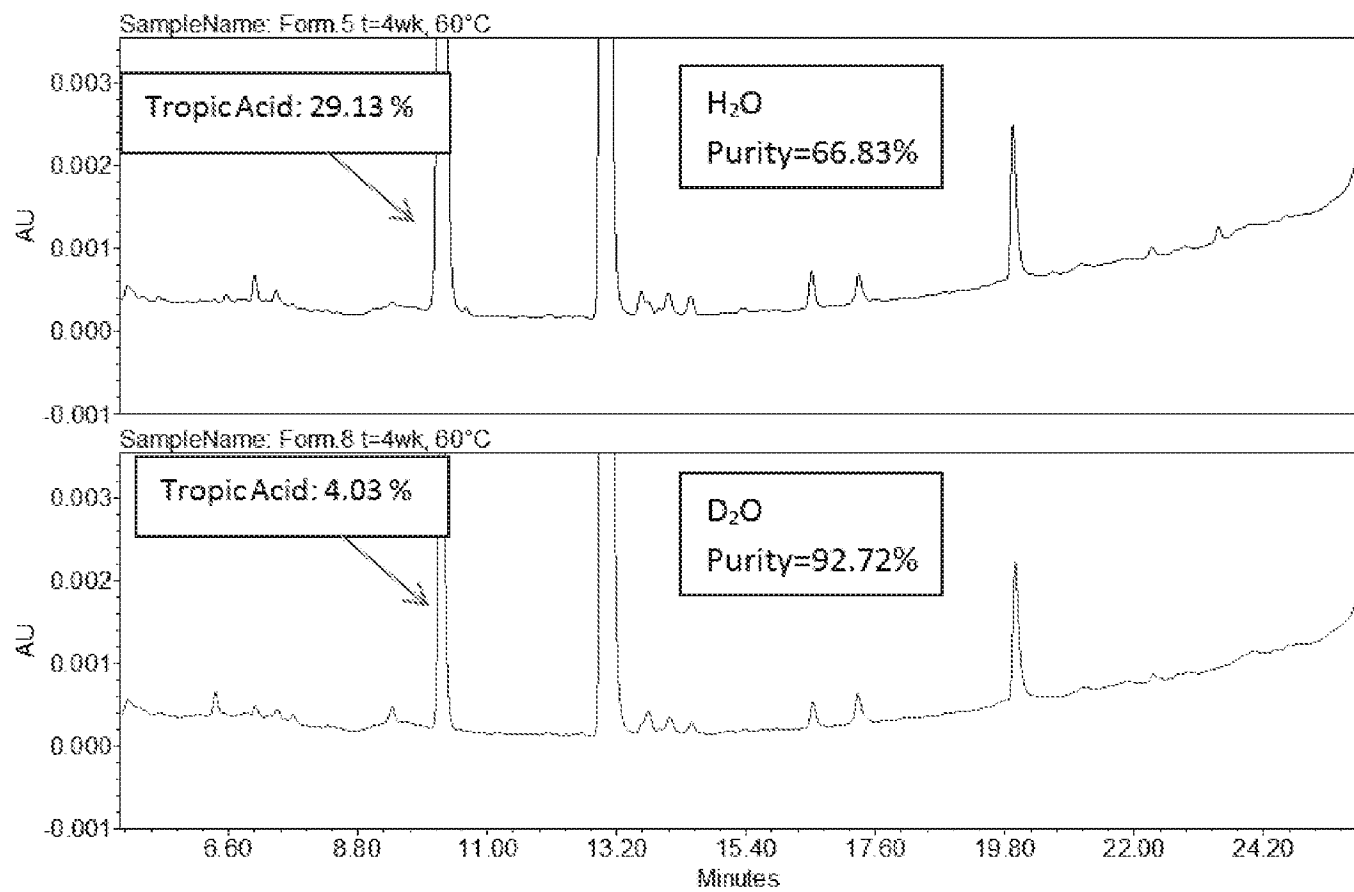


Fig. 6

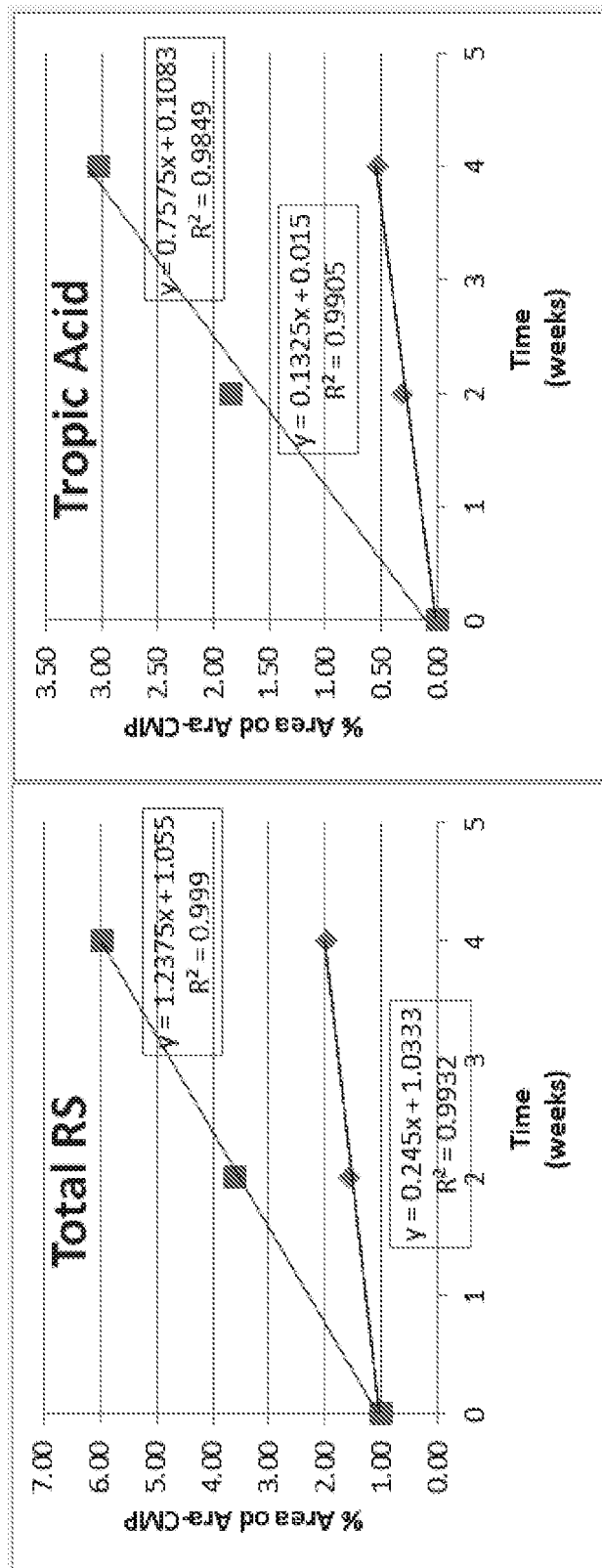


