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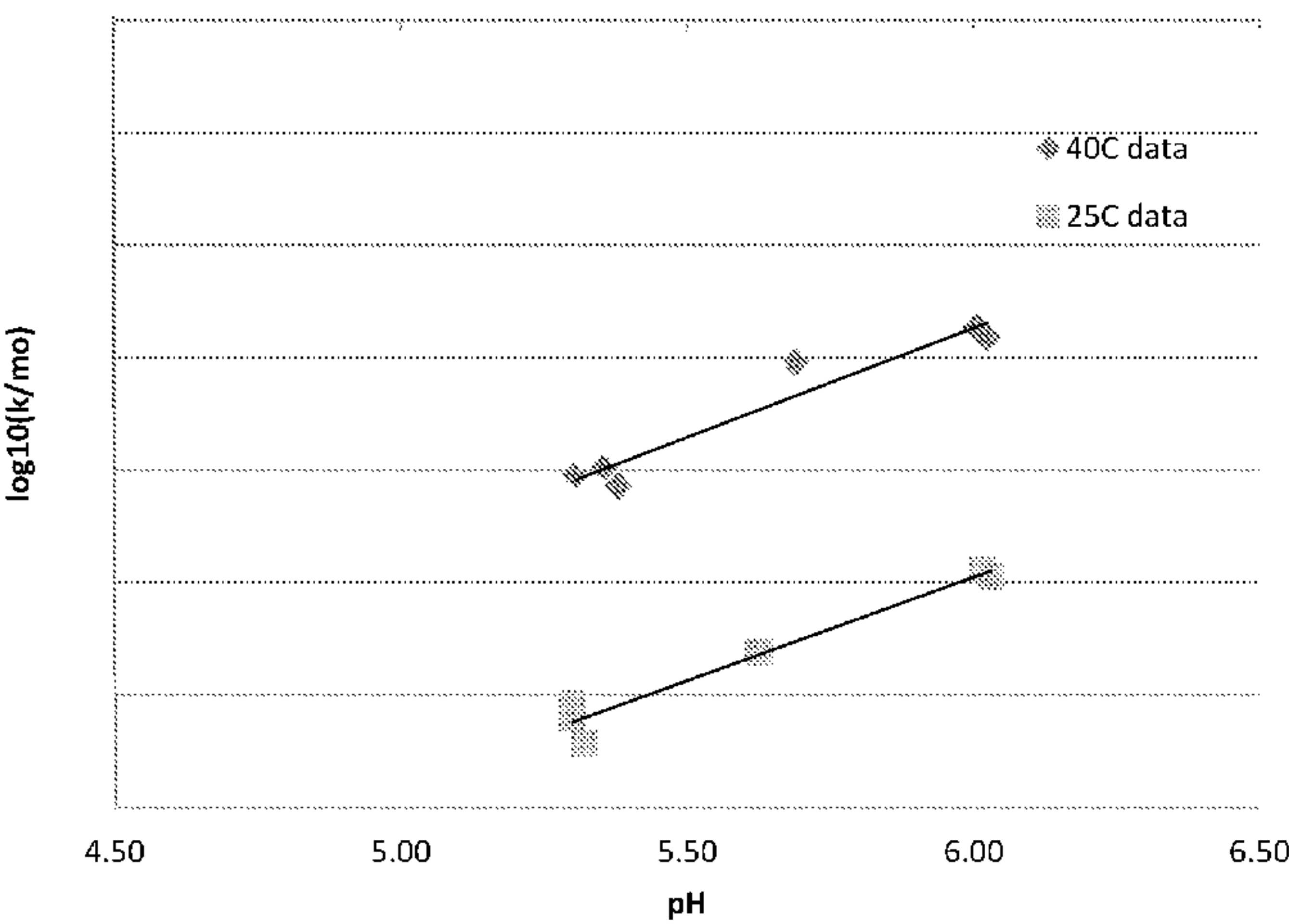
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(54) Title: OPHTHALMIC COMPOSITIONS COMPRISING D2O

log Rate Constant of Tropic Acid Formation vs pH



pH	log10(k/mo) at 40C	log10(k/mo) at 25C
5.3	4.8	4.5
5.7	5.2	4.9
6.1	5.6	5.3

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. Further disclosed herein is an ophthalmic composition including a low concentration of an ophthalmic agent and deuterated water. Further disclosed herein is an ophthalmic including a low concentration of an ophthalmic agent and various ratios of water to deuterated water.

[Continued on next page]

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- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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OPHTHALMIC COMPOSITIONS COMPRISING D2O**CROSS-REFERENCE**

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 63/080,617 filed on September 18, 2020 and U.S. Provisional Patent Application No. 62/948,761 filed on December 16, 2019, each of which is incorporated by reference in its 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 comprising from about 0.001 wt% to about 0.5 wt% of a muscarinic antagonist and deuterated water, at a pH of from about 4.2 to about 7.9, wherein the ophthalmic composition is substantially free of a benzalkonium chloride preservative. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition is substantially free of a preservative selected from cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition has no detectable amount of a benzalkonium chloride preservative. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition has no detectable amount of benzalkonium chloride. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition has no detectable amount of a preservative. In some embodiments of an ophthalmic composition described herein, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine, homatropine, or a combination thereof. In some embodiments of an ophthalmic composition described herein, the muscarinic antagonist is atropine or a pharmaceutically acceptable salt of atropine. In some embodiments of an ophthalmic composition described herein, 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 4.5 after an extended period of time under a storage condition. In some embodiments of an ophthalmic composition described herein, 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 an extended period of time under a storage condition. In some embodiments of an ophthalmic composition described herein, 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 an extended period of time under a storage condition. In some embodiments of an ophthalmic composition described herein, 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 of an ophthalmic composition described herein, the storage condition has a storage temperature of from about 0°C to about 30°C, 2°C to about 10°C, or from about 16°C to about 26°C. In some embodiments of an ophthalmic composition described herein, the muscarinic antagonist is present in the ophthalmic composition at a concentration of one of: from about 0.001 wt% to about 0.40 wt%, from about 0.001 wt% to about 0.30 wt%, from about 0.001 wt% to about 0.20 wt%, from about 0.001 wt% to about 0.10 wt%, from about 0.001 wt% to about 0.09 wt%, from about 0.001 wt% to about 0.08 wt%, from about 0.001 wt% to about 0.07 wt%, from about 0.001 wt% to about 0.06 wt%, from about 0.001 wt% to about 0.05 wt%, 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 of an ophthalmic composition described herein, the muscarinic antagonist is present in the ophthalmic composition at a concentration from about 0.001 wt% to about 0.10 wt%. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition further comprises 0.004 wt% to about 0.20 wt% citrate. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition further comprises an osmolarity adjusting agent. In some embodiments of an ophthalmic composition described herein, the osmolarity adjusting agent is sodium chloride. In some embodiments of an ophthalmic composition described herein, the sodium chloride is present in the ophthalmic composition at a concentration of one of: from about 0.01 wt% to about 1.0 wt%, from about 0.05 wt% to about 1.5 wt%, from about 0.075 wt% to about 2.0 wt%, or from about 0.1 wt% to about 3.0 wt%. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition further comprises a buffering agent. In some embodiments of an ophthalmic composition described herein, the buffering 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. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof. In some embodiments of an ophthalmic composition described herein, 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 of an ophthalmic composition described herein, 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. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition further comprises a pH adjusting agent. In some embodiments of an ophthalmic

composition described herein, the pH adjusting agent comprises DCl, HCl, NaOH, NaOD, CD₃COOD, C₆D₈O₇, CH₃COOH, C₆H₈O₇, or combinations thereof. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition comprises one of: less than 5% of water (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 of an ophthalmic composition described herein, the ophthalmic composition is not formulated as an injectable formulation. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition is formulated as an ophthalmic solution for treatment of pre-myopia, myopia, progression of myopia, or slowing progression of myopia.

[0004] Provided herein are ophthalmic compositions comprising from about 0.001 wt% to about 0.5 wt% of a muscarinic antagonist, deuterated water, at a pH of from about 4.2 to about 7.9, and one or more sodium phosphate buffers. In some embodiments of an ophthalmic composition described herein, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine, homatropine, or a combination thereof. In some embodiments of an ophthalmic composition described herein, the muscarinic antagonist is atropine or a pharmaceutically acceptable salt of atropine. In some embodiments of an ophthalmic composition described herein, a first sodium phosphate buffer of the one or more sodium phosphate buffers is monosodium phosphate anhydrous. In some embodiments of an ophthalmic composition described herein, the monosodium phosphate anhydrous is present in the ophthalmic composition at a concentration of about 0.004 wt% to about 0.20 wt%. In some embodiments of an ophthalmic composition described herein, a second sodium phosphate buffer of the one or more sodium phosphate buffers is disodium phosphate anhydrous. In some embodiments of an ophthalmic composition described herein, the disodium phosphate anhydrous is present in the ophthalmic composition at a concentration of about 0.050 wt% to about 2.0 wt%. In some embodiments of an ophthalmic composition described herein, 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 4.5 after an extended period of time under a storage condition. In some embodiments of an ophthalmic composition described herein, 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 an extended period of time under a storage condition. In some embodiments of an ophthalmic composition described herein, 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 an extended period of time under a storage condition. In some embodiments of an ophthalmic composition described herein, 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 of an ophthalmic composition described herein, the storage condition has a storage temperature of from about 0°C to about 30°C, 2°C to about 10°C or from about 16°C to about 26°C. In some embodiments of an ophthalmic composition described herein, the muscarinic antagonist is present in the ophthalmic composition at a concentration of one of: from about 0.001 wt% to about 0.40 wt%, from about 0.001 wt% to about 0.30 wt%, from about 0.001 wt% to about 0.20 wt%, from about 0.001 wt% to about 0.10 wt%, from about 0.001 wt% to about 0.09 wt%, from about 0.001 wt% to about 0.08 wt%, from about 0.001 wt% to about 0.07 wt%, from about 0.001 wt% to about 0.06 wt%, from about 0.001 wt% to about 0.05 wt%, 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 of an ophthalmic composition described herein, the muscarinic antagonist is present in the ophthalmic composition at a concentration from about 0.001 wt% to about 0.10 wt%. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition is essentially free of citrate and acetate buffering agents. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition further comprises an osmolarity adjusting agent. In some embodiments of an ophthalmic composition described herein, the osmolarity adjusting agent is sodium chloride. In some embodiments of an ophthalmic composition described herein, the sodium chloride is present in the ophthalmic composition at a concentration of one of: from about 0.01 wt% to about 1.0 wt%, from about 0.05 wt% to about 1.5 wt%, from about 0.075 wt% to about 2.0 wt%, or from about 0.1 wt% to about 3.0 wt%. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition is free of a preservative selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition is substantially free of a benzalkonium chloride preservative. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition is substantially free of any preservative. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition further comprises a buffering agent. In some embodiments of an ophthalmic composition described herein, the buffering 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. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition further comprises EDTA. In some embodiments of an ophthalmic composition described herein, the EDTA is present in the ophthalmic composition at a concentration of 0.01 wt% to about 0.50 wt%. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof. In some embodiments of an ophthalmic composition described herein, 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 of an ophthalmic composition described herein, 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. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition further comprises a pH adjusting agent. In some embodiments of an ophthalmic composition described herein, the pH adjusting agent comprises DCl, HCl, NaOH, NaOD, CD₃COOD, C₆D₈O₇, CH₃COOH, C₆H₈O₇, or combinations thereof. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition comprises one of: less than 5% of water (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 of an ophthalmic composition described herein, the ophthalmic composition is not formulated as an injectable formulation. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition is formulated as an ophthalmic solution for treatment of pre-myopia, myopia, progression of myopia, or slowing progression of myopia.

[0005] Provided herein are ophthalmic compositions comprising from about 0.001 wt% to about 0.5 wt% of a muscarinic antagonist, deuterated water, at a pH of from about 4.2 to about 7.9, and 0.01 wt% to about 0.50 wt% EDTA. In some embodiments of an ophthalmic composition described herein, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine, homatropine, or a combination thereof. In some embodiments of an ophthalmic composition described herein, the muscarinic antagonist is atropine or pharmaceutically acceptable salt of atropine. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition further comprises one or more sodium phosphate buffers. In some embodiments of an ophthalmic composition described herein, a first sodium phosphate buffer of the one or more sodium phosphate buffers is monosodium phosphate anhydrous. In some embodiments of an ophthalmic composition described herein, the monosodium phosphate anhydrous is present in the ophthalmic composition at a concentration of about 0.004 wt% to about 0.20 wt%. In some embodiments of an ophthalmic composition described herein, a second sodium phosphate of the one or more sodium phosphate buffers is disodium phosphate anhydrous. In some embodiments of an ophthalmic composition described herein, the disodium phosphate anhydrous is present in the ophthalmic composition at a concentration of about 0.050 wt% to about 2.0 wt%. In some embodiments of an ophthalmic composition described herein, 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 4.5 after an extended period of time under a storage condition. In some embodiments of an ophthalmic composition described herein, 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 an extended period of time

under a storage condition. In some embodiments of an ophthalmic composition described herein, 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 an extended period of time under a storage condition. In some embodiments of an ophthalmic composition described herein, 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 of an ophthalmic composition described herein, the storage condition has a storage temperature of from about 0°C to about 30°C, 2°C to about 10°C, or from about 16°C to about 26°C. In some embodiments of an ophthalmic composition described herein, the muscarinic antagonist is present in the ophthalmic composition at a concentration of one of: from about 0.001 wt% to about 0.40 wt%, from about 0.001 wt% to about 0.30 wt%, from about 0.001 wt% to about 0.20 wt%, from about 0.001 wt% to about 0.10 wt%, from about 0.001 wt% to about 0.09 wt%, from about 0.001 wt% to about 0.08 wt%, from about 0.001 wt% to about 0.07 wt%, from about 0.001 wt% to about 0.06 wt%, from about 0.001 wt% to about 0.05 wt%, 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 of an ophthalmic composition described herein, the muscarinic antagonist is present in the ophthalmic composition at a concentration from about 0.001 wt% to about 0.10 wt%. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition further comprises 0.004 wt% to about 0.20 wt% citrate. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition further comprises an osmolarity adjusting agent. In some embodiments of an ophthalmic composition described herein, the osmolarity adjusting agent is sodium chloride. In some embodiments of an ophthalmic composition described herein, the sodium chloride is present in the ophthalmic composition at a concentration of one of: from about 0.01 wt% to about 1.0 wt%, from about 0.05 wt% to about 1.5 wt%, from about 0.075 wt% to about 2.0 wt%, or from about 0.1 wt% to about 3.0 wt%. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition is free of a preservative selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition is substantially free of a benzalkonium chloride preservative. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition is substantially free of any preservative. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition further comprises a buffering agent. In some embodiments of an ophthalmic composition described herein, the buffering 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. In some embodiments of an

ophthalmic composition described herein, the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof. In some embodiments of an ophthalmic composition described herein, 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 of an ophthalmic composition described herein, 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. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition further comprises a pH adjusting agent. In some embodiments of an ophthalmic composition described herein, the pH adjusting agent comprises DCl, HCl, NaOH, NaOD, CD_3COOD , $\text{C}_6\text{D}_8\text{O}_7$, CH_3COOH , $\text{C}_6\text{H}_8\text{O}_7$, or combinations thereof. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition comprises one of: less than 5% of water (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 . In some embodiments of an ophthalmic composition described herein, the ophthalmic composition is not formulated as an injectable formulation. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition is formulated as an ophthalmic solution for treatment of pre-myopia, myopia, progression of myopia, or slowing progression of myopia.

[0006] Provided herein are ophthalmic compositions comprising from about 0.001 wt% to about 0.5 wt% of a muscarinic antagonist, deuterated water, at a pH of from about 4.2 to about 7.9, and water, wherein a ratio of the water to the deuterated water is in a range of about 99:1 to about 1:99. In some embodiments of an ophthalmic composition described herein, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscyne, scopolamine, tropicamide, cyclopentolate, pirenzepine, homatropine, or a combination thereof. In some embodiments of an ophthalmic composition described herein, the muscarinic antagonist is atropine or pharmaceutically acceptable salt of atropine. In some embodiments of an ophthalmic composition described herein, 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 4.5 after an extended period of time under a storage condition. In some embodiments of an ophthalmic composition described herein, 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 an extended period of time under a storage condition. In some embodiments of an ophthalmic composition described herein, 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 an extended period of time under a storage condition. In some embodiments of an ophthalmic composition described herein, 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 of an ophthalmic composition described herein, the storage condition has a storage temperature of from about 0°C to about 30°C, 2°C to about 10°C, or from about 16°C to about 26°C. In some embodiments of an ophthalmic composition described herein, the muscarinic antagonist is present in the ophthalmic composition at a concentration of one of: from about 0.001 wt% to about 0.40 wt%, from about 0.001 wt% to about 0.30 wt%, from about 0.001 wt% to about 0.20 wt%, from about 0.001 wt% to about 0.10 wt%, from about 0.001 wt% to about 0.09 wt%, from about 0.001 wt% to about 0.08 wt%, from about 0.001 wt% to about 0.07 wt%, from about 0.001 wt% to about 0.06 wt%, from about 0.001 wt% to about 0.05 wt%, 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 of an ophthalmic composition described herein, the muscarinic antagonist is present in the ophthalmic composition at a concentration from about 0.001 wt% to about 0.10 wt%. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition further comprises 0.004 wt% to about 0.20 wt% citrate. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition further comprises one or more sodium phosphate buffers. In some embodiments of an ophthalmic composition described herein, a first sodium phosphate buffer of the one or more sodium phosphate buffers is monosodium phosphate anhydrous. In some embodiments of an ophthalmic composition described herein, the monosodium phosphate anhydrous is present in the ophthalmic composition at a concentration of about 0.004 wt% to about 0.20 wt%. In some embodiments of an ophthalmic composition described herein, a second sodium phosphate of the one or more sodium phosphate buffers is disodium phosphate anhydrous. In some embodiments of an ophthalmic composition described herein, the disodium phosphate anhydrous is present in the ophthalmic composition at a concentration of about 0.050 wt% to about 2.0 wt%. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition further comprises an osmolarity adjusting agent. In some embodiments of an ophthalmic composition described herein, the osmolarity adjusting agent is sodium chloride. In some embodiments of an ophthalmic composition described herein, the sodium chloride is present in the ophthalmic composition at a concentration of one of: from about 0.01 wt% to about 1.0 wt%, from about 0.05 wt% to about 1.5 wt%, from about 0.075 wt% to about 2.0 wt%, or from about 0.1 wt% to about 3.0 wt%. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition is free of a preservative selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition is substantially free of a benzalkonium chloride preservative. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition is substantially free of any preservative. In some embodiments of an ophthalmic composition described herein, the ophthalmic

composition further comprises a buffering agent. In some embodiments of an ophthalmic composition described herein, the buffering 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. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition further comprises EDTA. In some embodiments of an ophthalmic composition described herein, the EDTA is present in the ophthalmic composition at a concentration of 0.01 wt% to about 0.50 wt%. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof. In some embodiments of an ophthalmic composition described herein, 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 of an ophthalmic composition described herein, 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. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition further comprises a pH adjusting agent. In some embodiments of an ophthalmic composition described herein, the pH adjusting agent comprises DCl, HCl, NaOH, NaOD, CD₃COOD, C₆D₈O₇, CH₃COOH, C₆H₈O₇, or combinations thereof. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition is not formulated as an injectable formulation. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition is formulated as an ophthalmic solution for treatment of pre-myopia, myopia, progression of myopia, or slowing progression of myopia. In some embodiments of an ophthalmic composition described herein, a ratio of the water to the deuterated water is in a range of about 95:5 to about 5:95, or in a range of about 90:10 to about 10:90, or in a range of about 80:20 to about 20:80, or in a range of about 80:20 to about 30:70, or in a range of about 80:30 to about 40:60, or in a range of about 90:10 to about 50:50, or in a range of about 80:20 to about 60:40. In some embodiments of an ophthalmic composition described herein, a ratio of the water to the deuterated water is about 50:50. In some embodiments of an ophthalmic composition described herein, the muscarinic antagonist is present in the ophthalmic composition at a concentration of from about 0.01 wt% to about 0.03 wt%. In some embodiments of an ophthalmic composition described herein, the muscarinic antagonist is present in the ophthalmic composition at a concentration of from about 0.01 wt% to about 0.05 wt%. In some embodiments of an ophthalmic composition described herein, the muscarinic antagonist is present in the ophthalmic composition at a concentration of about 0.01 wt%. In some embodiments of an ophthalmic composition described herein, the muscarinic antagonist is present in the ophthalmic composition at a concentration of about 0.03 wt%. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition is substantially free of a benzalkonium chloride preservative. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition has no detectable amount of a benzalkonium chloride preservative. In some embodiments of an ophthalmic composition described herein, the ophthalmic

composition has no detectable amount of a preservative. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition has a pH from about 5.1 to about 6.0. In some embodiments of an ophthalmic composition described herein, the ophthalmic composition has a pH from about 5.54 to about 5.59.

[0007] Provided herein are ophthalmic compositions comprising from about 0.001 wt% to about 0.5 wt% of a muscarinic antagonist and deuterated water, at a pH of from about 4.2 to about 7.9, wherein the ophthalmic composition is substantially free of a benzalkonium chloride preservative. In some embodiments, the ophthalmic composition is substantially free of a preservative selected from cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof. In some embodiments, the ophthalmic composition has no detectable amount of a benzalkonium chloride preservative. In some embodiments, the ophthalmic composition has no detectable amount of benzalkonium chloride. In some embodiments, the ophthalmic composition has no detectable amount of a preservative. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine or a pharmaceutically acceptable salt of atropine. In some embodiments, the muscarinic antagonist is present in the ophthalmic composition at a concentration of one of: from about 0.001 wt% to about 0.40 wt%, from about 0.001 wt% to about 0.30 wt%, from about 0.001 wt% to about 0.20 wt%, from about 0.001 wt% to about 0.10 wt%, from about 0.001 wt% to about 0.09 wt%, from about 0.001 wt% to about 0.08 wt%, from about 0.001 wt% to about 0.07 wt%, from about 0.001 wt% to about 0.06 wt%, from about 0.001 wt% to about 0.05 wt%, 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 muscarinic antagonist is present in the ophthalmic composition at a concentration from about 0.001 wt% to about 0.10 wt%. In some embodiments, the ophthalmic composition further comprises 0.004 wt% to about 0.20 wt% citrate. In some embodiments, the ophthalmic composition further comprises an osmolarity adjusting agent. In some embodiments, the osmolarity adjusting agent is sodium chloride. In some embodiments, the sodium chloride is present in the ophthalmic composition at a concentration of one of: from about 0.01 wt% to about 1.0 wt%, from about 0.05 wt% to about 1.5 wt%, from about 0.075 wt% to about 2.0 wt%, or from about 0.1 wt% to about 3.0 wt%. In some embodiments, the ophthalmic composition further comprises a buffering agent. In some embodiments, the buffering 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. In some embodiments, the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof. In some embodiments, the ophthalmic composition further comprises a pH adjusting agent. In some embodiments, the pH adjusting agent comprises DCl, HCl, NaOH, NaOD, CD₃COOD, C₆D₈O₇,

CH₃COOH, C₆H₈O₇, or combinations thereof. In some embodiments, the ophthalmic composition comprises less than about 10% of a degradant of the muscarinic antagonist formed from degradation of the muscarinic antagonist.

[0008] Provided herein are ophthalmic compositions comprising from about 0.001 wt% to about 0.5 wt% of a muscarinic antagonist, deuterated water, at a pH of from about 4.2 to about 7.9, and one or more sodium phosphate buffers, wherein at least one sodium phosphate buffer of the one or more sodium phosphate buffers is present in the ophthalmic composition at a concentration of about 0.004 wt% to about 0.20 wt%. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine or a pharmaceutically acceptable salt of atropine. In some embodiments, a first sodium phosphate buffer of the one or more sodium phosphate buffers is monosodium phosphate anhydrous. In some embodiments, the monosodium phosphate anhydrous is present in the ophthalmic composition at a concentration of about 0.004 wt% to about 0.20 wt%. In some embodiments, a second sodium phosphate buffer of the one or more sodium phosphate buffers is disodium phosphate anhydrous. In some embodiments, the disodium phosphate anhydrous is present in the ophthalmic composition at a concentration of about 0.050 wt% to about 2.0 wt%. In some embodiments, the muscarinic antagonist is present in the ophthalmic composition at a concentration of one of: from about 0.001 wt% to about 0.40 wt%, from about 0.001 wt% to about 0.30 wt%, from about 0.001 wt% to about 0.20 wt%, from about 0.001 wt% to about 0.10 wt%, from about 0.001 wt% to about 0.09 wt%, from about 0.001 wt% to about 0.08 wt%, from about 0.001 wt% to about 0.07 wt%, from about 0.001 wt% to about 0.06 wt%, from about 0.001 wt% to about 0.05 wt%, 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 muscarinic antagonist is present in the ophthalmic composition at a concentration from about 0.001 wt% to about 0.10 wt%. In some embodiments, the ophthalmic composition is essentially free of citrate and acetate buffering agents. In some embodiments, the ophthalmic composition further comprises an osmolarity adjusting agent. In some embodiments, the osmolarity adjusting agent is sodium chloride. In some embodiments, the sodium chloride is present in the ophthalmic composition at a concentration of one of: from about 0.01 wt% to about 1.0 wt%, from about 0.05 wt% to about 1.5 wt%, from about 0.075 wt% to about 2.0 wt%, or from about 0.1 wt% to about 3.0 wt%. In some embodiments, the ophthalmic composition is free of a preservative selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof. In some embodiments, the ophthalmic composition is substantially free of a benzalkonium chloride preservative. In some embodiments, the ophthalmic composition is substantially free of any preservative. In some embodiments, the ophthalmic composition further comprises a buffering agent. In some embodiments, the buffering 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. In some embodiments, the ophthalmic composition further comprises EDTA. In some embodiments, the EDTA is present in the ophthalmic composition at a concentration of 0.01 wt% to about 0.50 wt%. In some embodiments, the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof. In some embodiments, the ophthalmic composition further comprises a pH adjusting agent. In some embodiments, the pH adjusting agent comprises DCl, HCl, NaOH, NaOD, CD₃COOD, C₆D₈O₇, CH₃COOH, C₆H₈O₇, or combinations thereof.

[0009] Provided herein are ophthalmic compositions comprising from about 0.001 wt% to about 0.5 wt% of a muscarinic antagonist, deuterated water, at a pH of from about 4.2 to about 7.9, and 0.01 wt% to about 0.50 wt% EDTA. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine or pharmaceutically acceptable salt of atropine. In some embodiments, the ophthalmic composition further comprises one or more sodium phosphate buffers. In some embodiments, a first sodium phosphate buffer of the one or more sodium phosphate buffers is monosodium phosphate anhydrous. In some embodiments, the sodium phosphate anhydrous is present in the ophthalmic composition at a concentration of about 0.004 wt% to about 0.20 wt%. In some embodiments, a second sodium phosphate of the one or more sodium phosphate buffers is disodium phosphate anhydrous. In some embodiments, the disodium phosphate anhydrous is present in the ophthalmic composition at a concentration of about 0.050 wt% to about 2.0 wt%. In some embodiments, the muscarinic antagonist is present in the ophthalmic composition at a concentration of one of: from about 0.001 wt% to about 0.40 wt%, from about 0.001 wt% to about 0.30 wt%, from about 0.001 wt% to about 0.20 wt%, from about 0.001 wt% to about 0.10 wt%, from about 0.001 wt% to about 0.09 wt%, from about 0.001 wt% to about 0.08 wt%, from about 0.001 wt% to about 0.07 wt%, from about 0.001 wt% to about 0.06 wt%, from about 0.001 wt% to about 0.05 wt%, 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 muscarinic antagonist is present in the ophthalmic composition at a concentration from about 0.001 wt% to about 0.10 wt%. In some embodiments, the ophthalmic composition further comprises 0.004 wt% to about 0.20 wt% citrate. In some embodiments, the ophthalmic composition further comprises an osmolarity adjusting agent. In some embodiments, the osmolarity adjusting agent is sodium chloride. In some embodiments, the sodium chloride is present in the ophthalmic composition at a concentration of one of: from about 0.01 wt% to about 1.0 wt%, from about 0.05 wt% to about 1.5 wt%, from about 0.075 wt% to about 2.0 wt%, or from about 0.1 wt% to about 3.0 wt%. In some embodiments, the ophthalmic composition is free of a preservative selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium,

polyhexamethylene biguanide, or combinations thereof. In some embodiments, the ophthalmic composition is substantially free of a benzalkonium chloride preservative. In some embodiments, the ophthalmic composition is substantially free of any preservative. In some embodiments, the ophthalmic composition further comprises a buffering agent. In some embodiments, the buffering 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. In some embodiments, the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof. In some embodiments, the ophthalmic composition further comprises a pH adjusting agent. In some embodiments, the pH adjusting agent comprises DCl, HCl, NaOH, NaOD, CD₃COOD, C₆D₈O₇, CH₃COOH, C₆H₈O₇, or combinations thereof.

