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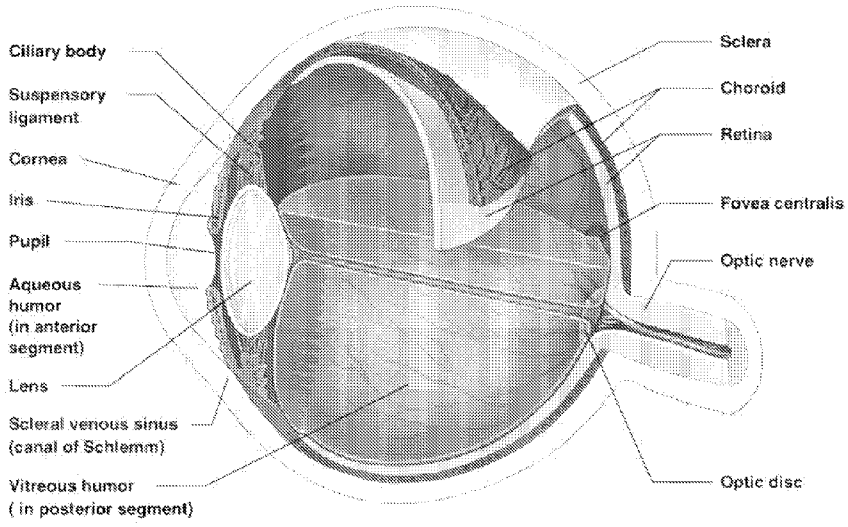
(54) Title: D_2O STABILIZED PHARMACEUTICAL FORMULATIONS

Fig. 1



(57) Abstract: Provided herein is an ophthalmic composition formulated in deuterated water. Also disclosed herein are methods of treating, ameliorating, or reducing ophthalmic conditions or diseases by administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition as described herein.

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D_2O STABILIZED PHARMACEUTICAL FORMULATIONS

CROSS REFERENCE

[0001] This application claims the benefit of U.S. provisional patent application serial number 62/168,538, filed May 29, 2015, which is herein 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 D_2O stabilized pharmaceutical compositions and formulations.

[0004] According to one aspect, an ophthalmic composition disclosed herein comprises an ophthalmic agent and deuterated water, at a pD of from about 4 to about 8.

[0005] According to another aspect, an ophthalmic composition disclosed herein comprises an ophthalmic agent and deuterated water, at a pD of from about 4 to about 8, wherein the ophthalmic agent is not a muscarinic antagonist, and wherein the ophthalmic agent does not extend singlet oxygen lifetime.

[0006] In some embodiments, the ophthalmic agent comprises aflibercept (also known as VEGF Trap), 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, 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, scopolomine (L-hyoscine), hydroxyzine, ipratropium, pirenzapine, solifenacin, darifenacin, benzatropine, mebeverine, procyclidine, aclidinium bromide, trihexyphenidyl/benzhexol, tolterodine, or any combinations thereof.

[0007] In some embodiments, the ophthalmic composition comprises at least about 80% of the ophthalmic agent based on initial concentration after extended period of time under storage condition. In some embodiments, the ophthalmic composition comprises at least about 85% of the ophthalmic agent based on initial concentration after extended period of time under storage condition. In some embodiments, the ophthalmic composition comprises at least about 90% of the ophthalmic agent based on initial concentration after extended period of time under storage condition. In some embodiments, the ophthalmic composition comprises at least about 95% of the ophthalmic agent based on initial concentration after extended period of time under storage condition. In some embodiments, the ophthalmic composition comprises at least about 97% of the ophthalmic agent based on initial concentration after extended period of time under storage condition. In some embodiments, the ophthalmic composition comprises at least about 98% of the ophthalmic agent based on initial concentration after extended period of time under storage condition. In some embodiments, the ophthalmic composition comprises at least about 99% of the ophthalmic agent based on initial concentration after extended period of time under storage condition.

[0008] In some embodiments, the ophthalmic composition has a pD of less than about 8 after extended period of time under storage condition. In some embodiments, the ophthalmic composition has a pD of less than about 7.5 after extended period of time under storage condition. In some embodiments, the ophthalmic composition has a pD of less than about 7 after extended period of time under storage condition. In some embodiments, the ophthalmic composition has a pD of less than about 6.5 after extended period of time under storage condition. In some embodiments, the ophthalmic composition has a pD of less than about 6

after extended period of time under storage condition. In some embodiments, the ophthalmic composition has a pD of less than about 5.5 after extended period of time under storage condition. In some embodiments, the ophthalmic composition has a pD of less than about 5 after extended period of time under storage condition. In some embodiments, the ophthalmic composition has a pD of less than about 4.5 after extended period of time under storage condition. In some embodiments, the ophthalmic composition has a pD of less than about 4 after extended period of time under storage condition.

[0009] In some embodiments, the ophthalmic composition has a pD that is about 0.4 unit higher than the measured pH.

[0010] In some embodiments, the ophthalmic composition further has a potency of at least 80% after extended period of time under storage condition. In some embodiments, the ophthalmic composition further has a potency of at least 85% after extended period of time under storage condition. In some embodiments, the ophthalmic composition further has a potency of at least 90% after extended period of time under storage condition. In some embodiments, the ophthalmic composition further has a potency of at least 93% after extended period of time under storage condition. In some embodiments, the ophthalmic composition further has a potency of at least 95% after extended period of time under storage condition. In some embodiments, the ophthalmic composition further has a potency of at least 97% after extended period of time under storage condition. In some embodiments, the ophthalmic composition further has a potency of at least 98% after extended period of time under storage condition. In some embodiments, the ophthalmic composition further has a potency of at least 99% after extended period of time under storage condition.

[0011] In some embodiments, the extended period of time is about 1 week. In some embodiments, extended period of time is about 2 weeks. In some embodiments, the extended period of time is about 3 weeks. In some embodiments, the extended period of time is about 1 month. In some embodiments, the extended period of time is about 2 months. In some embodiments, the extended period of time is about 3 months. In some embodiments the extended period of time is about 4 months. In some embodiments, the extended period of time is about 5 months. In some embodiments, the extended period of time is about 6 months. In some embodiments, the extended period of time is about 8 months. In some embodiments, the extended period of time is about 10 months. In some embodiments, the extended period of time is about 12 months. In some embodiments, the extended period of time is about 18 months. In some embodiments, the extended period of time is about 24 months. In some embodiments, the extended period of time is about 36 months. In some embodiments, the extended period of time is about 4 years. In some embodiments, the extended period of time is about 5 years.

[0012] In some embodiments, the ophthalmic composition of any one of the claims 1-44, wherein the storage condition has a storage temperature of from about 16°C to about 30°C or about 20°C to about 25°C. In some embodiments, the storage condition has a relative humidity of about 60%. In some embodiments, the ophthalmic composition of any one of the claims 1-45, wherein the storage condition has a relative humidity of about 75%.

[0013] In some embodiments, the ophthalmic composition is in the form of an aqueous solution.

[0014] In some embodiments, the ophthalmic agent is present in the formulation at a concentration of from about 0.001 wt% to about 20 wt%.

[0015] In some embodiments, the ophthalmic composition further comprises an osmolarity adjusting agent. In some embodiments, the osmolarity adjusting agent is sodium chloride.

[0016] In some embodiments the ophthalmic composition further comprises a preservative. In some embodiments, the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof.

[0017] In some embodiments, the ophthalmic composition further comprises a buffer agent. In some embodiments, the buffer agent is selected from borates, borate-polyol complexes, phosphate buffering agents, citrate buffering agents, acetate buffering agents, carbonate buffering agents, organic buffering agents, amino acid buffering agents, or combinations thereof.

[0018] In some embodiments, the ophthalmic composition further comprises a tonicity adjusting agent. In some embodiments, the tonicity adjusting agent is selected from sodium chloride, sodium nitrate, sodium sulfate, sodium bisulfate, potassium chloride, calcium chloride, magnesium chloride, zinc chloride, potassium acetate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium thiosulfate, magnesium sulfate, disodium hydrogen phosphate, sodium dihydrogen phosphate, potassium dihydrogen phosphate, dextrose, mannitol, sorbitol, dextrose, sucrose, urea, propylene glycol, glycerin, or a combination thereof.

[0019] In some embodiments, the ophthalmic composition is stored in a plastic container.

[0020] In some embodiments, the ophthalmic composition has a dose-to-dose ophthalmic agent concentration variation of less than 50%. In some embodiments, the ophthalmic composition has a dose-to-dose ophthalmic agent concentration variation of less than 40%. In some embodiments, the ophthalmic composition has a dose-to-dose ophthalmic agent concentration variation of less than 30%. In some embodiments, the ophthalmic composition has a dose-to-dose ophthalmic agent concentration variation of less than 20%. In some embodiments, the ophthalmic composition has a dose-to-dose ophthalmic agent concentration variation of less than

10%. In some embodiments, the ophthalmic composition has a dose-to-dose ophthalmic agent concentration variation of less than 5%.

[0021] In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 10 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 8 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 5 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 3 consecutive doses. In some embodiments, the dose-to-dose ophthalmic agent concentration variation is based on 2 consecutive doses.

[0022] In some embodiments, the ophthalmic composition has a pD of from about 4 to about 8. In some embodiments, the ophthalmic composition has a pD of from about 4.5 to about 7.5. In some embodiments the ophthalmic composition has a pD of from about 5 to about 7.0. In some embodiments, the ophthalmic composition has a pD of from about 6 to about 7.0.

[0023] In some embodiments, the ophthalmic composition further comprises a pD adjusting agent.

[0024] In some embodiments, the ophthalmic composition further comprises a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutically acceptable carrier further comprises at least one viscosity-enhancing agent. In some embodiments, the viscosity-enhancing agent is selected from cellulose-based polymers, polyoxyethylene-polyoxypropylene triblock copolymers, dextran-based polymers, polyvinyl alcohol, dextrin, polyvinylpyrrolidone, polyalkylene glycols, chitosan, collagen, gelatin, hyaluronic acid, or combinations thereof.

[0025] In some embodiments, the ophthalmic composition comprises less than 60% of H_2O. In some embodiments, the ophthalmic composition comprises less than 55% of H_2O. In some embodiments, the ophthalmic composition comprises less than 50% of H_2O. In some embodiments, the ophthalmic composition comprises less than 45% of H_2O. In some embodiments, the ophthalmic composition comprises less than 40% of H_2O. In some embodiments, the ophthalmic composition comprises less than 35% of H_2O. In some embodiments, the ophthalmic composition comprises less than 30% of H_2O. In some embodiments, the ophthalmic composition comprises less than 25% of H_2O. In some embodiments, the ophthalmic composition comprises less than 20% of H_2O. In some embodiments, the ophthalmic composition comprises less than 15% of H_2O.

[0026] In some embodiments, the ophthalmic composition comprises less than 10% of H_2O. In some embodiments, the ophthalmic composition comprises less than 8% of H_2O. In some embodiments, the ophthalmic composition comprises less than 6% of H_2O. In some

embodiments, the ophthalmic composition comprises less than 5% of H_2O. In some embodiments, the ophthalmic composition comprises less than 4% of H_2O. In some embodiments, the ophthalmic composition comprises less than 3% of H_2O. In some embodiments, the ophthalmic composition comprises less than 2% of H_2O. In some embodiments, the ophthalmic composition comprises less than 1% of H_2O. In some embodiments, the ophthalmic composition comprises less than 0.5% of H_2O. In some embodiments, the ophthalmic composition comprises less than 0.1% of H_2O. In some embodiments, the ophthalmic composition comprises 0% of H_2O.

[0027] In some embodiments, the ophthalmic composition is formulated as an ophthalmic solution for the treatment of an ophthalmic condition or disease.

[0028] In some embodiments, the ophthalmic agent is not atropine. In some embodiments, the ophthalmic agent is not atropine sulfate. In some embodiment, the ophthalmic agent is not a muscarinic antagonist.

[0029] In some embodiments, the ophthalmic agent is not an alpha-amino-carboxylic acid or an alpha-hydroxy-carboxylic acid. In some embodiments, the ophthalmic agent is not benactyzine hydrochloride.

[0030] In some embodiments, the ophthalmic agent quenches photogenerated singlet oxygen species in the composition. In some embodiments, the ophthalmic composition is not saturated with oxygen. In some embodiments, the ophthalmic composition does not comprise a photosensitizer.

[0031] In some embodiments, the ophthalmic agent is dissolved in the ophthalmic composition. In some embodiments, the ophthalmic agent is suspended in the ophthalmic composition.

[0032] According to another aspect, a method of treating an ophthalmic condition or disease comprises administering to an eye of an individual in need thereof an effective amount of the ophthalmic composition disclosed in the present disclosure. According to another aspect, a method of ameliorating or reducing an ophthalmic condition or disease comprises administering to an eye of an individual in need thereof an effective amount of the ophthalmic composition disclosed in the present disclosure.

[0033] 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 a day. 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 moths, 1 year, 2 years, 3

years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 11 years, or 12-15 years. In some embodiments, the ophthalmic composition is administered only once.

[0034] In some embodiments, the ophthalmic composition is stored below room temperature prior to first use. In some embodiments, the ophthalmic composition is stored at between about 2 °C to about 10 °C prior to first use. In some embodiments, the ophthalmic composition is stored at between about 4 °C to about 8 °C prior to first use.

[0035] In some embodiments the ophthalmic composition is stored at room temperature prior to first use. In some embodiments, the ophthalmic composition is stored at between about 16 °C to about 26 °C prior to first use.

[0036] In some embodiments, the ophthalmic composition is stored below room temperature after first use. In some embodiments, the ophthalmic composition is stored at between about 2 °C to about 10 °C after first use. In some embodiments, the ophthalmic composition is stored at between about 4 °C to about 8 °C after first use.

[0037] In some embodiments, the ophthalmic composition is stored at room temperature after first use. In some embodiments, the ophthalmic composition is stored at between about 16 °C to about 26 °C after first use.

[0038] Other features and technical effects of the methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only.

BRIEF DESCRIPTION OF THE DRAWINGS

[0039] The novel features of the disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the disclosure are utilized, and the accompanying drawings of which:

[0040] Fig. 1 illustrates a conceptual representation of the eye anatomy.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0041] The present disclosure recognizes that stability and eye tolerance are parameters to consider when formulating an ophthalmic composition. In some instances, to extend the shelf-life or stability of an ophthalmic composition, the pH of the composition is subsequently reduced. In some instances, the lowered pH reduces or prevents base catalyzed hydrolysis and thereby stabilizes the active agent. However, in some cases, the formulation with the reduced pH leads to poor eye tolerance as the acidic formulation stings the eye, leading to tear

production. In such cases, the tears then dilute the composition and/or wash the composition out of the eye, thereby reducing the effectiveness of the ophthalmic composition.

[0042] In addition, the present disclosure recognizes that deuterated water stabilizes ophthalmic compositions. In some cases, the deuterated water is a weak acid as compared to H_2O, as such deuterated water comprises a lower concentration of the reactive species (e.g., -OD) which in some instances leads to base catalyzed hydrolysis of an active agent in the ophthalmic composition. As such, in some instances compositions comprising deuterated water leads to reduced base catalyzed hydrolysis when compared to compositions comprising H_2O. In some instances, deuterated water further lowers the buffering capacity of an ophthalmic composition, leading to less tear reflex in the eye.

[0043] Disclosed herein are ophthalmic compositions that comprise an ophthalmic agent and deuterated water, at a pD of from about 4 to about 8. Also disclosed herein are ophthalmic solutions that comprise an ophthalmic agent and deuterated water, at a pD of from about 4 to about 8. Further disclosed herein are methods of treating an ophthalmic condition or disease that comprises administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition or an ophthalmic solution described *infra*. Additionally disclosed herein are methods of ameliorating or reducing an ophthalmic condition or disease that comprises administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition or an ophthalmic solution described *infra*.

Ophthalmic Agents

[0044] Disclosed herein are pharmaceutical compositions formulated in the presence of deuterated water. As used herein, deuterated water refers to D_2O, DHO, heavy water, and/or deuterium oxide. In some instances, the pharmaceutical compositions are ophthalmic compositions containing one or more ophthalmic agents. In some cases, the ophthalmic compositions are formulated as an aqueous solution, gel, or as an ointment.

[0045] In some embodiments, the ophthalmic agents used in the ophthalmic compositions are susceptible to degradation through hydrolysis. In some embodiment, the ophthalmic agents used in the ophthalmic compositions are susceptible to degradation through base-catalyzed hydrolysis.

[0046] In some embodiments, ophthalmic agents include anti-angiogenic ophthalmic agents, mydriatics, antimydriatic agents, ophthalmic anesthetics, ophthalmic anti-infectives, ophthalmic anti-inflammatory agents, ophthalmic antihistamines and decongestants, ophthalmic diagnostic agents, ophthalmic glaucoma agents, ophthalmic lubricants and irrigation agents, ophthalmic steroids, ophthalmic steroids with anti-infectives, or ophthalmic surgical agents.

[0047] In some embodiments, an ophthalmic composition formulated in the presence of deuterated water include anti-angiogenic ophthalmic agents, mydriatics, antimydriatic agents, ophthalmic anesthetics, ophthalmic anti-infectives, ophthalmic anti-inflammatory agents, ophthalmic antihistamines and decongestants, ophthalmic diagnostic agents, ophthalmic glaucoma agents, ophthalmic lubricants and irrigation agents, ophthalmic steroids, ophthalmic steroids with anti-infectives, ophthalmic surgical agents, or combinations thereof.

[0048] Anti-angiogenic ophthalmic agents are vascular endothelial growth factor (VEGF) antagonists that prevent generation of new blood vessels by a process termed neovascularization. In some instances, anti-angiogenic ophthalmic agents are used to inhibit neovascularization in age related macular degeneration. In some instances, anti-angiogenic ophthalmic agents are used to treat diabetic macular edema, diabetic retinopathy, or macular edema. In some embodiments, macular edema is a swelling or thickening of the eye's macula, or the region of the eye responsible for central vision. In some embodiments, diabetic retinopathy refers to damages to the blood vessels in the retina. Examplary anti-angiogenic ophthalmic agents include, but are not limited to, aflibercept (also known as VEGF Trap) (e.g., Eylea), ranibizumab (e.g., Lucentis), or pegaptanib (e.g., Macugen).

[0049] In some embodiments, an ophthalmic composition formulated in the presence of deuterated water includes anti-angiogenic ophthalmic agents such as for example aflibercept (also known as VEGF Trap), ranibizumab, or pegaptanib. In some embodiments, an ophthalmic composition formulated in the presence of deuterated water includes aflibercept (also known as VEGF Trap), ranibizumab, pegaptanib, or combinations thereof.

[0050] Mydriatic agents are agents that dilate the pupil of the eye. In some instances, mydriatics are used to treat eye dryness, redness, or itching, uveitis, organophosphate poisoning, or inflammary eye conditions such as iritis and cyclitis. Examplary mydriatic agents include, but are not limited to, cyclopentolate (e.g., Cyclogyl, Ak-Pentolate, Cylate, Ocu-Pentolate, or Pentolair), phenylephrine (e.g., AK-Dilate, AK-Nefrin, Altafrin, Isopto Frin, Mydfrin, Neo-synephrine Ophthalmic, Neofrin, Ocu-Phrin, Prefrin, or Refresh Redness Relief), homatropine (e.g., Homatropaire, Isopto Homatropine), scopolamine (e.g., Isopto Hyoscine), cyclopentolate/phenylephrine (e.g., Cyclomydril), phenylephrine/scopolamine (e.g., Murocoll 2), tropicamide (e.g., Mydral, Ocu-Tropic, or Tropicacyl), ketorolac/phenylephrine (e.g., Omidria), or hydroxyamphetamine/tropicamide (e.g., Paremyd).

[0051] In some embodiments, an ophthalmic composition formulated in the presence of deuterated water includes mydriatic agents such as for example cyclopentolate, phenylephrine, homatropine, scopolamine, cyclopentolate/phenylephrine, phenylephrine/scopolamine, tropicamide, ketorolac/phenylephrine, or hydroxyamphetamine/tropicamide. In some

embodiments, an ophthalmic composition formulated in the presence of deuterated water includes cyclopentolate, phenylephrine, homatropine, scopolamine, cyclopentolate/phenylephrine, phenylephrine/scopolamine, tropicamide, ketorolac/phenylephrine, hydroxyamphetamine/tropicamide, or combinations thereof. In some embodiments, an ophthalmic composition formulated in the presence of deuterated water does not include atropine, atropine sulfate, noratropine, atropine-N-oxide, tropine, tropic acid, or atropine methonitrate. In some embodiments, an ophthalmic composition formulated in the presence of deuterated water does not include atropine. In some embodiments, an ophthalmic composition formulated in the presence of deuterated water does not include atropine sulfate.

[0052] Antimydriatic agents are agents that decrease the size of the pupil. Examplary antimydriatic agents include, but are not limited to, cysteamine (e.g., Cystaran), ocriplasmin (e.g., Jetrea), mitomycin (e.g., Mitosol), or dapiprazole (e.g., Rev-Eyes).

[0053] In some embodiments, an ophthalmic composition formulated in the presence of deuterated water includes antimydriatic agents such as for example cysteamine, ocriplasmin, mitomycin, or dapiprazole. In some embodiments, an ophthalmic composition formulated in the presence of deuterated water includes cysteamine, ocriplasmin, mitomycin, dapiprazole, or combinations thereof.

[0054] Ophthalmic anesthetics are local anesthetics that block pain signals at the nerve endings in the eyes. Examplary ophthalmic anesthetics include, but are not limited to, lidocaine (e.g., Akten), proparacaine (e.g., Alcaine, Ocu-Caine, Ophthetic, or Parcaine), tetracaine (e.g., Altacaine, Opticaine, or TetraVisc), or benoxinate (or oxybuprocaine) (e.g., Novesine, Novesin).

[0055] In some embodiments, an ophthalmic composition formulated in the presence of deuterated water includes ophthalmic anesthetics such as for example lidocaine, proparacaine, tetracaine, or benoxinate. In some embodiments, an ophthalmic composition formulated in the presence of deuterated water includes lidocaine, proparacaine, tetracaine, benoxinate, or combinations thereof.

[0056] Ophthalmic anti-infectives are ophthalmic formulations that comprise antibiotics and/or antiviral agents. In some embodiments, ophthalmic anti-infectives are used to treat blepharitis, blepharoconjunctivitis, CMV retinitis, conjunctivitis, corneal ulcer, eye dryness or redness, Herpes Simplex dendritic keratitis, Herpetic keratitis, hordeolum, keratitis, keratoconjunctivitis, neonatol conjunctivitis, or trachoma, or are used during surgery. Examplary ophthalmic anti-infectives include, but are not limited to, azithromycin (e.g., Azasite), bacitracin (e.g., AK-Tracin, Ocu-Tracin), besifloxacin (e.g., Besivance), boric acid (e.g., Collyrium Fresh), chloramphenicol (e.g., AK-Chlor, Chloromycetin ophthalmic, Chloroptic, Ocu-Chlor), ciprofloxacin (e.g., Ciloxan), erythromycin (e.g., Eyemycin, Ilotycin, Roymicin), ganciclovir

(e.g., Vitrasert, Zirgan), gatifloxacin (e.g., Zymar, Zymaxid), gentamicin (e.g., Garamycin ophthalmic, Genoptic, Gentacidin, Gentak, Gentasol, Ocu-Mycin), idoxuridine (e.g., Herplex), levofloxacin (e.g., Iquix, Quixin), moxifloxacin (e.g., Vigamox, Moxeza), natamycin (e.g., Natacyn), norfloxacin (e.g., Chibroxin), ofloxacin (e.g., Ocuflox), bacitracin/polymyxin b (e.g., Polysporin ophthalmic, AK-Poly-Bac, Polycin-B, Polytracin ophthalmic), tobramycin (e.g., Tobrex, AK-Tob, Tomycine), polymyxin b/trimethoprim (e.g., Polytrim), povidone iodine (e.g., Betadine ophthalmic solution), trifluridine (e.g., Viroptic), gramicidin/neomycin/polymyxin b (e.g., AK-Spore, AK-Spore ointment, Neocidin ophthalmic solution), sulfacetamide sodium (e.g., AK-Sulf, Bleph-10, Cetamide, Isopto Cetamide), sulfisoxazole (e.g., Gantrisin ophthalmic), bacitracin/neomycin/polymyxin b (e.g., Neocidin, Neocin, Ocu-Spore-B, Ocutricin), oxytetracycline/polymyxin b (e.g., Terak, Tetramycin with Polymyxin B sulfate), phenylephrine/sulfacetamide sodium (e.g., Vasosulf), or vidarabine (e.g., Vira-A).

[0057] In some embodiments, an ophthalmic composition formulated in the presence of deuterated water includes ophthalmic anti-infectives such as for example 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, or vidarabine. In some embodiments, an ophthalmic composition formulated in the presence of deuterated water includes 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, or combinations thereof.

[0058] Ophthalmic anti-inflammatory agents are agents that reduce pain and/or inflammation of the eye. In some embodiments, ophthalmic anti-inflammatory agents are used to treat conjunctivitis, corneal ulcer, keratoconjunctivitis, keratoconjunctivitis sicca, postoperative increased intraocular pressure, postoperative ocular inflammation, or seasonal allergic conjunctivitis. In some embodiments, ophthalmic anti-inflammatory agents are used to inhibit intraoperative miosis. In some instances, ophthalmic anti-inflammatory agents are used during corneal refractive surgery. Examplary ophthalmic anti-inflammatory agents include, but are not limited to, bromfenac (e.g., Bromday, Xibrom), nepafenac (e.g., Nevanac), ketorolac (e.g.,

Acular, Acular LS, Acular PF, Acuvail), cyclosporine (e.g., Restasis), flurbiprofen (e.g., Ocufen), suprofen (e.g., Profenal), or diclofenac (e.g., Voltaren ophthalmic).

[0059] In some embodiments, an ophthalmic composition formulated in the presence of deuterated water includes ophthalmic anti-inflammatory agents such as for example bromfenac, nepafenac, ketorolac, cyclosporine, flurbiprofen, suprofen, or diclofenac. In some embodiments, an ophthalmic composition formulated in the presence of deuterated water includes bromfenac, nepafenac, ketorolac, cyclosporine, flurbiprofen, suprofen, diclofenac, or combinations thereof.

[0060] Ophthalmic antihistamines are antihistamines that block the histamine receptors that cause for example runny eyes, redness, itching, and the like. Ophthalmic decongestants are sympathomimetic agents that relieve redness of the eye. Examplary ophthalmic antihistamines and decongestants include, but are not limited to, alcaftadine (e.g., Lastacaft), azelastine (e.g., Optivar), bepotastine (e.g., Bepreve), cromolyn (e.g., Opticrom, Crolom), emedastine (e.g., Emadine), epinastine (e.g., Elestat), ketotifen (e.g., Alaway, Zaditor, Claritin Eye, Zyrtec Itchy Eye Drops), levocabastine (e.g., Livostin), lodoxamide (e.g., Alomide), nedocromil (e.g., Alocril), naphazoline (e.g., AK-Con, Albalon, All Clear, Allerest eye drops, Allersol, Clear Eyes, Ocu-Zoline, VasoClear, Vasocon), naphazoline/pheniramine (e.g., Visine-A, Opcon-A, Eye Allergy Relief), naphazoline/zinc sulfate (e.g., Clear Eyes ACR, VasoClear A), olopatadine (e.g., Patanol, Pataday, Pazeo), oxymetazoline (e.g., OcuClear), pemirolast (e.g., Alamast), phenylephrine (e.g., AK-Dilate, AK-Nefrin, Altafrin, Isopto Frin, Mydfrin, Neofrin, Ocu-Phrin, Prefrin, Refresh redness Relief), phenylephrine/zinc sulfate (e.g., Zincfrin), tetrahydrozoline (e.g., Visine original, Altazine, Geneyes, Opti-Clear, Optigene 3), or tetrahydrozoline/zinc sulfate (e.g., Visine totality multi-symptom relief).

[0061] In some embodiments, an ophthalmic composition formulated in the presence of deuterated water includes ophthalmic antihistamines and decongestants such as for example alcaftadine, azelastine, bepotastine, cromolyn, emedastine, epinastine, ketotifen, levocabastine, lodoxamide, nedocromil, naphazoline, naphazoline/pheniramine, naphazoline/zinc sulfate, olopatadine, oxymetazoline, pemirolast, phenylephrine, phenylephrine/zinc sulfate, tetrahydrozoline, or tetrahydrozoline/zinc sulfate. In some embodiments, an ophthalmic composition formulated in the presence of deuterated water includes alcaftadine, azelastine, bepotastine, cromolyn, emedastine, epinastine, ketotifen, levocabastine, lodoxamide, nedocromil, naphazoline, naphazoline/pheniramine, naphazoline/zinc sulfate, olopatadine, oxymetazoline, pemirolast, phenylephrine, phenylephrine/zinc sulfate, tetrahydrozoline, tetrahydrozoline/zinc sulfate, or combinations thereof.

[0062] Ophthalmic diagnostic agents are fluorescent molecules used for diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature. Examplary ophthalmic diagnostic

agents include, but are not limited to, fluorescein (e.g., AK-Fluor, BioGlo, Ful-Glo), fluorescein/proparacaine (e.g., Flucaine, Fluoracaine), benoxinate/fluorescein (e.g., Flurox), indocyanine green (e.g., IC-Green), or trypan blue (e.g., MembraneBlue, VisinBlue).

[0063] In some embodiments, an ophthalmic composition formulated in the presence of deuterated water includes ophthalmic diagnostic agents such as for example fluorescein, fluorescein/proparacaine, benoxinate/fluorescein, indocyanine green, or trypan blue. In some embodiments, an ophthalmic composition formulated in the presence of deuterated water includes fluorescein, fluorescein/proparacaine, benoxinate/fluorescein, indocyanine green, trypan blue, or combinations thereof.

[0064] Ophthalmic glaucoma agents are agents that reduce eye pressure in glaucoma. In some instances, ophthalmic glaucoma agents are also used to treat intraocular hypertension, postoperative increased intraocular pressure, or production of miosis. Examplary ophthalmic glaucoma agents include, but are not limited to, acetylcholine (e.g., Miochol-E), apraclonidine (e.g., Iopidine), betaxolol (e.g., Betoptic, Betoptic S), bimatoprost (e.g., Lumigan),brimonidine (e.g., Alphagan, Alphagan P), brinzolamide (e.g., Azopt), brimonidine/brinzolamide (e.g., Simbrinza), carbachol (e.g., Carbastat, Carboptic, Isopto Carbachol, Miostat), carteolol (e.g., Ocupress), demecarium bromide (e.g., Humorsol Ocumeter), dipivefrin (e.g., Propine), dorzolamide (e.g., Trusopt), dorzolamide/timolol (e.g., Cosopt, Cosopt PF, Combigan), echothiophate iodide (e.g., phospholine iodide), epinephrine (e.g., Epifrin, Epinal, Eppy/N, Glaucon), epinephrine/pilocarpine (e.g., E-Pilo-1, Epilo-2, P1E1, P2E1, P3E1, P4E1, P6E1), latanoprost (e.g., Xalatan), levobunolol (e.g., AK-Beta, Betagan), levobetaxolol (e.g., Betaxon), metipranolol (e.g., OptiPranolol), physostigmine (e.g., Eserine sulfate ophthalmic), pilocarpine (e.g., Isopto Carpine, Ocu-Carpine, Pilopine HS, Pilostat), tafluprost (e.g., Zioptan), timolol (e.g., Betimol, Timoptic Ocudose, Istalol, Timoptic, Timoptic-XE), travoprost (e.g., Travatan, Travatan Z, Izba), or unoprostone (e.g., Rescula).

[0065] In some embodiments, an ophthalmic composition formulated in the presence of deuterated water includes ophthalmic glaucoma agents such as for example 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, or unoprostone. In some embodiments, an ophthalmic composition formulated in the presence of deuterated water includes 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, or combinations thereof.

[0066] In some embodiments, ophthalmic lubricants and irrigation agents are used to treat dry and/or irritated eyes. Examplary ophthalmic lubricants and irrigation agents include, but are not limited to, artificial tear from Hypotears, System Balance, FreshKote, GenTeal, TheraTears, Lacrisert, Tears Again, Lacri-Lube S.O.P, Systane, Oasis Tears, Artificial Tears, Celluvisc, Clear Eyes CLR, Comfort Tears, Dry Eye Relief, Isopto Tears, Liquitears, Lubricant Eye drops, Lubrifresh PM, Moisture Drops, Murocel, Opti-Free Rewitting Drops, Optive, Puralube Tears, Refresh, Soothe, Sterilube, Tears Naturale, Tears Renew, Ultra Fresh, or Visine Tears. In some embodiments, artificial tear preparations include carboxymethyl cellulose, polyvinyl alcohol, hydroxypropyl methylcellulose, hydroxypropyl cellulose, and hyaluronic acid.

[0067] In some embodiments, an ophthalmic composition formulated in the presence of deuterated water includes ophthalmic lubricants and irrigation agents such as for example artificial tear. In some embodiments, an ophthalmic composition formulated in the presence of deuterated water includes artificial tear.

[0068] In some embodiments, ophthalmic steroids are used to treat conjunctivitis, cyclitis, diabetic macular edema, eye dryness/redness/itches, eyelash hypotrichosis, iritis, keratitis, macular edema, postoperative ocular inflammation, rosacea, seasonal allergic conjunctivitis, steroid responsive inflammatory conditions, temporal arteritis, uveitis, or vitrectomy. Examplary ophthalmic steroids include, but are not limited to, dexamethasone (e.g., Ozurdex, AK-Dex, Decadron Ocumeter, Dexasol, Maxidex, Ocu-Dex), difluprednate (e.g., Durezol), fluocinolone (e.g., Retisert, Iluvien), fluorometholone (e.g., FML Forte Liquifilm, Flarex, Fluor-Op, FML, FML S.O.P.), loteprednol (e.g., Alrex, Lotemax), medrysone (e.g., HMS), prednisolone (e.g., AK-Pred, Econopred, Econopred Plus, Inflamase Forte, Inflamase Mild, Omnipred, Pred Forte, Prednisol), rimexolone (e.g., Vexol), or triamcinolone (e.g., Triesence, Trivaris).

[0069] In some embodiments, an ophthalmic composition formulated in the presence of deuterated water includes ophthalmic steroids such as for example dexamethasone, difluprednate, fluocinolone, fluorometholone, loteprednol, medrysone, prednisolone, rimexolone, or triamcinolone. In some embodiments, an ophthalmic composition formulated in the presence of deuterated water includes dexamethasone, difluprednate, fluocinolone, fluorometholone, loteprednol, medrysone, prednisolone, rimexolone, triamcinolone, or combinations thereof.

[0070] Examplary ophthalmic steroids with anti-infectives include, but are not limited to, fluorometholone/sulfacetamide sodium (e.g., FML-S Liquifilm), dexamethasone/neomycin (e.g., Neo-Decadron, AK-Neo-Dex, Neo-Decadron Ocumeter, Neo-Dex, Neo-Dexair),

dexamethasone/tobramycin (e.g., TobraDex, Tobradex ST), dexamethasone/neomycin/polymyxin b (e.g., Neo-Poly-Dex, Maxitrol, AK-Trol, Dexacidin, Dexacine, Dexasporin, Methadex, Ocu-Trol), loteprednol/tobramycin (e.g., Zylet), prednisolone/sulfacetamide sodium (e.g., Blephamide, Blephamide S.O.P., AK-Cide, Cetapred, Isopto Cetapred, Metimyd, Ocu-Lone C, Vasocidin), bacitracin/hydrocortisone/neomycin/polymyxin b (e.g., Cortisporin Ophthalmic ointment, Cortomycin eye ointment, Neo-Poly-Bac, Neotricin HC, Triple Antibiotic HC ophthalmic ointment), hydrocortisone/neomycin/polymyxin b (e.g., Cortisporin ophthalmic suspension, Cortomycin suspension), chloramphenicol/hydrocortisone/polymyxin b (e.g., Ophthocort), neomycin/polymyxin b/prednisolone (e.g., Poly Pred), or gentamicin/prednisolone (e.g., Pred-G, Pred-G S.O.P.).

[0071] In some embodiments, an ophthalmic composition formulated in the presence of deuterated water includes ophthalmic steroids with anti-infectives such as for example 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, or gentamicin/prednisolone. In some embodiments, an ophthalmic composition formulated in the presence of deuterated water includes 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, or combinations thereof.

[0072] Examplary ophthalmic surgical agents include, but are not limited to, ketorolac/phenylephrine (e.g., Omidria).

[0073] In some embodiments, an ophthalmic composition formulated in the presence of deuterated water includes ophthalmic surgical agents such as for example ketorolac/phenylephrine. In some embodiments, an ophthalmic composition formulated in the presence of deuterated water includes ketorolac/phenylephrine.

[0074] In some embodiments, an ophthalmic composition formulated in the presence of deuterated water includes diphenhydramine, dimenhydrinate, dicyclomine, flavoxate, oxybutynin, tiotropium, hyoscine, scopolomine (L-hyoscine), hydroxyzine, ipratropium, pirenzapine, solifenacin, darifenacin, benzatropine, mebeverine, procyclidine, aclidinium bromide, trihexyphenidyl/benzhexol, tolterodine, or a combination thereof.

[0075] In some embodiments, an ophthalmic composition formulated in the presence of deuterated water includes aflibercept (also known as VEGF Trap), 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, 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, scopolomine (L-hyoscine), hydroxyzine, ipratropium, pirenzapine, solifenacin, darifenacin, benzatropine, mebeverine, procyclidine, aclidinium bromide, trihexyphenidyl/benzhexol, tolterodine, or any combinations thereof.

Ophthalmic Composition

[0076] Provided herein is an ophthalmic composition for the treatment of an ophthalmic disorder or condition in which the ophthalmic composition is formulated with deuterated water.

In some aspects, the ophthalmic composition is stable at different temperatures, at different relative humidity, and with a potency of at least 80% relative to the ophthalmic agent. In additional aspects, the ophthalmic composition has a lowered buffering capacity. In such 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 equivalent ophthalmic formulation or solution formulated in H_2O.

[0077] In some aspects, described herein is an ophthalmic composition that does not have a dose-to-dose variation. In some aspects, described herein is an ophthalmic composition that is stable at different temperatures, at different relative humidity, and with a potency of at least 80% relative to the ophthalmic agent.

[0078] 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, increased stability, reduced or limited systemic exposure, or combinations thereof.

Ophthalmic Solution Composition or Formulation

[0079] Disclosed herein, in certain embodiments, is an ophthalmic composition formulated as an aqueous solution. In some embodiments, the ophthalmic composition comprises an ophthalmic agent and deuterated water. As used herein, deuterated water refers to D_2O, DHO, heavy water, and/or deuterium oxide.

[0080] In some embodiments, the composition comprises at least about 80% of the ophthalmic agent for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 81% of the ophthalmic agent for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 82% of the ophthalmic agent for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 83% of the ophthalmic agent for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 84% of the ophthalmic agent for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 85% of the ophthalmic agent for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 86% of the ophthalmic agent for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 87% of the ophthalmic agent for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 88% of the ophthalmic agent for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 89% of the ophthalmic agent for an extended period of time under

storage condition. In some embodiments, the composition comprises at least about 90% of the ophthalmic agent for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 91% of the ophthalmic agent for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 92% of the ophthalmic agent for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 93% of the ophthalmic agent for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 94% of the ophthalmic agent for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 95% of the ophthalmic agent for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 96% of the ophthalmic agent for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 97% of the ophthalmic agent for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 98% of the ophthalmic agent for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 99% of the ophthalmic agent for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 99.5% of the ophthalmic agent for an extended period of time under storage condition. In some embodiments, the composition comprises at least about 99.9% of the ophthalmic agent for an extended period of time under storage condition.

[0081] In some embodiments, the composition has a potency of at least about 80% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least about 81% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least about 82% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least about 83% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least about 84% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least about 85% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least about 86% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least about 87% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least about 88% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least about 89% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least 90% after extended

period of time under storage condition. In some embodiments, the composition has a potency of at least 91% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least 92% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least 93% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least 94% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least 95% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least 96% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least 97% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least 98% after extended period of time under storage condition. In some embodiments, the composition has a potency of at least 99% after extended period of time under storage condition.

[0082] 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, 6 years, 7 years, 8 years, 9 years, 10 years, 15 years, 30 years, or more.

[0083] In some embodiments, the temperature of the storage condition is between about 2°C and about 70°C. In some embodiments, the temperature of the storage condition is between about 2°C and about 65°C, about 8°C and about 65°C, about 10°C and about 65°C, 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

2°C and about 10°C. In some embodiments, the temperature of the storage condition is between about 20°C and 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.

[0084] 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%.

[0085] In some embodiments, the composition comprises less than 60% of H_2O. In some embodiments, the composition comprises less than 55% of H_2O. In some embodiments, the composition comprises less than 50% of H_2O. In some embodiments, the composition comprises less than 45% of H_2O. In some embodiments, the composition comprises less than 40% of H_2O. In some embodiments, the composition comprises less than 35% of H_2O. In some embodiments, the composition comprises less than 30% of H_2O. In some embodiments, the composition comprises less than 25% of H_2O. In some embodiments, the composition comprises less than 20% of H_2O. In some embodiments, the composition comprises less than 15% of H_2O. In some embodiments, the composition comprises less than 10% of H_2O. In some embodiments, the composition comprises less than 9% of H_2O. In some embodiments, the composition comprises less than 8% of H_2O. In some embodiments, the composition comprises less than 7% of H_2O. In some embodiments, the composition comprises less than 6% of H_2O.

[0086] In some embodiments, the composition comprises from less than 5% of H_2O to less than 0.1% of H_2O. In some embodiments, the composition comprises less than 5% of H_2O. In some embodiments, the composition comprises less than 4.5% of H_2O. In some embodiments, the composition comprises less than 4% of H_2O. In some embodiments, the composition comprises less than 3.5% of H_2O. In some embodiments, the composition comprises less than 3% of H_2O. In some embodiments, the composition comprises less than 2.5% of H_2O. In some embodiments, the composition comprises less than 2% of H_2O. In some embodiments, the composition comprises less than 1.5% of H_2O. In some embodiments, the composition comprises less than 1% of H_2O. In some embodiments, the composition comprises less than 0.5% of H_2O. In some embodiments, the composition comprises less than 0.4% of H_2O. In some embodiments, the composition comprises less than 0.3% of H_2O. In some embodiments, the composition comprises less than 0.2% of H_2O. In some embodiments, the composition comprises less than 0.1% of H_2O. In some embodiments, the composition comprises 0% of H_2O.

[0087] In some embodiments, the composition has a pD of between about 3 and about 9, about 4 and about 8, about 4.5 and about 7.8, about 5 and about 7.5, or about 5.5 and about 7. In some

embodiments, the composition has a pD of less than about 8. In some embodiments, the composition has a pD of less than about 7.9. In some embodiments, the composition has a pD of less than about 7.8. In some embodiments, the composition has a pD of less than about 7.7. In some embodiments, the composition has a pD of less than 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 composition has a pD of less than about 3.9. In some embodiments, the composition has a pD of less than about 3.8. In some embodiments, the composition has a pD of less than about 3.7. In some embodiments, the composition has a pD of less than about 3.6. In some embodiments, the composition has a pD of less than about 3.5.

[0088] In some embodiments, the composition comprising deuterated water has a lowered buffering capacity than an equivalent composition comprising H_2O. 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 H_2O. In some embodiments, the lowered buffering capacity allows the composition to induce less tear reflex than an equivalent composition comprising H_2O.

[0089] In some instances, the composition comprising deuterated water stabilizes the ophthalmic agent. In some embodiments, this is due to a lower concentration of the reactive species (e.g., -OD) in the D_2O aqueous system compared to the concentration of the reactive species (e.g., -OH) in an equivalent H_2O aqueous system. In some cases, base catalysis leads to the presence of degradant from the ophthalmic agent. In some cases, with a lower concentration of the reactive species that causes degradant formation, the ophthalmic solution is more stable in a D_2O aqueous system than compared to an equivalent H_2O 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 H_2O.

[0090] In some embodiments, the composition comprises less than 20% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 15% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 10% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 5% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 2.5% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 2.0% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 1.5% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 1.0% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.5% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.4% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage

condition. In some embodiments, the composition comprises less than 0.3% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.2% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition comprises less than 0.1% of major degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition.

[0091] In some embodiments, the composition does not extend singlet oxygen lifetime upon irradiation with UV. In some instances, one or more of the ophthalmic agents described herein does not extend singlet oxygen lifetime upon irradiation with UV. In some instances, one or more of the ophthalmic agents described herein is a radical scavenger, which quenches photogenerated singlet oxygen species within the composition. In some instances, one or more of the ophthalmic agents selected from: 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, 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, artifical 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, scopolomine (L-hyoscine), hydroxyzine, ipratropium, pirenzapine, solifenacin, darifenacin, benzatropine, mebeverine, procyclidine, aclidinium bromide, trihexyphenidyl/benzhexol, and tolterodine, does not extend singlet oxygen lifetime upon irradiation with UV or quenches photogenerated singlet oxygen species within the composition. In some cases, the ophthalmic agent is not an alpha-amino-carboxylic acid or an alpha-hydroxy-carboxylic acid. In some cases, the ophthalmic agent is not benactyzine hydrochloride. In some cases, the ophthalmic composition is not saturated with oxygen. In additional cases, the ophthalmic composition does not comprise a photosensitizer.