Fig. 7

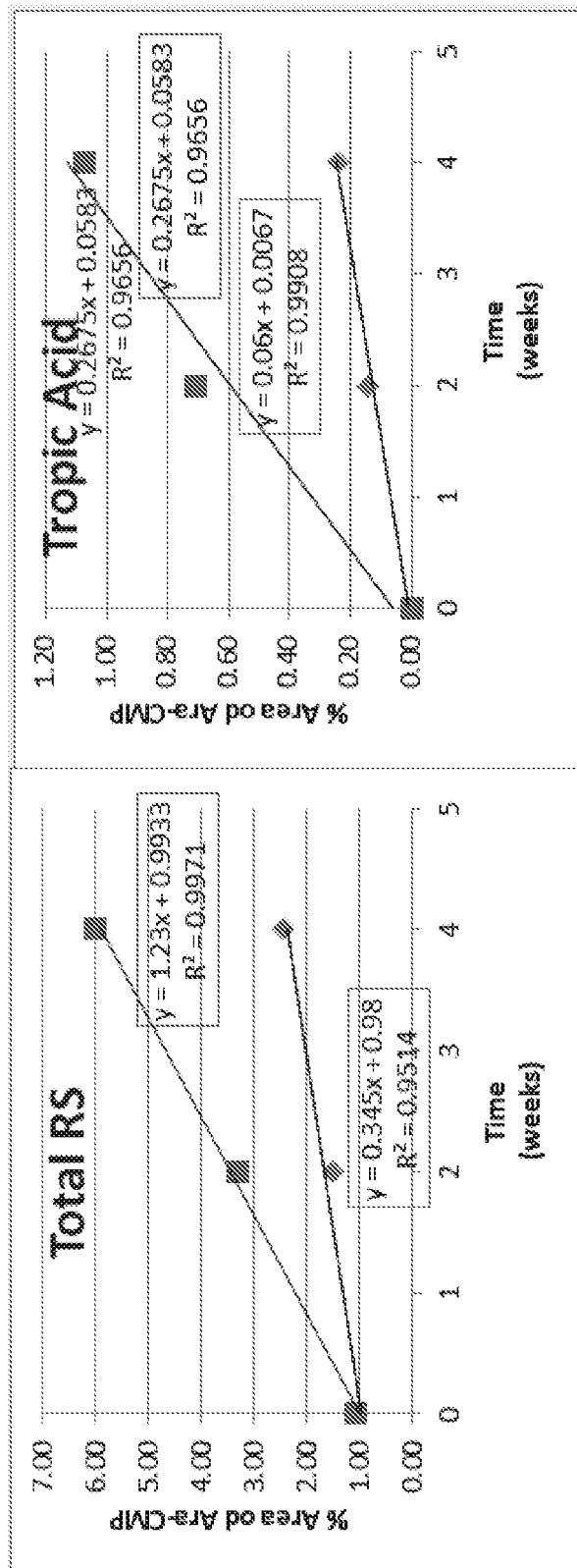


