COMPOSITIONS AND METHODS FOR THE TREATMENT OF PRESBYOPIA

BACKGROUND OF THE INVENTION

[001] As a person ages the minimum distance from the eye at which an object will come into focus, provided distance vision is corrected or is excellent unaided, increases. For example, a 10 year-old can focus on an object or a "focal point" only three inches (0.072 meters) from their eye while still retaining excellent distance vision; a 40 year-old at six inches (0.15 meters); and a 60 year-old at an inconvenient 39 inches (1.0 meter). This condition of increasing minimum focal length in individuals with excellent unaided distance vision is called presbyopia, loosely translated as "old-man eye".

[002] Excellent unaided distance vision is also known as emmetropia. The inability to focus on distant focal points is known as myopia and the inability to focus on near focal points is known as hyperopia. Specifically, "distance" vision is considered any focal point 1 meter or more from the eye and near vision is any focal point less than 1 meter from the eye. The minimum focal length at which an object will come into focus is known as the "near point". The change in focus from distance to the near point and any focal point in between is called accommodation. Accommodation is often measured in diopters. Diopters are calculated by taking the reciprocal of the focal length (in meters). For example, the decrease in accommodation from a 10 year-old eye to a 60 year-old eye is about 13 diopters ($1 \div 0.072$ meters = 13.89 diopters; $1 \div 1$ meter = 1 diopter).

[003] The highest incidence of first complaint of presbyopia occurs in people ages 42-44. Presbyopia occurs because as a person ages the eye's accommodative ability which uses near reflex-pupil constriction, convergence of the eyes and particularly ciliary muscle contraction, decreases. This reduction in accommodation results in an inadequate change in the normal thickening and increased curvature of the anterior surface of the lens that is necessary for the shift in focus from distant objects to near objects. Important near focus tasks affected by presbyopia include viewing computer screens (21 inches) and reading print (16 inches).

[004] Presbyopia is a normal and inevitable effect of ageing and is the first unmistakable sign for many in their forties that they are getting older. One study found that more than 1 billion people worldwide were presbyopic in 2005. This same study predicted that number to almost double by the year 2050. If everyone over the age of 45 is considered to be presbyopic, then an

estimated 122 million people in the United States alone had presbyopia in 2010. As baby boomers reach the critical age, this number is only going to increase.

[005] Presbyopia carries with it a stigma resulting from the limitation in ability to quickly function at many tasks requiring focusing at both distant and near points, which once occurred almost immediately. In the presbyopic patient, these tasks can be performed only by the use of eyeglasses, contact lenses or after undergoing invasive surgery. One such optical modification, the monovision procedure, can be executed with the use of glasses, contact lenses or even surgery. The monovision procedure corrects one eye for near focus and the other eye for distance focus. However, monovision correction is normally accompanied by loss of depth perception and distance vision particularly in dim light (e.g. night). Other surgical procedures that have been developed to relieve presbyopia include: (1) the implantation of intraocular lenses (INTRACOR®; registered trademark of Technolas Perfect Vision GMBH); (2) reshaping of the cornea (PresbyLASIK and conductive keratoplasty); (3) scleral band expansion; and (4) implantation of corneal inlays (Flexivue Microlens®; registered trademark of PresbiBio LLC, Kamra®; registered trademark of AcuFocus, Inc. and Vue+). Kamra® corneal inlays manufactured by AcuFocus work by inlaying a pinhole on the cornea to increase the depth of focus.

[006] A similar effect can be achieved with general miotic agents, such as pilocarpine (a non-selective muscarinic acetylcholine receptor agonist), carbachol (a non-selective muscarinic acetylcholine receptor agonist), and phospholine iodide (an acetylcholinesterase inhibitor). These general miotics can induce a pinhole pupil at sufficient concentrations to achieve pupils below 2.0 mm and potentially extend depth of focus much like an inlay, but at concentrations sufficient to cause pinhole pupil diamters of 2.0 mm or less these agents trigger increased ciliary muscle contraction and induce accommodation of any remaining reserves, improving near vision at the expense of distance vision in individuals who still retain some accommodative function. The side effects of ciliary spasm induced migraine like brow pain and blurred distance vision from induced myopia beyond the ability of a pinhole pupil to correct then necessitate using weaker concentrations with much shorter acting and more marginal effect, such as found with pilocarpine. In such cases even slight hyperopia helps offset the induced myopia while even very small increments of myopia, which is very common, exacerbate it. In extreme cases, such

ciliary muscle spasms may possibly be associated with anterior chamber shallowing and pull on the ora serrata of the retina, resulting in a retinal tear and or retinal detachment.

[007] Miotic agents have been described in various patent and patent applications for the treatment of presbyopia. US Patent Nos. 6,291,466 and 6,410,544 describe the use of pilocarpine to regulate the contraction of ciliary muscles to restore the eye to its resting state and potentially restore its accommodative abilities.

[008] US Patent No. 8,524,758 describes the use of pilocarpine with the non-steroidal anti-inflammatory, diclofenac, to reduce brow ache from ciliary spasm and increase the time in which the ciliary muscle contraction is regulated. International PCT Application Publication WO/2013/041967 describes the use of pilocarpine with oxymetazoline or meloxicam to temporarily overcome ocular conditions such as presbyopia.

[009] US Patent No. 8,299,079 (HEK Development LLC) describes the use of direct acting general miotic agents such as pilocarpine, carbachol and phospholine iodide with the alpha 2 selective vasoconstrictor brimonidine at a concentration from 0.05% to 3.0% w/v. However, the use of brimonidine concentrations of about 0.20% (or any at or above 0.05%) w/v induces ciliary spasm with often migraine intensity brow and/or head aches, and frequently results in increased rebound hyperemia. For example, rebound redness occurs in 25% of patients using brimonidine 0.20% w/v (Alphagan®, registered trademark of Allergan, Inc.) twice daily.

[010] US Patent Application Publication No. 2014/0113946 describes the use of pilocarpine with the alpha 1 and mild alpha 2 agonist vasoconstrictor oxymetazoline, demonstrating limitations in distance sharpness and duration, whereby a cohort largely restricted to mild hyperopes is required to neutralize the induced myopia (Table 1). Of the 16 eyes treated only three were -0.25 to -0.50 diopters, and eight were mildly hyperopic. Of the -0.50 diopter eyes two were reduced to 20.40 distance. Further, duration was limited as full effect became diminished in about four hours. Pupil size range was from 2.0 mm to 2.7 mm, where enhanced near effect and distance sharpness from depth of focus was minimal to absent.

[011] These attempts at miotic treatment for presbyopia all induce transient myopia of several diopters reducing distance vision to about legal blindness or worse at the expense of improved near vision for the full duration of their action, typically lasting several hours. This myopic effect is amplified by the exponential drop off in distance acuity with even small increments of nominal myopia in terms of unaided untreated vision. For example, a person having mild myopia (e.g.

spherical equivalents of -0.25 D, -0.50 D) that is usually associated with glasses free distance vision, typically will have several lines of distance vision loss after instillation of pilocarpine 1% (i.e. spherical equivalent of -0.75 D.).

[012] Miotics historically used to treat glaucoma, other than pilocarpine, particularly aceclidine, are also associated with ciliary spasm, brow and/or headache, and myopic blur. Further, aceclidine is unstable in solution. Normally, aceclidine is stored in a two-bottle system; one bottle containing the lyophilized aceclidine and the second bottle containing the diluent necessary to reconstitute the lyophilized aceclidine before topical instillation. However, the primary issue with its use as a presbyopic miotic is the attendant pain and in some cases distance blur that may be induced.

[013] U.S. Patent No. 9,089,562 describes a composition containing aceclidine combined with a cycloplegic agent, such that in preferred embodiments aceclidine 1.45% is combined with tropicamide 0.042%. The addition of the cycloplegic agent at extremely low concentratnos (less than 0.10%) surprisingly still results in pupil miosis and allows for useful distance and improved near vision without ciliary spasm (often a migraine like brow ache that can be extremely painful and disabling), which is induced by the use of aceclidine alone. Further, aceclidine and the cycloplegic agent require particular narrowly defined ratios and ranges of concentrations relative to each other such that complications in the manufacturing and regulatory process, particularly the need for lyophilization of aceclidine to allow its stable storage, and attendant effects of cryoprotectant / lyoprotectant (hereinafter referred to as "cryoprotectant") required, where it is a discovery of the present invention the addition of a cryoprotectant such as a polyol, in a preferred embodiment mannitol, results in reduced efficacy of the defined ranges and ratios of concentrations of US 9,089,562. Due to these medical and practical inefficiencies, it is discovered an aceclidine composition requiring same or slightly higher concentrations of aceclidine and much lower concentrations than US 9,089,562 or in some cases no cycloplegic agent, while allowing for formulation modifications to lyophilize aceclidine would be preferred for the treatment of presbyopia with necessary commercially stable formulations. However, to date, no aceclidine composition with amounts of cycloplegic agent lower than that claimed in US 9,089,562 has been effective to treat presbyopia because, as mentioned above, aceclidine alone, particularly young and middle-aged presbyopes (ages 45 to 58), severe ciliary spasms and may cause accommodative induced distance blur in some subjects.

[014] Thus, there is a need in the art for a treatment of presbyopia that is non-invasive and convenient with minimal side effects. Specifically, there is a need for an ophthalmological composition that will allow a person suffering from presbyopia to focus on near objects without significant side effects such as diminished distance vision, blurred vision, pain, redness, impaired night driving or incapacitating dim light vision, induced nasal congestion, or risk of retinal detachment. Further, there is a need in the art for a reduction or elimination of the need for a cycloplegic agent to be used with aceclidine potentially enhancing duration and efficacy, as well as for means of storage of stable aceclidine compositions, where such compositions preferably enhance both distance and near depth of focus allowing pupil miosis to a 1.50 to 2.0 mm range without clinically significant side effects.