Ophthalmic Agent Concentration

[0092] In some embodiments, the compositions described herein have a concentration of ophthalmic agent between about 0.001% to about 20%, between about 0.005% to about 10%, between about 0.010% to about 5%, between about 0.015% to about 1%, between about 0.020% to about 0.5%, between about 0.025% to about 0.1%, 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 is chemically converted into the ophthalmic agent after the administration of the ophthalmic composition. In a non-limiting example, the ophthalmic prodrug has a chemical bond that is cleavable by one or more enzymes in tears. In some embodiments, the ophthalmic agent is aflibercept (also known as VEGF Trap), 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, 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, scopolomine (L-hyoscine), hydroxyzine, ipratropium, pirenzapine, solifenacin, darifenacin, benzatropine, mebeverine, procyclidine, aclidinium bromide, trihexyphenidyl/benzhexol, or tolterodine.

[0093] 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 racemic mixture of D- and L-isomers; and some ophthalmic compositions disclosed herein includes optically enriched in favor of an ophthalmically active L-isomer.

Aqueous Solution Stability

[0094] 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.

[0095] 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.

[0096] 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 cases, the polyols are 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.

[0097] 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.

[0098] 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.

[0099] In some cases, citrate buffering agents include citric acid and sodium citrate.

[00100] In some instances, acetate buffering agents include acetic acid, potassium acetate, and sodium acetate.

[00101] In some instances, carbonate buffering agents include sodium bicarbonate and sodium carbonate.

[00102] In some cases, organic buffering agents include Good's Buffer, such as for example 2-(N-morpholino)ethanesulfonic acid (MES), *N*-(2-Acetamido)iminodiacetic acid, *N*-(Carbamoylmethyl)iminodiacetic acid (ADA), piperazine-N,N'-bis(2-ethanesulfonic acid (PIPES), N-(2-acetamido)-2-aminoethanesulfonic acid (ACES), β-Hydroxy-4-morpholinepropanesulfonic acid, 3-Morpholino-2-hydroxypropanesulfonic acid (MOPSO), cholamine chloride, 3-(N-morpholino)propansulfonic 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, glycinamide, bicine or N-tris(hydroxymethyl)methyl-3-aminopropanesulfonic acid sodium (TAPS); glycine; and diethanolamine (DEA).

[00103] 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.

[00104] In some instances, the composition described herein further comprises a tonicity adjusting agent. Tonicity adjusting agent is an agent introduced into a preparation such as an ophthalmic composition to reduce local irritation by preventing osmotic shock at the site of application. In some instances, buffer solution and/or a pD adjusting agent that broadly maintains the ophthalmic solution at a particular ion concentration and pD are considered as tonicity adjusting agents. In some cases, tonicity adjusting agents include various salts, such as halide salts of a monovalent cation. In some cases, tonicity adjusting agents include mannitol, sorbitol, dextrose, sucrose, urea, and glycerin. In some instances, suitable tonicity adjustors comprise sodium chloride, sodium nitrate, sodium sulfate, sodium bisulfate, potassium chloride, calcium chloride, magnesium chloride, zinc chloride, potassium acetate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium thiosulfate, magnesium sulfate, disodium hydrogen phosphate, sodium dihydrogen phosphate, potassium dihydrogen phosphate, dextrose, mannitol, sorbitol, dextrose, sucrose, urea, propylene glycol, glycerin, or a combination thereof.

[00105] 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.

[00106] In some cases, the composition described herein further comprises a pD adjusting agent. In some cases, the pD adjusting agent used is an acid or a base. In some embodiments, the base is oxides, hydroxides, carbonates, bicarbonates and the likes. In some cases, 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 cases, the acid is mineral acid and organic acids such as hydrochloric acid, nitric acid, phosphoric acid, acetic acid, citric acid, fumaric acid, malic acid tartaric acid and the likes or their deuterated equivalents. In some instances, the pD adjusting agent includes, but is not limited to, acetate, bicarbonate, ammonium chloride, citrate, phosphate, pharmaceutically acceptable salts thereof and combinations or mixtures thereof. In some embodiments, the pD adjusting agent comprises DCl and NaOD.

[00107] In some instances, the composition has a pD of between about 3 and about 9, about 4 and about 8, about 4.5 and about 7.8, about 5 and about 7.5, or about 5.5 and about 7. In some embodiments, the composition has a pD of less than about 8. In some embodiments, the composition has a pD of less than about 7.9. In some embodiments, the composition has a pD of less than about 7.8. In some embodiments, the composition has a pD of less than about 7.7. In some embodiments, the composition has a pD of less than 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 composition has a pD of less than about 3.9. In some embodiments, the composition has a pD of less than about 3.8. In some embodiments, the composition has a pD of less than about 3.7. In some embodiments, the composition has a pD of less than about 3.6. In some embodiments, the composition has a pD of less than about 3.5. In some embodiments, the pD is the pD of the composition after extended period of time under storage condition.

[00108] In some instances, the composition has an initial pD of between about 3 and about 9, about 4 and about 8, about 4.5 and about 7.8, about 5 and about 7.5, or about 5.5 and about 7. In some embodiments, the composition has an initial pD of about 8. 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. In some embodiments, the composition has an initial pD of about 3.9. In some embodiments, the composition has an initial pD of about 3.8. In some embodiments, the composition has an initial pD of about 3.7. In some embodiments, the composition has an initial pD of about 3.6. In some embodiments, the composition has an initial pD of about 3.5.

[00109] 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 3 and about 9, about 4 and about 8, about 4.5 and about 7.8, about 5 and about 7.5, or about 5.5 and about 7. In some embodiments, a stable composition comprises a pD of less than about 8. In some embodiments, a stable composition comprises a pD of less than about 7.9. In some embodiments, a stable composition comprises a pD of less than about 7.8. In some embodiments, a stable composition comprises a pD of less than about 7.7. In some embodiments, a stable composition comprises a pD of less than 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. In some embodiments, a stable composition comprises a pD of less than about 3.9. In some embodiments, a stable composition comprises a pD of less than about 3.8. In some embodiments, a stable composition comprises a pD of less than about 3.7. In some embodiments, a stable composition comprises a pD of less than about 3.6. In some embodiments, a stable composition comprises a pD of less than about 3.5.

[00110] As described elsewhere herein, in some instances, the D_2O aqueous system stabilizes an ophthalmic composition. In some embodiments, this is due to a lower concentration of the reactive species (e.g., -OD) in the D_2O aqueous system compared to the concentration of the reactive species (e.g., -OH) in an equivalent H_2O aqueous system. In some instances, the concentration of the reactive species (e.g., -OD) in the D_2O aqueous system is about one third less than the concentration of the reactive species (e.g., -OH) in the equivalent H_2O aqueous system. In some cases, this is due to a lower or smaller dissociation constant of D_2O than H_2O. For example, the $K_a(H_2O)$ is $1x10^{-14}$, whereas the $K_a(D_2O)$ is $1x10^{-15}$. As such, D_2O is a weaker acid than H_2O. In some cases, base catalyzed hydrolysis leads to the presence of a degradant from the ophthalmic agent. In some cases, with a lower concentration of the reactive species that causes degradant formation, the ophthalmic solution is more stable in a D_2O aqueous system than compared to an equivalent H_2O 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 H_2O.

[00111] In some embodiments, the presence of deuterated water shifts the pKa of the buffer. In some embodiments, the presence of deuterated water allows for the ophthalmic composition to simulate the stability of a lower pH system. In some instances, the buffer capacity of the ophthalmic composition is lowered, thereby allowing a faster shift in pH. In some instances, the lowered buffering capacity of the ophthalmic composition when administered into the eye allows the ophthalmic composition to reach physiological pH at a faster rate than compared to an ophthalmic composition formulated in H_2O. 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 H_2O.

[00112] In some instances, the composition described herein further comprises a disinfecting agent. In some cases, disinfecting agents include polymeric biguanides, polymeric quarternary ammonium compounds, chlorites, bisbiguanides, chlorite compounds (e.g. potassium chlorite, sodium chlorite, calcium chlorite, magnesium chlorite, or mixtures thereof), and a combination thereof.

[00113] 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).

[00114] 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%.

[00115] 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.

[00116] 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), polyprolyene (PP), polystyrene (PS), fluorine treated HDPE, post consumer resin (PCR), K-resine (SBC), or bioplastic. In some embodiments, the material of the plastic container comprises LDPE.

[00117] In some embodiments, the composition described herein is stored in a plastic container. In some embodiments, the composition stored in a plastic container has a pD of between about 3 and about 9, about 4 and about 8, about 4.5 and about 7.9, or about 4.9 and about 7.5. In some embodiments, the composition stored in a plastic container has a pD of less than about 8. In some embodiments, the composition stored in a plastic container has a pD of less than about 7.9. In some embodiments, the composition stored in a plastic container has a pD of less than about 7.8. In some embodiments, the composition stored in a plastic container has a pD of less than about 7.7. In some embodiments, the composition stored in a plastic container has a pD of less than about 7.6. In some embodiments, the composition stored in a plastic container has a pD of less than about 7.5. In some embodiments, the composition stored in a plastic container has a pD of less than about 7.4. In some embodiments, the composition stored in a plastic container has a pD of less than about 7.3. In some embodiments, the composition stored in a plastic container has a pD of less than about 7.2. In some embodiments, the composition stored in a plastic container has a pD of less than about 7.1. In some embodiments, the composition stored in a plastic container has a pD of less than about 7. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.9. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.8. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.7. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.6. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.5. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.4. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.3. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.2. In some embodiments, the composition stored in a plastic container has a pD of less than about 6.1. In some embodiments, the composition stored in a plastic container has a pD of less than about 6. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.9. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.8. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.7. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.6. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.5. In some embodiments, the composition

stored in a plastic container has a pD of less than about 5.4. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.3. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.2. In some embodiments, the composition stored in a plastic container has a pD of less than about 5.1. In some embodiments, the composition stored in a plastic container has a pD of less than about 5. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.9. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.8. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.7. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.6. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.5. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.4. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.3. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.2. In some embodiments, the composition stored in a plastic container has a pD of less than about 4.1. In some embodiments, the composition stored in a plastic container has a pD of less than about 4. In some embodiments, the composition stored in a plastic container has a pD of less than about 3.9. In some embodiments, the composition stored in a plastic container has a pD of less than about 3.8. In some embodiments, the composition stored in a plastic container has a pD of less than about 3.7. In some embodiments, the composition stored in a plastic container has a pD of less than about 3.6. In some embodiments, the composition stored in a plastic container has a pD of less than about 3.5.

[00118] In some embodiments, the composition stored in a plastic container has a potency of at least 80% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 85% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 90% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 93% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 95% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 97% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 98% after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container has a potency of at least 99% after extended period of time under storage condition. In some instances, the storage condition comprises a temperature of about 2°C, 4°C,

8°C, 10°C, 15°C, 20°C, 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, at least 24 months, at least 36 months, at least 3 years, at least 4 years, at least 5 years, or more.

[00119] In some embodiments, the composition stored in a plastic container has a potency of at least 80% at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container has a potency of at least 85% at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container has a potency of at least 90% at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container has a potency of at least 93% at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container has a potency of at least 95% at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container has a potency of at least 97% at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container has a potency of at least 98% at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a plastic container has a potency of at least 99% at a temperature of about 25°C, about 40°C, or about 60°C.

[00120] 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, at least 24 months, at least 36 months, at least 3 years, at least 4 years, at least 5 years, or more. 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, at least 24 months, at least 36 months, at least 3 years, at least 4 years, at least 5 years, or more. 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, at least 24 months, at least 36 months, at least 3 years, at least 4 years, at least 5 years, or more. 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, at least 24 months, at least 36 months, at least 3 years, at least 4 years, at least 5 years, or more. 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, at least 24 months, at least 36 months, at least 3 years, at least 4 years, at least 5 years, or more. 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, at least 24 months, at least 36 months, at least 3 years, at least 4 years, at least 5 years, or more. 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, at least 24 months, at least 36 months, at least 3 years, at least 4 years, at least 5 years, or more. 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, at least 24 months, at least 36 months, at least 3 years, at least 4 years, at least 5 years, or more.

[00121] In some embodiments, the composition stored in a plastic container comprises less than 20% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container comprises less than 15% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container comprises less than 10% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container comprises less than 5% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition.

[00122] In some embodiments, the composition stored in a plastic container comprises from less than 2.5% of primary degradant to less than 0.1% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In

some embodiments, the composition stored in a plastic container comprises less than 2.5% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container comprises less than 2.0% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container comprises less than 1.5% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container comprises less than 1.0% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container comprises less than 0.5% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container comprises less than 0.4% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container comprises less than 0.3% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container comprises less than 0.2% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some embodiments, the composition stored in a plastic container comprises less than 0.1% of primary degradant based on the concentration of the ophthalmic agent after extended period of time under storage condition. In some instances, the storage condition comprises a temperature of about 25°C, about 40°C, or about 60°C. In some instances, the extended period of time is at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, at least 24 months, at least 36 months, at least 3 years, at least 4 years, at least 5 years, or more.

[00123] 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.

[00124] 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.

[00125] 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.

[00126] In some embodiments, the composition stored in a plastic container comprises from less than 2.5% of primary degradant to less than 0.1% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 2.5% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 2.0% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 1.5% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 1.0% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the

composition stored in a plastic container comprises less than 0.5% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 0.4% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 0.3% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 0.2% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the composition stored in a plastic container comprises less than 0.1% of primary degradant based on the concentration of the ophthalmic agent for a period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 8 months, at least 10 months, at least 12 months, at least 18 months, or at least 24 months.

[00127] 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.

[00128] 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.

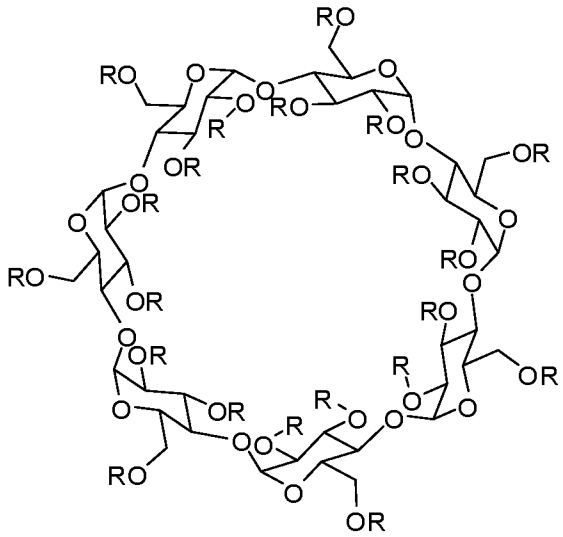
[00129] In some embodiments, the composition stored in a glass container has a potency of less than 60% at a temperature of about 25°C, about 40°C, or about 60°C. In some embodiments, the composition stored in a glass container has a potency of less than 60% for a period of at least 1 week, at least 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, at least 24 months, at least 36 months, at least 3 years, at least 4 years, at least 5 years, or more.

[00130] In some embodiments, the composition stored in a glass container is less stable than a composition stored in a plastic container.

[00131] 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.

[00132] 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.

[00133] 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 cases, 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 (HPβCD).



R = H
β-cyclodextrin

R = $CH_2CH(OH)CH_3$
hydroxypropyl β-cyclodextrin

[00134] 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 (HPβCD) is commercially available as a pyrogen free product. It is a nonhygroscopic white powder that readily dissolves in water. HPβCD 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.

[00135] 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.

[00136] 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.

[00137] 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.

[00138] 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.

[00139] 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 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.

[00140] 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.

[00141] 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.

[00142] 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, at least about 6 months, at least about 12 months, at least about 18 months, at least about 24 months, at least about 36 months, at least about 3 years, at least about 4 years, at least about 5 years, or at least about 10 years 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.

[00143] In other embodiments, an additional surfactant (co-surfactant) and/or buffering agent is combined with one or more of the pharmaceutically acceptable vehicles previously described herein so that the surfactant and/or buffering agent maintains the product at an optimal pD for stability. Suitable co-surfactants include, but are not limited to: a) natural and synthetic lipophilic agents, e.g., phospholipids, cholesterol, and cholesterol fatty acid esters and derivatives thereof; b) nonionic surfactants, which include for example, polyoxyethylene fatty alcohol esters, sorbitan fatty acid esters (Spans), polyoxyethylene sorbitan fatty acid esters (e.g., polyoxyethylene (20) sorbitan monooleate (Tween 80), polyoxyethylene (20) sorbitan monostearate (Tween 60), polyoxyethylene (20) sorbitan monolaurate (Tween 20) and other Tweens, sorbitan esters, glycerol esters, e.g., Myrj and glycerol triacetate (triacetin), polyethylene glycols, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, polysorbate 80, poloxamers, poloxamines, polyoxyethylene castor oil derivatives (e.g., Cremophor® RH40, Cremphor A25, Cremphor A20, Cremophor® EL) and other Cremophors, sulfosuccinates, alkyl sulphates (SLS); PEG glyceryl fatty acid esters such as PEG-8 glyceryl caprylate/caprate (Labrasol), PEG-4 glyceryl caprylate/caprate (Labrafac Hydro WL 1219), PEG-32 glyceryl laurate (Gelucire 444/14), PEG-6 glyceryl mono oleate (Labrafil M 1944 CS), PEG-6 glyceryl linoleate (Labrafil M 2125 CS); propylene glycol mono- and di-fatty acid esters, such as propylene glycol laurate, propylene glycol caprylate/caprate; Brij® 700, ascorbyl-6-palmitate, stearylamine, sodium lauryl sulfate, polyoxethyleneglycerol triiricinoleate, and any combinations or mixtures thereof; c) anionic surfactants include, but are not limited to, calcium carboxymethylcellulose, sodium carboxymethylcellulose, sodium sulfosuccinate, dioctyl, sodium alginate, alkyl polyoxyethylene sulfates, sodium lauryl sulfate, triethanolamine stearate, potassium laurate, bile salts, and any combinations or mixtures thereof; and d) cationic surfactants such as cetyltrimethylammonium bromide, and lauryldimethylbenzyl-ammonium chloride.

[00144] 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%.

[00145] 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.

pD

[00146] In some embodiments, the pD of a composition described herein is adjusted (e.g., by use of a buffer and/or a pD adjusting agent) to an ophthalmically compatible pD range of from about 3 and about 9, about 4 to about 8, about 4.5 to about 7.5, or about 5 to about 7. In some embodiments, the ophthalmic composition has a pD of from about 5.0 to about 7.0. In some embodiments, the ophthalmic composition has a pD of from about 5.5 to about 7.0. In some embodiments, the ophthalmic composition has a pD of from about 6.0 to about 7.0.

[00147] In some embodiments, useful formulations include one or more pD adjusting agents or buffering agents. Suitable pD adjusting agents or buffers include, but are not limited to acetate, bicarbonate, ammonium chloride, citrate, phosphate, deuterated forms of acetate, bicarbonate, ammonium chloride, citrate, phosphate, pharmaceutically acceptable salts thereof and combinations or mixtures thereof. In some embodiments, the pD adjusting agents or buffers include deuterated hydrochloric acid (DCl), deuterated sodium hydroxide (NaOD), deuterated acetic acid (CD_3COOD), or deuterated citric acid ($C_6D_8O_7$).

[00148] In one embodiment, when one or more buffers are utilized in the formulations of the present disclosure, they are combined, e.g., with a pharmaceutically acceptable vehicle and are present in the final formulation, e.g., in an amount ranging from about 0.1% to about 20%, from about 0.5% to about 10%. In certain embodiments of the present disclosure, the amount of buffer included in the gel formulations are an amount such that the pD of the gel formulation does not interfere with the body's natural buffering system.

[00149] In one embodiment, diluents are also used to stabilize compounds because they provide a more stable environment. Salts dissolved in buffered solutions (which also provide pD control or maintenance) are utilized as diluents in the art, including, but not limited to a phosphate buffered saline solution.

[00150] In some embodiments, the pD is calculated according to the formula disclosed in Glasoe *et al.*, "Use of glass electrodes to measure acidities in deuterium oxide," J. Physical Chem. 64(1): 188-190 (1960). In some embodiment, the pD is calculated as pD = pH* + 0.4, in which

pH* is the measured or observed pH of the ophthalmic composition formulated in a solution comprising deuterated water (e.g., D_2O).

[00151] In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 3 and about 9, about 4 and about 8, between about 4.5 and about 8, between about 4.9 and about 7.9, between about 5.4 and about 7.9, between about 5.9 and about 7.9, between about 6.4 and about 7.9, or between about 7.4 and about 7.9. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4.5-7.5, between about 5.0 and about 7.5, between about 5.5 and about 7.5, between about 6.0 and about 7.5, or between about 7.0 and about 7.5. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4.5-7.0, between about 5.0 and about 7.0, between about 5.5 and about 7.0, between about 6.0 and about 7.0, or between about 6.5 and about 7.0. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4.9-7.4, between about 5.4 and about 7.4, between about 5.9 and about 7.4, between about 6.4 and about 7.4, or between about 6.9 and about 7.4. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4.5-6.5, between about 5.0 and about 6.5, between about 5.5 and about 6.5, or between about 6.0 and about 6.5. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4.9-6.9, between about 5.4 and about 6.9, between about 5.9 and about 6.9, or between about 6.4 and about 6.9. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4.5-6.0, between about 5.0 and about 6.0, or between about 5.5 and about 6.0. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4.9-6.4, between about 5.4 and about 6.4, or between about 5.9 and about 6.4. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4.5-5.5, or between about 5.0 and about 5.5. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4.9-5.9, or between about 5.4 and about 5.9. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4.5-5.0. In some embodiments, the ophthalmic aqueous, gel, or ointment composition described herein has a pD of between about 4.9-5.4.

[00152] In some embodiments, the ophthalmic composition is an ophthalmic aqueous composition. In some instances, the ophthalmic aqueous composition has a pD of between about 3 and about 9, about 4 and about 8, about 4.5 and about 7.8, about 5 and about 7.5, or about 5.5 and about 7. In some embodiments, the ophthalmic aqueous composition has a pD of about 8.

In some embodiments, the ophthalmic aqueous composition has a pD of about 7.9. In some embodiments, the ophthalmic aqueous composition has a pD of about 7.8. In some embodiments, the ophthalmic aqueous composition has a pD of about 7.7. In some embodiments, the ophthalmic aqueous composition has a pD of about 7.6. In some embodiments, the ophthalmic aqueous composition has a pD of about 7.5. In some embodiments, the ophthalmic aqueous composition has a pD of about 7.4. In some embodiments, the ophthalmic aqueous composition has a pD of about 7.3. In some embodiments, the ophthalmic aqueous composition has a pD of about 7.2. In some embodiments, the ophthalmic aqueous composition has a pD of about 7.1. In some embodiments, the ophthalmic aqueous composition has a pD of about 7. In some embodiments, the ophthalmic aqueous composition has a pD of about 6.9. In some embodiments, the ophthalmic aqueous composition has a pD of about 6.8. In some embodiments, the ophthalmic aqueous composition has a pD of about 6.7. In some embodiments, the ophthalmic aqueous composition has a pD of about 6.6. In some embodiments, the ophthalmic aqueous composition has a pD of about 6.5. In some embodiments, the ophthalmic aqueous composition has a pD of about 6.4. In some embodiments, the ophthalmic aqueous composition has a pD of about 6.3. In some embodiments, the ophthalmic aqueous composition has a pD of about 6.2. In some embodiments, the ophthalmic aqueous composition has a pD of about 6.1. In some embodiments, the ophthalmic aqueous composition has a pD of about 6. In some embodiments, the ophthalmic aqueous composition has a pD of about 5.9. In some embodiments, the ophthalmic aqueous composition has a pD of about 5.8. In some embodiments, the ophthalmic aqueous composition has a pD of about 5.7. In some embodiments, the ophthalmic aqueous composition has a pD of about 5.6. In some embodiments, the ophthalmic aqueous composition has a pD of about 5.5. In some embodiments, the ophthalmic aqueous composition has a pD of about 5.4. In some embodiments, the ophthalmic aqueous composition has a pD of about 5.3. In some embodiments, the ophthalmic aqueous composition has a pD of about 5.2. In some embodiments, the ophthalmic aqueous composition has a pD of about 5.1. In some embodiments, the ophthalmic aqueous composition has a pD of about 5. In some embodiments, the ophthalmic aqueous composition has a pD of about 4.9. In some embodiments, the ophthalmic aqueous composition has a pD of about 4.8. In some embodiments, the ophthalmic aqueous composition has a pD of about 4.7. In some embodiments, the ophthalmic aqueous composition has a pD of about 4.6. In some embodiments, the ophthalmic aqueous composition has a pD of about 4.5. In some embodiments, the ophthalmic aqueous composition has a pD of about 4.4. In some embodiments, the ophthalmic aqueous composition has a pD of about 4.3. In some embodiments, the ophthalmic aqueous composition has a pD of about 4.2. In some

embodiments, the ophthalmic aqueous composition has a pD of about 4.1. In some embodiments, the ophthalmic aqueous composition has a pD of about 4. In some embodiments, the ophthalmic aqueous composition has a pD of about 3.9. In some embodiments, the ophthalmic aqueous composition has a pD of about 3.8. In some embodiments, the ophthalmic aqueous composition has a pD of about 3.7. In some embodiments, the ophthalmic aqueous composition has a pD of about 3.6. In some embodiments, the ophthalmic aqueous composition has a pD of about 3.5. In some embodiments, the pD is an initial pD of the ophthalmic aqueous composition. In some embodiments, the pD is the pD of the ophthalmic aqueous composition after extended period of time under storage condition.

[00153] In some instances, the ophthalmic aqueous composition has an initial pD of between about 3 and about 9, about 4 and about 8, about 4.5 and about 7.8, about 5 and about 7.5, or about 5.5 and about 7. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 8. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7.9. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7.8. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7.7. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7.6. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7.5. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7.4. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7.3. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7.2. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7.1. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 7. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.9. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.8. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.7. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.6. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.5. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.4. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.3. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.2. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6.1. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 6. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.9. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.8. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.7. In some

embodiments, the ophthalmic aqueous composition has an initial pD of about 5.6. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.5. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.4. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.3. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.2. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5.1. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 5. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 4.9. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 4.8. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 4.7. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 4.6. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 4.5. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 4.4. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 4.3. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 4.2. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 4.1. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 4. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 3.9. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 3.8. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 3.7. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 3.6. In some embodiments, the ophthalmic aqueous composition has an initial pD of about 3.5.

[00154] In some instances, the ophthalmic aqueous composition has a pD of between about 3 and about 9, about 4 and about 8, about 4.5 and about 7.8, about 5 and about 7.5, or about 5.5 and about 7. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 8. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 7.9. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 7.8. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 7.7. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 7.6. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 7.5. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 7.4. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 7.3. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 7.2. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 7.1. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 7. In some

embodiments, the ophthalmic aqueous composition has a pD of less than about 6.9. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 6.8. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 6.7. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 6.6. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 6.5. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 6.4. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 6.3. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 6.2. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 6.1. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 6. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 5.9. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 5.8. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 5.7. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 5.6. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 5.5. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 5.4. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 5.3. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 5.2. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 5.1. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 5. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 4.9. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 4.8. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 4.7. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 4.6. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 4.5. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 4.4. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 4.3. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 4.2. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 4.1. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 4. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 3.9. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 3.8. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 3.7. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 3.6. In some embodiments, the ophthalmic aqueous composition has a pD of less than about 3.5. In some

embodiments, the pD is the pD of the ophthalmic aqueous composition after extended period of time under storage condition.

[00155] In some embodiments, the pD of the ophthalmic aqueous composition described herein is associated with the stability of the ophthalmic aqueous composition. In some embodiments, a stable composition comprises a pD of between about 3 and about 9, about 4 and about 8, about 4.5 and about 7.8, about 5 and about 7.5, or about 5.5 and about 7. In some embodiments, a stable composition comprises a pD of less than about 8. In some embodiments, a stable composition comprises a pD of less than about 7.9. In some embodiments, a stable composition comprises a pD of less than about 7.8. In some embodiments, a stable composition comprises a pD of less than about 7.7. In some embodiments, a stable composition comprises a pD of less than 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. In some embodiments, a stable composition comprises a pD of less than about 3.9. In some embodiments, a stable composition comprises a pD of less than about 3.8. In some embodiments, a stable composition comprises a pD of less than about 3.7. In some embodiments, a stable composition comprises a pD of less than about 3.6. In some embodiments, a stable composition comprises a pD of less than about 3.5.

[00156] In some embodiments, the D_2O aqueous system stabilizes an ophthalmic agent. In some embodiments, this is due to a lower concentration of the reactive species (e.g., -OD) in the D_2O aqueous system compared to the concentration of the reactive species (e.g., -OH) in an equivalent H_2O aqueous system. In some instances, the concentration of the reactive species (e.g., -OD) in the D_2O aqueous system is about one third less than the concentration of the reactive species (e.g., -OH) in the equivalent H_2O aqueous system. In some cases, this is due to a lower or smaller dissociation constant of D_2O than H_2O. For example, the $K_a(H_2O)$ is $1x10^{-14}$, whereas the $K_a(D_2O)$ is $1x10^{-15}$. As such, D_2O is a weaker acid than H_2O. In some cases, base catalysis leads to the presence of a degradant from the ophthalmic agent. In some cases, with a lower concentration of the reactive species that causes degradant formation, the ophthalmic solution is more stable in a D_2O aqueous system than compared to an equivalent H_2O 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 H_2O.

[00157] In some embodiments, the presence of deuterated water shifts the pKa of the buffer. In some embodiments, the presence of deuterated water allows for the ophthalmic composition to simulate the stability of a lower pH system. In some instances, the buffer capacity of the ophthalmic composition is lowered, thereby allowing a faster shift in pH. In some instances, the lowered buffering capacity of the ophthalmic composition when administered into the eye allows the ophthalmic composition to reach physiological pH at a faster rate than compared to an ophthalmic composition formulated in H_2O. 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 H_2O.

[00158] In some embodiment, the ophthalmic gel or ointment composition described herein has a pD of about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, about 4, about 4.1, about 4.2, about 4.3, about 4.4, about 4.5, about 4.6, about 4.7, about 4.8, about 4.9, about 5.0, about 5.1, about 5.2, about 5.3, about 5.4, about 5.5, about 5.6, about 5.7, about 5.8, about 5.9, about 6.0, about 6.1, about 6.2, about 6.3, about 6.4, about 6.5, about 6.6, about 6.7, about 6.8, about 6.9, about 7.0, about 7.1, about 7.2, about 7.3, about 7.4, about 7.5, about 7.6, about 7.7, about 7.8, or about 7.9.

[00159] In some embodiment, the pD of the ophthalmic aqueous, gel, or ointment composition described herein is suitable for sterilization (e.g., by filtration or aseptic mixing or heat treatment and/or autoclaving (e.g., terminal sterilization)) of ophthalmic formulations described herein. As used in in the present disclosure, the term "aqueous composition" includes compositions that are based on D_2O.

[00160] In some embodiments, the pharmaceutical formulations described herein are stable with respect to pD over a period of any of at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 4 weeks, at least about 5 weeks, at least about 6 weeks, at least about 7 weeks, at least about 8 weeks, at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about 18 months, at least about 24 months, at least about 3 years, at least about 4 years, at least about 5 years, at least about 6 years, at least about 7 years, at least about 8 years, at least about 9 years, at least about 10 years, at least about 15 years, at least about 20 years, at least about 30 years, or more. In other embodiments, the formulations described herein are stable with respect to pD over a period of at least about 1 week. In other embodiments, the formulations described herein are stable with respect to pD over a period of at least about 2 weeks. In other embodiments, the formulations described herein are stable with respect to pD over a period of at least about 3 weeks. In other embodiments, the formulations described herein are stable with respect to pD over a period of at least about 1 month. Also described herein are formulations that are stable with respect to pD over a period of at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 12 months, at least about 18 months, at least about 2 years, or more.

Aqueous Solution Dose-To-Dose Uniformity

[00161] 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.

[00162] In some cases, described herein include ophthalmic aqueous compositions which provide a dose-to-dose uniform concentrations. In some instances, the dose-to-dose uniform concentration does not present significant variations of drug content from one dose to another. In some instances, the dose-to-dose uniform concentration does provide consistent drug content from one dose to another.

[00163] 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%.

[00164] 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.

[00165] 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.

[00166] 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 an ophthalmic agent in the expressed drops are determined using a reverse-phase HPLC method.

Aqueous Solution Viscosity

[00167] 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 $1s^{-1}$.

[00168] 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.

[00169] 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.

Osmolarity

[00170] In some embodiments, a composition disclosed herein is formulated in order to not disrupt the ionic balance of the eye. In some embodiments, a composition disclosed herein has an ionic balance that is the same as or substantially the same as the eye. In some embodiments, a composition disclosed herein does not does not disrupt the ionic balance of the eye.

[00171] As used herein, "practical osmolarity/osmolality" or "deliverable osmolarity/osmolality" means the osmolarity/osmolality of a composition as determined by measuring the osmolarity/osmolality of the ophthalmic agent and all excipients except the gelling and/or the thickening agent (e.g., polyoxyethylene-polyoxypropylene copolymers, carboxymethylcellulose or the like). The practical osmolarity of a composition disclosed herein is measured by a suitable method, e.g., a freezing point depression method as described in Viegas et. al., Int. J. Pharm., 1998, 160, 157-162. In some instances, the practical osmolarity of a composition disclosed herein is measured by vapor pressure osmometry (e.g., vapor pressure depression method) that allows for determination of the osmolarity of a composition at higher temperatures. In some instances, vapor pressure depression method allows for determination of the osmolarity of a composition comprising a gelling agent (e.g., a thermoreversible polymer) at a higher temperature wherein the gelling agent is in the form of a gel.

[00172] In some embodiments, the osmolarity at a target site of action (e.g., the eye) is about the same as the delivered osmolarity of a composition described herein. In some embodiments, a composition described herein has a deliverable osmolarity of about 150 mOsm/L to about 500 mOsm/L, about 250 mOsm/L to about 500 mOsm/L, about 250 mOsm/L to about 350 mOsm/L, about 280 mOsm/L to about 370 mOsm/L or about 250 mOsm/L to about 320 mOsm/L.

[00173] 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

osmolarity 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.

[00174] In some embodiments, suitable tonicity adjusting agents include, but are not limited to any pharmaceutically acceptable sugar, salt or any combinations or mixtures thereof, such as, but not limited to dextrose, glycerin, mannitol, sorbitol, sodium chloride, and other electrolytes. In some instances, the tonicity adjusting agent is selected from sodium chloride, sodium nitrate, sodium sulfate, sodium bisulfate, potassium chloride, calcium chloride, magnesium chloride, zinc chloride, potassium acetate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium thiosulfate, magnesium sulfate, disodium hydrogen phosphate, sodium dihydrogen phosphate, potassium dihydrogen phosphate, dextrose, mannitol, sorbitol, dextrose, sucrose, urea, propylene glycol, glycerin, or a combination thereof.

[00175] 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.

Sterility

[00176] 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.

[00177] 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

[00178] 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. $10^{7}/cm^{2}$) of unusually small microorganisms, such as Brevundimonas diminuta (ATCC 19146).

[00179] 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.

[00180] 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 (Tgel) 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).

[00181] 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 is reduced or eliminated through the use of specific pD ranges for buffer components and specific proportions of viscosity enhancing agents in the formulations. In some embodiments, the choice of an appropriate viscosity enhancing

agents or thermosetting polymer allows for sterilization of formulations described herein by filtration. In some embodiments, the use of an appropriate thermosetting polymer or other viscosity enhancing agents in combination with a specific pD range for the formulation allows for high temperature sterilization of formulations described with substantially no degradation of the therapeutic agent or the polymeric excipients. An advantage of the methods of sterilization provided herein is that, in certain instances, the formulations are subjected to terminal sterilization via autoclaving without any loss of the ophthalmic agent and/or excipients and/or viscosity enhancing agents during the sterilization step and are rendered substantially free of microbes and/or pyrogens.

Radiation Sterilization

[00182] 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

[00183] Many methods are available for sterilization by the application of high heat. One method is through the use of a saturated steam autoclave. In this method, saturated steam at a temperature of at least 121 °C is allowed to contact the object to be sterilized. The transfer of heat is either directly to the microorganism, in the case of an object to be sterilized, or indirectly to the microorganism by heating the bulk of an aqueous solution to be sterilized. This method is widely practiced as it allows flexibility, safety and economy in the sterilization process.

Microorganisms

[00184] 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.

[00185] 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.

[00186] Testing for *E. coli* and *Salmonella* includes the use of lactose broths incubated at 30 – 35 ^{o}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.

[00187] 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

[00188] 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 vary 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.

[00189] In some embodiments, the ophthalmic formulation has less than about 5 EU/kg of formulation. In other embodiments, the ophthalmic formulation has less than about 4 EU/kg of formulation. In additional embodiments, the ophthalmic formulation has less than about 3 EU/kg of formulation. In some embodiments, the ophthalmic formulation has less than about 5 EU/kg Product. In other embodiments, the ophthalmic formulation has less than about 1 EU/kg Product. In additional embodiments, the ophthalmic formulation has less than about 0.2 EU/kg Product. In some embodiments, the ophthalmic formulation has less than about 5 EU/g of unit or Product. In other embodiments, the ophthalmic formulation has less than about 4 EU/ g of unit or Product. In additional embodiments, the ophthalmic formulation has less than about 3 EU/g of unit or Product. In some embodiments, the ophthalmic formulation has less than about 5 EU/mg of unit or Product. In other embodiments, the ophthalmic formulation has less than about 4 EU/ mg of unit or Product. In additional embodiments, the ophthalmic formulation has less than about 3 EU/mg of unit or Product. In certain embodiments, ophthalmic formulations described herein contain from about 1 to about 5 EU/mL of formulation. In certain embodiments, ophthalmic formulations described herein contain from about 2 to about 5 EU/mL

of formulation, from about 3 to about 5 EU/mL of formulation, or from about 4 to about 5 EU/mL of formulation.

[00190] 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.

[00191] 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 amebocyte lysate test are both specified in the United States Pharmacopeia Chapters <85> and <151> (USP23/NF 18, Biological Tests, The United States Pharmacopeial 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 amebocyte 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.

Ophthalmic Agent-Mucus Penetrating Particle (MPP) Composition

[00192] Mucus-penetrating particles (MPPs) are particles that rapidly traverse mucus (e.g. human mucus). In some cases, MPPs comprise of a nanoparticle with a particle size of between about 200nm and 500nm. In some instances, the nanoparticle is further coated with a mucus penetrating agent. In some instances, a composition described herein is formulated with MPPs for mucus penetration. In some instances, an ophthalmic composition described herein is formulated with MPPs for mucus penetration. In some embodiments, an ophthalmic agent includes aflibercept (also known as VEGF Trap), 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, 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, scopolomine (L-hyoscine), hydroxyzine, ipratropium, pirenzapine, solifenacin, darifenacin, benzatropine, mebeverine, procyclidine, aclidinium bromide, trihexyphenidyl/benzhexol, tolterodine, or any combinations thereof. 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).

[00193] 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.

[00194] In some embodiments, the nanoparticle is coated with a mucus penetrating agent. In some instances, the mucus penetrating agent comprises any suitable material, such as a hydrophobic material, a hydrophilic material, and/or an amphiphilic material. In some instances, the mucus penetrating agent is a polymer. In some instances, the polymer a synthetic polymer (i.e., a polymer not produced in nature). In other embodiments, the polymer is a natural polymer (e.g. , a protein, polysaccharide, rubber). In certain embodiments, the polymer is a surface active polymer. In certain embodiments, the polymer is a non-ionic polymer. In certain embodiments, the polymer is a non-ionic block copolymer. In some embodiments, the polymer is a diblock copolymer, a triblock copolymer, e.g., e.g., where one block is a hydrophobic polymer and another block is a hydrophilic polymer. In some instances, the polymer is charged or uncharged.

[00195] Additional examples of suitable polymers include, but are not limited to, polyamines, polyethers, polyamides, polyesters, polycarbamates, polyureas, polycarbonates, polystyrenes, polyimides, polysulfones, polyurethanes, polyacetylenes, polyethylenes, polyethyeneimines, 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.

[00196] In some cases, an ophthalmic agent is present in the MPP formulation at a concentration of between about 0.001 wt% and about 20 wt%, between about 0.01% to about 15%, between about 0.05% to about %10, between about 0.1% to about 5%, or between about 0.5% to about 1% of the ophthalmic agent, or pharmaceutically acceptable prodrug or salt thereof, by weight of the composition. In some instances, additional agents such as buffers, pD adjusting agents, and/or preservatives are formulated in the MPP formulation.

[00197] 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. 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.

[00198] 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 embodiments, 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.

[00199] In some embodiments, any suitable solvent is used for milling. In some instances, the choice of solvent depends on factors such as the solid material 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. Suitable solvents include 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 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, pD modifier, and other pharmaceutical excipients. In other embodiments, an organic solvent is used. In some embodiments, a pharmaceutical agent 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.

[00200] 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).

Ophthalmic Gel Composition

[00201] 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.

[00202] 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.

[00203] In some embodiments, the ophthalmic composition is an ophthalmic gel, and wherein the ophthalmically acceptable carrier comprises deuterated 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.

[00204] 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.

[00205] 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.

[00206] 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.

[00207] 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.

[00208] 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.

[00209] In some instances, the ophthalmic gel composition comprises an ophthalmic agent 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, polymethacrilic acid (PMMA), polyethylene glycol (PEG), pseudolatexes, xyloglucans, or combinations thereof.

[00210] 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.

[00211] 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.

[00212] 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.

[00213] In certain embodiments, the enhanced viscosity formulation is characterized by a phase transition between room temperature and body temperature (including an individual with a serious fever, e.g., up to about 42 °C). In some embodiments, the phase transition occurs at 1 °C

below body temperature, at 2 °C below body temperature, at 3 °C below body temperature, at 4 °C below body temperature, at 6 °C below body temperature, at 8 °C below body temperature, or at 10 °C below body temperature. In some embodiments, the phase transition occurs at about 15 °C below body temperature, at about 20 °C below body temperature or at about 25 °C below body temperature. In specific embodiments, the gelation temperature (Tgel) of a formulation described herein is about 20 °C, about 25 °C, or about 30 °C. In certain embodiments, the gelation temperature (Tgel) of a formulation described herein is about 35 °C, or about 40 °C. Included within the definition of body temperature is the body temperature of a healthy individual, or an unhealthy individual, including an individual with a fever (up to ~42 °C). In some embodiments, the pharmaceutical compositions described herein are liquids at about room temperature and are administered at or about room temperature.

[00214] 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.

[00215] 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.

[00216] In an alternative embodiment, the thermogel is a PEG-PLGA-PEG triblock copolymer (Jeong etal, Nature (1997), 388:860-2; Jeong etal, J. Control. Release (2000), 63:155-63; Jeong etal, 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 coploymers 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.

[00217] 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.

[00218] Since the polymer systems of thermosetting gels dissolve more completely at reduced temperatures, methods of solubilization include adding the required amount of polymer to the amount of water to be used at reduced temperatures. Generally after wetting the polymer by shaking, the mixture is capped and placed in a cold chamber or in a thermostatic container at about 0-10 °C in order to dissolve the polymer. The mixture is stirred or shaken to bring about a more rapid dissolution of the thermosetting gel polymer. The ophthalmic agent and various additives such as buffers, salts, and preservatives are subsequently added and dissolved. In some instances the pharmaceutically agent is suspended if it is insoluble in water. The pD is modulated by the addition of appropriate buffering agents.

Ophthalmic Ointment Composition

[00219] 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

[00220] 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.

[00221] Ointments are formulated using hydrophobic, hydrophilic, or water-emulsifying bases to provide preparations that are immiscible, miscible, or emulsifiable with skin secretions. In some instances, 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.).

[00222] 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.

[00223] The present disclosure further recognizes that ophthalmic drugs 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.

[00224] 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.

[00225] 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.

[00226] 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.

[00227] 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.

[00228] 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.

[00229] 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.

[00230] 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.

[00231] Polyethoxylated castor oils are reaction products of natural or hydrogenated castor oils and ethylene glycol. 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.; H_2O content (%, KF)=ca. 0.03.

[00232] Poly(ethylene-glycols) are used in some embodiments as the agent for dispersing and/or dissolving the ophthalmic drug in the ointment base according to the present disclosure. Suitable poly(ethylene-glycol)s are typically mixtures of polymeric compounds of the general formula H—(OCH2—CH2)nOH, wherein the index n typically ranges 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.

[00233] 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.

[00234] 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.

Gel/Ointment Viscosity

[00235] 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 $1s^{-1}$.

[00236] 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.

[00237] 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.

[00238] 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.

[00239] 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).

Gel/Ointment Dose-To-Dose Uniformity

[00240] 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.

[00241] In some cases, described herein include ophthalmic gel compositions which provide a dose-to-dose uniform concentrations. In some instances, the dose-to-dose uniform concentration does not present significant variations of drug content from one dose to another. In some instances, the dose-to-dose uniform concentration does provide consistent drug content from one dose to another.

[00242] In some cases, described herein include ophthalmic ointment compositions which provide a dose-to-dose uniform concentrations. In some instances, the dose-to-dose uniform concentration does not present significant variations of drug content from one dose to another. In some instances, the dose-to-dose uniform concentration does provide consistent drug content from one dose to another.