[0010] Provided herein are ophthalmic compositions comprising from about 0.001 wt% to about 0.5 wt% of a muscarinic antagonist, deuterated water, at a pH of from about 4.2 to about 7.9, and water, wherein a ratio of the water to the deuterated water is in a range of 60:40 to 99:1. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine, homatropine, or a combination thereof. In some embodiments, the muscarinic antagonist is atropine or pharmaceutically acceptable salt of atropine. In some embodiments, the muscarinic antagonist is present in the ophthalmic composition at a concentration of one of: from about 0.001 wt% to about 0.40 wt%, from about 0.001 wt% to about 0.30 wt%, from about 0.001 wt% to about 0.20 wt%, from about 0.001 wt% to about 0.10 wt%, from about 0.001 wt% to about 0.09 wt%, from about 0.001 wt% to about 0.08 wt%, from about 0.001 wt% to about 0.07 wt%, from about 0.001 wt% to about 0.06 wt%, from about 0.001 wt% to about 0.05 wt%, 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 muscarinic antagonist is present in the ophthalmic composition at a concentration from about 0.001 wt% to about 0.10 wt%. In some embodiments, a ratio of the water to the deuterated water is in a range of about 80:20 to about 60:40. In some embodiments, a ratio of the water to the deuterated water is about 65:35. In some embodiments, a ratio of the water to the deuterated water is about 90:10. In some embodiments, the muscarinic antagonist is present in the ophthalmic composition at a concentration of from about 0.01 wt% to about 0.05 wt%. In some embodiments, the muscarinic antagonist is present in the ophthalmic composition at a concentration of from about 0.01 wt% to about 0.03 wt%. In some embodiments, the muscarinic antagonist is present in the ophthalmic composition at a concentration of about 0.01 wt%. In some embodiments, the muscarinic antagonist is present in the ophthalmic composition at a concentration of about 0.03 wt%. In some embodiments, the ophthalmic composition is substantially free of a benzalkonium chloride preservative. In some embodiments, the ophthalmic composition has no detectable amount of a benzalkonium chloride preservative. In some embodiments, the ophthalmic composition has no detectable amount of a preservative. In some embodiments, the ophthalmic composition has a pH from about 5.1 to about 6.0.

In some embodiments, the ophthalmic composition has a pH from about 5.54 to about 5.59. In some embodiments, the ophthalmic composition further comprises 0.004 wt% to about 0.20 wt% citrate. In some embodiments, the ophthalmic composition further comprises one or more sodium phosphate buffers. In some embodiments, a first sodium phosphate buffer of the one or more sodium phosphate buffers is monosodium phosphate anhydrous. In some embodiments, the monosodium phosphate anhydrous is present in the ophthalmic composition at a concentration of about 0.004 wt% to about 0.20 wt%. In some embodiments, a second sodium phosphate of the one or more sodium phosphate buffers is disodium phosphate anhydrous. In some embodiments, the disodium phosphate anhydrous is present in the ophthalmic composition at a concentration of about 0.050 wt% to about 2.0 wt%. In some embodiments, the ophthalmic composition further comprises an osmolarity adjusting agent. In some embodiments, the osmolarity adjusting agent is sodium chloride. In some embodiments, the sodium chloride is present in the ophthalmic composition at a concentration of one of: from about 0.01 wt% to about 1.0 wt%, from about 0.05 wt% to about 1.5 wt%, from about 0.075 wt% to about 2.0 wt%, or from about 0.1 wt% to about 3.0 wt%. In some embodiments, the ophthalmic composition is free of a preservative selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof. In some embodiments, the ophthalmic composition is substantially free of a benzalkonium chloride preservative. In some embodiments, the ophthalmic composition is substantially free of any preservative. In some embodiments, the ophthalmic composition further comprises a buffering agent. In some embodiments, the buffering 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. In some embodiments, the ophthalmic composition further comprises EDTA. In some embodiments, the EDTA is present in the ophthalmic composition at a concentration of 0.01 wt% to about 0.50 wt%. In some embodiments, the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof. In some embodiments, the ophthalmic composition further comprises a pH adjusting agent. In some embodiments, the pH adjusting agent comprises DCl, HCl, NaOH, NaOD, CD₃COOD, C₆D₈O₇, CH₃COOH, C₆H₈O₇, or combinations thereof. In some embodiments, the ophthalmic composition comprises less than about 10% of a degradant of the muscarinic antagonist formed from degradation of the muscarinic antagonist.

[0011] Provided herein are ophthalmic compositions, wherein the ophthalmic composition is formulated as an ophthalmic solution for treatment of pre-myopia, myopia, progression of myopia, or slowing progression of myopia.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] The novel features of the inventions disclosed herein are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present inventions will be

obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the inventions are utilized, and the accompanying drawings of which:

[0013] FIG. 1 shows a first order rate plot.

[0014] FIG. 2 shows the rate of tropic acid formation per month for ophthalmic compositions at 25°C (black bars) or 40°C (white bars).

[0015] FIG. 3 shows relationships of the ratio between tropic acid formation rate constants at 25°C and 40°C to the ratio of deuterated water to water in ophthalmic compositions (v/v).

[0016] FIG. 4 shows experimentally determined relationships between tropic acid formation and pH of ophthalmic compositions, in accordance with embodiments.

[0017] FIG. 5 shows experimentally determined relationships between tropic acid formation rate and ratios of deuterated water to water (v/v) in ophthalmic compositions, in accordance with embodiments.

[0018] FIG. 6 shows relationships between perceived pH and ratios of deuterated water to water in ophthalmic compositions (v/v), in accordance with embodiments.

[0019] FIG. 7 shows relationships between rate constant of tropic acid formation (k/mo) at 25°C and ratios of deuterated water to water in ophthalmic compositions (v/v), in accordance with embodiments.

[0020] FIG. 8 shows experimentally determined rate constants of tropic acid formation (k/mo) of ophthalmic compositions, in accordance with embodiments.

[0021] FIG. 9 shows the effect of pH and temperature on rate of tropic acid formation (100% D₂O).

DETAILED DESCRIPTION OF THE DISCLOSURE

[0022] 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.

[0023] Further, the present disclosure recognizes the need for an ophthalmic composition stabilized without the need for a preservative. The present disclosure recognizes a need for an ophthalmic composition that is substantially free of a preservative.

[0024] The present disclosure recognizes that a 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.

[0025] 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.

[0026] 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.

[0027] Still further, the present disclosure recognizes that some muscarinic antagonist (e.g. atropine) liquid compositions formulated at lower concentrations (e.g. 0.001% to 0.50%) present stability challenges that are less so in higher concentrations. Without wishing to be bound by any particular theory, it is contemplated that some muscarinic antagonists (e.g. atropine) contribute 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 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.

[0028] 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.

[0029] 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.

[0030] **Ophthalmic Compositions**

[0031] 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 0.50 wt% or from about 0.001 wt% to about 0.10 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.

[0032] 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 0.50 wt% or from about 0.001 wt% to about 0.10 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.

[0033] 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, scopolamine (L-hyoscine), hydroxyzine, ipratropium, tropicamide, cyclopentolate, pirenzepine, 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, scopolamine, tropicamide, cyclopentolate, pirenzepine, 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.

[0034] 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, scopolamine (L-hyoscine), hydroxyzine, ipratropium, tropicamide, cyclopentolate, pirenzepine, 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, scopolamine, tropicamide, cyclopentolate, pirenzepine, or homatropine. In some embodiments, the muscarinic antagonist is atropine or a pharmaceutically acceptable salt or prodrug thereof.

[0035] 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, scopolamine (L-hyoscine), hydroxyzine, ipratropium, tropicamide, cyclopentolate, pirenzepine, 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, scopolamine, tropicamide, cyclopentolate, pirenzepine, homatropine, or any combination thereof. In some embodiments, the muscarinic antagonist is atropine or a pharmaceutically acceptable salt or prodrug thereof.

[0036] 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, scopolamine (L-hyoscine), hydroxyzine, ipratropium, tropicamide, cyclopentolate, pirenzepine, homatropine, solifenacin, darifenacin, benztropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, or tolterodine; in combination with one or more of sympathetic agonists: phenylephrine or hydroxyamphetamine.

[0037] According to another aspect of the disclosure, described herein is an ophthalmic composition comprising one or more ophthalmic agents. In some instances, a first ophthalmic agent of the one or more ophthalmic agents is a muscarinic antagonist. In some instances, a second ophthalmic agent of the one or more ophthalmic agent is aflibercept, ranibizumab, pegaptanib, cyclopentolate, phenylephrine, homatropine, scopolamine, cyclopentolate/phenylephrine, phenylephrine/scopolamine, tropicamide, ketorolac/phenylephrine, hydroxyamphetamine/tropicamide, cysteamine, ocriplasmin, mitomycin, dapiprazole, lidocaine, proparacaine, 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/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, benztropine, mebeverine, procyclidine, acridinium bromide,

trihexyphenidyl/benzhexol, tolterodine, aceclidine, or any combinations thereof. In some embodiments, the ophthalmic agent is aceclidine, tropicamide, pilocarpine, or combinations thereof.

[0038] According to another aspect of the disclosure, described herein is an ophthalmic composition comprising an ophthalmic agent, wherein the ophthalmic agent is aflibercept, ranibizumab, pegaptanib, cyclopentolate, phenylephrine, homatropine, scopolamine, cyclopentolate/phenylephrine, phenylephrine/scopolamine, tropicamide, ketorolac/phenylephrine, hydroxyamphetamine/tropicamide, cysteamine, ocriplasmin, mitomycin, dapiprazole, lidocaine, proparacaine, 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/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, benztropine, mebeverine, procyclidine, aclidinium bromide, trihexyphenidyl/benzhexol, tolterodine, aceclidine, or any combinations thereof. In some embodiments, the ophthalmic agent is aceclidine, tropicamide, pilocarpine, or combinations thereof.

[0039] In some embodiments, the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof. In some embodiments, the ophthalmic composition is substantially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof. In some instances, the ophthalmic composition has no detectable amount of procaine and benactyzine, or pharmaceutically acceptable salts thereof.

[0040] 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 0.50 wt% or from about 0.001 wt% to about 0.10 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.

[0041] Provided herein is an ophthalmic composition containing low concentrations of atropine or a pharmaceutically acceptable salt or prodrug thereof. In some embodiments, the ophthalmic composition includes from about 0.001 wt% to about 0.50 wt% or from about 0.001 wt% to about 0.10 wt% of atropine or a pharmaceutically acceptable salt or prodrug thereof 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.

[0042] In some embodiments, the ophthalmic disorder or condition is pre-myopia, myopia or progression of myopia.

[0043] 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. 1 wt% or higher).

[0044] 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 0.50 wt% or from about 0.001 wt% to about 0.10 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.

[0045] In some embodiments of an ophthalmic composition described herein, the muscarinic antagonist is present in the ophthalmic composition at a concentration of one of: from about 0.001 wt% to about 0.40 wt%, from about 0.001 wt% to about 0.30 wt%, from about 0.001 wt% to about 0.20 wt%, from about 0.001 wt% to about 0.10 wt%, from about 0.001 wt% to about 0.09 wt%, from about 0.001 wt% to about 0.08 wt%, from about 0.001 wt% to about 0.07 wt%, from about 0.001 wt% to about 0.06 wt%, from about 0.001 wt% to about 0.05 wt%, 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 of an ophthalmic composition described herein, the muscarinic antagonist is present in the ophthalmic composition at a concentration from about 0.001 wt% to about 0.10 wt%. In some embodiments of an ophthalmic composition described herein, the muscarinic antagonist is atropine or its pharmaceutically acceptable salt.

[0046] In some embodiments of an ophthalmic composition described herein, the atropine or its pharmaceutically acceptable salt is present in the ophthalmic composition at a concentration of one of: from about 0.001 wt% to about 0.40 wt%, from about 0.001 wt% to about 0.30 wt%, from about 0.001 wt% to about 0.20 wt%, from about 0.001 wt% to about 0.10 wt%, from about 0.001 wt% to about 0.09 wt%, from about 0.001 wt% to about 0.08 wt%, from about 0.001 wt% to about 0.07 wt%, from about 0.001 wt% to about 0.06 wt%, from about 0.001 wt% to about 0.05 wt%, 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 of an ophthalmic composition described herein, the atropine or its pharmaceutically acceptable salt is present in the ophthalmic composition at a concentration from about 0.001 wt% to about 0.10 wt%.

[0047] In some embodiments of an ophthalmic composition described herein, the muscarinic antagonist is present in the ophthalmic composition at a concentration of one of: from about 0.001 mg/g to about 0.40 mg/g, from about 0.001 mg/g to about 0.30 mg/g, from about 0.001 mg/g to about 0.20 mg/g, from about 0.001 mg/g to about 0.10 mg/g, from about 0.001 mg/g to about 0.09 mg/g, from about 0.01 mg/g to about 0.40 mg/g, from about 0.01 mg/g to about 0.30 mg/g, from about 0.01 mg/g to about 0.20 mg/g, from about 0.01 mg/g to about 0.10 mg/g, from about 0.01 mg/g to about 0.09 mg/g, from about 0.01 mg/g to about 0.08 mg/g, from about 0.01 mg/g to about 0.07 mg/g, from about 0.01 mg/g to about 0.06 mg/g, from about 0.01 mg/g to about 0.05 mg/g, from about 0.01 mg/g to about 0.04 mg/g, from about 0.01 mg/g to about 0.03 mg/g, from about 0.01 mg/g to about 0.025 mg/g, from about 0.01 mg/g to about 0.02 mg/g, from about 0.01 mg/g to about 0.1 mg/g, from about 0.01 mg/g to about 0.25 mg/g, from about 0.01 mg/g to about 0.5 mg/g, from about 0.01 mg/g to about 0.75 mg/g, from about 0.01 mg/g to about 1.0 mg/g. In some embodiments of an ophthalmic composition described herein, the muscarinic antagonist is present in the ophthalmic composition at a concentration from about 0.01 mg/g to about 0.5 mg/g.

[0048] In some embodiments of an ophthalmic composition described herein, the atropine or its pharmaceutically acceptable salt is present in the ophthalmic composition at a concentration of one of: from about 0.001 mg/g to about 0.40 mg/g, from about 0.001 mg/g to about 0.30 mg/g, from about 0.001 mg/g to about 0.20 mg/g, from about 0.001 mg/g to about 0.10 mg/g, from about 0.001 mg/g to about 0.09 mg/g, from about 0.01 mg/g to about 0.40 mg/g, from about 0.01 mg/g to about 0.30 mg/g, from about 0.01 mg/g to about 0.20 mg/g, from about 0.01 mg/g to about 0.10 mg/g, from about 0.01 mg/g to about 0.09 mg/g, from about 0.01 mg/g to about 0.08 mg/g, from about 0.01 mg/g to about 0.07 mg/g, from about 0.01 mg/g to about 0.06 mg/g, from about 0.01 mg/g to about 0.05 mg/g, from about 0.01 mg/g to about 0.04 mg/g, from about 0.01 mg/g to about 0.03 mg/g, from about 0.01 mg/g to about 0.025 mg/g, from about 0.01 mg/g to about 0.02 mg/g, from about 0.01 mg/g to about 0.1 mg/g, from about 0.01 mg/g to about 0.25 mg/g, from about 0.01 mg/g to about 0.5 mg/g, from about 0.01 mg/g to about 0.75 mg/g, from about 0.01 mg/g to about 1.0 mg/g. In some embodiments of an ophthalmic

composition described herein, the atropine or its pharmaceutically acceptable salt is present in the ophthalmic composition at a concentration from about 0.01 mg/g to about 0.5 mg/g.

[0049] In some embodiments of an ophthalmic composition described herein, the muscarinic antagonist is present in the ophthalmic composition at a concentration of one of: from about 0.0001 mg to about 0.040 mg, from about 0.0001 mg to about 0.030 mg, from about 0.0001 mg to about 0.020 mg, from about 0.0001 mg to about 0.010 mg, from about 0.0001 mg to about 0.009 mg, from about 0.001 mg to about 0.040 mg, from about 0.001 mg to about 0.030 mg, from about 0.001 mg to about 0.020 mg, from about 0.001 mg to about 0.010 mg, from about 0.001 mg to about 0.009 mg, from about 0.001 mg to about 0.008 mg, from about 0.001 mg to about 0.007 mg, from about 0.001 mg to about 0.006 mg, from about 0.001 mg to about 0.005 mg, from about 0.001 mg to about 0.004 mg, from about 0.001 mg to about 0.003 mg, from about 0.001 mg to about 0.0025 mg, from about 0.001 mg to about 0.002 mg, from about 0.001 mg to about 0.01 mg, from about 0.001 mg to about 0.025 mg, from about 0.001 mg to about 0.05 mg, from about 0.001 mg to about 0.075 mg, from about 0.001 mg to about 1.0 mg. In some embodiments of an ophthalmic composition described herein, the muscarinic antagonist is present in the ophthalmic composition at a concentration from about 0.0003 mg to about 0.025 mg or 0.001 mg to about 0.05 mg.

[0050] In some embodiments of an ophthalmic composition described herein, the atropine or its pharmaceutically acceptable salt is present in the ophthalmic composition at a concentration of one of: from about 0.0001 mg to about 0.040 mg, from about 0.0001 mg to about 0.030 mg, from about 0.0001 mg to about 0.020 mg, from about 0.0001 mg to about 0.010 mg, from about 0.0001 mg to about 0.009 mg, from about 0.001 mg to about 0.040 mg, from about 0.001 mg to about 0.030 mg, from about 0.001 mg to about 0.020 mg, from about 0.001 mg to about 0.010 mg, from about 0.001 mg to about 0.009 mg, from about 0.001 mg to about 0.008 mg, from about 0.001 mg to about 0.007 mg, from about 0.001 mg to about 0.006 mg, from about 0.001 mg to about 0.005 mg, from about 0.001 mg to about 0.004 mg, from about 0.001 mg to about 0.003 mg, from about 0.001 mg to about 0.0025 mg, from about 0.001 mg to about 0.002 mg, from about 0.001 mg to about 0.01 mg, from about 0.001 mg to about 0.025 mg, from about 0.001 mg to about 0.05 mg, from about 0.001 mg to about 0.075 mg, from about 0.001 mg to about 1.0 mg. In some embodiments of an ophthalmic composition described herein, the atropine or its pharmaceutically acceptable salt is present in the ophthalmic composition at a concentration from about 0.0003 mg to about 0.025 mg or 0.001 mg to about 0.05 mg.

[0051] 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.

[0052] 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.

[0053] 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.

[0054] Described herein, in some embodiments, is an ophthalmic composition substantially free of a preservative. In some instances, composition substantially free of benzalkonium chloride preservative. In some instances, the composition has no detectable amount of a benzalkonium chloride preservative. In some instances, the composition has no detectable amount of a benzalkonium chloride. In some instances, the composition is substantially free of a preservative selected from cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof. In some instances, the composition has no detectable amount of a preservative. In some instances, the composition is substantially free of any preservative.

[0055] In some embodiments, the ophthalmic composition comprises one more sodium phosphate buffers. In some instances, a sodium phosphate of the one or more sodium phosphate buffers is monosodium phosphate anhydrous. In some instances, a sodium phosphate of the one or more sodium phosphate buffers is disodium phosphate anhydrous. The concentration of the sodium phosphate, in some embodiments, is between about 0.001% to about 0.20%, between about 0.004% to about 0.20%, between about 0.005% to about 0.20%, between about 0.010% to about 0.20%, between about 0.015% to about 0.20%, between about 0.020% to about 0.20%, between about 0.025% to about 0.20%, between about 0.030% to about 0.20%, between about 0.035% to about 0.20%, between about 0.040% to about 0.20%, or between about 0.045% to about 0.20% by weight of the composition. In some embodiments, the sodium phosphate is between about 0.01% to about 2.0%, between about 0.04% to about 2.0%, between about 0.05% to about 2.0%, between about 0.010% to about 2.0%, between about 0.015% to about 2.0%, between about 0.020% to about 2.0%, between about 0.025% to about 2.0%, between about 0.030% to about 2.0%, between about 0.035% to about 2.0%, between about 0.040% to about 2.0%, or between about 0.045% to about 2.0% by weight of the composition. In some instances, the sodium phosphate is present in the ophthalmic composition at a concentration of at least or about 0.001%, 0.002%, 0.003%, 0.004%, 0.005%, 0.006%, 0.007%, 0.008%, 0.009%, 0.010%, 0.020%, 0.030%, 0.040%, 0.050%, 0.060%, 0.070%, 0.080%, 0.090%, 0.10%, 0.20%, 0.30%, 0.40%, 0.50%, 0.60%, 0.70%, 0.80%, 0.90%, 1.0%, 2.0%, 3.0%, 4.0%, or more than 4.0% by weight of the composition.

[0056] Described herein, in some embodiments, is an ophthalmic composition comprising EDTA. In some embodiments, EDTA is present in the composition at about 0.001%, 0.005%, 0.010%, 0.015%, 0.020%, 0.025%, 0.030%, 0.035%, 0.040%, 0.045%, 0.050%, 0.055%, 0.060%, 0.065%, 0.070%, 0.075%, 0.080%, 0.085%, 0.090%, 0.095%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1.0%, 1.5%, 2.0%, 2.5%, or 3.0%. In some embodiments, EDTA is present in the composition from about 0.01% to about 0.05%, from about 0.01% to about 0.04%, from about 0.01% to about 0.03%, from about 0.01% to about 0.025%, from about 0.01% to about 0.02%, from about 0.001% to about 0.01%, from about 0.001% to about 0.008%, or from about 0.001% to about 0.005%. In some cases, the percentage is a weight percentage.

[0057] Described herein, in some embodiments, is an ophthalmic composition comprising variations ratios of water (H₂O) to deuterated water (D₂O). In some instances, the ratio of the water to the deuterated water is in a range of about 99:1 to about 1:99. In some instances, the ratio of the water to the deuterated water is in a range of about 99:1 to about 5:95, about 99:1 to about 10:90, about 99:1 to about 20:80, about 99:1 to about 30:70, about 99:1 to about 40:60, about 99:1 to about 50:50, about 99:1 to about 60:40, about 99:1 to about 70:30, about 99:1 to about 80:20, or about 99:1 to about 90:10. In some instances, the ratio of the water to the deuterated water is in a range of about 5:95 to about 1:99, about 10:90 to about 1:99, about 20:80 to about 1:99, about 30:70 to about 1:99, about 40:60 to about 1:99, about 50:50 to about 1:99, about 60:40 to about 1:99, about 70:30 to about 1:99, about 80:20 to about 1:99, or about 90:10 to about 1:99. In some instances, the ratio of the water to the deuterated water is about 99:1, about 98:2, about 97:3, about 96:4, about 95:5, about 94:6, about 93:7, about 92:8, about 91:9, about 90:10, about 89:11, about 88:12, about 87:13, about 86:14, about 85:15, about 84:16, about 83:17, about 82:18, about 81:19, about 80:20, about 79:21, about 78:22, about 77:23, about 76:24, about 75:25, about 74:26, about 73:27, about 72:28, about 71:29, about 70:30, about 69:31, about 68:32, about 67:33, about 66:34, about 65:35, about 64:36, about 63:37, about 62:38, about 61:39, about 60:40, about 59:41, about 58:42, about 57:43, about 56:44, about 55:45, about 54:46, about 53:47, about 52:48, about 51:49, about 50:50, about 49:51, about 48:52, about 47:53, about 46:54, about 45:55, about 44:56, about 43:57, about 42:58, about 41:59, about 40:60, about 39:61, about 38:62, about 37:63, about 36:64, about 35:65, about 34:66, about 33:67, about 32:68, about 31:69, about 30:70, about 29:71, about 28:72, about 27:73, about 26:74, about 25:75, about 24:76, about 23:77, about 22:78, about 21:79, about 20:80, about 19:81, about 18:82, about 17:83, about 16:84, about 15:85, about 14:86, about 13:87, about 12:88, about 11:89, about 10:90, about 9:91, about 8:92, about 7:93, about 6:94, about 5:95, about 4:96, about 3:97, about 2:98, or about 1:99.

[0058] Ophthalmic Solution Compositions

[0059] 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 0.50 wt% or from about 0.001 wt% to about 0.10 wt% of a muscarinic antagonist and deuterated water. As used herein, deuterated water refers to D₂O, DHO, heavy water, and/or deuterium oxide. DHO comprises a mixture of H₂O and D₂O.

[illegible]

In some embodiments, the concentration of the ophthalmic agent (e.g. muscarinic antagonist) is based on an initial concentration after an extended period of time under a storage condition.

[0061] In some embodiments, the composition has a potency of at least about 80% after extended period of time under a storage condition. In some embodiments, the composition has a potency of at least about 81% after extended period of time under a storage condition. In some embodiments, the composition has a potency of at least about 82% after extended period of time under a storage condition. In some embodiments, the composition has a potency of at least about 83% after extended period of time under a storage condition. In some embodiments, the composition has a potency of at least about 84% after extended period of time under a storage condition. In some embodiments, the composition has a potency of at least about 85% after extended period of time under a storage condition. In some embodiments, the composition has a potency of at least about 86% after extended period of time under a storage condition. In some embodiments, the composition has a potency of at least about 87% after extended period of time under a storage condition. In some embodiments, the composition has a potency of at least about 88% after extended period of time under a storage condition. In some embodiments, the composition has a potency of at least about 89% after extended period of time under a storage condition. In some embodiments, the composition has a potency of at least 90% after extended period of time under a storage condition. In some embodiments, the composition has a potency of at least 91% after extended period of time under a storage condition. In some embodiments, the composition has a potency of at least 92% after extended period of time under a storage condition. In some embodiments, the composition has a potency of at least 93% after extended period of time under a storage condition. In some embodiments, the composition has a potency of at least 94% after extended period of time under a storage condition. In some embodiments, the composition has a potency of at least 95% after extended period of time under a storage condition. In some embodiments, the composition has a potency of at least 96% after extended period of time under a storage condition. In some embodiments, the composition has a potency of at least 97% after extended period of time under a storage condition. In some embodiments, the composition has a potency of at least 98% after extended period of time under a storage condition. In some embodiments, the composition has a potency of at least 99% after extended period of time under a storage condition.

[0062] 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.

[0063] 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 between about 0°C to about 30°C, 2°C to about 10°C, or from about 16°C to about 26°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.

[0064] 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%.

[0065] 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.

[0066] 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.

[0067] In some embodiments, the composition has a pH of between about 4 and about 8, about 4.2 to about 7.9, about 4.5 and about 7.8, about 5 and about 7.5, about 4.9 and about 6.1, about 5.0 and about 6.0, about 5.2 and about 6.1, about 5.5 and about 7, or about 5.5 and 5.6, for example when measured at about 25 °C. In some embodiments, the composition has a pH of between about 4 and about 8, about 4.2 to about 7.9, about 4.5 and about 7.8, about 5 and about 7.5, about 4.9 and about 6.1, about 5.0 and about 6.0, about 5.2 and about 6.1, about 5.5 and about 7, or about 5.5 and 5.6, for example when measured at about 40 °C. In some embodiments, the composition has a pH of about 8.0. In some embodiments, the composition has a pH of about 7.9. In some embodiments, the composition has a pH of about 7.8. In some embodiments, the composition has a pH of about 7.7. In some embodiments, the composition has a pH of about 7.6. In some embodiments, the composition has a pH of less than about 7.5. In some embodiments, the composition has a pH of less than about 7.4. In some embodiments, the composition has a pH of less than about 7.3. In some embodiments, the composition has a pH of less than about 7.2. In some embodiments, the composition has a pH of less than about 7.1. In some embodiments, the composition has a pH of less than about 7. In some embodiments, the composition has a pH of less than about 6.9. In some embodiments, the composition has a pH of less than about 6.8. In some embodiments, the composition has a pH of less than about 6.7. In some embodiments, the composition has a pH of less than about 6.6. In some embodiments, the composition has a pH of less than about 6.5. In some embodiments, the composition has a pH of less than about 6.4. In some embodiments, the composition has a pH of less than about 6.3. In some embodiments, the composition has a pH of less than about 6.2. In some embodiments, the composition has a pH of less than about 6.1. In some embodiments, the composition has a pH of less than about 6. In some embodiments, the composition has a pH of less than about 5.9. In some embodiments, the composition has a pH of less than about 5.8. In some embodiments, the composition has a pH of less than about 5.7. In some embodiments, the composition has a pH of less than about 5.6. In some embodiments, the composition has a pH of less than about 5.5. In some embodiments, the composition has a pH of less than about 5.4. In some embodiments, the composition has a pH of less than about 5.3. In some embodiments, the composition has a pH of less than about 5.2. In some embodiments, the composition has a pH of less than about 5.1. In some embodiments, the composition has a pH of less than about 5. In some embodiments, the composition has a pH of less than about 4.9. In some embodiments, the composition has a pH of less than about 4.8. In some embodiments, the composition has a pH of less than about 4.7. In some embodiments, the composition has a pH of less than about 4.6. In some embodiments, the composition has a pH of less than about 4.5. In some embodiments, the composition has a pH of less than about 4.4. In some embodiments, the composition has a pH of less than about 4.3. In some embodiments, the composition has a pH of less than about 4.2. In some embodiments, the composition has a pH of less than about 4.1. In some embodiments, the composition has a pH of less than about 4.