SUMMARY OF THE INVENTION

[015] In certain embodiments, the present invention is directed to compositions and methods for the treatment of presbyopia.

[016] In certain embodiments, the present invention is directed to compositions and methods for the treatment of presbyopia comprising a muscarinic agonist, wherein the muscarinic agonist preferentially activates M1 and M3 muscarinic acetylcholine receptors. In still more preferred embodiments the muscarinic agonist is more highly selective for M1 than M3. In certain embodiments, the present invention is directed to compositions and methods for the treatment of presbyopia comprising a muscarinic agonist that preferentially activates M1 and M3 muscarinic acetylcholine receptors.

[017] In certain embodiments, the present invention is directed to compositions and methods for the treatment of presbyopia comprising a muscarinic agonist selected from the group consisting of aceclidine, talsaclidine, sabcomeline, cevimeline, WAY-132983, AFB267B (NGX267), AC-42, AC-260584, 77-LH-28-1, and LY593039 or any pharmaceutically acceptable salts, esters, analogues, prodrugs or derivatives thereof.

[018] In certain embodiments, the present invention is directed to compositions and methods for the treatment of presbyopia comprising a muscarinic agonist that activates only M1 muscarinic acetylcholine receptors.

[019] In certain other embodiments, the present invention is directed to an ophthalmological composition for the treatment of presbyopia comprising aceclidine.

[020] In certain preferred embodiments, the present invention is directed to ophthalmological compositions for the treatment of presbyopia comprising aceclidine, preferably at a concentration from about 0.25% to about 2.0% w/v, and a cycloplegic agent, preferably tropicamide.

[021] In certain preferred embodiments, the present invention is directed ophthalmological compositions for the treatment of presbyopia comprising aceclidine, preferably at a concentration from about 0.25% to about 2.0% w/v and a cryoprotectant, preferably a polyol, preferably mannitol at a concentration from about 1.0% to about 10.0% w/v, more preferably 2.5% w/v. In certain preferred embodiments, the present invention is directed to ophthalmological compositions for the treatment of presbyopia comprising:

about 1.75% w/v aceclidine;

about 2.5% w/v mannitol; and

optionally about 0.004% to 0.015% w/v tropicamide.

[022] In certain preferred embodiments, the present invention is directed to ophthalmological compositions for the treatment of presbyopia comprising:

about 1.75% w/v aceclidine;

about 2.5% w/v mannitol;

about 1.0% to about 6.0% w/v of a nonionic surfactant;

about 0.1% to about 2.25% w/v hydroxypropylmethyl cellulose; and

optionally about 0.004% to 0.015% w/v tropicamide.

[023] In certain preferred embodiments, the present invention is directed to ophthalmological compositions for the treatment of presbyopia comprising:

about 1.75% w/v aceclidine;

about 2.5% w/v mannitol;

about 1.0% to about 6.0% w/v of a nonionic surfactant, preferably the nonionic surfactant is selected from a polysorbate, tyloxapol, a poloxamer, a cyclodextrin, vitamin E TPGS and a polyoxyl, more preferably polysorbate 80, even more preferably from about 1.0% to about 5.0% w/v polysorbate 80 and most preferably from about 2.0% to about 4.0% w/v polysorbate 80;

about 0.1% to about 2.25% w/v hydroxypropylmethyl cellulose, more preferably from about 0.75% to about 1.5% w/v hydroxypropylmethyl cellulose and most preferably from about 1.0% to about 1.25% w/v hydroxypropylmethyl cellulose;

about 0.10% to about 0.12% w/v sorbic acid;
about 0.005% to about 0.02% w/v benzalkonium chloride; and
optionally about 0.004% to 0.015% w/v tropicamide.

[024] In certain preferred embodiments, the present invention is directed to ophthalmological compositions for the treatment of presbyopia comprising:

about 1.75% w/v aceclidine;
about 2.5% w/v mannitol;

about 1.0% to about 6.0% w/v of a nonionic surfactant, preferably the nonionic surfactant is selected from a polysorbate, tyloxapol, a poloxamer, a cyclodextrin, vitamin E TPGS and a polyoxyl, more preferably polysorbate 80, even more preferably from about 1.0% to about 5.0% w/v polysorbate 80 and most preferably from about 2.0% to about 4.0% w/v polysorbate 80;

about 0.1% to about 2.25% w/v hydroxypropylmethyl cellulose, more preferably from about 0.75% to about 1.5% w/v hydroxypropylmethyl cellulose and most preferably from about 1.0% to about 1.25% w/v hydroxypropylmethyl cellulose;

about 0.10% to about 0.12% w/v sorbic acid;
about 0.005% to about 0.02% w/v benzalkonium chloride;
one or more antioxidants selected from the group consisting of ethylenediaminetetraacetic acid (EDTA), ethylenediaminetetraacetic acid dihydrate, sodium citrate and citrate buffer, preferably selected from the group consisting of ethylenediaminetetraacetic acid dihydrate and sodium citrate or citrate buffer; and
optionally about 0.004% to 0.015% w/v tropicamide.

[025] In certain preferred embodiments, the present invention is directed to ophthalmological compositions for the treatment of presbyopia comprising:

about 1.75% w/v aceclidine;

optionally, about 0.004% to 0.015% w/v tropicamide;

about 1.0% to about 6.0% w/v of a nonionic surfactant;

about 0.1% to about 2.25% w/v hydroxypropylmethyl cellulose;

about 0.10% to about 0.12% w/v sorbic acid; and

about 0.005% to about 0.02% w/v benzalkonium chloride,

wherein the composition is maintained at a temperature from about 2 to about 8 degrees celsius.

[026] In certain preferred embodiments, the present invention is directed to ophthalmological compositions for the treatment of presbyopia comprising:

about 1.75% w/v aceclidine;

about 2.5% w/v mannitol;

about 4.0% w/v polysorbate 80;

about 1.25% w/v hydroxypropylmethyl cellulose;

about 0.12% w/v sorbic acid;

about 0.1% w/v ethylenediaminetetraacetic acid dihydrate;

about 0.02% w/v benzalkonium chloride; and

about 0.1% w/v sodium citrate or citrate buffer.

[027] In certain preferred embodiments, the present invention is directed to ophthalmological compositions for the treatment of presbyopia comprising:

about 1.75% w/v aceclidine;

about 2.5% w/v mannitol;

about 4.0% w/v polysorbate 80;

about 1.25% w/v hydroxypropylmethyl cellulose;

about 0.12% w/v sorbic acid;

about 0.1% w/v ethylenediaminetetraacetic acid dihydrate;

about 0.02% w/v benzalkonium chloride;

about 0.1% w/v sodium citrate or citrate buffer; and

about 0.01% w/v tropicamide.

[028] In a preferred embodiment the concentration of hydroxypropylmethyl cellulose is from about 0.1% to about 2.25% w/v, more preferably from about 0.75% to about 1.5% w/v and most preferably from about 1.0% to about 1.25% w/v. Preferably, the concentration of

hydroxypropylmethyl cellulose is such that the viscosity is from about 1 to about 10,000 cps prior to instillation, more preferably from about 200 to about 500 cps and most preferably about 400 cps.

[029] In another preferred embodiment, opththalmological compositions of the present invention comprise one or more antioxidants selected from the group consisting of ethylenediaminetetraacetic acid ("EDTA"), ethylenediaminetetraacetic acid dihydrate, sodium citrate and citrate buffer, preferably 0.1% w/v ethylenediaminetetraacetic acid dihydrate; and 0.1% w/v sodium citrate or citrate buffer.

[030] In another preferred embodiment, the nonionic surfactant is selected from a polysorbate, tyloxapol, a poloxamer, a cyclodextrin, vitamin E TPGS and a polyoxyl, preferably polysorbate 80, more preferably 4.0% w/v polysorbate 80.

[031] In another preferred embodiment, opththalmological compositions of the present invention have a pH of about 4.0 to about 8.0 for tropicamide free compositions and from about 4.0 to about 6.0 in compositions containing tropicamide and more preferably 5.0 in compositions, regardless of tropicamide content.

[032] In certain preferred embodiments, the present invention is directed ophthalmological compositions for the treatment of presbyopia comprising aceclidine, preferably at a concentration from about 0.25% to about 2.0% w/v, a cryoprotectant, preferably a polyol, preferably mannitol at a concentration from about 1.0% to about 10.0% w/v, more preferably 2.5% w/v, and a nonionic surfactant, preferably the nonionic surfactant is selected from the group consisting of a polysorbate, a polyoxyl castor oil, a polyoxyl stearate, a poloxamer, a polyethylene glycol, a polyoxyethylene glycol alkyl ether, tyloxapol and 2-[[10,13-dimethyl-17-(6-methylheptan-2-yl)-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-yl]oxy]ethanol, more preferably polysorbate 80 or polyoxyl 35 castor oil, more preferably at a concentration of about 0.5% to about 10.0% w/v, more preferably from about 1.0% to about 7.0% w/v, even more preferably about 2.5% or 3.5% w/v.