[00243] 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%.

[00244] 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.

[00245] 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.

[00246] 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 is 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 an ophthalmic agent in the expressed drops are determined using a reverse-phase HPLC method.

Methods of Treatment

[00247] Disclosed herein are methods of treating one or more ophthalmic conditions or diseases by administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition described *supra*. Also disclosed herein are methods of ameliorating or reducing one or more ophthalmic conditions or diseases by administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition described *supra*.

[00248] In some embodiments, the ophthalmic condition or disease includes a condition or disease associated with the eyelid, the lacrimal system, or the orbit (Fig. 1). In some

embodiments, the lacrimal system encompasses the orbital structures for tear production and drainage. In some embodiments, the lacrimal system comprises the lacrimal gland responsible for tear production, excretory ducts which convey the fluid to the surface of the eye, lacrimal canaliculi, lacrimal sac, and nasolacrimal duct. In some embodiments, the orbit encompasses the eye and its associated appendages. In some embodiments, an ophthalmic composition described herein is administered to an eye of an individual in need thereof for a condition or disease associated with the eyelid, lacrimal system or the orbit.

[00249] In some embodiments, the ophthalmic condition or disease includes a condition or disease associated with the conjunctiva, sclera, cornea, iris, or ciliary body (Fig. 1). Conjunctiva lines the inside of the eyelids and covers the sclera. Sclera, or the white of the eye, is an opaque, fibrous, protective outer layer of the eye. Cornea is the transparent front part of the eye that covers the iris, pupil, and anterior chamber. Iris is a thin, circular structure in the eye responsible for controlling the diameter and size of the pupil and therefore the amount of light reaching the retina. Ciliary body includes the ciliary muscle, which controls the shape of the lens and the ciliary epithelium, which produces the aqueous humor. In some embodiments, an ophthalmic composition described herein is administered to an eye of an individual in need thereof for a condition or disease associated with conjunctiva, sclera, cornea, iris, or ciliary body.

[00250] In some embodiments, the ophthalmic condition or disease includes a condition or disease associated with the choroid or retina (Fig. 1). Choroid, also known as choroidea or choroid coat, is the vascular layer of the eye containing connective tissue and is in between the retina and the sclera. Retina is the third and inner coat of the eye and is a light-sensitive tissue layer. In some embodiments, an ophthalmic composition described herein is administered to an eye of an individual in need thereof for a condition or disease associated with choroid or retina.

[00251] In some embodiments, the ophthalmic condition or disease includes a condition or disease associated with the lens (Fig. 1). The lens or crystalline lens is a transparent, biconvex structure in the eye that in combination with the cornea helps to refract light to be focused on the retina. In some embodiments, an ophthalmic composition described herein is administered to an eye of an individual in need thereof for a condition or disease associated with the lens.

[00252] In some embodiments, the ophthalmic conditions or diseases include, but are not limited to, Acanthamoeba keratitis, Bell's palsy, blepharochalasis, blepharitis, chalazion, cataract, cyclitis, cytomegalovirus (CMV) retinitis, chorioretinal inflammation, conjunctivitis (e.g., allergy related conjunctivitis or conjunctivitis due to infection), neonatol conjunctivitis, corneal neovascularization, corneal ulcer, dermatitis, diabetic retinopathy, dry eye syndrome, dacryoadenitis, dacryostenosis, endophthalmitis, epiphora, episcleritis, eye impetigo, eyelash hypotrichosis, Fuchs' dystrophy (also known as Fuchs' corneal endothelial dystrophy or FCED),

glaucoma, hypermetropia, iritis, keratoconjunctivitis, keratoconjunctivitis sicca, macular degeneration (e.g., Stargardt's disease), macular dystrophy, macular edema (e.g., diabetic macular edema), myopia, ocular hypertension, loiasis, ocular rosacea, onchocerciasis (or known as river blindness or Robles disease), optic neuritis and optic neuropathy, keratitis (e.g., bacterial keratitis, fungal keratitis, parasitic keratitis, or viral keratitis), pinguecular and pterygium, production of miosis, scleritis, steroid responsive inflammatory conditions, stye (or hordeolum), temporal arteritis, Thygeson's superficial punctate keratopathy (TSPK), trachoma, organophosphate poisoning, basal cell carcinoma, squamous carcinoma, sebaceous carcinoma, malignant melanoma, orbital lymphoma, uveitis, uveal melanoma, retinoblastoma, medulloepithelioma, or primary intraocular lymphoma. In some embodiments, viral keratitis includes ocular herpes or Herpetic keratitis, or Herpes Simplex dendritic keratitis.

[00253] In some embodiments, viruses that cause viral eye infections include Herpes simplex virus, Epstein Barr virus, or influenza virus.

[00254] In some embodiments, fungi that cause fungal eye infections include *Arthrobotrys oligospora*, *Aspergillus versicolar*, *Candida*, *Cladosporium*, *Cephaliophora irregularis*, *Exophiala*, *Fusarium* (e.g., *Fusarium solani*), *Phoma*, or *Scedosporium* (e.g., *Scedosporium prolificans*).

[00255] In some embodiments, bacteria that cause bacterial eye infections include *Chlamydia trachomatis, N. meningitidis, Staphylococcus aureus, S. epidermidis, S. pneumoniae, Streptococcus* spp., or *Pseudomonas aeruginosa.*

[00256] In some embodiments, parasites that cause eye infections include *Demodex*, *Leishmania*, nematode such as *Loa loa*, *Simulium*, *Toxoplasma gondii,* or *Toxocara.*

[00257] In some embodiments, the ophthalmic condition or disease refers to a condition or disease that requires surgery. In some embodiments, one or more of the ophthalmic compositions is administered before, during, or after surgery, or for surgery-related complications. Examplary surgeries include laser eye surgery, cataract surgery, glaucoma surgery, canaloplasty, refractive surgery, corneal surgery, vitrectomy, eye muscle surgery, and oculoplastic surgery. In some embodiments, surgery-related complications include postoperative increased intraocular pressure and postoperative ocular inflammation.

[00258] In some embodiments, the ophthalmic condition or disease refers to a condition or disease that requires aid of a diagnostic agent for visualization. In some embodiments, one or more of the ophthalmic compositions is administered as a diagnostic agent for visualization.

[00259] In some embodiments, an ophthalmic composition is administered as part of a normal or routine eye examination procedure. In some embodiments, the normal or routine eye

examination procedure is an eye exam. In some embodiments, an ophthalmic composition comprising a mydriatic agent is administered for dilation of the pupil during an eye exam.

[00260] 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.

[00261] 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 ºC to about 10 ºC prior to first use. In some embodiments of the disclosed method, the ophthalmic composition is stored at about 2 ºC, about 3 ºC, about 4 ºC, about 5 ºC, about 6 ºC, about 7 ºC, about 8 ºC, about 9 ºC, or about 10 ºC prior to first use. In some embodiments of the disclosed method, the ophthalmic composition is stored at between about 4 ºC to about 8 ºC prior to first use.

[00262] 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 ºC to about 26 ºC after to first use. In some embodiments of the disclosed method, the ophthalmic composition is stored at about 16 ºC, about 17 ºC, about 18 ºC, about 19 ºC, about 20 ºC, about 21 ºC, about 22 ºC, about 23 ºC, about 24 ºC, about 25 ºC, or about 26 ºC after to first use.

[00263] 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.

[00264] 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.

[00265] 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.

[00266] 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 a day. 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 moths, 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 11 years, or 12-15 years. In some embodiments, the ophthalmic composition is administered only once.

[00267] 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%.

[00268] 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.

[00269] 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.

[00270] 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%.

[00271] 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.

[00272] 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.

[00273] In some embodiments, the initial administration is a particular ophthalmic agent and the subsequent administration a different formulation or ophthalmic agent.

Kits/Articles of Manufacture

[00274] The disclosure also provides kits for treating one or more ophthalmic conditions or diseases described herein. 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 abating, reducing, or ameliorating the symptoms of one or more of the ophthalmic conditions or diseases described herein.

[00275] 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.

[00276] 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.

[00277] 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.

[00278] 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.

Terminology

[00279] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the claimed subject

matter belongs. It is to be understood that the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of any subject matter claimed. In this application, the use of the singular includes the plural unless specifically stated otherwise. It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. In this application, the use of "or" means "and/or" unless stated otherwise. Furthermore, use of the term "including" as well as other forms, such as "include," "includes," and "included," is not limiting.

[00280] As used herein, ranges and amounts is expressed as “about” a particular value or range. About also includes the exact amount. Hence “about 5 µg” means “about 5 µg” and also “5 µg.” Generally, the term “about” includes an amount that is expected to be within experimental error.

[00281] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in the application including, but not limited to, patents, patent applications, articles, books, manuals, and treatises are hereby expressly incorporated by reference in their entirety for any purpose.

[00282] The terms “subject” and “individual”, as included herein, are used interchangeably. None of the terms are to be interpreted as requiring the supervision of a medical professional (e.g., a doctor, nurse, physician’s assistant, orderly, hospice worker).

EXAMPLES

Example 1 – Ophthalmic Formulations

[00283] Exemplary compositions for preparation of ophthalmic formulations are described in Tables 1-5.

Table 1 —Aqueous Solution Formulation

Ingredient	Quantity (mg/g)	Concentration (wt%)
Ophthalmic agent	0.01-200	0.001-20 (wt%)
Buffer agent and/or pD adjusting agent (e.g. , borates and/or DCl)	-	q.s. for pD=4-8
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	-	q.s. to prevent the growth of or to destroy microorganism introduced into the solution
Tonicity and/or Osmolarity adjustor (e.g. NaCl, mannitol, etc)	-	q.s. to 0.5-2.0 wt%
Deuterated Water	-	q.s. to 100 wt%

Table 2 —Aqueous Solution Formulation

Ingredient	Quantity (mg/g)	Concentration (wt%)
Ophthalmic agent	0.01-50	0.001-5 (wt%)
Buffer agent and/or pD adjusting agent (e.g. , borates and/or DCl)	-	q.s. for pD=4-8
Preservative (e.g. benzalkonium chloride, cetrimonium sodium perborate, etc.)	-	q.s. to prevent the growth of or to destroy microorganism introduced into the solution
Tonicity and/or Osmolarity adjustor (e.g. NaCl, mannitol, etc)	-	q.s. to 0.5-2.0 wt%
Deuterated Water	-	q.s. to 100 wt%

Table 3 —Cellulose Gel Formulation

Ingredient	Quantity (mg/g)	Concentration (wt%)
Ophthalmic agent	0.01-200	0.001-20 (wt%)
Viscosity enhancing agent (e.g. hydroxypropyl methylcellulose)	10-50	1-5 (wt%)
Buffer agent and/or pD adjusting agent (e.g. , sodium acetate and/or DCl)	-	q.s. for pD=4-8
Stabilizer (e.g. EDTA, cyclodextrin, etc.)	-	q.s. for low degradation of ophthalmic agent
Osmolarity modifier (e.g. NaCl)	-	q.s. 150-500 mOsm/L
Deuterated Water	-	q.s. to 100 wt%

Table 4 —Thermosetting Gel Formulation

Ingredient	Quantity (mg/g)	Concentration (wt%)
Ophthalmic agent	0.01-200	0.001-20 (wt%)
Viscosity enhancing agent (e.g. poloxamer 407)	100-250	10-25 (wt%)
Buffer agent and/or pD adjusting agent (e.g. , sodium acetate and/or DCl)	-	q.s. for pH=4.2-7.9
Stabilizer (e.g. EDTA, cyclodextrin, etc.)	-	q.s. for low degradation of ophthalmic agent
Osmolarity modifier (e.g. NaCl)	-	q.s. 150-500 mOsm/L
Deuterated Water	-	q.s. to 100 wt%

Table 5 — Ointment Formulation

Ingredient	Quantity (g) for 1000 mL solution	Concentration in 1000 mL aqueous solution
Ophthalmic agent	0.01-200	0.001-20 (wt%)
Dispersing agent (e.g. polyethyleneglycol, and/or polyethoxylated castor oil and/or C12-C20 alcohol	10-200	1-20 (wt%)
Buffering agent pD adjusting agent (e.g. DCl)	-	q.s. for pD=4-8
Stabilizer (e.g. EDTA, cyclodextrin, etc.)	-	q.s. for low degradation of ophthalmic agent
Osmolarity modifier (e.g. NaCl)	-	q.s. 150-500 mOsm/L
Ointment base (e.g. wool wax and/or petrolatum and/or liquid paraffin)		q.s. to 100 wt%

Example 2 - Preparation of an Aqueous Solution Formulation Containing 0.01% an ophthalmic agent in D_2O

[00284] Stock 1% Solution

[00285] In a 100mL solution, 1 gram of an ophthalmic agent, and 0.77 g of NaCl (and other ingredients/components preferably in their dry state) are added along with a quantity sufficient to equal 100mL sterile deuterated water for injection. The solution is mixed in an appropriately sized beaker with a stir bar on a hot plate until all of the solid powders have dissolved and the

solution has become clear with no visible particles. Next, the stir bar is removed, and the solution is poured into a filter bottle and vacuum filtered through a 0.22 micron pothyethersulfone membrane filter into a sterile bottle. The filter top is removed from the sterile stock bottle and the stock bottle is capped for storage with a sterile bottle cap.

[00286] Diluted 0.01% Solution

[00287] 0.3mL of the 1% solution is combined with a quantity sufficient to achieve 30mL total of sterile 0.9% Sodium Chloride For Injection USP. The solution is thoroughly mixed. The pD of the solution is recorded. A 0.22 micron filter is placed on the tip of the syringe and the solution is aliquotted into separate sterile containers.

Example 3 – Stability Analysis

[00288] Five 0.01% ophthalmic solutions are prepared from the 1% ophthalmic stock solution (preparation as described in Example 2). The pD of the five solutions are 4.5, 5, 5.5, 6, and 6.5 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 aliquotted into separate sterile containers according to Table 6.

Table 6. Container Filling Outline

Type of Container	Volume of 0.01% Ophthalmic Drug Product in Container	Total Containers Filled
Sterile Eyedroppers	5-mL	12
Sterile Glass Vials	5-mL	12

[00289] 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: 40ºC with 75% relative humidity (RH) (samples were transferred from 2-8ºC condition after 3 days), 25ºC with 60% RH, and 60ºC. 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 aliquotted 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 7.

Table 7. 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

[00290] Arrhenius based shelf life predictions are calculated. These predictions are based on an assumption that the degradation is first order (linear).

Example 4 – Dose Uniformity (10-Dose)

[00291] 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 an ophthalmic agent in the expressed drops are determined using a reverse-phase HPLC method.

Example 5 – Dose Uniformity (5-Dose)

[00292] 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 an ophthalmic agent in the expressed drops are determined using a reverse-phase HPLC method.

Example 6 – Dose Uniformity (2-Dose)

[00293] 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 an ophthalmic agent in the expressed drops are determined using a reverse-phase HPLC method.

Example 7 - Effect of pD on Ophthalmic Acceptance in Guinea Pigs

[00294] A cohort of guinea pigs is administered 50 µL of ophthalmic formulations having different pD values described herein. For example, ophthalmic formulations comprising H_2O or deuterated water (e.g., D_2O) are administered to the animals. Animal behavior is recorded at predetermined time intervals to evaluate the acceptance of the ophthalmic formulations

Example 8 – In vivo Rabbit Eye Irritation Test

[00295] The exemplary compositions disclosed herein are subjected to rabbit eye irritation test to evalaute 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 9 – Safety and Efficacy Studies of Ophthalmic Aqueous Formulation

[00296] A clinical trial is performed to investigate the efficacy and safety of ophthalmic aqueous formulations described herein in patents. In some cases, the study is open-label, single blind, or double blind study. Patient selection criteria includes an ophthalmic condition of interest, and additional factors such as age, sex, and/or health conditions.

[00297] The patients are randomized to receive 5%, 1%, or 0.1% of an ophthalmic aqueous formulation formulated in deuterated water (e.g., D_2O) once nightly in one or both eyes. Allocation ratio is defined based on the patient population.

[00298] The patients are evaluated on day 0 (baseline), day 14, day 30, and then at 2, 3, 4, 5, 6, 8, 10, 12, 18, 20, 24, and 36 months.

[00299] The primary outcome is condition or disease progression over the time period of the study. Safety is assessed by adverse events including allergic reactions, irritation, or development of blurring of vision in one or both eyes.

Example 10 – Preparation of an Ointment Formulation

[00300] An ophthalmic agent is mixed with the dispersing agent (e.g. polyethyleneglycol) under heating and sonication and this mixture is further thoroughly mixed with a molten ointment base (e.g. a mixture of wool wax, white petrolatum, and liquid paraffin). The mixture is placed in a pressure vessel, and sterilized at 125 °C for 30-45 minutes and cooled to room temperature. In another embodiment, autoclaving is conducted under nitrogen. The resulting ophthalmic ointment is aseptically filled into pre-sterilized containers (e.g. tubes).

[00301] While preferred embodiments of the present disclosure have been shown and described herein, such embodiments are provided by way of example only. Various alternatives to the embodiments described herein are optionally employed in practicing the disclosure. It is intended that the following claims define the scope of the disclosure and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

WHAT IS CLAIMED IS:

1. An ophthalmic composition comprising an ophthalmic agent and deuterated water, at a pD of from about 4 to about 8, wherein the ophthalmic agent is not a muscarinic antagonist, and wherein the ophthalmic agent does not extend singlet oxygen lifetime.

2. The ophthalmic composition of claim 1, wherein the ophthalmic agent comprises 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, 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, artifical 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, scopolomine (L-hyoscine), hydroxyzine, ipratropium, pirenzapine, solifenacin, darifenacin, benzatropine, mebeverine,

procyclidine, aclidinium bromide, trihexyphenidyl/benzhexol, tolterodine, or any combinations thereof.

3. The ophthalmic composition of claim 1 or 2, wherein the ophthalmic composition comprises at least one of: about 80%, about 85%, about 90%, about 95%, about 97%, about 98%, or about 99% of the ophthalmic agent based on initial concentration after extended period of time under storage condition.

4. The ophthalmic composition of any one of the claims 1-3, wherein the ophthalmic composition has a pD of one of: less than about 8, less than about 7.5, less than about 7, less than about 6.5, less than about 6, less than about 5.5, less than about 5, less than about 4.5, or less than about 4 after extended period of time under storage condition.

5. The ophthalmic composition of any one of the claims 1-4, wherein the ophthalmic composition further has a potency of one of: at least 80%, at least 85%, at least 90%, at least 93%, at least 95%, at least 97%, at least 98%, at least 99% after extended period of time under storage condition.

6. The ophthalmic composition of any one of the claims 1-5, wherein the extended period of time is one of: about 1 week, about 2 weeks, about 3 weeks, about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 8 months, about 10 months, about 12 months, about 18 months, about 24 months, about 36 months, about 4 years, or about 5 years.

7. The ophthalmic composition of any one of the claims 1-6, wherein the storage condition has a storage temperature of from about 16°C to about 30°C or from about 20°C to about 25°C.

8. The ophthalmic composition of any one of the claims 1-7, wherein the ophthalmic agent is present in the formulation at a concentration of from about 0.001 wt% to about 20 wt%.

9. The ophthalmic composition of claim 1, wherein the ophthalmic composition further comprises an osmolarity adjusting agent, a preservative, a buffer agent, a tonicity adjusting agent, a pD adjusting agent, or a combination thereof.

10. The ophthalmic composition of claim 9, wherein the osmolarity adjusting agent is sodium chloride.

11. The ophthalmic composition of claim 9, wherein the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof.

12. The ophthalmic composition of claim 9, wherein the buffer agent is selected from borates, borate-polyol complexes, phosphate buffering agents, citrate buffering agents, acetate

buffering agents, carbonate buffering agents, organic buffering agents, amino acid buffering agents, or combinations thereof.

13. The ophthalmic composition of claim 9, wherein the tonicity adjusting agent is selected from sodium chloride, sodium nitrate, sodium sulfate, sodium bisulfate, potassium chloride, calcium chloride, magnesium chloride, zinc chloride, potassium acetate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium thiosulfate, magnesium sulfate, disodium hydrogen phosphate, sodium dihydrogen phosphate, potassium dihydrogen phosphate, dextrose, mannitol, sorbitol, dextrose, sucrose, urea, propylene glycol, glycerin, or a combination thereof.

14. The ophthalmic composition of any one of the claims 1-13, wherein the ophthalmic composition has a dose-to-dose ophthalmic agent concentration variation of one of: less than 50%, less than 40%, less than 30%, less than 20%, less than 10%, or less than 5%.

15. The ophthalmic composition of any one of the claims 1-14, wherein the ophthalmic composition has a pD of one of: from about 4 to about 8, from about 4.5 to about 7.5, from about 5 to about 7.0, or from about 6 to about 7.0.

16. The ophthalmic composition of any one of the claims 1-15, further comprising a pharmaceutically acceptable carrier.

17. The ophthalmic composition of claim 16, wherein the pharmaceutically acceptable carrier further comprises at least one viscosity-enhancing agent.

18. The ophthalmic composition of claim 17, wherein 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.

19. The ophthalmic composition of any one of the claims 1-18, wherein the ophthalmic composition comprises one of: less than 10% of H_2O, less than 8% of H_2O, less than 6% of H_2O, less than 5% of H_2O, less than 4% of H_2O, less than 3% of H_2O, less than 2% of H_2O, less than 1% of H_2O, less than 0.5% of H_2O, less than 0.1% of H_2O, or 0% of H_2O.

20. The ophthalmic composition of any one of the claims 1-19, wherein the ophthalmic agent is not atropine or atropine sulfate.

21. The ophthalmic composition of any one of the claims 1-20, wherein the ophthalmic agent is not an alpha-amino-carboxylic acid or an alpha-hydroxy-carboxylic acid.

22. The ophthalmic composition of any one of the claims 1-21, wherein the ophthalmic agent is not benactyzine hydrochloride.

23. The ophthalmic composition of any one of the claims 1-22, wherein the ophthalmic agent quenches photogenerated singlet oxygen species in the composition.

24. The ophthalmic composition of any one of the claims 1-23, wherein the ophthalmic composition is not saturated with oxygen.

25. The ophthalmic composition of any one of the claims 1-24, wherein the ophthalmic composition does not comprise a photosensitizer.

26. The ophthalmic composition of any one of the claims 1-25, wherein the ophthalmic agent is dissolved in the ophthalmic composition or is suspended in the ophthalmic composition.

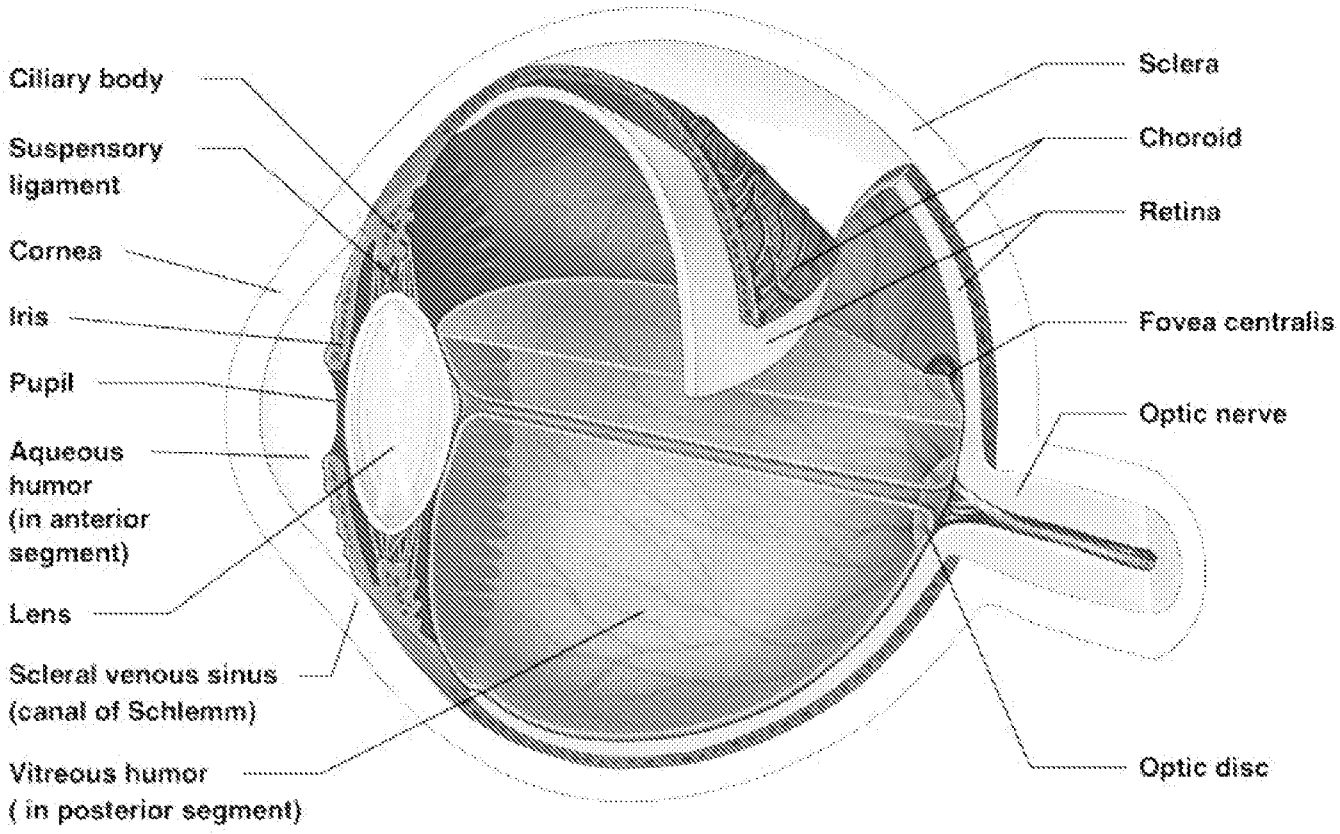
27. A method of treating an ophthalmic condition or disease comprising administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition of claims 1-26.

28. A method of ameliorating or reducing an ophthalmic condition or disease comprising administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition of claims 1-26.

29. The method of claim 27 or 28, wherein the ophthalmic composition is stored below room temperature prior to first use or is stored at between about 2 °C to about 10 °C prior to first use.

30. The method of claim 27 or 28, wherein the ophthalmic composition is stored below room temperature after first use, is stored at between about 2 °C to about 10 °C after first use, or is stored at between about 16 °C to about 26 °C after first use.

Fig. 1


Ciliary body
Suspensory ligament
Cornea
Iris
Pupil
Aqueous humor (in anterior segment)
Lens
Scleral venous sinus (canal of Schlemm)
Vitreous humor (in posterior segment)
Sclera
Choroid
Retina
Fovea centralis
Optic nerve
Optic disc

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/34823

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 9/00, 31/00, 47/02, 47/30; A61P 27/02 (2016.01)
CPC - A61K 9/00, 31/00, 47/02, 47/30
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC (8) - A61F 9/00; A61K 9/00, 9/08, 31/00, 47/02, 47/30; A61P 27/02 (2016.01);
CPC - A61K 9/00, 9/08, 9/0048, 31/00, 47/02, 47/30

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, Other Countries (INPADOC), RU, AT, CH, TH, BR, PH); EBSCO; Google/Google Scholar; PubMed; ophthalmic composition, ophthalmic agent, deuterated water, singlet oxygen, aflibercept, ranibizumab, cyclpentolate, tropicamide, tetracaine, azelastine, oxymetazoline, phenylephrine, tetrahydrozoline, osmolarity adjusting agent, pD, tonicity

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 7,691,099 B2 (BERRY, MJ) 6 April 2010; column 2, lines 23-36	1-2, 3/1-2, 9-13
Y	US 8,980,839 B2 (MITRA, AK et al.) 17 March 2015; column 10, lines 57-67; column 11, lines 1-11; column 12, lines 19-33	1-2, 3/1-2, 9-13
Y	(U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION) Guidance for Industry Q1A (R2) Stability Testing of New Drug Substances and Products. November 2003 [retrieved on 27 July 2016]. Retrieved from the internet; URL: <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073369.pdf>; page 1, third paragraph; page 2, fourth-fifth paragraphs; page 4, sixth-seventh paragraphs; page 11, first-fourth paragraphs	3/1-2

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 July 2016 (27.07.2016)	23 AUG 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/34823

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-8 and 14-30
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

(19)中华人民共和国国家知识产权局

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代理人 郑霞

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A61K 47/02(2006.01)
A61K 47/30(2006.01)
A61P 27/02(2006.01)

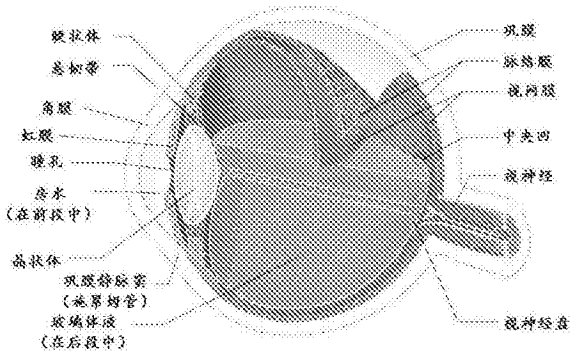
权利要求书3页 说明书59页 附图1页

(54)发明名称

D_2O稳定化的药物制剂

(57)摘要

本文提供了一种在氘化水中配制的眼用组合物。本文还公开了通过向有需要的个体的眼睛施用有效量的本文所述眼用组合物来治疗、改善或减轻眼科病况或疾病的方法。



CN 107847432 A

1.一种包含眼用剂和氘化水的眼用组合物，其pD为约4至约8，其中所述眼用剂不是毒蕈碱拮抗剂，并且其中所述眼用剂不延长单线态氧寿命。

2.如权利要求1所述的眼用组合物，其中所述眼用剂包括阿柏西普、雷珠单抗、培加尼布、环喷托酯、苯福林、后马托品、东莨菪碱、环喷托酯/苯福林、苯福林/东莨菪碱、托吡卡胺、酮咯酸/苯福林、羟苯丙胺/托吡卡胺、半胱胺、奥克纤溶酶、丝裂霉素、达哌唑、利多卡因、丙美卡因、丁卡因、丁氧普鲁卡因、阿奇霉素、杆菌肽、贝西沙星、硼酸、氯霉素、环丙沙星、红霉素、更昔洛韦、加替沙星、庆大霉素、碘苷、左氧氟沙星、莫西沙星、纳他霉素、诺氟沙星、氧氟沙星、杆菌肽/多粘菌素b、妥布霉素、多粘菌素b/甲氧苄啶、聚维酮碘、曲氟尿苷、短杆菌肽/新霉素/多粘菌素b、磺胺醋酰钠、磺胺异噁唑、杆菌肽/新霉素/多粘菌素b、土霉素/多粘菌素b、苯福林/磺胺醋酰钠、阿糖腺苷、溴芬酸、奈帕芬胺、酮咯酸、环孢菌素、氟比洛芬、舒洛芬、双氯芬酸、阿卡他定、氮䓬斯汀、贝他斯汀、色甘酸、依美斯汀、依匹斯汀、酮替芬、左卡巴斯汀、洛度沙胺、奈多罗米、萘甲唑啉、萘甲唑啉/非尼拉敏、萘甲唑啉/硫酸锌、奥洛他定、羟甲唑啉、吡嘧司特、苯福林、苯福林/硫酸锌、四氢唑啉、四氢唑啉/硫酸锌、荧光素、荧光素/丙美卡因、丁氧普鲁卡因/荧光素、吲哚菁绿、台盼蓝、乙酰胆碱、安普乐定、倍他洛尔、比马前列素、溴莫尼定、布林佐胺、溴莫尼定/布林佐胺、卡巴胆碱、卡替洛尔、地美溴铵、地匹福林、多佐胺、多佐胺/噻吗洛尔、依可碘酯、肾上腺素、肾上腺素/毛果芸香碱、拉坦前列素、左布诺洛尔、左倍他洛尔、美替洛尔、毒扁豆碱、毛果芸香碱、他氟前列素、噻吗洛尔、曲伏前列素、乌诺前列酮、人造泪液、地塞米松、二氟泼尼酯、氟轻松、氟米龙、氯替泼诺、甲羟松、泼尼松龙、利美索龙、曲安西龙、氟米龙/磺胺醋酰钠、地塞米松/新霉素、地塞米松/妥布霉素、地塞米松/新霉素/多粘菌素b、氯替泼诺/妥布霉素、泼尼松龙/磺胺醋酰钠、杆菌肽/氢化可的松/新霉素/多粘菌素b、氢化可的松/新霉素/多粘菌素b、氯霉素/氢化可的松/多粘菌素b、新霉素/多粘菌素b/泼尼松龙、庆大霉素/泼尼松龙、酮咯酸/苯福林、苯海拉明、茶苯海明、双环维林、黄酮哌酯、奥昔布宁、噻托溴铵、莨菪碱、scopolomine(L-莨菪碱)、羟嗪、异丙托铵、哌仑西平、索利那新、达非那新、苯扎托品、美贝维林、丙环定、阿地溴铵、三己芬迪/苯海索、托特罗定或其任何组合。

3.如权利要求1或2所述的眼用组合物，其中在储存条件下在延长的时间段后，基于初始浓度，所述眼用组合物包含以下至少之一：约80％、约85％、约90％、约95％、约97％、约98％或约99％的所述眼用剂。

4.如权利要求1-3中任一项所述的眼用组合物，其中在储存条件下在延长的时间段后，所述眼用组合物具有以下之一的pD：小于约8、小于约7.5、小于约7、小于约6.5、小于约6、小于约5.5、小于约5、小于约4.5或小于约4。

5.如权利要求1-4中任一项所述的眼用组合物，其中在储存条件下在延长的时间段后，所述眼用组合物还具有以下之一的效力：至少80％、至少85％、至少90％、至少93％、至少95％、至少97％、至少98％、至少99％。

6.如权利要求1-5中任一项所述的眼用组合物，其中所述延长的时间段为以下之一：约1周、约2周、约3周、约1个月、约2个月、约3个月、约4个月、约5个月、约6个月、约8个月、约10个月、约12个月、约18个月、约24个月、约36个月、约4年或约5年。

7.如权利要求1-6中任一项所述的眼用组合物，其中所述储存条件具有约16℃至约30

℃或约20℃至约25℃的储存温度。

8.如权利要求1-7中任一项所述的眼用组合物，其中所述眼用剂以约0.001wt％至约20wt％的浓度存在于制剂中。

9.如权利要求1所述的眼用组合物，其中所述眼用组合物进一步包含摩尔渗透压浓度调节剂、防腐剂、缓冲剂、张力调节剂、pD调节剂或其组合。

10.如权利要求9所述的眼用组合物，其中所述摩尔渗透压浓度调节剂为氯化钠。

11.如权利要求9所述的眼用组合物，其中所述防腐剂选自苯扎氯铵、西曲铵、过硼酸钠、稳定化的氧氯复合物、SofZia、聚季铵盐-1、氯丁醇、依地酸二钠、聚六亚甲基双胍或其组合。

12.如权利要求9所述的眼用组合物，其中所述缓冲剂选自硼酸盐、硼酸盐-多元醇复合物、磷酸盐缓冲剂、柠檬酸盐缓冲剂、乙酸盐缓冲剂、碳酸盐缓冲剂、有机缓冲剂、氨基酸缓冲剂或其组合。

13.如权利要求9所述的眼用组合物，其中所述张力调节剂选自氯化钠、硝酸钠、硫酸钠、硫酸氢钠、氯化钾、氯化钙、氯化镁、氯化锌、乙酸钾、乙酸钠、碳酸氢钠、碳酸钠、硫代硫酸钠、硫酸镁、磷酸氢二钠、磷酸二氢钠、磷酸二氢钾、右旋糖、甘露醇、山梨醇、葡萄糖、蔗糖、尿素、丙二醇、甘油或其组合。

14.如权利要求1-13中任一项所述的眼用组合物，其中所述眼用组合物具有以下之一的剂量间眼用剂浓度变化：小于50％、小于40％、小于30％、小于20％、小于10％或小于5％。

15.如权利要求1-14中任一项所述的眼用组合物，其中所述眼用组合物具有以下之一的pD：约4至约8、约4.5至约7.5、约5至约7.0或约6至约7.0。

16.如权利要求1-15中任一项所述的眼用组合物，其进一步包含药学上可接受的载体。

17.如权利要求16所述的眼用组合物，其中所述药学上可接受的载体进一步包含至少一种粘度增强剂。

18.如权利要求17所述的眼用组合物，其中所述粘度增强剂选自基于纤维素的聚合物、聚氧乙烯-聚氧丙烯三嵌段共聚物、基于葡聚糖的聚合物、聚乙烯醇、糊精、聚乙烯吡咯烷酮、聚亚烷基二醇、壳聚糖、胶原、明胶、透明质酸或其组合。

19.如权利要求1-18中任一项所述的眼用组合物，其中所述眼用组合物包含以下之一：少于10％的H_2O、少于8％的H_2O、少于6％的H_2O、少于5％的H_2O、少于4％的H_2O、少于3％的H_2O、少于2％的H_2O、少于1％的H_2O、少于0.5％的H_2O、少于0.1％的H_2O或0％的H_2O。

20.如权利要求1-19中任一项所述的眼用组合物，其中所述眼用剂不是阿托品或硫酸阿托品。

21.如权利要求1-20中任一项所述的眼用组合物，其中所述眼用剂不是α-氨基-羧酸或α-羟基-羧酸。

22.如权利要求1-21中任一项所述的眼用组合物，其中所述眼用剂不是盐酸贝那替嗪。

23.如权利要求1-22中任一项所述的眼用组合物，其中所述眼用剂猝灭所述组合物中光生成的单线态氧种类。

24.如权利要求1-23中任一项所述的眼用组合物，其中所述眼用组合物未用氧饱和。

25.如权利要求1-24中任一项所述的眼用组合物，其中所述眼用组合物不包含光敏剂。

26.如权利要求1-25中任一项所述的眼用组合物，其中所述眼用剂溶解在所述眼用组

合物中或悬浮在所述眼用组合物中。

27.一种治疗眼科病况或疾病的方法，其包括向有需要的个体的眼睛施用有效量的如权利要求1-26所述的眼用组合物。

28.一种改善或减轻眼科病况或疾病的方法，其包括向有需要的个体的眼睛施用有效量的如权利要求1-26所述的眼用组合物。

29.如权利要求27或28所述的方法，其中所述眼用组合物在首次使用前储存在低于室温的温度下，或在首次使用前储存在约2℃至约10℃。

30.如权利要求27或28所述的方法，其中所述眼用组合物在首次使用后储存在低于室温的温度下，在首次使用后储存在约2℃至约10℃，或在首次使用后储存在约16℃至约26℃。

D_2O稳定化的药物制剂

交叉引用

[0001] 本申请要求于2015年5月29日提交的美国临时专利申请系列号62/168,538的权益，该美国临时申请在此通过引用整体并入本文。

背景技术

[0002] 药物制剂的有效期基于活性成分的降解。

发明内容

[0003] 本文提供了D_2O稳定化的药物组合物和制剂。

[0004] 根据一个方面，本文公开的眼用组合物包含眼用剂和氘化水，其pD为约4至约8。

[0005] 根据另一方面，本文公开的眼用组合物包含眼用剂和氘化水，其pD为约4至约8，其中该眼用剂不是毒蕈碱拮抗剂，并且其中该眼用剂不延长单线态氧寿命。

[0006] 在一些实施方案中，所述眼用剂包括阿柏西普(也称为VEGFTrap)、雷珠单抗、培加尼布、环喷托酯、苯福林、后马托品、东莨菪碱、环喷托酯/苯福林、苯福林/东莨菪碱、托吡卡胺、酮咯酸/苯福林、羟苯丙胺/托吡卡胺、半胱胺、奥克纤溶酶、丝裂霉素、达哌唑、利多卡因、丙美卡因、丁卡因、丁氧普鲁卡因、阿奇霉素、杆菌肽、贝西沙星、硼酸、氯霉素、环丙沙星、红霉素、更昔洛韦、加替沙星、庆大霉素、碘苷、左氧氟沙星、莫西沙星、纳他霉素、诺氟沙星、氧氟沙星、杆菌肽/多粘菌素b、妥布霉素、多粘菌素b/甲氧苄啶、聚维酮碘、曲氟尿苷、短杆菌肽/新霉素/多粘菌素b、磺胺醋酰钠、磺胺异噁唑、杆菌肽/新霉素/多粘菌素b、土霉素/多粘菌素b、苯福林/磺胺醋酰钠、阿糖腺苷、溴芬酸、奈帕芬胺、酮咯酸、环孢菌素、氟比洛芬、舒洛芬、双氯芬酸、阿卡他定、氮䓬斯汀、贝他斯汀、色甘酸、依美斯汀、依匹斯汀、酮替芬、左卡巴斯汀、洛度沙胺、奈多罗米、萘甲唑啉、萘甲唑啉/非尼拉敏、萘甲唑啉/硫酸锌、奥洛他定、羟甲唑啉、吡嘧司特、苯福林、苯福林/硫酸锌、四氢唑啉、四氢唑啉/硫酸锌、荧光素、荧光素/丙美卡因、丁氧普鲁卡因/荧光素、吲哚菁绿、台盼蓝、乙酰胆碱、安普乐定、倍他洛尔、比马前列素、溴莫尼定、布林佐胺、溴莫尼定/布林佐胺、卡巴胆碱、卡替洛尔、地美溴铵、地匹福林、多佐胺、多佐胺/噻吗洛尔、依可碘酯、肾上腺素、肾上腺素/毛果芸香碱、拉坦前列素、左布诺洛尔、左倍他洛尔、美替洛尔、毒扁豆碱、毛果芸香碱、他氟前列素、噻吗洛尔、曲伏前列素、乌诺前列酮、人造泪液、地塞米松、二氟泼尼酯、氟轻松、氟米龙、氯替泼诺、甲羟松、泼尼松龙、利美索龙、曲安西龙、氟米龙/磺胺醋酰钠、地塞米松/新霉素、地塞米松/妥布霉素、地塞米松/新霉素/多粘菌素b、氯替泼诺/妥布霉素、泼尼松龙/磺胺醋酰钠、杆菌肽/氢化可的松/新霉素/多粘菌素b、氢化可的松/新霉素/多粘菌素b、氯霉素/氢化可的松/多粘菌素b、新霉素/多粘菌素b/泼尼松龙、庆大霉素/泼尼松龙、酮咯酸/苯福林、苯海拉明、茶苯海明、双环维林、黄酮哌酯、奥昔布宁、噻托溴铵、莨菪碱、scopolomine(L-莨菪碱)、羟嗪、异丙托铵、哌仑西平、索利那新、达非那新、苯扎托品、美贝维林、丙环定、阿地溴铵、三己芬迪/苯海索、托特罗定或其任何组合。

[0007] 在一些实施方案中，在储存条件下在延长的时间段后，基于初始浓度，所述眼用组

合物包含至少约80％的眼用剂。在一些实施方案中，在储存条件下在延长的时间段后，基于初始浓度，所述眼用组合物包含至少约85％的眼用剂。在一些实施方案中，在储存条件下在延长的时间段后，基于初始浓度，所述眼用组合物包含至少约90％的眼用剂。在一些实施方案中，在储存条件下在延长的时间段后，基于初始浓度，所述眼用组合物包含至少约95％的眼用剂。在一些实施方案中，在储存条件下在延长的时间段后，基于初始浓度，所述眼用组合物包含至少约97％的眼用剂。在一些实施方案中，在储存条件下在延长的时间段后，基于初始浓度，所述眼用组合物包含至少约98％的眼用剂。在一些实施方案中，在储存条件下在延长的时间段后，基于初始浓度，所述眼用组合物包含至少约99％的眼用剂。

[0008] 在一些实施方案中，在储存条件下在延长的时间段后，所述眼用组合物具有小于约8的pD。在一些实施方案中，在储存条件下在延长的时间段后，所述眼用组合物具有小于约7.5的pD。在一些实施方案中，在储存条件下在延长的时间段后，所述眼用组合物具有小于约7的pD。在一些实施方案中，在储存条件下在延长的时间段后，所述眼用组合物具有小于约6.5的pD。在一些实施方案中，在储存条件下在延长的时间段后，所述眼用组合物具有小于约6的pD。在一些实施方案中，在储存条件下在延长的时间段后，所述眼用组合物具有小于约5.5的pD。在一些实施方案中，在储存条件下在延长的时间段后，所述眼用组合物具有小于约5的pD。在一些实施方案中，在储存条件下在延长的时间段后，所述眼用组合物具有小于约4.5的pD。在一些实施方案中，在储存条件下在延长的时间段后，所述眼用组合物具有小于约4的pD。

[0009] 在一些实施方案中，所述眼用组合物的pD比所测量的pH高约0.4个单位。

[0010] 在一些实施方案中，在储存条件下在延长的时间段后，所述眼用组合物还具有至少80％的效力。在一些实施方案中，在储存条件下在延长的时间段后，所述眼用组合物还具有至少85％的效力。在一些实施方案中，在储存条件下在延长的时间段后，所述眼用组合物还具有至少90％的效力。在一些实施方案中，在储存条件下在延长的时间段后，所述眼用组合物还具有至少93％的效力。在一些实施方案中，在储存条件下在延长的时间段后，所述眼用组合物还具有至少95％的效力。在一些实施方案中，在储存条件下在延长的时间段后，所述眼用组合物还具有至少97％的效力。在一些实施方案中，在储存条件下在延长的时间段后，所述眼用组合物还具有至少98％的效力。在一些实施方案中，在储存条件下在延长的时间段后，所述眼用组合物还具有至少99％的效力。