[0068] In some embodiments, the composition has a pD of between about 4 and about 8, about 4.2 to about 7.9, about 4.5 and about 7.8, about 5 and about 7.5, about 5.5 and about 7, about 5.3 and about 6.5, about 5.4 and about 6.4, about 5.6 and about 6.5, or about 5.9 and 6.0, for example when measured at

about 25 °C. In some embodiments, the composition has a pD of between about 4 and about 8, about 4.2 to about 7.9, about 4.5 and about 7.8, about 5 and about 7.5, about 5.5 and about 7, about 5.3 and about 6.5, about 5.4 and about 6.4, about 5.6 and about 6.5, or about 5.9 and 6.0, for example when measured at about 40 °C. In some embodiments, the composition has a pD of about 8.0. In some embodiments, the composition has a pD of about 7.9. In some embodiments, the composition has a pD of about 7.8. In some embodiments, the composition has a pD of about 7.7. In some embodiments, the composition has a pD of about 7.6. 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.

[0069] 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.

[0070] 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 purely 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 purely 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.

[0071] 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 a 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 a storage condition.

[0072] 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 a 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 a 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 a 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 a 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 a 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 a 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 a 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 a 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 a 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 a storage condition. In some embodiments, the major degradant is tropic acid.

[0073] In some embodiments, the composition has a potency of at least 80% at a temperature of about 0°C, about 2°C, about 5°C, about 10°C, about 15°C, about 25°C, about 40°C, or about 60°C. In some embodiments, the composition has a potency of at least 85% at a temperature of about 0°C, about 2°C, about 5°C, about 10°C, about 15°C, about 25°C, about 40°C, or about 60°C. In some embodiments, the composition has a potency of at least 90% at a temperature of about 0°C, about 2°C, about 5°C, about

[illegible]

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.

[0075] In some embodiments, the composition comprises less than 20% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under a storage condition. In some embodiments, the composition comprises less than 15% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under a storage condition. In some embodiments, the composition comprises less than 10% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under a storage condition. In some embodiments, the composition comprises less than 5% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under a storage condition.

[0076] In some embodiments, the composition 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 a storage condition. In some embodiments, the composition comprises less than 2.5% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under a storage condition. In some embodiments, the composition comprises less than 2.0% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under a storage condition. In some embodiments, the composition comprises less than 1.5% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under a storage condition. In some embodiments, the composition comprises less than 1.0% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under a storage condition. In some embodiments, the composition comprises less than 0.5% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under a storage condition. In some embodiments, the composition comprises less than 0.4% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under a storage condition. In some embodiments, the composition comprises less than 0.3% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under a storage condition. In some embodiments, the composition comprises less than 0.2% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under a storage condition. In some embodiments, the composition comprises less than 0.1% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under a storage condition. In some instances, a storage condition comprises a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, a storage condition comprises a temperature is between about 0°C to about 30°C, 2°C to about 10°C, or from about 16°C to about 26°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.

[0077] In some embodiments, the composition 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 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 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 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.

[0078] In some embodiments, the composition 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 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 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 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 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 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 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 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 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 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.

[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. 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] Described herein, in some embodiments, is an ophthalmic composition comprising various ratios of water (H₂O) to deuterated water (D₂O). In some instances, the ratio of the water to the deuterated water is in a range of about 99:1 to about 1:99. In some instances, the ratio of the water to the deuterated water is in a range of about 99:1 to about 5:95, about 99:1 to about 10:90, about 99:1 to about 20:80, about 99:1 to about 30:70, about 99:1 to about 40:60, about 99:1 to about 50:50, about 99:1 to about 60:40, about 99:1 to about 70:30, about 99:1 to about 80:20, or about 99:1 to about 90:10. In some instances, the ratio of the water to the deuterated water is in a range of about 5:95 to about 1:99, about 10:90 to about 1:99, about 20:80 to about 1:99, about 30:70 to about 1:99, about 40:60 to about 1:99,

about 50:50 to about 1:99, about 60:40 to about 1:99, about 70:30 to about 1:99, about 80:20 to about 1:99, or about 90:10 to about 1:99. In some instances, the ratio of the water to the deuterated water is in a range of about 95:5 to about 5:95, or in a range of about 90:10 to about 10:90, or in a range of about 80:20 to about 20:80, or in a range of about 80:20 to about 30:70, or in a range of about 80:30 to about 40:60, or in a range of about 90:10 to about 50:50, or in a range of about 80:20 to about 60:40. In some instances, the ratio of the water to the deuterated water is in a range of about 95:5 to about 5:95, or in a range of about 90:10 to about 10:90, or in a range of about 80:20 to about 20:80, or in a range of about 80:20 to about 30:70, or in a range of about 80:30 to about 40:60, or in a range of about 90:10 to about 50:50, or in a range of about 80:20 to about 60:40. In some instances, the ratio of the water to the deuterated water is about 99:1, about 98:2, about 97:3, about 96:4, about 95:5, about 94:6, about 93:7, about 92:8, about 91:9, about 90:10, about 89:11, about 88:12, about 87:13, about 86:14, about 85:15, about 84:16, about 83:17, about 82:18, about 81:19, about 80:20, about 79:21, about 78:22, about 77:23, about 76:24, about 75:25, about 74:26, about 73:27, about 72:28, about 71:29, about 70:30, about 69:31, about 68:32, about 67:33, about 66:34, about 65:35, about 64:36, about 63:37, about 62:38, about 61:39, about 60:40, about 59:41, about 58:42, about 57:43, about 56:44, about 55:45, about 54:46, about 53:47, about 52:48, about 51:49, about 50:50, about 49:51, about 48:52, about 47:53, about 46:54, about 45:55, about 44:56, about 43:57, about 42:58, about 41:59, about 40:60, about 39:61, about 38:62, about 37:63, about 36:64, about 35:65, about 34:66, about 33:67, about 32:68, about 31:69, about 30:70, about 29:71, about 28:72, about 27:73, about 26:74, about 25:75, about 24:76, about 23:77, about 22:78, about 21:79, about 20:80, about 19:81, about 18:82, about 17:83, about 16:84, about 15:85, about 14:86, about 13:87, about 12:88, about 11:89, about 10:90, about 9:91, about 8:92, about 7:93, about 6:94, about 5:95, about 4:96, about 3:97, about 2:98, or about 1:99. In some instances, the ratio of the water to the deuterated water is in a range of about 100:0. In some instances, the ratio of the water to the deuterated water is in a range of about 0:100.

[0081] 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.

[0082] In some instances, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine, homatropine, or a combination thereof. In some cases, the muscarinic antagonist is atropine. In some cases, the muscarinic antagonist is atropine sulfate. In some embodiments, the muscarinic antagonist is atropine or a pharmaceutically acceptable salt or prodrug thereof.

[0083] 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.

[0084] According to another aspect of the disclosure, described herein is an ophthalmic composition comprising one or more ophthalmic agents. In some instances, a first ophthalmic agent of the one or

more ophthalmic agents is a muscarinic antagonist. In some instances, a second ophthalmic agent of the one or more ophthalmic agent is aflibercept, ranibizumab, pegaptanib, cyclopentolate, phenylephrine, homatropine, scopolamine, cyclopentolate/phenylephrine, phenylephrine/scopolamine, tropicamide, ketorolac/phenylephrine, hydroxyamphetamine/tropicamide, cysteamine, ocriplasmin, mitomycin, dapiprazole, lidocaine, proparacaine, 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/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, benztropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, tolterodine, aceclidine, or any combinations thereof. In some embodiments, the ophthalmic agent is aceclidine, tropicamide, pilocarpine, or combinations thereof.

[0085] According to another aspect of the disclosure, described herein is an ophthalmic composition comprising an ophthalmic agent, wherein the ophthalmic agent is aflibercept, ranibizumab, pegaptanib, cyclopentolate, phenylephrine, homatropine, scopolamine, cyclopentolate/phenylephrine, phenylephrine/scopolamine, tropicamide, ketorolac/phenylephrine, hydroxyamphetamine/tropicamide, cysteamine, ocriplasmin, mitomycin, dapiprazole, lidocaine, proparacaine, 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/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, benztropine, mebeverine, procyclidine, aclidinium bromide, trihexyphenidyl/benzhexol, tolterodine, aceclidine, or any combinations thereof. In some embodiments, the ophthalmic agent is aceclidine, tropicamide, pilocarpine, or combinations thereof.

[0086] 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.

[0087] 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.

[0088] 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.

[0089] 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%.

[0090] 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%.

[0091] In some instances, the ophthalmic composition further comprises an osmolarity adjusting agent. In some cases, the osmolarity adjusting agent is sodium chloride.

[0092] 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.

[0093] 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.

[0094] 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.

[0095] In some instances, the ophthalmic composition further comprises a penetration agent. In some instances, the penetration agent is benzalkonium chloride.

[0096] 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).

[0097] 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.

[0098] 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, from about 4.9 and about 6.1, from about 5.0 and about 6.0, from about 5.2 and about 6.1, or from about 5.5 and 5.6, for example when measured at 25 °C. 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, from about 4.9 and

about 6.1, from about 5.0 and about 6.0, from about 5.2 and about 6.1, or from about 5.5 and 5.6, for example when measured at 40 °C.

[0099] 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.

[00100] 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.

[00101] In some instances, the ophthalmic composition further comprises a pharmaceutically acceptable carrier.

[00102] In some instances, the ophthalmic composition is formulated as an ophthalmic solution for treatment of an ophthalmic disorder. In some cases, the ophthalmic disorder or condition is pre-myopia, myopia, or progression of myopia. In some instances, the ophthalmic composition is formulated for slowing the progression of myopia.

[00103] In some instances, the ophthalmic composition is not formulated as an injectable formulation.

[00104] **Ophthalmic Agent Concentration**

[00105] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.5%, between about 0.005% to about 0.5%, between about 0.010% to about 0.5%, between about 0.015% to about 0.5%, between about 0.020% to about 0.5%, between about 0.025% to about 0.5%, between about 0.030% to about 0.5%, between about 0.035% to about 0.1%, between about 0.040% to about 0.5%, or between about 0.045% to about 0.5% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some instances, the prodrug of the ophthalmic agent (e.g. muscarinic antagonist) is chemically converted into the ophthalmic agent (e.g. muscarinic antagonist) after the administration of the ophthalmic composition. In a non-limiting example, the muscarinic antagonist prodrug has a chemical bond that is cleavable by one or more enzymes in tears. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine, 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 an optically enriched in favor of the more ophthalmically active L-isomer. In some instances, the ophthalmic agent is aflibercept, ranibizumab, pegaptanib, cyclopentolate, phenylephrine, homatropine, scopolamine, cyclopentolate/phenylephrine, phenylephrine/scopolamine, tropicamide, ketorolac/phenylephrine,

hydroxyamphetamine/tropicamide, cysteamine, ocriplasmin, mitomycin, dapiprazole, lidocaine, proparacaine, 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/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, benztropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, tolterodine, aceclidine, or any combinations thereof. In some embodiments, the ophthalmic agent is aceclidine, tropicamide, pilocarpine, or combinations thereof.

[00106] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.45%, between about 0.005% to about 0.45%, between about 0.010% to about 0.45%, between about 0.015% to about 0.45%, between about 0.020% to about 0.45%, between about 0.025% to about 0.45%, between about 0.030% to about 0.45%, between about 0.035% to about 0.45%, or between about 0.040% to about 0.45% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine, 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. In some instances, the ophthalmic agent is aflibercept, ranibizumab, pegaptanib, cyclopentolate, phenylephrine, homatropine, scopolamine,

cyclopentolate/phenylephrine, phenylephrine/scopolamine, tropicamide, ketorolac/phenylephrine, hydroxyamphetamine/tropicamide, cysteamine, ocriplasmin, mitomycin, dapiprazole, lidocaine, proparacaine, 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/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, aceclidine, or any combinations thereof. In some embodiments, the ophthalmic agent is aceclidine, tropicamide, pilocarpine, or combinations thereof.

[00107] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.40%, between about 0.005% to about 0.40%, between about 0.010% to about 0.40%, between about 0.015% to about 0.40%, between about 0.020% to about 0.40%, between about 0.025% to about 0.40%, between about 0.030% to about 0.40%, or between about 0.035% to about 0.40% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine, 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. In some instances, the ophthalmic agent is aflibercept, ranibizumab, pegaptanib, cyclopentolate,

phenylephrine, homatropine, scopolamine, cyclopentolate/phenylephrine, phenylephrine/scopolamine, tropicamide, ketorolac/phenylephrine, hydroxyamphetamine/tropicamide, cysteamine, ocriplasmin, mitomycin, dapiprazole, lidocaine, proparacaine, 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/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, aceclidine, or any combinations thereof. In some embodiments, the ophthalmic agent is aceclidine, tropicamide, pilocarpine, or combinations thereof.

[00108] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.35%, between about 0.005% to about 0.35%, between about 0.010% to about 0.35%, between about 0.015% to about 0.35%, between about 0.020% to about 0.35%, between about 0.025% to about 0.35%, between about 0.030% to about 0.35%, or between about 0.035% to about 0.35% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine, 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. In some instances, the ophthalmic agent is aflibercept, ranibizumab, pegaptanib, cyclopentolate, phenylephrine, homatropine, scopolamine, cyclopentolate/phenylephrine, phenylephrine/scopolamine, tropicamide, ketorolac/phenylephrine, hydroxyamphetamine/tropicamide, cysteamine, ocriplasmin, mitomycin, dapiprazole, lidocaine, proparacaine, 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/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, benztropine, mebeverine, procyclidine, aclidinium bromide, trihexyphenidyl/benzhexol, tolterodine, aceclidine, or any combinations thereof. In some embodiments, the ophthalmic agent is aceclidine, tropicamide, pilocarpine, or combinations thereof.

[00109] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.30%, between about 0.005% to about 0.30%, between about 0.010% to about 0.30%, between about 0.015% to about 0.30%, between about 0.020% to about 0.30%, between about 0.025% to about 0.30%, between about 0.030% to about 0.30%, or between about 0.030% to about 0.30% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine, 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. In some instances, the ophthalmic agent is aflibercept, ranibizumab, pegaptanib, cyclopentolate, phenylephrine, homatropine, scopolamine, cyclopentolate/phenylephrine, phenylephrine/scopolamine, tropicamide, ketorolac/phenylephrine, hydroxyamphetamine/tropicamide, cysteamine, ocriplasmin, mitomycin, dapiprazole, lidocaine, proparacaine, 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/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, benztropine, mebeverine, procyclidine, aclidinium bromide, trihexyphenidyl/benzhexol, tolterodine, aceclidine, or any combinations thereof. In some embodiments, the ophthalmic agent is aceclidine, tropicamide, pilocarpine, or combinations thereof.

[00110] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.25%, between about 0.005% to about 0.25%, between about 0.010% to about 0.25%, between about 0.015% to about 0.25%, between about 0.020% to about 0.25%, between about 0.025% to about 0.25%, between about 0.030% to about 0.25%, or between about 0.035% to about 0.25% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine,

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. In some instances, the ophthalmic agent is aflibercept, ranibizumab, pegaptanib, cyclopentolate, phenylephrine, homatropine, scopolamine, cyclopentolate/phenylephrine, phenylephrine/scopolamine, tropicamide, ketorolac/phenylephrine, hydroxyamphetamine/tropicamide, cysteamine, ocriplasmin, mitomycin, dapiprazole, lidocaine, proparacaine, 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/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, benztropine, mebeverine, procyclidine, aclidinium bromide, trihexyphenidyl/benzhexol, tolterodine, aceclidine, or any combinations thereof. In some embodiments, the ophthalmic agent is aceclidine, tropicamide, pilocarpine, or combinations thereof.

[00111] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.20%, between about 0.005% to about 0.20%, between about 0.010% to about 0.20%, between about 0.015% to about 0.20%, between about 0.020% to about 0.20%, between about 0.025% to about 0.20%, between about 0.030% to about 0.20%, or between about 0.035% to about 0.20% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-

N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine, 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. In some instances, the ophthalmic agent is aflibercept, ranibizumab, pegaptanib, cyclopentolate, phenylephrine, homatropine, scopolamine, cyclopentolate/phenylephrine, phenylephrine/scopolamine, tropicamide, ketorolac/phenylephrine, hydroxyamphetamine/tropicamide, cysteamine, ocriplasmin, mitomycin, dapiprazole, lidocaine, proparacaine, 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/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, benztropine, mebeverine, procyclidine, aclidinium bromide, trihexyphenidyl/benzhexol, tolterodine, aceclidine, or any combinations thereof. In some embodiments, the ophthalmic agent is aceclidine, tropicamide, pilocarpine, or combinations thereof.

[00112] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.15%, between about 0.005% to about 0.15%, between about 0.010% to about 0.15%, between about 0.015% to about 0.15%, between about 0.020% to about 0.15%, between about 0.025% to about 0.15%, between about 0.030% to about 0.15%, or between about 0.035% to about 0.15% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In

some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine, 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. In some instances, the ophthalmic agent is aflibercept, ranibizumab, pegaptanib, cyclopentolate, phenylephrine, homatropine, scopolamine, cyclopentolate/phenylephrine, phenylephrine/scopolamine, tropicamide, ketorolac/phenylephrine, hydroxyamphetamine/tropicamide, cysteamine, ocriplasmin, mitomycin, dapiprazole, lidocaine, proparacaine, 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/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, benztropine, mebeverine, procyclidine, aclidinium bromide, trihexyphenidyl/benzhexol, tolterodine, aceclidine, or any combinations thereof. In some embodiments, the ophthalmic agent is aceclidine, tropicamide, pilocarpine, or combinations thereof.

[00113] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.1%, between about 0.005% to about 0.1%, between about 0.010% to about 0.1%, between about 0.015% to about 0.1%, between about 0.020% to about 0.1%, between about 0.025% to about 0.1%, between about 0.030% to about 0.1%, between about 0.035% to about 0.1%, between about 0.040% to about 0.1%, or between about 0.045% to about 0.1% of the

ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine, 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. In some instances, the ophthalmic agent is aflibercept, ranibizumab, pegaptanib, cyclopentolate, phenylephrine, homatropine, scopolamine, cyclopentolate/phenylephrine, phenylephrine/scopolamine, tropicamide, ketorolac/phenylephrine, hydroxyamphetamine/tropicamide, cysteamine, ocriplasmin, mitomycin, dapiprazole, lidocaine, proparacaine, 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/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, aceclidine, or any combinations thereof. In some embodiments, the ophthalmic agent is aceclidine, tropicamide, pilocarpine, or combinations thereof.

[00114] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.095%, between about 0.005% to about 0.095%, between about 0.010% to about 0.095%², between about 0.015% to about 0.095%², between about 0.020% to about 0.095%, between about 0.025% to about 0.095%, between about 0.030% to about 0.095%, between about

0.035% to about 0.095%, or between about 0.040% to about 0.095% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine, 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. In some instances, the ophthalmic agent is aflibercept, ranibizumab, pegaptanib, cyclopentolate, phenylephrine, homatropine, scopolamine, cyclopentolate/phenylephrine, phenylephrine/scopolamine, tropicamide, ketorolac/phenylephrine, hydroxyamphetamine/tropicamide, cysteamine, ocriplasmin, mitomycin, dapiprazole, lidocaine, proparacaine, 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/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, benztropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, tolterodine, aceclidine, or any combinations thereof. In some embodiments, the ophthalmic agent is aceclidine, tropicamide, pilocarpine, or combinations thereof.

[00115] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.090%, between about 0.005% to about 0.090%, between about 0.010% to about 0.090%, between about 0.015% to about 0.090%, between about 0.020% to about

0.090%, between about 0.025% to about 0.090%, between about 0.030% to about 0.090%, between about 0.035% to about 0.090% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine, 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. In some instances, the ophthalmic agent is aflibercept, ranibizumab, pegaptanib, cyclopentolate, phenylephrine, homatropine, scopolamine, cyclopentolate/phenylephrine, phenylephrine/scopolamine, tropicamide, ketorolac/phenylephrine, hydroxyamphetamine/tropicamide, cysteamine, ocriplasmin, mitomycin, dapiprazole, lidocaine, proparacaine, 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/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, benztropine, mebeverine, procyclidine, aclidinium bromide, trihexyphenidyl/benzhexol, tolterodine, aceclidine, or any combinations thereof. In some embodiments, the ophthalmic agent is aceclidine, tropicamide, pilocarpine, or combinations thereof.

[00116] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.085%, between about 0.005% to about 0.085%, between about

0.010% to about 0.085%, between about 0.015% to about 0.085%, between about 0.020% to about 0.085%, between about 0.025% to about 0.085%, between about 0.030% to about 0.085%, between about 0.035% to about 0.085% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine, 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. In some instances, the ophthalmic agent is aflibercept, ranibizumab, pegaptanib, cyclopentolate, phenylephrine, homatropine, scopolamine, cyclopentolate/phenylephrine, phenylephrine/scopolamine, tropicamide, ketorolac/phenylephrine, hydroxyamphetamine/tropicamide, cysteamine, ocriplasmin, mitomycin, dapiprazole, lidocaine, proparacaine, 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/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, benztropine, mebeverine, procyclidine, aclidinium bromide, trihexyphenidyl/benzhexol, tolterodine, aceclidine, or any combinations thereof. In some embodiments, the ophthalmic agent is aceclidine, tropicamide, pilocarpine, or combinations thereof.

[00117] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.080%, between about 0.005% to about 0.080%, between about 0.010% to about 0.080%, between about 0.015% to about 0.080%, between about 0.020% to about 0.080%, between about 0.025% to about 0.080%, between about 0.030% to about 0.080%, between about 0.035% to about 0.080% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine, 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. In some instances, the ophthalmic agent is aflibercept, ranibizumab, pegaptanib, cyclopentolate, phenylephrine, homatropine, scopolamine, cyclopentolate/phenylephrine, phenylephrine/scopolamine, tropicamide, ketorolac/phenylephrine, hydroxyamphetamine/tropicamide, cysteamine, ocriplasmin, mitomycin, dapiprazole, lidocaine, proparacaine, 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/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, benztropine, mebeverine, procyclidine, aclidinium bromide, trihexyphenidyl/benzhexol, tolterodine, aceclidine, or any

combinations thereof. In some embodiments, the ophthalmic agent is aceclidine, tropicamide, pilocarpine, or combinations thereof.

[00118] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.075%, between about 0.005% to about 0.075%, between about 0.010% to about 0.075%, between about 0.015% to about 0.075%, between about 0.020% to about 0.075%, between about 0.025% to about 0.075%, between about 0.030% to about 0.075%, between about 0.035% to about 0.075% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine, 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. In some instances, the ophthalmic agent is aflibercept, ranibizumab, pegaptanib, cyclopentolate, phenylephrine, homatropine, scopolamine, cyclopentolate/phenylephrine, phenylephrine/scopolamine, tropicamide, ketorolac/phenylephrine, hydroxyamphetamine/tropicamide, cysteamine, ocriplasmin, mitomycin, dapiprazole, lidocaine, proparacaine, 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/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, benztatropine,

mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, tolterodine, aceclidine, or any combinations thereof. In some embodiments, the ophthalmic agent is aceclidine, tropicamide, pilocarpine, or combinations thereof.

[00119] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.070%, between about 0.005% to about 0.070%, between about 0.010% to about 0.070%, between about 0.015% to about 0.070%, between about 0.020% to about 0.070%, between about 0.025% to about 0.070%, between about 0.030% to about 0.070%, between about 0.035% to about 0.070% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine, 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. In some instances, the ophthalmic agent is aflibercept, ranibizumab, pegaptanib, cyclopentolate, phenylephrine, homatropine, scopolamine, cyclopentolate/phenylephrine, phenylephrine/scopolamine, tropicamide, ketorolac/phenylephrine, hydroxyamphetamine/tropicamide, cysteamine, ocriplasmin, mitomycin, dapiprazole, lidocaine, proparacaine, 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/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, benztropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, tolterodine, aceclidine, or any combinations thereof. In some embodiments, the ophthalmic agent is aceclidine, tropicamide, pilocarpine, or combinations thereof.

[00120] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.065%, between about 0.005% to about 0.065%, between about 0.010% to about 0.065%, between about 0.015% to about 0.065%, between about 0.020% to about 0.065%, between about 0.025% to about 0.065%, between about 0.030% to about 0.065%, between about 0.035% to about 0.065% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine, 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. In some instances, the ophthalmic agent is aflibercept, ranibizumab, pegaptanib, cyclopentolate, phenylephrine, homatropine, scopolamine, cyclopentolate/phenylephrine, phenylephrine/scopolamine, tropicamide, ketorolac/phenylephrine, hydroxyamphetamine/tropicamide, cysteamine, ocriplasmin, mitomycin, dapiprazole, lidocaine, proparacaine, 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/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, benztropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, tolterodine, aceclidine, or any combinations thereof. In some embodiments, the ophthalmic agent is aceclidine, tropicamide, pilocarpine, or combinations thereof.

[00121] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.060%, between about 0.005% to about 0.060%, between about 0.010% to about 0.060%, between about 0.015% to about 0.060%, between about 0.020% to about 0.060%, between about 0.025% to about 0.060%, between about 0.030% to about 0.060%, between about 0.035% to about 0.060% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine, 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. In some instances, the ophthalmic agent is aflibercept, ranibizumab, pegaptanib, cyclopentolate, phenylephrine, homatropine, scopolamine, cyclopentolate/phenylephrine, phenylephrine/scopolamine, tropicamide, ketorolac/phenylephrine, hydroxyamphetamine/tropicamide, cysteamine, ocriplasmin, mitomycin, dapiprazole, lidocaine, proparacaine, 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/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, aceclidine, or any combinations thereof. In some embodiments, the ophthalmic agent is aceclidine, tropicamide, pilocarpine, or combinations thereof.

[00122] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.055%, between about 0.005% to about 0.055%, between about 0.010% to about 0.055%, between about 0.015% to about 0.055%, between about 0.020% to about 0.055%, between about 0.025% to about 0.055%, between about 0.030% to about 0.055%, between about 0.035% to about 0.055% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine, 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. In some instances, the ophthalmic agent is aflibercept, ranibizumab, pegaptanib, cyclopentolate, phenylephrine, homatropine, scopolamine, cyclopentolate/phenylephrine, phenylephrine/scopolamine, tropicamide, ketorolac/phenylephrine, hydroxyamphetamine/tropicamide, cysteamine, ocriplasmin, mitomycin, dapiprazole, lidocaine, proparacaine, 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/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, benztropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, tolterodine, aceclidine, or any combinations thereof. In some embodiments, the ophthalmic agent is aceclidine, tropicamide, pilocarpine, or combinations thereof.

[00123] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.050%, between about 0.005% to about 0.050%, between about 0.010% to about 0.050%, between about 0.015% to about 0.050%, between about 0.020% to about 0.050%, between about 0.025% to about 0.050%, between about 0.030% to about 0.050%, between about 0.035% to about 0.050%, between about 0.040% to about 0.050%, or between about 0.045% to about 0.050% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some instances, the prodrug of the ophthalmic agent (e.g. muscarinic antagonist) is chemically converted into the ophthalmic agent (e.g. muscarinic antagonist) after the administration of the ophthalmic composition. In a non-limiting example, the muscarinic antagonist prodrug has a chemical bond that is cleavable by one or more enzymes in tears. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine, 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. In some instances, the ophthalmic agent is aflibercept, ranibizumab, pegaptanib, cyclopentolate, phenylephrine, homatropine, scopolamine, cyclopentolate/phenylephrine, phenylephrine/scopolamine, tropicamide, ketorolac/phenylephrine, hydroxyamphetamine/tropicamide, cysteamine, ocriplasmin, mitomycin, dapiprazole, lidocaine, proparacaine, 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/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, aceclidine, or any combinations thereof. In some embodiments, the ophthalmic agent is aceclidine, tropicamide, pilocarpine, or combinations thereof.

[00124] 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, scopolamine, tropicamide, cyclopentolate, pirenzepine, 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. In some instances, the ophthalmic agent is aflibercept, ranibizumab, pegaptanib, cyclopentolate, phenylephrine, homatropine, scopolamine, cyclopentolate/phenylephrine, phenylephrine/scopolamine, tropicamide, ketorolac/phenylephrine, hydroxyamphetamine/tropicamide, cysteamine, ocriplasmin, mitomycin, dapiprazole, lidocaine, proparacaine, 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/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, benztropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, tolterodine, aceclidine, or any combinations thereof. In some embodiments, the ophthalmic agent is aceclidine, tropicamide, pilocarpine, or combinations thereof.

[00125] 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 ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine, 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. In some instances, the ophthalmic agent is aflibercept, ranibizumab, pegaptanib, cyclopentolate, phenylephrine, homatropine, scopolamine, cyclopentolate/phenylephrine, phenylephrine/scopolamine, tropicamide, ketorolac/phenylephrine, hydroxyamphetamine/tropicamide, cysteamine, ocriplasmin, mitomycin, dapiprazole, lidocaine, proparacaine, 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/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, benztropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, tolterodine, aceclidine, or any combinations thereof. In some embodiments, the ophthalmic agent is aceclidine, tropicamide, pilocarpine, or combinations thereof.