[033] In certain preferred embodiments, the present invention is directed ophthalmological compositions for the treatment of presbyopia comprising aceclidine, preferably at a concentration from about 0.25% to about 2.0% w/v, more preferably 1.75% w/v, a cryoprotectant, preferably a polyol, preferably mannitol at a concentration from about 1.0% to about 10.0% w/v, more preferably 2.5% w/v, tropicamide, preferably at a concentration from about 0.004% to about

0.025% w/v, more preferably about 0.005% to about 0.007%, a nonionic surfactant, preferably polysorbate 80, more preferably at a concentration of about 0.5% to about 10.0% w/v, more preferably from about 2.0% to about 6.0% w/v, even more preferably about 2.5% to about 4.0% w/v and a viscosity agent, preferably selected from the group consisting of a cellulose derivative, hyaluronate, a carbomer and a gum, more preferably high molecular weight carboxymethyl cellulose or carbomer 940, preferably at a concentration from about 1.0% to about 2.0% w/v, and more preferably about 1.35% to 1.45% w/v and even more preferably about 1.42% w/v, or other viscosity agent such as hydroxypropylmethyl cellulose, preferably at a concentration from about 1.0% to about 2.0%, and more preferably about about 0.50% to 1.95%, wherein initial viscosity of the composition prior to instillation in the eye may range from about 25 to about 10,000 centipoise, and more preferably about 100 to about 5,000 centipoise and may be non-Newtonian and or induce tear secretion resulting in minimal blur, and or with minimal blur at high shear (intrablink) vs. low shear (between blinks) after instillation.

[034] In certain preferred embodiments, the present invention is directed ophthalmological compositions for the treatment of presbyopia comprising aceclidine, preferably at a concentration from about 0.25% to about 2.0% w/v, more preferably 1.75% w/v, a cryoprotectant, preferably a polyol, preferably mannitol at a concentration from about 1.0% to about 10.0% w/v, more preferably 2.5% w/v, tropicamide, preferably at a concentration from about 0.004% to about 0.025% w/v, more preferably about 0.005% to about 0.007%, a nonionic surfactant, preferably polysorbate 80, more preferably at a concentration of about 0.5% to about 10.0% w/v, more preferably from about 2.0% to about 6.0% w/v, even more preferably about 2.5% to about 4.0% w/v, a viscosity agent, preferably selected from the group consisting of a cellulose derivative, hyaluronate, carbomer 940 and a gum, more preferably high molecular weight carboxymethyl cellulose or carbomer 940, preferably at a concentration from about 1.0% to about 2.0% w/v, and more preferably about 1.35% to 1.45% w/v and even more preferably about 1.42% w/v, or other viscosity agent such as hydroxypropylmethyl cellulose, preferably at a concentration from about 0.5% to about 1.75%, and more preferably about 0.75% or 1.5%, most preferably from about 1.0% to about 1.5%, and most preferably at about 1.05% to 1.25%, wherein initial viscosity of the composition prior to instillation in the eye may range from about 25 to about 10,000 centipoise, and more preferably about 100 to about 5000 centipoise and may be non-Newtonian with minimal blur at high shear (intrablink) vs. low shear (between blinks) after instillation, and

a preservative, preferably selected from the group consisting of benzalkonium chloride ("BAK"), sorbic acid and oxychloro complex.

[035] In certain other embodiments, the present invention is directed to a method of stabilizing a composition comprising aceclidine comprising storing the composition in a container having a headspace at a temperature from about 2 degrees Celsius to about 8 degrees Celsius, preferably at about 5 degrees Celsius.

[035a] In certain other embodiments, the present invention is directed to a method of stabilizing a composition comprising aceclidine comprising storing the composition in a container having a headspace at a temperature from about 2 degrees Celsius to about 8 degrees Celsius, preferably at about 5 degrees Celsius, wherein the term "about" is defined as ±10% of each particular value.

[036] In certain other embodiments, the compositions of the present invention are filled into the container having a headspace under an inert gas overlay, preferably nitrogen, preferably the headspace is purged with an inert gas overlay, preferably nitrogen.

[037] In certain other embodiments, the present invention is directed to a method of stabilizing a composition comprising aceclidine, a viscosity agent, and a nonionic surfactant comprising storing the composition in a container having a headspace at a temperature from about 2 degrees Celsius to about 8 degrees Celsius, wherein the composition is filled into the container under a nitrogen overlay and the headspace is purged with nitrogen and wherein the composition provides a low shear (1/sec) viscosity from about 50 to about 1000 centipoise and a high shear (1:1000/sec) of about 0.5 or less centipoise.

[037a] In certain other embodiments, the present invention is directed to a method of stabilizing a composition comprising aceclidine, a viscosity agent, and a nonionic surfactant comprising storing the composition in a container having a headspace at a temperature from about 2 degrees Celsius to about 8 degrees Celsius, wherein the composition is filled into the container under a nitrogen overlay and the headspace is purged with nitrogen and wherein the composition provides a low shear (1/sec) viscosity from about 50 to about 1000 centipoise and a high shear (1:1000/sec) of about 0.5 or less centipoise, wherein the term "about" is defined as ± 10% of each particular value.

[038] In certain other embodiments, the container of the present invention comprises a closure and a vessel wherein a portion of the closure and a portion of the vessel are sealed with an anti-leaching material selected from the group consisting of biaxially-oriented polyethylene

terephthalate, polytetrafluorethylene and aluminum foil, preferably biaxially-oriented polyethylene terephthalate.

[039] In certain other embodiments, the container of the present invention is disposed in a second container that is formed with or lined with an anti-leaching material selected from the group consisting of biaxially-oriented polyethylene terephthalate, polytetrafluorethylene and aluminum foil, preferably biaxially-oriented polyethylene terephthalate.

[040] In certain other embodiments, the present invention is directed to a method of stabilizing a composition comprising aceclidine comprising storing the composition in a container having a headspace at a temperature from about 22 degrees Celsius to about 25 degrees Celsius, wherein the container comprises a closure and a vessel wherein a portion of the closure and a portion of the vessel are sealed with an anti-leaching material selected from the group consisting of biaxially-oriented polyethylene terephthalate, polytetrafluorethylene and aluminum foil and/or the container is disposed in a second container that is formed with or lined with biaxially-oriented polyethylene terephthalate, polytetrafluorethylene and aluminum foil.

[040a] In certain other embodiments, the present invention is directed to a method of stabilizing a composition comprising aceclidine comprising storing the composition in a container having a headspace at a temperature from about 22 degrees Celsius to about 25 degrees Celsius, wherein the container comprises a closure and a vessel wherein a portion of the closure and a portion of the vessel are sealed with an anti-leaching material selected from the group consisting of biaxially-oriented polyethylene terephthalate, polytetrafluorethylene and aluminum foil and/or the container is disposed in a second container that is formed with or lined with biaxially-oriented polyethylene terephthalate, polytetrafluorethylene and aluminum foil, wherein the term "about" is defined as ± 10% of each particular value.

[041] In certain other embodiments, the second container comprises a second closure, wherein the second closure provides an airtight seal.

[042] In certain other embodiments, the the airtight seal is resealable.

[043] In certain other embodiments, aceclidine is at a concentration from about 0.25% to about 4.0% w/v aceclidine.

[044] In certain other embodiments, the methods of the present invention provide at least 90% stability of aceclidine for at least 7 months, at least 8 months, at least 12 months, at least 15 months, at least 18 months, at least 20 months or at least 22 months.

[045] In certain other embodiments, the compositions of the present invention further comprises a viscosity agent, a polysorbate, a cryoprotectant and a preservative.

[046] In certain other embodiments, the viscosity agent provides a viscosity of at least 50 centipoise, at least 100 centipoise, or at least 200 centipoise.

[047] In certain other embodiments, the cryoprotectant is selected from the group consisting of a a polyol, a sugar, an alcohol, a lower alkanol, a lipophilic solvent, a hydrophilic solvent, a bulking agent, a solubilizer, a surfactant, an antioxidant, a cyclodextrin, a maltodextrin, colloidal silicon dioxide, polyvinyl alcohol, 2-methyl-2,4-pentanediol, cellobiose, gelatin, polyethylene glycol (PEG), dimethyl sulfoxide (DMSO), formamide, antifreeze protein 752 or a combination thereof.

[048] In certain other embodiments, the preservative is selected from the group consisting of benzalkonium chloride, sorbate, an antioxidant and a combination thereof.

[049] In certain other embodiments, the antioxidant is selected from the group consisting of sodium ascorbate, sodium bisulfate, ~~soidum~~sodium metabisulfite, n-acetyl cysteine or a combination thereof.

[050] In certain other embodiments, the present invention is directed to a method of stabilizing a composition comprising aceclidine, hydroxypropylmethyl cellulose, polysorbate 80, mannitol, sorbate and an antioxidant selected from the group consisting of sodium ascorbate, sodium bisulfate, ~~soidum~~sodium metabisulfite, n-acetyl cysteine or a combination thereof comprising storing the composition in a container having a headspace at a temperature from about 2 degrees Celsius to about 8 degrees Celsius, wherein the composition is filled into the container under an inert gas overlay, preferably nitrogen and the headspace is purged with an inert gas, preferably nitrogen.

[050a] In certain other embodiments, the present invention is directed to a method of stabilizing a composition comprising aceclidine, hydroxypropylmethyl cellulose, polysorbate 80, mannitol, sorbate and an antioxidant selected from the group consisting of sodium ascorbate, sodium bisulfate, sodium metabisulfite, n-acetyl cysteine or a combination thereof comprising storing the composition in a container having a headspace at a temperature from about 2 degrees Celsius to about 8 degrees Celsius, wherein the composition is filled into the container under an inert gas overlay, preferably nitrogen and the headspace is purged with an inert gas, preferably nitrogen, wherein the term “about” is defined as ± 10% of each particular value.

[051] In certain other embodiments, the aceclidine is at a concentration from about 0.25% to about 4.00% w/v, the hydroxypropylmethyl cellulose is at a concentration from about 0.75% to about 1.25% w/v, polysorbate 80 is at a concentration from about 2% to about 4% w/v, mannitol is at a concentration from about 2% to about 4% w/v, sorbate is at a concentration from about 0.10% to about 0.12% w/v and the antioxidant is at a concentration from about 0.10% to about 0.25% w/v.