[0011] 在一些实施方案中，所述延长的时间段为约1周。在一些实施方案中，延长的时间段为约2周。在一些实施方案中，所述延长的时间段为约3周。在一些实施方案中，所述延长的时间段为约1个月。在一些实施方案中，所述延长的时间段为约2个月。在一些实施方案中，所述延长的时间段为约3个月。在一些实施方案中，所述延长的时间段为约4个月。在一些实施方案中，所述延长的时间段为约5个月。在一些实施方案中，所述延长的时间段为约6个月。在一些实施方案中，所述延长的时间段为约8个月。在一些实施方案中，所述延长的时间段为约10个月。在一些实施方案中，所述延长的时间段为约12个月。在一些实施方案中，所述延长的时间段为约18个月。在一些实施方案中，所述延长的时间段为约24个月。在一些实施方案中，所述延长的时间段为约36个月。在一些实施方案中，所述延长的时间段为约4年。在一些实施方案中，所述延长的时间段为约5年。

[0012] 在一些实施方案中，如权利要求1-44中任一项所述的眼用组合物，其中所述储存

条件具有约16℃至约30℃或约20℃至约25℃的储存温度。在一些实施方案中，所述储存条件具有约60％的相对湿度。在一些实施方案中，如权利要求1-45中任一项所述的眼用组合物，其中所述储存条件具有约75％的相对湿度。

[0013] 在一些实施方案中，所述眼用组合物为水溶液的形式。

[0014] 在一些实施方案中，所述眼用剂以约0.001wt％至约20wt％的浓度存在于制剂中。

[0015] 在一些实施方案中，所述眼用组合物进一步包含摩尔渗透压浓度调节剂。在一些实施方案中，该摩尔渗透压浓度调节剂为氯化钠。

[0016] 在一些实施方案中，所述眼用组合物进一步包含防腐剂。在一些实施方案中，所述防腐剂选自苯扎氯铵、西曲铵、过硼酸钠、稳定化的氧基氯复合物、SofZia、聚季铵盐-1、氯丁醇、依地酸二钠、聚六亚甲基双胍或其组合。

[0017] 在一些实施方案中，所述眼用组合物进一步包含缓冲剂。在一些实施方案中，所述缓冲剂选自硼酸盐、硼酸盐-多元醇复合物、磷酸盐缓冲剂、柠檬酸盐缓冲剂、乙酸盐缓冲剂、碳酸盐缓冲剂、有机缓冲剂、氨基酸缓冲剂或其组合。

[0018] 在一些实施方案中，所述眼用组合物进一步包含张力调节剂。在一些实施方案中，所述张力调节剂选自氯化钠、硝酸钠、硫酸钠、硫酸氢钠、氯化钾、氯化钙、氯化镁、氯化锌、乙酸钾、乙酸钠、碳酸氢钠、碳酸钠、硫代硫酸钠、硫酸镁、磷酸氢二钠、磷酸二氢钠、磷酸二氢钾、右旋糖、甘露醇、山梨醇、葡萄糖、蔗糖、尿素、丙二醇、甘油或其组合。

[0019] 在一些实施方案中，所述眼用组合物储存在塑料容器中。

[0020] 在一些实施方案中，所述眼用组合物具有小于50％的剂量间眼用剂浓度变化。在一些实施方案中，所述眼用组合物具有小于40％的剂量间眼用剂浓度变化。在一些实施方案中，所述眼用组合物具有小于30％的剂量间眼用剂浓度变化。在一些实施方案中，所述眼用组合物具有小于20％的剂量间眼用剂浓度变化。在一些实施方案中，所述眼用组合物具有小于10％的剂量间眼用剂浓度变化。在一些实施方案中，所述眼用组合物具有小于5％的剂量间眼用剂浓度变化。

[0021] 在一些实施方案中，所述剂量间眼用剂浓度变化基于10个连续的剂量。在一些实施方案中，所述剂量间眼用剂浓度变化基于8个连续的剂量。在一些实施方案中，所述剂量间眼用剂浓度变化基于5个连续的剂量。在一些实施方案中，所述剂量间眼用剂浓度变化基于3个连续的剂量。在一些实施方案中，所述剂量间眼用剂浓度变化基于2个连续的剂量。

[0022] 在一些实施方案中，所述眼用组合物具有约4至约8的pD。在一些实施方案中，所述眼用组合物具有约4.5至约7.5的pD。在一些实施方案中，所述眼用组合物具有约5至约7.0的pD。在一些实施方案中，所述眼用组合物具有约6至约7.0的pD。

[0023] 在一些实施方案中，所述眼用组合物进一步包含pD调节剂。

[0024] 在一些实施方案中，所述眼用组合物进一步包含药学上可接受的载体。在一些实施方案中，该药学上可接受的载体进一步包含至少一种粘度增强剂。在一些实施方案中，该粘度增强剂选自基于纤维素的聚合物、聚氧乙烯-聚氧丙烯三嵌段共聚物、基于葡聚糖的聚合物、聚乙烯醇、糊精、聚乙烯吡咯烷酮、聚亚烷基二醇、壳聚糖、胶原、明胶、透明质酸或其组合。

[0025] 在一些实施方案中，所述眼用组合物包含少于60％的H_2O。在一些实施方案中，所述眼用组合物包含少于55％的H_2O。在一些实施方案中，所述眼用组合物包含少于50％的

H_2O。在一些实施方案中，所述眼用组合物包含少于45％的H_2O。在一些实施方案中，所述眼用组合物包含少于40％的H_2O。在一些实施方案中，所述眼用组合物包含少于35％的H_2O。在一些实施方案中，所述眼用组合物包含少于30％的H_2O。在一些实施方案中，所述眼用组合物包含少于25％的H_2O。在一些实施方案中，所述眼用组合物包含少于20％的H_2O。在一些实施方案中，所述眼用组合物包含少于15％的H_2O。

[0026] 在一些实施方案中，所述眼用组合物包含少于10％的H_2O。在一些实施方案中，所述眼用组合物包含少于8％的H_2O。在一些实施方案中，所述眼用组合物包含少于6％的H_2O。在一些实施方案中，所述眼用组合物包含少于5％的H_2O。在一些实施方案中，所述眼用组合物包含少于4％的H_2O。在一些实施方案中，所述眼用组合物包含少于3％的H_2O。在一些实施方案中，所述眼用组合物包含少于2％的H_2O。在一些实施方案中，所述眼用组合物包含少于1％的H_2O。在一些实施方案中，所述眼用组合物包含少于0.5％的H_2O。在一些实施方案中，所述眼用组合物包含少于0.1％的H_2O。在一些实施方案中，所述眼用组合物包含0％的H_2O。

[0027] 在一些实施方案中，所述眼用组合物被配制为用于治疗眼科病况或疾病的眼用溶液。

[0028] 在一些实施方案中，所述眼用剂不是阿托品。在一些实施方案中，所述眼用剂不是硫酸阿托品。在一些实施方案中，所述眼用剂不是毒蕈碱拮抗剂。

[0029] 在一些实施方案中，所述眼用剂不是α-氨基-羧酸或α-羟基-羧酸。在一些实施方案中，所述眼用剂不是盐酸贝那替嗪。

[0030] 在一些实施方案中，所述眼用剂猝灭组合物中光生成的单线态氧种类。在一些实施方案中，所述眼用组合物未用氧饱和。在一些实施例中，所述眼用组合物不包含光敏剂。

[0031] 在一些实施方案中，所述眼用剂溶解在所述眼用组合物中。在一些实施例中，所述眼用剂悬浮于所述眼用组合物中。

[0032] 根据另一个方面，治疗眼科病况或疾病的方法包括向有需要的个体的眼睛施用有效量的本发明公开的眼用组合物。根据另一个方面，改善或减轻眼科病况或疾病的方法包括向有需要的个体的眼睛施用有效量的本发明公开的眼用组合物。

[0033] 在一些实施方案中，所述眼用组合物在延长的时间段内以预定的时间间隔施用。在一些实施方案中，所述眼用组合物一天施用一次。在一些实施方案中，所述眼用组合物每天施用一次。在一些实施方案中，所述眼用组合物每隔一天施用一次。在一些实施方案中，所述眼用组合物在1周、2周、1个月、2个月、3个月、6个月、1年、2年、3年、4年、5年、6年、7年、8年、9年、10年、11年或12-15年内施用。在一些实施方案中，所述眼用组合物仅施用一次。

[0034] 在一些实施方案中，所述眼用组合物在首次使用前储存在低于室温的温度下。在一些实施方案中，所述眼用组合物在首次使用前储存在约2℃至约10℃。在一些实施方案中，所述眼用组合物在首次使用前储存在约4℃至约8℃。

[0035] 在一些实施方案中，所述眼用组合物在首次使用前储存在室温下。在一些实施方案中，所述眼用组合物在首次使用前储存在约16℃至约26℃。

[0036] 在一些实施方案中，所述眼用组合物在首次使用后储存在低于室温的温度下。在一些实施方案中，所述眼用组合物在首次使用后储存在约2℃至约10℃。在一些实施方案中，所述眼用组合物在首次使用后储存在约4℃至约8℃。

[0037] 在一些实施方案中，所述眼用组合物在首次使用后储存在室温下。在一些实施方

案中，所述眼用组合物在首次使用后储存在约16℃至约26℃。

[0038] 通过以下详细描述，本文所述方法和组合物的其他特征和技术效果将变得显而易见。然而，应当理解，该详细描述和特定实施例虽然指示特定的实施方案，但仅以说明的方式给出。

附图说明

[0039] 本发明的新颖特征在所附的权利要求书中具体阐述。通过参考以下对利用本发明原理的说明性实施方案加以阐述的详细描述以及附图，将获得对本发明的特征和优点的更好的理解，在这些附图中：

[0040] 图1示出了眼睛解剖学的概念图示。

具体实施方式

[0041] 本发明认识到稳定性和眼睛耐受性是配制眼用组合物时要考虑的参数。在一些情况下，为了延长眼用组合物的保质期或稳定性，随后降低该组合物的pH。在一些情况下，降低的pH降低或防止碱催化的水解，从而使活性剂稳定。然而，在一些情况下，pH降低的制剂导致眼睛耐受性较差，因为酸性制剂刺激眼睛，导致泪液产生。在这样的情况下，泪液然后稀释所述组合物并且/或者将组合物洗出眼外，由此降低眼用组合物的有效性。

[0042] 另外，本发明认识到，氘化水使眼用组合物稳定。在一些情况下，与H_2O相比，氘化水为弱酸，于是氘化水包含较低浓度的反应性种类(例如-OD)，在一些情况下该反应性种类导致眼用组合物中活性剂的碱催化水解。因此，在一些情况下，与包含H_2O的组合物相比，包含氘化水的组合物导致碱催化的水解减少。在一些情况下，氘化水进一步降低了眼用组合物的缓冲能力，从而导致眼中较少的泪反射。

[0043] 本文公开了包含眼用剂和氘化水的眼用组合物，其pD为约4至约8。本文还公开了包含眼用剂和氘化水的眼用溶液，其pD为约4至约8。本文进一步公开了治疗眼科病况或疾病的方法，其包括向有需要的个体的眼睛施用有效量的下文描述的眼用组合物或眼用溶液。另外，本文公开了改善或减轻眼科病况或疾病的方法，其包括向有需要的个体的眼睛施用有效量的下文描述的眼用组合物或眼用溶液。

眼用剂

[0044] 本文公开了在氘化水的存在下配制的药物组合物。如本文所用的，氘化水是指D_2O、DHO、重水和/或氧化氘。在一些情况下，所述药物组合物是含有一种或多种眼用剂的眼用组合物。在一些情况下，所述眼用组合物被配制为水溶液、凝胶或软膏。

[0045] 在一些实施方案中，在所述眼用组合物中使用的眼用剂易于通过水解而降解。在一些实施方案中，在所述眼用组合物中使用的眼用剂易于通过碱催化的水解而降解。

[0046] 在一些实施方案中，所述眼用剂包括抗血管生成眼用剂、散瞳药、抗散瞳药、眼用麻醉药、眼用抗感染药、眼用抗炎药、眼用抗组胺药和减充血药、眼科诊断剂、眼科青光眼药、眼用润滑剂和灌洗剂、眼用类固醇、眼用类固醇结合抗感染药或眼科手术剂。

[0047] 在一些实施方案中，在氘化水的存在下配制的眼用组合物包含抗血管生成眼用剂、散瞳药、抗散瞳药、眼用麻醉药、眼用抗感染药、眼用抗炎药、眼用抗组胺药和减充血药、眼科诊断剂、眼科青光眼药、眼用润滑剂和灌洗剂、眼用类固醇、眼用类固醇结合抗感染药、

眼科手术剂,或其组合。

[0048] 抗血管生成眼用剂是阻止通过被称为新血管形成的过程生成新血管的血管内皮生长因子(VEGF)拮抗剂。在一些情况下,抗血管生成眼用剂用来抑制年龄相关性黄斑变性中的新血管形成。在一些情况下,抗血管生成眼用剂用来治疗糖尿病黄斑水肿、糖尿病视网膜病变或黄斑水肿。在一些实施方案中,黄斑水肿是眼睛黄斑或眼睛负责中央视觉的区域的肿胀或增厚。在一些实施方案中,糖尿病视网膜病变是指对视网膜中的血管的损害。示例性抗血管生成眼用剂包括但不限于阿柏西普(也称为VEGF Trap)(例如Eylea)、雷珠单抗(例如Lucentis)或培加尼布(例如Macugen)。

[0049] 在一些实施方案中,在氘化水的存在下配制的眼用组合物包含抗血管生成眼用剂,例如阿柏西普(也称为VEGF Trap)、雷珠单抗或培加尼布。在一些实施方案中,在氘化水的存在下配制的眼用组合物包含阿柏西普(也称为VEGF Trap)、雷珠单抗、培加尼布或其组合。

[0050] 散瞳药是扩张眼睛瞳孔的药剂。在一些情况下,散瞳药用来治疗眼睛干燥、发红或瘙痒,葡萄膜炎,有机磷中毒,或炎性眼睛病况,如虹膜炎和睫状体炎。示例性散瞳药包括但不限于环喷托酯(例如,Cyclogyl,Ak-Pentolate,Cylate,Ocu-Pentolate或Pentolair)、苯福林(例如,AK-Dilate,AK-Nefrin,Altafrin,Isopto Frin,Mydfrin、Neo-synephrine Ophthalmic,Neofrin,Ocu-Phrin,Prefrin或Refresh Redness Relief)、后马托品(例如,Homatropaire,Isopto Homatropine)、东莨菪碱(例如Isopto Hyoscine)、环喷托酯/苯福林(例如Cyclomydril)、苯福林/东莨菪碱(例如Murocoll 2)、托吡卡胺(例如Mydral,Ocu-Tropic或Tropicacyl)、酮咯酸/苯福林(例如Omidria)或羟苯丙胺/托吡卡胺(例如Paremyd)。

[0051] 在一些实施方案中,在氘化水的存在下配制的眼用组合物包含散瞳药,例如环喷托酯、苯福林、后马托品、东莨菪碱、环喷托酯/苯福林、苯福林/东莨菪碱、托吡卡胺、酮咯酸/苯福林或羟苯丙胺/托吡卡胺。在一些实施方案中、在氘化水的存在下配制的眼用组合物包含环喷托酯、苯福林、后马托品、东莨菪碱、环喷托酯/苯福林、苯福林/东莨菪碱、托吡卡胺、酮咯酸/苯福林、羟苯丙胺/托吡卡胺,或其组合。在一些实施方案中、在氘化水的存在下配制的眼用组合物不包含阿托品、硫酸阿托品、去甲阿托品、阿托品-N-氧化物、托品、托品酸或甲硝阿托品。在一些实施方案中,在氘化水的存在下配制的眼用组合物不包含阿托品。在一些实施方案中,在氘化水的存在下配制的眼用组合物不包含硫酸阿托品。

[0052] 抗散瞳药是减少瞳孔大小的药剂。示例性的抗散瞳药包括但不限于半胱胺(例如Cystaran)、奥克纤溶酶(例如Jetrea)、丝裂霉素(例如Mitosol)或达哌唑(例如Rev-Eyes)。

[0053] 在一些实施方案中,在氘化水的存在下配制的眼用组合物包含抗散瞳药,例如半胱胺、奥克纤溶酶、丝裂霉素或达哌唑。在一些实施方案中,在氘化水的存在下配制的眼用组合物包含半胱胺、奥克纤溶酶、丝裂霉素、达哌唑或其组合。

[0054] 眼用麻醉药是阻断眼睛中神经末梢的疼痛信号的局部麻醉剂。示例性的眼用麻醉药包括但不限于利多卡因(例如Akten)、丙美卡因(例如Alcaine,Ocu-Caine,Ophthetic或Parcaine)、丁卡因(例如Altacaine,Opticaine或TetraVisc)或丁氧普鲁卡因(或奥布卡因)(例如Novesine,Novesin)。

[0055] 在一些实施方案中,在氘化水的存在下配制的眼用组合物包含眼用麻醉药,例如

利多卡因、丙美卡因、丁卡因或丁氧普鲁卡因。在一些实施方案中，在氘化水的存在下配制的眼用组合物包含利多卡因、丙美卡因、丁卡因、丁氧普鲁卡因或其组合。

[0056] 眼用抗感染药是包含抗生素和/或抗病毒剂的眼用制剂。在一些实施方案中，眼用抗感染药用来治疗睑炎、睑缘结膜炎、CMV视网膜炎、结膜炎、角膜溃疡、眼干燥或发红、树状单纯疱疹性角膜炎、疱疹性角膜炎、麦粒肿、角膜炎、角膜结膜炎、新生儿结膜炎或沙眼，或者在手术过程中使用。示例性的眼用抗感染药包括但不限于阿奇霉素(例如Azasite)、杆菌肽(例如AK-Tracin，Ocu-Tracin)、贝西沙星(例如Besivance)、硼酸(例如Collyrium Fresh)、氯霉素(例如，AK-Chlor，眼用氯霉素，Chloroptic，Ocu-Chlor)、环丙沙星(例如Ciloxan)、红霉素(例如Ciloxan，Ilotycin，Roymicin)、更昔洛韦(例如Vitrasert，Zirgan)、加替沙星(例如Zymar，Zymaxid)、庆大霉素(例如，Garamycin ophthalmic，Genoptic，Gentacidin，Gentak，Gentasol，Ocu-Mycin)、碘苷(例如Herplex)、左氧氟沙星(例如Iquix，Quixin)、莫西沙星(例如Vigamox，Moxeza)、纳他霉素(例如Natacyn)、诺氟沙星(例如，Chibroxin)、氧氟沙星(例如Ocuflox)、杆菌肽/多粘菌素b(例如Polysporin ophthalmic，AK-Poly-Bac，Polycin-B，Polytracin ophthalmic)、妥布霉素(例如Tobrex，AK-Tob，Tomycine)、多粘菌素b/甲氧苄啶(例如Polytrim)、聚维酮碘(例如Betadine眼用溶液)、曲氟尿苷(例如Viroptic)、短杆菌肽/新霉素/多粘菌素b(例如，AK-Spore，AK-Spore软膏，Neocidin眼用溶液)、磺胺醋酰钠(例如AK-Sulf，Bleph-10，Cetamide，Isopto Cetamide)、磺胺异噁唑(例如Gantrisin ophthalmic)、杆菌肽/新霉素/多粘菌素b(例如Neocidin，Neocin，Ocu-Spore-B，Ocutricin)、土霉素/多粘菌素b(例如，Terak，四霉素与多粘菌素B硫酸盐)、苯福林/磺胺醋酰钠(例如Vasosulf)或阿糖腺苷(例如Vira-A)。

[0057] 在一些实施方案中，在氘化水的存在下配制的眼用组合物包含眼用抗感染药，例如阿奇霉素、杆菌肽、贝西沙星、硼酸、氯霉素、环丙沙星、红霉素、更昔洛韦、加替沙星、庆大霉素、碘苷、左氧氟沙星、莫西沙星、纳他霉素、诺氟沙星、氧氟沙星、杆菌肽/多粘菌素b、妥布霉素、多粘菌素b/甲氧苄啶、聚维酮碘、曲氟尿苷、短杆菌肽/新霉素/多粘菌素b、磺胺醋酰钠、磺胺异噁唑、杆菌肽/新霉素/多粘菌素b、土霉素/多粘菌素b、苯福林/磺胺醋酰钠或阿糖腺苷。在一些实施方案中、在氘化水的存在下配制的眼用组合物包含阿奇霉素、杆菌肽、贝西沙星、硼酸、氯霉素、环丙沙星、红霉素、更昔洛韦、加替沙星、庆大霉素、碘苷、左氧氟沙星、莫西沙星、那他霉素、诺氟沙星、氧氟沙星、杆菌肽/多粘菌素b、妥布霉素、多粘菌素b/甲氧苄啶、聚维酮碘、曲氟尿苷、短杆菌肽/新霉素/多粘菌素b、磺胺醋酰钠、磺胺异噁唑、杆菌肽/新霉素/多粘菌素b、土霉素/多粘菌素b、苯福林/磺胺醋酰钠、阿糖腺苷或其组合。

[0058] 眼用抗炎药是减轻眼睛的疼痛和/或炎症的药剂。在一些实施方案中，眼用抗炎药用来治疗结膜炎、角膜溃疡、角膜结膜炎、干燥性角膜结膜炎、术后眼内压升高、术后眼部炎症或季节性变应性结膜炎。在一些实施方案中，使用眼用抗炎药来抑制术中瞳孔缩小。在一些情况下，在角膜屈光手术过程中使用眼用抗炎药。示例性眼用抗炎药包括但不限于溴芬酸(例如Bromday，Xibrom)、奈帕芬胺(例如Nevanac)、酮咯酸(例如Acular，Acular LS，Acular PF，Acuvail)、环孢菌素(例如Restasis)、氟比洛芬(例如Ocufen)、舒洛芬(例如Profenal)或双氯芬酸(例如Voltaren ophthalmic)。

[0059] 在一些实施方案中，在氘化水的存在下配制的眼用组合物包含眼用抗炎药，例如溴芬酸、奈帕芬胺、酮咯酸、环孢菌素、氟比洛芬、舒洛芬或双氯芬酸。在一些实施方案中，在

氘化水的存在下配制的眼用组合物包含溴芬酸、奈帕芬胺、酮咯酸、环孢菌素、氟比洛芬、舒洛芬、双氯芬酸或其组合。

[0060] 眼用抗组胺药是阻断导致例如眼睛流泪、发红、瘙痒等的组胺受体的抗组胺药。眼用减充血药是缓解眼睛发红的拟交感神经药剂。示例性眼用抗组胺药和减充血药包括但不限于阿卡他定(例如Lastacaft)、氮䓬斯汀(例如Optivar)、贝他斯汀(例如Bepreve)、色甘酸(例如Opticrom,Crolom)、依美斯汀(例如Emadine)、依匹斯汀(例如,Elestat)、酮替芬(例如Alaway,Zaditor,Claritin Eye,Zyrtec Itchy滴眼剂)、左卡巴斯汀(例如Livostin)、洛度沙胺(例如Alomide)、奈多罗米(例如Alocril)、萘甲唑啉(例如AK-Con,Albalon,All Clear,Allerest滴眼剂,Allersol,Clear Eyes,Ocu-Zoline,VasoClear,Vasocon)、萘甲唑啉/非尼拉敏(例如,Visine-A,Opcon-A,Eye Allergy Relief)、萘甲唑啉/硫酸锌(例如Clear Eyes ACR,VasoClear A)、奥洛他定(例如Patanol,Pataday,Pazeo)、羟甲唑啉(例如OcuClear)、吡嘧司特(例如Alamast)、苯福林(例如AK-Dilate,AK-Nefrin,Altafrin,Isopto Frin,Mydfrin,Neofrin,Ocu-Phrin,Prefrin,Refresh redness Relief)、苯福林/硫酸锌(例如Zincfrin)、四氢唑啉(例如Visine original,Altazine,Geneyes,Opti-Clear,Optigene 3)或四氢唑啉/硫酸锌(例如Visine totality多症状缓解剂)。

[0061] 在一些实施方案中,在氘化水的存在下配制的眼用组合物包含眼用抗组胺药和减充血药,例如阿卡他定、氮䓬斯汀、贝他斯汀、色甘酸、依美斯汀、依匹斯汀、酮替芬、左卡巴斯汀、洛度沙胺、奈多罗米、萘甲唑啉、萘甲唑啉/非尼拉敏、萘甲唑啉/硫酸锌、奥洛他定、羟甲唑啉、吡嘧司特、苯福林、苯福林/硫酸锌、四氢唑啉或四氢唑啉/硫酸锌。在一些实施方案中、在氘化水的存在下配制的眼用组合物包含阿卡他定、氮䓬斯汀、贝他斯汀、色甘酸、依美斯汀、依匹斯汀、酮替芬、左卡巴斯汀、洛度沙胺、奈多罗米、萘甲唑啉、萘甲唑啉/非尼拉敏、萘甲唑啉/硫酸锌、奥洛他定、羟甲唑啉、吡嘧司特、苯福林、苯福林/硫酸锌、四氢唑啉、四氢唑啉/硫酸锌或其组合。

[0062] 眼科诊断剂是诊断性荧光素血管造影术或视网膜和虹膜脉管系统血管镜检查使用的荧光分子。示例性的眼科诊断剂包括但不限于荧光素(例如AK-Fluor,BioGlo,Ful-Glo)、荧光素/丙美卡因(例如Flucaine,Fluoracaine)、丁氧普鲁卡因/荧光素(例如Flurox)、吲哚菁绿(例如IC-Green)或台盼蓝(例如MembraneBlue,VisinBlue)。

[0063] 在一些实施方案中,在氘化水的存在下配制的眼用组合物包含眼科诊断剂,例如荧光素、荧光素/丙美卡因、丁氧普鲁卡因/荧光素、吲哚菁绿或台盼蓝。在一些实施方案中,在氘化水的存在下配制的眼用组合物包含荧光素、荧光素/丙美卡因、丁氧普鲁卡因/荧光素、吲哚菁绿、台盼蓝或其组合。

[0064] 眼科青光眼药是降低青光眼的眼压的药剂。在一些情况下,眼科青光眼药还用来治疗眼内高压、术后眼内压升高或产生瞳孔缩小。示例性的眼科青光眼药包括但不限于乙酰胆碱(例如Miochol-E)、安普乐定(例如Iopidine)、倍他洛尔(例如Betoptic,Betoptic S)、比马前列素(例如Lumigan)、溴莫尼定(例如Alphagan,Alphagan P)、布林佐胺(例如Azopt)、溴莫尼定/布林佐胺(例如Simbrinza)、卡巴胆碱(例如Carbastat,Carboptic,Isopto Carbachol,Miostat)、卡替洛尔(例如Ocupress)、地美溴铵(例如Humorsol

Ocumeter)、地匹福林(例如,Propine)、多佐胺(例如Trusopt)、多佐胺/噻吗洛尔(例如Cosopt,Cosopt PF,Combigan)、依可碘酯(例如碘二乙氧磷酰硫胆碱)、肾上腺素(例如Epifrin,Epinal,Eppy/N,Glaucon)、肾上腺素/毛果芸香碱(例如,E-Pilo-1,Epilo-2,P1E1,P2E1,P3E1,P4E1,P6E1)、拉坦前列素(例如Xalatan)、左布诺洛尔(例如AK-Beta,Betagan)、左倍他洛尔(例如,Betaxon)、美替洛尔(例如OptiPranolol)、毒扁豆碱(例如眼用硫酸毒扁豆碱)、毛果芸香碱(例如Isopto Carpine,Ocu-Carpine,Pilopine HS,Pilostat)、他氟前列素(例如Zioptan)、噻吗洛尔(例如Betimol,Timoptic Ocudose,Istalol,Timoptic,Timoptic-XE)、曲伏前列素(例如Travatan,Travatan Z,Izba)或乌诺前列酮(例如Rescula)。

[0065] 在一些实施方案中,在氘化水的存在下配制的眼用组合物包含眼科青光眼药,例如乙酰胆碱、安普乐定、倍他洛尔、比马前列素、溴莫尼定、布林佐胺、溴莫尼定/布林佐胺、卡巴胆碱、卡替洛尔、地美溴铵、地匹福林、多佐胺、多佐胺/噻吗洛尔、依可碘酯、肾上腺素、肾上腺素/毛果芸香碱、拉坦前列素、左布诺洛尔、左倍他洛尔、美替洛尔、毒扁豆碱、毛果芸香碱、他氟前列素、噻吗洛尔、曲伏前列素或乌诺前列酮。在一些实施方案中、在氘化水的存在下配制的眼用组合物包含乙酰胆碱、安普乐定、倍他洛尔、比马前列素、溴莫尼定、布林佐胺、溴莫尼定/布林佐胺、卡巴胆碱、卡替洛尔、地美溴铵、地匹福林、多佐胺、多佐胺/噻吗洛尔、依可碘酯、肾上腺素、肾上腺素/毛果芸香碱、拉坦前列素、左布诺洛尔、左倍他洛尔、美替洛尔、毒扁豆碱、毛果芸香碱、他氟前列素、噻吗洛尔、曲伏前列素、乌诺前列酮或其组合。

[0066] 在一些实施方案中,眼用润滑剂和灌洗剂用来治疗干眼和/或发炎的眼睛。示例性的眼用润滑剂和灌洗剂包括但不限于来自Hypotears、System Balance、FreshKote、GenTeal、TheraTears、Lacrisert、Tears Again、Lacri-Lube S.O.P、Systane、Oasis Tears、Artificial Tears、Celluvisc、Clear Eyes CLR、Comfort Tears、Dry Eye Relief、Isopto Tears、Liquitears、Lubricant Eye drops、Lubrifresh PM、Moisture Drops、Murocel、Opti-Free Rewitting Drops、Optive、Puralube Tears、Refresh、Soothe、Sterilube、Tears Naturale、Tears Renew、Ultra Fresh或Visine Tears的人造泪液。在一些实施方案中,人造泪液制剂包括羧甲基纤维素、聚乙烯醇、羟丙基甲基纤维素、羟丙基纤维素和透明质酸。

[0067] 在一些实施方案中,在氘化水的存在下配制的眼用组合物包含眼用润滑剂和灌洗剂,例如人造泪液。在一些实施方案中,在氘化水的存在下配制的眼用组合物包含人造泪液。

[0068] 在一些实施方案中,眼用类固醇用来治疗结膜炎、睫状体炎、糖尿病黄斑水肿、眼睛干燥/发红/瘙痒、睫毛稀少症、虹膜炎、角膜炎、黄斑水肿、术后眼部炎症、红斑痤疮、季节性变应性结膜炎、类固醇反应性炎性病况、颞动脉炎、葡萄膜炎或玻璃体切除术。示例性眼用类固醇包括但不限于地塞米松(例如Ozurdex,AK-Dex,Decadron Ocumeter,Dexasol,Maxidex,Ocu-Dex)、二氟泼尼酯(例如Durezol)、氟轻松(例如Retisert,Iluvien)、氟米龙(例如、FML Forte Liquifilm,Flarex,Fluor-Op,FML,FMLS.O.P.)、氯替泼诺(例如Alrex,Lotemax)、甲羟松(HMS)、泼尼松龙(例如AK-Pred,Econopred,Econopred Plus,Inflamase Forte,Inflamase Mild,Omnipred,Pred Forte,Prednisol)、利美索龙(例如Vexol)或曲安西龙(例如Triesence,Trivaris)。

[0069] 在一些实施方案中，在氘化水的存在下配制的眼用组合物包含眼用类固醇，例如地塞米松、二氟泼尼酯、氟轻松、氟米龙、氯替泼诺、甲羟松、泼尼松龙、利美索龙或曲安西龙。在一些实施方案中，在氘化水的存在下配制的眼用组合物包含地塞米松、二氟泼尼酯、氟轻松、氟米龙、氯替泼诺、甲羟松、泼尼松龙、利美索龙、曲安西龙或其组合。

[0070] 示例性眼用类固醇结合抗感染药包括但不限于氟米龙/磺胺醋酰钠(例如FML-S Liquifilm)、地塞米松/新霉素(例如Neo-Decadron,AK-Neo-Dex,Neo-Decadron Ocumeter,Neo-Dex,Neo-Dexair)、地塞米松/妥布霉素(例如TobraDex,Tobradex ST)、地塞米松/新霉素/多粘菌素b(例如Neo-Poly-Dex,Maxitrol,AK-Trol,Dexacidin,Dexacine,Dexasporin,Methadex,Ocu-Trol)、氯替泼诺/妥布霉素(例如Zylet)、泼尼松龙/磺胺醋酰钠(例如Blephamide,Blephamide S.O.P.,AK-Cide,Cetapred,Isopto Cetapred,Metimyd,Ocu-Lone C,Vasocidin)、杆菌肽/氢化可的松/新霉素/多粘菌素b(例如,Cortisporin眼用软膏,Cortomycin眼软膏,Neo-Poly-Bac,Neotricin HC,Triple Antibiotic HC眼用软膏)、氢化可的松/新霉素/多粘菌素b(例如,Cortisporin眼用悬浮液,Cortomycin悬浮液)、氯霉素/氢化可的松/多粘菌素b(例如Ophthocort)、新霉素/多粘菌素b/泼尼松龙(例如Poly Pred)或庆大霉素/泼尼松龙(例如Pred-G,Pred-G S.O.P.)。

[0071] 在一些实施方案中，在氘化水的存在下配制的眼用组合物包含眼用类固醇结合抗感染药，例如氟米龙/磺胺醋酰钠、地塞米松/新霉素、地塞米松/妥布霉素、地塞米松/新霉素/多粘菌素b、氯替泼诺/妥布霉素、泼尼松龙/磺胺醋酰钠、杆菌肽/氢化可的松/新霉素/多粘菌素b、氢化可的松/新霉素/多粘菌素b、氯霉素/氢化可的松/多粘菌素b、新霉素/多粘菌素b/泼尼松龙或庆大霉素/泼尼松龙。在一些实施方案中，在氘化水的存在下配制的眼用组合物包含氟米龙/磺胺醋酰钠、地塞米松/新霉素、地塞米松/妥布霉素、地塞米松/新霉素/多粘菌素b、氯替泼诺/妥布霉素、泼尼松龙/磺胺醋酰钠、杆菌肽/氢化可的松/新霉素/多粘菌素b、氢化可的松/新霉素/多粘菌素b、氯霉素/氢化可的松/多粘菌素b、新霉素/多粘菌素b/泼尼松龙、庆大霉素/泼尼松龙或其组合。

[0072] 示例性的眼科手术剂包括但不限于酮咯酸/苯福林(例如Omidria)。

[0073] 在一些实施方案中，在氘化水的存在下配制的眼用组合物包含眼科手术剂，例如酮咯酸/苯福林。在一些实施方案中，在氘化水的存在下配制的眼用组合物包含酮咯酸/苯福林。

[0074] 在一些实施方案中，在氘化水的存在下配制的眼用组合物包含苯海拉明、茶苯海明、双环维林、黄酮哌酯、奥昔布宁、噻托溴铵、莨菪碱、scopolomine(L-莨菪碱)、羟嗪、异丙托铵、哌仑西平、索利那新、达非那新、苯扎托品、美贝维林、丙环定、阿地溴铵、三己芬迪/苯海索、托特罗定或其任何组合。

[0075] 在一些实施方案中，在氘化水的存在下配制的眼用组合物包含阿柏西普(也称为VEGF Trap)、雷珠单抗、培加尼布、环喷托酯、苯福林、后马托品、东莨菪碱、环喷托酯/苯福林、苯福林/东莨菪碱、托吡卡胺、酮咯酸/苯福林、羟苯丙胺/托吡卡胺、半胱胺、奥克纤溶酶、丝裂霉素、达哌唑、利多卡因、丙美卡因、丁卡因、丁氧普鲁卡因、阿奇霉素、杆菌肽、贝西沙星、硼酸、氯霉素、环丙沙星、红霉素、更昔洛韦、加替沙星、庆大霉素、碘苷、左氧氟沙星、莫西沙星、纳他霉素、诺氟沙星、氧氟沙星、杆菌肽/多粘菌素b、妥布霉素、多粘菌素b/甲氧苄啶、聚维酮碘、曲氟尿苷、短杆菌肽/新霉素/多粘菌素b、磺胺醋酰钠、磺胺异噁唑、杆菌

肽/新霉素/多粘菌素b、土霉素/多粘菌素b、苯福林/磺胺醋酰钠、阿糖腺苷、溴芬酸、奈帕芬胺、酮咯酸、环孢菌素、氟比洛芬、舒洛芬、双氯芬酸、阿卡他定、氮䓬斯汀、贝他斯汀、色甘酸、依美斯汀、依匹斯汀、酮替芬、左卡巴斯汀、洛度沙胺、奈多罗米、萘甲唑啉、萘甲唑啉/非尼拉敏、萘甲唑啉/硫酸锌、奥洛他定、羟甲唑啉、吡嘧司特、苯福林、苯福林/硫酸锌、四氢唑啉、四氢唑啉/硫酸锌、荧光素、荧光素/丙美卡因、丁氧普鲁卡因/荧光素、吲哚菁绿、台盼蓝、乙酰胆碱、安普乐定、倍他洛尔、比马前列素、溴莫尼定、布林佐胺、溴莫尼定/布林佐胺、卡巴胆碱、卡替洛尔、地美溴铵、地匹福林、多佐胺、多佐胺/噻吗洛尔、依可碘酯、肾上腺素、肾上腺素/毛果芸香碱、拉坦前列素、左布诺洛尔、左倍他洛尔、美替洛尔、毒扁豆碱、毛果芸香碱、他氟前列素、噻吗洛尔、曲伏前列素、乌诺前列酮、人造泪液、地塞米松、二氟泼尼酯、氟轻松、氟米龙、氯替泼诺、甲羟松、泼尼松龙、利美索龙、曲安西龙、氟米龙/磺胺醋酰钠、地塞米松/新霉素、地塞米松/妥布霉素、地塞米松/新霉素/多粘菌素b、氯替泼诺/妥布霉素、泼尼松龙/磺胺醋酰钠、杆菌肽/氢化可的松/新霉素/多粘菌素b、氢化可的松/新霉素/多粘菌素b、氯霉素/氢化可的松/多粘菌素b、新霉素/多粘菌素b/泼尼松龙、庆大霉素/泼尼松龙、酮咯酸/苯福林、苯海拉明、茶苯海明、双环维林、黄酮哌酯、奥昔布宁、噻托溴铵、莨菪碱、scopolomine(L-莨菪碱)、羟嗪、异丙托铵、哌仑西平、索利那新、达非那新、苯扎托品、美贝维林、丙环定、阿地溴铵、三己芬迪/苯海索、托特罗定或其任何组合。

眼用组合物

[0076] 本文提供了用于治疗眼科病症或病况的眼用组合物，其中该眼用组合物用氘化水配制。在一些方面，该眼用组合物在不同的温度下、在不同的相对湿度下是稳定的，并且相对于眼用剂具有至少80％的效力。在另外的方面，该眼用组合物具有降低的缓冲能力。在这样的情况下，该眼用组合物在施用到眼睛中时降低的缓冲能力使得该眼用组合物达到生理pH的速率比在H_2O中配制的等效眼用制剂或溶液更快。

[0077] 在一些方面，本文描述了不具有剂量间变化的眼用组合物。在一些方面，本文描述了一种眼用组合物，其在不同的温度下、在不同的相对湿度下是稳定的，并且相对于眼用剂具有至少80％的效力。

[0078] 在其他方面，本文所述包括将眼用组合物配制成眼用凝胶或眼用软膏。例如，本文所述的一些眼用凝胶或眼用软膏允许期望的剂量间均匀性、提高的稳定性、降低或受限的全身暴露或其组合。

眼用溶液组合物或制剂

[0079] 在某些实施方案中，本文公开了一种配制成水溶液的眼用组合物。在一些实施方案中，该眼用组合物包含眼用剂和氘化水。如本文所用的，氘化水是指D_2O、DHO、重水和/或氧化氘。

[0080] 在一些实施方案中，在储存条件下在延长的时间段内，所述组合物包含至少约80％的眼用剂。在一些实施方案中，在储存条件下在延长的时间段内，所述组合物包含至少约81％的眼用剂。在一些实施方案中，在储存条件下在延长的时间段内，所述组合物包含至少约82％的眼用剂。在一些实施方案中，在储存条件下在延长的时间段内，所述组合物包含至少约83％的眼用剂。在一些实施方案中，在储存条件下在延长的时间段内，所述组合物包含至少约84％的眼用剂。在一些实施方案中，在储存条件下在延长的时间段内，所述组合物包含至少约85％的眼用剂。在一些实施方案中，在储存条件下在延长的时间段内，所述组合

物包含至少约86％的眼用剂。在一些实施方案中，在储存条件下在延长的时间段内，所述组合物包含至少约87％的眼用剂。在一些实施方案中，在储存条件下在延长的时间段内，所述组合物包含至少约88％的眼用剂。在一些实施方案中，在储存条件下在延长的时间段内，所述组合物包含至少约89％的眼用剂。在一些实施方案中，在储存条件下在延长的时间段内，所述组合物包含至少约90％的眼用剂。在一些实施方案中，在储存条件下在延长的时间段内，所述组合物包含至少约91％的眼用剂。在一些实施方案中，在储存条件下在延长的时间段内，所述组合物包含至少约92％的眼用剂。在一些实施方案中，在储存条件下在延长的时间段内，所述组合物包含至少约93％的眼用剂。在一些实施方案中，在储存条件下在延长的时间段内，所述组合物包含至少约94％的眼用剂。在一些实施方案中，在储存条件下在延长的时间段内，所述组合物包含至少约95％的眼用剂。在一些实施方案中，在储存条件下在延长的时间段内，所述组合物包含至少约96％的眼用剂。在一些实施方案中，在储存条件下在延长的时间段内，所述组合物包含至少约97％的眼用剂。在一些实施方案中，在储存条件下在延长的时间段内，所述组合物包含至少约98％的眼用剂。在一些实施方案中，在储存条件下在延长的时间段内，所述组合物包含至少约99％的眼用剂。在一些实施方案中，在储存条件下在延长的时间段内，所述组合物包含至少约99.5％的眼用剂。在一些实施方案中，在储存条件下在延长的时间段内，所述组合物包含至少约99.9％的眼用剂。

[0081] 在一些实施方案中，在储存条件下在延长的时间段后，所述组合物具有至少约80％的效力。在一些实施方案中，在储存条件下在延长的时间段后，所述组合物具有至少约81％的效力。在一些实施方案中，在储存条件下在延长的时间段后，所述组合物具有至少约82％的效力。在一些实施方案中，在储存条件下在延长的时间段后，所述组合物具有至少约83％的效力。在一些实施方案中，在储存条件下在延长的时间段后，所述组合物具有至少约84％的效力。在一些实施方案中，在储存条件下在延长的时间段后，所述组合物具有至少约85％的效力。在一些实施方案中，在储存条件下在延长的时间段后，所述组合物具有至少约86％的效力。在一些实施方案中，在储存条件下在延长的时间段后，所述组合物具有至少约87％的效力。在一些实施方案中，在储存条件下在延长的时间段后，所述组合物具有至少约88％的效力。在一些实施方案中，在储存条件下在延长的时间段后，所述组合物具有至少约89％的效力。在一些实施方案中，在储存条件下在延长的时间段后，所述组合物具有至少90％的效力。在一些实施方案中，在储存条件下在延长的时间段后，所述组合物具有至少91％的效力。在一些实施方案中，在储存条件下在延长的时间段后，所述组合物具有至少92％的效力。在一些实施方案中，在储存条件下在延长的时间段后，所述组合物具有至少93％的效力。在一些实施方案中，在储存条件下在延长的时间段后，所述组合物具有至少94％的效力。在一些实施方案中，在储存条件下在延长的时间段后，所述组合物具有至少95％的效力。在一些实施方案中，在储存条件下在延长的时间段后，所述组合物具有至少96％的效力。在一些实施方案中，在储存条件下在延长的时间段后，所述组合物具有至少97％的效力。在一些实施方案中，在储存条件下在延长的时间段后，所述组合物具有至少98％的效力。在一些实施方案中，在储存条件下在延长的时间段后，所述组合物具有至少99％的效力。

[0082] 在一些实施方案中，所述延长的时间段为至少1周。在一些实施方案中，所述延长的时间段为至少2周。在一些实施方案中，所述延长的时间段为至少3周。在一些实施方案

中，所述延长的时间段为至少1个月。在一些实施方案中，所述延长的时间段为至少2个月。在一些实施方案中，所述延长的时间段为至少3个月。在一些实施方案中，所述延长的时间段为至少4个月。在一些实施方案中，所述延长的时间段为至少5个月。在一些实施方案中，所述延长的时间段为至少6个月。在一些实施方案中，所述延长的时间段为至少7个月。在一些实施方案中，所述延长的时间段为至少8个月。在一些实施方案中，所述延长的时间段为至少9个月。在一些实施方案中，所述延长的时间段为至少10个月。在一些实施方案中，所述延长的时间段为至少11个月。在一些实施方案中，所述延长的时间段为至少12个月(即1年)。在一些实施方案中，所述延长的时间段为至少18个月(即1.5年)。在一些实施方案中，所述延长的时间段为至少24个月(即2年)。在一些实施方案中，所述延长的时间段为至少36个月(即3年)。所述延长的时间段为至少3年。在一些实施方案中，所述延长的时间段为至少5年、6年、7年、8年、9年、10年、15年、30年或更长。