Fig. 8

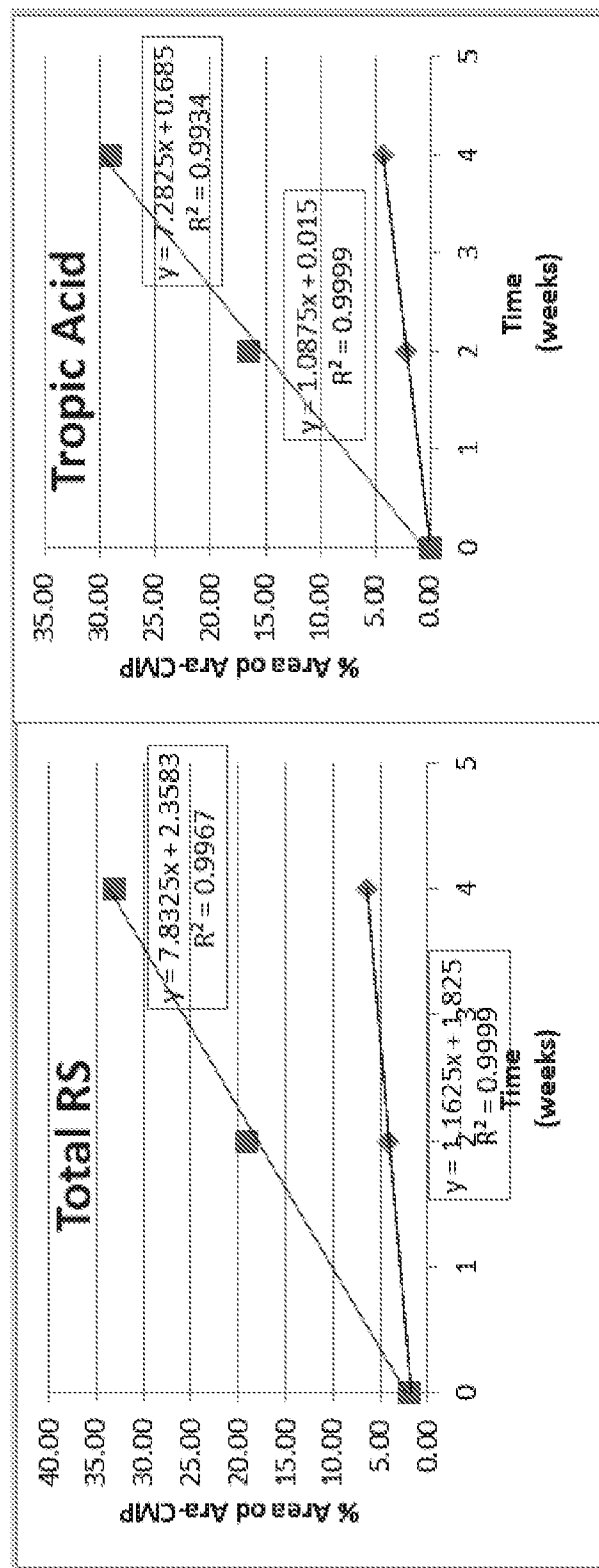


Fig. 9