[052] In certain other embodiments the present invention is directed to a container comprising aceclidine prepared by the process comprising the steps of:

a) providing a container;

b) filling the container with a composition comprising aceclidine under an inert gas overlay, prefereably nitrogen;

c) purging a headspace created during the filling step b) with an inert gas, preferably nitrogen;

d) capping the container; and

e) optionally, storing the container at a temperature from about 2 to about 8 degrees Celsius.

[052a] In certain other embodiments the present invention is directed to a container comprising aceclidine prepared by the process comprising the steps of:

a) providing a container;

b) filling the container with a composition comprising aceclidine under an inert gas overlay, prefereably nitrogen;

c) purging a headspace created during the filling step b) with an inert gas, preferably nitrogen;

d) capping the container; and

e) optionally, storing the container at a temperature from about 2 to about 8 degrees Celsius, wherein the term "about" is defined as ± 10% of each particular value.

[053] In certain other embodiments the present invention is directed to a composition comprising from about 0.25% to about 4.0% w/v aceclidine and one or more means of stabilizing the composition selected from the group consisting of filling the composition into a container under an inert gas overlay, preferably nitrogen and purging a headspace created during filling with the inert gas overlay, preferably nitrogen, having a total viscosity of the composition of at

least 50 centipoise or more, adding a preservative to the composition selected from the group consisting of sorbate, ~~benzalkonim~~benzalkonium chloride, sodium ascorbate, sodium bisulfate, ~~soidum~~sodium metabisulfite, n-acetyl cysteine and a combination thereof,
wherein the composition is stored at a temperature from about 2 to about 8 degrees Celsisus and wherein w/v denotes weight by total volume of the composition.

[053a] In certain other embodiments the present invention is directed to a composition comprising from about 0.25% to about 4.0% w/v aceclidine and one or more means of stabilizing the composition selected from the group consisting of filling the composition into a container under an inert gas overlay, preferably nitrogen and purging a headspace created during filling with the inert gas overlay, preferably nitrogen, having a total viscosity of the composition of at least 50 centipoise or more, adding a preservative to the composition selected from the group consisting of sorbate, benzalkonium chloride, sodium ascorbate, sodium bisulfate, sodium metabisulfite, n-acetyl cysteine and a combination thereof,
wherein the composition is stored at a temperature from about 2 to about 8 degrees Celsisus and wherein w/v denotes weight by total volume of the composition, wherein the term "about" is defined as ± 10% of each particular value.

[054] In certain other embodiments, the present invention is directed to a method of treating presbyopia comprising administering to a subject in need thereof a composition of the present invention.

[055] In certain other embodiments, the present invention is directed to a method of treating presbyopia comprising administering to a subject in need thereof an ophthalmological composition of the present invention, wherein near vision acuity of the subject is improved by about 4 lines of resolution or more for at least 8 hours, where it is discovered the addition of a nonionic surfactant at 0.50% to 10%, and more preferably 1.0% to 6.0%, and still more preferably at 3.0% to 5.0%; and optionally one or more of the following: increased viscosity such as in a preferred embodiment about 400 cps using hydroxypropylmethyl cellulose at 1.25%; and addition of a preservative combination of BAK, sorbate and antioxidant combination of one or more of EDTA and citrate; thereby further improve one or more of i) reduced redness; ii) increased lines of near improvement without distance blur; iii) excellent comfort; and iv) enhanced duration.

[056] In certain other embodiments, the present invention is directed to a method of treating a refractive error of the eye in a subject in need thereof comprising administering to a subject in need thereof a pharmaceutically acceptable amount of a composition of the present invention wherein the refractive error of the eye is selected from presbyopia, myopia, hyperopia, astigmatism or a combination thereof.

[057] In certain other embodiments, the present invention is directed to a method of treating a refractive error of the eye comprising administering to a patient in need thereof a pharmaceutically acceptable amount of a composition of the present invention, wherein the size of the pupil is reduced to from about 1.5 to about 2.5 millimeters, preferably from about 1.7 to about 2.2 millimeters and wherein the refractive error is selected from the group consisting of a range of distance corrected vision for mild to moderate hyperopia of 3.0 D or less; mild to moderate myopia of -5.0 D or less; regular astigmatism of 3.0 D or less; uncorrected distance vision for emmetropes of + 0. 50 to -0.50 spheq with regular astigmatism of 0.75 D or less; corneal irregular astigmatism, an ectasia induced corneal irregularity, a pellucid induced corneal irregularity, a higher order aberration and a refractive surgery induced higher order aberration.

[058] The present invention is further directed to a method of increasing the visual depth of field (i.e. depth of focus) secondary to pupil miosis, comprising administering to a subject in need thereof a pharmaceutically effective amount of an ophthalmological composition of the present invention.

[059] The present invention is further directed to a method of reducing the side effects of ophthalmic aceclidine administration by modulating the agonist effect on the ciliary body of the eye such that ciliary spasm, ciliary induced brow ache, and/or ciliary induced headache are substantially reduced or eliminated.

[060] The present invention is further directed to a method of allowing binocular physiologic topical presbyopic correction.

[061] The present invention is further directed to a method of eliminating the need for monocular limitation due to distance blur, or reduced to treatment of mild hyperopes to counteract induced myopic blur, as typically associated with pilocarpine, or pilocarpine and alpha agonist combinations.

[062] The present invention is further directed to a method of improving near vision by increasing accommodation without reduction in distance vision sharpness. This is achieved by

simultaneously increasing incremental accommodation, modulated so that while sufficient to provide additive near vision enhancement, it remains at a rate of induction and total degree of accommodation such that the associated myopic blur does not break through the ability of the simultaneously induced pupil miosis pinhole effect to filter the refractive error and maintain distance sharpness.

[063] The present invention is further directed to a method of increasing the visual depth perception upon improving near vision unaided comprising administering to a subject in need thereof a pharmaceutically effective amount of an ophthalmological composition of the present invention in both eyes (binocular vision), wherein such binocularity further enhances near vision beyond that of either eye separately.

[064] The present invention is further directed to a method of improving vision in a subject with ammetropia (vision abnormality), comprising administering to a subject in need thereof a pharmaceutically effective amount of a composition of the present invention.

[065] The present invention is further directed to a method of improving vision in a subject with ammetropia, comprising administering to a subject in need thereof a pharmaceutically effective amount of a composition of the present invention, wherein ammetropia is selected from the group consisting of nearsightedness, farsightedness, regular astigmatism, irregular astigmatism and high degrees of regular astigmatism.

[066] The present invention is further directed at eliminating optical aberrations induced by corneal irregularity, opacities, or very high degrees of regular astigmatism that include regions adjacent or peripheral to the central 1.5 mm optical zone, and thereby inducing improved visual acuity and quality of vision by filtering out these aberrant optics in those suffering from irregular astigmatism or high degrees of more regular astigmatism, such as occurs in conditions such as keratoconus, photorefractive keratectomy induced corneal haze, diffuse lamellar keratitis ("DLK") (post-lasik DLK), other iatrogenic corneal induced irregularity such as cataract incision, glaucoma filtering blebs, implanted glaucoma valves, corneal inlays with or without removal, ectasia post corneal surgery (lasik), and secondary to infection.

[067] The present invention is further directed at improving acuity relative to existing uncorrected refractive error. Upon this improved acuity, patients now requiring toric contact lenses for astigmatism with reduced comfort and optics that may shift during each blink may in many cases require only non-toric soft contact lenses or no contact lenses. Further, those

requiring gas permeable contact lenses may no longer require contact lenses or only require much more comfortable soft contact lenses. Patients with high degrees of astigmatism may now require no correction or reduced astigmatic correction. Patients with small to moderate degrees of nearsightedness may require less correction or no longer require correction. Patients with small to moderate degrees of hyperopia (farsightedness) may require no correction or reduced correction.

[068] The present invention is directed to methods and ophthalmological compositions for improving eye sight. In a preferred embodiment the present invention is directed to methods and ophthalmological compositions for the treatment of presbyopia. In a more preferred embodiment the present invention is directed to ophthalmological compositions comprising aceclidine.

[069] The present invention is directed to methods of treating irregular astigmatism, keratoconic ectasia, and low myopia, or hyperopia, with or without astigmatism, comprising administering to a subject in need thereof an ophthalmological composition of the present invention.

[070] The present invention is further directed to a method of stabilizing aceclidine comprising providing a first composition comprising about 1.75% w/v aceclidine and about 2.5% w/v mannitol in a first chamber and a second composition comprising about 0.01% w/v tropicamide, about 4.0% w/v polysorbate 80, about 1.25% w/v hydroxypropylmethyl cellulose, about 0.10% to 0.12% w/v sorbic acid, about 0.1% w/v ethylenediaminetetraacetic acid dihydrate, about 0.02% w/v benzalkonium chloride and about 0.1% w/v sodium citrate or citrate buffer in a second chamber, wherein upon mixing the first composition and the second composition the efficacy of aceclidine is maintained for at least one month.

[071] The present invention is further directed to a method of stabilizing aceclidine comprising storing a composition of the present invention at from 0 degrees Celsius to 8 degrees Celsius.

[072] The present invention is further directed to a method of inhibiting microbial and fungal growth comprising the following steps:

providing an ophthalmological composition comprising about 1.75% w/v aceclidine, about 2.5% w/v mannitol, about 0.01% w/v tropicamide, about 4.0% w/v polysorbate 80 and about 1.25% w/v hydroxypropylmethyl cellulose;

adding from about 0.10% to 0.12% w/v sorbic acid; and

adding one or more of about 0.1% w/v ethylenediaminetetraacetic acid dihydrate and about 0.1% w/v sodium citrate or citrate buffer.

BRIEF DESCRIPTION OF THE FIGURES

[073] Figure 1 is a graphical representation of the effects of pilocarpine and aceclidine with or without tropicamide and with or without a carrier on near and distance vision in a patient over the age of 45.

