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

[0002a] In an aspect of the present disclosure, there is provided 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.

[0002b] In another aspect of the present disclosure, there is provided 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.

[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 ~~embodiment~~examples 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 ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition has no detectable amount of a benzalkonium chloride preservative. In some ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition has no detectable amount of benzalkonium chloride. In some ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition has no detectable amount of a preservative. In some ~~embodiment~~examples 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 ~~embodiment~~examples of an ophthalmic composition described herein, the muscarinic antagonist is atropine or a pharmaceutically acceptable salt of atropine. In some ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples of an ophthalmic composition described herein, the storage condition has a storage temperature of from about 0ºC to about 30ºC, 2ºC to about 10ºC, or from about 16ºC to about 26ºC. In some ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition further comprises 0.004 wt% to about 0.20 wt% citrate. In some ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition further comprises an osmolarity adjusting agent. In some ~~embodiment~~examples of an ophthalmic composition described herein, the osmolarity adjusting agent is sodium chloride. In some ~~embodiment~~examples 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 ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition further comprises a buffering agent. In some ~~embodiment~~examples 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 ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof. In some ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition further comprises a pH adjusting agent. In some ~~embodiment~~examples of an ophthalmic

composition described herein, the pH adjusting agent comprises DCl, HCl, NaOH, NaOD, CD_3COOD, $C_6D_8O_7$, CH_3COOH, $C_6H_8O_7$, or combinations thereof. In some ~~embodiment~~examples 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 ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition is not formulated as an injectable formulation. In some ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples of an ophthalmic composition described herein, the muscarinic antagonist is atropine or a pharmaceutically acceptable salt of atropine. In some ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples of an ophthalmic composition described herein, the storage condition has a storage temperature of from about 0ºC to about 30ºC, 2ºC to about 10ºC or from about 16ºC to about 26ºC. In some ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition is essentially free of citrate and acetate buffering agents. In some ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition further comprises an osmolarity adjusting agent. In some ~~embodiment~~examples of an ophthalmic composition described herein, the osmolarity adjusting agent is sodium chloride. In some ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition is substantially free of a benzalkonium chloride preservative. In some ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition is substantially free of any preservative. In some ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition further comprises a buffering agent. In some ~~embodiment~~examples 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 ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition further comprises EDTA. In some ~~embodiment~~examples 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 ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof. In some ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition further comprises a pH adjusting agent. In some ~~embodiment~~examples of an ophthalmic composition described herein, the pH adjusting agent comprises DCl, HCl, NaOH, NaOD, CD_3COOD, $C_6D_8O_7$, CH_3COOH, $C_6H_8O_7$, or combinations thereof. In some ~~embodiment~~examples 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 ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition is not formulated as an injectable formulation. In some ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples of an ophthalmic composition described herein, the muscarinic antagonist is atropine or pharmaceutically acceptable salt of atropine. In some ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition further comprises one or more sodium phosphate buffers. In some ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples of an ophthalmic composition described herein, a second sodium phosphate of the one or more sodium phosphate buffers is disodium phosphate anhydrous. In some ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples of an ophthalmic composition described herein, the storage condition has a storage temperature of from about 0ºC to about 30ºC, 2ºC to about 10ºC, or from about 16ºC to about 26ºC. In some ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition further comprises 0.004 wt% to about 0.20 wt% citrate. In some ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition further comprises an osmolarity adjusting agent. In some ~~embodiment~~examples of an ophthalmic composition described herein, the osmolarity adjusting agent is sodium chloride. In some ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition is substantially free of a benzalkonium chloride preservative. In some ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition is substantially free of any preservative. In some ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition further comprises a buffering agent. In some ~~embodiment~~examples 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 ~~embodiment~~examples of an