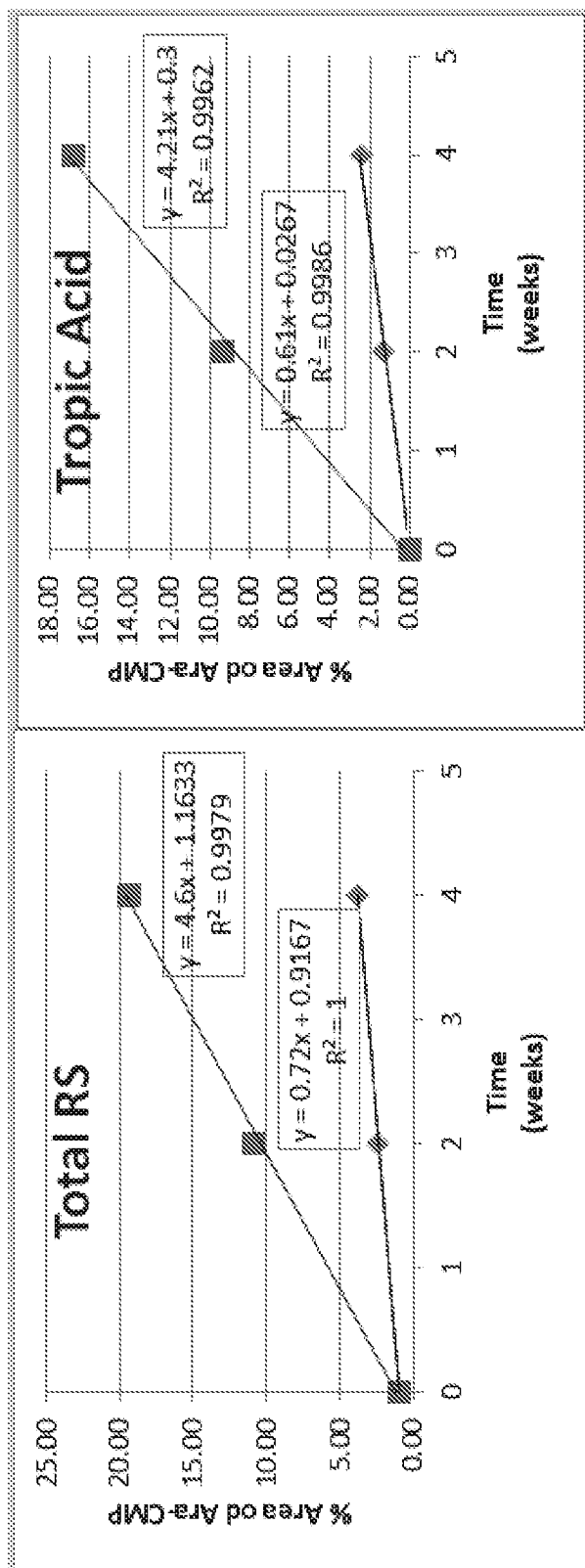
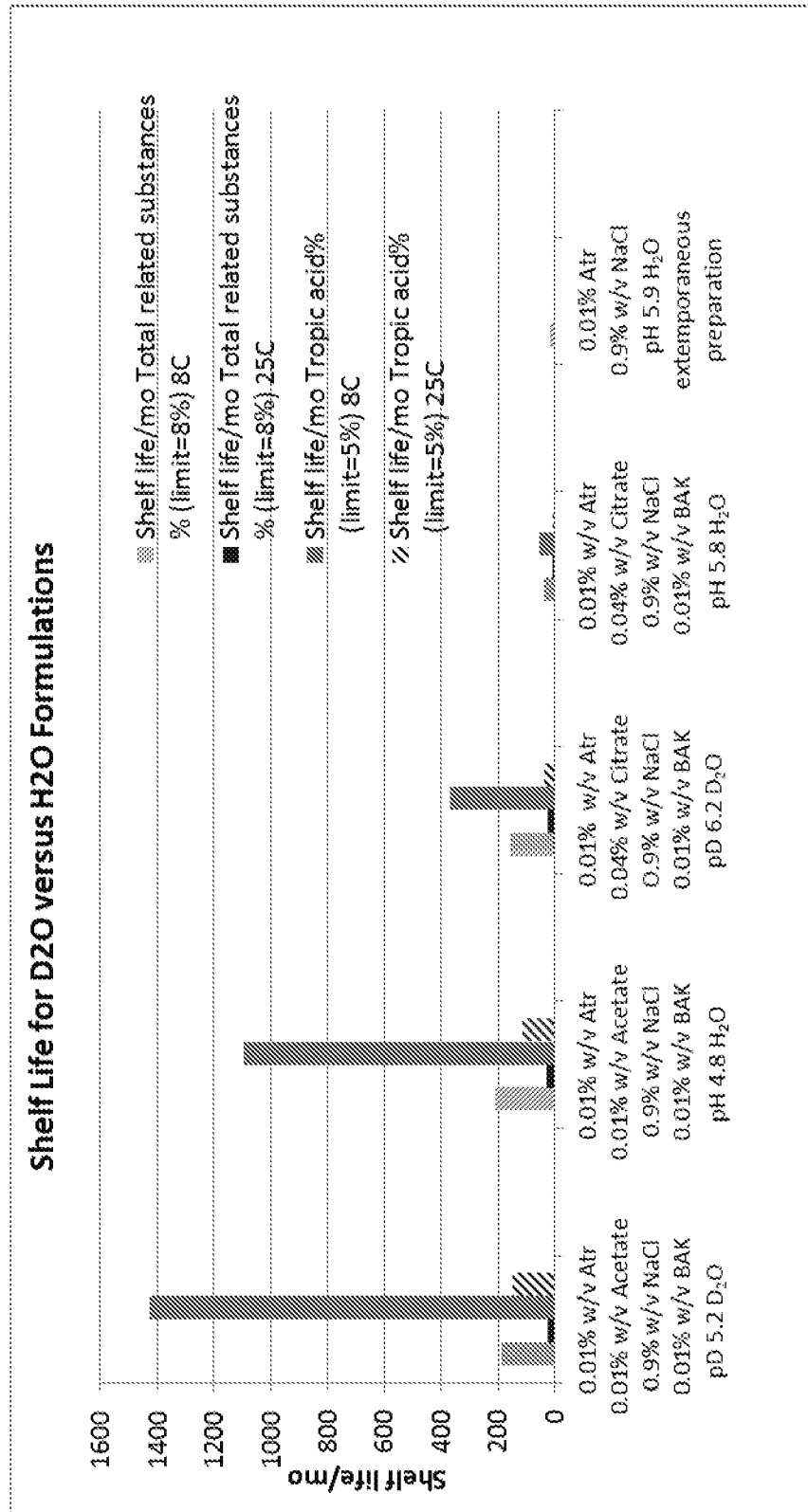