[074] Figure 2 is a graphical representation of the effects of addition of non-ionic surfactants and viscosity agents on near vision acuity and duration of effect. Line-Hours denotes lines improved times duration of effect.

[075] Figure 3 is a graphical representation of the Efficacy Index for formulas #L33-#L94. Box color denotes a comfort level of good for white, fair for cross-hatched and poor for black.

[076] Figure 4 is a graphical representation of percent stability of aceclidine cold storage compositions at 5 and 25 degrees Celsius over 30 months.

DETAILED DESCRIPTION OF THE INVENTION

[077] The present invention is directed to compositions and methods of treating presbyopia, irregular astigmatism, and/or refractive error, comprising administering to a patient in need thereof a pharmaceutical composition comprising a muscarinic agonist that preferentially activates M1 and M3 muscarinic acetylcholine receptors, preferably activate M1 more than M3 and most preferably aceclidine or its derivatives. Aceclidine has been surprisingly and unexpectedly discovered to provide enhanced presbyopic reversal with negligible side effects day or night (when viewing includes one or more direct or reflected light sources) using compositions of the present invention.

[078] Aceclidine is traditionally used as a treatment for glaucoma. When aceclidine is used to treat glaucoma it is normally stored in a two-bottle system; one bottle containing the lyophilized aceclidine and the second bottle containing the diluent necessary to reconstitute the lyophilized aceclidine before topical instillation. Romano J.H., Double-blind cross-over comparison of aceclidine and pilocarpine in open-angle glaucoma, *Brit J Ophthal*, Aug 1970, 54(8), 510-521. It is a further aspect of the present invention to provide an aqueous aceclidine composition that is stable in combination with cold chain storage. It is yet a further aspect of the present invention to provide a method of stabilizing aqueous aceclidine by combining effective excipients, pH ranges and temperature ranges.

[079] The compositions and methods of the present invention treat presbyopia by improving depth of focus in patients with presbyopia by administering an ophthalmological composition to the eye that reduces pupil dilation in the dark or in dim light, produces a particular degree and duration of miosis without accommodation, provides cosmetic whitening and/or induce redness prophylaxis. The compositions and methods of the present invention also do not cause significant pupil rebound, tachyphylaxis, ciliary spasms, induction of myopia or reduction in distance vision. Additionally, the compositions and methods of the present invention allow for the further improvement in visual acuity and depth perception of binocular (both eyes) treatment. The ophthalmological composition of the present invention surprisingly creates a pupil of from about 1.5 to about 2.4 mm at the anterior iris plane and about 2.0 mm at the corneal surface. Not wishing to be held to particular theory the clinical effect appears to involve both with modulated increase in accommodative tone and enhanced pinhole near depth of focus for improved near vision, estimated to be about -1.25 D or less, but restricted in power to remain wihin the range of pinhole correction for distance, found to be about -1.00 D or less creating a sum increase that may in some cases create a near vision add of +2.00 D or more without distance blur; and with a reduction or ablation of the redness that is otherwise a hallmark of the use of miotic agents. The pupil miosis of the present invention with such modulation and restriction of peak accommodative tone is superior to the pinhole effect of the Kamra® and Flexivue Microlens® corneal inlays, allowing binocular treatment without peak dimming. Pupil miosis of the present invention with modulated accommodation is also superior to inlays because the constriction of the actual pupil does not result in the attendant severe night vision disturbance caused by the light scattering borders of the pre-corneal pinholes created by the inlays. Further pupil miosis provides a greater field of vision and transmission of more focused light, and in a discovered optimal pupil range of about 1.5 mm to 2.1 mm using formulation discoveries of the present invention does so with negligible to mild and very tolerable dimming and enhanced contrast, distance vision, reduced glare at night, and improved near vision.

[080] The use of aceclidine has a minimal effect on the longitudinal ciliary muscle, thus reducing risk of retinal detachment when compared to the use of general muscarinic agonists such as pilocarpine and carbachol. The further inclusion of a cycloplegic agent resulted in only 0.04 mm of anterior chamber shallowing. Aceclidine, particularly as enhanced for the present invention, also has greater magnitude, duration, and control of minimum pupil diameter than

conventional pilocarpine with or without alpha agonists, and less anterior chamber inflammation with chronic use. Compositions of the present invention achieve these advantages by allowing both pinhole near vision depth perception benefit and modest accommodative increase below the threshold of induced myopic distance blur through the miotic pupil, whereby, not wishing to be held to particular theory, it is believed the rate of miosis and the rate of accommodative increase maintain a synchronous balance in preferred embodiments allowing pinhole correction of otherwise induced accommodative blur in prior art applications of miotics for presbyopic correction. This combination thus is found to avoid the distance blur typically seen in patients as a response to pilocarpine and/or carbachol induced miosis without the formulation discoveries of the present invention, as well as the excessive accommodative myopia and ciliary spasm manifested as brow ache or generalized migraine-like headache.

[081] Such conventional formulations of pilocarpine, in order to effect any reasonable duration of effect, are still restricted to less than or equal to about 4 hours in most cases, as the high ratio of accommodation to pupillary miosis requires minimal concentrations of pilocarpine of about 1.0% to minimize but not eliminate distance induced myopic blur and ciliary spasm. Further pilocarpine must be instilled monocularly to minimize intolerable distance blur to a still bothersome 2-3 lines of distance blur. Even instilled monocularly, pilocarpine still may create bothersome attendant distance blur and must be restricted to about 1.0%. Upon instillation of 1.0% pilocarpine pupil size is about 2.3 mm or larger in most subjects and thereby restricts any significant pinhole depth perception benefit as well as any pinhole filtering of induced myopic rays. The restriction to about 1.0% for these conventional formulations of pilocarpine with the attendant short duration and still bothersome but reduced distance blur in emmetropes or myopes (somewhat neutralized in low hyperopes) are attempts to prevent extremely strong accommodation of 5D to 11 D well known to occur at higher concentrations of pilocarpine.

[082] Any effects on accommodation may be further reduced or totally eliminated in preferred embodiments by combining a miotic with a cycloplegic agent in a narrow and particular ratio of miotic to cycloplegic, where such ratios as discovered for US 9, 089,562, such as about 35:1 for a preferred embodiment, become greatly increased for the present invention in the presence of cryoprotectant as to a factor of about 300% - 700%. Aceclidine is capable of producing the increased depth of focus by both pupil miosis below 2.3 mm and modest accommodation described in the present invention. Particularly enhanced miosis occurs with use of compositions

of the present invention. This enhanced miosis makes it possible to use an α-2 agonist at very low concentrations if desired to reduce mild eye redness. Other combinations of inactive ingredients reduce or effectively eliminate induced redness without such agonists. Further, due to the apparent and surprisingly selective nature of aceclidine, and the commercially stable aceclidine formulation discoveries of the present invention, administration to the eye of compositions of the present invention result in a net strongly enhanced near vision acuity from both pupil miotic pinhole effect and moderate modulated ciliary accommodation. These beneficial effects are accompanied by a filtering pupil effect, which eliminates any distance blur from the accommodation, correcting residual refractive error and optical aberrations as may exist to in many cases improve distance vision as well. Thus, the administration of aceclidine results in pupil miosis without excessive accommodation and attendant distance blur. However, aceclidine alone may cause substantial redness and brow ache. Without formulation enhancement of the present invention such as requiring cycloplegic agent, cryoprotectant or both, aceclidine may produce either less than optimal pupil miosis at low concentrations or at higher concentrations require more than desired peak miosis to attain satisfactory duration of greater than 3-4 hours. However the use of a cycloplegic agent has been found to be highly sensitive to other inactive ingredients in the formulation not usually associated with effects on active agents, and particularly for cryoprotectants as found to be preferred commercially for aceclidine reduce or eliminate the need for this cycloplegic requirement to extremely low concentrations in a preferred embodiment, rendering 0.042% sufficiently high when a cryoprotectant is present (e.g. a polyol such as mannitol) to cause substantial loss of efficacy. Further, aceclidine without formulation enhancements of the present invention causes dimming of vision in dim or absent lighting as well as ciliary pain above a reasonably tolerable threshold that may last for an hour or more and be similar to a severe migraine headache.

[083] Certain embodiments of the present invention enhance the discovered preferred degree of pupillary miosis by providing a consistent range of effect of about 1.50 – 2.20 mm for most patients using a preferred embodiment of a nonionic surfactant and viscosity agent. Similar benefit may be achieved using other permeation enhancers, particularly hydroxypropylmethyl cellulose, high viscosity carboxymethyl cellulose, Carbopol® (polyacrylic acid or carbomer), and various viscosity additives that increase drug residence time, such as xanthan gums, guar gum, alginate, and other *in situ* gels well known to experts in the art. It is well known to experts in the

art that the exact concentration of a specific viscosity agent will depend on both the molecular weight for that agent selected and the concentration, such that for increased molecular weight a reduced concentration can have the same viscosity. The present invention further prevents nasal congestion otherwise occurring when substantial aceclidine levels reach the nasal mucosa, due to the rheologic properties of the preferred embodiment.

[084] The combination of aceclidine and a low concentration of a selective α-2 adrenergic receptor agonist (α-2 agonist or α-2 adrenergic agonist), such as fadolmidine, brimonidine or guanfacine, allows for the desired miotic effect with diminished or no redness. The use of low concentrations of a selective α-2 agonist results in substantial reduction of hyperemia with greatly reduced risk of rebound hyperemia that is found in concentrations of about 0.06% w/v or more. Furthermore, the use of low concentrations of selective α-2 agonist does not adversely modify the pupil constriction caused by aceclidine. In contrast, the use of brimonidine 0.20% w/v, when topically applied for pupil modulation for night vision, result in tachyphylaxis of pupil modulation due to α-2 receptor upregulation in almost 100% of treated subjects within four weeks of use.