[00126] 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, scopolamine, tropicamide, cyclopentolate, pirenzepine, 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. In some instances, the ophthalmic agent is aflibercept, ranibizumab, pegaptanib, cyclopentolate, phenylephrine, homatropine, scopolamine, cyclopentolate/phenylephrine, phenylephrine/scopolamine, tropicamide, ketorolac/phenylephrine, hydroxyamphetamine/tropicamide, cysteamine, ocriplasmin, mitomycin, dapiprazole, lidocaine, proparacaine, 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/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, benztropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, tolterodine, aceclidine, or any combinations thereof. In some embodiments, the ophthalmic agent is aceclidine, tropicamide, pilocarpine, or combinations thereof.

[00127] 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 ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine, 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. In some instances, the ophthalmic agent is aflibercept, ranibizumab, pegaptanib, cyclopentolate, phenylephrine, homatropine, scopolamine, cyclopentolate/phenylephrine, phenylephrine/scopolamine, tropicamide, ketorolac/phenylephrine, hydroxyamphetamine/tropicamide, cysteamine, ocriplasmin, mitomycin, dapiprazole, lidocaine, proparacaine, 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/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, benztropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, tolterodine, aceclidine, or any combinations thereof. In some embodiments, the ophthalmic agent is aceclidine, tropicamide, pilocarpine, or combinations thereof.

[00128] 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, scopolamine, tropicamide, cyclopentolate, pirenzepine, 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. In some instances, the ophthalmic agent is aflibercept, ranibizumab, pegaptanib, cyclopentolate, phenylephrine, homatropine, scopolamine, cyclopentolate/phenylephrine, phenylephrine/scopolamine, tropicamide, ketorolac/phenylephrine, hydroxyamphetamine/tropicamide, cysteamine, ocriplasmin, mitomycin, dapiprazole, lidocaine, proparacaine, 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/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, benztropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, tolterodine, aceclidine, or any combinations thereof. In some embodiments, the ophthalmic agent is aceclidine, tropicamide, pilocarpine, or combinations thereof.

[00129] 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 ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine, 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. In some instances, the ophthalmic agent is aflibercept, ranibizumab, pegaptanib, cyclopentolate, phenylephrine, homatropine, scopolamine, cyclopentolate/phenylephrine, phenylephrine/scopolamine, tropicamide, ketorolac/phenylephrine, hydroxyamphetamine/tropicamide, cysteamine, ocriplasmin, mitomycin, dapiprazole, lidocaine, proparacaine, 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/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, benztropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, tolterodine, aceclidine, or any combinations thereof. In some embodiments, the ophthalmic agent is aceclidine, tropicamide, pilocarpine, or combinations thereof.

[00130] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.015%, between about 0.005% to about 0.015%, or between about 0.010% to about 0.015% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine, 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. In some instances, the ophthalmic agent is aflibercept, ranibizumab, pegaptanib, cyclopentolate, phenylephrine, homatropine, scopolamine, cyclopentolate/phenylephrine, phenylephrine/scopolamine, tropicamide, ketorolac/phenylephrine, hydroxyamphetamine/tropicamide, cysteamine, ocriplasmin, mitomycin, dapiprazole, lidocaine, proparacaine, 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/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, benztropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, tolterodine, aceclidine, or any combinations thereof. In some embodiments, the ophthalmic agent is aceclidine, tropicamide, pilocarpine, or combinations thereof.

[00131] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 0.010%, between about 0.005% to about 0.010%, or between about 0.008% to about 0.010% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine, 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. In some instances, the ophthalmic agent is aflibercept, ranibizumab, pegaptanib, cyclopentolate, phenylephrine, homatropine, scopolamine, cyclopentolate/phenylephrine, phenylephrine/scopolamine, tropicamide, ketorolac/phenylephrine, hydroxyamphetamine/tropicamide, cysteamine, ocriplasmin, mitomycin, dapiprazole, lidocaine, proparacaine, 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/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, benztropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, tolterodine, aceclidine, or any combinations thereof. In some embodiments, the ophthalmic agent is aceclidine, tropicamide, pilocarpine, or combinations thereof.

[00132] 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%, 0.050%, 0.055%, 0.060%, 0.065%, 0.070%, 0.075%, 0.080%, 0.085%, 0.090%, 0.095%, or 0.1% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some embodiments, the compositions described herein have a concentration of ophthalmic agent of from about 0.001% to about 0.05%, from about 0.001% to about 0.04%, from about 0.001% to about 0.03%, from about 0.001% to about 0.025%, from about 0.001% to about 0.02%, from about 0.001% to about 0.01%, from about 0.001% to about 0.008%, or from about 0.001% to about 0.005%. In some embodiments, the ophthalmic agent is a muscarinic antagonist. In some embodiments, the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine, 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. In some instances, the ophthalmic agent is aflibercept, ranibizumab, pegaptanib, cyclopentolate, phenylephrine, homatropine, scopolamine, cyclopentolate/phenylephrine, phenylephrine/scopolamine, tropicamide, ketorolac/phenylephrine, hydroxyamphetamine/tropicamide, cysteamine, ocriplasmin, mitomycin, dapiprazole, lidocaine, proparacaine, 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/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, benztropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, tolterodine, aceclidine, or any combinations thereof. In some embodiments, the ophthalmic agent is aceclidine, tropicamide, pilocarpine, or combinations thereof.

[00133] 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).

[00134] Solution Stability

[00135] 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.

[00136] 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.

[00137] 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.

[00138] 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.

[00139] 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.

[00140] In some cases, citrate buffering agents include citric acid and sodium citrate. In some instances, the citrate buffering agent comprises citrate. In some instances, the citrate is present in the ophthalmic composition at a concentration of between about 0.001% to about 0.20%, between about 0.004% to about 0.20%, between about 0.005% to about 0.20%, between about 0.010% to about 0.20%, between about 0.015% to about 0.20%, between about 0.020% to about 0.20%, between about 0.025% to about 0.20%, between about 0.030% to about 0.20%, between about 0.035% to about 0.20%, between about 0.040% to about 0.20%, or between about 0.045% to about 0.20% by weight of the composition. In some instances, the citrate is present in the ophthalmic composition at a concentration of at least or about 0.001%, 0.002%, 0.003%, 0.004%, 0.005%, 0.006%, 0.007%, 0.008%, 0.009%, 0.010%, 0.020%, 0.030%, 0.040%, 0.050%, 0.060%, 0.070%, 0.080%, 0.090%, 0.10%, 0.20%, 0.30%, or 0.40% by weight of the composition.

[00141] In some instances, acetate buffering agents include acetic acid, potassium acetate, and sodium acetate.

[00142] In some instances, carbonate buffering agents include sodium bicarbonate and sodium carbonate.

[00143] 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).

[00144] 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.

[00145] Described herein, in some embodiments, is a composition essentially free of a citrate buffering agent, an acetate buffering agent, or a combination thereof. In some embodiments, the composition is substantially free of a citrate buffering agent, an acetate buffering agent, or a combination thereof. In some instances, the composition has no detectable amount of a citrate buffering agent, an acetate buffering agent, or a combination thereof.

[00146] 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, or a combination thereof.

[00147] 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.

[00148] 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 pH 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 pH adjusting agent comprises DCl and NaOD. In some embodiments, the pH adjusting agent comprises DCl, HCl, NaOH, NaOD, CD_3COOD , $\text{C}_6\text{D}_8\text{O}_7$, CH_3COOH , $\text{C}_6\text{H}_8\text{O}_7$, or combinations thereof.

[00149] In some instances, the pH adjusting agent is present in the ophthalmic composition at a concentration of between about 0.001% to about 0.20%, between about 0.004% to about 0.20%, between about 0.005% to about 0.20%, between about 0.010% to about 0.20%, between about 0.015% to about 0.20%, between about 0.020% to about 0.20%, between about 0.025% to about 0.20%, between about 0.030% to about 0.20%, between about 0.035% to about 0.20%, between about 0.040% to about 0.20%, or between about 0.045% to about 0.20% by weight of the composition. In some instances, the pH adjusting agent is present in the ophthalmic composition at a concentration of at least or about 0.001%, 0.002%, 0.003%, 0.004%, 0.005%, 0.006%, 0.007%, 0.008%, 0.009%, 0.010%, 0.020%, 0.030%, 0.040%, 0.050%, 0.060%, 0.070%, 0.080%, 0.090%, 0.10%, 0.20%, 0.30%, or 0.40% by weight of the composition. In some instances, the pH 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 pH adjusting agent comprises DCl and NaOD.

[00150] In some instances, the pH adjusting agent is citrate. In some instances, the citrate is present in the ophthalmic composition at a concentration of between about 0.001% to about 0.20%, between about 0.004% to about 0.20%, between about 0.005% to about 0.20%, between about 0.010% to about 0.20%, between about 0.015% to about 0.20%, between about 0.020% to about 0.20%, between about 0.025% to about 0.20%, between about 0.030% to about 0.20%, between about 0.035% to about 0.20%, between about 0.040% to about 0.20%, or between about 0.045% to about 0.20% by weight of the composition. In some instances, the citrate is present in the ophthalmic composition at a concentration of at least or about 0.001%, 0.002%, 0.003%, 0.004%, 0.005%, 0.006%, 0.007%, 0.008%, 0.009%, 0.010%, 0.020%, 0.030%, 0.040%, 0.050%, 0.060%, 0.070%, 0.080%, 0.090%, 0.10%, 0.20%, 0.30%, or 0.40% by weight of the composition.

[00151] In some cases, the composition described herein further comprises one or more sodium phosphate buffers. Exemplary sodium phosphate buffers include, but are not limited to, monosodium phosphate (sodium dihydrogen phosphate), disodium phosphate, trisodium phosphate, monosodium phosphate anhydrous, disodium phosphate anhydrous, and trisodium phosphate anhydrous. In some instances, a sodium phosphate of the one or more sodium phosphate buffers is monosodium phosphate. In some instances, a sodium phosphate of the one or more sodium phosphate buffers is disodium phosphate. In some instances, a sodium phosphate of the one or more sodium phosphate buffers is

anhydrous. In some instances, a sodium phosphate of the one or more sodium phosphate buffers is monosodium phosphate anhydrous. In some instances, a sodium phosphate of the one or more sodium phosphate buffers is disodium phosphate anhydrous.

[00152] The concentration of the sodium phosphate, in some embodiments, is between about 0.001% to about 0.20%, between about 0.004% to about 0.20%, between about 0.005% to about 0.20%, between about 0.010% to about 0.20%, between about 0.015% to about 0.20%, between about 0.020% to about 0.20%, between about 0.025% to about 0.20%, between about 0.030% to about 0.20%, between about 0.035% to about 0.20%, between about 0.040% to about 0.20%, or between about 0.045% to about 0.20% by weight of the composition. In some embodiments, the sodium phosphate is between about 0.01% to about 2.0%, between about 0.04% to about 2.0%, between about 0.05% to about 2.0%, between about 0.010% to about 2.0%, between about 0.015% to about 2.0%, between about 0.020% to about 2.0%, between about 0.025% to about 2.0%, between about 0.030% to about 2.0%, between about 0.035% to about 2.0%, between about 0.040% to about 2.0%, or between about 0.045% to about 2.0% by weight of the composition. In some instances, the sodium phosphate is present in the ophthalmic composition at a concentration of at least or about 0.001%, 0.002%, 0.003%, 0.004%, 0.005%, 0.006%, 0.007%, 0.008%, 0.009%, 0.010%, 0.020%, 0.030%, 0.040%, 0.050%, 0.060%, 0.070%, 0.080%, 0.090%, 0.10%, 0.20%, 0.30%, 0.40%, 0.50%, 0.60%, 0.70%, 0.80%, 0.90%, 1.0%, 2.0%, 3.0%, 4.0%, or more than 4.0% by weight of the composition.

[00153] The concentration of the monosodium phosphate anhydrous, in some embodiments, is between about 0.001% to about 0.20%, between about 0.004% to about 0.20%, between about 0.005% to about 0.20%, between about 0.010% to about 0.20%, between about 0.015% to about 0.20%, between about 0.020% to about 0.20%, between about 0.025% to about 0.20%, between about 0.030% to about 0.20%, between about 0.035% to about 0.20%, between about 0.040% to about 0.20%, or between about 0.045% to about 0.20% by weight of the composition. In some embodiments, the monosodium phosphate anhydrous is between about 0.01% to about 2.0%, between about 0.04% to about 2.0%, between about 0.05% to about 2.0%, between about 0.010% to about 2.0%, between about 0.015% to about 2.0%, between about 0.020% to about 2.0%, between about 0.025% to about 2.0%, between about 0.030% to about 2.0%, between about 0.035% to about 2.0%, between about 0.040% to about 2.0%, or between about 0.045% to about 2.0% by weight of the composition. In some instances, the monosodium phosphate anhydrous is present in the ophthalmic composition at a concentration of at least or about 0.001%, 0.002%, 0.003%, 0.004%, 0.005%, 0.006%, 0.007%, 0.008%, 0.009%, 0.010%, 0.020%, 0.030%, 0.040%, 0.050%, 0.060%, 0.070%, 0.080%, 0.090%, 0.10%, 0.20%, 0.30%, 0.40%, 0.50%, 0.60%, 0.70%, 0.80%, 0.90%, 1.0%, 2.0%, 3.0%, 4.0%, or more than 4.0% by weight of the composition.

[00154] The concentration of the disodium phosphate anhydrous, in some embodiments, is between about 0.001% to about 0.20%, between about 0.004% to about 0.20%, between about 0.005% to about 0.20%, between about 0.010% to about 0.20%, between about 0.015% to about 0.20%, between about 0.020% to about 0.20%, between about 0.025% to about 0.20%, between about 0.030% to about 0.20%, between about 0.035% to about 0.20%, between about 0.040% to about 0.20%, or between about 0.045%

to about 0.20% by weight of the composition. In some embodiments, the disodium phosphate anhydrous is between about 0.01% to about 2.0%, between about 0.04% to about 2.0%, between about 0.05% to about 2.0%, between about 0.010% to about 2.0%, between about 0.015% to about 2.0%, between about 0.020% to about 2.0%, between about 0.025% to about 2.0%, between about 0.030% to about 2.0%, between about 0.035% to about 2.0%, between about 0.040% to about 2.0%, or between about 0.045% to about 2.0% by weight of the composition. In some instances, the disodium phosphate anhydrous is present in the ophthalmic composition at a concentration of at least or about 0.001%, 0.002%, 0.003%, 0.004%, 0.005%, 0.006%, 0.007%, 0.008%, 0.009%, 0.010%, 0.020%, 0.030%, 0.040%, 0.050%, 0.060%, 0.070%, 0.080%, 0.090%, 0.10%, 0.20%, 0.30%, 0.40%, 0.50%, 0.60%, 0.70%, 0.80%, 0.90%, 1.0%, 2.0%, 3.0%, 4.0%, or more than 4.0% by weight of the composition.

[00155] In some instances, the composition has a pH of between about 4 and about 8, about 4.2 to about 7.9, 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 pH of about 8.0. In some embodiments, the composition has a pH of about 7.9. In some embodiments, the composition has a pH of about 7.8. In some embodiments, the composition has a pH of about 7.7. In some embodiments, the composition has a pH of about 7.6. In some embodiments, the composition has a pH of less than about 7.5. In some embodiments, the composition has a pH of less than about 7.4. In some embodiments, the composition has a pH of less than about 7.3. In some embodiments, the composition has a pH of less than about 7.2. In some embodiments, the composition has a pH of less than about 7.1. In some embodiments, the composition has a pH of less than about 7. In some embodiments, the composition has a pH of less than about 6.9. In some embodiments, the composition has a pH of less than about 6.8. In some embodiments, the composition has a pH of less than about 6.7. In some embodiments, the composition has a pH of less than about 6.6. In some embodiments, the composition has a pH of less than about 6.5. In some embodiments, the composition has a pH of less than about 6.4. In some embodiments, the composition has a pH of less than about 6.3. In some embodiments, the composition has a pH of less than about 6.2. In some embodiments, the composition has a pH of less than about 6.1. In some embodiments, the composition has a pH of less than about 6. In some embodiments, the composition has a pH of less than about 5.9. In some embodiments, the composition has a pH of less than about 5.8. In some embodiments, the composition has a pH of less than about 5.7. In some embodiments, the composition has a pH of less than about 5.6. In some embodiments, the composition has a pH of less than about 5.5. In some embodiments, the composition has a pH of less than about 5.4. In some embodiments, the composition has a pH of less than about 5.3. In some embodiments, the composition has a pH of less than about 5.2. In some embodiments, the composition has a pH of less than about 5.1. In some embodiments, the composition has a pH of less than about 5. In some embodiments, the composition has a pH of less than about 4.9. In some embodiments, the composition has a pH of less than about 4.8. In some embodiments, the composition has a pH of less than about 4.7. In some embodiments, the composition has a pH of less than about 4.6. In some embodiments, the composition has a pH of less than about 4.5. In some embodiments, the composition has a pH of less than about 4.4. In some embodiments, the composition has a pH of less

than about 4.3. In some embodiments, the composition has a pH of less than about 4.2. In some embodiments, the composition has a pH of less than about 4.1. In some embodiments, the composition has a pH of less than about 4. In some embodiments, the pH is the pH of the composition after extended period of time under a storage condition.

[00156] In some instances, the composition has a pD of between about 4 and about 8, about 4.2 to about 7.9, 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 about 8.0. In some embodiments, the composition has a pD of about 7.9. In some embodiments, the composition has a pD of about 7.8. In some embodiments, the composition has a pD of about 7.7. In some embodiments, the composition has a pD of about 7.6. 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 a storage condition.

[00157] In some instances, the composition has an initial pH of between about 4 and about 8, about 4.2 to about 7.9, about 4.5 and about 7.8, about 5 and about 7.5, or about 5.5 and about 7. In some

[illegible]

[00158] In some instances, the composition has an initial pD of between about 4 and about 8, about 4.2 to about 7.9, 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 8.0. In some embodiments, the composition has an initial pD of about 7.9. In some embodiments, the composition has an initial pD of about 7.8. In some embodiments, the composition has an initial pD of about 7.7. In some embodiments, the composition has an initial pD of about 7.6. 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.

[00159] In some embodiments, the pH of the composition described herein is associated with the stability of the composition. In some embodiments, a stable composition comprises a pH of between about 4 and about 8, about 4.2 to about 7.9, 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 pH of about 8.0. In some embodiments, a stable composition comprises a pH of about 7.9. In some embodiments, a stable composition comprises a pH of about 7.8. In some embodiments, a stable composition comprises a pH of about 7.7. In some embodiments, a stable composition comprises a pH of about 7.6. In some embodiments, a stable composition comprises a pH of less than about 7.5. In some embodiments, a stable composition comprises a pH of less than about 7.4. In some embodiments, a stable composition comprises a pH of less than about 7.3. In some embodiments, a stable composition comprises a pH of less than about 7.2. In some embodiments, a stable composition comprises a pH of less than about 7.1. In some embodiments, a stable composition comprises a pH of less than about 7. In some embodiments, a stable composition comprises a pH of less than about 6.9. In some embodiments, a stable composition comprises a pH of less than about 6.8. In some embodiments, a stable composition comprises a pH of less than about 6.7. In some embodiments, a stable composition comprises a pH of less than about 6.6. In some embodiments, a stable composition comprises a pH of less than about 6.5. In some embodiments, a stable composition comprises a pH of less than about 6.4. In some embodiments, a stable composition comprises a pH of less than about 6.3. In some embodiments, a stable composition

comprises a pH of less than about 6.2. In some embodiments, a stable composition comprises a pH of less than about 6.1. In some embodiments, a stable composition comprises a pH of less than about 6. In some embodiments, a stable composition comprises a pH of less than about 5.9. In some embodiments, a stable composition comprises a pH of less than about 5.8. In some embodiments, a stable composition comprises a pH of less than about 5.7. In some embodiments, a stable composition comprises a pH of less than about 5.6. In some embodiments, a stable composition comprises a pH of less than about 5.5. In some embodiments, a stable composition comprises a pH of less than about 5.4. In some embodiments, a stable composition comprises a pH of less than about 5.3. In some embodiments, a stable composition comprises a pH of less than about 5.2. In some embodiments, a stable composition comprises a pH of less than about 5.1. In some embodiments, a stable composition comprises a pH of less than about 5. In some embodiments, a stable composition comprises a pH of less than about 4.9. In some embodiments, a stable composition comprises a pH of less than about 4.8. In some embodiments, a stable composition comprises a pH of less than about 4.7. In some embodiments, a stable composition comprises a pH of less than about 4.6. In some embodiments, a stable composition comprises a pH of less than about 4.5. In some embodiments, a stable composition comprises a pH of less than about 4.4. In some embodiments, a stable composition comprises a pH of less than about 4.3. In some embodiments, a stable composition comprises a pH of less than about 4.2. In some embodiments, a stable composition comprises a pH of less than about 4.1. In some embodiments, a stable composition comprises a pH of less than about 4.

[00160] 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 4.2 to about 7.9, 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 about 8.0. In some embodiments, a stable composition comprises a pD of about 7.9. In some embodiments, a stable composition comprises a pD of about 7.8. In some embodiments, a stable composition comprises a pD of about 7.7. In some embodiments, a stable composition comprises a pD of about 7.6. 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.

[00161] 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 purely 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 purely 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 purely 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.

[00162] 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.

[00163] In some instances, the composition described herein further comprises a disinfecting agent. In some cases, disinfecting agents include polymeric biguanides, polymeric quaternary ammonium compounds, chlorites, bisbiguanides, chlorite compounds (e.g. potassium chlorite, sodium chlorite, calcium chlorite, magnesium chlorite, or mixtures thereof), and a combination thereof.

[00164] 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*).

[00165] 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%.

[00166] 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.

[00167] The ophthalmic composition as described herein, in some embodiments, is substantially free of a preservative. In some instances, the ophthalmic composition is substantially free of a benzalkonium chloride preservative. In some instances, the composition has no detectable amount of a benzalkonium chloride preservative. In some instances, the composition has no detectable amount of a benzalkonium chloride. In some instances, the composition is substantially free of a preservative selected from cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof. In some instances, the composition has no detectable amount of a preservative. In some instances, the composition is substantially free of any preservative.

[00168] 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-resin (SBC), or bioplastic. In some embodiments, the material of the plastic container comprises LDPE.

[00169] 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 pH of between about 4 and about 8, about 4.2 to about 7.9, 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 pH of about 7.9. In some embodiments, the composition

[illegible]

[illegible]

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.

[00171] In some embodiments, the composition stored in a plastic container has a potency of at least 80% after extended period of time under a 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 a 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 a 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 a 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 a 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 a 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 a 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 a 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.

[00172] In some embodiments, the composition stored in a plastic container has a potency of at least 80% at a temperature of about 0°C, about 2°C, about 5°C, about 10°C, about 15°C, 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 0°C, about 2°C, about 5°C, about 10°C, about 15°C, 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 0°C, about 2°C, about 5°C, about 10°C, about 15°C, 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 0°C, about 2°C, about 5°C, about 10°C, about 15°C, 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 0°C, about 2°C, about 5°C, about 10°C, about 15°C, 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 0°C, about 2°C, about 5°C, about 10°C, about 15°C, 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 0°C, about 2°C, about 5°C, about 10°C, about 15°C, 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 0°C, about 2°C, about 5°C, about 10°C, about 15°C, 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 80%, at least 85%, at least 90%, at least 93%, at least 95%, at least 97%, at least 98%, or at least 99% at a temperature of from about 0°C to about 30°C, 2°C to about 10°C or from about 16°C to about 26°C.

[00173] In some embodiments, the composition stored in a plastic container has a potency of at least 80% for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container has a potency of at least 85% for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container has a potency of at least 90% for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container has a potency of at least 93% for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container has a potency of at least 95% for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container has a potency of at least 97% for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container has a potency of at least 98% for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container has a potency of at least 99% for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months.

[00174] 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 a 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 a 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 a 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 a storage condition.

[00175] 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 a 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 a 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 a 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 a 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 a 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 a 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 a 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 a 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 a 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 a storage condition. In some instances, a storage condition comprises a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, a storage condition comprises a temperature is between about 0°C to about 30°C, 2°C to about 10°C, or from about 16°C to about 26°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.

[00176] 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.

[00177] 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.

[00178] In some embodiments, the composition stored in a plastic container comprises less than 20% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 15% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 10% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months,

at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 5% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months.

[illegible]

least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 0.2% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 0.1% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months.

[00180] 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 borosilicate glass vial.

[00181] In some embodiments, the composition stored in a glass container has a pH of higher than about 7. In some embodiments, the composition stored in a glass container has a pH of higher than about 7.5. In some embodiments, the composition stored in a glass container has a pH of higher than about 8. In some embodiments, the composition stored in a glass container has a pH of higher than about 8.5. In some embodiments, the composition stored in a glass container has a pH of higher than about 9.

[00182] 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.

[00183] 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.

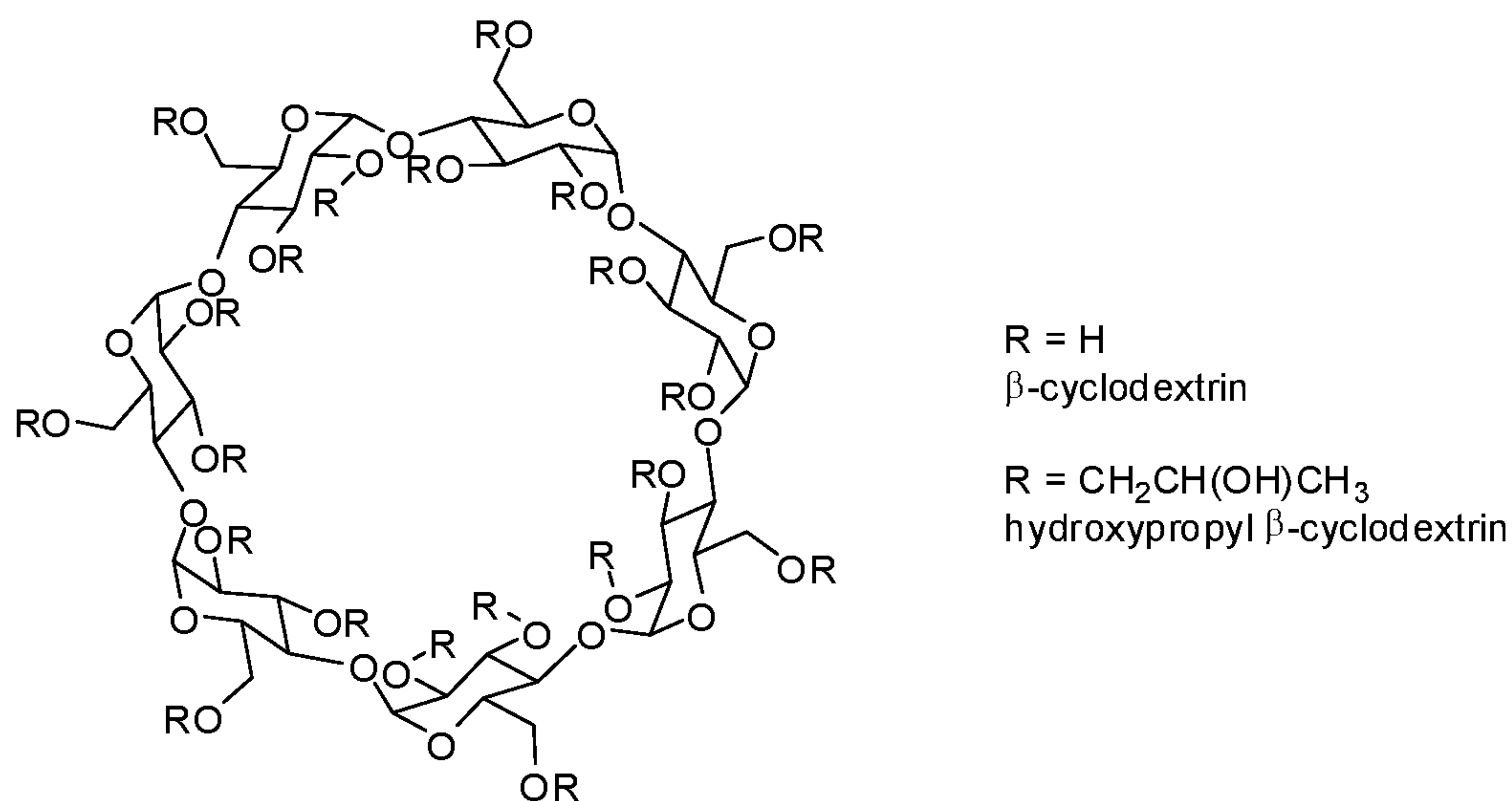
[00184] In some embodiments, the composition stored in a glass container is less stable than a composition stored in a plastic container.

[00185] 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.

[00186] 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.

[00187] 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).



[00188] 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.

[00189] 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.

[00190] 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.

[00191] 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.

[00192] 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. In some embodiments, the stabilizer is EDTA.