Fig. 10



Electronic Acknowledgement Receipt

EFS ID:	26330989
Application Number:	15208537
International Application Number:	
Confirmation Number:	1009
Title of Invention:	OPHTHALMIC COMPOSITION
First Named Inventor/Applicant Name:	Gregory I. OSTROW
Customer Number:	021971
Filer:	Xiaofan Yang/Angie Hirano
Filer Authorized By:	Xiaofan Yang
Attorney Docket Number:	46682-701.301
Receipt Date:	12-JUL-2016
Filing Date:	
Time Stamp:	20:20:30
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		46682-701-301_Application.pdf	598058	yes	108
			bde1c201f19ef203a42ae49c633bcb07dd4cd80e		

	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Specification		1	103	
	Claims		104	107	
	Abstract		108	108	
Warnings:					
Information:					
2	Oath or Declaration filed	46682-701-301_Declarations.pdf	197785	no	3
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3	Transmittal of New Application	46682-701-301_Transmittal.pdf	276964	no	2
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4	Application Data Sheet	46682-701-301_ADS.pdf	1823490	no	9
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5	Drawings-only black and white line drawings	46682-701-301_Figures.pdf	184617	no	10
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U.S. CONTINUATION APPLICATION

OPHTHALMIC COMPOSITION

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OPHTHALMIC COMPOSITION

BACKGROUND OF THE DISCLOSURE

[0001] Pharmaceutical formulations have an expiration date which is based on the degradation of the active ingredient.

SUMMARY OF THE DISCLOSURE

[0002] 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.

[0003] 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 atropine sulfate.

[0004] 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.

[0005] 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).

[0006] 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).

[0007] 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.

[0008] 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.

[0009] 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%.

[0010] 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%.

[0011] 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.

[0012] 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).

[0013] In some embodiments, the composition is in a form of an aqueous solution.

[0014] In some embodiments, the composition further comprises an osmolarity adjusting agent. In some embodiments, the osmolarity adjusting agent is sodium chloride.

[0015] 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.

[0016] 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.

[0017] 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.

[0018] 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).

[0019] In some embodiments, the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof.

[0020] 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.

[0021] In some embodiments, the composition further comprises a pD adjusting agent. In some embodiments, the pD adjusting agent comprises DCl, NaOD, CD_3COOD , or $\text{C}_6\text{D}_8\text{O}_7$.

[0022] 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.

[0023] 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 .

[0024] 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 .

[0025] 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.

[0026] 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.

[0027] In some embodiments, the ophthalmic composition is not formulated as an injectable formulation.

[0028] In some embodiments, the ophthalmic composition is formulated as an ophthalmic solution for the treatment of pre-myopia, myopia, or progression of myopia.

[0029] 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 at between about 2 °C to about 10 °C prior to first use. In some embodiments, the ophthalmic composition is stored at between about 16 °C to about 26 °C after first use.

[0030] 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.

[0031] 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

[0032] 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:

[0033] 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.

[0034] 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.

[0035] Fig. 3 illustrates mass balance at 4 weeks and at 60°C condition for atropine sulfate formulations disclosed in Example 9.

[0036] 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.

[0037] 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.

[0038] Fig. 6 illustrates comparison of total RS and tropic acid for atropine sulfate (0.025%) formulation (Formulation 4) at pH 4.8 in H₂O.

[0039] Fig. 7 illustrates comparison of total RS and tropic acid for atropine sulfate (0.01%) formulation (Formulation 7) at pD 5.2 in D₂O.

[0040] Fig. 8 illustrates comparison of total RS and tropic acid for atropine sulfate (0.01%) formulation (Formulation 5) at pH 5.8 in H₂O.

[0041] Fig. 9 illustrates comparison of total RS and tropic acid for atropine sulfate (0.025%) formulation (Formulation 6) at pH 5.8 in H₂O.

[0042] Fig. 10 illustrates estimated shelf lives for D₂O and H₂O formulations disclosed in Examples 11 and 12.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0043] 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.

[0044] 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.

[0045] 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.

[0046] 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.

[0047] 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.

[0048] 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.

[0049] 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.

[0050] Ophthalmic Muscarinic Antagonist Composition

[0051] 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.

[0052] 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.

[0053] 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, benzatropine, 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.

[0054] 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, benzatropine, 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.

[0055] 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, benzatropine, 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.

[0056] 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, benzatropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, or tolterodine; in combination with one or more of sympathetic agonists: phenylephrine or hydroxyamphetamine.

[0057] 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.

[0058] 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.

[0059] In some embodiments, the ophthalmic disorder or condition is pre-myopia, myopia or progression of myopia.

[0060] 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).

[0061] 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.

[0062] 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.

[0063] 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.

[0064] 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.

[0065] Ophthalmic Solution Muscarinic Antagonist Composition

[0066] 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.

[0067] 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

[illegible]

[illegible]

[0069] 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.

[0070] 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.

[0071] 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%.

[0072] 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.

[0073] 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.

[0074] 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.

[0075] 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.

[0076] 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.

[0077] 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.

[0078] 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.

[0079] 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.

[0080] Ophthalmic Muscarinic Antagonist Concentration

[0081] 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, 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.