[085] Unexpectedly, the addition of a cycloplegic agent results in reduction of any brow ache or associated discomfort by further reducing the degree of ciliary spasms on topical instillation without impairing the miotic response. More unexpectedly and surprisingly, the ratio of 1.40% aceclidine to about 0.040% tropicamide in a preferred embodiment of U.S. Patent No. 9,089,562 (35:1) becomes about 1.75% aceclidine to about 0.004% to 0.010% tropicamide (350:1, 175:1 respectively) in the presence of mannitol, where 2.5% provides better effect than 4.0%.

[086] The lack of impairment of the miotic response is an unexpected surprising discovery, as particular cycloplegic agents, such as tropicamide, have known pupil dilating effects at concentrations as low as 0.01% w/v (Grünberger J. et al., The pupillary response test as a method to differentiate various types of dementia, Neuropsychiatr, 2009, 23(1), pg 57). More specifically cycloplegic agents cause pupil mydriasis (i.e. dilation of the radial muscle of the iris). Further, the addition of a cycloplegic agent to the miotic agent unexpectedly increases the time at which the pupil maintains the desired size range without becoming too restricted. Peak miotic effect at 30 – 60 minutes can be titrated in inverse relation to the cycloplegic concentration. The concentrations of tropicamide discovered in the present invention apparently cause more relaxation of the ciliary muscle than the iris radial musculature. In fact, iris

mydriasis is discovered to be suppressed by the addition of tropicamide to compositions containing concentrations of aceclidine used in the present invention, with instead a more consistent level of miosis for the duration of the miotic effect. Additionally and quite surprisingly, unexpectedly, and beneficially the addition of tropicamide can reduce the degree of peak pupil miosis without inducing mydriasis thereby creating a more constant and ideal pupil size throughout the drug induced miosis. This more consistent pupil size allows for beneficial near and distance vision without the adverse dimming or loss of resolution due to diffraction limits at the very reduced pupil sizes seen at peak pupil miosis (e.g. 1.25 mm).

[087] Previously, in US 9,089,562, it was surprisingly found that the addition of at least 0.04% w/v cycloplegic agent resulted in an abatement of ciliary side effects caused by the administration of aceclidine (1.40%) to the eye, in a preferred embodiment, but such formulations are not as constituted sufficiently stable for commercial use, and typically have a duration of about five to six hours maximum.

[088] Several additional discoveries of the present invention allow for commercially stable aceclidine formulations with enhanced efficacy and duration:

[089] Equally or more surprising than the synergistic effects of cyloplegics of 0.040% added to aceclidine 1.40%, is the discovery of the present invention that combination of aceclidine 1.50% -2.0%, and preferably about 1.75% and a cryoprotectant, preferably a polyol, in a preferred embodiment mannitol, particularly at 0.5% to 4.0% and most preferably about 2.5%, can achieve a similar pupil range with reduced or absent ciliary side effects. The cryoprotectant when combined with aceclidine can then be combined to allow lyophilization without degradation of aceclidine and simultaneously further reduce or eliminate the need for a cycloplegic agent for the present invention vs. the teachings of cycloplegic concentration ranges required in US 9,089,562. Optionally, the addition of a cryoprotectant can therefore also be used to greatly reduce (i.e. no more than 0.025% w/v cycloplegic agent, preferably 0.004% to 0.015% and most preferably 0.005% to 0.010%) the concentration of cycloplegic required to further eliminate mild, but potentially bothersome, ciliary side effects particularly in younger presbyopes and further modulate pupil miosis over aceclidine and a cryoprotectant combinations alone, reducing and in most cases eliminating any bothersome peak concentration dimming, as found in preferred embodiments of the present invention. In preferred embodiments it is discovered that aceclidine about 1.50% - 2.0% and more preferably 1.75% and mannitol about 0.5% - 4.0% and more

preferably 2.5% provide optimal concentration combinations for the present invention, that are necessary but not sufficient for about 3 lines of near improvement and 5 or more hours duration desired for an effective topical presbyopic composition, where additional formulation discoveries can further enhance the desired clinical near improvement magnitude and duration;

[090] It is surprisingly discovered that adding a viscosity agent to compositions described in a. above only modestly improves magnitude and duration, however when first adding a nonionic surfactant, such as polyoxyl stearate or polysorbate 80, optimal concentrations are discovered that provide greatly improved magnitude and duration for the present invention, to which viscosity may then provide added duration much more substantially than when added alone. For polysorbate 80 or polyoxyl 40 stearate concentrations of 1.0% to 10.0%, and more preferably about 2.5% to 5.0% w/v have been found to be beneficial;

[091] When formulation improvements of a. and b. above are combined, preferred embodiments such as aceclidine 1.75%, mannitol 2.5%, and polysorbate 80 2.75% result. Viscosity agents such as high viscosity carboxymethyl cellulose ("CMC") are surprisingly discovered to moderately enhance magnitude and greatly enhance duration, unlike with formulations in a. above alone. High molecular weight CMC concentrations of 0.75% to 1.75%, and most preferably about 1.40%, or hydroxypropylmethyl cellulose ("HPMC") at about 0.25% to 2.0%, more preferably about 0.50% or 1.50%, and most preferably about 1.0% to 1.25%, when combined result now in about +3 lines of near vision improvement or greater, at a duration of 5 – 10 hours, at a mean of about 7 hours or greater vs. pilocarpine 1.0% of about less than 4 hours;

[092] Not wishing to be held to particular theory citrate in combination with EDTA as a preferred embodiment buffer appears to 1) reduce redness; 2) enhance sorbate preservative shelf life, and in combination of the above with BAK 0.005% to 0.02% (0.02% preferred) further enhances near vision lines to about 4 lines and duration to about 8 to 12 hours.

[093] Additionally 0.5% or 1.5% sodium chloride is added in a preferred embodiment. Optionally, sodium chloride may be substituted with boric acid, preferably at 0.35% or potassium borate, preferably at 0.47%;

[094] Not wishing to be held to particular theory, it appears the addition of nonionic surfactant at optimized concentration of about 2.5% to 5.0% enhances permeation of aceclidine into the eye, which may relate to optimal micellar size particularly once of micromicallar or nanomicellar

range. This increased permeation coincides with the desirable increase in magnitude and duration and absent tropicamide but in the presence of mannitol with slight increases in ciliary sensation and dimming. Therefore in the presence of the combined formulation enhancements of a-d. above, where a cycloplegic agent is no longer required for a-d. above, addition of a nonionic surfactant at concentrations found to be preferred may be further improved with much lower concentrations of a cycloplegic agent than those found in US 9.089,562, such as the use of about 0.042% tropicamide with aceclidine 1.40%. For the present invention then preferred embodiments include aceclidine of about 1.75%, mannitol 2.5%, polysorbate 80 of about 2.5% to 5.0%, CMC of about 1.42%, or HPMC of about 1.8% and tropicamide of about 0.004% - 0.010%, more preferably about 0.005% to 0.007%, and most preferably about 0.005% - 0.006%. Micelle formation above the critical micellar concentration may allow for micelles to spread across the tear film surface and spread at low concentrations to cover this surface, while at higher concentrations these micelles becoming increasingly contracted and "squeezed" along the surface. Not wishing to be held to particular theory, it is believed at an optimal concentration a minimal micelle diameter is achieved before significant multiple lamellae (layering) occurs. It is believed that at the optimal concentration nanomicelles of about 100 to 250 nm along the surface are achieved surrounding the highly charged and hydrophilic aceclidine, facilitating its penetration through the very lipophilic epithelium;

[095] Not wishing to be held to particular theory the addition of BAK 0.02% to sorbate about 0.10%, EDTA about 0.10%, in a preferred composition of aceclidine 1.75%, mannitol 2.5%, tropicamide 0.01%, and citrate buffer (1 to 100 mM 3-5 mM preferred) is above the BAK critical micellar concentration. BAK, being a cationic surfactant, and BAK micelles, creating an ionic micellar gradient with + charge NH4+ quaternary nitrogen bring on the polar heads aggregating outside and lipophilic alkyl chain on the hydrophobic tails aggregating on the inside may cause significant similar aceclidine alignment due to its dipole with quaternary NH3 nucleophilic or NH4 protonated nitrogens oriented along the outside polar heads and more hydrophobic carbonyls C=O along hydrophobic BAK micellar tails these preventing, greatly reducing, or moderately reducing collisions of any nonionic aceclidine molecules - the nucleophiles - which if oriented in solution such that randomly they collide with another aceclidine carbonyl will result in chemical conversion of that aceclidine via nucleophilic attack at its targeted carbonyl, which can recur from such nucleophiles to other aceclidines so oriented repeatedly and cause loss of

stability without such BAK orientation via 0.005% and preferably 0.01% to 0.02% most preferred micelles. The concentration of such nonionic nucleophiles at a preferred pH in the preferred embodiment is relatively low, but the ability of these nonionic nucleophiles to destabilize adjacent aceclidines repeatedly without themselves degrading is otherwise high. The result may be improved potency for 1 month plus of a mixed solution once opened in a dual chamber bottle and mixing occurs of lyophilized aceclidine/mannitol with the remainder of the formulation in the diluent and or improved stability sufficient for commercialization in solution, either at room temperature or via cold chain;

[096] It is discovered that BAK alone does not provide sufficient bacterial and fungal preservative efficacy but that BAK and sorbate, or sorbate alone satisfactorily preserve diluent and or mixed solutions of the invention;

[097] Not to be wishing to be held to particular theory preferred embodiments of the present invention such as containing 1.25% hydroxypropyl methyl cellulose may have a viscosity of about 400 cps prior to instillation, yet unlike conventional high viscosity artificial tear formulations such as Celluvisc® at about 400 cps, which may blur vision for 10-20 minutes or Liquigel® at about 100 cps, which causes similar but slightly reduced blurring causes only about 60 seconds of blur dissipating rapidly with an influx of tear secretion; where both a nonnewtonian reduction in viscosity at high shear (such as about 1/1000 sec during a blink, and aceclidine parasympathetic trigger of tear secretion as a sialogen may contribute.

