

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**

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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

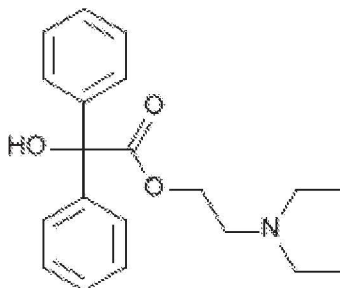
In the Office Action, the Patent Office cites WoldeMussie for allegedly teaching ophthalmic formulations containing a muscarinic antagonist; and Wildsoet for allegedly teaching atropine being used as a muscarinic antagonist in ophthalmic formulations (page 6 of the Office Action). Applicant notes that 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

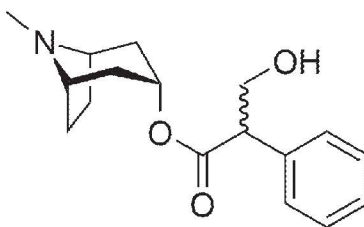
The Office Action cites Teva for allegedly teaching the following:

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,

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