[0082] 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.

[0083] 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.

[0084] 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.

[0085] 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.

[0086] 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.

[0087] 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.

[0088] 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, 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.

[0089] 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.

[0090] 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.

[0091] 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).

[0092] Aqueous Solution Stability

[0093] 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.

[0094] 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.

[0095] 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.

[0096] 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.

[0097] 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.

[0098] In some cases, citrate buffering agents include citric acid and sodium citrate.

[0099] In some instances, acetate buffering agents include acetic acid, potassium acetate, and sodium acetate.

[00100] In some instances, carbonate buffering agents include sodium bicarbonate and sodium carbonate.

[00101] 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-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).

[00102] 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.

[00103] 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.

[00104] 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.

[00105] 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.

[00106] 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.

[00107] 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.

[00108] 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.

[00109] 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.

[00110] In some embodiments, the presence of deuterated water shifts the pKa 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.

[00111] 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.

[00112] 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*).

[00113] 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%.

[00114] 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.

[00115] 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.

[00116] 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.

[00117] 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.

[00118] 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.

[illegible]

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.

[00120] 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.

[00121] 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.

[00122] 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.

[00123] 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.

[00124] 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.

[00125] 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.

[00126] 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.

[00127] 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.

[00128] 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.

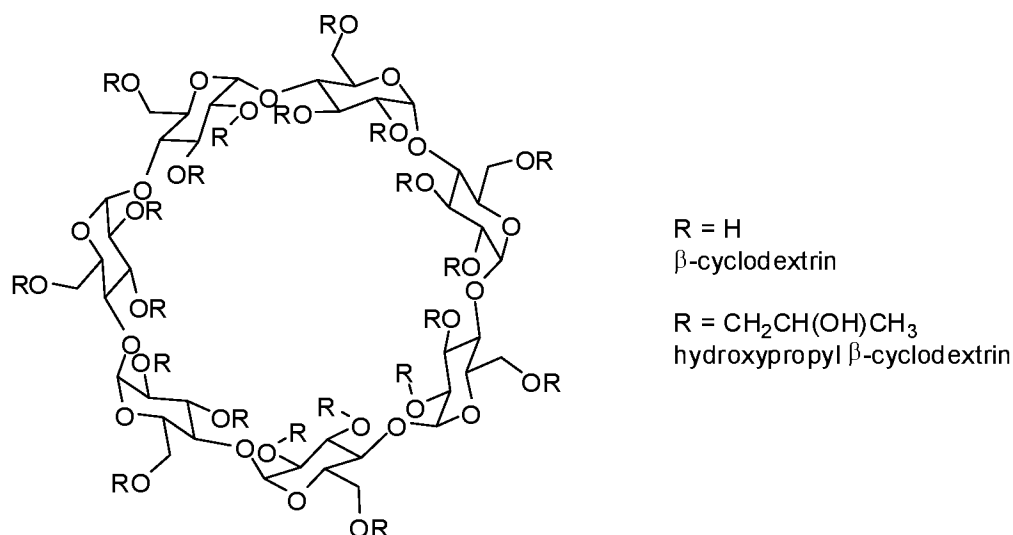
[00129] In some embodiments, the composition stored in a glass container is less stable than a composition stored in a plastic container.

[00130] 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.

[00131] 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.

[00132] 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).



[00133] 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.

[00134] 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.

[00135] 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.

[00136] 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.

[00137] 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.

[00138] 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.

[00139] 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.

[00140] 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.

[00141] 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.

[00142] 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.

[00143] 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%.

[00144] 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.

[00145] pD

[00146] 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.

[00147] 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), deuterated sodium hydroxide (NaOD), deuterated acetic acid (CD₃COOD), or deuterated citric acid (C₆D₈O₇).

[00148] 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.

[00149] 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.

[00150] 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 $pD = pH^* + 0.4$, in which pH^* is the measured or observed pH of the ophthalmic composition formulated in a solution comprising deuterated water (e.g., D_2O).

[00151] 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.

[00152] 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.

[00153] 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

[illegible]

[00154] 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,

[illegible]

the pD is the pD of the ophthalmic aqueous composition after extended period of time under storage condition.

[00155] 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.

[00156] 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.

[00157] 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.

[00158] 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.

[00159] 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.

[00160] 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.

[00161] Aqueous Solution Dose-To-Dose Uniformity

[00162] 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.

[00163] 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.

[00164] 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%.

[00165] 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.

[00166] 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.

[00167] 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.

[00168] **Aqueous Solution Viscosity**

[00169] 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} .

[00170] 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.

[00171] 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.

[00172] **Osmolarity**

[00173] 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.

[00174] 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.

[00175] 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.

[00176] 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.

[00177] 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.

[00178] 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.

[00179] **Sterility**

[00180] 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.

[00181] 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

[00182] 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 μ m. 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).

[00183] 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.

[00184] 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).

[00185] 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

[00186] 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

[00187] 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

[00188] 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.

[00189] 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.

[00190] 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.

[00191] 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

[00192] 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.

[00193] 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.

[00194] 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.