[098] General miotic agents, such as pilocarpine, carbachol and phospholine diesterase, are capable of causing pupil miosis resulting in improved near vision of presbyopic patients. However, there is an inverse reduction in distance vision associated with these general miotic agents from miosis at peak effect and accommodation that is not seen with aceclidine. The co-administration of a cycloplegic agent with aceclidine surprisingly results in an attenuation of this reduction in distance vision.

[099] Comfort, safety, and efficacy of a preferred embodiment of an ophthalmological composition of the present invention results from the presence of a nonionic surfactant, such as cyclodextrin alpha, beta, or gamma chains, preferably 2-hydroxypropyl beta-cyclodextrin ("HPβCD"), and, sulfobutyl ether derivative of β-cyclodextrin (Captisol®), a polyoxyl alkyl such as polyoxyl 40 stearate and polyoxyl 35 castor oil, or a poloxamer such as poloxamer 108 and poloxamer 407, a polysorbate such as polysorbate 80 or Brij® 35(Brij is a registered trademark

of Uniqema Americas LLC); a viscosity enhancing agent, such as carboxymethyl cellulose ("CMC"); a tonicity adjustor, such as sodium chloride; a preservative, such as benzalkonium chloride and a pH from about 5.0 to about 8.0. Further, an increase in the concentration of the nonionic surfactant may result in reduced redness. Specifically, increasing polysorbate from 0.10% to 0.50 - 1.0% results in reduced redness. Further, increasing CMC or Carbopol® 940 from 0.50% to 1.5% w/v (preferably 1.40 – 1.43% w/v) results in enhanced near vision, both quantitative improvement and duration improvement.

[0100] The viscosity of compositions of the present invention comprising a viscosity agent may be from about 1 to about 10,000 cps prior to topical instillation in the eye. As a result of the shear force applied to the composition as it exits the device used for administration the viscosity is lowered to a range from about 1 to about 25 cps at the high shear of blinking, and 50 cps to 200 cps at the low shear between blinks, allowing greater drop retention with less spillage and less nasolacrimal drainage and systemic absorption upon topical instillation.

Definitions

[0101] As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from a combination of the specified ingredients in the specified amounts.

[0102] The term "stabilizing", as used herein, refers to any process which facilitates and/or enables an active agent to remain in solution. The term "stabilizing", as used herein, also refers to any means or process which inhibits and/or reduces the tendency of a muscarinic agonist, including aceclidine, to degrade.

[0103] As used herein, all numerical values relating to amounts, weights, and the like, that are defined as "about" each particular value is plus or minus 10%. For example, the phrase "about 5% w/v" is to be understood as "4.5% to 5.5% w/v." Therefore, amounts within 10% of the claimed value are encompassed by the scope of the claims.

[0104] As used herein "% w/v" refers to the percent weight of the total composition.

[0105] As used herein the term "subject" refers but is not limited to a person or other animal.

[0106] As used herein, the term "container" refers to a pharmaceutically acceptable container comprising a chamber suitable to house a liquid drug product. Containers include, for example, vials, syringes, capsules, and ampoules.

[0107] As used herein "headspace" refers to the area within the chamber of the container between the composition and the cap when the cap is oriented away from the pull of gravity.

[0108] As used herein, the term "cap" or "closure" refers to any article capable of preventing the composition from exiting the container.

[0109] The term muscarinic receptor agonist ("muscarinic agonist") encompasses agonists that activate muscarinic acetylcholine receptors ("muscarinic receptors"). Muscarinic receptors are divided into five subtypes named M1-M5. Muscarinic agonists of the present invention include those muscarinic agonists that preferentially activate M1 and M3 receptors over M2, M4 and M5 receptors ("M1/M3 agonists"). M1/M3 agonists include but are not limited to aceclidine, xanomeline, talsaclidine, sabcomeline, cevimeline, alvameline, arecoline, milameline, SDZ-210-086, YM-796, RS-86, CDD-0102A (5-[3-ethyl-1,2,4-oxasdiazol-5-yl]-1,4,5,6-tetrahydropyrimidine hydrocholoride), N-arylurea-substituted 3-morpholine arecolines, VUO255-035 (N-[3-oxo-3-[4-(4-pyridinyl)-1-piperazinyl]propyl]-2,1,3-benzothiadiazole-4-sulfonamide), benzylquinolone carboxylic acid (BQCA), WAY-132983, AFB267B (NGX267), AC-42, AC-260584, chloropyrazines including but not limited to L-687, 306, L-689-660, 77-LH-28-1, LY593039, and any quiniclidine ring with one or more carbon substitutions particularly that include an ester, sulfur, or 5 or 6 carbon ring structure including with substituted nitrogen(s) and or oxygen(s), or any pharmaceutically acceptable salts, esters, analogues, prodrugs or derivatives thereof. A preferred M1/M3 agonist is aceclidine. In a preferred embodiment, muscarinic agonist of the present invention include those muscarinic agonist that preferentially activate M1 and M3 over M2, M4, and M5; and even more preferably activate M1 over M3. In a more preferred embodiment muscarinic agonist of the present invention include those muscarinic agonists that only activate M1.

[0110] The term "aceclidine" encompasses its salts, esters, analogues, prodrugs and derivatives including, but not limited to, aceclidine as a racemic mixture, aceclidine (+) enantiomer, aceclidine (-) enantiomer, aceclidine analogues, including, but not limited to, highly M1 selective 1,2,5 thiadiazole substituted analogues like those disclosed in Ward. J.S. et al., 1,2,5-Thiadiazole analogues of aceclidine as potent m1 muscarinic agonists, *J Med Chem*, 1998, Jan. 29, 41(3), 379-392 and aceclidine prodrugs including but not limited to carbamate esters.

[0111] The term "selective α-2 adrenergic receptor agonists" or "α-2 agonist" encompasses all α-2 adrenergic receptor agonists which have a binding affinity of 900 fold or greater for α-2 over

α-1 adrenergic receptors, or 300 fold or greater for α-2a or α-2b over α-1 adrenergic receptors. The term also encompasses pharmaceutically acceptable salts, esters, prodrugs, and other derivatives of selective α-2 adrenergic receptor agonists.

[0112] The term “inert gas” refers to gases that are chemically inert and do not react with other compounds. Inert gases include, but are not limited to, helium, neon, argon, krypton, xenon, radon and nitrogen.

[0113] The term “low concentrations” or “low-dose” of alpha-2 adrenergic receptor agonists refers to concentrations from between about 0.0001% to about 0.065% w/v; more preferably, from about 0.001% to about 0.035% w/v; even more preferably, from about 0.01% to about 0.035% w/v; and even more preferably, from about 0.03% to about 0.035% w/v.

[0114] The term “brimonidine” encompasses, without limitation, brimonidine salts and other derivatives, and specifically includes, but is not limited to, brimonidine tartrate, 5-bromo-6-(2-imidazolin-2-ylamino)quinoxaline D-tartrate, and Alphagan®.

[0115] The terms “treating” and “treatment” refer to reversing, alleviating, inhibiting, or slowing the progress of the disease, disorder, or condition to which such terms apply, or one or more symptoms of such disease, disorder, or condition.

[0116] The term “pharmaceutically acceptable” describes a material that is not biologically or otherwise undesirable (i.e. without causing an unacceptable level of undesirable biological effects or interacting in a deleterious manner).

[0117] As used herein, the term “pharmaceutically effective amount” refers to an amount sufficient to effect a desired biological effect, such as a beneficial result, including, without limitation, prevention, diminution, amelioration or elimination of signs or symptoms of a disease or disorder. Thus, the total amount of each active component of the pharmaceutical composition or method is sufficient to show a meaningful subject benefit. Thus, a "pharmaceutically effective amount" will depend upon the context in which it is being administered. A pharmaceutically effective amount may be administered in one or more prophylactic or therapeutic administrations.

[0118] The term "prodrugs" refers to compounds, including, but not limited to, monomers and dimers of the compounds of the invention, which have cleavable groups and become, under physiological conditions, compounds which are pharmaceutically active *in vivo*.

[0119] As used herein “salts” refers to those salts which retain the biological effectiveness and properties of the parent compounds and which are not biologically or otherwise harmful at the dosage administered. Salts of the compounds of the present inventions may be prepared from inorganic or organic acids or bases.

[0120] The term “higher order aberrations” refers to aberrations in the visual field selected from starbursts, halos (spherical aberration), double vision, multiple images, smeared vision, coma and trefoil.

[0121] The term “cold chain” refers to storage at temperatures from about 2 to about 8 °C from manufacture to immediately prior to administration.

[0122] The compounds of the present invention can be used in the form of pharmaceutically acceptable salts derived from inorganic or organic acids or bases. The phrase "pharmaceutically acceptable salt" means those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well-known in the art. For example, S. M. Berge et al. describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66: *1 et seq.*

[0123] The salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention or separately by reacting a free base function with a suitable organic acid. Representative acid addition salts include, but are not limited to acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate (isothionate), lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmitoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, phosphate, glutamate, bicarbonate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; arylalkyl halides like benzyl and phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained. Examples of acids which can be employed

to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, hydrobromic acid, hyaluronic acid, malic acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, malic acid, maleic acid, methanosulfonic acid, succinic acid and citric acid.