[0083] 在一些实施方案中，所述储存条件的温度为约2℃至约70℃。在一些实施方案中，所述储存条件的温度为约2℃至约65℃、约8℃至约65℃、约10℃至约65℃、约25℃至约65℃、约30℃至约60℃、约35℃至约55℃或约40℃至约50℃。在一些实施方案中，所述储存条件的温度为约2℃至约10℃。在一些实施方案中，所述储存条件的温度为约20℃至约26℃。在一些实施方案中，所述储存条件的温度为约25℃。在一些实施方案中，所述储存条件的温度为约40℃。在一些实施方案中，所述储存条件的温度为约60℃。

[0084] 在一些实施方案中，所述储存条件的相对湿度为约50％至约80％，或约60％至约75％。在一些实施方案中，所述储存条件的相对湿度为约60％。在一些实施方案中，所述储存条件的相对湿度为约75％。

[0085] 在一些实施方案中，所述组合物包含少于60％的H_2O。在一些实施方案中，所述组合物包含少于55％的H_2O。在一些实施方案中，所述组合物包含少于50％的H_2O。在一些实施方案中，所述组合物包含少于45％的H_2O。在一些实施方案中，所述组合物包含少于40％的H_2O。在一些实施方案中，所述组合物包含少于35％的H_2O。在一些实施方案中，所述组合物包含少于30％的H_2O。在一些实施方案中，所述组合物包含少于25％的H_2O。在一些实施方案中，所述组合物包含少于20％的H_2O。在一些实施方案中，所述组合物包含少于15％的H_2O。在一些实施方案中，所述组合物包含少于10％的H_2O。在一些实施方案中，所述组合物包含少于9％的H_2O。在一些实施方案中，所述组合物包含少于8％的H_2O。在一些实施方案中，所述组合物包含少于7％的H_2O。在一些实施方案中，所述组合物包含少于6％的H_2O。

[0086] 在一些实施方案中，所述组合物包含少于5％的H_2O到少于0.1％的H_2O。在一些实施方案中，所述组合物包含少于5％的H_2O。在一些实施方案中，所述组合物包含少于4.5％的H_2O。在一些实施方案中，所述组合物包含少于4％的H_2O。在一些实施方案中，所述组合物包含少于3.5％的H_2O。在一些实施方案中，所述组合物包含少于3％的H_2O。在一些实施方案中，所述组合物包含少于2.5％的H_2O。在一些实施方案中，所述组合物包含少于2％的H_2O。在一些实施方案中，所述组合物包含少于1.5％的H_2O。在一些实施方案中，所述组合物包含少于1％的H_2O。在一些实施方案中，所述组合物包含少于0.5％的H_2O。在一些实施方案中，所述组合物包含少于0.4％的H_2O。在一些实施方案中，所述组合物包含少于0.3％的H_2O。在一些实施方案中，所述组合物包含少于0.2％的H_2O。在一些实施方案中，所述组合物包含少于0.1％的H_2O。在一些实施方案中，所述组合物包含0％的H_2O。

[0087] 在一些实施方案中，所述组合物具有约3至约9、约4至约8、约4.5至约7.8、约5至约7.5或约5.5至约7的pD。在一些实施方案中，所述组合物具有小于约8的pD。在一些实施方案中，所述组合物具有小于约7.9的pD。在一些实施方案中，所述组合物具有小于约7.8的pD。在一些实施方案中，所述组合物具有小于约7.7的pD。在一些实施方案中，所述组合物具有小于约7.6的pD。在一些实施方案中，所述组合物具有小于约7.5的pD。在一些实施方案中，所述组合物具有小于约7.4的pD。在一些实施方案中，所述组合物具有小于约7.3的pD。在一些实施方案中，所述组合物具有小于约7.2的pD。在一些实施方案中，所述组合物具有小于约7.1的pD。在一些实施方案中，所述组合物具有小于约7的pD。在一些实施方案中，所述组合物具有小于约6.9的pD。在一些实施方案中，所述组合物具有小于约6.8的pD。在一些实施方案中，所述组合物具有小于约6.7的pD。在一些实施方案中，所述组合物具有小于约6.6的pD。在一些实施方案中，所述组合物具有小于约6.5的pD。在一些实施方案中，所述组合物具有小于约6.4的pD。在一些实施方案中，所述组合物具有小于约6.3的pD。在一些实施方案中，所述组合物具有小于约6.2的pD。在一些实施方案中，所述组合物具有小于约6.1的pD。在一些实施方案中，所述组合物具有小于约6的pD。在一些实施方案中，所述组合物具有小于约5.9的pD。在一些实施方案中，所述组合物具有小于约5.8的pD。在一些实施方案中，所述组合物具有小于约5.7的pD。在一些实施方案中，所述组合物具有小于约5.6的pD。在一些实施方案中，所述组合物具有小于约5.5的pD。在一些实施方案中，所述组合物具有小于约5.4的pD。在一些实施方案中，所述组合物具有小于约5.3的pD。在一些实施方案中，所述组合物具有小于约5.2的pD。在一些实施方案中，所述组合物具有小于约5.1的pD。在一些实施方案中，所述组合物具有小于约5的pD。在一些实施方案中，所述组合物具有小于约4.9的pD。在一些实施方案中，所述组合物具有小于约4.8的pD。在一些实施方案中，所述组合物具有小于约4.7的pD。在一些实施方案中，所述组合物具有小于约4.6的pD。在一些实施方案中，所述组合物具有小于约4.5的pD。在一些实施方案中，所述组合物具有小于约4.4的pD。在一些实施方案中，所述组合物具有小于约4.3的pD。在一些实施方案中，所述组合物具有小于约4.2的pD。在一些实施方案中，所述组合物具有小于约4.1的pD。在一些实施方案中，所述组合物具有小于约4的pD。在一些实施方案中，所述组合物具有小于约3.9的pD。在一些实施方案中，所述组合物具有小于约3.8的pD。在一些实施方案中，所述组合物具有小于约3.7的pD。在一些实施方案中，所述组合物具有小于约3.6的pD。在一些实施方案中，所述组合物具有小于约3.5的pD。

[0088] 在一些实施方案中，包含氘化水的组合物具有相比于包含H_2O的等效组合物降低的缓冲能力。如本文别处所述，在一些实施方案中，降低的缓冲能力允许包含氘化水的组合物以比包含H_2O的组合物更快的速率正常化至生理pH。在一些实施方案中，降低的缓冲能力允许该组合物相比于包含H_2O的等效组合物诱导更少的泪反射。

[0089] 在一些情况下，包含氘化水的组合物使眼用剂稳定。在一些实施方案中，这是由于与等效H_2O水性系统中反应性种类(例如-OH)的浓度相比，D_2O水性系统中反应性种类(例如-OD)的浓度更低。在一些情况下，碱催化导致存在来自眼用剂的降解物。在一些情况下，在引起降解物形成的反应性物质的浓度较低时，眼用溶液在D_2O水性系统中比在等效H_2O水性系统中更稳定。在一些实施方案中，相对于用H_2O配制的眼用组合物，用氘化水配制的眼用组合物允许更稳定的眼用组合物。

[0090] 在一些实施方案中，在储存条件下在延长的时间段后，基于眼用剂的浓度，所述组合物包含少于20％的主要降解物。在一些实施方案中，在储存条件下在延长的时间段后，基于眼用剂的浓度，所述组合物包含少于15％的主要降解物。在一些实施方案中，在储存条件下在延长的时间段后，基于眼用剂的浓度，所述组合物包含少于10％的主要降解物。在一些实施方案中，在储存条件下在延长的时间段后，基于眼用剂的浓度，所述组合物包含少于5％的主要降解物。在一些实施方案中，在储存条件下在延长的时间段后，基于眼用剂的浓度，所述组合物包含少于2.5％的主要降解物。在一些实施方案中，在储存条件下在延长的时间段后，基于眼用剂的浓度，所述组合物包含少于2.0％的主要降解物。在一些实施方案中，在储存条件下在延长的时间段后，基于眼用剂的浓度，所述组合物包含少于1.5％的主要降解物。在一些实施方案中，在储存条件下在延长的时间段后，基于眼用剂的浓度，所述组合物包含少于1.0％的主要降解物。在一些实施方案中，在储存条件下在延长的时间段后，基于眼用剂的浓度，所述组合物包含少于0.5％的主要降解物。在一些实施方案中，在储存条件下在延长的时间段后，基于眼用剂的浓度，所述组合物包含少于0.4％的主要降解物。在一些实施方案中，在储存条件下在延长的时间段后，基于眼用剂的浓度，所述组合物包含少于0.3％的主要降解物。在一些实施方案中，在储存条件下在延长的时间段后，基于眼用剂的浓度，所述组合物包含少于0.2％的主要降解物。在一些实施方案中，在储存条件下在延长的时间段后，基于眼用剂的浓度，所述组合物包含少于0.1％的主要降解物。

[0091] 在一些实施方案中，所述组合物在用UV照射时不延长单线态氧寿命。在一些情况下，本文所述的一种或多种眼用剂在用UV照射时不延长单线态氧寿命。在一些情况下，本文所述的一种或多种眼用剂是自由基清除剂，其猝灭组合物内光生成的单线态氧种类。在一些情况下，一种或多种选自以下的眼用剂不会在用UV照射时延长单线态氧寿命或猝灭组合物内光生成的单态氧种类：阿柏西普、雷珠单抗、培加尼布、环喷托酯、苯福林、后马托品、东莨菪碱、环喷托酯/苯福林、苯福林/东莨菪碱、托吡卡胺、酮咯酸/苯福林、羟苯丙胺/托吡卡胺、半胱胺、奥克纤溶酶、丝裂霉素、达哌唑、利多卡因、丙美卡因、丁卡因、丁氧普鲁卡因、阿奇霉素、杆菌肽、贝西沙星、硼酸、氯霉素、环丙沙星、红霉素、更昔洛韦、加替沙星、庆大霉素、碘苷、左氧氟沙星、莫西沙星、纳他霉素、诺氟沙星、氧氟沙星、杆菌肽/多粘菌素b、妥布霉素、多粘菌素b/甲氧苄啶、聚维酮碘、曲氟尿苷、短杆菌肽/新霉素/多粘菌素b、磺胺醋酰钠、磺胺异噁唑、杆菌肽/新霉素/多粘菌素b、土霉素/多粘菌素b、苯福林/磺胺醋酰钠、阿糖腺苷、溴芬酸、奈帕芬胺、酮咯酸、环孢菌素、氟比洛芬、舒洛芬、双氯芬酸、阿卡他定、氮䓬斯汀、贝他斯汀、色甘酸、依美斯汀、依匹斯汀、酮替芬、左卡巴斯汀、洛度沙胺、奈多罗米、萘甲唑啉、萘甲唑啉/非尼拉敏、萘甲唑啉/硫酸锌、奥洛他定、羟甲唑啉、吡嘧司特、苯福林、苯福林/硫酸锌、四氢唑啉、四氢唑啉/硫酸锌、荧光素、荧光素/丙美卡因、丁氧普鲁卡因/荧光素、吲哚菁绿、台盼蓝、乙酰胆碱、安普乐定、倍他洛尔、比马前列素、溴莫尼定、布林佐胺、溴莫尼定/布林佐胺、卡巴胆碱、卡替洛尔、地美溴铵、地匹福林、多佐胺、多佐胺/噻吗洛尔、依可碘酯、肾上腺素、肾上腺素/毛果芸香碱、拉坦前列素、左布诺洛尔、左倍他洛尔、美替洛尔、毒扁豆碱、毛果芸香碱、他氟前列素、噻吗洛尔、曲伏前列素、乌诺前列酮、人造泪液、地塞米松、二氟泼尼酯、氟轻松、氟米龙、氯替泼诺、甲羟松、泼尼松龙、利美索龙、曲安西龙、氟米龙/磺胺醋酰钠、地塞米松/新霉素、地塞米松/妥布霉素、地塞米松/新霉素/多粘菌素b、氯替泼诺/妥布霉素、泼尼松龙/磺胺醋酰钠、杆菌肽/氢化可的松/新霉素/多粘菌素b、氢化

可的松/新霉素/多粘菌素b、氯霉素/氢化可的松/多粘菌素b、新霉素/多粘菌素b/泼尼松龙、庆大霉素/泼尼松龙、酮咯酸/苯福林、苯海拉明、茶苯海明、双环维林、黄酮哌酯、奥昔布宁、噻托溴铵、莨菪碱、scopolomine(L-莨菪碱)、羟嗪、异丙托铵、哌仑西平、索利那新、达非那新、苯扎托品、美贝维林、丙环定、阿地溴铵、三己芬迪/苯海索和托特罗定。在一些情况下,所述眼用剂不是α-氨基-羧酸或α-羧基-羧酸。在一些情况下,所述眼用剂不是盐酸贝那替嗪。在一些情况下,所述眼用组合物未用氧饱和。在其他情况下,所述眼用组合物不包含光敏剂。

眼用剂浓度

[0092] 在一些实施方案中,按组合物的重量计,本文所述的组合物具有以下浓度的眼用剂:约0.001%至约20%、约0.005%至约10%、约0.010%至约5%、约0.015%至约1%、约0.020%至约0.5%、约0.025%至约0.1%、约0.030%至约0.050%、约0.035%至约0.050%、约0.040%至约0.050%或约0.045%至约0.050%的眼用剂或其药学上可接受的前药或盐。在一些情况下,在施用眼用组合物后,眼用剂的前药以化学方式转化为眼用剂。在非限制性实例中,该眼用前药具有可被泪液中的一种或多种酶切割的化学键。在一些实施方案中,所述眼用剂是阿柏西普(也称为VEGF Trap)、雷珠单抗、培加尼布、环喷托酯、苯福林、后马托品、东莨菪碱、环喷托酯/苯福林、苯福林/东莨菪碱、托吡卡胺、酮咯酸/苯福林、羟苯丙胺/托吡卡胺、半胱胺、奥克纤溶酶、丝裂霉素、达哌唑、利多卡因、丙美卡因、丁卡因、丁氧普鲁卡因、阿奇霉素、杆菌肽、贝西沙星、硼酸、氯霉素、环丙沙星、红霉素、更昔洛韦、加替沙星、庆大霉素、碘苷、左氧氟沙星、莫西沙星、纳他霉素、诺氟沙星、氧氟沙星、杆菌肽/多粘菌素b、妥布霉素、多粘菌素b/甲氧苄啶、聚维酮碘、曲氟尿苷、短杆菌肽/新霉素/多粘菌素b、磺胺醋酰钠、磺胺异噁唑、杆菌肽/新霉素/多粘菌素b、土霉素/多粘菌素b、苯福林/磺胺醋酰钠、阿糖腺苷、溴芬酸、奈帕芬胺、酮咯酸、环孢菌素、氟比洛芬、舒洛芬、双氯芬酸、阿卡他定、氮䓬斯汀、贝他斯汀、色甘酸、依美斯汀、依匹斯汀、酮替芬、左卡巴斯汀、洛度沙胺、奈多罗米、萘甲唑啉、萘甲唑啉/非尼拉敏、萘甲唑啉/硫酸锌、奥洛他定、羟甲唑啉、吡嘧司特、苯福林、苯福林/硫酸锌、四氢唑啉、四氢唑啉/硫酸锌、荧光素、荧光素/丙美卡因、丁氧普鲁卡因/荧光素、吲哚菁绿、台盼蓝、乙酰胆碱、安普乐定、倍他洛尔、比马前列素、溴莫尼定、布林佐胺、溴莫尼定/布林佐胺、卡巴胆碱、卡替洛尔、地美溴铵、地匹福林、多佐胺、多佐胺/噻吗洛尔、依可碘酯、肾上腺素、肾上腺素/毛果芸香碱、拉坦前列素、左布诺洛尔、左倍他洛尔、美替洛尔、毒扁豆碱、毛果芸香碱、他氟前列素、噻吗洛尔、曲伏前列素、乌诺前列酮、人造泪液、地塞米松、二氟泼尼酯、氟轻松、氟米龙、氯替泼诺、甲羟松、泼尼松龙、利美索龙、曲安西龙、氟米龙/磺胺醋酰钠、地塞米松/新霉素、地塞米松/妥布霉素、地塞米松/新霉素/多粘菌素b、氯替泼诺/妥布霉素、泼尼松龙/磺胺醋酰钠、杆菌肽/氢化可的松/新霉素/多粘菌素b、氢化可的松/新霉素/多粘菌素b、氯霉素/氢化可的松/多粘菌素b、新霉素/多粘菌素b/泼尼松龙、庆大霉素/泼尼松龙、酮咯酸/苯福林、苯海拉明、茶苯海明、双环维林、黄酮哌酯、奥昔布宁、噻托溴铵、莨菪碱、scopolomine(L-莨菪碱)、羟嗪、异丙托铵、哌仑西平、索利那新、达非那新、苯扎托品、美贝维林、丙环定、阿地溴铵、三己芬迪/苯海索或托特罗定。

[0093] 如本文所述,所述眼用剂包括光学纯的立体异构体、光学富集的立体异构体和立体异构体的外消旋混合物。例如,本文公开的一些眼用组合物包含D-和L-异构体的外消旋

混合物;并且本文公开的一些眼用组合物包括为有利于眼科活性L-异构体而光学富集的。

水溶液稳定性

[0094] 在一些实施方案中,本文所述的组合物包含缓冲液。在一些实施方案中,缓冲液选自硼酸盐、硼酸盐-多元醇复合物、磷酸盐缓冲剂、柠檬酸盐缓冲剂、乙酸盐缓冲剂、碳酸盐缓冲剂、有机缓冲剂、氨基酸缓冲剂或其组合。在一些实施方案中,本文所述的组合物包含含有氘化水的缓冲液。在一些实施方案中,氘化缓冲液选自在氘化水中配制的硼酸盐、硼酸盐-多元醇复合物、磷酸盐缓冲剂、柠檬酸盐缓冲剂、乙酸盐缓冲剂、碳酸盐缓冲剂、有机缓冲剂、氨基酸缓冲剂或其组合。

[0095] 在一些情况下,硼酸盐包括硼酸、硼酸的盐、其他药学上可接受的硼酸盐及其组合。在一些情况下,硼酸盐包括硼酸、硼酸钠、硼酸钾、硼酸钙、硼酸镁、硼酸锰以及其他这样的硼酸盐。

[0096] 如本文所用的,术语多元醇包括在相对于彼此不呈反式构型的两个相邻碳原子的每一个上具有至少一个羟基的任何化合物。在一些情况下,多元醇是链状或环状、取代或未取代的,或其混合物,只要所得复合物是水溶性的并且是药学上可接受的即可。在一些情况下,多元醇的实例包括:糖、糖醇、糖酸和糖醛酸。在一些情况下,多元醇包括但不限于:甘露醇、甘油、木糖醇和山梨醇。

[0097] 在一些实施方案中,磷酸盐缓冲剂包括磷酸;碱金属磷酸盐,诸如磷酸氢二钠、磷酸二氢钠、磷酸三钠、磷酸氢二钾、磷酸二氢钾和磷酸三钾;碱土金属磷酸盐,诸如磷酸钙、磷酸氢钙、磷酸二氢钙、磷酸二氢镁、磷酸二镁(磷酸氢镁)和磷酸三镁;磷酸铵,诸如磷酸氢二铵和磷酸二氢铵;或其组合。在一些情况下,磷酸盐缓冲剂为酸酐。在一些情况下,磷酸盐缓冲剂为水合物。

[0098] 在一些实施方案中,硼酸盐-多元醇复合物包括在美国专利号6,503,497中描述的那些。在一些情况下,硼酸盐-多元醇复合物包含约0.01%w/v至约2.0%w/v的量的硼酸盐以及约0.01%w/v至约5.0%w/v的量的一种或多种多元醇。

[0099] 在一些情况下,柠檬酸盐缓冲剂包括柠檬酸和柠檬酸钠。

[0100] 在一些情况下,乙酸盐缓冲剂包括乙酸、乙酸钾和乙酸钠。

[0101] 在一些情况下,碳酸盐缓冲剂包括碳酸氢钠和碳酸钠。

[0102] 在一些情况下,有机缓冲剂包括Good缓冲液,诸如2-(N-吗啉基)乙磺酸(MES)、N-(2-乙酰胺基)亚氨基二乙酸、N-(氨基甲酰基甲基)亚氨基二乙酸(ADA)、哌嗪-N,N'-双(2-乙磺酸)(PIPES)、N-(2-乙酰胺基)-2-氨基乙磺酸(ACES)、β-羟基-4-吗啉丙磺酸、3-吗啉基-2-羟基丙磺酸(MOPSO)、胆胺氯化物、3-(N-吗啉基)丙磺酸(MOPS)、N,N-双(2-羟乙基)-2-氨基乙磺酸(BES)、2-[(2-羟基-1,1-双(羟甲基)乙基)氨基]乙磺酸(TES)、4-(2-羟乙基)-1-哌嗪乙磺酸(HEPES)、3-(N,N-双[2-羟乙基]氨基)-2-羟基丙磺酸(DIPSO)、乙酰胺基甘氨酸、3-{[1,3-二羟基-2-(羟甲基)-2-丙基]氨基}-2-羟基-1-丙磺酸(TAPSO)、哌嗪-1,4-双(2-羟基丙磺酸)(POPSO)、4-(2-羟乙基)哌嗪-1-(2-羟基丙磺酸)水合物(HEPPSO)、3-[4-(2-羟乙基)-1-哌嗪基]丙磺酸(HEPPS)、N-三(羟甲基)甲基甘氨酸(tricine)、甘氨酰胺、N,N-二羟乙基甘氨酸(bicine)或N-三(羟甲基)甲基-3-氨基丙磺酸钠(TAPS);甘氨酸;以及二乙醇胺(DEA)。

[0103] 在一些情况下,氨基酸缓冲剂包括牛磺酸、天冬氨酸及其盐(例如钾盐等)、E-氨基

己酸等。

[0104] 在一些情况下，本文所述的组合物进一步包含张力调节剂。张力调节剂是引入到诸如眼用组合物的制剂中以通过在施加部位处阻止渗透休克来减少局部刺激的试剂。在一些情况下，将眼用溶液宽泛地维持在特定离子浓度和pD下的缓冲溶液和/或pD调节剂被视为张力调节剂。在一些情况下，张力调节剂包括各种盐，诸如单价阳离子的卤盐。在一些情况下，张力调节剂包括甘露醇、山梨醇、右旋糖、蔗糖、尿素和甘油。在一些情况下，合适的张力调节剂包括氯化钠、硝酸钠、硫酸钠、硫酸氢钠、氯化钾、氯化钙、氯化镁、氯化锌、乙酸钾、乙酸钠、碳酸氢钠、碳酸钠、硫代硫酸钠、硫酸镁、磷酸氢二钠、磷酸二氢钠、磷酸二氢钾、右旋糖、甘露醇、山梨醇、葡萄糖、蔗糖、尿素、丙二醇、甘油或其组合。

[0105] 在一些情况下，本文所述的组合物中张力调节剂的浓度为约0.5％至约2.0％。在一些情况下，本文所述的组合物中张力调节剂的浓度为约0.7％至约1.8％、约0.8％至约1.5％，或约1％至约1.3％。在一些情况下，张力调节剂的浓度为约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％或1.9％。在一些情况下，所述百分比为重量百分比。

[0106] 在一些情况下，本文所述的组合物进一步包含pD调节剂。在一些实施方案中，所用的pD调节剂为酸或碱。在一些实施方案中，该碱为氧化物、氢氧化物、碳酸盐、碳酸氢盐等。在一些情况下，该氧化物为金属氧化物，如氧化钙、氧化镁等；氢氧化物为碱金属和碱土金属的氢氧化物，如氢氧化钠、氢氧化钾、氢氧化钙等或它们的氘化等效物，而碳酸盐为碳酸钠、碳酸氢钠、碳酸氢钾等。在一些情况下，该酸为无机酸和有机酸，如盐酸、硝酸、磷酸、乙酸、柠檬酸、富马酸、苹果酸、酒石酸等或它们的氘化等效物。在一些情况下，该pD调节剂包括但不限于乙酸盐、碳酸氢盐、氯化铵、柠檬酸盐、磷酸盐、其药学上可接受的盐及其组合或混合物。在一些实施方案中，该pD调节剂包括DCl和NaOD。

[0107] 在一些情况下，所述组合物具有约3至约9、约4至约8、约4.5至约7.8、约5至约7.5或约5.5至约7的pD。在一些实施方案中，该组合物具有小于约8的pD。在一些实施方案中，该组合物具有小于约7.9的pD。在一些实施方案中，该组合物具有小于约7.8的pD。在一些实施方案中，该组合物具有小于约7.7的pD。在一些实施方案中，该组合物具有小于约7.6的pD。在一些实施方案中，该组合物具有小于约7.5的pD。在一些实施方案中，该组合物具有小于约7.4的pD。在一些实施方案中，该组合物具有小于约7.3的pD。在一些实施方案中，该组合物具有小于约7.2的pD。在一些实施方案中，该组合物具有小于约7.1的pD。在一些实施方案中，该组合物具有小于约7的pD。在一些实施方案中，该组合物具有小于约6.9的pD。在一些实施方案中，该组合物具有小于约6.8的pD。在一些实施方案中，该组合物具有小于约6.7的pD。在一些实施方案中，该组合物具有小于约6.6的pD。在一些实施方案中，该组合物具有小于约6.5的pD。在一些实施方案中，该组合物具有小于约6.4的pD。在一些实施方案中，该组合物具有小于约6.3的pD。在一些实施方案中，该组合物具有小于约6.2的pD。在一些实施方案中，该组合物具有小于约6.1的pD。在一些实施方案中，该组合物具有小于约6的pD。在一些实施方案中，该组合物具有小于约5.9的pD。在一些实施方案中，该组合物具有小于约5.8的pD。在一些实施方案中，该组合物具有小于约5.7的pD。在一些实施方案中，该组合物具有小于约5.6的pD。在一些实施方案中，该组合物具有小于约5.5的pD。在一些实施方案中，该组合物具有小于约5.4的pD。在一些实施方案中，该组合物具有小于约5.3的pD。在一些实施

方案中，该组合物具有小于约5.2的pD。在一些实施方案中，该组合物具有小于约5.1的pD。在一些实施方案中，该组合物具有小于约5的pD。在一些实施方案中，该组合物具有小于约4.9的pD。在一些实施方案中，该组合物具有小于约4.8的pD。在一些实施方案中，该组合物具有小于约4.7的pD。在一些实施方案中，该组合物具有小于约4.6的pD。在一些实施方案中，该组合物具有小于约4.5的pD。在一些实施方案中，该组合物具有小于约4.4的pD。在一些实施方案中，该组合物具有小于约4.3的pD。在一些实施方案中，该组合物具有小于约4.2的pD。在一些实施方案中，该组合物具有小于约4.1的pD。在一些实施方案中，该组合物具有小于约4的pD。在一些实施方案中，该组合物具有小于约3.9的pD。在一些实施方案中，该组合物具有小于约3.8的pD。在一些实施方案中，该组合物具有小于约3.7的pD。在一些实施方案中，该组合物具有小于约3.6的pD。在一些实施方案中，该组合物具有小于约3.5的pD。在一些实施方案中，该pD为在储存条件下在延长的时间段后所述组合物的pD。

[0108] 在一些情况下，所述组合物具有约3至约9、约4至约8、约4.5至约7.8、约5至约7.5或约5.5至约7的初始pD。在一些实施方案中，该组合物具有约8的初始pD。在一些实施方案中，该组合物具有约7.9的初始pD。在一些实施方案中，该组合物具有约7.8的初始pD。在一些实施方案中，该组合物具有约7.7的初始pD。在一些实施方案中，该组合物具有约7.6的初始pD。在一些实施方案中，该组合物具有约7.5的初始pD。在一些实施方案中，该组合物具有约7.4的初始pD。在一些实施方案中，该组合物具有约7.3的初始pD。在一些实施方案中，该组合物具有约7.2的初始pD。在一些实施方案中，该组合物具有约7.1的初始pD。在一些实施方案中，该组合物具有约7的初始pD。在一些实施方案中，该组合物具有约6.9的初始pD。在一些实施方案中，该组合物具有约6.8的初始pD。在一些实施方案中，该组合物具有约6.7的初始pD。在一些实施方案中，该组合物具有约6.6的初始pD。在一些实施方案中，该组合物具有约6.5的初始pD。在一些实施方案中，该组合物具有约6.4的初始pD。在一些实施方案中，该组合物具有约6.3的初始pD。在一些实施方案中，该组合物具有约6.2的初始pD。在一些实施方案中，该组合物具有约6.1的初始pD。在一些实施方案中，该组合物具有约6的初始pD。在一些实施方案中，该组合物具有约5.9的初始pD。在一些实施方案中，该组合物具有约5.8的初始pD。在一些实施方案中，该组合物具有约5.7的初始pD。在一些实施方案中，该组合物具有约5.6的初始pD。在一些实施方案中，该组合物具有约5.5的初始pD。在一些实施方案中，该组合物具有约5.4的初始pD。在一些实施方案中，该组合物具有约5.3的初始pD。在一些实施方案中，该组合物具有约5.2的初始pD。在一些实施方案中，该组合物具有约5.1的初始pD。在一些实施方案中，该组合物具有约5的初始pD。在一些实施方案中，该组合物具有约4.9的初始pD。在一些实施方案中，该组合物具有约4.8的初始pD。在一些实施方案中，该组合物具有约4.7的初始pD。在一些实施方案中，该组合物具有约4.6的初始pD。在一些实施方案中，该组合物具有约4.5的初始pD。在一些实施方案中，该组合物具有约4.4的初始pD。在一些实施方案中，该组合物具有约4.3的初始pD。在一些实施方案中，该组合物具有约4.2的初始pD。在一些实施方案中，该组合物具有约4.1的初始pD。在一些实施方案中，该组合物具有约4的初始pD。在一些实施方案中，该组合物具有约3.9的初始pD。在一些实施方案中，该组合物具有约3.8的初始pD。在一些实施方案中，该组合物具有约3.7的初始pD。在一些实施方案中，该组合物具有约3.6的初始pD。在一些实施方案中，该组合物具有约3.5的初始pD。

[0109] 在一些实施方案中，本文所述的组合物的pD与该组合物的稳定性有关。在一些实

施方案中，稳定的组合物具有约3至约9、约4至约8、约4.5至约7.8、约5至约7.5或约5.5至约7的pD。在一些实施方案中，稳定的组合物具有小于约8的pD。在一些实施方案中，稳定的组合物具有小于约7.9的pD。在一些实施方案中，稳定的组合物具有小于约7.8的pD。在一些实施方案中，稳定的组合物具有小于约7.7的pD。在一些实施方案中，稳定的组合物具有小于约7.6的pD。在一些实施方案中，稳定的组合物具有小于约7.5的pD。在一些实施方案中，稳定的组合物具有小于约7.4的pD。在一些实施方案中，稳定的组合物具有小于约7.3的pD。在一些实施方案中，稳定的组合物具有小于约7.2的pD。在一些实施方案中，稳定的组合物具有小于约7.1的pD。在一些实施方案中，稳定的组合物具有小于约7的pD。在一些实施方案中，稳定的组合物具有小于约6.9的pD。在一些实施方案中，稳定的组合物具有小于约6.8的pD。在一些实施方案中，稳定的组合物具有小于约6.7的pD。在一些实施方案中，稳定的组合物具有小于约6.6的pD。在一些实施方案中，稳定的组合物具有小于约6.5的pD。在一些实施方案中，稳定的组合物具有小于约6.4的pD。在一些实施方案中，稳定的组合物具有小于约6.3的pD。在一些实施方案中，稳定的组合物具有小于约6.2的pD。在一些实施方案中，稳定的组合物具有小于约6.1的pD。在一些实施方案中，稳定的组合物具有小于约6的pD。在一些实施方案中，稳定的组合物具有小于约5.9的pD。在一些实施方案中，稳定的组合物具有小于约5.8的pD。在一些实施方案中，稳定的组合物具有小于约5.7的pD。在一些实施方案中，稳定的组合物具有小于约5.6的pD。在一些实施方案中，稳定的组合物具有小于约5.5的pD。在一些实施方案中，稳定的组合物具有小于约5.4的pD。在一些实施方案中，稳定的组合物具有小于约5.3的pD。在一些实施方案中，稳定的组合物具有小于约5.2的pD。在一些实施方案中，稳定的组合物具有小于约5.1的pD。在一些实施方案中，稳定的组合物具有小于约5的pD。在一些实施方案中，稳定的组合物具有小于约4.9的pD。在一些实施方案中，稳定的组合物具有小于约4.8的pD。在一些实施方案中，稳定的组合物具有小于约4.7的pD。在一些实施方案中，稳定的组合物具有小于约4.6的pD。在一些实施方案中，稳定的组合物具有小于约4.5的pD。在一些实施方案中，稳定的组合物具有小于约4.4的pD。在一些实施方案中，稳定的组合物具有小于约4.3的pD。在一些实施方案中，稳定的组合物具有小于约4.2的pD。在一些实施方案中，稳定的组合物具有小于约4.1的pD。在一些实施方案中，稳定的组合物具有小于约4的pD。在一些实施方案中，稳定的组合物具有小于约3.9的pD。在一些实施方案中，稳定的组合物具有小于约3.8的pD。在一些实施方案中，稳定的组合物具有小于约3.7的pD。在一些实施方案中，稳定的组合物具有小于约3.6的pD。在一些实施方案中，稳定的组合物具有小于约3.5的pD。

[0110] 如本文别处所述，在一些情况下，D_2O水性系统使眼用组合物稳定。在一些实施方案中，这是由于与等效H_2O水性系统中反应性种类(例如-OH)的浓度相比，D_2O水性系统中反应性种类(例如-OD)的浓度更低。在一些情况下，D_2O水性系统中反应性种类(例如-OD)的浓度比等效H_2O水性系统中反应性种类(例如-OH)的浓度低约三分之一。在一些情况下，这是由于D_2O的离解常数低于或小于H_2O。例如，$K_a(H_2O)$为$1x10^{-14}$，而$K_a(D_2O)$为$1x10^{-15}$。因此，D_2O是比H_2O更弱的酸。在一些情况下，碱催化水解导致存在来自眼用剂的降解物。在一些情况下，在引起降解物形成的反应性物质的浓度较低时，眼用溶液在D_2O水性系统中比在等效H_2O水性系统中更稳定。在一些实施方案中，相对于用H_2O配制的眼用组合物，用氘化水配制的眼用组合物允许更稳定的眼用组合物。

[0111] 在一些实施方案中，氘化水的存在改变了缓冲液的pKa。在一些实施方案中，氘化水的存在允许眼用组合物模拟更低pH的系统的稳定性。在一些情况下，眼用组合物的缓冲能力得以降低，从而允许pH的更快改变。在一些情况下，眼用组合物在施用于眼中时降低的缓冲能力允许该眼用组合物以比在H_2O中配制的眼用组合物更快的速率达到生理pH。在一些情况下，与用H_2O配制的眼用组合物相比，用氘化水配制的眼用组合物允许在眼中更少的眼泪产生或更少的泪反射。

[0112] 在一些情况下，本文所述的组合物进一步包含消毒剂。在一些情况下，消毒剂包括聚合双胍、聚合季铵化合物、亚氯酸盐、二双胍、亚氯酸盐化合物(例如亚氯酸钾、亚氯酸钠、亚氯酸钙、亚氯酸镁或其混合物)及其组合。

[0113] 在一些情况下，本文所述的组合物进一步包含防腐剂。在一些情况下，防腐剂以一定浓度添加至本文所述的组合物中，以防止引入至该组合物中的微生物的生长或破坏该微生物。在一些情况下，微生物是指细菌(例如奇异变形杆菌(Proteus mirabilis)、粘质沙雷氏菌(Serratia marcesens))、病毒(例如单纯疱疹病毒、带状疱疹病毒)、真菌(例如来自镰孢(Fusarium)属的真菌)、酵母(例如白色假丝酵母(Candida albicans))、寄生虫(例如疟原虫(Plasmodium spp.)、颚口线虫(Gnathostoma spp.))、原生动物(例如兰伯贾第虫(Giardia lamblia))、线虫(例如盘尾丝虫(Onchocercus volvulus))、蠕虫(例如犬恶丝虫(Dirofilaria immitis))和/或阿米巴(例如棘阿米巴属(Acanthameoba))。

[0114] 在一些情况下，防腐剂的浓度为约0.0001％至约1％、约0.001％至约0.8％、约0.004％至约0.5％、约0.008％至约0.1％以及约0.01％至约0.08％。在一些情况下，防腐剂的浓度为约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％或1.0％。

[0115] 在一些实施方案中，防腐剂选自苯扎氯铵、西曲铵、过硼酸钠、稳定化的氧基氯复合物、SofZia(Alcon)、聚季铵盐-1、氯丁醇、依地酸二钠和聚六亚甲基双胍。

[0116] 在一些实施方案中，本文所述的组合物储存在塑料容器中。在一些实施方案中，该塑料容器的材料包括高密度聚乙烯(HDPE)、低密度聚乙烯(LDPE)、聚对苯二甲酸乙二醇酯(PET)、聚氯乙烯(PVC)、聚丙烯(PP)、聚苯乙烯(PS)、氟处理的HDPE、消费后再生(post-consumer)树脂(PCR)、K-树脂(SBC)或生物塑料。在一些实施方案中，该塑料容器的材料包括LDPE。

[0117] 在一些实施方案中，本文所述的组合物储存在塑料容器中。在一些实施方案中，储存在塑料容器中的组合物具有约3至约9、约4至约8、约4.5至约7.9或约4.9至约7.5的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约8的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约7.9的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约7.8的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约7.7的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约7.6的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约7.5的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约7.4的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约7.3的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约7.2的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约7.1的pD。在一些实施方案中，储存在塑

料容器中的组合物具有小于约7的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约6.9的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约6.8的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约6.7的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约6.6的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约6.5的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约6.4的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约6.3的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约6.2的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约6.1的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约6的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约5.9的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约5.8的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约5.7的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约5.6的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约5.5的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约5.4的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约5.3的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约5.2的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约5.1的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约5的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约4.9的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约4.8的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约4.7的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约4.6的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约4.5的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约4.4的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约4.3的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约4.2的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约4.1的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约4的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约3.9的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约3.8的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约3.7的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约3.6的pD。在一些实施方案中，储存在塑料容器中的组合物具有小于约3.5的pD。

[0118] 在一些实施方案中，在储存条件下在延长的时间段后，储存在塑料容器中的组合物具有至少80％的效力。在一些实施方案中，在储存条件下在延长的时间段后，储存在塑料容器中的组合物具有至少85％的效力。在一些实施方案中，在储存条件下在延长的时间段后，储存在塑料容器中的组合物具有至少90％的效力。在一些实施方案中，在储存条件下在延长的时间段后，储存在塑料容器中的组合物具有至少93％的效力。在一些实施方案中，在储存条件下在延长的时间段后，储存在塑料容器中的组合物具有至少95％的效力。在一些实施方案中，在储存条件下在延长的时间段后，储存在塑料容器中的组合物具有至少97％的效力。在一些实施方案中，在储存条件下在延长的时间段后，储存在塑料容器中的组合物具有至少98％的效力。在一些实施方案中，在储存条件下在延长的时间段后，储存在塑料容器中的组合物具有至少99％的效力。在一些情况下，该储存条件包括约2℃、4℃、8℃、10℃、15℃、20℃、约25℃、约40℃或约60℃的温度。在一些情况下，该延长的时间段为至少1周、至

少2周、至少3周、至少1个月、至少2个月、至少3个月、至少4个月、至少5个月、至少6个月、至少8个月、至少10个月、至少12个月、至少18个月、至少24个月、至少36个月、至少3年、至少4年、至少5年或更长。

[0119] 在一些实施方案中，储存在塑料容器中的组合物在约25℃、约40℃或约60℃的温度下具有至少80％的效力。在一些实施方案中，储存在塑料容器中的组合物在约25℃、约40℃或约60℃的温度下具有至少85％的效力。在一些实施方案中，储存在塑料容器中的组合物在约25℃、约40℃或约60℃的温度下具有至少90％的效力。在一些实施方案中，储存在塑料容器中的组合物在约25℃、约40℃或约60℃的温度下具有至少93％的效力。在一些实施方案中，储存在塑料容器中的组合物在约25℃、约40℃或约60℃的温度下具有至少95％的效力。在一些实施方案中，储存在塑料容器中的组合物在约25℃、约40℃或约60℃的温度下具有至少97％的效力。在一些实施方案中，储存在塑料容器中的组合物在约25℃、约40℃或约60℃的温度下具有至少98％的效力。在一些实施方案中，储存在塑料容器中的组合物在约25℃、约40℃或约60℃的温度下具有至少99％的效力。

[0120] 在一些实施方案中，储存在塑料容器中的组合物在至少1周、至少2周、至少3周、至少1个月、至少2个月、至少3个月、至少4个月、至少5个月、至少6个月、至少8个月、至少10个月、至少12个月、至少18个月、至少24个月、至少36个月、至少3年、至少4年、至少5年或更长的时间段内具有至少80％的效力。在一些实施方案中，储存在塑料容器中的组合物在至少1周、至少2周、至少3周、至少1个月、至少2个月、至少3个月、至少4个月、至少5个月、至少6个月、至少8个月、至少10个月、至少12个月、至少18个月、至少24个月、至少36个月、至少3年、至少4年、至少5年或更长的时间段内具有至少85％的效力。在一些实施方案中，储存在塑料容器中的组合物在至少1周、至少2周、至少3周、至少1个月、至少2个月、至少3个月、至少4个月、至少5个月、至少6个月、至少8个月、至少10个月、至少12个月、至少18个月、至少24个月、至少36个月、至少3年、至少4年、至少5年或更长的时间段内具有至少90％的效力。在一些实施方案中，储存在塑料容器中的组合物在至少1周、至少2周、至少3周、至少1个月、至少2个月、至少3个月、至少4个月、至少5个月、至少6个月、至少8个月、至少10个月、至少12个月、至少18个月、至少24个月、至少36个月、至少3年、至少4年、至少5年或更长的时间段内具有至少93％的效力。在一些实施方案中，储存在塑料容器中的组合物在至少1周、至少2周、至少3周、至少1个月、至少2个月、至少3个月、至少4个月、至少5个月、至少6个月、至少8个月、至少10个月、至少12个月、至少18个月、至少24个月、至少36个月、至少3年、至少4年、至少5年或更长的时间段内具有至少95％的效力。在一些实施方案中，储存在塑料容器中的组合物在至少1周、至少2周、至少3周、至少1个月、至少2个月、至少3个月、至少4个月、至少5个月、至少6个月、至少8个月、至少10个月、至少12个月、至少18个月、至少24个月、至少36个月、至少3年、至少4年、至少5年或更长的时间段内具有至少97％的效力。在一些实施方案中，储存在塑料容器中的组合物在至少1周、至少2周、至少3周、至少1个月、至少2个月、至少3个月、至少4个月、至少5个月、至少6个月、至少8个月、至少10个月、至少12个月、至少18个月、至少24个月、至少36个月、至少3年、至少4年、至少5年或更长的时间段内具有至少98％的效力。在一些实施方案中，储存在塑料容器中的组合物在至少1周、至少2周、至少3周、至少1个月、至少2个月、至少3个月、至少4个月、至少5个月、至少6个月、至少8个月、至少10个月、至少12个月、至少18个月、至少24个月、至少36个月、至少3年、至少4年、至少5年或更长的时间段内具

有至少99%的效力。

[0121] 在一些实施方案中，在储存条件下在延长的时间段后，基于眼用剂的浓度，储存在塑料容器中的组合物包含少于20%的主要降解物。在一些实施方案中，在储存条件下在延长的时间段后，基于眼用剂的浓度，储存在塑料容器中的组合物包含少于15%的主要降解物。在一些实施方案中，在储存条件下在延长的时间段后，基于眼用剂的浓度，储存在塑料容器中的组合物包含少于10%的主要降解物。在一些实施方案中，在储存条件下在延长的时间段后，基于眼用剂的浓度，储存在塑料容器中的组合物包含少于5%的主要降解物。

[0122] 在一些实施方案中，在储存条件下在延长的时间段后，基于眼用剂的浓度，储存在塑料容器中的组合物包含少于2.5%的主要降解物到少于0.1%的主要降解物。在一些实施方案中，在储存条件下在延长的时间段后，基于眼用剂的浓度，储存在塑料容器中的组合物包含少于2.5%的主要降解物。在一些实施方案中，在储存条件下在延长的时间段后，基于眼用剂的浓度，储存在塑料容器中的组合物包含少于2.0%的主要降解物。在一些实施方案中，在储存条件下在延长的时间段后，基于眼用剂的浓度，储存在塑料容器中的组合物包含少于1.5%的主要降解物。在一些实施方案中，在储存条件下在延长的时间段后，基于眼用剂的浓度，储存在塑料容器中的组合物包含少于1.0%的主要降解物。在一些实施方案中，在储存条件下在延长的时间段后，基于眼用剂的浓度，储存在塑料容器中的组合物包含少于0.5%的主要降解物。在一些实施方案中，在储存条件下在延长的时间段后，基于眼用剂的浓度，储存在塑料容器中的组合物包含少于0.4%的主要降解物。在一些实施方案中，在储存条件下在延长的时间段后，基于眼用剂的浓度，储存在塑料容器中的组合物包含少于0.3%的主要降解物。在一些实施方案中，在储存条件下在延长的时间段后，基于眼用剂的浓度，储存在塑料容器中的组合物包含少于0.2%的主要降解物。在一些实施方案中，在储存条件下在延长的时间段后，基于眼用剂的浓度，储存在塑料容器中的组合物包含少于0.1%的主要降解物。在一些情况下，储存条件包含约25℃、约40℃或约60℃的温度。在一些情况下，所述延长的时间段为至少1周、至少2周、至少3周、至少1个月、至少2个月、至少3个月、至少4个月、至少5个月、至少6个月、至少8个月、至少10个月、至少12个月、至少18个月、至少24个月、至少36个月、至少3年、至少4年、至少5年或更长。