ophthalmic composition described herein, the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof. In some ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition further comprises a pH adjusting agent. In some ~~embodiment~~examples of an ophthalmic composition described herein, the pH adjusting agent comprises DCl, HCl, NaOH, NaOD, CD_3COOD, $C_6D_8O_7$, CH_3COOH, $C_6H_8O_7$, or combinations thereof. In some ~~embodiment~~examples 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 ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition is not formulated as an injectable formulation. In some ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples of an ophthalmic composition described herein, the muscarinic antagonist is atropine or pharmaceutically acceptable salt of atropine. In some ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples of an ophthalmic composition described herein, the storage condition has a storage temperature of from about 0ºC to about 30ºC, 2ºC to about 10ºC, or from about 16ºC to about 26ºC. In some ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition further comprises 0.004 wt% to about 0.20 wt% citrate. In some ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition further comprises one or more sodium phosphate buffers. In some ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples of an ophthalmic composition described herein, a second sodium phosphate of the one or more sodium phosphate buffers is disodium phosphate anhydrous. In some ~~embodiment~~examples 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 ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition further comprises an osmolarity adjusting agent. In some ~~embodiment~~examples of an ophthalmic composition described herein, the osmolarity adjusting agent is sodium chloride. In some ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition is substantially free of a benzalkonium chloride preservative. In some ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition is substantially free of any preservative. In some ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic

composition further comprises a buffering agent. In some ~~embodiment~~examples 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 ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition further comprises EDTA. In some ~~embodiment~~examples 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 ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof. In some ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition further comprises a pH adjusting agent. In some ~~embodiment~~examples of an ophthalmic composition described herein, the pH adjusting agent comprises DCl, HCl, NaOH, NaOD, CD_3COOD, $C_6D_8O_7$, CH_3COOH, $C_6H_8O_7$, or combinations thereof. In some ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition is not formulated as an injectable formulation. In some ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples of an ophthalmic composition described herein, a ratio of the water to the deuterated water is about 50:50. In some ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples 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 ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition is substantially free of a benzalkonium chloride preservative. In some ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition has no detectable amount of a benzalkonium chloride preservative. In some ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic

composition has no detectable amount of a preservative. In some ~~embodiment~~examples of an ophthalmic composition described herein, the ophthalmic composition has a pH from about 5.1 to about 6.0. In some ~~embodiment~~examples 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 ~~embodiment~~examples, 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 ~~embodiment~~examples, the ophthalmic composition has no detectable amount of a benzalkonium chloride preservative. In some ~~embodiment~~examples, the ophthalmic composition has no detectable amount of benzalkonium chloride. In some ~~embodiment~~examples, the ophthalmic composition has no detectable amount of a preservative. In some ~~embodiment~~examples, 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 ~~embodiment~~examples, the muscarinic antagonist is atropine or a pharmaceutically acceptable salt of atropine. In some ~~embodiment~~examples, 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 ~~embodiment~~examples, the muscarinic antagonist is present in the ophthalmic composition at a concentration from about 0.001 wt% to about 0.10 wt%. In some ~~embodiment~~examples, the ophthalmic composition further comprises 0.004 wt% to about 0.20 wt% citrate. In some ~~embodiment~~examples, the ophthalmic composition further comprises an osmolarity adjusting agent. In some ~~embodiment~~examples, the osmolarity adjusting agent is sodium chloride. In some ~~embodiment~~examples, 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 ~~embodiment~~examples, the ophthalmic composition further comprises a buffering agent. In some ~~embodiment~~examples, 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 ~~embodiment~~examples, the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof. In some ~~embodiment~~examples, the ophthalmic composition further comprises a pH adjusting agent. In some ~~embodiment~~examples, the pH adjusting agent comprises DCl, HCl, NaOH, NaOD, CD_3COOD, $C_6D_8O_7$,