[00193] Stabilizing agents, in some embodiments, are present in the composition at about 0.001%, 0.005%, 0.010%, 0.015%, 0.020%, 0.025%, 0.030%, 0.035%, 0.040%, 0.045%, 0.050%, 0.055%, 0.060%, 0.065%, 0.070%, 0.075%, 0.080%, 0.085%, 0.090%, 0.095%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1.0%, 1.5%, 2.0%, 2.5%, or 3.0%. In some embodiments, the stabilizing agent is present in the composition from about 0.001% to about 0.05%, from about 0.001% to about 0.04%, from about 0.001% to about 0.03%, from about 0.001% to about 0.025%, from about 0.001% to about 0.02%, from about 0.001% to about 0.01%, from about 0.001% to about 0.008%, or from about 0.001% to about 0.005%. In some cases, the percentage is a weight percentage.

[00194] In some embodiments, EDTA is present in the composition at about 0.001%, 0.005%, 0.010%, 0.015%, 0.020%, 0.025%, 0.030%, 0.035%, 0.040%, 0.045%, 0.050%, 0.055%, 0.060%, 0.065%, 0.070%, 0.075%, 0.080%, 0.085%, 0.090%, 0.095%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1.0%, 1.5%, 2.0%, 2.5%, or 3.0%. In some embodiments, EDTA is present in the composition from about 0.01% to about 0.05%, from about 0.01% to about 0.04%, from about 0.01% to about 0.03%, from about 0.01% to about 0.025%, from about 0.01% to about 0.02%, from about 0.001%

to about 0.01%, from about 0.001% to about 0.008%, or from about 0.001% to about 0.005%. In some cases, the percentage is a weight percentage.

[00195] 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.

[00196] 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.

[00197] 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.

[00198] 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.

[00199] 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 pH 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.

[00200] 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%.

[00201] 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.

[00202] pH

[00203] In some embodiments, the pH of a composition described herein is adjusted (e.g., by use of a buffer and/or a pH adjusting agent) to an ophthalmically compatible pH range of from about 4 to about 8, about 4.2 to about 7.9, about 4.5 to about 7.5, or about 5 to about 7. In some embodiments, the ophthalmic composition has a pH of from about 5.0 to about 7.0. In some embodiments, the ophthalmic composition has a pH of from about 5.5 to about 7.0. In some embodiments, the ophthalmic composition has a pH of from about 6.0 to about 7.0.

[00204] In some embodiments, useful formulations include one or more pH adjusting agents or buffering agents. Suitable pH 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 pH adjusting agents or buffers include deuterated hydrochloric acid (DCl), deuterated sodium hydroxide (NaOD), deuterated acetic acid (CD₃COOD), or deuterated citric acid (C₆D₈O₇).

[00205] 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 pH of the gel formulation does not interfere with the body's natural buffering system.

[00206] 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 pH control or maintenance) are utilized as diluents in the art, including, but not limited to a phosphate buffered saline solution. In some embodiments, pH and pD of the present disclosure are based on the apparent (measured) pH of a system, using an electrode calibrated with aqueous buffers. In the case of a 100% D₂O system the apparent pH will be less than the pD ($-\log_{10}[\text{molar deuteron concentration}]$) of the system by approximately 0.44 units. In the case of a 100% H₂O system, the apparent pH is the pH ($-\log_{10}[\text{molar proton concentration}]$) of the system. In the case of a mixed H₂O/D₂O system, the apparent pH is less than the pH of the system by approximately 0-0.44 units depending on the ratio between H₂O and D₂O.

[00207] 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 embodiments, the pD is calculated as $\text{pD} = \text{pH} + 0.4$, in which pH is the measured or observed pH of the ophthalmic composition formulated in a solution comprising deuterated water (e.g., D₂O).

[00208] In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pH 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 pH 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 pH 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 pH 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 pH 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 pH 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 pH

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 pH 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 pH 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 pH 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 pH of between about 4.5-5.0. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pH of between about 4.9-5.4.

[00209] In some embodiments, the ophthalmic composition is an ophthalmic aqueous composition. In some instances, the ophthalmic aqueous composition has a pH of between about 4 and about 8, about 4.2 to about 7.9, 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 pH of about 8.0. In some embodiments, the ophthalmic aqueous composition has a pH of about 7.9. In some embodiments, the ophthalmic aqueous composition has a pH of about 7.8. In some embodiments, the ophthalmic aqueous composition has a pH of about 7.7. In some embodiments, the ophthalmic aqueous composition has a pH of about 7.6. In some embodiments, the ophthalmic aqueous composition has a pH of about 7.5. In some embodiments, the ophthalmic aqueous composition has a pH of about 7.4. In some embodiments, the ophthalmic aqueous composition has a pH of about 7.3. In some embodiments, the ophthalmic aqueous composition has a pH of about 7.2. In some embodiments, the ophthalmic aqueous composition has a pH of about 7.1. In some embodiments, the ophthalmic aqueous composition has a pH of about 7. In some embodiments, the ophthalmic aqueous composition has a pH of about 6.9. In some embodiments, the ophthalmic aqueous composition has a pH of about 6.8. In some embodiments, the ophthalmic aqueous composition has a pH of about 6.7. In some embodiments, the ophthalmic aqueous composition has a pH of about 6.6. In some embodiments, the ophthalmic aqueous composition has a pH of about 6.5. In some embodiments, the ophthalmic aqueous composition has a pH of about 6.4. In some embodiments, the ophthalmic aqueous composition has a pH of about 6.3. In some embodiments, the ophthalmic aqueous composition has a pH of about 6.2. In some embodiments, the ophthalmic aqueous composition has a pH of about 6.1. In some embodiments, the ophthalmic aqueous composition has a pH of about 6. In some embodiments, the ophthalmic aqueous composition has a pH of about 5.9. In some embodiments, the ophthalmic aqueous composition has a pH of about 5.8. In some embodiments, the ophthalmic aqueous composition has a pH of about 5.7. In some embodiments, the ophthalmic aqueous composition has a pH of about 5.6. In some embodiments, the ophthalmic aqueous composition has a pH of about 5.5. In some embodiments, the ophthalmic aqueous composition has a pH of about 5.4. In some embodiments, the ophthalmic aqueous composition has a pH of about 5.3. In some embodiments, the ophthalmic aqueous composition has a pH of about 5.2. In some embodiments, the ophthalmic aqueous composition has a pH of about 5.1. In some embodiments, the ophthalmic aqueous composition has a pH of about 5. In some embodiments, the ophthalmic aqueous composition has a pH of about 4.9. In some embodiments, the ophthalmic aqueous

composition has a pH of about 4.8. In some embodiments, the ophthalmic aqueous composition has a pH of about 4.7. In some embodiments, the ophthalmic aqueous composition has a pH of about 4.6. In some embodiments, the ophthalmic aqueous composition has a pH of about 4.5. In some embodiments, the ophthalmic aqueous composition has a pH of about 4.4. In some embodiments, the ophthalmic aqueous composition has a pH of about 4.3. In some embodiments, the ophthalmic aqueous composition has a pH of about 4.2. In some embodiments, the ophthalmic aqueous composition has a pH of about 4.1. In some embodiments, the ophthalmic aqueous composition has a pH of about 4. In some embodiments, the pH is an initial pH of the ophthalmic aqueous composition. In some embodiments, the pH is the pH of the ophthalmic aqueous composition after extended period of time under a storage condition.

[00210] In some instances, the ophthalmic aqueous composition has an initial pH of between about 4 and about 8, about 4.2 to about 7.9, 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 pH of about 8.0. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 7.9. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 7.8. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 7.7. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 7.6. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 7.5. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 7.4. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 7.3. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 7.2. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 7.1. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 7. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 6.9. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 6.8. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 6.7. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 6.6. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 6.5. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 6.4. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 6.3. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 6.2. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 6.1. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 6. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 5.9. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 5.8. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 5.7. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 5.6. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 5.5. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 5.4. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 5.3. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 5.2. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 5.1. In some embodiments,

the ophthalmic aqueous composition has an initial pH of about 5. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 4.9. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 4.8. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 4.7. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 4.6. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 4.5. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 4.4. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 4.3. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 4.2. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 4.1. In some embodiments, the ophthalmic aqueous composition has an initial pH of about 4.

[00211] In some instances, the ophthalmic aqueous composition has a pH of between about 4 and about 8, about 4.9 to about 7.2, 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 pH of about 8.0. In some embodiments, the ophthalmic aqueous composition has a pH of about 7.9. In some embodiments, the ophthalmic aqueous composition has a pH of about 7.8. In some embodiments, the ophthalmic aqueous composition has a pH of about 7.7. In some embodiments, the ophthalmic aqueous composition has a pH of about 7.6. In some embodiments, the ophthalmic aqueous composition has a pH of less than about 7.5. In some embodiments, the ophthalmic aqueous composition has a pH of less than about 7.4. In some embodiments, the ophthalmic aqueous composition has a pH of less than about 7.3. In some embodiments, the ophthalmic aqueous composition has a pH of less than about 7.2. In some embodiments, the ophthalmic aqueous composition has a pH of less than about 7.1. In some embodiments, the ophthalmic aqueous composition has a pH of less than about 7. In some embodiments, the ophthalmic aqueous composition has a pH of less than about 6.9. In some embodiments, the ophthalmic aqueous composition has a pH of less than about 6.8. In some embodiments, the ophthalmic aqueous composition has a pH of less than about 6.7. In some embodiments, the ophthalmic aqueous composition has a pH of less than about 6.6. In some embodiments, the ophthalmic aqueous composition has a pH of less than about 6.5. In some embodiments, the ophthalmic aqueous composition has a pH of less than about 6.4. In some embodiments, the ophthalmic aqueous composition has a pH of less than about 6.3. In some embodiments, the ophthalmic aqueous composition has a pH of less than about 6.2. In some embodiments, the ophthalmic aqueous composition has a pH of less than about 6.1. In some embodiments, the ophthalmic aqueous composition has a pH of less than about 6. In some embodiments, the ophthalmic aqueous composition has a pH of less than about 5.9. In some embodiments, the ophthalmic aqueous composition has a pH of less than about 5.8. In some embodiments, the ophthalmic aqueous composition has a pH of less than about 5.7. In some embodiments, the ophthalmic aqueous composition has a pH of less than about 5.6. In some embodiments, the ophthalmic aqueous composition has a pH of less than about 5.5. In some embodiments, the ophthalmic aqueous composition has a pH of less than about 5.4. In some embodiments, the ophthalmic aqueous composition has a pH of less than about 5.3. In some embodiments, the ophthalmic aqueous composition has a pH of less than about 5.2. In

some embodiments, the ophthalmic aqueous composition has a pH of less than about 5.1. In some embodiments, the ophthalmic aqueous composition has a pH of less than about 5. In some embodiments, the ophthalmic aqueous composition has a pH of less than about 4.9. In some embodiments, the ophthalmic aqueous composition has a pH of less than about 4.8. In some embodiments, the ophthalmic aqueous composition has a pH of less than about 4.7. In some embodiments, the ophthalmic aqueous composition has a pH of less than about 4.6. In some embodiments, the ophthalmic aqueous composition has a pH of less than about 4.5. In some embodiments, the ophthalmic aqueous composition has a pH of less than about 4.4. In some embodiments, the ophthalmic aqueous composition has a pH of less than about 4.3. In some embodiments, the ophthalmic aqueous composition has a pH of less than about 4.2. In some embodiments, the ophthalmic aqueous composition has a pH of less than about 4.1. In some embodiments, the ophthalmic aqueous composition has a pH of less than about 4. In some embodiments, the pH is the pH of the ophthalmic aqueous composition after extended period of time under a storage condition.

[00212] In some embodiments, the pH 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 pH of between about 4 and about 8, about 4.2 to about 7.9, 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 pH of about 8.0. In some embodiments, a stable composition comprises a pH of about 7.9. In some embodiments, a stable composition comprises a pH of about 7.8. In some embodiments, a stable composition comprises a pH of about 7.7. In some embodiments, a stable composition comprises a pH of about 7.6. In some embodiments, a stable composition comprises a pH of less than about 7.5. In some embodiments, a stable composition comprises a pH of less than about 7.4. In some embodiments, a stable composition comprises a pH of less than about 7.3. In some embodiments, a stable composition comprises a pH of less than about 7.2. In some embodiments, a stable composition comprises a pH of less than about 7.1. In some embodiments, a stable composition comprises a pH of less than about 7. In some embodiments, a stable composition comprises a pH of less than about 6.9. In some embodiments, a stable composition comprises a pH of less than about 6.8. In some embodiments, a stable composition comprises a pH of less than about 6.7. In some embodiments, a stable composition comprises a pH of less than about 6.6. In some embodiments, a stable composition comprises a pH of less than about 6.5. In some embodiments, a stable composition comprises a pH of less than about 6.4. In some embodiments, a stable composition comprises a pH of less than about 6.3. In some embodiments, a stable composition comprises a pH of less than about 6.2. In some embodiments, a stable composition comprises a pH of less than about 6.1. In some embodiments, a stable composition comprises a pH of less than about 6. In some embodiments, a stable composition comprises a pH of less than about 5.9. In some embodiments, a stable composition comprises a pH of less than about 5.8. In some embodiments, a stable composition comprises a pH of less than about 5.7. In some embodiments, a stable composition comprises a pH of less than about 5.6. In some embodiments, a stable composition comprises a pH of less than about 5.5. In some embodiments, a stable composition comprises a pH of less than about 5.4. In

some embodiments, a stable composition comprises a pH of less than about 5.3. In some embodiments, a stable composition comprises a pH of less than about 5.2. In some embodiments, a stable composition comprises a pH of less than about 5.1. In some embodiments, a stable composition comprises a pH of less than about 5. In some embodiments, a stable composition comprises a pH of less than about 4.9. In some embodiments, a stable composition comprises a pH of less than about 4.8. In some embodiments, a stable composition comprises a pH of less than about 4.7. In some embodiments, a stable composition comprises a pH of less than about 4.6. In some embodiments, a stable composition comprises a pH of less than about 4.5. In some embodiments, a stable composition comprises a pH of less than about 4.4. In some embodiments, a stable composition comprises a pH of less than about 4.3. In some embodiments, a stable composition comprises a pH of less than about 4.2. In some embodiments, a stable composition comprises a pH of less than about 4.1. In some embodiments, a stable composition comprises a pH of less than about 4.

[00213] 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 purely 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 purely 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 purely 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.

[00214] 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.

[00215] In some embodiment, the ophthalmic gel or ointment composition described herein has a pH 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.

[00216] In some embodiment, the pH of the ophthalmic aqueous, gel, or ointment composition described herein is suitable for sterilization (e.g., by filtration or aseptic mixing or heat treatment and/or autoclaving (e.g., terminal sterilization) of ophthalmic formulations described herein. As used in in the present disclosure, the term “aqueous composition” includes compositions that are based on D₂O.

[00217] In some embodiments, the pharmaceutical formulations described herein are stable with respect to pH 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 pH over a period of at least about 1 week. In other embodiments, the formulations described herein are stable with respect to pH over a period of at least about 2 weeks. In other embodiments, the formulations described herein are stable with respect to pH over a period of at least about 3 weeks. In other embodiments, the formulations described herein are stable with respect to pH over a period of at least about 1 month. Also described herein are formulations that are stable with respect to pH 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.

[00218] **Aqueous Solution Dose-To-Dose Uniformity**

[00219] 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.

[00220] In some embodiments, a drop comprises at least or about 10 microliters (μL), 15 μL, 20 μL, 25 μL, 30 μL, 35 μL, 40 μL, 45 μL, 50 μL, 75 μL, 100 μL, 125 μL, 150 μL, or more than 150 μL. In some embodiments, a drop comprises about 10 μL to about 100 μL, about 10 μL to about 75 μL, about 10 μL to about 50 μL, about 20 μL to about 100 μL, about 25 μL to about 75 μL, about 50 μL to about 75 μL, or about 50 μL to about 100 μL.

[00221] In some cases, described herein include ophthalmic aqueous compositions which provide 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.

[00222] 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%.

[00223] 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.

[00224] 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.

[00225] 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.

[00226] **Aqueous Solution Viscosity**

[00227] 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 $1s^{-1}$.

[00228] 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.

[00229] 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.

[00230] **Osmolarity**

[00231] 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 disrupt the ionic balance of the eye.

[00232] 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 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.

[00233] 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.

[00234] 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.

[00235] In some embodiments, suitable osmolality 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.

[00236] In some instances, the osmolality adjusting agent is present in the composition between about 0.01% and about 3.0%. In some instances, the osmolality adjusting agent is present in the composition 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 osmolality adjusting agent is present in the composition from about 0.01 wt% to about 1.0 wt%, from about 0.05 wt% to about 1.5 wt%, from about 0.075 wt% to about 2.0 wt%, or from about 0.1 wt% to about 3.0 wt%. In some instances, the osmolality adjusting agent is present in the composition 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 instances, the osmolality adjusting agent is present in the composition 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%, 1.0%, 2.0%, 3.0%, 4.0%, or more than 4.0%. In some cases, the percentage is a weight percentage.

[00237] In some embodiments, the osmolality adjusting agent is sodium chloride. In some instances, the sodium chloride is present in the composition between about 0.01% and about 3.0%. In some

instances, the sodium chloride is present in the composition 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 sodium chloride is present in the composition from about 0.01 wt% to about 1.0 wt%, from about 0.05 wt% to about 1.5 wt%, from about 0.075 wt% to about 2.0 wt%, or from about 0.1 wt% to about 3.0 wt%. In some instances, the sodium chloride is present in the composition 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 instances, the sodium chloride is present in the composition 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%, 1.0%, 2.0%, 3.0%, 4.0%, or more than 4.0%. In some cases, the percentage is a weight percentage.

[00238] 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.

[00239] **Sterility**

[00240] 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.

[00241] 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

[00242] 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).

[00243] 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.

[00244] 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).

[00245] Accordingly, provided herein are methods for sterilization of ophthalmic formulations that prevent degradation of polymeric components (e.g., thermosetting and/or other viscosity enhancing agents) and/or the ophthalmic agent during the process of sterilization. In some embodiments, degradation of the ophthalmic agent (e.g., a muscarinic antagonist such as atropine or atropine sulfate) is reduced or eliminated through the use of specific pH ranges for buffer components and specific proportions of viscosity enhancing agents in the formulations. In some embodiments, the choice of an appropriate viscosity enhancing agents or thermosetting polymer allows for sterilization of formulations described herein by filtration. In some embodiments, the use of an appropriate thermosetting polymer or other viscosity enhancing agents in combination with a specific pH range for the formulation allows for high temperature sterilization of formulations described with substantially no degradation of the therapeutic agent or the polymeric excipients. An advantage of the methods of sterilization provided herein is that, in certain instances, the formulations are subjected to terminal sterilization via autoclaving without any loss of the ophthalmic agent and/or excipients and/or viscosity enhancing agents during the sterilization step and are rendered substantially free of microbes and/or pyrogens.

Radiation Sterilization

[00246] 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

[00247] 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.

Sterilization by Ethylene Oxide

[00248] In some embodiments, the methods disclosed herein comprise sterilizing the formulation (or components thereof) using ethylene oxide (EtO) sterilization. In some instances, the method for ethylene oxide sterilization comprises injecting a chamber or sterilizing unit using a sterilant or sterilizing agent. In some instances, the sterilant or sterilizing agent is a gas sterilant. In some instances, the sterilant or sterilizing agent is ethylene oxide. In some instances, the gas sterilant is ethylene oxide.

Microorganisms

[00249] 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.

[00250] 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.

[00251] 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.

[00252] 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

[00253] 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.

[00254] 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 2 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.

[00255] 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.

[00256] 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.

[00257] Ophthalmic Mucus Penetrating Particle (MPP) Compositions

[00258] 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 200 nm and 500 nm. 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, the ophthalmic agent is aflibercept, ranibizumab, pegaptanib, cyclopentolate, phenylephrine, homatropine, scopolamine, cyclopentolate/phenylephrine, phenylephrine/scopolamine, tropicamide, ketorolac/phenylephrine, hydroxyamphetamine/tropicamide, cysteamine, ocriplasmin, mitomycin, dapiprazole, lidocaine, proparacaine, 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/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, benztropine, mebeverine, procyclidine, acridinium bromide, trihexyphenidyl/benzhexol, tolterodine, aceclidine, or any combinations thereof. In some embodiments, the ophthalmic agent is aceclidine, tropicamide, pilocarpine, or combinations thereof.

[00259] 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, pirenzepine, homatropine, solifenacin, darifenacin, benztropine, 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 MMPs for mucus penetration. In a non-limiting example, the MMPs for use in the disclosed composition is obtained from Kala Pharmaceuticals, Inc. (100 Beaver Street #201, Waltham, MA 02453).

[00260] 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.

[00261] 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.

[00262] 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.

[00263] 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.

[00264] 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.

[00265] 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.

[00266] In some embodiments, any suitable solvent is used for milling. In some cases, the choice of solvent is dependent 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.

[00267] 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.

[00268] **Ophthalmic Gel Compositions**

[00269] 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.

[00270] 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.

[00271] 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.

[00272] 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.

[00273] 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.

[00274] 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.

[00275] 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.

[00276] 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.

[00277] In some instances, the ophthalmic gel composition comprises an ophthalmic agent such as 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.

[00278] 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. In some instances, the permeation enhancer is EDTA. In some

embodiments, EDTA is present in the composition at about 0.001%, 0.005%, 0.010%, 0.015%, 0.020%, 0.025%, 0.030%, 0.035%, 0.040%, 0.045%, 0.050%, 0.055%, 0.060%, 0.065%, 0.070%, 0.075%, 0.080%, 0.085%, 0.090%, 0.095%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1.0%, 1.5%, 2.0%, 2.5%, or 3.0%. In some embodiments, EDTA is present in the composition from about 0.001% to about 0.05%, from about 0.001% to about 0.04%, from about 0.001% to about 0.03%, from about 0.001% to about 0.025%, from about 0.001% to about 0.02%, from about 0.001% to about 0.01%, from about 0.001% to about 0.008%, or from about 0.001% to about 0.005%. In some cases, the percentage is a weight percentage.

[00279] 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.

[00280] 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.

[00281] 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.

[00282] 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.

[00283] 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.

[00284] 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.

[00285] 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.

[00286] 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 pH is modulated by the addition of appropriate buffering agents.

[00287] Ophthalmic Ointment Compositions

[00288] 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.

[00289] 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.

[00290] 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.).

[00291] 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.

[00292] 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.

[00293] 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.

[00294] 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.

[00295] 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.

[00296] 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.

[00297] 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.

[00298] 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.

[00299] 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.

[00300] 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.

[00301] 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 $\text{H}-(\text{OCH}_2-\text{CH}_2)_n\text{OH}$, 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.

[00302] 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.

[00303] 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.

[00304] **Gel/Ointment Viscosity**

[00305] 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} .

[00306] 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 50,0000 and 1,000,000 centipoise.

[00307] 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.

[00308] 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.

[00309] 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).

[00310] Gel/Ointment Dose-To-Dose Uniformity

[00311] 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.

[00312] In some cases, described herein include ophthalmic gel compositions which provide 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.

[00313] In some cases, described herein include ophthalmic ointment compositions which provide 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.

[00314] 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%.

[00315] 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.

[00316] 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.

[00317] 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.

[00318] **Methods of Treatment**

[00319] Disclosed herein are methods of arresting myopia development or slowing progression of myopia 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.

[00320] 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. In some embodiments, the ophthalmic composition is not formulated as an injectable formulation.

[00321] In some embodiments, the ophthalmic composition is formulated as an ophthalmic solution for treatment of pre-myopia, myopia, progression of myopia, or slowing progression of myopia.

[00322] 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.

[00323] 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 first use.

[00324] 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.

[00325] 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.

[00326] 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.

[00327] 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.

[00328] 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%.

[00329] 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.

[00330] 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.

[00331] 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%.

[00332] 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.

[00333] 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.

[00334] In some embodiments, the initial administration is a particular ophthalmic agent and the subsequent administration a different formulation or ophthalmic agent.

[00335] **Fluid-Dispensing Device**

[00336] In certain embodiments, described herein include an ophthalmic product, which comprises a fluid-dispensing device comprising a reservoir and a dispensing tip fitted onto the reservoir, and the composition described herein, wherein the composition is dispensed from the dispensing tip into an eye of an individual in need thereof. In some instances, the composition in the reservoir is substantially preservative-free. In other instances, the composition in the reservoir comprises a preservative, but is filtered prior to dispensing from the dispensing tip, and the dispensed composition is substantially preservative-free.

[00337] In some embodiments, the ophthalmic composition comprises a muscarinic antagonist. In some cases, the ophthalmic product comprises a fluid-dispensing device comprising a reservoir and a dispensing tip fitted onto the reservoir; and an ophthalmic composition comprising from about 0.001 wt% to about 0.05 wt% of a muscarinic antagonist and deuterated water, at a pH of from about 4.2 to

about 7.9, in the reservoir; wherein the ophthalmic composition is dispensed from the dispensing tip into an eye of an individual in need thereof, and wherein the dispensed ophthalmic composition is substantially preservative-free.

[00338] In some embodiments, the ophthalmic composition comprises an ophthalmic agent. In some cases, the ophthalmic product comprises a fluid-dispensing device comprising a reservoir and a dispensing tip fitted onto the reservoir; and an ophthalmic composition comprising an ophthalmic agent and deuterated water, at a pH of from about 4 to about 8, in the reservoir; wherein the ophthalmic agent is not a muscarinic antagonist and does not extend singlet oxygen lifetime, wherein the ophthalmic composition is dispensed from the dispensing tip into an eye of an individual in need thereof, and wherein the dispensed ophthalmic composition is substantially preservative-free.

[00339] In some embodiments, the ophthalmic composition is dispensed from a single-dose container. In some embodiments, the ophthalmic composition is dispensed using a unidose system. In some embodiments, the ophthalmic composition is dispensed from a multi-dose container. In some embodiments, the single-dose container or multi-dose container is disposable. In some embodiments, the ophthalmic composition is dispensed from a single-dose or multi-dose container provided as an ampule. In some embodiments, the ophthalmic composition is dispensed from a first container that contains the ophthalmic formulation comprising the muscarinic antagonist (e.g., atropine or atropine sulfate), wherein the first container is configured as a disposable single-dose container or a multi-dose container, and a second container enclosing the first container and comprising one or more buffering agents. In some instances, the ophthalmic composition in the container is substantially preservative-free. In some instances, the ophthalmic composition in the container comprises a preservative, but is filtered prior to dispensing, and the dispensed ophthalmic composition is substantially preservative-free.

[00340] In some embodiments, the container comprises a polymeric material, for example, polyvinyl chloride (PVC) plastics or non-PVC plastics. In some instances, the 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-resin (SBC), or bioplastic. In some embodiments, the material of the reservoir comprises ethylene vinyl acetate (EVA) and block copolymers such as Kraton®. In some cases, the container comprises high-density polyethylene (HDPE). In some cases, the container comprises low-density polyethylene (LDPE). In some cases, the container comprises polyethylene terephthalate (PET). In some cases, the container comprises polypropylene (PP). In some cases, the container comprises polystyrene (PS). In some cases, the material of the reservoir comprises ethylene vinyl acetate (EVA).

[00341] As used herein, the term “substantially preservative-free” or “substantially free of a preservative” refers to the composition as having one of: less than about 1%, less than about 0.5%, less than about 0.4%, less than about 0.3%, less than about 0.2%, less than about 0.1%, less than about 0.01%, or less than about 0.001% of a preservative. In some instances, the term refers to the composition as having 0% of a preservative, or preservative-free.

[00342] In some embodiments, the reservoir comprises of a polymeric material, for example, polyvinyl chloride (PVC) plastics or non-PVC plastics. In some instances, the material of the reservoir 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-resin (SBC), or bioplastic. In some embodiments, the material of the reservoir comprises ethylene vinyl acetate (EVA) and block copolymers such as Kraton®. In some cases, the material of the reservoir comprises high-density polyethylene (HDPE). In some cases, the material of the reservoir comprises low-density polyethylene (LDPE). In some cases, the material of the reservoir comprises polyethylene terephthalate (PET). In some cases, the material of the reservoir comprises polypropylene (PP). In some cases, the material of the reservoir comprises polystyrene (PS). In some cases, the material of the reservoir comprises ethylene vinyl acetate (EVA).

[00343] In some instances, the reservoir further comprises a plasticizer. Exemplary plasticizer includes families of phthalate esters such as di-2-ethylhexylphthalate (DEHP), mono-(2-ethylhexyl) phthalate (MEHP), and triethylhexyltrimellitate (TEHTM); citrate esters such as acetyltri-n-hexyl citrate, acetyltri-n-(hexyl/octyl/decyl) citrate, acetyltri-n-(octyl/decyl) citrate, and n-butyryltri-n-hexyl citrate; and non-phthalate plasticizers such as TEHTM, di(isononyl) cyclohexane-1,2-dicarboxylate (DINCH), or n-butyryltri-n-hexyl citrate.

[00344] In some embodiments, the reservoir is at least partially elastically deformable so as to dispense the ophthalmic composition by pressing on the reservoir.

[00345] In some embodiments, the reservoir comprises glass.