[00195] 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.

[00196] Ophthalmic Muscarinic Antagonist-Mucus Penetrating Particle (MPP) Composition

[00197] 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).

[00198] 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.

[00199] 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.

[00200] 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.

[00201] 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.

[00202] 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.

[00203] 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.

[00204] 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.

[00205] 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.

[00206] Ophthalmic Gel Muscarinic Antagonist Composition

[00207] 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.

[00208] 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.

[00209] 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.

[00210] 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.

[00211] 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.

[00212] 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.

[00213] 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.

[00214] 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.

[00215] 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.

[00216] 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.

[00217] 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.

[00218] 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.

[00219] 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.

[00220] 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.

[00221] 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.

[00222] 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.

[00223] 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.

[00224] 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.

[00225] Ophthalmic Ointment Muscarinic Antagonist Composition

[00226] 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

[00227] 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.

[00228] 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.).

[00229] 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.

[00230] 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.

[00231] 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.

[00232] 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.

[00233] 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.

[00234] 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.

[00235] 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.

[00236] 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.

[00237] 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.

[00238] 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.

[00239] 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.

[00240] 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.

[00241] 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.

[00242] **Gel/Ointment Viscosity**

[00243] 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 $1s^{-1}$.

[00244] 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.

[00245] 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.

[00246] 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.

[00247] 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).

[00248] Gel/Ointment Dose-To-Dose Uniformity

[00249] 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.

[00250] 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.

[00251] 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.

[00252] 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%.

[00253] 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.

[00254] 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.

[00255] 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.

[00256] **Methods of Treatment**

[00257] 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.

[00258] 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 dispensing tube.

[00259] 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.

[00260] 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.

[00261] 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.

[00262] 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.

[00263] 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.

[00264] 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.

[00265] 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%.

[00266] 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.

[00267] 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.

[00268] 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%.

[00269] 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.

[00270] 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.

[00271] In some embodiments, the initial administration is a particular ophthalmic agent and the subsequent administration a different formulation or ophthalmic agent.

[00272] **Kits/Articles of Manufacture**

[00273] 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.

[00274] 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.

[00275] 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.

[00276] 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.

[00277] 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

[00278] 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 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

[00279] Stock 1% Solution

[00280] 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.

[00281] Diluted 0.01% Solution

[00282] 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

[00283] Stock 1% Solution

[00284] 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.

[00285] Diluted 0.01% Solution

[00286] 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

[00287] 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

[00288] 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 µm
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 ± 3 °C
Autosampler Temperature	5 ± 3 °C
Run Time	6.0 minutes
Injection Volume	10 µL*
Needle Wash Solution	90/10 Water: Acetonitrile

* Modified from original method to maintain sensitivity at 100 µg/mL nominal.

[00289] 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.

[00290] 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.

[00291] 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

[00292] 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

[00293] 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)

[00294] 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)

[00295] 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)

[00296] 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

[00297] 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

[00298] 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.

[00299] 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

[00300] 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.

[00301] 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.

[00302] 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.

[00303] 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.

[00304] The percentage of tropic acid observed for each of the formulations at t=4 weeks and at 60°C are as follow:

[00305] Formulation 1- Tropic acid observed is 0.54%.

[00306] Formulation 2-Tropic acid observed is 0.93%.

[00307] Formulation 3-Tropic acid observed is 1.58%.

[00308] Formulation 4-Tropic acid observed is 3.03%.

[00309] Formulation 5-Tropic acid observed is 29.13%.

[00310] Formulation 6-Tropic acid observed is 16.84%.

[00311] Formulation 7-Tropic acid observed is 1.07%.

[00312] Formulation 8-Tropic acid observed is 4.03%.

[00313] 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 pH 5.2 (Formulation 7), see Fig. 4. In addition, in the formulation containing citric acid at pH 6.2 (Formulation 8), the deuterated water also stabilizes atropine sulfate, see Fig. 5.

[00314] 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

[00315] 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	25/60	107.2	107.1	109.1

pH 5.8	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

[00316] 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.

[00317] 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	25/60	5.31	5.10	5.24

(pD)	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

[00318] 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)).

[00319] 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

[00320] Activation energy was calculated for the eight formulations disclosed in Example 9 and comparison with a reference standard was made with Formulations 4-7.

[00321] 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 +/- 3* 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	Poor

	Corr	Corr	
2	12.2	Poor	
		Corr	
3	Poor	18.3	
	Corr		
4	16.8	18.1	
5	19.8	19.7	
6	19.2	20.0	
7	13.2	15.5	
8	Poor	18.9	
	Corr		
Mean	16.2	18.4	Kcal/mole
Stdev	3.4	1.6	
RSD	21%	9%	

[00322] 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

[00323] 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

[00324] At pD 6.2, the deuterated formulation (Formulation 8) has a predicted shelf life of close to 2 years at 30°C.

[00325] 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

[00326] 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)

[00327] 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.