CH_3COOH, $C_6H_8O_7$, or combinations thereof. In some ~~embodiment~~examples, 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 ~~embodiment~~examples, 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 ~~embodiment~~examples, the muscarinic antagonist is atropine or a pharmaceutically acceptable salt of atropine. In some ~~embodiment~~examples, a first sodium phosphate buffer of the one or more sodium phosphate buffers is monosodium phosphate anhydrous. In some ~~embodiment~~examples, 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 ~~embodiment~~examples, a second sodium phosphate buffer of the one or more sodium phosphate buffers is disodium phosphate anhydrous. In some ~~embodiment~~examples, 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 ~~embodiment~~examples, 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 ~~embodiment~~examples, the muscarinic antagonist is present in the ophthalmic composition at a concentration from about 0.001 wt% to about 0.10 wt%. In some ~~embodiment~~examples, the ophthalmic composition is essentially free of citrate and acetate buffering agents. In some ~~embodiment~~examples, the ophthalmic composition further comprises an osmolarity adjusting agent. In some ~~embodiment~~examples, the osmolarity adjusting agent is sodium chloride. In some ~~embodiment~~examples, 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 ~~embodiment~~examples, 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 ~~embodiment~~examples, the ophthalmic composition is substantially free of a benzalkonium chloride preservative. In some ~~embodiment~~examples, the ophthalmic composition is substantially free of any preservative. In some ~~embodiment~~examples, the ophthalmic composition further comprises a buffering agent. In some ~~embodiment~~examples, 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 ~~embodiment~~examples, the ophthalmic composition further comprises EDTA. In some ~~embodiment~~examples, the EDTA is present in the ophthalmic composition at a concentration of 0.01 wt% to about 0.50 wt%. In some ~~embodiment~~examples, the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof. In some ~~embodiment~~examples, the ophthalmic composition further comprises a pH adjusting agent. In some ~~embodiment~~examples, the pH adjusting agent comprises DCl, HCl, NaOH, NaOD, CD_3COOD, $C_6D_8O_7$, CH_3COOH, $C_6H_8O_7$, 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 ~~embodiment~~examples, 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 ~~embodiment~~examples, the muscarinic antagonist is atropine or pharmaceutically acceptable salt of atropine. In some ~~embodiment~~examples, the ophthalmic composition further comprises one or more sodium phosphate buffers. In some ~~embodiment~~examples, a first sodium phosphate buffer of the one or more sodium phosphate buffers is monosodium phosphate anhydrous. In some ~~embodiment~~examples, 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 ~~embodiment~~examples, a second sodium phosphate of the one or more sodium phosphate buffers is disodium phosphate anhydrous. In some ~~embodiment~~examples, 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 ~~embodiment~~examples, 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 ~~embodiment~~examples, the muscarinic antagonist is present in the ophthalmic composition at a concentration from about 0.001 wt% to about 0.10 wt%. In some ~~embodiment~~examples, the ophthalmic composition further comprises 0.004 wt% to about 0.20 wt% citrate. In some ~~embodiment~~examples, the ophthalmic composition further comprises an osmolarity adjusting agent. In some ~~embodiment~~examples, the osmolarity adjusting agent is sodium chloride. In some ~~embodiment~~examples, 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 ~~embodiment~~examples, 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 ~~embodiment~~examples, the ophthalmic composition is substantially free of a benzalkonium chloride preservative. In some ~~embodiment~~examples, the ophthalmic composition is substantially free of any preservative. In some ~~embodiment~~examples, the ophthalmic composition further comprises a buffering agent. In some ~~embodiment~~examples, 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 ~~embodiment~~examples, the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof. In some ~~embodiment~~examples, the ophthalmic composition further comprises a pH adjusting agent. In some ~~embodiment~~examples, the pH adjusting agent comprises DCl, HCl, NaOH, NaOD, CD_3COOD, $C_6D_8O_7$, CH_3COOH, $C_6H_8O_7$, 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 ~~embodiment~~examples, 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 ~~embodiment~~examples, the muscarinic antagonist is atropine or pharmaceutically acceptable salt of atropine. In some ~~embodiment~~examples, 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 ~~embodiment~~examples, the muscarinic antagonist is present in the ophthalmic composition at a concentration from about 0.001 wt% to about 0.10 wt%. In some ~~embodiment~~examples, a ratio of the water to the deuterated water is in a range of about 80:20 to about 60:40. In some ~~embodiment~~examples, a ratio of the water to the deuterated water is about 65:35. In some ~~embodiment~~examples, a ratio of the water to the deuterated water is about 90:10. In some ~~embodiment~~examples, 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 ~~embodiment~~examples, 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 ~~embodiment~~examples, the muscarinic antagonist is present in the ophthalmic composition at a concentration of about 0.01 wt%. In some ~~embodiment~~examples, the muscarinic antagonist is present in the ophthalmic composition at a concentration of about 0.03 wt%. In some ~~embodiment~~examples, the ophthalmic composition is substantially free of a benzalkonium chloride preservative. In some ~~embodiment~~examples, the ophthalmic composition has no detectable amount of a benzalkonium chloride preservative. In some ~~embodiment~~examples, the ophthalmic composition has no detectable amount of a preservative. In some ~~embodiment~~examples, the ophthalmic composition has a pH from about 5.1 to about 6.0.