[00346] In some embodiments, the reservoir stores multiple unit doses of the composition described herein.

[00347] In some embodiments, the fluid-dispensing device described herein is a multi-dose fluid-dispensing device.

[00348] In some embodiments, the fluid-dispensing device described herein enables storage of a preservative-free or substantially preservative-free composition. In some cases, the fluid-dispensing device is a multi-dose preservative-free device.

[00349] In some instances, a fluid-dispensing device from Aptar Pharma (AptarGroup) is utilized for delivery of a composition described herein. In some cases, the composition is preservative-free.

[00350] In some cases, a fluid-dispensing device from Nemera La Verpillière S.A.S. is utilized for delivery of a composition described herein. In some cases, a fluid-dispensing device as described in U.S. Patent no. 8,986,266 and/or 8,863,998 is utilized for delivery of a composition described herein. In some cases, the composition is preservative-free.

[00351] In some cases, a fluid-dispensing device from CIS Pharma is utilized for delivery of a composition described herein. In some cases, the composition is preservative-free.

[00352] In some embodiments, the fluid-dispensing device described herein optionally comprises an atomizer, a pump, or a mister. In such cases, a mechanical system such as a pump, a mister, or an atomizer is incorporated into the fluid-dispensing device to facilitate delivery of the composition

described herein and optionally to facilitate dose uniformity (e.g., between each administration, minimize excessive drug volume, and/or enhance droplet uniformity). In additional cases, a mechanical system such as a pump, a mister, or an atomizer is incorporated into the fluid-dispensing device to enhance and/or optimize the amount of drug delivered to the eye.

[00353] In some instances, an atomizer and/or pump system from Aero Pump GMBH (Adelphi Healthcare Packaging) is utilized with the fluid-dispensing device and the composition described herein. In some instances, a multiple-dosage fluid-dispensing device from Aero Pump GMBH is utilized for delivery of the composition described herein. In some cases, a fluid-dispensing device as described in U.S. Patent Publication 2016/279663 and/or 2015/076174 (Aero Pump GMBH) is utilized with the fluid-dispensing device and the composition described herein.

[00354] In some embodiments, a fluid-dispensing device from Eyenovia, Inc. is utilized for delivery of the composition described herein. In some cases, a fluid-dispensing device comprising one or more of a delivery system and/or component described in U.S. Patents and Patent Publications 9,539,604, 9,087,145, 9,463,486, or 2012/143152 are utilized for delivery of the composition described herein.

[00355] In some cases, a fluid-dispensing device comprising one or more of a delivery system and/or component from Kedalion Therapeutics is utilized for delivery of the composition described herein.

[00356] In some cases, a fluid-dispensing device comprising one or more of a delivery system and/or component from Aptar Pharma (e.g., a pump dispensing system) is utilized for delivery of the composition described herein.

[00357] In some embodiments, the fluid-dispensing device optionally comprises an internal filter or membrane. In some instances, the internal filter or membrane is located within the fluid-dispensing device at a position capable of removing a preservative from the ophthalmic composition prior to dispensing the ophthalmic composition into the eye of the individual. In some instances, the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof. In some instances, the internal filter or membrane is located within the fluid-dispensing device at a position capable of removing a preservative selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof, from the ophthalmic composition prior to dispensing the ophthalmic composition into the eye of the individual. In some instances, the internal filter or membrane is located within the fluid-dispensing device at a position capable of removing a preservative selected from benzalkonium chloride (BAK, BAC, or BKC) from the ophthalmic composition prior to dispensing the ophthalmic composition into the eye of the individual. In some cases, the internal filter or membrane is located at the junction connecting the dispensing tip to the reservoir. In other cases, the internal filter or membrane is located within the dispensing tip.

[00358] In some instances, the internal filter or membrane is located within the fluid-dispensing device at a position capable of removing a microorganism and/or an endotoxin from the ophthalmic composition prior to dispensing the ophthalmic composition into the eye of the individual. In some cases,

the internal filter or membrane is located at the junction connecting the dispensing tip to the reservoir. In other cases, the internal filter or membrane is located within the dispensing tip. In some cases, the ophthalmic composition is a preservative-free composition.

[00359] In some cases, the internal filter or membrane comprises cellulose acetate, cellulose nitrate, nylon, polyether sulfone (PES), polypropylene (PP), polyvinyl difluoride (PVDF), silicone, polycarbonate, or a combination thereof.

[00360] In some embodiments, a filter system from TearClear is utilized with a fluid-dispensing device and composition described herein. In some cases, a filter system from TearClear removes a preservative from the composition described herein in-situ, e.g., the filter system is within the fluid-dispensing device which removes a preservative from the composition as the composition is passed from the filter and dispensed into the eye of an individual.

[00361] In some cases, the dispensed composition comprises one of: less than about 1%, less than about 0.5%, less than about 0.4%, less than about 0.3%, less than about 0.2%, less than about 0.1%, less than about 0.01%, less than about 0.001%, or less than about 0.0001% of a preservative. In some cases, the dispensed composition is preservative-free.

[00362] In some instances, the droplet volume dispensed from the fluid-dispensing device described herein is from about 0.1 μL to about 50 μL . In some instances, the droplet volume is one of: about 0.1 μL to about 40 μL , about 0.5 μL to about 30 μL , about 1 μL to about 30 μL , about 5 μL to about 20 μL , about 10 μL to about 20 μL , about 5 μL to about 40 μL , about 5 μL to about 30 μL , about 6 μL to about 8 μL , about 6 μL to about 7 μL , about 7 μL to about 8 μL , about 10 μL to about 40 μL , or about 10 μL to about 30 μL . In some cases, the droplet volume dispensed from the fluid-dispensing device described herein is about 0.1 μL , about 0.2 μL , about 0.3 μL , about 0.4 μL , about 0.5 μL , about 1 μL , about 5 μL , about 6 μL , about 7 μL , about 8 μL , about 9 μL , about 10 μL , about 20 μL , about 30 μL , about 40 μL , or about 50 μL .

[00363] In some embodiments, the linear size or diameter of the droplet when spherical is about 1 up to less than 100 microns. In some cases, the linear size or diameter of the droplet is about 20 to 100 microns, about 1 to 20 microns, 1-15 microns, 1-10 microns, 8-20 microns, 8-15 microns, 8-12 microns, or 1-5 microns. In the context of an aerosol or mist, the size of the droplet is, for example, 1-5 microns, 1-10 microns, less than 10 microns, greater than 10 microns, or up to 100 microns.

[00364] In some cases, the diameter of the droplet is calculated using the equation $V=4\pi r^3$ where the diameter=2r.

[00365] In some instances, the fluid-dispensing device is suitable for dispensing the composition described herein having a viscosity described herein. In some cases, the composition has a viscosity of up to 500 cP, up to 600 cP, up to 1000 cP, up to 10,000 cP, or up to 50,000 cP.

[00366] In some instances, the fluid-dispensing device described herein facilitates at least 60%, 70%, 80%, 85%, 90%, 95%, or 99% of the ejected mass of a droplet deposited on the eye of an individual. In some cases, the fluid-dispensing device described herein facilitates at least 70% of the ejected mass of a droplet to be deposited on the eye of an individual. In some cases, the fluid-dispensing device described

herein facilitates at least 80% of the ejected mass of a droplet to be deposited on the eye of an individual. In some cases, the fluid-dispensing device described herein facilitates at least 90% of the ejected mass of a droplet to be deposited on the eye of an individual. In some cases, the fluid-dispensing device described herein facilitates at least 95% of the ejected mass of a droplet to be deposited on the eye of an individual. In some cases, the fluid-dispensing device described herein facilitates at least 99% of the ejected mass of a droplet to be deposited on the eye of an individual.

[00367] Kits/Articles of Manufacture

[00368] 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.

[00369] 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.

[00370] 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.

[00371] 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.

[00372] 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

[00373] Exemplary compositions for preparation of ophthalmic formulations are described in Tables 1-18. Table 19 shows compositions of ophthalmic formulation #1 to ophthalmic formulation #20.

Table 1

Ingredient	Concentration (wt%)
Atropine or pharmaceutically acceptable salt of atropine	0.001-0.50 (wt%)
Buffer agent and/or pH adjusting agent (e.g., borates, citrate and/or DCl, citrate)	q.s. for pH=4.2-7.9 and q.s. for 0.004 wt%-0.20 wt%
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	0.001-0.10 (wt%)
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

Ingredient	Concentration (wt%)
Atropine or pharmaceutically acceptable salt of atropine	0.001-0.50 (wt%)
Buffer agent and/or pH adjusting agent (e.g., borates, citrate and/or DCl, citrate)	q.s. for pH=4.2-7.9 and q.s. for 0.004 wt%-0.20 wt%
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	0%
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

Ingredient	Concentration (wt%)
Atropine	0.001-0.50 (wt%)
Buffer agent (monosodium phosphate anhydrous, disodium phosphate anhydrous) and/or pH adjusting agent (e.g., borates and/or DCl)	q.s. for pH=4.2-7.9 .s. for 0.004 wt%-0.20 wt%
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	0%
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

Ingredient	Concentration (wt%)
Atropine	0.001-0.50 (wt%)
Buffer agent (monosodium phosphate anhydrous, disodium phosphate anhydrous) and/or pH adjusting agent (e.g., borates and/or DCl)	q.s. for pH=4.2-7.9 .s. for 0.004 wt%-0.20 wt%
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	0%
Tonicity and/or Osmolarity adjustor (e.g. NaCl, mannitol, etc)	q.s. to 0.5-2.0 wt%
Stabilizing agent (e.g. EDTA)	0.01-0.50 (wt%)
Deuterated Water	q.s. to 100 wt%

Table 5

Ingredient	Concentration (wt%)
Atropine or pharmaceutically acceptable salt of atropine	0.001-0.50 (wt%)
Buffer agent and/or pH adjusting agent (e.g., borates, citrate and/or DCl, citrate)	q.s. for pH=4.2-7.9 and q.s. for 0.004 wt%-0.20 wt%
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	0%
Tonicity and/or Osmolarity adjustor (e.g. NaCl, mannitol, etc)	q.s. to 0.5-2.0 wt%
Water (H ₂ O) : Deuterated Water (D ₂ O)	99:1-1:99

Table 6

Ingredient	Concentration (wt%)
Atropine or pharmaceutically acceptable salt of atropine	0.001-0.50 (wt%)
Buffer agent and/or pH adjusting agent (e.g., borates, citrate and/or DCl, citrate)	q.s. for pH=4.2-7.9 and q.s. for 0.004 wt%-0.20 wt%

Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	0%
Tonicity and/or Osmolarity adjustor (e.g. NaCl, mannitol, etc)	q.s. to 0.5-2.0 wt%
Water (H ₂ O) : Deuterated Water (D ₂ O)	10:90-30:70

Table 7

Ingredient	Concentration (wt%)
Atropine or pharmaceutically acceptable salt of atropine	0.001-0.50 (wt%)
Buffer agent and/or pH adjusting agent (e.g., borates, citrate and/or DCl, citrate)	q.s. for pH=4.2-7.9 and q.s. for 0.004 wt%-0.20 wt%
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	0%
Tonicity and/or Osmolarity adjustor (e.g. NaCl, mannitol, etc)	q.s. to 0.5-2.0 wt%
Water (H ₂ O) : Deuterated Water (D ₂ O)	40:60-60:40

Table 8

Ingredient	Concentration (wt%)
Atropine or pharmaceutically acceptable salt of atropine	0.001-0.50 (wt%)
Buffer agent and/or pH adjusting agent (e.g., borates, citrate and/or DCl, citrate)	q.s. for pH=4.2-7.9 and q.s. for 0.004 wt%-0.20 wt%
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	0%
Tonicity and/or Osmolarity adjustor (e.g. NaCl, mannitol, etc)	q.s. to 0.5-2.0 wt%
Water (H ₂ O) : Deuterated Water (D ₂ O)	40:60-20:80

Table 9

Ingredient	Concentration (wt%)
Atropine or pharmaceutically acceptable salt of atropine	0.001-0.50 (wt%)
Buffer agent and/or pH adjusting agent (e.g., borates, citrate and/or DCl, citrate)	q.s. for pH=4.2-7.9 and q.s. for 0.004 wt%-0.20 wt%
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	0%
Tonicity and/or Osmolarity adjustor (e.g. NaCl, mannitol, etc)	q.s. to 0.5-2.0 wt%
Water (H ₂ O) : Deuterated Water (D ₂ O)	10:90-20:80

Table 10

Ingredient	Concentration (wt%)
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Atropine or pharmaceutically acceptable salt of atropine	0.001-0.10 (wt%)
Buffer agent and/or pH adjusting agent (e.g., borates, citrate and/or DCl, citrate)	q.s. for pH=4.2-7.9 and q.s. for 0.004 wt%-0.20 wt%
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	0.001-0.10 (wt%)
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 11

Ingredient	Concentration (wt%)
Atropine or pharmaceutically acceptable salt of atropine	0.001-0.10 (wt%)
Buffer agent and/or pH adjusting agent (e.g., borates, citrate and/or DCl, citrate)	q.s. for pH=4.2-7.9 and q.s. for 0.004 wt%-0.20 wt%
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	0%
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 12

Ingredient	Concentration (wt%)
Atropine	0.001-0.10 (wt%)
Buffer agent (monosodium phosphate anhydrous, disodium phosphate anhydrous) and/or pH adjusting agent (e.g., borates and/or DCl)	q.s. for pH=4.2-7.9 .s. for 0.004 wt%-0.20 wt%
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	0%
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 13

Ingredient	Concentration (wt%)
Atropine	0.001-0.10 (wt%)
Buffer agent (monosodium phosphate anhydrous, disodium phosphate anhydrous) and/or pH adjusting agent (e.g., borates and/or DCl)	q.s. for pH=4.2-7.9 and q.s. for 0.004 wt%-0.20 wt%
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	0%

Tonicity and/or Osmolarity adjustor (e.g. NaCl, mannitol, etc)	q.s. to 0.5-2.0 wt%
Stabilizing agent (e.g. EDTA)	0.01-0.50 (wt%)
Deuterated Water	q.s. to 100 wt%

Table 14

Ingredient	Concentration (wt%)
Atropine or pharmaceutically acceptable salt of atropine	0.001-0.10 (wt%)
Buffer agent and/or pH adjusting agent (e.g., borates, citrate and/or DCl, citrate)	q.s. for pH=4.2-7.9 and q.s. for 0.004 wt%-0.20 wt%
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	0%
Tonicity and/or Osmolarity adjustor (e.g. NaCl, mannitol, etc)	q.s. to 0.5-2.0 wt%
Water (H ₂ O) : Deuterated Water (D ₂ O)	99:1-1:99

Table 15

Ingredient	Concentration (wt%)
Atropine or pharmaceutically acceptable salt of atropine	0.001-0.10 (wt%)
Buffer agent and/or pH adjusting agent (e.g., borates, citrate and/or DCl, citrate)	q.s. for pH=4.2-7.9 and q.s. for 0.004 wt%-0.20 wt%
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	0%
Tonicity and/or Osmolarity adjustor (e.g. NaCl, mannitol, etc)	q.s. to 0.5-2.0 wt%
Water (H ₂ O) : Deuterated Water (D ₂ O)	10:90-30:70

Table 16

Ingredient	Concentration (wt%)
Atropine or pharmaceutically acceptable salt of atropine	0.001-0.10 (wt%)
Buffer agent and/or pH adjusting agent (e.g., borates, citrate and/or DCl, citrate)	q.s. for pH=4.2-7.9 and q.s. for 0.004 wt%-0.20 wt%
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	0%
Tonicity and/or Osmolarity adjustor (e.g. NaCl, mannitol, etc)	q.s. to 0.5-2.0 wt%
Water (H ₂ O) : Deuterated Water (D ₂ O)	40:60-60:40

Table 17

Ingredient	Concentration (wt%)
Atropine or pharmaceutically acceptable salt of atropine	0.001-0.10 (wt%)

Buffer agent and/or pH adjusting agent (e.g., borates, citrate and/or DCl, citrate)	q.s. for pH=4.2-7.9 and q.s. for 0.004 wt%-0.20 wt%
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	0%
Tonicity and/or Osmolarity adjustor (e.g. NaCl, mannitol, etc)	q.s. to 0.5-2.0 wt%
Water (H ₂ O) : Deuterated Water (D ₂ O)	40:60-20:80

Table 18

Ingredient	Concentration (wt%)
Atropine or pharmaceutically acceptable salt of atropine	0.001-0.10 (wt%)
Buffer agent and/or pH adjusting agent (e.g., borates, citrate and/or DCl, citrate)	q.s. for pH=4.2-7.9 and q.s. for 0.004 wt%-0.20 wt%
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	0%
Tonicity and/or Osmolarity adjustor (e.g. NaCl, mannitol, etc)	q.s. to 0.5-2.0 wt%
Water (H ₂ O) : Deuterated Water (D ₂ O)	10:90-20:80

Table 19. Compositions of Ophthalmic Formulations #1-#20

System	Ophthalmic Formulation	Atropine (% w/v)	BAK (% w/v)	Buffer Species*	DTA (% w/v)	% D ₂ O (% v/v)	pH at 25°C
0.01SYD-BAK	#1	0.01	0	Citrate	0	100	5.59
0.03SYD	#2	0.03	0	Citrate	0	100	5.60
0.01SYD	#3	0.01	0.01	Citrate	0	100	5.60
0.01SYD-BAK + Pho	#4	0.01	0	Phosphate	0	100	5.51
0.01SYD-BAK + Pho +EDTA	#5	0.01	0	Phosphate	0.1	100	5.49
0.01SYD 80% D ₂ O	#6	0.01	0.01	Citrate	0	80	5.74
0.01SYD 50% D ₂ O	#7	0.01	0.01	Citrate	0	50	5.59
0.01SYD 25% D ₂ O	#8	0.01	0.01	Citrate	0	25	5.49
0.01SYD 10% D ₂ O	#9	0.01	0.01	Citrate	0	10	5.45
0.03SYD 50% D ₂ O	#10	0.03	0.01	Citrate	0	50	5.54
0.01SYD -BAK 50% D ₂ O	#11	0.01	0	Citrate	0	50	5.55
0.01SYD -BAK +Pho +EDTA 50% D ₂ O	#12	0.01	0	Phosphate	0.1	50	5.61

0.01SYD 0% D ₂ O pH 5.3	#13	0.01	0.01	Citrate	0	0	5.30
0.01SYD-BAK 0% D ₂ O pH 5.3	#14	0.01	0	Citrate	0	0	5.30
0.03SYD-BAK 0% D ₂ O pH 5.3	#15	0.03	0	Citrate	0	0	5.32
0.01SYD 0% D ₂ O pH 6.0	#16	0.01	0.01	Citrate	0	0	6.02
0.01SYD-BAK 0% D ₂ O pH 5.6	#17	0.01	0	Citrate	0	0	5.63
0.01SYD-BAK 0% D ₂ O pH 6.0	#18	0.01	0	Citrate	0	0	6.03
0.01SYD -BAK 100% D ₂ O pH* 4.9	#19	0.01	0	Citrate	0	100	4.94
0.01SYD -BAK 100% D ₂ O pH* 5.2	#20	0.01	0	Citrate	0	100	5.24

* In some embodiments, citric acid is added at 0.04% w/v and the pH adjusted with NaOH or HCl in the appropriate solvent. The formulation is made isotonic with 0.9% (w/v) NaCl. In some cases, phosphate buffer consists of 0.044% monosodium phosphate anhydrous + 0.863% disodium phosphate anhydrous and the pH adjusted with NaOH or HCl in the appropriate solvent. The formulation is made isotonic with 0.04% (w/v) NaCl in some embodiments.

Example 2 - Preparation of an Aqueous Solution Formulation Containing 0.1%, 0.03%, and 0.01%

Atropine in D₂O

[00374] Stock 1% Solution

[00375] In a 100 mL 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 100 mL sterile deuterated water for injection. The solution is mixed in an appropriately sized beaker with a stir bar on a hot plate until all of the solid powders have dissolved and the solution has become clear with no visible particles. Next, the stir bar is removed, and the solution is poured into a filter bottle and vacuum filtered through a 0.22 micron polyethersulfone membrane filter into a sterile bottle. The filter top is removed from the sterile stock bottle and the stock bottle is capped for storage with a sterile bottle cap.

[00376] Diluted 0.1% Solution

[00377] 3.0 mL of the 1% solution is combined with a quantity sufficient to achieve 30 mL total of sterile 0.9% Sodium Chloride for Injection USP (e.g., 0.9% Sodium Chloride Injection, USP) to generate a 0.1% solution. The solution is thoroughly mixed. The pH of the solution is recorded. A 0.22 micron filter is placed on the tip of the syringe and the solution is aliquoted into separate sterile containers.

[00378] Diluted 0.01% Solution

[00379] 3.0 mL of the 0.1% solution is combined with a quantity sufficient to achieve 30 mL total of sterile 0.9% Sodium Chloride for Injection USP (e.g., 0.9% Sodium Chloride Injection, USP) to generate a 0.01% solution. The solution is thoroughly mixed. The pH of the solution is recorded. A 0.22 micron filter is placed on the tip of the syringe and the solution is aliquoted into separate sterile containers.

[00380] Diluted 0.03% Solution

[00381] 3.0 mL of the 0.1% solution is combined with a quantity sufficient to achieve 10 mL total of sterile 0.9% Sodium Chloride for Injection USP (e.g., 0.9% Sodium Chloride Injection, USP) to generate a 0.03% solution. The solution is thoroughly mixed. The pH of the solution is recorded. A 0.22 micron filter is placed on the tip of the syringe and the solution is aliquoted into separate sterile containers.

Example 3 – Stability Analysis

[00382] Five 0.1% atropine sulfate solutions are prepared from the 1% atropine sulfate stock solution (preparation as described in Example 2). The pH of the five solutions is 5.87, 5.97, 5.90, 6.24, and 6.16 for solutions 1-5, respectively. Each solution is thoroughly mixed. A 0.22 micron filter is placed on the tip of the syringe and the solution is aliquoted into separate sterile containers according to Table 20.

Table 20. 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

[00383] The samples are then stored at different conditions for stability analysis. The samples are analyzed at different time points up to 2 months. The storage conditions include: 40°C with 75% relative humidity (RH) (samples are transferred from 2-8°C condition after 3 days), 25°C with 60% RH, and 60°C. The time points are 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 are removed and allowed to equilibrate to ambient conditions. Once equilibrated, both the plastic eyedropper and the glass vials are inverted 3 times. The solution in the eyedroppers is transferred to an HPLC vial in a drop wise fashion through the dropper. The solution in the glass vial is aliquoted into an HPLC vial using a glass Pasteur pipette. The samples are then tested for purity and potency using the UPLC method listed in Table 21.

Table 21. 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.

[00384] Stability data for the 0.10% atropine sulfate solutions and Arrhenius based shelf life predictions are determined.

Example 4 – Stability Analysis of Ophthalmic Formulations #1-#20

[00385] Stability was analyzed for ophthalmic formulations #1-#20 using methods described in Example 3. A major route of atropine degradation is base-catalyzed hydrolysis to form tropic acid. The formation of tropic acid is the shelf life limiting factor of formulations in many cases. Data regarding formation of tropic acid over time for each of ophthalmic formulations #1-#20 were analyzed and the first order rate constants for tropic acid formation was calculated. Data is shown in **FIG. 1**, and consist of a plot of $\ln(A_0/A_t)$ against time, where A_0 is the initial concentration of atropine and A_t is the concentration at time t . The concentration at time t was closely approximated by subtracting the increase in tropic acid concentration from the initial concentration of atropine. The first order rate constant is given by the gradient of the line (**FIG. 1**).

Example 5 – Kinetics of Tropic Acid Formation

[00386] First order rate constants of tropic acid formation were determined and correlated with the pH measurements for ophthalmic formulations #1-#20. Sufficient buffer was present in each of ophthalmic formulations #1-#20 to keep the pH constant with time. The pH of ophthalmic formulations #1-#20 was measured at multiple time points according to Example 4 and were averaged to yield a more accurate value. These data were fitted to a kinetic model and were found to be first order with respect to atropine concentration. **FIGS. 2-3** show the first order rate constants determined for each of ophthalmic formulations #1-#20 at each of 25°C (k_{25}/mo) and 40°C (k_{40}/mo).

Example 6 - The Effect of pH on Tropic Acid Formation Rate Constants

[00387] The log of the first order rate constant for tropic acid formation for ophthalmic formulations #13-#18 (atropine sulfate hydrolysis) was found. In many cases, the first order rate constant for tropic acid formation is the shelf life limiting factor for a composition. The data shows that the log of the first order rate constant for tropic acid formation follows a linear relationship with pH. The data also shows that the log of the first order rate constant for tropic acid formation has a slope of approximately 1 (0.92 in the case of 25°C data, and 0.97 in the case of 40°C data), indicating that tropic acid is produced by a specific base catalyzed degradation (**FIG. 4**).

Example 7 - The Effect of D₂O in D₂O/H₂O Mixtures on the rate of tropic acid formation

[00388] To compare stability in D₂O/H₂O mixtures, the differences in pH between the formulations needed to be adjusted. Since the degradation rate is proportional to the hydroxide/deuteroxide ion concentration, the first order rate constants to a standard measured pH was adjusted using a pH of 5.6. After adjusting for pH differences in the apparent (measured) pH, the first order rate constant for tropic acid formation was found to have a linear relationship with the amount of D₂O in the formulation (% volume) (**FIG. 5**).

Example 8 - The Effect of D₂O/H₂O Ratio on Perceived pH in Ophthalmic Compositions

[00389] The effect of deuterium oxide water (D₂O) to water (H₂O) ration in ophthalmic compositions is presented. In the case of 100% water, the measured pH corresponds to the actual $-\log_{10}[\text{H}^+]$, the negative log 10 of the hydronium ion concentration. It is contemplated that the species H⁺ does not exist in solution and is actually H₃O⁺. In the case of 100% deuterium oxide the measured pH can be correlated to pD (the negative log 10 of the deuteronium ion concentration, [D₃O⁺]) by the expression $\text{pD}=\text{pH}+0.41$. For example, if two solutions of atropine sulfate are formulated at a measured pH of 5.6, one 100% H₂O and the other 100% D₂O, on administration to the eye, the former will be perceived by the patient as pH 5.60 whereas the latter will be perceived as less acidic at pD 6.01 and closer to the physiological pH of the eye (tear fluid pH is close to 7.0). In terms of how this impacts a patient receiving a deuterium oxide solution as an ophthalmic drop, the pertinent factor in terms of tolerability in the eye, in many cases, is pD since this defines how close the solution is to the physiological pH of the tear film. Ideally ophthalmic solutions should be as close as possible to the physiological pH of the corneal tear film (approximately pH 7.0).

[00390] For intermediate compositions of H₂O and D₂O the effective pH will consist of the summation of hydronium and deuteronium ions, which can be used to calculate the sum concentration of OH⁻ and OD⁻, which are the catalytic species affecting the rate of degradation of atropine to tropic acid. To a first approximation, the 0.41 pH unit offset from the measured pH can be assumed to decrease linearly as more water is added to a deuterium oxide system (FIG. 6).

[00391] This is consistent with the linear decrease in rate of degradation with increasing D₂O content seen in FIG. 5. In this way, the pD/pH of a D₂O/H₂O system was estimated (FIG. 6), and its effect on the rate of tropic acid formation was also estimated. FIG. 7 combines observations made of the effect of increasing D₂O content on the rate of formation of tropic acid and the perceived pH of the ophthalmic composition (e.g., eyedrop). As shown in these data, increasing the D₂O content resulted in more stable formulations while also increasing the perceived pH of the eyedrop, which is counterintuitive for a base-catalyzed degradation.

Example 9 - Overall Assessment of Ophthalmic Formulations #1-#20

[00392] This example shows the evaluation of pH and shelf life stability of ophthalmic formulations #1-#20 presented in Example 1.

[00393] *Ophthalmic Formulations #1-#12*

[00394] FIG. 2 shows that each of ophthalmic formulations #1-#12 meet the criteria for 24 month stability at 25 °C, as their rate constants are each below the black “2 yr shelf life at 25 °C” line that was determined based on atropine concentration and rate constant. While 9 of 10 tested ophthalmic formulations with at least a 50% v/v composition of deuterium oxide (D₂O) to water (H₂O) (e.g., ophthalmic formulations #1-#7 and #10-#11) passed the commonly applied accelerated stability criteria of 6 months at 40 °C, tested ophthalmic formulations with less than a 50% v/v composition of deuterium oxide to water (e.g., ophthalmic formulations #8 and #9) did not pass the 6 months at 40 °C stability

criterion. These data indicate that ophthalmic formulations having at least a 50:50 mixture of D₂O to H₂O are strong clinical candidates (e.g., in compositions formulated to a measured pH close to 5.6). It is contemplated that compositions can be formulated at lower D₂O content than 50:50, for example, when the measured pH of formulations is lowered. It is noted that the numbers presented across the top of the chart (“Max pH to meet 6 mo at 40 °C”) indicate the maximum pH at which an ophthalmic formulation can be adjusted to and still meet stability criteria for storage at 6 months at 40 °C (e.g., as indicated on the graph by the thick horizontal black line just under 0.0140 k/mo). The data also indicates that citric acid buffer is significantly better than the phosphate buffer system in terms of reduced tropic acid formation. Comparison of formulations 1 and 3 (both 100% D₂O) showed BAK has no effect on the rate of degradation.