[0123] 在一些实施方案中，基于眼用剂的浓度，储存在塑料容器中的组合物在约25℃、约40℃或约60℃的温度下包含少于20%的主要降解物。在一些实施方案中，基于眼用剂的浓度，储存在塑料容器中的组合物在约25℃、约40℃或约60℃的温度下包含少于15%的主要降解物。在一些实施方案中，基于眼用剂的浓度，储存在塑料容器中的组合物在约25℃、约40℃或约60℃的温度下包含少于10%的主要降解物。在一些实施方案中，基于眼用剂的浓度，储存在塑料容器中的组合物在约25℃、约40℃或约60℃的温度下包含少于5%的主要降解物。

[0124] 在一些实施方案中，基于眼用剂的浓度，储存在塑料容器中的组合物在约25℃、约40℃或约60℃的温度下包含少于2.5%的主要降解物到少于0.1%的主要降解物。在一些实施方案中，基于眼用剂的浓度，储存在塑料容器中的组合物在约25℃、约40℃或约60℃的温度下包含少于2.5%的主要降解物。在一些实施方案中，基于眼用剂的浓度，储存在塑料容器中的组合物在约25℃、约40℃或约60℃的温度下包含少于2.0%的主要降解物。在一些实施方案中，基于眼用剂的浓度，储存在塑料容器中的组合物在约25℃、约40℃或约60℃的温

度下包含少于1.5%的主要降解物。在一些实施方案中，基于眼用剂的浓度，储存在塑料容器中的组合物在约25℃、约40℃或约60℃的温度下包含少于1.0%的主要降解物。在一些实施方案中，基于眼用剂的浓度，储存在塑料容器中的组合物在约25℃、约40℃或约60℃的温度下包含少于0.5%的主要降解物。在一些实施方案中，基于眼用剂的浓度，储存在塑料容器中的组合物在约25℃、约40℃或约60℃的温度下包含少于0.4%的主要降解物。在一些实施方案中，基于眼用剂的浓度，储存在塑料容器中的组合物在约25℃、约40℃或约60℃的温度下包含少于0.3%的主要降解物。在一些实施方案中，基于眼用剂的浓度，储存在塑料容器中的组合物在约25℃、约40℃或约60℃的温度下包含少于0.2%的主要降解物。在一些实施方案中，基于眼用剂的浓度，储存在塑料容器中的组合物在约25℃、约40℃或约60℃的温度下包含少于0.1%的主要降解物。

[0125] 在一些实施方案中，基于眼用剂的浓度，储存在塑料容器中的组合物在至少1周、至少2周、至少3周、至少1个月、至少2个月、至少3个月、至少4个月、至少5个月、至少6个月、至少8个月、至少10个月、至少12个月、至少18个月或至少24个月的时间段内包含少于20%的主要降解物。在一些实施方案中，基于眼用剂的浓度，储存在塑料容器中的组合物在至少1周、至少2周、至少3周、至少1个月、至少2个月、至少3个月、至少4个月、至少5个月、至少6个月、至少8个月、至少10个月、至少12个月、至少18个月或至少24个月的时间段内包含少于15%的主要降解物。在一些实施方案中，基于眼用剂的浓度，储存在塑料容器中的组合物在至少1周、至少2周、至少3周、至少1个月、至少2个月、至少3个月、至少4个月、至少5个月、至少6个月、至少8个月、至少10个月、至少12个月、至少18个月或至少24个月的时间段内包含少于10%的主要降解物。在一些实施方案中，基于眼用剂的浓度，储存在塑料容器中的组合物在至少1周、至少2周、至少3周、至少1个月、至少2个月、至少3个月、至少4个月、至少5个月、至少6个月、至少8个月、至少10个月、至少12个月、至少18个月或至少24个月的时间段内包含少于5%的主要降解物。

[0126] 在一些实施方案中，基于眼用剂的浓度，储存在塑料容器中的组合物在至少1周、至少2周、至少3周、至少1个月、至少2个月、至少3个月、至少4个月、至少5个月、至少6个月、至少8个月、至少10个月、至少12个月、至少18个月或至少24个月的时间段内包含少于2.5%的主要降解物到少于0.1%的主要降解物。在一些实施方案中，基于眼用剂的浓度，储存在塑料容器中的组合物在至少1周、至少2周、至少3周、至少1个月、至少2个月、至少3个月、至少4个月、至少5个月、至少6个月、至少8个月、至少10个月、至少12个月、至少18个月或至少24个月的时间段内包含少于2.5%的主要降解物。在一些实施方案中，基于眼用剂的浓度，储存在塑料容器中的组合物在至少1周、至少2周、至少3周、至少1个月、至少2个月、至少3个月、至少4个月、至少5个月、至少6个月、至少8个月、至少10个月、至少12个月、至少18个月或至少24个月的时间段内包含少于2.0%的主要降解物。在一些实施方案中，基于眼用剂的浓度，储存在塑料容器中的组合物在至少1周、至少2周、至少3周、至少1个月、至少2个月、至少3个月、至少4个月、至少5个月、至少6个月、至少8个月、至少10个月、至少12个月、至少18个月或至少24个月的时间段内包含少于1.5%的主要降解物。在一些实施方案中，基于眼用剂的浓度，储存在塑料容器中的组合物在至少1周、至少2周、至少3周、至少1个月、至少2个月、至少3个月、至少4个月、至少5个月、至少6个月、至少8个月、至少10个月、至少12个月、至少18个月或至少24个月的时间段内包含少于1.0%的主要降解物。在一些实施方案中，基于眼

用剂的浓度，储存在塑料容器中的组合物在至少1周、至少2周、至少3周、至少1个月、至少2个月、至少3个月、至少4个月、至少5个月、至少6个月、至少8个月、至少10个月、至少12个月、至少18个月或至少24个月的时间段内包含少于0.5％的主要降解物。在一些实施方案中，基于眼用剂的浓度，储存在塑料容器中的组合物在至少1周、至少2周、至少3周、至少1个月、至少2个月、至少3个月、至少4个月、至少5个月、至少6个月、至少8个月、至少10个月、至少12个月、至少18个月或至少24个月的时间段内包含少于0.4％的主要降解物。在一些实施方案中，基于眼用剂的浓度，储存在塑料容器中的组合物在至少1周、至少2周、至少3周、至少1个月、至少2个月、至少3个月、至少4个月、至少5个月、至少6个月、至少8个月、至少10个月、至少12个月、至少18个月或至少24个月的时间段内包含少于0.3％的主要降解物。在一些实施方案中，基于眼用剂的浓度，储存在塑料容器中的组合物在至少1周、至少2周、至少3周、至少1个月、至少2个月、至少3个月、至少4个月、至少5个月、至少6个月、至少8个月、至少10个月、至少12个月、至少18个月或至少24个月的时间段内包含少于0.2％的主要降解物。在一些实施方案中，基于眼用剂的浓度，储存在塑料容器中的组合物在至少1周、至少2周、至少3周、至少1个月、至少2个月、至少3个月、至少4个月、至少5个月、至少6个月、至少8个月、至少10个月、至少12个月、至少18个月或至少24个月的时间段内包含少于0.1％的主要降解物。

[0127] 在一些实施方案中，本文所述的组合物储存在玻璃容器中。在一些实施方案中，该玻璃容器为玻璃小瓶，诸如例如，I型、II型或III型玻璃小瓶。在一些实施方案中，该玻璃容器为I型玻璃小瓶。在一些实施方案中，该I型玻璃小瓶为硼硅酸盐玻璃小瓶。

[0128] 在一些实施方案中，储存在玻璃容器中的组合物具有高于约7的pD。在一些实施方案中，储存在玻璃容器中的组合物具有高于约7.5的pD。在一些实施方案中，储存在玻璃容器中的组合物具有高于约8的pD。在一些实施方案中，储存在玻璃容器中的组合物具有高于约8.5的pD。在一些实施方案中，储存在玻璃容器中的组合物具有高于约9的pD。

[0129] 在一些实施方案中，储存在玻璃容器中的组合物在约25℃、约40℃或约60℃的温度下具有低于60％的效力。在一些实施方案中，储存在玻璃容器中的组合物在至少1周、至少2周、至少3周、至少1个月、至少2个月、至少3个月、至少4个月、至少5个月、至少6个月、至少8个月、至少10个月、至少12个月、至少18个月、至少24个月、至少36个月、至少3年、至少4年、至少5年或更长的时间段内具有低于60％的效力。

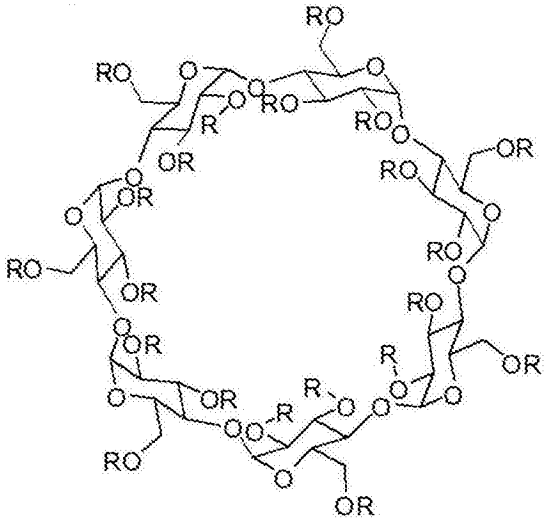
[0130] 在一些实施方案中，储存在玻璃容器中的组合物不如储存在塑料容器中的组合物稳定。

[0131] 在一些实施方案中，所述组合物储存在暗处。在一些情况下，所述组合物在光的存在下储存。在一些情况下，光为户内光、室内光或阳光。在一些情况下，所述组合物在光的存在下储存时稳定。

[0132] 在一些实施方案中，本文所述的组合物被配制成水溶液。在一些实施方案中，该水溶液为稳定水溶液。在一些情况下，该水溶液储存在如上所述的塑料容器中。在一些情况下，该水溶液不储存在玻璃容器中。在一些情况下，该水溶液储存在暗处。在一些情况下，该水溶液在光的存在下储存。在一些情况下，该水溶液在光的存在下稳定。

[0133] 在特定实施方案中，眼科上可接受的制剂备选地包含环糊精。环糊精是含有6、7或8个吡喃葡萄糖单元的环状寡糖，分别被称作α-环糊精、β-环糊精或γ-环糊精。环糊精具有增强水溶性的亲水外部和形成腔的疏水内部。在水性环境中，其他分子的疏水部分通常进

入环糊精的疏水腔以形成包合物。另外，环糊精还能够与不在疏水腔内部的分子发生其他类型的非键合相互作用。环糊精的每个吡喃葡萄糖单元具有三个游离羟基，或者在α-环糊精上具有18个羟基，在β-环糊精上具有21个羟基，而在γ-环糊精上具有24个羟基。在一些情况下，这些羟基中的一个或多个与许多试剂中的任一种反应以形成很多种环糊精衍生物，包括羟丙基醚、磺酸盐和磺基烷基醚。以下示出了β-环糊精和羟丙基-β-环糊精(HPβCD)的结构。



[0134] 在一些实施方案中，在本文所述的药物组合物中使用环糊精改善了药物的溶解性。包合物与增强溶解性的许多情况有关；然而，环瑚精与不溶性化合物之间的其他相互作用也改善了溶解性。羟丙基-β-环糊精(HPβCD)作为无热原产品可商购获得。其为易溶于水的不吸湿性白色粉末。HPβCD是热稳定的，并且在中性pH下不降解。因此，环糊精改善了治疗剂在组合物或制剂中的溶解性。因此，在一些实施方案中，包含环糊精以提高眼科上可接受的眼用剂在本文所述制剂内的溶解度。另外，在其他实施方案中，环糊精在本文所述的制剂内充当控制释放赋形剂。

[0135] 仅举例而言，使用的环糊精衍生物包括α-环糊精、β-环糊精、γ-环糊精、羟乙基-β-环糊精、羟丙基-γ-环糊精、硫酸化β-环糊精、硫酸化α-环糊精、磺丁基醚β-环糊精。

[0136] 在本文公开的组合物和方法中使用的环糊精的浓度根据生理化学性质、药代动力学性质、副作用或不良事件、制剂考虑因素或与治疗性眼用剂或其盐或前药或与组合物中其他赋形剂的性质有关的其他因素而变化。因此，在某些情况下，在根据本文公开的组合物和方法中使用的环糊精的浓度或量将根据需要而变化。在使用时，利用本文所述的原理、实例和教导来选择在本文所述的任何制剂中提高眼用剂的溶解度和/或起到控制释放赋形剂作用所需的环糊精的量。

[0137] 在本文公开的眼科上可接受的制剂中有用的其他稳定剂包括，例如，脂肪酸、脂肪醇、醇、长链脂肪酸酯、长链醚、脂肪酸的亲水性衍生物、聚乙烯吡咯烷酮、聚乙烯醚、聚乙烯醇、烃、疏水性聚合物、吸湿聚合物及其组合。在一些实施方案中，还使用稳定剂的酰胺类似物。在其他实施方案中，所选稳定剂改变制剂的疏水性，改善制剂中各种组分的混合，控制配方中的水分含量，或控制相的流动性。

[0138] 在其他实施方案中，稳定剂以足以抑制眼用剂降解的量存在。这样的稳定剂的实例包括但不限于：甘油、甲硫氨酸、硫代甘油、EDTA、抗坏血酸、聚山梨醇酯80、聚山梨醇酯

20、精氨酸、肝素、硫酸葡聚糖、环糊精、戊聚糖多硫酸酯和其他类肝素、二价阳离子如镁和锌或其组合。

[0139] 对于眼科上可接受的制剂有用的其他稳定剂包括一种或多种抗聚集添加剂，以通过降低蛋白质聚集率增强眼用制剂的稳定性。所选的抗聚集添加剂取决于眼用剂所暴露的病况的性质。例如，经历搅拌和热应力的某些制剂与经历冻干和重建的制剂需要不同的抗聚集添加剂。仅举例而言，有用的抗聚集添加剂包括尿素、胍氯化物、简单氨基酸(诸如甘氨酸或精氨酸)、糖、多元醇、聚山梨醇酯、聚合物(诸如聚乙二醇和葡聚糖)、烷基糖(诸如烷基糖苷)和表面活性剂。

[0140] 在需要的情况下，其他有用的制剂任选地包含一种或多种眼科上可接受的抗氧化剂以增强化学稳定性。仅举例而言，合适的抗氧化剂包括抗坏血酸、甲硫氨酸、硫代硫酸钠和焦亚硫酸钠。在一个实施方案中，抗氧化剂选自金属螯合剂、含硫醇的化合物和其他一般稳定剂。

[0141] 其他有用的组合物包含一种或多种眼科上可接受的表面活性剂以增强物理稳定性或用于其他目的。合适的非离子型表面活性剂包括但不限于聚氧乙烯脂肪酸甘油酯和植物油，例如聚氧乙烯(60)氢化蓖麻油；以及聚氧乙烯烷基醚和烷基苯基醚，例如，辛苯聚醇10、辛苯聚醇40。

[0142] 在一些实施方案中，本文所述的眼科上可接受的药物制剂在储存条件(例如室温)下在至少约1天、至少约2天、至少约3天、至少约4天、至少约5天、至少约6天、至少约1周、至少约2周、至少约3周、至少约4周、至少约5周、至少约6周、至少约7周、至少约8周、至少约3个月、至少约4个月、至少约5个月、至少约6个月、至少约12个月、至少约18个月、至少约24个月、至少约36个月、至少约3年、至少约4年、至少约5年或至少约10年中的任何时间段内在化合物降解方面稳定(例如少于30％降解、少于25％降解、少于20％降解、少于15％降解、少于10％降解、少于8％降解、少于5％降解、少于3％降解、少于2％降解或少于5％降解)。在其他实施方案中，本文所述的制剂在至少约1周的时间段内关于化合物降解稳定。本文还描述了在至少约1个月的时间段内关于化合物降解稳定的制剂。

[0143] 在其他实施方案中，额外的表面活性剂(共表面活性剂)和/或缓冲剂与本文之前所述的一种或多种药学上可接受的媒介物组合，以使该表面活性剂和/或缓冲剂将产品维持在关于稳定性的最佳pD。合适的共表面活性剂包括但不限于：a)天然和合成的亲脂剂，例如磷脂、胆固醇和胆固醇脂肪酸酯及其衍生物；b)非离子型表面活性剂，其包括例如聚氧乙烯脂肪醇酯、失水山梨醇脂肪酸酯(Span)、聚氧乙烯失水山梨醇脂肪酸酯(例如，聚氧乙烯(20)失水山梨醇单油酸酯(吐温80)、聚氧乙烯(20)失水山梨醇单硬脂酸酯(吐温60)、聚氧乙烯(20)失水山梨醇单月桂酸酯(吐温20)和其他吐温)、失水山梨醇酯、甘油酯(例如Myrj和三乙酸甘油酯(三醋精))、聚乙二醇、十六烷醇、十八十六醇(cetostearyl alcohol)、十八烷醇、聚山梨醇酯80、泊洛沙姆(poloxamer)、泊洛沙胺(poloxamine)、聚氧乙烯蓖麻油衍生物(例如Cremophor® RH40、Cremphor A25、Cremphor A20、Cremophor® EL)和其他Cremophor、磺基琥珀酸酯、烷基硫酸酯(SLS)；PEG甘油脂肪酸酯，诸如PEG-8甘油辛酸酯/癸酸酯(Labrasol)、PEG-4甘油辛酸酯/癸酸酯(Labrafac Hydro WL 1219)、PEG-32甘油月桂酸酯(Gelucire 444/14)、PEG-6甘油单油酸酯(Labrafil M 1944CS)、PEG-6甘油亚油酸酯(Labrafil M 2125CS)；丙二醇单脂肪酸酯和丙二醇二脂肪酸酯，诸如丙二醇月桂酸酯、丙

二醇辛酸酯/癸酸酯；Brij®700、抗坏血酸基-6-棕榈酸酯、十八胺、月桂基硫酸钠、聚氧乙烯甘油三蓖麻油酸酯及其任意组合或混合物；c)阴离子型表面活性剂，包括但不限于羧甲基纤维素钙、羧甲基纤维素钠、磺基琥珀酸钠、二辛基、海藻酸钠、烷基聚氧乙烯硫酸酯、月桂基硫酸钠、三乙醇胺硬脂酸酯、月桂酸钾、胆盐及其任意组合或混合物；以及d)阳离子型表面活性剂，诸如十六烷基三甲基溴化铵和十二烷基二甲基苄基-氯化铵。

[0144] 在又一个实施方案中，当一种或多种共表面活性剂在本发明的眼科上可接受的制剂中使用时，它们例如与药学上可接受的媒介物组合，并以例如在约0.1％至约20％、约0.5％至约10％范围内的量存在于最终制剂中。

[0145] 在一个实施方案中，所述表面活性剂具有0至20的HLB值。在其他实施方案中，所述表面活性剂具有0至3、4至6、7至9、8至18、13至15、10至18的HLB值。

pD

[0146] 在一些实施方案中，将本文所述的组合物的pD调节(例如，通过使用缓冲液和/或pD调节剂)至在约3至约9、约4至约8、约4.5至约7.5或约5至约7范围内的眼科相容pD。在一些实施方案中，该眼用组合物具有约5.0至约7.0的pD。在一些实施方案中，该眼用组合物具有约5.5至约7.0的pD。在一些实施方案中，该眼用组合物具有约6.0至约7.0的pD。

[0147] 在一些实施方案中，有用的制剂包含一种或多种pD调节剂或缓冲剂。合适的pD调节剂或缓冲液包括但不限于乙酸盐、碳酸氢盐、氯化铵、柠檬酸盐、磷酸盐、氘化形式的乙酸盐、碳酸氢盐、氯化铵、柠檬酸盐、磷酸盐、其药学上可接受的盐及其组合或混合物。在一些实施方案中，pD调节剂或缓冲液包括氘化盐酸(DCl)、氘化氢氧化钠(NaOD)、氘化乙酸(CD_3COOD)或氘化柠檬酸($C_6D_8O_7$)。

[0148] 在一个实施方案中，当一种或多种缓冲液在本发明的制剂中使用时，它们例如与药学上可接受的媒介物组合，并以例如在约0.1％至约20％、约0.5％至约10％范围内的量存在于最终制剂中。在本发明的某些实施方案中，凝胶制剂中包含的缓冲液的量为使得该凝胶制剂的pD不干扰身体的天然缓冲系统的量。

[0149] 在一个实施方案中，还使用稀释剂来稳定化合物，因为它们提供了更稳定的环境。在本领域中使用溶于缓冲溶液的盐(其也提供pD控制或维持)作为稀释剂，包括但不限于磷酸盐缓冲盐水溶液。

[0150] 在一些实施方案中，根据Glasoe等人，“Use of glass electrodes to measure acidities in deuterium oxide,”J.Physical Chem.64(1):188-190(1960)中公开的公式计算pD。在一些实施方案中，pD计算为pD＝pH*+0.4，其中pH*为在包含氘化水(例如D_2O)的溶液中配制的眼用组合物的测量或观察到的pH。

[0151] 在一些实施方案中，本文所述的眼用水性、凝胶或软膏组合物具有约3至约9、约4至约8、约4.5至约8、约4.9至约7.9、约5.4至约7.9、约5.9至约7.9、约6.4至约7.9或约7.4至约7.9的pD。在一些实施方案中，本文所述的眼用水性、凝胶或软膏组合物具有约4.5-7.5、约5.0至约7.5、约5.5至约7.5、约6.0至约7.5或约7.0至约7.5的pD。在一些实施方案中，本文所述的眼用水性、凝胶或软膏组合物具有约4.5-7.0、约5.0至约7.0、约5.5至约7.0、约6.0至约7.0或约6.5至约7.0的pD。在一些实施方案中，本文所述的眼用水性、凝胶或软膏组合物具有约4.9-7.4、约5.4至约7.4、约5.9至约7.4、约6.4至约7.4或约6.9至约7.4的pD。在一些实施方案中，本文所述的眼用水性、凝胶或软膏组合物具有约4.5-6.5、约5.0至约6.5、

约5.5至约6.5或约6.0至约6.5的pD。在一些实施方案中，本文所述的眼用水性、凝胶或软膏组合物具有约4.9-6.9、约5.4至约6.9、约5.9至约6.9或约6.4至约6.9的pD。在一些实施方案中，本文所述的眼用水性、凝胶或软膏组合物具有约4.5-6.0、约5.0至约6.0或约5.5至约6.0的pD。在一些实施方案中，本文所述的眼用水性、凝胶或软膏组合物具有约4.9-6.4、约5.4至约6.4或约5.9至约6.4的pD。在一些实施方案中，本文所述的眼用水性、凝胶或软膏组合物具有约4.5-5.5或约5.0至约5.5的pD。在一些实施方案中，本文所述的眼用水性、凝胶或软膏组合物具有约4.9-5.9或约5.4至约5.9的pD。在一些实施方案中，本文所述的眼用水性、凝胶或软膏组合物具有约4.5-5.0的pD。在一些实施方案中，本文所述的眼用水性、凝胶或软膏组合物具有约4.9-5.4的pD。

[0152] 在一些实施方案中，所述眼用组合物为眼用水性组合物。在一些情况下，该眼用水性组合物具有约3至约9、约4至约8、约4.5至约7.8、约5至约7.5或约5.5至约7的pD。在一些实施方案中，该眼用水性组合物具有约8的pD。在一些实施方案中，该眼用水性组合物具有约7.9的pD。在一些实施方案中，该眼用水性组合物具有约7.8的pD。在一些实施方案中，该眼用水性组合物具有约7.7的pD。在一些实施方案中，该眼用水性组合物具有约7.6的pD。在一些实施方案中，该眼用水性组合物具有约7.5的pD。在一些实施方案中，该眼用水性组合物具有约7.4的pD。在一些实施方案中，该眼用水性组合物具有约7.3的pD。在一些实施方案中，该眼用水性组合物具有约7.2的pD。在一些实施方案中，该眼用水性组合物具有约7.1的pD。在一些实施方案中，该眼用水性组合物具有约7的pD。在一些实施方案中，该眼用水性组合物具有约6.9的pD。在一些实施方案中，该眼用水性组合物具有约6.8的pD。在一些实施方案中，该眼用水性组合物具有约6.7的pD。在一些实施方案中，该眼用水性组合物具有约6.6的pD。在一些实施方案中，该眼用水性组合物具有约6.5的pD。在一些实施方案中，该眼用水性组合物具有约6.4的pD。在一些实施方案中，该眼用水性组合物具有约6.3的pD。在一些实施方案中，该眼用水性组合物具有约6.2的pD。在一些实施方案中，该眼用水性组合物具有约6.1的pD。在一些实施方案中，该眼用水性组合物具有约6的pD。在一些实施方案中，该眼用水性组合物具有约5.9的pD。在一些实施方案中，该眼用水性组合物具有约5.8的pD。在一些实施方案中，该眼用水性组合物具有约5.7的pD。在一些实施方案中，该眼用水性组合物具有约5.6的pD。在一些实施方案中，该眼用水性组合物具有约5.5的pD。在一些实施方案中，该眼用水性组合物具有约5.4的pD。在一些实施方案中，该眼用水性组合物具有约5.3的pD。在一些实施方案中，该眼用水性组合物具有约5.2的pD。在一些实施方案中，该眼用水性组合物具有约5.1的pD。在一些实施方案中，该眼用水性组合物具有约5的pD。在一些实施方案中，该眼用水性组合物具有约4.9的pD。在一些实施方案中，该眼用水性组合物具有约4.8的pD。在一些实施方案中，该眼用水性组合物具有约4.7的pD。在一些实施方案中，该眼用水性组合物具有约4.6的pD。在一些实施方案中，该眼用水性组合物具有约4.5的pD。在一些实施方案中，该眼用水性组合物具有约4.4的pD。在一些实施方案中，该眼用水性组合物具有约4.3的pD。在一些实施方案中，该眼用水性组合物具有约4.2的pD。在一些实施方案中，该眼用水性组合物具有约4.1的pD。在一些实施方案中，该眼用水性组合物具有约4的pD。在一些实施方案中，该眼用水性组合物具有约3.9的pD。在一些实施方案中，该眼用水性组合物具有约3.8的pD。在一些实施方案中，该眼用水性组合物具有约3.7的pD。在一些实施方案中，该眼用水性组合物具有约3.6的pD。在一些实施方案中，该眼用水性组合物具有约3.5的

pD。在一些实施方案中，该pD为该眼用水性组合物的初始pD。在一些实施方案中，该pD为在储存条件下在延长的时间段后该眼用水性组合物的pD。

[0153] 在一些情况下，所述眼用水性组合物具有约3至约9、约4至约8、约4.5至约7.8、约5至约7.5或约5.5至约7的初始pD。在一些实施方案中，该眼用水性组合物具有约8的初始pD。在一些实施方案中，该眼用水性组合物具有约7.9的初始pD。在一些实施方案中，该眼用水性组合物具有约7.8的初始pD。在一些实施方案中，该眼用水性组合物具有约7.7的初始pD。在一些实施方案中，该眼用水性组合物具有约7.6的初始pD。在一些实施方案中，该眼用水性组合物具有约7.5的初始pD。在一些实施方案中，该眼用水性组合物具有约7.4的初始pD。在一些实施方案中，该眼用水性组合物具有约7.3的初始pD。在一些实施方案中，该眼用水性组合物具有约7.2的初始pD。在一些实施方案中，该眼用水性组合物具有约7.1的初始pD。在一些实施方案中，该眼用水性组合物具有约7的初始pD。在一些实施方案中，该眼用水性组合物具有约6.9的初始pD。在一些实施方案中，该眼用水性组合物具有约6.8的初始pD。在一些实施方案中，该眼用水性组合物具有约6.7的初始pD。在一些实施方案中，该眼用水性组合物具有约6.6的初始pD。在一些实施方案中，该眼用水性组合物具有约6.5的初始pD。在一些实施方案中，该眼用水性组合物具有约6.4的初始pD。在一些实施方案中，该眼用水性组合物具有约6.3的初始pD。在一些实施方案中，该眼用水性组合物具有约6.2的初始pD。在一些实施方案中，该眼用水性组合物具有约6.1的初始pD。在一些实施方案中，该眼用水性组合物具有约6的初始pD。在一些实施方案中，该眼用水性组合物具有约5.9的初始pD。在一些实施方案中，该眼用水性组合物具有约5.8的初始pD。在一些实施方案中，该眼用水性组合物具有约5.7的初始pD。在一些实施方案中，该眼用水性组合物具有约5.6的初始pD。在一些实施方案中，该眼用水性组合物具有约5.5的初始pD。在一些实施方案中，该眼用水性组合物具有约5.4的初始pD。在一些实施方案中，该眼用水性组合物具有约5.3的初始pD。在一些实施方案中，该眼用水性组合物具有约5.2的初始pD。在一些实施方案中，该眼用水性组合物具有约5.1的初始pD。在一些实施方案中，该眼用水性组合物具有约5的初始pD。在一些实施方案中，该眼用水性组合物具有约4.9的初始pD。在一些实施方案中，该眼用水性组合物具有约4.8的初始pD。在一些实施方案中，该眼用水性组合物具有约4.7的初始pD。在一些实施方案中，该眼用水性组合物具有约4.6的初始pD。在一些实施方案中，该眼用水性组合物具有约4.5的初始pD。在一些实施方案中，该眼用水性组合物具有约4.4的初始pD。在一些实施方案中，该眼用水性组合物具有约4.3的初始pD。在一些实施方案中，该眼用水性组合物具有约4.2的初始pD。在一些实施方案中，该眼用水性组合物具有约4.1的初始pD。在一些实施方案中，该眼用水性组合物具有约4的初始pD。在一些实施方案中，该眼用水性组合物具有约3.9的初始pD。在一些实施方案中，该眼用水性组合物具有约3.8的初始pD。在一些实施方案中，该眼用水性组合物具有约3.7的初始pD。在一些实施方案中，该眼用水性组合物具有约3.6的初始pD。在一些实施方案中，该眼用水性组合物具有约3.5的初始pD。

[0154] 在一些情况下，所述眼用水性组合物具有约3至约9、约4至约8、约4.5至约7.8、约5至约7.5或约5.5至约7的pD。在一些实施方案中，该眼用水性组合物具有小于约8的pD。在一些实施方案中，该眼用水性组合物具有小于约7.9的pD。在一些实施方案中，该眼用水性组合物具有小于约7.8的pD。在一些实施方案中，该眼用水性组合物具有小于约7.7的pD。在一些实施方案中，该眼用水性组合物具有小于约7.6的pD。在一些实施方案中，该眼用水性组

合物具有小于约7.5的pD。在一些实施方案中，该眼用水性组合物具有小于约7.4的pD。在一些实施方案中，该眼用水性组合物具有小于约7.3的pD。在一些实施方案中，该眼用水性组合物具有小于约7.2的pD。在一些实施方案中，该眼用水性组合物具有小于约7.1的pD。在一些实施方案中，该眼用水性组合物具有小于约7的pD。在一些实施方案中，该眼用水性组合物具有小于约6.9的pD。在一些实施方案中，该眼用水性组合物具有小于约6.8的pD。在一些实施方案中，该眼用水性组合物具有小于约6.7的pD。在一些实施方案中，该眼用水性组合物具有小于约6.6的pD。在一些实施方案中，该眼用水性组合物具有小于约6.5的pD。在一些实施方案中，该眼用水性组合物具有小于约6.4的pD。在一些实施方案中，该眼用水性组合物具有小于约6.3的pD。在一些实施方案中，该眼用水性组合物具有小于约6.2的pD。在一些实施方案中，该眼用水性组合物具有小于约6.1的pD。在一些实施方案中，该眼用水性组合物具有小于约6的pD。在一些实施方案中，该眼用水性组合物具有小于约5.9的pD。在一些实施方案中，该眼用水性组合物具有小于约5.8的pD。在一些实施方案中，该眼用水性组合物具有小于约5.7的pD。在一些实施方案中，该眼用水性组合物具有小于约5.6的pD。在一些实施方案中，该眼用水性组合物具有小于约5.5的pD。在一些实施方案中，该眼用水性组合物具有小于约5.4的pD。在一些实施方案中，该眼用水性组合物具有小于约5.3的pD。在一些实施方案中，该眼用水性组合物具有小于约5.2的pD。在一些实施方案中，该眼用水性组合物具有小于约5.1的pD。在一些实施方案中，该眼用水性组合物具有小于约5的pD。在一些实施方案中，该眼用水性组合物具有小于约4.9的pD。在一些实施方案中，该眼用水性组合物具有小于约4.8的pD。在一些实施方案中，该眼用水性组合物具有小于约4.7的pD。在一些实施方案中，该眼用水性组合物具有小于约4.6的pD。在一些实施方案中，该眼用水性组合物具有小于约4.5的pD。在一些实施方案中，该眼用水性组合物具有小于约4.4的pD。在一些实施方案中，该眼用水性组合物具有小于约4.3的pD。在一些实施方案中，该眼用水性组合物具有小于约4.2的pD。在一些实施方案中，该眼用水性组合物具有小于约4.1的pD。在一些实施方案中，该眼用水性组合物具有小于约4的pD。在一些实施方案中，该眼用水性组合物具有小于约3.9的pD。在一些实施方案中，该眼用水性组合物具有小于约3.8的pD。在一些实施方案中，该眼用水性组合物具有小于约3.7的pD。在一些实施方案中，该眼用水性组合物具有小于约3.6的pD。在一些实施方案中，该眼用水性组合物具有小于约3.5的pD。在一些实施方案中，该pD为在储存条件下在延长的时间段后该眼用水性组合物的pD。

[0155] 在一些实施方案中，本文描述的眼用水性组合物的pD与该眼用水性组合物的稳定性相关。在一些实施方案中，稳定的组合物具有约3至约9、约4至约8、约4.5至约7.8、约5至约7.5或约5.5至约7的pD。在一些实施方案中，稳定的组合物具有小于约8的pD。在一些实施方案中，稳定的组合物具有小于约7.9的pD。在一些实施方案中，稳定的组合物具有小于约7.8的pD。在一些实施方案中，稳定的组合物具有小于约7.7的pD。在一些实施方案中，稳定的组合物具有小于约7.6的pD。在一些实施方案中，稳定的组合物具有小于约7.5的pD。在一些实施方案中，稳定的组合物具有小于约7.4的pD。在一些实施方案中，稳定的组合物具有小于约7.3的pD。在一些实施方案中，稳定的组合物具有小于约7.2的pD。在一些实施方案中，稳定的组合物具有小于约7.1的pD。在一些实施方案中，稳定的组合物具有小于约7的pD。在一些实施方案中，稳定的组合物具有小于约6.9的pD。在一些实施方案中，稳定的组合物具有小于约6.8的pD。在一些实施方案中，稳定的组合物具有小于约6.7的pD。在一些实施

方案中，稳定的组合物具有小于约6.6的pD。在一些实施方案中，稳定的组合物具有小于约6.5的pD。在一些实施方案中，稳定的组合物具有小于约6.4的pD。在一些实施方案中，稳定的组合物具有小于约6.3的pD。在一些实施方案中，稳定的组合物具有小于约6.2的pD。在一些实施方案中，稳定的组合物具有小于约6.1的pD。在一些实施方案中，稳定的组合物具有小于约6的pD。在一些实施方案中，稳定的组合物具有小于约5.9的pD。在一些实施方案中，稳定的组合物具有小于约5.8的pD。在一些实施方案中，稳定的组合物具有小于约5.7的pD。在一些实施方案中，稳定的组合物具有小于约5.6的pD。在一些实施方案中，稳定的组合物具有小于约5.5的pD。在一些实施方案中，稳定的组合物具有小于约5.4的pD。在一些实施方案中，稳定的组合物具有小于约5.3的pD。在一些实施方案中，稳定的组合物具有小于约5.2的pD。在一些实施方案中，稳定的组合物具有小于约5.1的pD。在一些实施方案中，稳定的组合物具有小于约5的pD。在一些实施方案中，稳定的组合物具有小于约4.9的pD。在一些实施方案中，稳定的组合物具有小于约4.8的pD。在一些实施方案中，稳定的组合物具有小于约4.7的pD。在一些实施方案中，稳定的组合物具有小于约4.6的pD。在一些实施方案中，稳定的组合物具有小于约4.5的pD。在一些实施方案中，稳定的组合物具有小于约4.4的pD。在一些实施方案中，稳定的组合物具有小于约4.3的pD。在一些实施方案中，稳定的组合物具有小于约4.2的pD。在一些实施方案中，稳定的组合物具有小于约4.1的pD。在一些实施方案中，稳定的组合物具有小于约4的pD。在一些实施方案中，稳定的组合物具有小于约3.9的pD。在一些实施方案中，稳定的组合物具有小于约3.8的pD。在一些实施方案中，稳定的组合物具有小于约3.7的pD。在一些实施方案中，稳定的组合物具有小于约3.6的pD。在一些实施方案中，稳定的组合物具有小于约3.5的pD。

[0156] 在一些实施方案中，D_2O水性系统使眼用剂稳定。在一些实施方案中，这是由于与等效H_2O水性系统中反应性种类(例如-OH)的浓度相比，D_2O水性系统中反应性种类(例如-OD)的浓度更低。在一些情况下，D_2O水性系统中反应性种类(例如-OD)的浓度比等效H_2O水性系统中反应性种类(例如-OH)的浓度低约三分之一。在一些情况下，这是由于D_2O的离解常数比H_2O更低或更小。例如，$K_a(H_2O)$为$1x10^{-14}$，而$K_a(D_2O)$为$1x10^{-15}$。因此，D_2O是比H_2O更弱的酸。在一些情况下，碱催化导致存在来自眼用剂的降解物。在一些情况下，在引起降解物形成的反应性物质的浓度较低时，眼用溶液在D_2O水性系统中比在等效H_2O水性系统中更稳定。在一些实施方案中，相对于用H_2O配制的眼用组合物，用氘化水配制的眼用组合物允许更稳定的眼用组合物。

[0157] 在一些实施方案中，氘化水的存在改变了缓冲液的pKa。在一些实施方案中，氘化水的存在允许眼用组合物模拟更低pH的系统的稳定性。在一些情况下，眼用组合物的缓冲能力得以降低，从而允许pH的更快改变。在一些情况下，眼用组合物在施用于眼中时降低的缓冲能力允许该眼用组合物以比在H_2O中配制的眼用组合物更快的速率达到生理pH。在一些情况下，与用H_2O配制的眼用组合物相比，用氘化水配制的眼用组合物允许在眼中更少的眼泪产生或更少的泪反射。

[0158] 在一些实施方案中，本文所述的眼用凝胶或软膏组合物具有约3.5、约3.6、约3.7、约3.8、约3.9、约4、约4.1、约4.2、约4.3、约4.4、约4.5、约4.6、约4.7、约4.8、约4.9、约5.0、约5.1、约5.2、约5.3、约5.4、约5.5、约5.6、约5.7、约5.8、约5.9、约6.0、约6.1、约6.2、约6.3、约6.4、约6.5、约6.6、约6.7、约6.8、约6.9、约7.0、约7.1、约7.2、约7.3、约7.4、约7.5、

约7.6、约7.7、约7.8或约7.9的pD。

[0159] 在一些实施方案中，本文所述的眼用水性、凝胶或软膏组合物的pD适于本文所述的眼用制剂的灭菌(例如，通过过滤或无菌混合或热处理和/或高压灭菌(例如，最终灭菌))。如在本公开内容中所用的，术语“水性组合物”包括基于D_2O的组合物。

[0160] 在一些实施方案中，本文所述的药物制剂在以下任一时间段内就pD而言是稳定的：至少约1天、至少约2天、至少约3天、至少约4天、至少约5天、至少约6天、至少约1周、至少约2周、至少约3周、至少约4周、至少约5周、至少约6周、至少约7周、至少约8周、至少约1个月、至少约2个月、至少约3个月、至少约4个月、至少约5个月、至少约6个月、至少约7个月、至少约8个月、至少约9个月、至少约10个月、至少约11个月、至少约12个月、至少约18个月、至少约24个月、至少约3年、至少约4年、至少约5年、至少约6年、至少约7年、至少约8年、至少约9年、至少约10年、至少约15年、至少约20年、至少约30年或更长的时间段。在其他实施方案中，本文所述的制剂在至少约1周的时间段内就pD而言是稳定的。在其他实施方案中，本文所述的制剂在至少约2周的时间段内就pD而言是稳定的。在其他实施方案中，本文所述的制剂在至少约3周的时间段内就pD而言是稳定的。在其他实施方案中，本文所述的制剂在至少约1个月的时间段内就pD而言是稳定的。本文还描述了在以下时间段内就pD而言稳定的制剂：至少约2个月、至少约3个月、至少约4个月、至少约5个月、至少约6个月、至少约12个月、至少约18个月、至少约2年或更长的时间段。

水溶液剂量间均匀性

[0161] 典型的眼用水溶液被包装在滴眼瓶中并以液滴的形式施用。例如，眼用水溶液的单一施用(即单一剂量)包括向患者眼中施用一滴、两滴、三滴或更多滴。在一些实施方案中，本文所述的眼用水溶液的一个剂量为来自滴眼瓶的一滴水溶液组合物。

[0162] 在一些情况下，本文所述包括提供剂量间均匀浓度的眼用水性组合物。在一些情况下，剂量间均匀浓度不呈现剂量间药物含量的显著变化。在一些情况下，剂量间均匀浓度提供了剂量间一致的药物含量。

[0163] 在一些实施方案中，所述组合物具有小于50％的剂量间眼用剂浓度变化。在一些实施方案中，所述组合物具有小于40％的剂量间眼用剂浓度变化。在一些实施方案中，所述组合物具有小于30％的剂量间眼用剂浓度变化。在一些实施方案中，所述组合物具有小于20％的剂量间眼用剂浓度变化。在一些实施方案中，所述组合物具有小于10％的剂量间眼用剂浓度变化。在一些实施方案中，所述组合物具有小于5％的剂量间眼用剂浓度变化。

[0164] 在一些实施方案中，所述剂量间眼用剂浓度变化基于10个连续的剂量。在一些实施方案中，所述剂量间眼用剂浓度变化基于8个连续的剂量。在一些实施方案中，所述剂量间眼用剂浓度变化基于5个连续的剂量。在一些实施方案中，所述剂量间眼用剂浓度变化基于3个连续的剂量。在一些实施方案中，所述剂量间眼用剂浓度变化基于2个连续的剂量。

[0165] 非沉降制剂应该不需要摇动来使药物均匀分散。“不需摇动”制剂比需要摇动的制剂潜在有利，简单原因在于患者的摇动行为是药物给药量的可变性的主要来源。已报道，尽管关于摇动的说明明确标注在标签上，但患者在施用剂量之前经常不摇动或忘记摇动他们需要摇动的眼用组合物。另一方面，即使对于摇动产品的那些患者，通常不能确定摇动的强度和/或持续时间是否足以使产品变均匀。在一些实施方案中，本文所述的眼用凝胶组合物和眼用软膏组合物是维持本文所述的剂量间均匀性的“不需摇动”制剂。

[0166] 为了评估剂量间均匀性，在测试开始之前，将含有眼用水性组合物、眼用凝胶组合物或眼用软膏组合物的滴瓶或管直立储存最少12小时。为了模拟这些产品的推荐给药，以预定的时间间隔从每个市售瓶或管中分配预定数目的滴或条持续延长的时间段，或直到瓶或管中不留下产品为止。将所有的滴和条分配至配衡的玻璃小瓶中，加盖，并储存在室温下直到进行分析。使用反相HPLC方法测定在所表示的滴中眼用剂的浓度。

水溶液粘度

[0167] 在一些实施方案中，所述组合物在约20℃下具有约10cp至约50,000cp的Brookfield RVDV粘度，并具有1s^{-1}的剪切速率。在一些实施方案中，所述组合物在约20℃下具有约100cp至约40,000cp的Brookfield RVDV粘度，并具有1s^{-1}的剪切速率。在一些实施方案中，所述组合物在约20℃下具有约500cp至约30,000cp的Brookfield RVDV粘度，并具有1s^{-1}的剪切速率。在一些实施方案中，所述组合物在约20℃下具有约1000cp至约20,000cp的Brookfield RVDV粘度，并具有1s^{-1}的剪切速率。在一些实施方案中，所述组合物在约20℃下具有约2000cp至约10,000cp的Brookfield RVDV粘度，并具有1s^{-1}的剪切速率。在一些实施方案中，所述组合物在约20℃下具有约4000cp至约8,000cp的Brookfield RVDV粘度，并具有1s^{-1}的剪切速率。