[00328] 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

[00329] 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	25/60	98.53	97.17	95.99

↓C D ₂ O pD 7.2	40/75		90.75	84.64
	60 °C		56.78	46.05

[00330] 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

[00331] 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 ↓ <i>A</i> 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 ↓ <i>C</i> 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 ↓ <i>C</i> 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>C</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 ↓ <i>A</i> 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 ↓ <i>C</i> 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 ↓ <i>C</i> 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 ↓ <i>C</i> 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

[00332] 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	25/60	4.85	4.44	4.61

↓A H ₂ O pH 4.8	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

[00333] 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%)	
	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 H ₂ O (Formulation 5)	37	5.2	54	5.5
0.01% Atr 0.9% w/v NaCl pH5.9 H ₂ O extemporaneous preparation	13.6	2.6		

[00334] 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

[00335] 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 14 – In vivo Rabbit Eye Irritation Test

[00336] 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

[00337] 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

[00338] 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

[00339] 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.

[00340] 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.

[00341] 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.

[00342] 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

[00343] 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.

[00344] 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.

[00345] 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.

[00346] 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.

[00347] 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

[00348] 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

[00349] 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

[00350] 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.

[00351] 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.

[00352] In some instances, 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 cases, the muscarinic antagonist is atropine. In some cases, the muscarinic antagonist is atropine sulfate.

[00353] 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.

[00354] 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.

[00355] 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.

[00356] 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.

[00357] 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%.

[00358] 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%.

[00359] In some instances, the ophthalmic composition further comprises an osmolarity adjusting agent. In some cases, the osmolarity adjusting agent is sodium chloride.

[00360] 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.

[00361] 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.

[00362] 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.

[00363] 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).

[00364] 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.

[00365] 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.

[00366] 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.

[00367] 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.

[00368] In some instances, the ophthalmic composition further comprises a pharmaceutically acceptable carrier.

[00369] 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.

[00370] In some instances, the ophthalmic composition is not formulated as an injectable formulation.

[00371] 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, scopolomine, 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 claim 1, 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 claim 1, 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 claim 1, 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 claim 1, 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.

8. The ophthalmic composition of claim 1, 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.
9. The ophthalmic composition of claim 1, 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%.
10. The ophthalmic composition of claim 1, wherein the ophthalmic composition further comprises an osmolarity adjusting agent.
11. The ophthalmic composition of claim 10, wherein the osmolarity adjusting agent is sodium chloride.
12. The ophthalmic composition of claim 1, wherein the ophthalmic composition further comprises a preservative.
13. The ophthalmic composition of claim 12, wherein the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof.
14. The ophthalmic composition of claim 1, wherein the ophthalmic composition further comprises a buffer agent.
15. The ophthalmic composition of claim 14, wherein 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.
16. The ophthalmic composition of claim 1, wherein the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof.

17. The ophthalmic composition of claim 1, 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%.
18. The ophthalmic composition of claim 17, wherein 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.
19. The ophthalmic composition of claim 1, wherein the ophthalmic composition further comprises a pD adjusting agent.
20. The ophthalmic composition of claim 19, wherein the pD adjusting agent comprises DCl, NaOD, CD₃COOD, or C₆D₈O₇.
21. The ophthalmic composition of claim 1, 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.
22. The ophthalmic composition of claim 1, wherein the ophthalmic composition is not formulated as an injectable formulation.
23. The ophthalmic composition of claim 1, wherein the ophthalmic composition is formulated as an ophthalmic solution for the treatment of pre-myopia, myopia, or progression of myopia.
24. An ophthalmic solution, 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.
25. The ophthalmic solution of claim 24, wherein 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.

26. The ophthalmic solution of claim 24, 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.
27. The ophthalmic solution of claim 24, wherein 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.
28. 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.
29. The method of claim 28, wherein the ophthalmic composition is stored at between about 2 °C to about 10 °C prior to first use.
30. The method of claim 28, wherein the ophthalmic composition is stored at between about 16 °C to about 26 °C after first use.

OPHTHALMIC COMPOSITION

ABSTRACT

[00372] 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.

PTO/AIA/01 (08-12)

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APPLICATION DATA SHEET (37 CFR 1.76)**Title of
Invention

OPHTHALMIC COMPOSITION

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 14/726,139filed on May 29, 2015

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 INVENTORInventor: Gregory J. OstrowDate (Optional): 6/1/15Signature: Gregory J. Ostrow

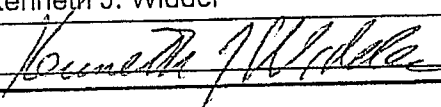
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Title of Invention	OPHTHALMIC COMPOSITION
As the below named inventor, I hereby declare that:	
This declaration is directed to: ☐ The attached application, or	
☒ United States application or PCT International application number <u>14/726,139</u>	
filed on <u>May 29, 2015</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.	
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LEGAL NAME OF INVENTOR	
Inventor: <u>Kenneth J. Widder</u> Date (Optional) : _____	
Signature: <u></u>	
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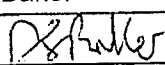
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LEGAL NAME OF INVENTOR

Inventor: David S. Baker Date (Optional): 6/3/15
Signature: 

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