[00395] *Ophthalmic Formulations #13-#20*

[00396] **FIG. 3** suggests that the presence or absence of BAK in an ophthalmic formulation has relatively little effect on shelf life (e.g., among H₂O systems). As is the case with ophthalmic formulations #1-#12 above, ophthalmic formulations with tropic acid formation constants less than that indicated by the “Max k for 6 mo shelf life” line are highly desirable, as degradation at 6 months is strongly temperature dependent and product experiencing inadvertent temperature variations on the market would be significantly less likely to experience a product recall. As can be seen, if formulated at a measured pH of 5.6 only the deuterium oxide systems (e.g., ophthalmic formulations #19 and #20) would meet this requirement, other tested ophthalmic formulations presented in **FIG 3**. (e.g., ophthalmic formulations #13-#18), which comprise water but no deuterium oxide, would need to be adjusted to a lower pH to meet the more stringent 6 month at 40 °C shelf life criterion.

Example 10 - The Effect of Deuterium Oxide Content on Activation Energy

[00397] Previous work has shown the kinetics of tropic acid formation fits the Arrhenius relationship with temperature. Although in these studies data has been accumulated at only two temperatures, the ratio of the first order rate constants at 40 °C and 25 °C should yield a value which is proportional to the exponential of the activation energy. A greater k_2/k_1 ratio is indicative of a greater activation energy for the system.

[00398] Results using this analysis are shown in **FIG. 8**. As can be seen, despite the scatter, the degradation reaction had a significantly higher E_a in pure water than in pure deuterium oxide (significant at a 99% confidence level). Interestingly, at any intermediate composition the activation energy appeared to be similar to 100% deuterium oxide. Consequently, another advantage of adding deuterium oxide to a solution of atropine was that the degradation reaction to tropic acid became much less affected by increases in temperature at 6 months. For a 100% H₂O system a 15 °C difference in temperature (from 25 °C to 40 °C) the rate of degradation to tropic acid increased 12-fold, by comparison for a system containing D₂O the increase was only 8-fold.

Example 11. Effect of pH and Temperature on rate of tropic acid formation (100% D₂O)

[00399] A plot of $\log(k)$ versus pH was generated. FIG. 9 shows that a plot of $\log(k)$ versus pH is linear with a slope of 1, both for D₂O systems and for H₂O systems, meaning the reaction is specific base catalyzed in both deuterium oxide and water systems. The degradation also followed Arrhenius kinetics in both solvent systems (linear plot of $\ln(k)$ versus $1/\text{Temperature}$).

[00400] Previous reports further demonstrated that the effect of dilution of a buffer system in D₂O with H₂O results in a linear decrease in pH (Practical corrections for p(H,D) measurements in mixed H₂O/D₂O biological buffer, Kenneth A. Robinson, Anal. Methods, 2017, 9, 2744–2750). This is due to effect of the deuterium oxide content on the pK_a of the acid or base present in the buffer system as well as the offset in the measurement generated by the pH probe (pH*). In 100% D₂O this offset is 0.41 pH units for an electrode calibrated using aqueous buffers. The paper cited above confirms that as a D₂O/buffer system is diluted with water, there was a linear reduction in this offset from 0.41 units to zero when the system reached effectively 100% water. This allowed for calculation of the effective acidity (concentration of proton and hydronium ions) for any water:deuterium oxide mixture.

Example 12– 1% Atropine Sulfate (Bausch + Lomb) Sample Analysis

[00401] The 1% atropine sulfate sample is obtained from Bausch + Lomb (Lot 198421). For comparison the pH of the 1% Atropine Sulfate drug product is determined in the neat solution as well as a sample that is diluted to the current nominal concentration (0.01% Atropine Sulfate) using the vehicle. Additionally a sample is diluted to the nominal concentration with method diluent. Both samples diluted to the nominal concentration are analyzed using the RP-UPLC method (Table 21).

Example 13 – Dose Uniformity (10-Dose)

[00402] 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 14 – Dose Uniformity (5-Dose)

[00403] 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 15 – Dose Uniformity (2-Dose)

[00404] 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 16– Formulation Stability Comparison and Determination of Shelf Life and Activation Energy

[00405] Atropine sulfate monohydrate (MP Bio; Lot Number 7825K) and tropic acid (Sigma Aldrich; Lot Number STBD6457V) are used for this experiment. Various formulations as described in Example 1 are analyzed at t=0, 2 weeks, and 4 weeks. The conditions that are tested include 40°C with 75% relative humidity (RH), 25°C with 60% RH, and 60°C. A RP-HPLC method is used to carry out the analysis.

[00406] Atropine sulfate purity, tropic acid degradation, atropine sulfate potency, and pH and pD stability are determined. Data is also used to determine shelf life and activation energy.

Example 17 - 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 18 – 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 19 – 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 is 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 is 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 are treated with the ophthalmic aqueous formulation, the ophthalmic carrier (without the ophthalmic agent), or FDM-only. The defocus-induced myopia groups are treated with the ophthalmic aqueous formulation, the ophthalmic carrier (without the ophthalmic agent), or defocus-only. The control groups are 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] 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

1. An ophthalmic composition comprising from about 0.001 wt% to about 0.5 wt% of a muscarinic antagonist and deuterated water, at a pH of from about 4.2 to about 7.9, wherein the ophthalmic composition is substantially free of a benzalkonium chloride preservative.
2. The ophthalmic composition of claim 1, wherein the ophthalmic composition is substantially free of a preservative selected from cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof.
3. The ophthalmic composition of any of claims 1 or 2, wherein the ophthalmic composition has no detectable amount of a benzalkonium chloride preservative.
4. The ophthalmic composition of any of claims 1-3, wherein the ophthalmic composition has no detectable amount of benzalkonium chloride.
5. The ophthalmic composition of any of claims 1-4, wherein the ophthalmic composition has no detectable amount of a preservative.
6. The ophthalmic composition of any of claims 1-5, wherein the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine, homatropine, or a combination thereof.
7. The ophthalmic composition of claim 1, wherein the muscarinic antagonist is atropine or a pharmaceutically acceptable salt of atropine.
8. The ophthalmic composition of claim 1, wherein the muscarinic antagonist is present in the ophthalmic composition at a concentration of one of: from about 0.001 wt% to about 0.40 wt%, from about 0.001 wt% to about 0.30 wt%, from about 0.001 wt% to about 0.20 wt%, from about 0.001 wt% to about 0.10 wt%, from about 0.001 wt% to about 0.09 wt%, from about 0.001 wt% to about 0.08 wt%, from about 0.001 wt% to about 0.07 wt%, from about 0.001 wt% to about 0.06 wt%, from about 0.001 wt% to about 0.05 wt%, from about 0.001 wt% to about 0.04 wt%, from about 0.001 wt% to about 0.03 wt%, from about 0.001 wt% to about 0.025 wt%, from about 0.001 wt% to about 0.02 wt%, from about 0.001 wt% to about 0.01 wt%, from about 0.001 wt% to about 0.008 wt%, or from about 0.001 wt% to about 0.005 wt%.
9. The ophthalmic composition of claim 1, wherein the muscarinic antagonist is present in the ophthalmic composition at a concentration from about 0.001 wt% to about 0.10 wt%.
10. The ophthalmic composition of any of claims 1-8, wherein the ophthalmic composition further comprises 0.004 wt% to about 0.20 wt% citrate.
11. The ophthalmic composition of any of claims 1-8, wherein the ophthalmic composition further comprises an osmolarity adjusting agent.
12. The ophthalmic composition of claim 11, wherein the osmolarity adjusting agent is sodium chloride.
13. The ophthalmic composition of claim 12, wherein the sodium chloride is present in the ophthalmic composition at a concentration of one of: from about 0.01 wt% to about 1.0 wt%,

- from about 0.05 wt% to about 1.5 wt%, from about 0.075 wt% to about 2.0 wt%, or from about 0.1 wt% to about 3.0 wt%.
14. The ophthalmic composition of any of claims 1-13, wherein the ophthalmic composition further comprises a buffering agent.
 15. The ophthalmic composition of claim 14, wherein the buffering 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 any of claims 1-15, wherein the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof.
 17. The ophthalmic composition of any of claims 1-16, wherein the ophthalmic composition further comprises a pH adjusting agent.
 18. The ophthalmic composition of claim 17, wherein the pH adjusting agent comprises DCl, HCl, NaOH, NaOD, CD₃COOD, C₆D₈O₇, CH₃COOH, C₆H₈O₇, or combinations thereof.
 19. The ophthalmic composition of claim 1, wherein the ophthalmic composition comprises less than about 10% of a degradant of the muscarinic antagonist formed from degradation of the muscarinic antagonist.
 20. An ophthalmic composition comprising from about 0.001 wt% to about 0.5 wt% of a muscarinic antagonist, deuterated water, at a pH of from about 4.2 to about 7.9, and one or more sodium phosphate buffers, wherein at least one sodium phosphate buffer of the one or more sodium phosphate buffers is present in the ophthalmic composition at a concentration of about 0.004 wt% to about 0.20 wt%.
 21. The ophthalmic composition of claim 20, wherein the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine, homatropine, or a combination thereof.
 22. The ophthalmic composition of claim 20, wherein the muscarinic antagonist is atropine or a pharmaceutically acceptable salt of atropine.
 23. The ophthalmic composition of claim 20, wherein a first sodium phosphate buffer of the one or more sodium phosphate buffers is monosodium phosphate anhydrous.
 24. The ophthalmic composition of claim 23, wherein the monosodium phosphate anhydrous is present in the ophthalmic composition at a concentration of about 0.004 wt% to about 0.20 wt%.
 25. The ophthalmic composition of claim 23, wherein a second sodium phosphate buffer of the one or more sodium phosphate buffers is disodium phosphate anhydrous.
 26. The ophthalmic composition of claim 25, wherein the disodium phosphate anhydrous is present in the ophthalmic composition at a concentration of about 0.050 wt% to about 2.0 wt%.
 27. The ophthalmic composition of claim 20, wherein the muscarinic antagonist is present in the ophthalmic composition at a concentration of one of: from about 0.001 wt% to about 0.40 wt%, from about 0.001 wt% to about 0.30 wt%, from about 0.001 wt% to about 0.20 wt%, from about

- 0.001 wt% to about 0.10 wt%, from about 0.001 wt% to about 0.09 wt%, from about 0.001 wt% to about 0.08 wt%, from about 0.001 wt% to about 0.07 wt%, from about 0.001 wt% to about 0.06 wt%, from about 0.001 wt% to about 0.05 wt%, 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%.
28. The ophthalmic composition of claim 20, wherein the muscarinic antagonist is present in the ophthalmic composition at a concentration from about 0.001 wt% to about 0.10 wt%.
29. The ophthalmic composition of claim 20, wherein the ophthalmic composition is essentially free of citrate and acetate buffering agents.
30. The ophthalmic composition of any of claims 20-29, wherein the ophthalmic composition further comprises an osmolarity adjusting agent.
31. The ophthalmic composition of claim 30, wherein the osmolarity adjusting agent is sodium chloride.
32. The ophthalmic composition of claim 31, wherein the sodium chloride is present in the ophthalmic composition at a concentration of one of: from about 0.01 wt% to about 1.0 wt%, from about 0.05 wt% to about 1.5 wt%, from about 0.075 wt% to about 2.0 wt%, or from about 0.1 wt% to about 3.0 wt%.
33. The ophthalmic composition of any of claims 20-32, wherein the ophthalmic composition is free of a preservative selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof.
34. The ophthalmic composition of claim 33, wherein the ophthalmic composition is substantially free of a benzalkonium chloride preservative.
35. The ophthalmic composition of any of claims 20-34, wherein the ophthalmic composition is substantially free of any preservative.
36. The ophthalmic composition of any of claims 20-35, wherein the ophthalmic composition further comprises a buffering agent.
37. The ophthalmic composition of claim 36, wherein the buffering 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.
38. The ophthalmic composition of any of claims 20-37, wherein the ophthalmic composition further comprises EDTA.
39. The ophthalmic composition of claim 38, wherein the EDTA is present in the ophthalmic composition at a concentration of 0.01 wt% to about 0.50 wt%.
40. The ophthalmic composition of any of claims 20-39, wherein the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof.

41. The ophthalmic composition of any of claims 20-40, wherein the ophthalmic composition further comprises a pH adjusting agent.
42. The ophthalmic composition of claim 41, wherein the pH adjusting agent comprises DCl, HCl, NaOH, NaOD, CD₃COOD, C₆D₈O₇, CH₃COOH, C₆H₈O₇, or combinations thereof.
43. An ophthalmic composition comprising from about 0.001 wt% to about 0.5 wt% of a muscarinic antagonist, deuterated water, at a pH of from about 4.2 to about 7.9, and 0.01 wt% to about 0.50 wt% EDTA.
44. The ophthalmic composition of claim 43, wherein the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine, homatropine, or a combination thereof.
45. The ophthalmic composition of claim 43, wherein the muscarinic antagonist is atropine or pharmaceutically acceptable salt of atropine.
46. The ophthalmic composition of any of claims 43-45, wherein the ophthalmic composition further comprises one or more sodium phosphate buffers.
47. The ophthalmic composition of claim 46, wherein a first sodium phosphate buffer of the one or more sodium phosphate buffers is monosodium phosphate anhydrous.
48. The ophthalmic composition of claim 47, wherein the sodium phosphate anhydrous is present in the ophthalmic composition at a concentration of about 0.004 wt% to about 0.20 wt%.
49. The ophthalmic composition of claim 46, wherein a second sodium phosphate of the one or more sodium phosphate buffers is disodium phosphate anhydrous.
50. The ophthalmic composition of claim 49, wherein the disodium phosphate anhydrous is present in the ophthalmic composition at a concentration of about 0.050 wt% to about 2.0 wt%.
51. The ophthalmic composition of claim 43, wherein the muscarinic antagonist is present in the ophthalmic composition at a concentration of one of: from about 0.001 wt% to about 0.40 wt%, from about 0.001 wt% to about 0.30 wt%, from about 0.001 wt% to about 0.20 wt%, from about 0.001 wt% to about 0.10 wt%, from about 0.001 wt% to about 0.09 wt%, from about 0.001 wt% to about 0.08 wt%, from about 0.001 wt% to about 0.07 wt%, from about 0.001 wt% to about 0.06 wt%, from about 0.001 wt% to about 0.05 wt%, 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%.
52. The ophthalmic composition of claim 43, wherein the muscarinic antagonist is present in the ophthalmic composition at a concentration from about 0.001 wt% to about 0.10 wt%.
53. The ophthalmic composition of any of claims 43-52, wherein the ophthalmic composition further comprises 0.004 wt% to about 0.20 wt% citrate.
54. The ophthalmic composition of any of claims 43-53, wherein the ophthalmic composition further comprises an osmolarity adjusting agent.

55. The ophthalmic composition of claim 54, wherein the osmolarity adjusting agent is sodium chloride.
56. The ophthalmic composition of claim 55, wherein the sodium chloride is present in the ophthalmic composition at a concentration of one of: from about 0.01 wt% to about 1.0 wt%, from about 0.05 wt% to about 1.5 wt%, from about 0.075 wt% to about 2.0 wt%, or from about 0.1 wt% to about 3.0 wt%.
57. The ophthalmic composition of any of claims 43-56, wherein the ophthalmic composition is free of a preservative selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof.
58. The ophthalmic composition of claim 57, wherein the ophthalmic composition is substantially free of a benzalkonium chloride preservative.
59. The ophthalmic composition of any of claims 43-58, wherein the ophthalmic composition is substantially free of any preservative.
60. The ophthalmic composition of any of claims 43-59, wherein the ophthalmic composition further comprises a buffering agent.
61. The ophthalmic composition of claim 60, wherein the buffering 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.
62. The ophthalmic composition of any of claims 43-61, wherein the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof.
63. The ophthalmic composition of any of claims 43-62, wherein the ophthalmic composition further comprises a pH adjusting agent.
64. The ophthalmic composition of claim 63, wherein the pH adjusting agent comprises DCl, HCl, NaOH, NaOD, CD₃COOD, C₆D₈O₇, CH₃COOH, C₆H₈O₇, or combinations thereof.
65. An ophthalmic composition comprising from about 0.001 wt% to about 0.5 wt% of a muscarinic antagonist, deuterated water, at a pH of from about 4.2 to about 7.9, and water, wherein a ratio of the water to the deuterated water is in a range of 60:40 to 99:1.
66. The ophthalmic composition of claim 65, wherein the muscarinic antagonist comprises atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, hyoscine, scopolamine, tropicamide, cyclopentolate, pirenzepine, homatropine, or a combination thereof.
67. The ophthalmic composition of claim 65, wherein the muscarinic antagonist is atropine or pharmaceutically acceptable salt of atropine.
68. The ophthalmic composition of claim 65, wherein the muscarinic antagonist is present in the ophthalmic composition at a concentration of one of: from about 0.001 wt% to about 0.40 wt%, from about 0.001 wt% to about 0.30 wt%, from about 0.001 wt% to about 0.20 wt%, from about 0.001 wt% to about 0.10 wt%, from about 0.001 wt% to about 0.09 wt%, from about 0.001 wt%

to about 0.08 wt%, from about 0.001 wt% to about 0.07 wt%, from about 0.001 wt% to about 0.06 wt%, from about 0.001 wt% to about 0.05 wt%, 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%.

69. The ophthalmic composition of claim 65, wherein the muscarinic antagonist is present in the ophthalmic composition at a concentration from about 0.001 wt% to about 0.10 wt%.
70. The ophthalmic composition of claim 65, wherein a ratio of the water to the deuterated water is in a range of about 80:20 to about 60:40.
71. The ophthalmic composition of claim 65, wherein a ratio of the water to the deuterated water is about 65:35.
72. The ophthalmic composition of claim 65, wherein a ratio of the water to the deuterated water is about 90:10.
73. The ophthalmic composition of claim 65, wherein the muscarinic antagonist is present in the ophthalmic composition at a concentration of from about 0.01 wt% to about 0.05 wt%.
74. The ophthalmic composition of claim 65, wherein the muscarinic antagonist is present in the ophthalmic composition at a concentration of from about 0.01 wt% to about 0.03 wt%.
75. The ophthalmic composition of claim 65, wherein the muscarinic antagonist is present in the ophthalmic composition at a concentration of about 0.01 wt%.
76. The ophthalmic composition of claim 65, wherein the muscarinic antagonist is present in the ophthalmic composition at a concentration of about 0.03 wt%.
77. The ophthalmic composition of any one of claims 65-76, wherein the ophthalmic composition is substantially free of a benzalkonium chloride preservative.
78. The ophthalmic composition of any one of claims 65-76, wherein the ophthalmic composition has no detectable amount of a benzalkonium chloride preservative.
79. The ophthalmic composition of any one of claims 65-76, wherein the ophthalmic composition has no detectable amount of a preservative.
80. The ophthalmic composition of claim 65, wherein the ophthalmic composition has a pH from about 5.1 to about 6.0.
81. The ophthalmic composition of claim 65, wherein the ophthalmic composition has a pH from about 5.54 to about 5.59.
82. The ophthalmic composition of any of claims 65-81, wherein the ophthalmic composition further comprises 0.004 wt% to about 0.20 wt% citrate.
83. The ophthalmic composition of any of claims 65-82, wherein the ophthalmic composition further comprises one or more sodium phosphate buffers.
84. The ophthalmic composition of claim 83, wherein a first sodium phosphate buffer of the one or more sodium phosphate buffers is monosodium phosphate anhydrous.

85. The ophthalmic composition of claim 84, wherein the monosodium phosphate anhydrous is present in the ophthalmic composition at a concentration of about 0.004 wt% to about 0.20 wt%.
86. The ophthalmic composition of claim 85, wherein a second sodium phosphate of the one or more sodium phosphate buffers is disodium phosphate anhydrous.
87. The ophthalmic composition of claim 86, wherein the disodium phosphate anhydrous is present in the ophthalmic composition at a concentration of about 0.050 wt% to about 2.0 wt%.
88. The ophthalmic composition of any of claims 65-87, wherein the ophthalmic composition further comprises an osmolarity adjusting agent.
89. The ophthalmic composition of any of claims 65-88, wherein the osmolarity adjusting agent is sodium chloride.
90. The ophthalmic composition of claim 89, wherein the sodium chloride is present in the ophthalmic composition at a concentration of one of: from about 0.01 wt% to about 1.0 wt%, from about 0.05 wt% to about 1.5 wt%, from about 0.075 wt% to about 2.0 wt%, or from about 0.1 wt% to about 3.0 wt%.
91. The ophthalmic composition of any of claims 65-90, wherein the ophthalmic composition is free of a preservative selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof.
92. The ophthalmic composition of claim 91, wherein the ophthalmic composition is substantially free of a benzalkonium chloride preservative.
93. The ophthalmic composition of any of claims 65-92, wherein the ophthalmic composition is substantially free of any preservative.
94. The ophthalmic composition of any of claims 65-93, wherein the ophthalmic composition further comprises a buffering agent.
95. The ophthalmic composition of claim 94, wherein the buffering 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.
96. The ophthalmic composition of any of claims 65-95, wherein the ophthalmic composition further comprises EDTA.
97. The ophthalmic composition of claim 96, wherein the EDTA is present in the ophthalmic composition at a concentration of 0.01 wt% to about 0.50 wt%.
98. The ophthalmic composition of any of claims 65-97, wherein the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof.
99. The ophthalmic composition of any of claims 65-98, wherein the ophthalmic composition further comprises a pH adjusting agent.
100. The ophthalmic composition of claim 99, wherein the pH adjusting agent comprises DCl, HCl, NaOH, NaOD, CD₃COOD, C₆D₈O₇, CH₃COOH, C₆H₈O₇, or combinations thereof.

101. The ophthalmic composition of claim 65, wherein the ophthalmic composition comprises less than about 10% of a degradant of the muscarinic antagonist formed from degradation of the muscarinic antagonist.
102. The ophthalmic composition of 1-101, wherein the ophthalmic composition is formulated as an ophthalmic solution for treatment of pre-myopia, myopia, progression of myopia, or slowing progression of myopia.