[0168] 在一些实施方案中，所述眼用水性制剂含有足以提供约500至50,000厘泊、约750至50,000厘泊、约1000至50,000厘泊、约1000至40,000厘泊、约2000至30,000厘泊、约3000至20,000厘泊、约4000至10,000厘泊或约5000至8000厘泊的粘度的粘度增强剂。

[0169] 在一些实施方案中，本文所述的组合物在体温下为低粘度组合物。在一些实施方案中，低粘度组合物含有约1％至约10％的粘度增强剂(例如胶凝组分，诸如聚氧乙烯-聚氧丙烯共聚物)。在一些实施方案中，低粘度组合物含有约2％至约10％的粘度增强剂(例如胶凝组分，诸如聚氧乙烯-聚氧丙烯共聚物)。在一些实施方案中，低粘度组合物含有约5％至约10％的粘度增强剂(例如胶凝组分，诸如聚氧乙烯-聚氧丙烯共聚物)。在一些实施方案中，低粘度组合物基本不含粘度增强剂(例如胶凝组分，诸如聚氧乙烯-聚氧丙烯共聚物)。在一些实施方案中，本文所述的低粘度眼用剂组合物提供约100cP至约10,000cP的表观粘度。在一些实施方案中，本文所述的低粘度眼用剂组合物提供约500cP至约10,000cP的表观粘度。在一些实施方案中，本文所述的低粘度眼用剂组合物提供约1000cP至约10,000cP的表观粘度。

容量摩尔渗透压浓度

[0170] 在一些实施方案中，本文公开的组合物被配制为不破坏眼睛的离子平衡。在一些实施方案中，本文公开的组合物具有与眼睛相同或基本相同的离子平衡。在一些实施方案中，本文公开的组合物不破坏眼睛的离子平衡。

[0171] 如本文所用的，“实际容量摩尔渗透压浓度(osmolarity)/重量摩尔渗透压浓度(osmolality)”或“可递送的容量摩尔渗透压浓度/重量摩尔渗透压浓度”意指如通过测量眼用剂和除了胶凝剂和/或增稠剂(例如聚氧乙烯-聚氧丙烯共聚物、羧甲基纤维素等)之外的所有赋形剂的容量摩尔渗透压浓度/重量摩尔渗透压浓度而确定的，组合物的容量摩尔渗透压浓度/重量摩尔渗透压浓度。本文公开的组合物的实际容量摩尔渗透压浓度通过合适的方法，例如，如在Viegas等人，Int.J.Pharm.，1998，160，157-162中描述的冰点降低法进行测量。在一些情况下，本文公开的组合物的实际容量摩尔渗透压浓度通过允许在较高

温度下测定组合物的容量摩尔渗透压浓度的蒸气压渗透压测定法(例如蒸气压降低法)进行测量。在一些情况下,蒸气压降低法允许在较高温度下测定包含胶凝剂(例如热可逆性聚合物)的组合物的容量摩尔渗透压浓度,其中该胶凝剂为凝胶形式。

[0172] 在一些实施方案中,在目标作用部位(例如眼)的容量摩尔渗透压浓度与本文所述的组合物的递送容量摩尔渗透压浓度大致相同。在一些实施方案中,本文所述的组合物具有约150mOsm/L至约500mOsm/L、约250mOsm/L至约500mOsm/L、约250mOsm/L至约350mOsm/L、约280mOsm/L至约370mOsm/L或约250mOsm/L至约320mOsm/L的可递送容量摩尔渗透压浓度。

[0173] 本文公开的眼用组合物的实际重量摩尔渗透压浓度为约100mOsm/kg至约1000mOsm/kg,约200mOsm/kg至约800mOsm/kg,约250mOsm/kg至约500mOsm/kg,或约250mOsm/kg至约320mOsm/kg,或约250mOsm/kg至约350mOsm/kg,或约280mOsm/kg至约320mOsm/kg。在一些实施方案中,本文所述的组合物具有约100mOsm/L至约1000mOsm/L、约200mOsm/L至约800mOsm/L、约250mOsm/L至约500mOsm/L、约250mOsm/L至约350mOsm/L、约250mOsm/L至约320mOsm/L或约280mOsm/L至约320mOsm/L的实际容量摩尔渗透压浓度。

[0174] 在一些实施方案中,合适的张力调节剂包括但不限于任何药学上可接受的糖、盐或其任意组合或混合物,诸如但不限于右旋糖、甘油、甘露醇、山梨醇、氯化钠和其他电解质。在一些情况下,张力调节剂选自氯化钠、硝酸钠、硫酸钠、硫酸氢钠、氯化钾、氯化钙、氯化镁、氯化锌、乙酸钾、乙酸钠、碳酸氢钠、碳酸钠、硫代硫酸钠、硫酸镁、磷酸氢二钠、磷酸二氢钠、磷酸二氢钾、右旋糖、甘露醇、山梨醇、葡萄糖、蔗糖、尿素、丙二醇、甘油或其组合。

[0175] 在一些实施方案中,本文所述的眼用组合物包含使组合物的重量摩尔渗透压浓度处于可接受范围内所需的量的一种或多种盐。这样的盐包括具有钠、钾或铵阳离子以及氯离子、柠檬酸根、抗坏血酸根、硼酸根、磷酸根、碳酸氢根、硫酸根、硫代硫酸根或亚硫酸氢根阴离子的那些盐;合适的盐包括氯化钠、氯化钾、硫代硫酸钠、亚硫酸氢钠和硫酸铵。

无菌性

[0176] 在一些实施方案中,所述组合物经灭菌。本文公开的实施方案内包括为了在人类中使用而对本文公开的药物组合物进行灭菌的手段和过程。目标是提供安全的药物产品,相对地不含导致感染的微生物。美国食品和药品管理局(U.S.Food and Drug Administration)已经在http://www.fda.gov/cder/guidance/5882fnl.htm可获得的出版物“Guidance for Industry:Sterile Drug Products Produced by Aseptic Processing”中提供了规章指导,该出版物通过引用而全文并入本文。

[0177] 如本文所用的,灭菌意指用来破坏或去除产品或包装中存在的微生物的过程。使用可用于目标和组合物的灭菌的任何合适的方法。可用于微生物的灭活的方法包括但不限于施加极端热、致死性化学品或γ辐射。在一些实施方案中,用于制备眼用制剂的过程包括使制剂经受选自热灭菌、化学灭菌、辐射灭菌或过滤除菌的灭菌方法。所用方法在很大程度上取决于待灭菌的装置或组合物的性质。许多灭菌方法的详细说明在由Lippincott,Williams&Wilkins出版的Remington:The Science and Practice of Pharmacy的第40章中给出,并且其关于该主题的内容通过引用而并入本文。

过滤

[0178] 过滤除菌是用来从溶液中去除但不破坏微生物的方法。使用膜过滤器过滤热敏性溶液。这样的过滤器为混合的纤维素酯(MCE)、聚偏二氟乙烯(PVF;也称作PVDF)或聚四氟乙

烯(PTFE)的薄的强均匀性聚合物，并具有在0.1-0.22μm范围内的孔径。任选地使用不同的过滤膜过滤具有不同特征的溶液。例如，PVF和PTFE膜很适合过滤有机溶剂，而水溶液则通过PVF或MCE膜进行过滤。过滤器装置可供在从附接至注射器的单使用点一次性过滤器到用于制造厂中的商业规模过滤器范围内的许多规模上使用。膜过滤器通过高压灭菌器或化学灭菌法进行灭菌。膜过滤系统的验证遵循标准化方案(Microbiological Evaluation of Filters for Sterilizing Liquids,Vol 4,No.3,Washington,D.C:Health Industry Manufacturers Association,1981)而进行，并涉及用已知量(约$10^7/cm^2$)的异常小的微生物如缺陷短波单胞菌(Brevundimonas diminuta)(ATCC 19146)攻击膜过滤器。

[0179] 药物组合物任选地通过穿过膜过滤器进行除菌。包含纳米粒子(美国专利号6,139,870)或多层囊泡(Richard等人，International Journal of Pharmaceutics(2006),312(1-2):144-50)的制剂适合于通过穿过0.22μm过滤器过滤除菌而不破坏其组织化结构。

[0180] 在一些实施方案中，本文公开的方法包括借助于过滤除菌使制剂(或其组分)灭菌。在包含热固性聚合物的眼用凝胶组合物中，在比本文所述制剂的凝胶温度(Tgel)低(例如，约5℃)的温度下，并且采用允许用蠕动泵在合理时间内过滤的粘度(例如低于100cP的理论值)进行过滤。

[0181] 因此，本文提供了眼用制剂的灭菌方法，该方法防止聚合组分(例如热固性和/或其他粘度增强剂)和/或眼用剂在灭菌过程期间的降解。在一些实施方案中，通过使用用于缓冲液组分的特定pD范围和制剂中粘度增强剂的特定比例来减少或消除眼用剂的降解。在一些实施方案中，适当的粘度增强剂或热固性聚合物的选择允许本文所述制剂通过过滤除菌。在一些实施方案中，适当的热固性聚合物或其他粘度增强剂与用于制剂的特定pD范围的组合使用允许所述制剂的高温灭菌，而治疗剂或聚合赋形剂基本不降解。本文提供的灭菌方法的优点在于，在某些情况下，制剂经受经由高压灭菌的最终灭菌，而在灭菌步骤期间眼用剂和/或赋形剂和/或粘度增强剂没有任何损失，并且使其基本不含微生物和/或致热原。

辐射灭菌

[0182] 辐射灭菌的一个优点是使多种类型的产品灭菌而没有热降解或其他损伤的能力。常用的辐射是β辐射或可替代的来自^{60}Co源的γ辐射。γ辐射的穿透能力允许其用于包括溶液、组合物和非均匀混合物在内的许多产品类型的灭菌。辐射的杀菌作用由γ辐射与生物大分子的相互作用而产生。该相互作用生成带电荷物质和自由基。随后的化学反应，诸如重排和交联过程，导致这些生物大分子的正常功能的损失。本文所述的制剂也任选地使用β辐射进行灭菌。

热灭菌

[0183] 许多方法可用于通过施加高热进行灭菌。一种方法是通过使用饱和蒸气高压灭菌器。在该方法中，使至少121℃的温度的饱和蒸气接触待灭菌的物体。在待灭菌的物体的情况下使热直接转移至微生物，或通过加热待灭菌的水溶液主体使热间接转移至微生物。该方法得到广泛使用，因为其使灭菌过程具有灵活性、安全性和经济性。

微生物

[0184] 在一些实施方案中，所述组合物基本不含微生物。可接受的生物负载或无菌性水平基于定义治疗上可接受的组合物的适用标准，包括但不限于美国药典(United States

Pharmacopeia)第<1111>章及以下等。例如,可接受的无菌性(例如生物负载)水平包括约10个菌落形成单位(cfu)/克制剂、约50cfu/克制剂、约100cfu/克制剂、约500cfu/克制剂或约1000cfu/克制剂。在一些实施方案中,对于制剂可接受的生物负载水平或无菌性包括少于10cfu/mL微生物剂、少于50cfu/mL微生物剂、少于500cfu/mL微生物剂或少于1000cfu/mL微生物剂。另外,可接受的生物负载水平或无菌性包括排除指定的不良微生物剂。举例而言,指定的不良微生物剂包括但不限于大肠杆菌(E.coli)、沙门氏菌(Salmonella sp.)、绿脓杆菌(Pseudomonas aeruginosa,P.aeruginosa)和/或其他特定微生物剂。

[0185] 无菌性保证质量控制、质量保证和验证过程的重要部分是无菌性测试的方法。仅举例而言,无菌性测试通过两种方法进行。第一种是直接接种,其中将待测组合物的样品添加至生长培养基中,并温育最长21天的一段时间。生长培养基的浊度指示污染。该方法的缺点包括主体材料的小的取样大小(这降低了灵敏度),以及基于目测的微生物生长的检测。一种替代方法是膜过滤无菌性测试。在该方法中,使一定体积的产品穿过小的膜滤纸。随后将滤纸置于培养基中以促进微生物生长。因为对整个主体产品进行取样,所以该方法具有更大灵敏度的优点。市售的Millipore Steritest无菌性测试系统任选地用于通过膜过滤无菌性测试进行测定。对于乳膏或软膏的过滤测试,使用Steritest过滤器系统No.TLHVSL210。对于乳液或粘性产品的过滤测试,使用Steritest过滤器系统No.TLAREM210或TDAREM210。对于预填充注射器的过滤测试,使用Steritest过滤器系统No.TTHASY210。对于分配为气溶胶或泡沫的材料的过滤测试,使用Steritest过滤器系统No.TTHVA210。对于安瓿或小瓶中的可溶性粉末的过滤测试,使用Steritest过滤器系统No.TTHADA210或TTHADV210。

[0186] 对大肠杆菌和沙门氏菌的测试包括使用在30-35℃下温育24-72小时的乳糖肉汤、在MacConkey和/或EMB琼脂中温育18-24小时,和/或使用Rappaport培养基。用于检测绿脓杆菌的测试包括使用NAC琼脂。美国药典第<62>章进一步列举了针对指定的不良微生物的测试程序。

[0187] 在某些实施方案中,本文所述的眼用制剂具有少于约60个菌落形成单位(CFU)、少于约50个菌落形成单位、少于约40个菌落形成单位或少于约30个菌落形成单位的微生物剂/克制剂。在某些实施方案中,本文所述的眼用制剂被配制成与眼等渗。

内毒素

[0188] 灭菌过程的另一方面是去除因杀死微生物而产生的副产物(下文中称为“产物”)。去热原的过程从样品中去除致热原。致热原是诱导免疫应答的内毒素或外毒素。内毒素的一个实例为在革兰氏阴性细菌的细胞壁中发现的脂多糖(LPS)分子。尽管灭菌程序如高压灭菌或环氧乙烷处理杀死了细菌,但LPS残留物诱导促炎性免疫应答,诸如脓毒性休克。因为内毒素的分子大小变化很大,所以内毒素的存在以“内毒素单位”(EU)表示。一个EU等同于100皮克的大肠杆菌LPS。在一些情况下,人类对低至5EU/kg体重发生应答。生物负载(例如微生物限度)和/或无菌性(例如内毒素水平)以本领域公认的任何单位表示。在某些实施方案中,与常规可接受的内毒素水平(例如,5EU/kg受试者体重)相比,本文所述的眼用组合物含有更低的内毒素水平(例如<4EU/kg受试者体重)。在一些实施方案中,该眼用制剂具有小于约5EU/kg受试者体重。在其他实施方案中,该眼用制剂具有小于约4EU/kg受试者体重。在其他实施方案中,该眼用制剂具有小于约3EU/kg受试者体重。在其他实施方案中,该眼用

制剂具有小于约2EU/kg受试者体重。

[0189] 在一些实施方案中，该眼用制剂具有小于约5EU/kg制剂。在其他实施方案中，该眼用制剂具有小于约4EU/kg制剂。在其他实施方案中，该眼用制剂具有小于约3EU/kg制剂。在一些实施方案中，该眼用制剂具有小于约5EU/kg产品。在其他实施方案中，该眼用制剂具有小于约1EU/kg产品。在其他实施方案中，该眼用制剂具有小于约0.2EU/kg产品。在一些实施方案中，该眼用制剂具有小于约5EU/g单元或产品。在其他实施方案中，该眼用制剂具有小于约4EU/g单元或产品。在其他实施方案中，该眼用制剂具有小于约3EU/g单元或产品。在一些实施方案中，该眼用制剂具有小于约5EU/mg单元或产品。在其他实施方案中，该眼用制剂具有小于约4EU/mg单元或产品。在其他实施方案中，该眼用制剂具有小于约3EU/mg单元或产品。在某些实施方案中，本文所述的眼用制剂含有约1至约5EU/mL制剂。在某些实施方案中，本文所述的眼用制剂含有约2至约5EU/mL制剂、约3至约5EU/mL制剂或约4至约5EU/mL制剂。

[0190] 在某些实施方案中，与常规可接受的内毒素水平(例如，0.5EU/mL制剂)相比，本文所述的眼用组合物含有更低的内毒素水平(例如<0.5EU/mL制剂)。在一些实施方案中，该眼用制剂具有小于约0.5EU/mL制剂。在其他实施方案中，该眼用制剂具有小于约0.4EU/mL制剂。在其他实施方案中，该眼用制剂具有小于约0.2EU/mL制剂。

[0191] 仅举例而言，通过几种方法进行致热原检测。适于无菌性的测试包括美国药典(USP)<71>Sterility Tests(第23版，1995)中所述的测试。兔致热原测试和鲎变形细胞溶解物测试均在美国药典第<85>章和第<151>章(USP23/NF 18,Biological Tests,The United States Pharmacopeial Convention,Rockville,MD,1995)中有详细说明。已经基于单核细胞活化-细胞因子测定开发了替代性致热原测定。已经开发了适于质量控制应用的均匀细胞系，并且已经证明了该均匀细胞系检测通过兔致热原测试和鲎变形细胞溶解物测试(Taktak等人,J.Pharm.Pharmacol.(1990),43:578-82)的样品中的致热性的能力。在另一个实施方案中，对眼用制剂进行去热原。在又一个实施方案中，眼用制剂的制备过程包括测试制剂的致热性。在某些实施方案中，本文所述的制剂基本不含致热原。

眼用剂-粘液渗透粒子(MPP)组合物

[0192] 粘液渗透粒子(MPP)为快速穿过粘液(例如人类粘液)的粒子。在一些情况下，MPP包括粒径为约200nm至500nm的纳米粒子。在一些情况下，该纳米粒子进一步涂覆有粘液渗透剂。在一些情况下，本文所述的组合物与MPP配制在一起以供粘液渗透。在一些情况下，本文公开的眼用组合物与MPP配制在一起以供粘液渗透。在一些实施方案中，眼用剂包括阿柏西普(也称为VEGF Trap)、雷珠单抗、培加尼布、环喷托酯、苯福林、后马托品、东莨菪碱、环喷托酯/苯福林、苯福林/东莨菪碱、托吡卡胺、酮咯酸/苯福林、羟苯丙胺/托吡卡胺、半胱胺、奥克纤溶酶、丝裂霉素、达哌唑、利多卡因、丙美卡因、丁卡因、丁氧普鲁卡因、阿奇霉素、杆菌肽、贝西沙星、硼酸、氯霉素、环丙沙星、红霉素、更昔洛韦、加替沙星、庆大霉素、碘苷、左氧氟沙星、莫西沙星、纳他霉素、诺氟沙星、氧氟沙星、杆菌肽/多粘菌素b、妥布霉素、多粘菌素b/甲氧苄啶、聚维酮碘、曲氟尿苷、短杆菌肽/新霉素/多粘菌素b、磺胺醋酰钠、磺胺异噁唑、杆菌肽/新霉素/多粘菌素b、土霉素/多粘菌素b、苯福林/磺胺醋酰钠、阿糖腺苷、溴芬酸、奈帕芬胺、酮咯酸、环孢菌素、氟比洛芬、舒洛芬、双氯芬酸、阿卡他定、氮䓬斯汀、贝他斯汀、色甘酸、依美斯汀、依匹斯汀、酮替芬、左卡巴斯汀、洛度沙胺、奈多罗米、萘甲唑啉、萘

甲唑啉/非尼拉敏、萘甲唑啉/硫酸锌、奥洛他定、羟甲唑啉、吡嘧司特、苯福林、苯福林/硫酸锌、四氢唑啉、四氢唑啉/硫酸锌、荧光素、荧光素/丙美卡因、丁氧普鲁卡因/荧光素、吲哚菁绿、台盼蓝、乙酰胆碱、安普乐定、倍他洛尔、比马前列素、溴莫尼定、布林佐胺、溴莫尼定/布林佐胺、卡巴胆碱、卡替洛尔、地美溴铵、地匹福林、多佐胺、多佐胺/噻吗洛尔、依可碘酯、肾上腺素、肾上腺素/毛果芸香碱、拉坦前列素、左布诺洛尔、左倍他洛尔、美替洛尔、毒扁豆碱、毛果芸香碱、他氟前列素、噻吗洛尔、曲伏前列素、乌诺前列酮、人造泪液、地塞米松、二氟泼尼酯、氟轻松、氟米龙、氯替泼诺、甲羟松、泼尼松龙、利美索龙、曲安西龙、氟米龙/磺胺醋酰钠、地塞米松/新霉素、地塞米松/妥布霉素、地塞米松/新霉素/多粘菌素b、氯替泼诺/妥布霉素、泼尼松龙/磺胺醋酰钠、杆菌肽/氢化可的松/新霉素/多粘菌素b、氢化可的松/新霉素/多粘菌素b、氯霉素/氢化可的松/多粘菌素b、新霉素/多粘菌素b/泼尼松龙、庆大霉素/泼尼松龙、酮咯酸/苯福林、苯海拉明、茶苯海明、双环维林、黄酮哌酯、奥昔布宁、噻托溴铵、莨菪碱、scopolomine(L-莨菪碱)、羟嗪、异丙托铵、哌仑西平、索利那新、达非那新、苯扎托品、美贝维林、丙环定、阿地溴铵、三己芬迪/苯海索、托特罗定或其任何组合。在非限制性实例中,用于在所公开的组合物中使用的MMP从Kala Pharmaceuticals,Inc.(100Beaver Street#201,Waltham,MA 02453)获得。

[0193] 在一些实施方案中,所述纳米粒子包括任何合适的材料,诸如有机材料、无机材料、聚合物或其组合。在一些情况下,该纳米粒子包括无机材料,诸如例如,金属(例如,Ag、Au、Pt、Fe、Cr、Co、Ni、Cu、Zn和其他过渡金属)、半导体(例如,硅、硅化合物和合金、硒化镉、硫化镉、砷化铟和磷化铟)或绝缘体(例如,陶瓷,诸如氧化硅)。在一些情况下,该纳米粒子包括有机材料,诸如合成聚合物和/或天然聚合物。合成聚合物的实例包括不可降解的聚合物如聚甲基丙烯酸酯和可降解的聚合物如聚乳酸、聚乙醇酸及其共聚物。天然聚合物的实例包括透明质酸、壳聚糖和胶原。

[0194] 在一些实施方案中,所述纳米粒子涂覆有粘液渗透剂。在一些情况下,该粘液渗透剂包括任何合适的材料,诸如疏水性材料、亲水性材料和/或两亲性材料。在一些情况下,该粘液渗透剂为聚合物。在一些情况下,该聚合物为合成聚合物(即,不是天然产生的聚合物)。在其他实施方案中,该聚合物为天然聚合物(例如,蛋白质、多糖、橡胶)。在某些实施方案中,该聚合物为表面活性聚合物。在某些实施方案中,该聚合物为非离子型聚合物。在某些实施方案中,该聚合物为非离子型嵌段共聚物。在一些实施方案中,该聚合物为二嵌段共聚物、三嵌段共聚物,例如,其中一个嵌段为疏水性聚合物而另一个嵌段为亲水性聚合物。在一些情况下,该聚合物带电荷或不带电荷。

[0195] 合适的聚合物的其他实例包括但不限于多胺、聚醚、聚酰胺、聚酯、聚氨基甲酸酯、聚脲、聚碳酸酯、聚苯乙烯、聚酰亚胺、聚砜、聚氨酯、聚乙炔、聚乙烯、聚乙烯亚胺、聚异氰酸酯、聚丙烯酸酯、聚甲基丙烯酸酯、聚丙烯腈和聚芳酯。具体聚合物的非限制性实例包括聚(己内酯)(PCL)、乙烯乙酸乙烯酯聚合物(EVA)、聚(乳酸)(PLA)、聚(L-乳酸)(PLLA)、聚(乙醇酸)(PGA)、聚(乳酸-共-乙醇酸)(PLGA)、聚(L-乳酸-共-乙醇酸)(PLLGA)、聚(D,L-丙交酯)(PDLA)、聚(L-丙交酯)(PLLA)、聚(D,L-丙交酯-共-己内酯)、聚(D,L-丙交酯-共-己内酯-共-乙交酯)、聚(D,L-丙交酯-共-PEO-共-D,L-丙交酯)、聚(D,L-丙交酯-共-PPO-共-D,L-丙交酯)、聚氰基丙烯酸烷基酯、聚氨酯、聚-L-赖氨酸(PLL)、甲基丙烯酸羟丙酯(HPMA)、聚(乙二醇)、聚-L-谷氨酸、聚(羟基酸)、聚酸酐、聚原酸酯、聚(酯酰胺)、聚酰胺、聚(酯醚)、

聚碳酸酯、聚亚烷基(诸如聚乙烯和聚丙烯)、聚亚烷基二醇(诸如聚(乙二醇)(PEG))、聚亚烷基氧化物(PEO)、聚亚烷基对苯二甲酸酯(诸如聚(乙烯对苯二甲酸酯))、聚乙烯醇(PVA)、聚乙烯醚、聚乙烯酯(诸如聚(乙酸乙烯酯))、聚乙烯卤化物(诸如聚(氯乙烯)(PVC))、聚乙烯吡咯烷酮、聚硅氧烷、聚苯乙烯(PS)、聚氨酯、衍生的纤维素(诸如烷基纤维素、羟烷基纤维素、纤维素醚、纤维素酯、硝酸纤维素、羟丙基纤维素、羧甲基纤维素)、丙烯酸的聚合物(诸如聚((甲基)丙烯酸甲酯)(PMMA)、聚((甲基)丙烯酸乙酯)、聚((甲基)丙烯酸丁酯)、聚((甲基)丙烯酸异丁酯)、聚((甲基)丙烯酸己酯)、聚((甲基)丙烯酸异癸酯)、聚((甲基)丙烯酸月桂酯)、聚((甲基)丙烯酸苯酯)、聚(丙烯酸甲酯)、聚(丙烯酸异丙酯)、聚(丙烯酸异丁酯)、聚(丙烯酸十八酯)(在本文中统称为"聚丙烯酸"))及其共聚物和混合物、聚二噁烷酮及其共聚物、聚羟基脂肪酸酯、聚(丙烯富马酸酯)、聚甲醛、泊洛沙姆、聚(原酸)酯(poly(ortho)ester)、聚(丁酸)、聚(戊酸)、聚(丙交酯-共-己内酯)和三亚甲基碳酸酯、聚乙烯吡咯烷酮。

[0196] 在一些情况下,按组合物的重量计,眼用剂以下列浓度存在于MPP制剂中:约0.001wt%至约20wt%、约0.01%至约15%、约0.05%至约10%、约0.1%至约5%或约0.5%至约1%的眼用剂或其药学上可接受的前药或盐。在一些情况下,将另外的试剂如缓冲液、pD调节剂和/或防腐剂配制在MPP制剂中。

[0197] 在一些情况下,使用任何合适的方法配制眼用剂-MPP组合物。在一些实施方案中,使用研磨法减小固体材料的大小以形成在微米至纳米大小范围内的粒子。干磨和湿磨法(诸如喷射研磨、冷冻研磨、球磨、介质研磨和均质化)是已知的并在本文所述的方法中使用。通常,在湿磨法中,将待用作纳米粒子的材料的悬浮液与具有或不具有赋形剂的研磨介质混合以减小粒径。干磨是其中待用作纳米粒子的材料与具有或不具有赋形剂的研磨介质混合以减小粒径的方法。在冷冻研磨法中,在冷却温度下将待用作纳米粒子的材料的悬浮液与具有或不具有赋形剂的研磨介质混合。

[0198] 在一些实施方案中,任何合适的研磨介质都用于研磨。在一些实施方案中,使用陶瓷和/或聚合材料和/或金属。合适材料的实例包括氧化锆、碳化硅、氧化硅、氮化硅、硅酸锆、氧化钇、玻璃、氧化铝(alumina)、α-氧化铝(alpha-alumina)、氧化铝(aluminum oxide)、聚苯乙烯、聚(甲基丙烯酸甲酯)、钛、钢。在一些实施方案中,研磨介质具有任何合适的大小。例如,研磨介质具有至少约0.1mm、至少约0.2mm、至少约0.5mm、至少约0.8mm、至少约1mm、至少约2mm或至少约5mm的平均直径。在一些情况下,研磨介质具有小于或等于约5mm、小于或等于约2mm、小于或等于约1mm、小于或等于约0.8、小于或等于约0.5mm或小于或等于约0.2mm的平均直径。上述范围的组合也是可能的(例如,至少约0.5毫米和小于或等于约1mm的平均直径)。其他范围也是可能的。

[0199] 在一些实施方案中,任何合适的溶剂都用于研磨。在一些情况下,溶剂的选择取决于以下因素:诸如所研磨的固体材料、所用的稳定剂/粘液渗透剂(例如,使得粒子粘液渗透的粘液渗透剂)的特定类型、所用的研磨材料以及其他因素。合适的溶剂是基本不溶解固体材料或研磨材料,但在适当程度上溶解稳定剂/粘液渗透剂的溶剂。溶剂的非限制性实例包括水、缓冲溶液、其他水溶液、醇(例如,乙醇、甲醇、丁醇)及其混合物,任选地包括其他组分,诸如药物赋形剂、聚合物、药物剂、盐、防腐剂、粘度调节剂、张力调节剂、掩味剂、抗氧化剂、pD调节剂和其他药物赋形剂。在其他实施方案中,使用有机溶剂。在一些实施方案中,药

物剂在这些或其他溶剂中具有任何合适的溶解度，诸如对于水溶解度或对于在涂覆溶液中的溶解度具有在一个或多个上述范围内的溶解度。

[0200] 在一些情况下，MPP为如WO2013/166385中所述的MPP。在一些情况下，MPP为如Lai等人，“Rapid transport of large polymeric nanoparticles in fresh undiluted human mucus,”PNAS 104(5):1482-1487(2007)中所述的MPP。在一些情况下，眼用剂-MPP组合物使用如WO2013/166385中所述的方法进行配制。在一些情况下，眼用剂-MPP组合物使用如Lai等人，“Rapid transport of large polymeric nanoparticles in fresh undiluted human mucus,”PNAS 104(5):1482-1487(2007)中所述的方法进行配制。

眼用凝胶组合物

[0201] 以多种方式定义凝胶。例如，美国药典将凝胶定义为由无机小粒子构成的悬浮液或由液体互相渗透的有机大分子组成的半固体系统。凝胶包括单相或两相系统。单相凝胶由以在所分散的大分子与液体之间不存在明显边界的方式均匀分布在整个液体中的有机大分子组成。一些单相凝胶由合成大分子(例如卡波姆)或由天然树胶(例如黄芪胶)制备。在一些实施方案中，单相凝胶通常是水性的，但也将使用醇和油制得。两相凝胶由小的离散粒子的网络组成。

[0202] 在一些实施方案中，凝胶也分类为疏水性或亲水性的。在某些实施方案中，疏水性凝胶的非限制性实例的基质包括具有与硅胶或铝或锌皂一起胶凝的聚乙烯或脂肪油的液体石蜡。相比之下，亲水性凝胶的非限制性实例的基质包括与合适的胶凝剂(例如，黄芪胶、淀粉、纤维素衍生物、羧基乙烯基聚合物和镁-铝硅酸盐)一起胶凝的水、甘油或丙二醇。在某些实施方案中，本文公开的组合物的流变学是假塑性、塑性、触变性或膨胀性的。

[0203] 在一些实施方案中，所述眼用组合物为眼用凝胶，并且其中眼科上可接受的载体包含氘化水和至少一种粘度增强剂。在一些实施方案中，该粘度增强剂选自基于纤维素的聚合物、聚氧乙烯-聚氧丙烯三嵌段共聚物、基于葡聚糖的聚合物、聚乙烯醇、糊精、聚乙烯吡咯烷酮、聚亚烷基二醇、壳聚糖、胶原、明胶、透明质酸或其组合。

[0204] 在一些实施方案中，本文所述的眼用凝胶组合物在局部施用之前(例如在室温下)为半固体或呈胶凝状态。例如，仅举例而言，用于这类凝胶的合适的粘度增强剂包括胶凝剂和悬浮剂。在一个实施方案中，增强粘度制剂不包含缓冲液。在其他实施方案中，增强粘度制剂包含药学上可接受的缓冲液。如果必要的话，任选地使用氯化钠或其他张力剂来调节张力。

[0205] 仅举例而言，眼科上可接受的粘度剂包括羟丙基甲基纤维素、羟乙基纤维素、聚乙烯吡咯烷酮、羧甲基纤维素、聚乙烯醇、硫酸软骨素钠、透明质酸钠。与目标眼部位相容的其他粘度增强剂包括但不限于阿拉伯胶(阿拉伯树胶)、琼脂、硅酸铝镁、海藻酸钠、硬脂酸钠、墨角藻、膨润土、卡波姆(carbomer)、角叉菜胶、卡波普(Carbopol)、黄原胶、纤维素、微晶纤维素(MCC)、长角豆胶(ceratonia)、甲壳质、羧甲基壳聚糖、角叉菜(chondrus)、右旋糖、红藻胶、明胶、印度树胶(Ghatti gum)、瓜尔胶、锂蒙脱石、乳糖、蔗糖、麦芽糊精、甘露醇、山梨醇、蜂蜜、玉米淀粉、小麦淀粉、米淀粉、马铃薯淀粉、明胶、梧桐胶、黄多糖胶、黄芪胶、乙基纤维素、乙基羟乙基纤维素、乙基甲基纤维素、甲基纤维素、羟乙基纤维素、羟乙基甲基纤维素、羟丙基纤维素、聚(甲基丙烯酸羟乙酯)、氧化聚明胶、果胶、聚明胶肽、聚维酮、碳酸丙烯酯、甲基乙烯基醚/马来酸酐共聚物(PVM/MA)、聚(甲基丙烯酸甲氧基乙酯)、聚(甲基丙烯酸

甲氧基乙氧基乙酯)、羟丙基纤维素、羟丙基甲基-纤维素(HPMC)、羧甲基-纤维素钠(CMC)、二氧化硅、聚乙烯吡咯烷酮(PVP:聚维酮)、Splenda®(右旋糖、麦芽糊精和三氯蔗糖)或其组合。在特定实施方案中,粘度增强赋形剂是MCC和CMC的组合。在另一个实施方案中,粘度增强剂是羧甲基壳聚糖或甲壳质和海藻酸盐的组合。甲壳质和海藻酸盐与本文公开的眼用剂的组合充当控制释放制剂,限制了眼用剂从制剂的扩散。此外,任选地使用羧甲基壳聚糖和海藻酸盐的组合来帮助增加眼用剂在眼中的摩尔渗透压浓度。

[0206] 在一些实施方案中为增强粘度制剂,其包含约0.1mM至约100mM的眼用剂、药学上可接受的粘度剂和注射用水,该粘度剂在水中的浓度足以提供具有约100cP至约100,000cP的最终粘度的增强粘度制剂。在某些实施方案中,凝胶的粘度在约100cP至约50,000cP、约100cP至约1,000cP、约500cP至约1500cP、约1000cP至约3000cP、约2000cP至约8,000cP、约4,000cP至约50,000cP、约10,000cP至约500,000cP、约15,000cP至约1,000,000cP的范围内。在其他实施方案中,当需要甚至更有粘性的介质时,生物相容性凝胶包含至少约35%、至少约45%、至少约55%、至少约65%、至少约70%、至少约75%或甚至至少约80%(重量)左右的眼用剂。在高度浓缩的样品中,生物相容性增强粘度制剂包含至少约25%、至少约35%、至少约45%、至少约55%、至少约65%、至少约75%、至少约85%、至少约90%或至少约95%(重量)或更多的眼用剂。

[0207] 在一个实施方案中,药学上可接受的增强粘度的眼科上可接受的制剂包含至少一种眼用剂和至少一种胶凝剂。用于制备凝胶制剂的合适的胶凝剂包括但不限于纤维素、纤维素衍生物、纤维素醚(例如,羧甲基纤维素、乙基纤维素、羟乙基纤维素、羟甲基纤维素、羟丙基甲基纤维素、羟丙基纤维素、甲基纤维素)、瓜尔胶、黄原胶、刺槐豆胶、海藻酸盐(例如海藻酸)、硅酸盐、淀粉、黄芪胶、羧基乙烯基聚合物、角叉菜胶、石蜡、凡士林及其任意组合或混合物。在一些其他实施方案中,使用羟丙基甲基纤维素(Methocel®)作为胶凝剂。在某些实施方案中,还使用本文所述的粘度增强剂作为用于本文所示的凝胶制剂的胶凝剂。

[0208] 在一些实施方案中,本文所述的眼用凝胶组合物为原位凝胶制剂。在一些情况下,原位凝胶形成基于眼用组合物的增加的角膜前停留时间,这改善了眼部生物利用度、角膜粘膜粘附、溶酶体相互作用和离子胶凝、改善的角膜吸收、热胶凝或其组合。在一些情况下,原位凝胶制剂由pH、温度、离子、UV或溶剂交换来活化。

[0209] 在一些情况下,所述眼用凝胶组合物包含眼用剂和一种或多种胶凝剂。在一些情况下,该胶凝剂包括但不限于泊洛沙姆(例如泊洛沙姆407)、季酮酸(tetronics)、乙基(羟乙基)纤维素、邻苯二甲酸乙酸纤维素(CAP)、卡波普(例如卡波普1342P NF、卡波普980NF)、海藻酸盐(例如低乙酰基结冷胶(Gelrite®))、结冷胶、透明质酸、pluronic(例如Pluronic F-127)、壳聚糖、聚乙烯醇(PVA)、聚乙烯吡咯烷酮(PVP)、葡聚糖、羟丙基甲基纤维素(HPMC)、羟乙基纤维素(HEC)、甲基纤维素(MC)、巯基化木葡聚糖、聚甲基丙烯酸(PMMA)、聚乙二醇(PEG)、假乳胶(pseudolatexe)、木葡聚糖或其组合。

[0210] 在一些情况下,原位凝胶形成进一步包括渗透增强剂。在一些情况下,该渗透增强剂包括表面活性剂(例如非离子型表面活性剂)、苯扎氯铵、EDTA、表面活性杂糖苷(heteroglycoside)、钙螯合剂、羟丙基β环糊精(HPβCD)、胆盐等。

[0211] 在一些实施方案中,根据使用的特定眼用剂、其他药物剂或赋形剂/添加剂,其他

凝胶制剂是有用的，并因此被视为落入本发明的范围内。例如，预期其他市售的基于甘油的凝胶、甘油衍生的化合物、结合或交联凝胶、基质、水凝胶和聚合物以及明胶及其衍生物、海藻酸盐和基于海藻酸盐的凝胶，以及甚至各种天然和合成水凝胶以及水凝胶衍生的化合物，均可用于本文所述的眼用剂制剂中。在一些实施方案中，眼科上可接受的凝胶包括但不限于海藻酸盐水凝胶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.)；甘油凝胶Elta®Hydrogel(Swiss-American Products,Inc.,Dallas,Tex.)和K-Y®Sterile(Johnson&Johnson)。在其他实施方案中，可生物降解的生物相容性凝胶也代表存在于本文所述和公开的眼科上可接受的制剂中的化合物。

[0212] 在一些实施方案中，所述粘度增强剂为基于纤维素的聚合物，其选自纤维素胶、烷基纤维素、羟基-烷基纤维素、羟基-烷基烷基纤维素、羧基-烷基纤维素或其组合。在一些实施方案中，该粘度增强剂为羟基-烷基烷基纤维素。在一些实施方案中，该粘度增强剂为羟丙基甲基纤维素。

[0213] 在某些实施方案中，所述增强粘度制剂的特征是在室温与体温(包括严重发热的个体，例如最高约42℃)之间的相变。在一些实施方案中，相变在低于体温1℃、低于体温2℃、低于体温3℃、低于体温4℃、低于体温6℃、低于体温8℃或低于体温10℃的温度下发生。在一些实施方案中，相变在低于体温约15℃、低于体温约20℃或低于体温约25℃的温度下发生。在特定实施方案中，本文所述的制剂的胶凝温度(Tgel)为约20℃、约25℃或约30℃。在某些实施方案中，本文所述的制剂的胶凝温度(Tgel)为约35℃或约40℃。体温的定义内包括健康个体或不健康个体的体温，包括发热(最高约42℃)个体的体温。在一些实施方案中，本文所述的药物组合物在大约室温下为液体并且在室温或大约室温下施用。

[0214] 聚氧丙烯和聚氧乙烯共聚物(例如聚氧乙烯-聚氧丙烯三嵌段共聚物)在并入水溶液中时形成热固性凝胶。这些聚合物具有在接近体温的温度下从液态变为凝胶态的能力，因此允许施加于目标眼部位的有用制剂。液态至凝胶态的相变取决于溶液中的聚合物浓度和成分。

[0215] 在一些实施方案中，本文所述的任何制剂中的热固性聚合物的量为制剂总重量的约10％、约15％、约20％、约25％、约30％、约35％或约40％。在一些实施方案中，本文所述的任何制剂中的热固性聚合物的量为制剂总重量的约10％、约11％、约12％、约13％、约14％、约15％、约16％、约17％、约18％、约19％、约20％、约21％、约22％、约23％、约24％或约25％。在一些实施方案中，本文所述的任何制剂中的热固性聚合物(例如泊洛沙姆407)的量为制剂总重量的约7.5％。在一些实施方案中，本文所述的任何制剂中的热固性聚合物(例如泊洛沙姆407)的量为制剂总重量的约10％。在一些实施方案中，本文所述的任何制剂中的热固性聚合物(例如泊洛沙姆407)的量为制剂总重量的约11％。在一些实施方案中，本文所述的任何制剂中的热固性聚合物(例如泊洛沙姆407)的量为制剂总重量的约12％。在一些实施方案中，本文所述的任何制剂中的热固性聚合物(例如泊洛沙姆407)的量为制剂总重量的约13％。在一些实施方案中，本文所述的任何制剂中的热固性聚合物(例如泊洛沙姆407)的量为制剂总重量的约14％。在一些实施方案中，本文所述的任何制剂中的热固性聚合物(例如泊洛沙姆407)的量为制剂总重量的约15％。在一些实施方案中，本文所述的任何

制剂中的热固性聚合物(例如泊洛沙姆407)的量为制剂总重量的约16%。在一些实施方案中,本文所述的任何制剂中的热固性聚合物(例如泊洛沙姆407)的量为制剂总重量的约17%。在一些实施方案中,本文所述的任何制剂中的热固性聚合物(例如泊洛沙姆407)的量为制剂总重量的约18%。在一些实施方案中,本文所述的任何制剂中的热固性聚合物(例如泊洛沙姆407)的量为制剂总重量的约19%。在一些实施方案中,本文所述的任何制剂中的热固性聚合物(例如泊洛沙姆407)的量为制剂总重量的约20%。在一些实施方案中,本文所述的任何制剂中的热固性聚合物(例如泊洛沙姆407)的量为制剂总重量的约21%。在一些实施方案中,本文所述的任何制剂中的热固性聚合物(例如泊洛沙姆407)的量为制剂总重量的约23%。在一些实施方案中,本文所述的任何制剂中的热固性聚合物(例如泊洛沙姆407)的量为制剂总重量的约25%。在一些实施方案中,本文所述的任何制剂中的增稠剂(例如胶凝剂)的量为制剂总重量的约1%、约5%、约10%或约15%。在一些实施方案中,本文所述的任何制剂中的增稠剂(例如胶凝剂)的量为制剂总重量的约0.5%、约1%、约1.5%、约2%、约2.5%、约3%、约3.5%、约4%、约4.5%或约5%。

[0216] 在替代实施方案中,所述热凝胶为PEG-PLGA-PEG三嵌段共聚物(Jeong等人,Nature(1997),388:860-2;Jeong等人,J.Control.Release(2000),63:155-63;Jeong等人,Adv.Drug Delivery Rev.(2002),54:37-51)。该聚合物在约5%w/w至约40%w/w的浓度内表现出溶胶-凝胶表现。根据期望的性质,PLGA共聚物中的丙交酯/乙交酯的摩尔比在约1:1至约20:1的范围内。所得共聚物可溶于水,并在室温下形成自由流动的液体,但在体温下形成水凝胶。市售的PEG-PLGA-PEG三嵌段共聚物是由Boehringer Ingelheim生产的RESOMER RGP t50106。该材料由50:50聚(DL-丙交酯-共-乙交酯)的PLGA共聚物和10%w/w的PEG组成,且具有约6000的分子量。

[0217] 其他可生物降解的热塑性聚酯包括AtriGel®(由Atrix Laboratories,Inc.提供)和/或在例如美国专利号5,324,519、4,938,763、5,702,716、5,744,153和5,990,194中公开的那些;其中合适的可生物降解的热塑性聚酯公开为热塑性聚合物。合适的可生物降解的热塑性聚酯的实例包括聚丙交酯、聚乙交酯、聚己内酯、其共聚物、其三元聚合物及其任意组合。在一些这样的实施方案中,合适的可生物降解的热塑性聚酯为聚丙交酯、聚乙交酯、其共聚物、其三元聚合物或其组合。在一个实施方案中,可生物降解的热塑性聚酯为具有羧基端基的50/50聚(DL-丙交酯-共-乙交酯);以组合物的约30wt.%至约40wt.%存在;并且具有约23,000至约45,000的平均分子量。或者,在另一个实施方案中,可生物降解的热塑性聚酯为没有羧基端基的75/25聚(DL-丙交酯-共-乙交酯);以组合物的约40wt.%至约50wt.%存在;并且具有约15,000至约24,000的平均分子量。在进一步或替代的实施方案中,根据聚合方法,聚(DL-丙交酯-共-乙交酯)的端基为羟基、羧基或酯。乳酸或乙醇酸的缩聚提供了具有末端羟基和羧基的聚合物。环状丙交酯或乙交酯单体与水、乳酸或乙醇酸的开环聚合提供了具有相同端基的聚合物。然而,环状单体与单官能醇如甲醇、乙醇或1-十二醇的开环提供了具有一个羟基和一个酯端基的聚合物。环状单体与二醇如1,6-己二醇或聚乙二醇的开环聚合提供了仅具有羟基端基的聚合物。