In some ~~embodiment~~examples, the ophthalmic composition has a pH from about 5.54 to about 5.59. In some ~~embodiment~~examples, the ophthalmic composition further comprises 0.004 wt% to about 0.20 wt% citrate. In some ~~embodiment~~examples, the ophthalmic composition further comprises one or more sodium phosphate buffers. In some ~~embodiment~~examples, a first sodium phosphate buffer of the one or more sodium phosphate buffers is monosodium phosphate anhydrous. In some ~~embodiment~~examples, 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 ~~embodiment~~examples, a second sodium phosphate of the one or more sodium phosphate buffers is disodium phosphate anhydrous. In some ~~embodiment~~examples, 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 ~~embodiment~~examples, the ophthalmic composition further comprises an osmolarity adjusting agent. In some ~~embodiment~~examples, the osmolarity adjusting agent is sodium chloride. In some ~~embodiment~~examples, 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 ~~embodiment~~examples, 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 ~~embodiment~~examples, the ophthalmic composition is substantially free of a benzalkonium chloride preservative. In some ~~embodiment~~examples, the ophthalmic composition is substantially free of any preservative. In some ~~embodiment~~examples, the ophthalmic composition further comprises a buffering agent. In some ~~embodiment~~examples, 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 ~~embodiment~~examples, the ophthalmic composition further comprises EDTA. In some ~~embodiment~~examples, the EDTA is present in the ophthalmic composition at a concentration of 0.01 wt% to about 0.50 wt%. In some ~~embodiment~~examples, the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof. In some ~~embodiment~~examples, the ophthalmic composition further comprises a pH adjusting agent. In some ~~embodiment~~examples, the pH adjusting agent comprises DCl, HCl, NaOH, NaOD, CD_3COOD, $C_6D_8O_7$, CH_3COOH, $C_6H_8O_7$, or combinations thereof. In some ~~embodiment~~examples, 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

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, CD_3COOD, $C_6D_8O_7$, CH_3COOH, $C_6H_8O_7$, 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, CD_3COOD, $C_6D_8O_7$, CH_3COOH, $C_6H_8O_7$, or combinations thereof.~~

~~43.~~1. 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.~~2. The ophthalmic composition of claim ~~43~~1, 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.~~3. The ophthalmic composition of claim ~~43~~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%.

~~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%.~~

53.4. The ophthalmic composition of ~~any of~~ claim~~s~~ 1~~43-52~~, wherein the ophthalmic composition further comprises 0.004 wt% to about 0.20 wt% citrate.

54.5. The ophthalmic composition of ~~any of~~ claim~~s~~ 1~~43-53~~, wherein the ophthalmic composition further comprises an osmolarity adjusting agent.

55.6. The ophthalmic composition of claim ~~54~~5, wherein the osmolarity adjusting agent is sodium chloride.

56.7. The ophthalmic composition of claim ~~55~~6, 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%.

57.8. The ophthalmic composition of ~~any of~~ claim~~s~~ 1~~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.~~

61.9. The ophthalmic composition of claim ~~60~~5, 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.~~

64.10. The ophthalmic composition of claim ~~63~~5, wherein the pH adjusting agent comprises DCl, HCl, NaOH, NaOD, CD_3COOD, $C_6D_8O_7$, CH_3COOH, $C_6H_8O_7$, or combinations thereof.

65.11. 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.

66.12. The ophthalmic composition of claim ~~65~~11, 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.~~13. The ophthalmic composition of claim ~~65~~11, 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.~~14. The ophthalmic composition of claim ~~65~~11, wherein a ratio of the water to the deuterated water is in a range of about 80:20 to about 60:40.

~~71.~~15. The ophthalmic composition of claim ~~65~~11, wherein a ratio of the water to the deuterated water is about 65:35.

~~72.~~16. The ophthalmic composition of claim ~~65~~11, 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.~~17. The ophthalmic composition of ~~any one of~~ claim~~s~~ 11~~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.~~18. The ophthalmic composition of ~~any one of~~ claim~~s~~ 11~~65-76~~, wherein the ophthalmic composition has no detectable amount of a preservative.

~~80.~~19. The ophthalmic composition of claim ~~65~~11, wherein the ophthalmic composition has a pH from about 5.1 to about 6.0.

~~81.~~20. The ophthalmic composition of claim ~~65~~11, 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, CD_3COOD, $C_6D_8O_7$, CH_3COOH, $C_6H_8O_7$, 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.