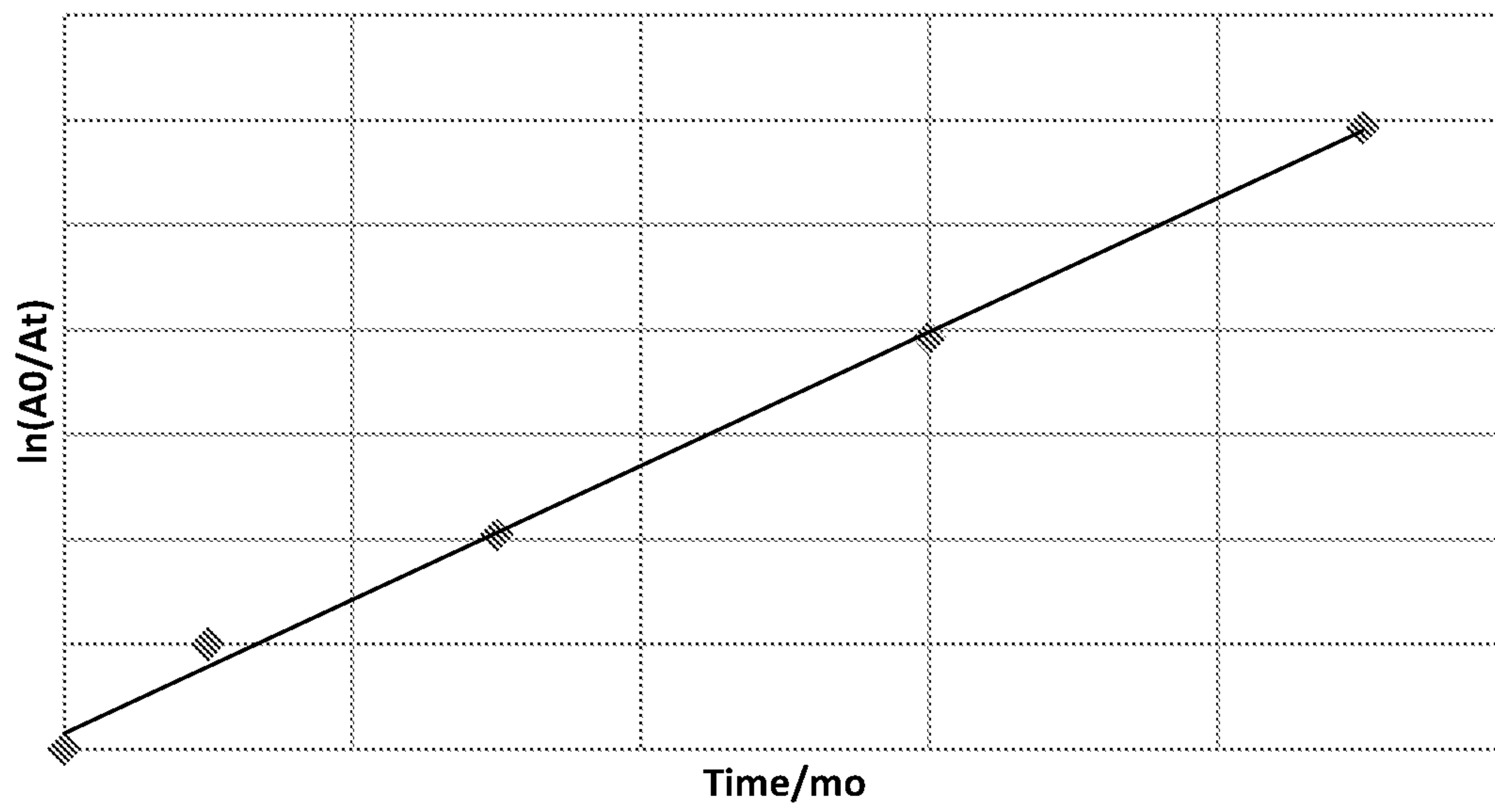


FIG. 1

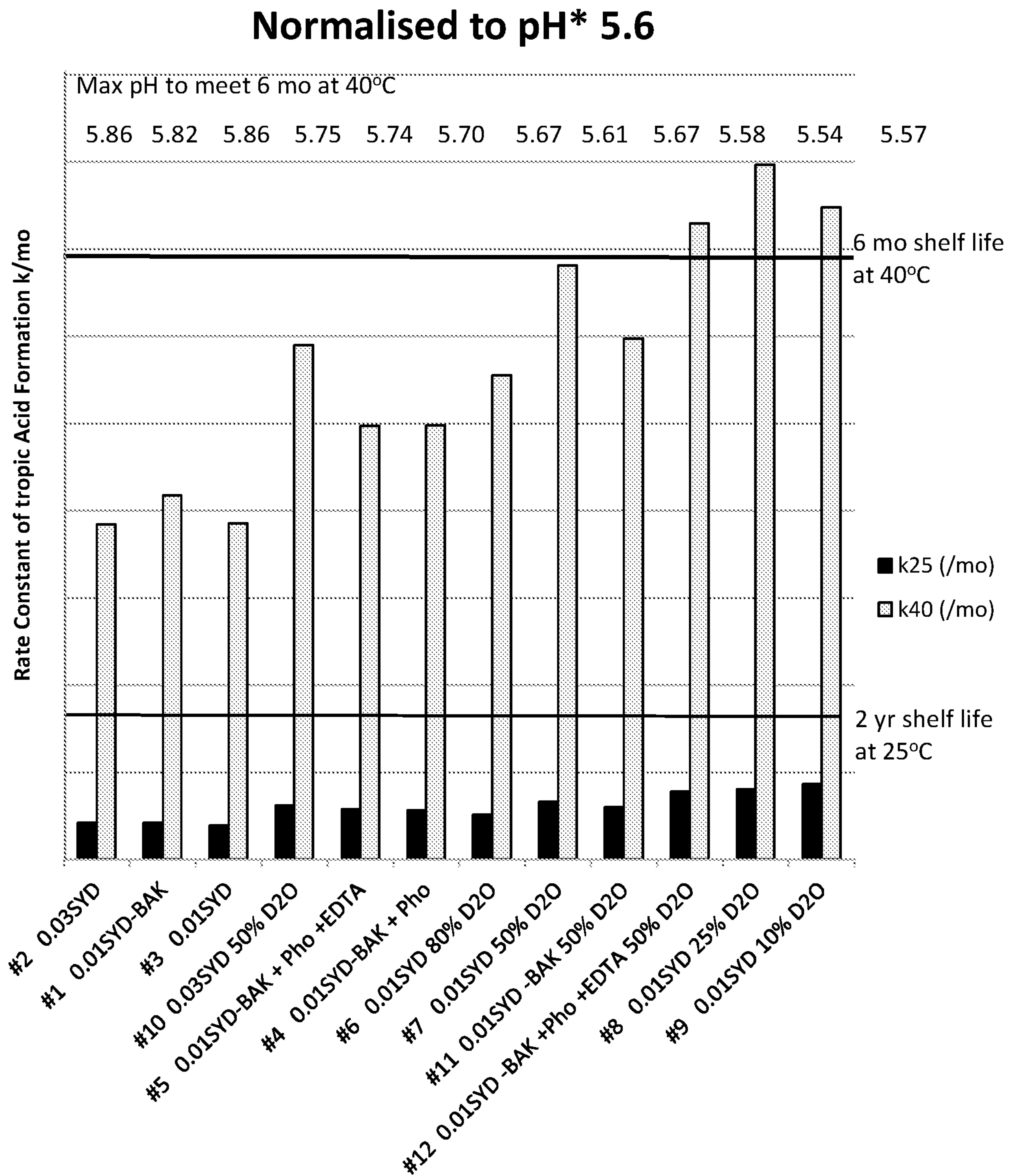


FIG. 2

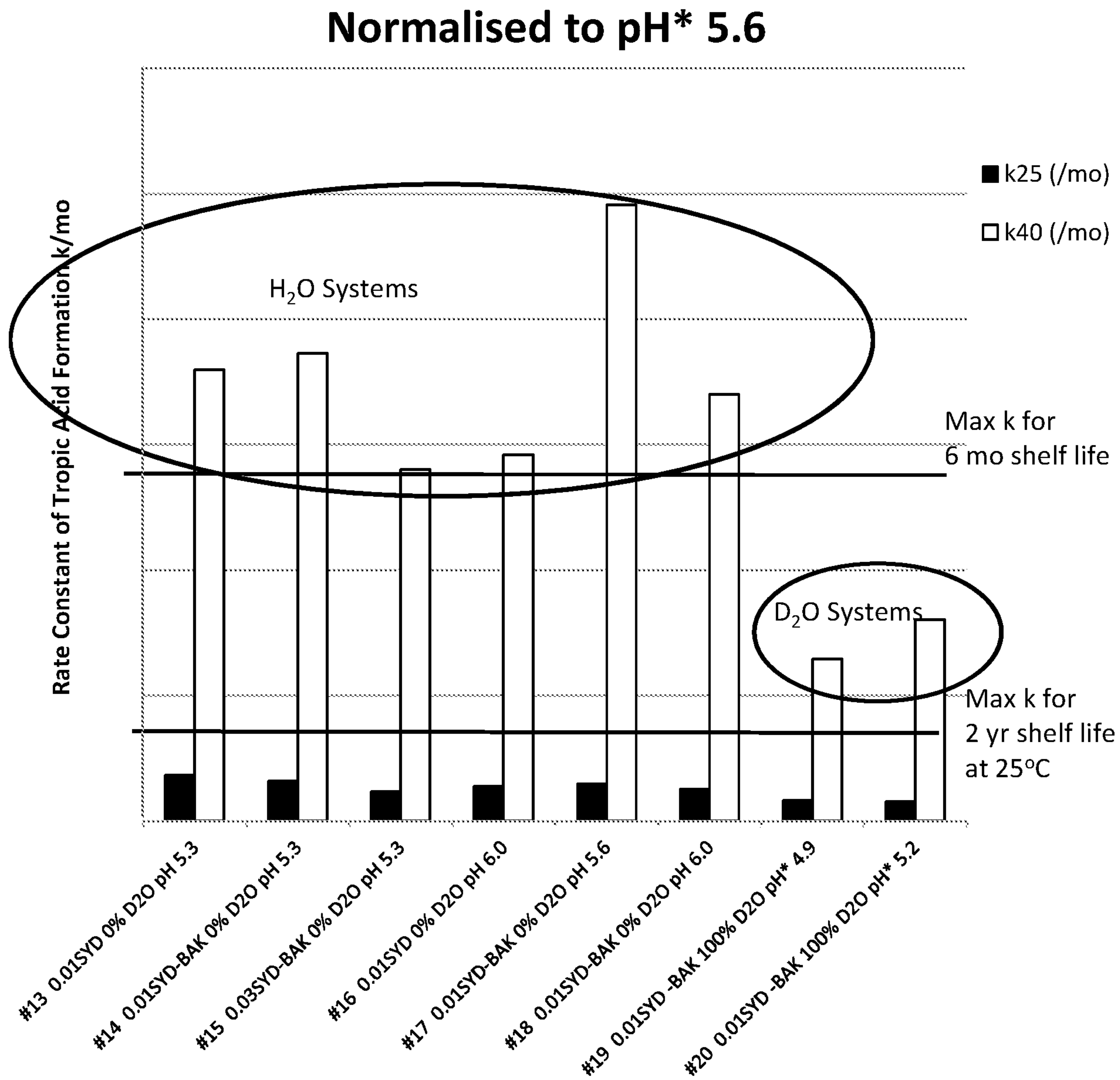


FIG. 3

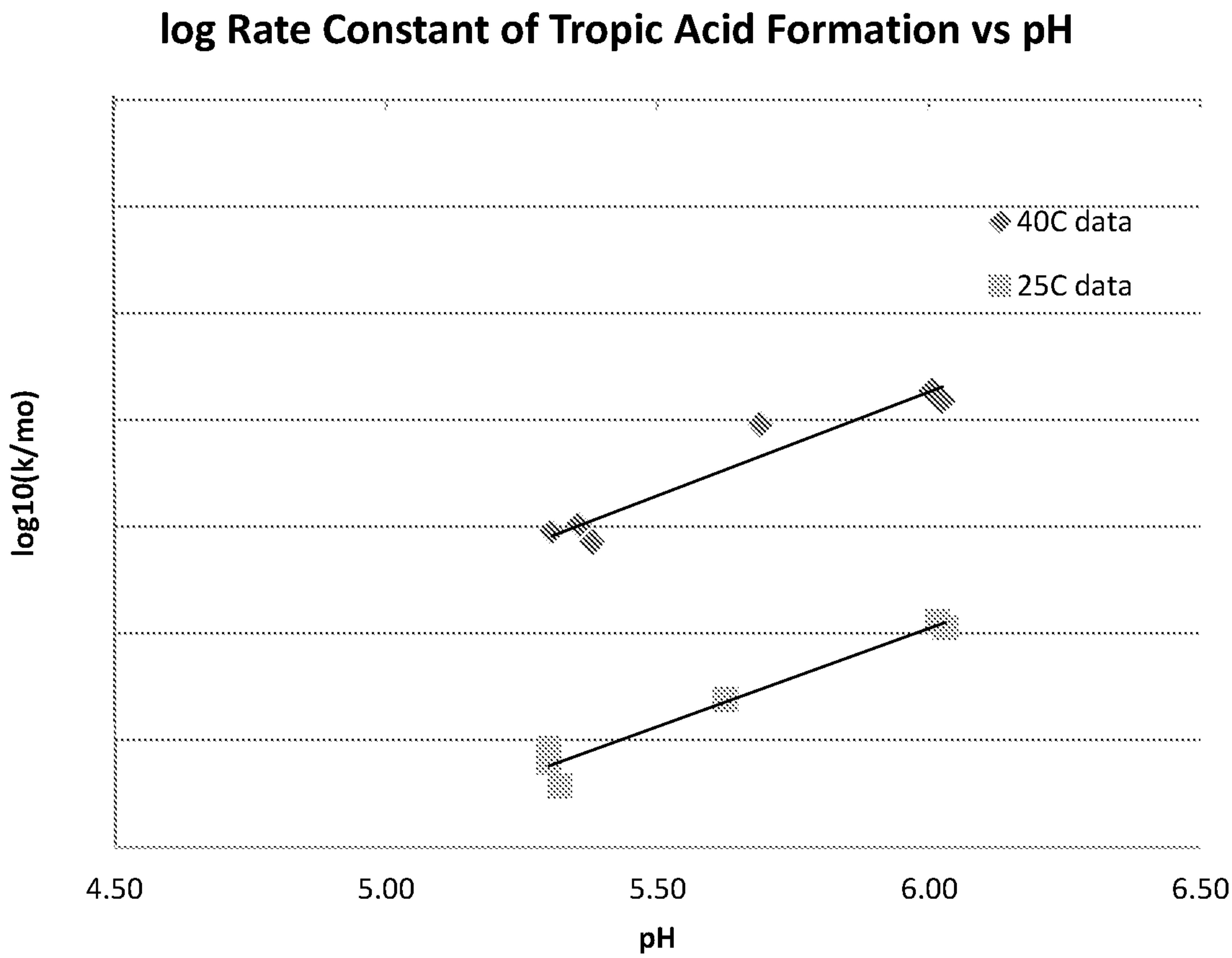


FIG. 4

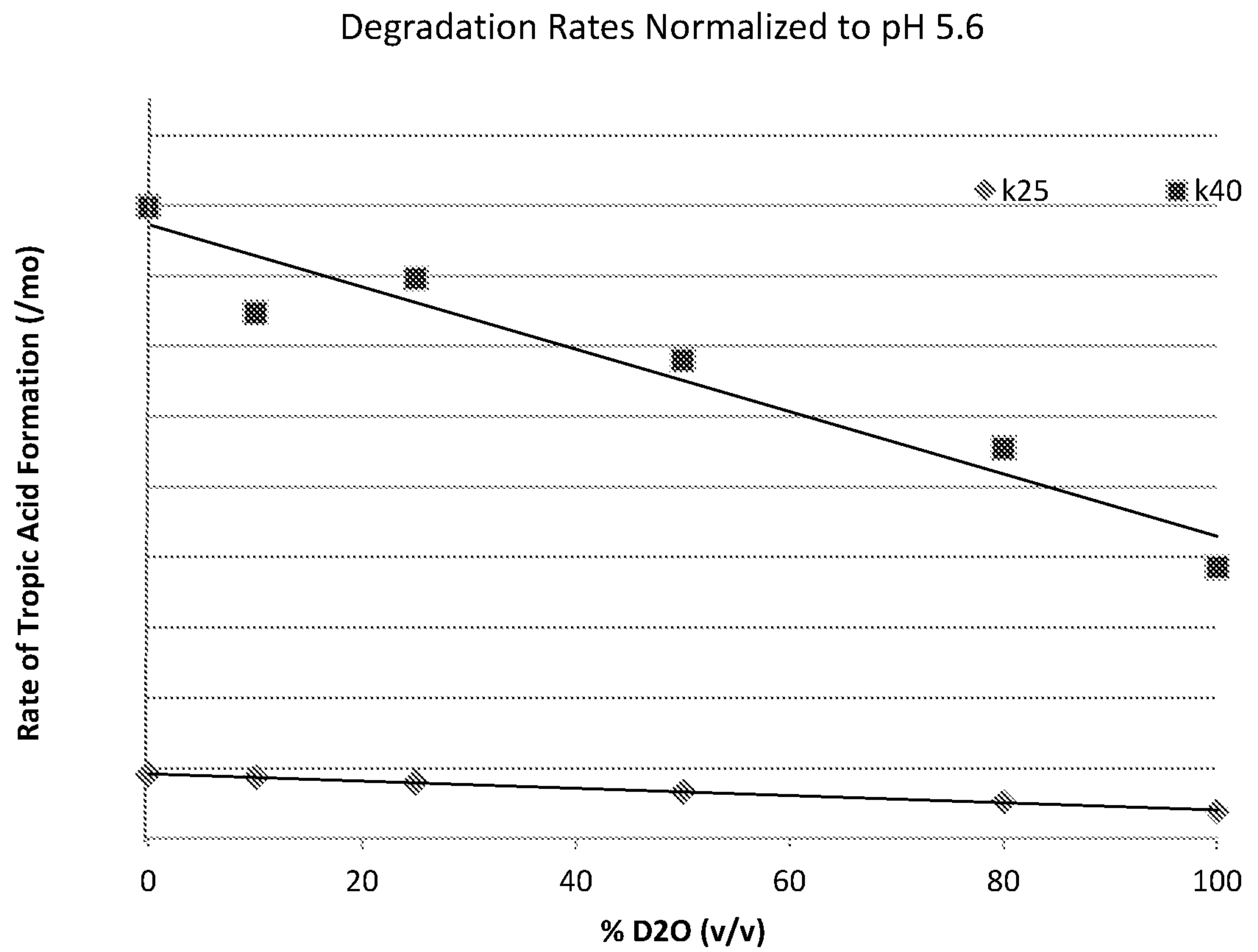


FIG. 5

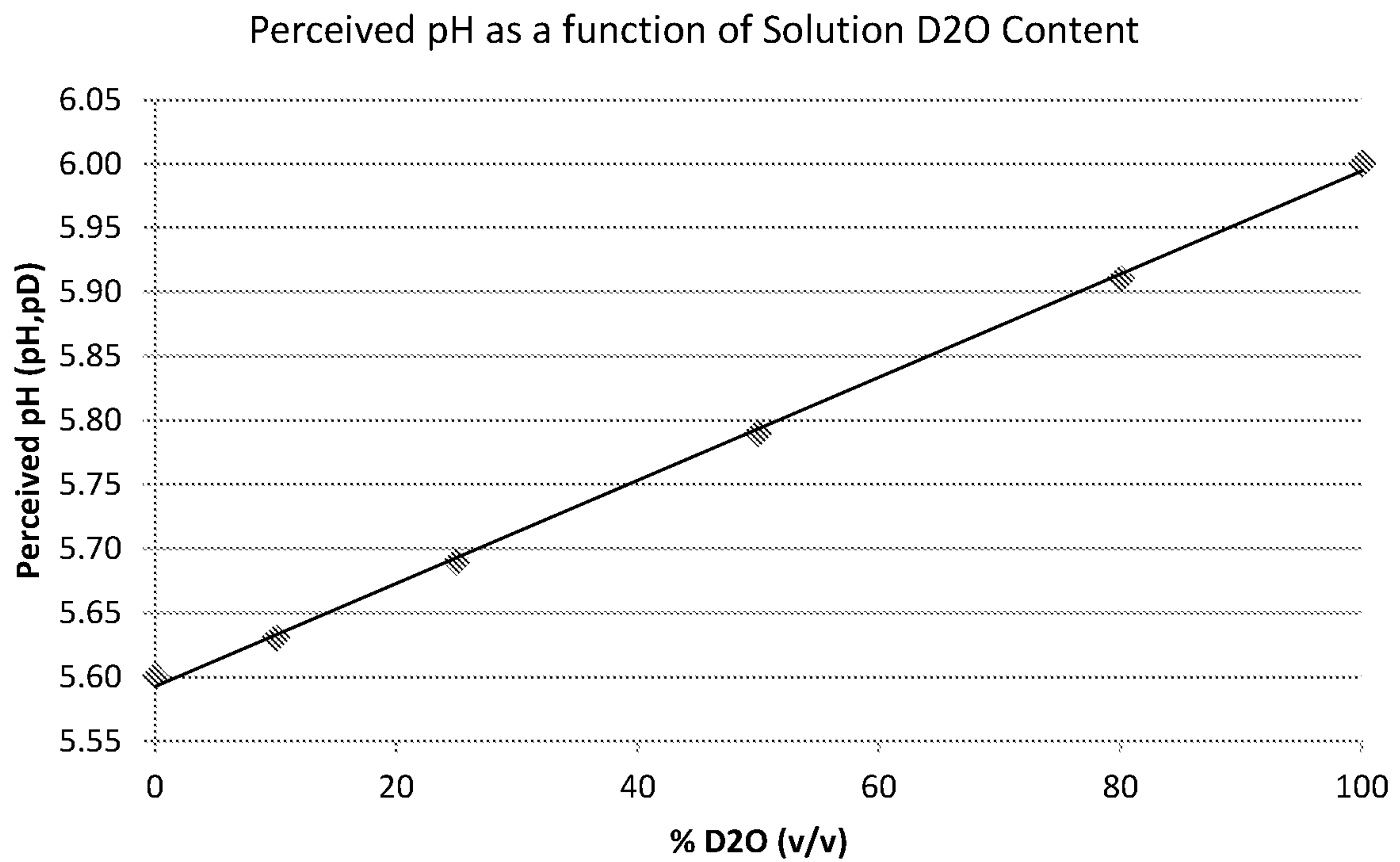


FIG. 6

25C Rate Constant of Tropic Acid Formation as a Function of % D2O (v/v). k adjusted to a measured pH of 5.6

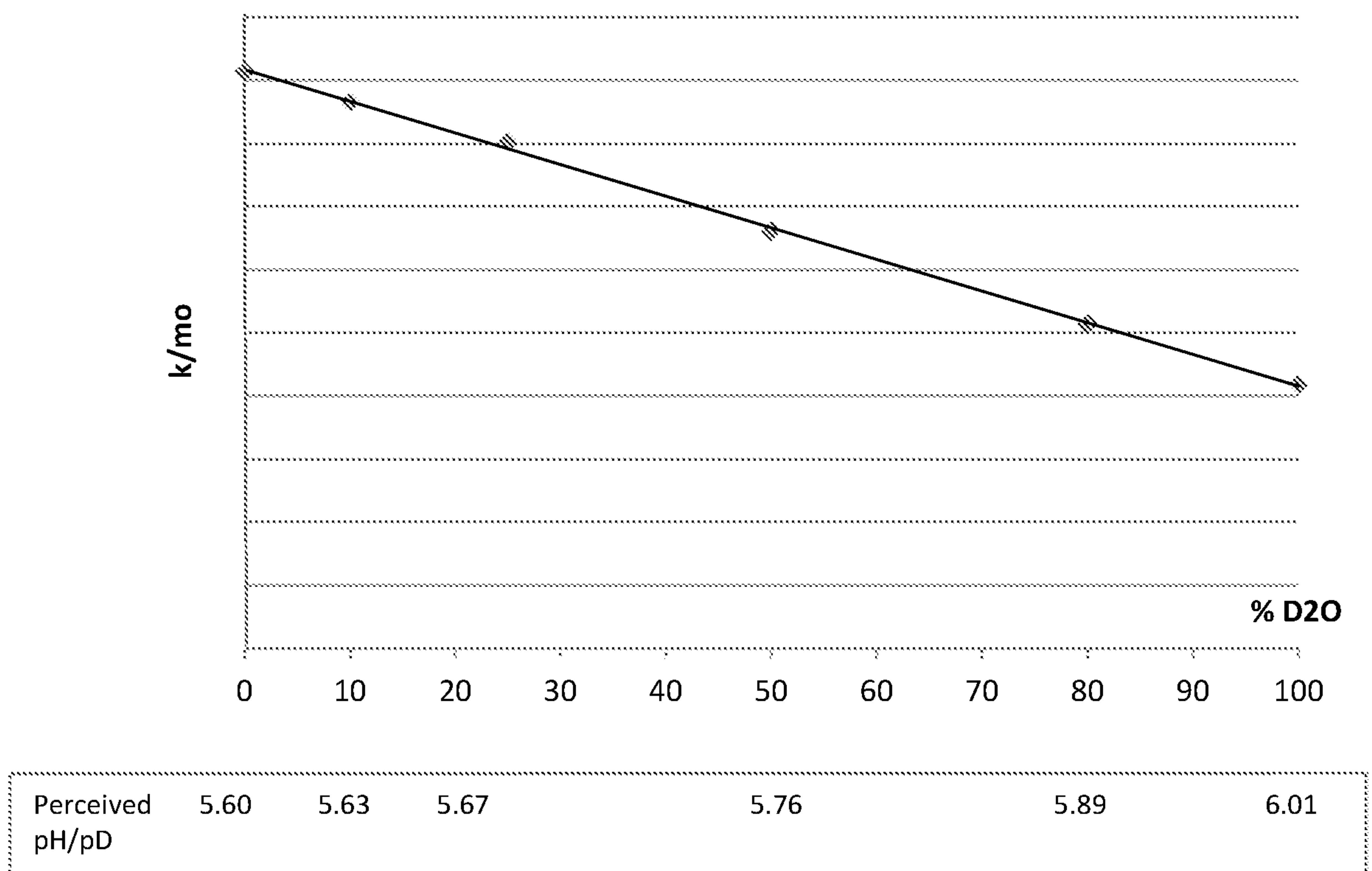


FIG. 7

Ratio of First Order Rate Constants

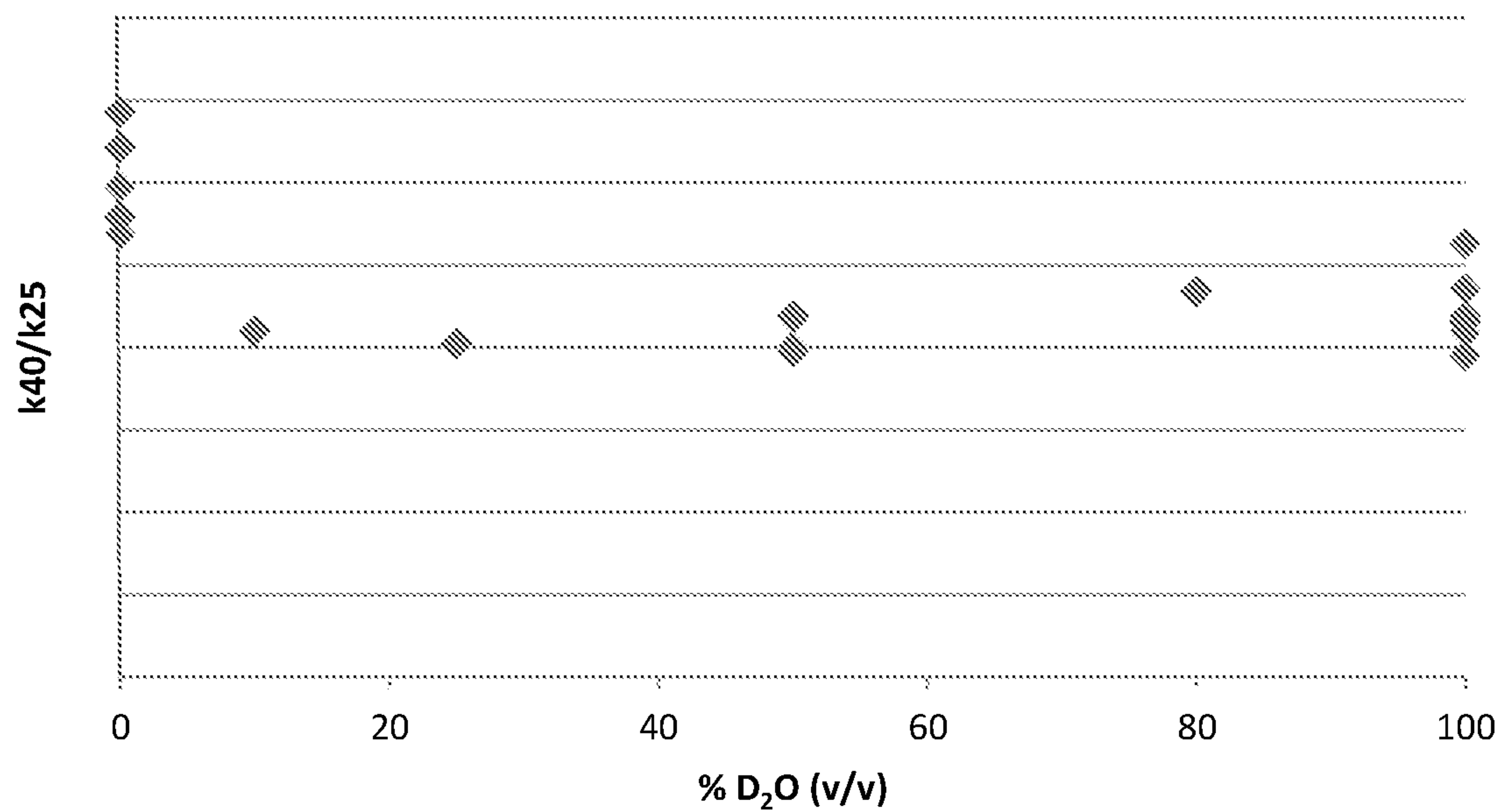


FIG. 8

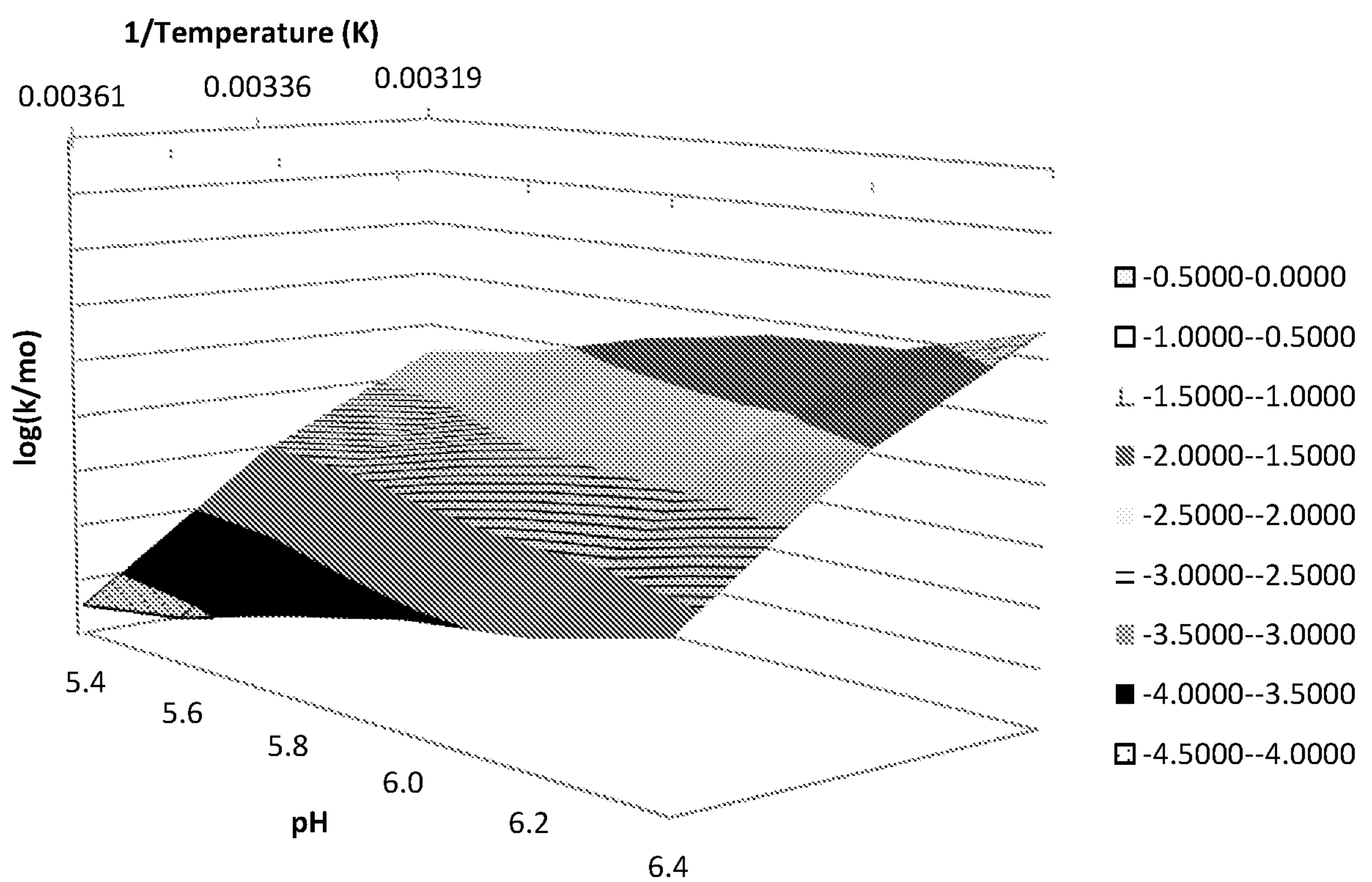


FIG. 9

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 20/65149

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/5575; A61K 47/26; A61K 47/44 (2021.01)

CPC - A61K 31/5575; A61K 47/14; A61K 47/26

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)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2018/0193326 A1(Sydnexis, Inc.) 12 July 2018 (12.07.2018); entire document, especially abstract, [0003], [0045], [0097], [0187], pg 33 TABLE 1-5, pg 34 TABLE 7	1-3, 7-9, 19-22, 27-29, 30/(20-22, 27-29), 31/(30/(20-22, 27-29)), 32/(31/(30/(20-22, 27-29))), 43-46, 49-52, 65-81, 101 ----- 23-26, 30/(23-26), 31/(30/(23-26)), 32/(31/(30/(23-26))), 47-48
Y	US 2008/0021106 A1 (Petit, II et al.) 24 January 2008 (24.01.2008); entire document, especially claim 1, claim 10-11	23-26, 30/(23-26), 31/(30/(23-26)), 32/(31/(30/(23-26))), 47-48
A	US 2018/0325888 A1 (Nevakar Inc.) 15 November 2018 (15.11.2018); entire document	1-3, 7-9, 19-32, 43-52, 65-81, 101
A	US 2004/0136915 A1 (Dugger, III et al.) 15 July 2004 (15.07.2004); entire document	1-3, 7-9, 19-32, 43-52, 65-81, 101

☒ 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

"D" document cited by the applicant in the international application

"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

15 February 2021

Date of mailing of the international search report

MAR 22 2021

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 20/65149

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2007/0254914 A1 (Wu et al.) 01 November 2007 (01.11.2007); entire document	1-3, 7-9, 19-32, 43-52, 65-81, 101

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 20/65149

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.: 4-6, 10-18, 33-42, 53-64, 82-100, 102
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.