[0218] 由于热固性凝胶的聚合物体系在降低的温度下溶解更完全,因此增溶方法包括在降低的温度下向待使用的一定量的水中添加所需量的聚合物。通常在通过摇动润湿聚合物后,将混合物加盖并置于约0-10℃下的冷却室或恒温容器中以溶解聚合物。搅拌或摇动混

合物以使热固性凝胶聚合物更快溶解。随后添加并溶解眼用剂和各种添加剂，诸如缓冲液、盐和防腐剂。在一些情况下，如果药物剂不溶于水，则使其悬浮。通过添加合适的缓冲剂调节pD。

眼用软膏组合物

[0219] 软膏是旨在外用于皮肤或粘膜的均匀粘性半固体制剂，最常见的是具有高粘度的脂性稠油(例如80％油-20％水)。软膏具有定义其含有的最大水量的水值(water number)。它们用作润肤剂或用于将活性成分施加于皮肤以用于保护、治疗或预防目的，并且其中封阻(occlusion)的程度是期望的。软膏在多个身体表面上局部使用。这些包括眼睛(眼软膏)、外阴、肛门和鼻的皮肤和粘膜。

[0220] 软膏的媒介物被称为软膏基质。基质的选择取决于软膏的临床适应证。不同类型的软膏基质为：烃基质，例如硬石蜡、软石蜡、微晶蜡和地蜡；吸收基质，例如羊毛脂、蜂蜡；水溶性基质，例如聚乙二醇200、300、400；乳化基质，例如乳化蜡、西曲溴铵；植物油，例如橄榄油、椰子油、芝麻油、杏仁油和花生油。

[0221] 使用疏水性、亲水性或水乳化基质配制软膏以提供与皮肤分泌物不混溶、混溶或可乳化的制剂。在一些情况下，软膏也来源于烃(脂肪)、吸收、水可去除或水溶性基质。活性剂分散于基质中，随后在药物渗透至目标部位(例如膜、皮肤等)后分开。

[0222] 在一些实施方案中，聚(乙二醇)、聚乙氧基蓖麻油(Cremophor®EL)、具有12-20个碳原子的醇或所述组分中两种或更多种的混合物是用于在软膏基质中(具体为在基本包含油性和烃组分的软膏基质中)分散和/或溶解有效量的眼用药物(具体为子囊霉素(ascomycin)和星形孢菌素(staurosporine)衍生物)的有效赋形剂，并且皮肤和眼组织对所得软膏很好地耐受。

[0223] 本发明进一步认识到，当组合物局部施用于眼睛表面(具体为所述患者的巩膜)时，并入本文所述的软膏组合物中的眼用药物靶向患者的脉络膜和/或视网膜。在一些实施方案中，眼用软膏组合物包含眼用药物、软膏基质和用于将所述药物分散和/或溶解在软膏基质中的试剂，该试剂选自聚(乙二醇)、聚乙氧基蓖麻油、具有12-20个碳原子的醇和所述组分中两种或更多种的混合物。

[0224] 在一些实施方案中，软膏基质包括眼科上可接受的油和脂肪基质，诸如天然蜡，例如白色和黄色蜂蜡、巴西棕榈蜡、羊毛蜡(羊毛脂)、纯化的羊毛脂、无水羊毛脂；石油蜡，例如硬石蜡、微晶蜡；烃，例如液体石蜡、白色和黄色软石蜡、白凡士林、黄凡士林；或其组合。

[0225] 以上提及的油和脂肪基质在例如英国药典(British Pharmacopoeia)第2001版或欧洲药典(European Pharmacopoeia)第3版中更详细地描述。

[0226] 基于组合物的总重量，软膏基质以约50％至约95％，优选70％至90％(重量)的量存在。

[0227] 优选的软膏基质包含一种或多种天然蜡(如上文所示的蜡)，优选羊毛蜡(羊毛脂)与一种或多种烃(如上文所示的烃)，优选软石蜡或凡士林，更优选与液体石蜡的组合中的一种或多种组合。

[0228] 上述的软膏基质的具体实施方案包含例如5-17重量份的羊毛脂和50-65重量份的白凡士林以及20-30重量份的液体石蜡。

[0229] 用于将眼用药物分散和/或溶解在软膏基质中的试剂选自聚(乙二醇)、聚乙氧基

蓖麻油、具有12-20个碳原子的醇和所述组分中两种或更多种的混合物。按整个半固体眼用组合物的重量计，该试剂优选以1-20百分比、更优选1-10百分比的量使用。

[0230] 具有12-20个碳原子的醇具体包括十八烷醇($C_{18}H_{37}OH$)、十六烷醇($C_{16}H_{33}OH$)及其混合物。优选所谓的十六十八醇，基本由十八烷醇和十六烷醇组成且优选包含不少于40重量%的十八烷醇并且十八烷醇和十六烷醇的总量达到至少90重量%的固体醇的混合物，以及包含不少于80重量%的十六十八醇和乳化剂(特别是十六十八烷基硫酸钠和/或月桂基硫酸钠，优选的量为不少于7重量%的乳化剂)的组合物。

[0231] 聚乙氧基蓖麻油是天然或氢化蓖麻油与乙二醇的反应产物。这样的产物以已知方式获得，例如通过天然或氢化蓖麻油或其部分与环氧乙烷以例如约1:30至约1:60的摩尔比反应，并且根据例如German Auslegeschriften 1,182,388和1,518,819中公开的方法从产物中任选地去除游离的聚乙二醇组分。尤其适合并优选的是以商品名Cremophor®EL市售的产品，其分子量(通过蒸汽渗透压测定法)＝约1630、皂化数＝约65-70，酸数＝约2，碘数＝约28-32且nD 25＝约1.471。适用于该类别的还有，例如，Nikkol®HCO-60，其为氢化蓖麻油与环氧乙烷的反应产物，表现出以下特征：酸数＝约0.3；皂化数＝约47.4；羟基值＝约42.5；pH(5%)＝约4.6；颜色APHA＝约40；m.p.＝约36.0℃；凝固点＝约32.4℃；H2O含量(%，KF)＝约0.03。

[0232] 根据本发明，聚(乙二醇)在一些实施方案中用作用于将眼用药物分散和/或溶解于软膏基质中的试剂。合适的聚(乙二醇)通常为通式$H-(OCH_2-CH_2)_nOH$的聚合化合物的混合物，其中下标n通常在4-230的范围内，并且平均分子量为约200至约10000。优选地，n为约6至约22的数字并且平均分子量在约300与约1000之间，更优选地，n在约6至约13的范围内并且平均分子量为约300至约600，最优选地，n具有约8.5至约9的值并且相对分子量为约400。合适的聚(乙二醇)易商购获得，例如平均分子量为约200、300、400、600、1000、1500、2000、3000、4000、6000、8000和10000的聚(乙二醇)。

[0233] 聚(乙二醇)，特别是上述段落中所述的优选类型，优选以整个半固体眼用组合物的1-10重量%，更优选1-5重量%的量使用。

[0234] 根据本公开内容的组合物的特别优选的实施方案包含用于将药物分散和/或溶解于软膏基质中的试剂，该试剂选自聚(乙二醇)、聚乙氧基蓖麻油并且优选所述组分的混合物。

凝胶/软膏粘度

[0235] 在一些实施方案中，所述组合物在约20℃下具有约10,000cp至约300,000cp的Brookfield RVDV粘度，并具有$1s^{-1}$的剪切速率。在一些实施方案中，所述组合物在约20℃下具有约15,000cp至约200,000cp的Brookfield RVDV粘度，并具有$1s^{-1}$的剪切速率。在一些实施方案中，所述组合物在约20℃下具有约50,000cp至约150,000cp的BrookfieldRVDV粘度，并具有$1s^{-1}$的剪切速率。在一些实施方案中，所述组合物在约20℃下具有约70,000cp至约130,000cp的Brookfield RVDV粘度，并具有$1s^{-1}$的剪切速率。在一些实施方案中，所述组合物在约20℃下具有约90,000cp至约110,000cp的Brookfield RVDV粘度，并具有$1s^{-1}$的剪切速率。

[0236] 在一些实施方案中，所述眼用凝胶制剂含有足以提供以下粘度的粘度增强剂：约500至1,000,000厘泊、约750至1,000,000厘泊、约1000至1,000,000厘泊、约1000至400,000

厘泊、约2000至100,000厘泊、约3000至50,000厘泊、约4000至25,000厘泊、约5000至20,000厘泊，或约6000至15,000厘泊。在一些实施方案中，该眼用凝胶制剂含有足以提供约50,0000至1,000,000厘泊的粘度的粘度增强剂。

[0237] 在一些实施方案中，本文所述的组合物在体温下为低粘度组合物。在一些实施方案中，低粘度组合物含有约1％至约10％的粘度增强剂(例如胶凝组分，诸如聚氧乙烯-聚氧丙烯共聚物)。在一些实施方案中，低粘度组合物含有约2％至约10％的粘度增强剂(例如胶凝组分，诸如聚氧乙烯-聚氧丙烯共聚物)。在一些实施方案中，低粘度组合物含有约5％至约10％的粘度增强剂(例如胶凝组分，诸如聚氧乙烯-聚氧丙烯共聚物)。在一些实施方案中，低粘度组合物基本不含粘度增强剂(例如胶凝组分，诸如聚氧乙烯-聚氧丙烯共聚物)。在一些实施方案中，本文所述的低粘度眼用剂组合物提供了约100cP至约10,000cP的表观粘度。在一些实施方案中，本文所述的低粘度眼用剂组合物提供了约500cP至约10,000cP的表观粘度。在一些实施方案中，本文所述的低粘度眼用剂组合物提供了约1000cP至约10,000cP的表观粘度。

[0238] 在一些实施方案中，本文所述的组合物在体温下为粘性组合物。在一些实施方案中，粘性组合物含有约10％至约25％的粘度增强剂(例如胶凝组分，诸如聚氧乙烯-聚氧丙烯共聚物)。在一些实施方案中，粘性组合物含有约14％至约22％的粘度增强剂(例如胶凝组分，诸如聚氧乙烯-聚氧丙烯共聚物)。在一些实施方案中，粘性组合物含有约15％至约21％的粘度增强剂(例如胶凝组分，诸如聚氧乙烯-聚氧丙烯共聚物)。在一些实施方案中，本文所述的粘性眼用组合物提供了约100,000cP至约1,000,000cP的表观粘度。在一些实施方案中，本文所述的粘性眼用组合物提供了约150,000cP至约500,000cP的表观粘度。在一些实施方案中，本文所述的粘性眼用组合物提供了约250,000cP至约500,000cP的表观粘度。在一些这样的实施方案中，粘性眼用组合物在室温下为液体，并且大约在室温与体温(包括严重发热，例如最高约42℃的个体)之间的温度下胶凝。在一些实施方案中，粘性眼用组合物作为单一疗法施用以治疗本文所述的眼科疾病或病况。

[0239] 在一些实施方案中，本文所示的凝胶制剂的粘度通过所述的任何方式来测量。例如，在一些实施方案中，使用LVDV-II+CP Cone Plate Viscometer和Cone Spindle CPE-40来计算本文所述的凝胶制剂的粘度。在其他实施方案中，使用Brookfield(轴和杯)粘度计来计算本文所述的凝胶制剂的粘度。在一些实施方案中，本文提及的粘度范围在室温下测量。在其他实施方案中，本文提及的粘度范围在体温下(例如，在健康人的平均体温下)测量。

凝胶/软膏剂量间均匀性

[0240] 典型的眼用凝胶被包装在滴眼瓶中并以液滴的形式施用。例如，眼用凝胶的单一施用(即单一剂量)包括向患者眼中施用一滴、两滴、三滴或更多滴。此外，典型的眼用软膏被包装在具有分配喷嘴(通过该喷嘴递送软膏条)的管或其他可挤压容器中。例如，眼用软膏的单一施用(即单一剂量)包括向患者眼中施用一条或多条。在一些实施方案中，本文所述的眼用凝胶的一个剂量为来自滴眼瓶的一滴凝胶组合物。在一些实施方案中，眼用软膏的一个剂量为通过分散管的喷嘴分配的一条软膏组合物。

[0241] 在一些情况下，本文所述包括提供剂量间均匀浓度的眼用凝胶组合物。在一些情况下，剂量间均匀浓度不呈现剂量间药物含量的显著变化。在一些情况下，剂量间均匀浓度

提供了剂量间一致的药物含量。

[0242] 在一些情况下，本文所述包括提供剂量间均匀浓度的眼用软膏组合物。在一些情况下，剂量间均匀浓度不呈现剂量间药物含量的显著变化。在一些情况下，剂量间均匀浓度提供了剂量间一致的药物含量。

[0243] 在一些实施方案中，所述组合物具有小于50％的剂量间眼用剂浓度变化。在一些实施方案中，所述组合物具有小于40％的剂量间眼用剂浓度变化。在一些实施方案中，所述组合物具有小于30％的剂量间眼用剂浓度变化。在一些实施方案中，所述组合物具有小于20％的剂量间眼用剂浓度变化。在一些实施方案中，所述组合物具有小于10％的剂量间眼用剂浓度变化。在一些实施方案中，所述组合物具有小于5％的剂量间眼用剂浓度变化。

[0244] 在一些实施方案中，所述剂量间眼用剂浓度变化基于10个连续的剂量。在一些实施方案中，所述剂量间眼用剂浓度变化基于8个连续的剂量。在一些实施方案中，所述剂量间眼用剂浓度变化基于5个连续的剂量。在一些实施方案中，所述剂量间眼用剂浓度变化基于3个连续的剂量。在一些实施方案中，所述剂量间眼用剂浓度变化基于2个连续的剂量。

[0245] 非沉降制剂应该不需要摇动来使药物均匀分散。“不需摇动”制剂比需要摇动的制剂潜在有利，简单原因在于患者的摇动行为是药物给药量的可变性的主要来源。已报道，尽管摇动的说明明确标注在标签上，但患者在施用剂量之前经常不摇动或忘记摇动他们需要摇动的眼用组合物。另一方面，即使对于摇动产品的那些患者，通常不能确定摇动的强度和/或持续时间是否足以使产品变均匀。在一些实施方案中，本文所述的眼用凝胶组合物和眼用软膏组合物是维持本文所述的剂量间均匀性的“不需摇动”制剂。

[0246] 为了评估剂量间均匀性，在测试开始之前，将含有眼用水性组合物、眼用凝胶组合物或眼用软膏组合物的滴瓶或管直立储存最少12小时。为了模拟这些产品的推荐给药，以预定的时间间隔从每个市售瓶或管分配预定数目的滴或条持续延长的时间段，或直到瓶或管中不留下产品为止。将所有的滴和条分配至配衡的玻璃小瓶中，加盖，并储存在室温下直到进行分析。使用反相HPLC方法测定在所表示的滴中眼用剂的浓度。

治疗方法

[0247] 本文公开了通过向有需要的个体的眼睛施用有效量的以上描述的眼用组合物来治疗一种或多种眼科病况或疾病的方法。本文还公开了通过向有需要的个体的眼睛施用有效量的以上描述的眼用组合物来改善或减轻一种或多种眼科病况或疾病的方法。

[0248] 在一些实施方案中，所述眼科病况或疾病包括与眼睑、泪器或眼眶(图1)有关的病况或疾病。在一些实施方案中，泪器包括用于产生并排出泪液的眼眶结构。在一些实施方案中，泪器包含负责产生泪液的泪腺、将流体运送到眼睛表面的分泌导管、泪小管、泪囊和鼻泪管。在一些实施方案中，眼眶包括眼睛及其相关附件。在一些实施方案中，针对与眼睑、泪器或眼眶相关的病况或疾病，将本文所述的眼用组合物施用至有需要的个体的眼睛。

[0249] 在一些实施方式中，所述眼科病况或疾病包括与结膜、巩膜、角膜、虹膜或睫状体(图1)相关的病况或疾病。结膜线衬于眼睑内侧并覆盖巩膜。巩膜，或眼白，是不透明的、纤维状、保护性眼睛外层。角膜是覆盖虹膜、瞳孔和前房的眼睛的透明前部。虹膜是眼睛中薄的圆形结构，负责控制瞳孔的直径和大小，因而控制到达视网膜的光量。睫状体包括睫状肌，睫状肌控制晶状体的形状和睫状体上皮，睫状体上皮产生房水。在一些实施方案中，针对与结膜、巩膜、角膜、虹膜或睫状体相关的病况或疾病，将本文所述的眼用组合物施用至

有需要的个体的眼睛。

[0250] 在一些实施方案中，所述眼科病况或疾病包括与脉络膜或视网膜(图1)相关的病况或疾病。脉络膜也称为头绪膜或脉络层，是含有结缔组织的眼睛血管层，位于视网膜与巩膜之间。视网膜是眼睛的第三层，也是内层，是光敏组织层。在一些实施方案中，针对与脉络膜或视网膜相关的病况或疾病，将本文所述的眼用组合物施用至有需要的个体的眼睛。

[0251] 在一些实施方案中，所述眼科病况或疾病包括与晶状体(图1)相关的病况或疾病。晶状体是眼睛中透明的双凸面结构，与角膜一起有助于折射光线以聚焦在视网膜上。在一些实施方案中，针对与晶状体相关的病况或疾病，将本文所述的眼用组合物施用至有需要的个体的眼睛。

[0252] 在一些实施方案中，所述眼科病况或疾病包括但不限于棘阿米巴角膜炎、贝尔麻痹、眼睑皮肤松弛症、睑炎、睑板腺囊肿、白内障、睫状体炎、巨细胞病毒(CMV)视网膜炎、脉络膜视网膜炎症、结膜炎(例如变态反应相关结膜炎或感染引起的结膜炎)、新生儿结膜炎、角膜新血管形成、角膜溃疡、皮炎、糖尿病视网膜病变、干眼综合征、泪腺炎、泪管狭窄、眼内炎、溢泪、巩膜外层炎、眼脓疱病、睫毛稀少症、Fuchs营养不良(也称为Fuchs角膜内皮营养不良或FCED)、青光眼、远视、虹膜炎、角膜结膜炎、干燥性角膜结膜炎、黄斑变性(例如Stargardt病)、黄斑营养不良、黄斑水肿(例如糖尿病黄斑水肿)、近视、眼高压、罗阿丝虫病、眼红斑痤疮、盘尾丝虫病(或称河盲症或Robles病)、视神经炎和视神经病、角膜炎(例如细菌性角膜炎、真菌性角膜炎、寄生性角膜炎或病毒性角膜炎)、睑裂斑和翼状胬肉、瞳孔缩小的产生、巩膜炎、类固醇反应性炎性病况、麦粒肿(或睑腺炎)、颞动脉炎、Thygeson浅层点状角膜病变(TSPK)、沙眼、有机磷中毒、基底细胞癌、鳞状细胞癌、皮脂腺癌、恶性黑素瘤、眼眶淋巴瘤、葡萄膜炎、葡萄膜黑素瘤、视网膜母细胞瘤、髓上皮瘤或原发性眼内淋巴瘤。在一些实施方案中，病毒性角膜炎包括眼疱疹或疱疹性角膜炎，或树状单纯疱疹性角膜炎。

[0253] 在一些实施方案中，引起病毒性眼睛感染的病毒包括单纯疱疹病毒、EB病毒或流感病毒。

[0254] 在一些实施方案中，引起真菌性眼睛感染的真菌包括少孢节丛孢(Arthrobotrys oligospora)、杂色曲霉(Aspergillus versicolar)、假丝酵母(Candida)、枝孢(Cladosporium)、不规则头梗霉(Cephaliophora irregularis)、外瓶霉(Exophiala)、镰孢(Fusarium)(例如腐皮镰孢(Fusarium solani))、茎点霉(Phoma)或丝孢菌(Scedosporium)(例如Scedosporium prolificans)。

[0255] 在一些实施方案中，引起细菌性眼睛感染的细菌包括沙眼衣原体(Chlamydia trachomatis)、脑膜炎奈瑟球菌(N.meningitidis)、金黄色葡萄球菌(Staphylococcus aureus)、表皮葡萄球菌(S.epidermidis)、肺炎链球菌(S.pneumoniae)、链球菌属的种(Streptococcus spp.)或绿脓杆菌。

[0256] 在一些实施方案中，引起眼睛感染的寄生虫包括蠕形螨(Demodex)、利什曼原虫(Leishmania)、线虫如罗阿丝虫(Loa loa)、蚋(Simulium)、刚地弓形虫(Toxoplasma gondii)或弓蛔虫(Toxocara)。

[0257] 在一些实施方案中，眼科病况或疾病是指需要手术的病况或疾病。在一些实施方案中，在手术之前、期间或之后或针对手术有关的并发症施用一种或多种眼用组合物。示例手术包括激光眼部手术、白内障手术、青光眼手术、管道成形术、屈光手术、角膜手术、玻璃

体切除术、眼肌肉手术和眼整形手术。在一些实施例中，手术相关的并发症包括术后增加的眼内压和术后眼部炎症。

[0258] 在一些实施方案中，眼科病况或疾病是指需要诊断剂辅助以便进行可视化的病况或疾病。在一些实施方案中，一种或多种眼用组合物作为用于可视化的诊断剂施用。

[0259] 在一些实施方案中，眼用组合物作为正常或常规眼睛检查程序的一部分施用。在一些实施例中，该正常或常规的眼睛检查程序是眼睛检查。在一些实施方案中，在眼科检查期间施用包含散瞳药的眼用组合物以扩张瞳孔。

[0260] 在一些实施方案中，本文所述的眼用水性制剂被包装在滴眼瓶中并以液滴的形式施用。例如，眼用水性制剂的单一施用(即单一剂量)包括向患者眼中施用一滴、两滴、三滴或更多滴。在一些实施方案中，本文所述的眼用凝胶制剂被包装在滴眼瓶中并以液滴的形式施用。例如，眼用凝胶的单一施用(即单一剂量)包括向患者眼中施用一滴、两滴、三滴或更多滴。在一些实施方案中，本文所述的眼用软膏制剂被包装在具有分配喷嘴(通过该喷嘴递送软膏条)的管或其他可挤压容器中。例如，眼用软膏的单一施用(即单一剂量)包括向患者眼中施用一条或多条。在一些实施方案中，本文所述的眼用水性制剂的一个剂量为来自滴眼瓶的一滴水性组合物。在一些实施方案中，本文所述的眼用凝胶的一个剂量为来自滴眼瓶的一滴凝胶组合物。在一些实施方案中，眼用软膏的一个剂量为通过分散管的喷嘴分配的一条软膏组合物。

[0261] 在所公开的方法的一些实施方案中，在首次使用前，将眼用组合物储存在低于室温的温度下。在所公开的方法的一些实施方案中，在首次使用前，将眼用组合物储存在约2℃至约10℃。在所公开的方法的一些实施方案中，在首次使用前，将眼用组合物储存在约2℃、约3℃、约4℃、约5℃、约6℃、约7℃、约8℃、约9℃或约10℃下。在所公开的方法的一些实施方案中，在首次使用前，将眼用组合物储存在约4℃至约8℃。

[0262] 在所公开的方法的一些实施方案中，在首次使用后，将眼用组合物储存在室温下。在所公开的方法的一些实施方案中，在首次使用后，将眼用组合物储存在约16℃至约26℃。在所公开的方法的一些实施方案中，在首次使用后，将眼用组合物储存在约16℃、约17℃、约18℃、约19℃、约20℃、约21℃、约22℃、约23℃、约24℃、约25℃或约26℃下。

[0263] 在一些实施方案中，所述眼用水性制剂如下施用：下拉将要施用的下眼睑并向眼睑内部施加预定量的水性制剂(例如1-3滴)。分配机构的眼用尖端不接触任何表面以避免污染和/或损伤。

[0264] 在一些实施方案中，所述眼用凝胶制剂如下施用：下拉将要施用的下眼睑并向眼睑内部施加预定量的凝胶(例如1-3滴)。分配机构的眼用尖端不接触任何表面以避免污染和/或损伤。

[0265] 在一些实施方案中，所述眼用软膏制剂如下施用：下拉将要施用的下眼睑并向眼睑内部施加少量的软膏(约0.25英寸)。分配机构的眼用尖端不接触任何表面以避免污染和/或损伤。

[0266] 在一些实施方案中，所述眼用组合物在延长的时间段内以预定的时间间隔施用。在一些实施方案中，该眼用组合物一天施用一次。在一些实施方案中，该眼用组合物每天施用一次。在一些实施方案中，该眼用组合物每隔一天施用一次。在一些实施方案中，该眼用组合物在1周、2周、1个月、2个月、3个月、6个月、1年、2年、3年、4年、5年、6年、7年、8年、9年、

10年、11年或12-15年内施用。在一些实施方案中，该眼用组合物仅施用一次。

[0267] 在一些实施方案中，所述眼用组合物以剂量间眼用剂浓度变化小于50％、小于40％、小于30％、小于20％、小于10％或小于5％的剂量施用。

[0268] 向有需要的个体施用组合物的次数取决于医疗专业人员的判断、病症、病症的严重程度以及个体对制剂的反应。在一些实施方案中，向患有轻度急性病况的有需要的个体施用本文公开的组合物一次。在一些实施方案中，向患有中度或重度急性病况的有需要的个体施用本文公开的组合物多于一次。在患者的病情没有改善的情况下，根据医生的判断，长期(即，在延长的时间段，包括患者生命的整个持续时间)施用眼用剂，以减轻或以其他方式控制或限制患者的疾病或病况的症状。

[0269] 在患者的病情没有改善的情况下，根据医生的判断，长期(即，在延长的时间段，包括患者生命的整个持续时间)施用眼用剂，以减轻或以其他方式控制或限制患者的疾病或病况的症状。

[0270] 在患者的状况确实得到改善的情况下，根据医生的判断，继续给予眼用剂的施用；或者，将所施用的药物的剂量暂时减少或暂时暂停某一时间长度(即“休药期”)。休药期的长度在2天与1年之间不等，仅举例而言，包括2天、3天、4天、5天、6天、7天、10天、12天、15天、20天、28天、35天、50天、70天、100天、120天、150天、180天、200天、250天、280天、300天、320天、350天和365天。休药期期间的剂量减少为10％-100％，仅举例而言，包括10％、15％、20％、25％、30％、35％、40％、45％、50％、55％、60％、65％、70％、75％、80％、85％、90％、95％和100％。

[0271] 一旦患者的眼睛病况发生改善，则如有必要，施用眼用剂的维持剂量。随后，任选地根据症状将施用的剂量或频率或两者降低至保持疾病、病症或病况改善的水平。在某些实施方案中，一旦有任何症状复发，则患者需要长期的间歇治疗。

[0272] 对应于这样的量的眼用剂的量将依赖于诸如具体化合物、疾病病况及其严重程度等因素，根据关于该病例的具体情况而变化，这些具体情况包括例如施用的具体眼用剂、给药途径、所治疗的病况、所治疗的目标区域和所治疗的受试者或宿主。所需剂量以单一剂量或作为同时(或在短时间段内)或以适当间隔施用的分开的剂量提供。

[0273] 在一些实施方案中，初始施用的是特定的眼用剂，而随后施用的是不同的制剂或眼用剂。

药剂盒/制品

[0274] 本发明还提供了用于治疗一种或多种本文描述的眼科病况或疾病的药剂盒。这样的药剂盒通常包含一种或多种本文公开的眼用组合物和关于使用该药剂盒的说明。本发明还涉及一种或多种眼用组合物在制备用于缓和、减轻或改善一种或多种本文所述眼科病况或疾病的症状的药物中的用途。

[0275] 在一些实施方案中，药剂盒包括载具、包装或被区室化为接纳一个或多个容器如小瓶、管等的容器，每个容器包含将在本文所述的方法中使用的一个单独要素。合适的容器包括，例如，瓶、小瓶、注射器和试管。在其他实施方案中，容器由诸如玻璃或塑料的多种材料形成。

[0276] 本文提供的制品含有包装材料。本文还提供了用于包装药物产品的包装材料。参见例如美国专利号5,323,907、5,052,558和5,033,252。药物包装材料的实例包括但不限于

滴瓶、管、泵、包、小瓶、容器、注射器、瓶和适于所选制剂以及预期给药和治疗方式的任何包装材料。涉及本文提供的宽范围的眼用组合物，其用于针对通过眼用剂向眼睛的控制释放施用而获益的任何疾病、病症或病况的多种治疗。

[0277] 在一些实施方案中，药剂盒包括一或多个附加容器，每个附加容器具有从商业和用户角度考虑对于使用本文所述制剂而言所期望的一种或多种不同材料(诸如冲洗剂、擦拭巾和/或装置)。这样的材料也包括列出内容物的标签和/或使用说明以及具有使用说明的包装插页。任选地包括一组说明。在另一个实施方案中，标签处于容器上或与容器相关联。在又一个实施方案中，当构成标签的字母、数字或其他字符附着、模制或蚀刻在容器本身上时，该标签处于容器上；当标签存在于也容纳容器的接纳器或托架内(例如作为包装插页)时，该标签与该容器相关联。在其他实施方案中，使用标签来指示内容物将用于具体治疗应用。在又一个实施方案中，标签也指示关于内容物例如在本文所述方法中的使用的指导。

[0278] 在某些实施方案中，所述眼用组合物在含有一个或多个单位剂型的分配器装置中提供，该单位剂型含有本文提供的化合物。在另一个实施方案中，该分配器装置伴随有给药说明。在又一个实施方案中，该分配器也伴随有由监管药物的制造、使用或销售的政府机构所规定形式的、与容器相关联的公告，该公告反映出该机构批准用于人类或兽医给药的药物形式。在另一个实施方案中，该公告例如是由美国食品和药品管理局批准用于处方药物的标记或已批准的产品插页。在又一个实施方案中，还制备了含有在相容性药物载体中配制的本文提供的化合物的组合物，将该组合物置于适当容器中，并标出用于治疗所示出的病况。

术语

[0279] 除非另外定义，否则本文使用的所有技术和科学术语具有与所请求保护的主题所属领域的技术人员通常理解的相同的含义。应当理解，前面的一般描述和下面的详细描述仅是示例性和解释性的，并不限制所请求保护的任何主题。在本申请中，除非另有具体说明，否则单数的使用包括复数。必须指出，如说明书和所附权利要求书中所使用的，单数形式“一种”、“一个”和“该”包括复数指代物，除非上下文另有明确说明。在本申请中，“或”的使用意味着“和/或”，除非另有说明。此外，术语“包括”以及其他形式如“包括”、“包含”和“含有”的使用不是限制性的。

[0280] 如本文所用，范围和量表示为“约”特定值或范围。“约”还包括确切的量。因此，“约5μg”是指“约5μg”以及“5μg”。通常，术语“约”包括预期在实验误差内的量。

[0281] 本文使用的章节标题仅用于组织目的，不应被解释为限制所描述的主题。本申请中引用的所有文件或部分文件(包括但不限于专利、专利申请、文章、书籍、手册和论文)都明确地通过引用全部并入本文以用于任何目的。

[0282] 如本文所包括的，术语“受试者”和“个体”可互换使用。这些术语均不被解释为要求医务专业人员(例如医生、护士、医师助理、护理员、临终关怀工作人员)的监督。

实施例

实施例1—眼用制剂

[0283] 表1-5中描述了用于制备眼用制剂的示例性组合物。

表1—水溶液制剂

成分	量（mg/g）	浓度（wt%）
眼用剂	0.01-200	0.001-20 (wt%)
缓冲剂和/或 pD 调节剂（例如硼酸盐和/或 DCl）	-	适量以达到 pD=4-8
防腐剂（例如苯扎氯铵、西曲铵、过硼酸钠等）	-	适量，以防止引入溶液中的微生物的生长或破坏该微生物
张力和/或摩尔渗透压浓度调节剂（例如 NaCl、甘露醇等）	-	适量，至 0.5-2.0 wt%
氘化水	-	适量，至 100 wt%

表2－水溶液制剂

成分	量（mg/g）	浓度（wt%）
眼用剂	0.01-50	0.001-5 (wt%)
缓冲剂和/或 pD 调节剂（例如硼酸盐和/或 DCl）	-	适量以达到 pD=4-8
防腐剂（例如苯扎氯铵、西曲铵、过硼酸钠等）	-	适量，以防止引入溶液中的微生物的生长或破坏该微生物
张力和/或摩尔渗透压浓度调节剂（例如 NaCl、甘露醇等）	-	适量，至 0.5-2.0 wt%
氘化水	-	适量，至 100 wt%

表3－纤维素凝胶制剂

成分	量（mg/g）	浓度（wt%）
眼用剂	0.01-200	0.001-20 (wt%)
粘度增强剂（例如羟丙基甲基纤维素）	10-50	1-5 (wt%)
缓冲剂和/或 pD 调节剂（例如乙酸钠和/或 DCl）	-	适量以达到 pD=4-8
稳定剂（例如 EDTA、环糊精等）	-	适量，以使眼用剂低降解
摩尔渗透压浓度调节剂（例如 NaCl）	-	适量，150-500 mOsm/L
氘化水	-	适量，至 100 wt%

表4—热固性凝胶制剂

成分	量（mg/g）	浓度（wt%）
眼用剂	0.01-200	0.001-20 (wt%)
粘度增强剂（例如泊洛沙姆 407）	100-250	10-25 (wt%)
缓冲剂和/或 pD 调节剂（例如乙酸钠和/或 DCl）	-	适量以达到 pH=4.2-7.9
稳定剂（例如 EDTA、环糊精等）	-	适量，以使眼用剂低降解
摩尔渗透压浓度调节剂（例如 NaCl）	-	适量，150-500 mOsm/L
氘化水	-	适量，至 100 wt%

表5—软膏制剂

成分	对于 1000 mL 溶液的量(g)	在 1000 mL 水溶液中的浓度
眼用剂	0.01-200	0.001-20 (wt%)
分散剂（例如聚乙二醇和/或聚乙氧基蓖麻油和/或 C12-C20 醇）	10-200	1-20 (wt%)
缓冲剂、pD 调节剂（例如 DCl）	-	适量以达到 pD=4-8
稳定剂（例如 EDTA、环糊精等）	-	适量，以使眼用剂低降解
摩尔渗透压浓度调节剂（例如 NaCl）	-	适量，150-500 mOsm/L
软膏基质（例如羊毛蜡和/或凡士林和/或液体石蜡）		适量，至 100 wt%

实施例2-在D_2O中含有0.01%眼用剂的水溶液制剂的制备

[0284] 1%储备溶液

[0285] 对于100mL溶液，添加1克眼用剂和0.77g NaCl(以及其他成分/组分，优选处于其干燥状态)以及足以等于100mL的量的无菌注射用氘化水。在热板上用搅拌棒使溶液在适当大小的烧杯中混合，直至所有固体粉末均已溶解且溶液已变澄清而无可见颗粒。接下来，取出搅拌棒，并将溶液倒入过滤瓶中，并通过0.22微米聚醚砜膜过滤器真空过滤至无菌瓶中。从无菌储存瓶去除过滤器顶部，并将储存瓶用无菌瓶盖盖上以便储存。。

[0286] 稀释的0.01%溶液

[0287] 将0.3mL的1%溶液与足以达到30mL总体积的量的无菌0.9%注射用氯化钠(USP)合并。使溶液完全混合。记录溶液的pD。将0.22微米过滤器置于注射器的尖端上，并将溶液等分至单独的无菌容器中。

实施例3-稳定性分析

[0288] 从1%眼用储备溶液(如实施例2所述制备)制备五种0.01%眼用溶液。对于溶液1-5，五种溶液的pH分别为4.5、5、5.5、6和6.5。使每种溶液完全混合。将0.22微米过滤器置于注射器的尖端上，并根据表6将溶液等分至单独的无菌容器中。

表6.容器填充概要

容器类型	容器中0.01%眼用药物产品的体积	填充的容器总数
无菌滴眼管	5-mL	12
无菌玻璃小瓶	5-mL	12

[0289] 然后将样品储存在不同的条件下以供稳定性分析。在不同的时间点直至2个月对样品进行分析。储存条件包括:40℃与75%相对湿度(RH)(3天后在2-8℃条件下转移样品)、25℃与60%RH,以及60℃。时间点为1周、2周、1个月和2个月。在每个时间点,将来自每一储存条件的一个塑料滴眼管(LDPE塑料)和一个玻璃小瓶取出,并使其平衡至环境条件。一经平衡,将塑料滴眼管和玻璃小瓶均颠倒3次。将滴眼管中的溶液经由滴管逐滴转移至HPLC小瓶中。使用玻璃Pasteur移液管将玻璃小瓶中的溶液等分至HPLC小瓶中。然后使用表7中列出的UPLC方法测试样品的纯度和效力。

表7.UPLC方法参数

参数	条件
柱	EMD, Hiber HR PurospherSTAR C-18, 100 x 2.1 mm, 2 μm
流动相/稀释剂	87:13, 50 mM 磷酸钾:乙腈, pH 3.5
流动	等梯度
流速	0.5 mL/min
检测波长	210 nm
柱温	30 ± 3 ℃
自动进样器温度	5 ± 3 ℃
运行时间	6.0 分钟
注射体积	10 μL*
洗针溶液	90/10 水:乙腈

[0290] 计算基于Arrhenius的保质期预测。这些预测基于降解是一阶(线性)的假设。

实施例4—剂量均匀性(10个剂量)

[0291] 为了评估剂量间均匀性,在测试开始之前,将含有眼用水性组合物的滴瓶直立储存预定的时间段(例如12小时)。为了模拟该产品的推荐给药,以预定的时间间隔(例如连续地,每1分钟、每10分钟、每小时或每24小时)从每瓶分配10滴水性组合物。所有滴都分配至配衡的玻璃小瓶中,加盖,并储存在室温下直至进行分析。使用反相HPLC方法来测定所表示的滴中眼用剂的浓度。

实施例5—剂量均匀性(5个剂量)

[0292] 为了评估剂量间均匀性，在测试开始之前，将含有眼用水性组合物的滴瓶直立储存预定的时间段(例如12小时)。为了模拟该产品的推荐给药，以预定的时间间隔(例如连续地，每1分钟、每10分钟、每小时或每24小时)从每瓶分配5滴水性组合物。所有滴都分配至配衡的玻璃小瓶中，加盖，并储存在室温下直至进行分析。使用反相HPLC方法来测定所表示的滴中眼用剂的浓度。

实施例6—剂量均匀性(2个剂量)

[0293] 为了评估剂量间均匀性，在测试开始之前，将含有眼用水性组合物的滴瓶直立储存预定的时间段(例如12小时)。为了模拟该产品的推荐给药，以预定的时间间隔(例如连续地，每1分钟、每10分钟、每小时或每24小时)从每瓶分配2滴水性组合物。所有滴都分配至配衡的玻璃小瓶中，加盖，并储存在室温下直至进行分析。使用反相HPLC方法来测定所表示的滴中眼用剂的浓度。

实施例7—pD对豚鼠中眼可接受性的影响

[0294] 向一组豚鼠施用50μL本文描述的具有不同pD值的眼用制剂。例如，向动物施用包含H_2O或氘化水(例如D_2O)的眼用制剂。以预定的时间间隔记录动物行为，以评价眼用制剂的可接受性。

实施例8—体内兔眼刺激测试

[0295] 使本文公开的示例性组合物经受兔眼刺激测试，以评价其安全性概况。在新西兰兔中利用眼刺激测试来对测试组合物进行测试(参见，例如Abraham M H等人，Draize rabbit eye test compatibility with eye irritation thresholds in humans:a quantitative structure-activity relationship analysis.Toxicol Sci.2003年12月;76(2):384-91.Epub 2003年9月26日;还参见Gettings S D等人，Acomparison of low volume,Draize and in vitro eye irritation test data.III.Surfactant-based formulations.Food Chem Toxicol.1998年3月;36(3):209-31)。该研究涉及向三只兔中每一只的右眼中单眼施用，并向其左眼施用相同体积的安慰剂。在组合物滴注后立即以及在滴注后4小时、24小时、48小时和72小时对兔进行检查，以记录眼刺激的体征/症状(如果存在)。测试组合物在兔眼的角膜、虹膜和结膜中未显示出刺激体征。

实施例9-眼用水性制剂的安全性和有效性研究

[0296] 进行临床试验以研究本文描述的眼用水性制剂在患者中的有效性和安全性。在一些情况下，该研究为开放标签、单盲或双盲研究。患者选择标准包括感兴趣的眼科病况以及诸如年龄、性别和/或健康状况等其他因素。

[0297] 将患者随机分配为在单眼或双眼中每夜接受一次在氘化水(例如D_2O)中配制的5%、1%或0.1%眼用水性制剂。基于患者群体来定义分配比。

[0298] 在第0天(基线)、14天、30天时对患者进行评价，随后在2个月、3个月、4个月、5个月、6个月、8个月、10个月、12个月、18个月、20个月、24个月和36个月时对患者进行评价。

[0299] 主要结果是在研究时段内的病况或疾病进展。通过包括变态反应、刺激或者单眼或双眼视力模糊的发展在内的不良事件来评价安全性。

实施例10-软膏制剂的制备

[0300] 在加热和超声处理下将眼用剂与分散剂(例如聚乙二醇)混合，并进一步将该混合物与熔化的软膏基质(例如羊毛蜡、白凡士林和液体石蜡的混合物)充分混合。将混合物置

于压力容器中，并在125℃下灭菌30-45分钟并冷却至室温。在另一个实施方案中，在氮气下进行高压灭菌。将所得眼用软膏无菌填充至预先灭菌的容器(例如管)中。

[0301] 尽管本文中已经示出并描述了本发明的优选实施方案，但这些实施方案仅以示例的方式提供。本文描述的实施方案的各种替代方案任选地在实施本发明中使用。目的在于以下述权利要求限定本发明的范围，并由此涵盖这些权利要求范围内的方法和结构及其等同项。

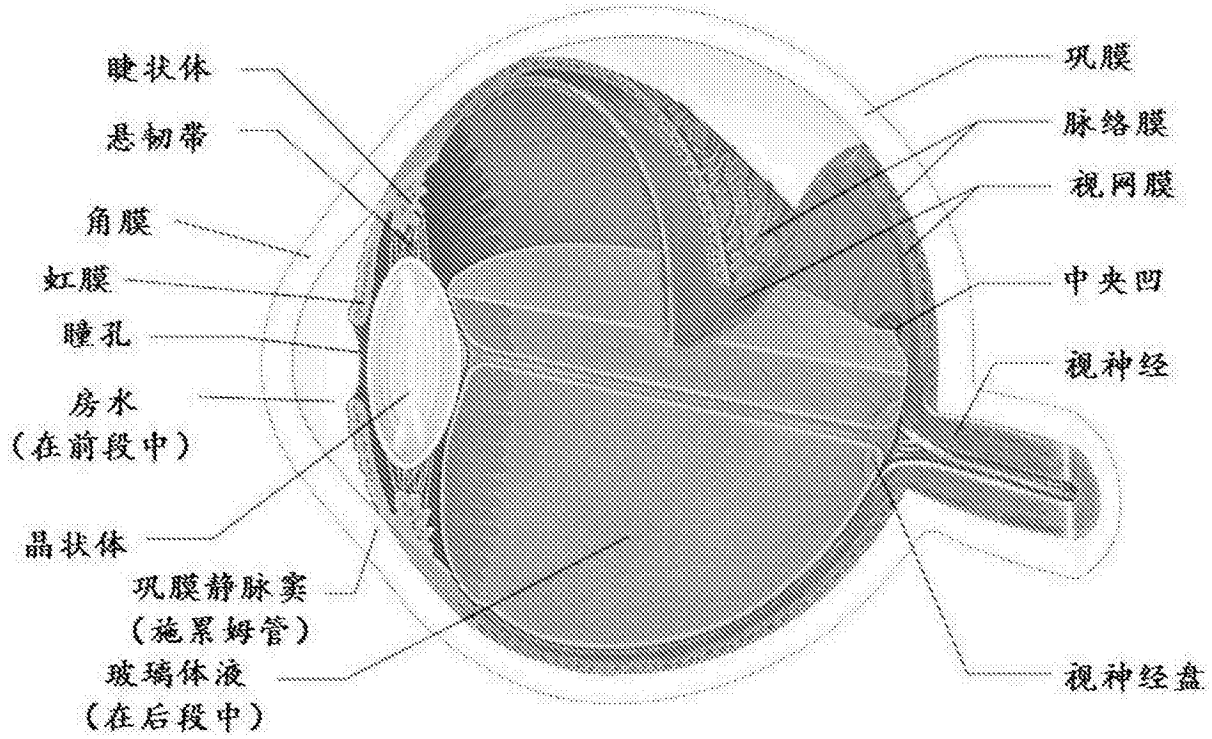

睫状体
悬韧带
角膜
虹膜
瞳孔
房水
（在前段中）
晶状体
巩膜静脉窦
（施累姆管）
玻璃体液
（在后段中）
巩膜
脉络膜
视网膜
中央凹
视神经
视神经盘

图1