[0124] Basic addition salts can be prepared *in situ* during the final isolation and purification of compounds of this invention by reacting a carboxylic acid-containing moiety with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia or an organic primary, secondary or tertiary amine. Pharmaceutically acceptable salts include, but are not limited to, cations based on alkali metals or alkaline earth metals such as lithium, sodium, potassium, calcium, magnesium and aluminum salts and the like and nontoxic quaternary ammonia and amine cations including ammonium, tetramethylammonium, tetraethylammonium, methylammonium, dimethylammonium, trimethylammonium, triethylammonium, diethylammonium, and ethylammonium among others. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, piperazine and the like.

[0125] The term "ester" as used herein is represented by the formula —OC(O)A^1 or —C(O)OA^1, where A^1 can be alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, a heteroaryl group or other suitable substituent.

Compositions of the Invention

[0126] In one embodiment, the present invention is directed to an ophthalmological composition comprising aceclidine. In a preferred embodiment, aceclidine is at a concentration from about 0.25% to about 2.0% w/v, more preferably from about 0.50% to about 1.90% w/v, still more preferably from about 1.65% to about 1.85% w/v, and most preferably about 1.75% w/v. As aceclidine is a tertiary amine with asymmetry, both a + and – optical isomer exist (where in some studies (+) is more potent and in others it is felt (-) may be more potent). For the above concentrations polarimetry demonstrated an exactly equal ratio of (+) and (–) isomer for these concentrations. Altering this ratio could therefore alter this concentration range proportional to a change in ratio.

[0127] The present invention is further directed to an ophthalmological composition comprising a muscarinic agonist, preferably a nonionic surfactant above its critical micellar concentration for the composition, and a viscosity enhancing agent; or alternatively an *in situ* gelling agent. In

preferred embodiments the initial viscosity of the composition on topical application is above 20 cps, preferably 50 cps, and more preferably above 70 cps at low shear (1/s).

[0128] Cryoprotectants are compounds that either prevent freezing or prevent damage to compounds during freezing. As used herein, the term "cryoprotectant" or "cryoprotectants" include lyoprotectants. Cryoprotectants suitable for use in the subject invention include, but are not limited to, a polyol, a sugar, an alcohol, a lower alkanol, a lipophilic solvent, a hydrophilic solvent, a bulking agent, a solubilizer, a surfactant, an antioxidant, a cyclodextrin, a maltodextrin, colloidal silicon dioxide, polyvinyl alcohol, glycine, 2-methyl-2,4-pentanediol, cellobiose, gelatin, polyethylene glycol (PEG), dimethyl sulfoxide (DMSO), formamide, antifreeze protein 752 or a combination thereof.

[0129] As used herein the term "polyol" refers to compounds with multiple hydroxyl functional groups available for organic reactions such as monomeric polyols such as glycerin, pentaerythritol, ethylene glycol and sucrose. Further, polyols may refer to polymeric polyols including glycerin, pentaerythritol, ethylene glycol and sucrose reacted with propylene oxide or ethylene oxide. In a preferred embodiment, polyols are selected from the group consisting of mannitol, glycerol, erythritol, lactitol, xylitol, sorbitol, isosorbide, ethylene glycol, propylene glycol, maltitol, threitol, arabitol and ribitol. In a more preferred embodiment, the polyol is mannitol.

[0130] Sugars suitable for use in the present invention as cryoprotectants include, but are not limited to, glucose, sucrose, trehalose, lactose, maltose, fructose and dextran.

[0131] In another preferred embodiment, alcohols include, but are not limited to, methanol.

[0132] In one embodiment, the present invention individually excludes each cryoprotectant from the definition of cryoprotectant.

[0133] Cryoprotectants may be at present in compositions of the present invention at a concentration from about 0.1% to about 99% w/v, preferably from about 1% to about 50% w/v, more preferably from about 1% to about 10% w/v.

[0134] As used herein "lower alkanols" include C1-C6 alkanols. Lower alkanols, suitable for use in the present invention include, but are not limited to, amyl alcohol, butanol, sec-butanol, t-butyl alcohol, n-butyl alcohol, ethanol, isobutanol, methanol. isopropanol and propanol.

[0135] Bulking agents suitable for use in the present invention include, but are not limited to, saccharide, polyvinylpyrrolidone, cyclodextrin and trehalose.

[0136] Solubilizers suitable for use in the present invention include, but are not limited to, cyclic amide, gentisic acid and cyclodextrins.

[0137] In a preferred embodiment, surfactants suitable for use in the present invention include, but are not limited to, nonionic surfactants, more preferably surfactants with a hydrophilic-lipophilic balance ("HLB") value of 1 to 18.

[0138] In a preferred embodiment, antioxidants suitable for use in the present invention include, but are not limited to, bisulfite, ascorbic acid, disodium- or tetrasodium ethylenediaminetetraacetic acid, citrate, butylated hydroxyanisole ("BHA"), butylated hydroxytoluene ("BHT"), a sulfoxylate, propyl gallate, an amino acid containing a thio group, and a thiol.

[0139] Nonionic surfactants suitable for the present invention include cyclodextrins, polyoxyl alkyls, poloxamers or combinations thereof, and may include in addition combinations with other nonionic surfactants such as polysorbates. Preferred embodiments include polyoxyl 40 stearate and optionally Poloxamer 108, Poloxamer 188, Poloxamer 407, Polysorbate 20, Polysorbate 80, ionically charged (e.g. anionic) beta - cyclodextrins with or without a butyrated salt (Captisol®) 2-hydroxypropyl beta cyclodextrin ("HPβCD"), alpha cyclodextrins, gamma cyclodextrins, Polyoxyl 35 castor oil, and Polyoxyl 40 hydrogenated castor oil or combinations thereof. Further, substitution of other nonionic surfactants compatible with ophthalmological use allows for similar formulation advantages, which may included but is not limited to one or more of a nonionizing surfactant such as poloxamer, poloxamer 103, poloxamer 123, and poloxamer 124, poloxamer 407, poloxamer 188, and poloxamer 338, any poloxamer analogue or derivative, polysorbate, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, any polysorbate analogue or derivative, cyclodextrin, hydroxypropyl-β- cyclodextrin, hydroxypropyl- γ-cyclodextrin, randomly methylated β-cyclodextrin, β-cyclodextrin sulfobutyl ether, γ-cyclodextrin sulfobutyl ether or glucosyl- β- cyclodextrin, any cyclodextrin analogue or derivative, polyoxyethylene, polyoxypropylene glycol, an polysorbate analogue or derivative, polyoxyethylene hydrogenated castor oil 60, polyoxyethylene (200) , polyoxypropylene glycol (70), polyoxyethylene hydrogenated castor oil, polyoxyethylene hydrogenated castor oil 60, polyoxyl, polyoxyl stearate, nonoxynol, octyphenol ethoxylates, nonyl phenol ethoxylates, capryols, lauroglycol, polyethylene glycol ("PEG"), Brij® 35, 78, 98, 700 (polyoxyethylene glycol alkyl ethers), glyceryl laurate, lauryl glucoside, decyl glucoside, or cetyl alcohol; or

zwitterion surfactants such as palmitoyl carnitine, cocamide DEA, cocamide DEA derivatives cocamidopropyl betaine, or trimethyl glycine betaine, N-2(2-acetamido)-2-aminoethane sulfonic acid (ACES), N-2-acetamido iminodiacetic acid (ADA), N,N-bis(2-hydroxyethyl)-2-aminoethane sulfonic acid (BES), 2-[Bis-(2-hydroxyethyl)-amino]-2-hydroxymethyl-propane-1,3-diol (Bis-Tris), 3-cyclohexylamino-1-propane sulfonic acid (CAPS), 2-cyclohexylamino-1-ethane sulfonic acid (CHES), N,N-bis(2-hydroxyethyl)-3-amino-2-hydroxypropane sulfonic acid (DIPSO), 4-(2-hydroxyethyl)-1-piperazine propane sulfonic acid (EPPS), N-2-hydroxyethylpiperazine-N′-2-ethane sulfonic acid (HEPES), 2-(N-morpholino)-ethane sulfonic acid (MES), 4-(N-morpholino)-butane sulfonic acid (MOBS), 2-(N-morpholino)-propane sulfonic acid (MOPS), 3-morpholino-2-hydroxypropanesulfonic acid (MOPSO), 1,4-piperazine-bis-(ethane sulfonic acid) (PIPES), piperazine-N,N′-bis(2-hydroxypropane sulfonic acid) (POPSO), N-tris(hydroxymethyl)methyl-2-aminopropane sulfonic acid (TAPS), N-[tris(hydroxymethyl)methyl]-3-amino-2-hydroxypropane sulfonic acid (TAPSO), N-tris(hydroxymethyl) methyl-2-aminoethane sulfonic acid (TES), 2-Amino-2-hydroxymethyl-propane-1,3-diol (Tris), tyloxapol, Solulan™ C-24 (2-[[10,13-dimethyl-17-(6-methylheptan-2-yl)-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-yl]oxy]ethanol) and Span® 20-80 (sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, and sorbitan monooleate). In certain embodiments the addition of an anionic surfactant such as sodium lauryl sulfate and or sodium ester lauryl sulfate may be preferred. In other embodiments the addition of polysorbate 80 is preferred. In addition to the above nonionic surfactants any nonionic surfactant is suitable for use in the present invention as long as the concentration of the nonionic surfactant is such that it is above the critical micellar concentration for that non-ionic surfactant. Preferably, the nonionic surfactants used in the present invention achieve submicron diameter micelles, more preferably less than 200 nanometers and more preferably less than 150 nanometers in diameter.

[0140] Ophthalmological *in situ* gels which may be substituted for or added in addition to one or more nonionic surfactants include but are not limited to gelatin, carbomers of various molecular weights including carbomer 934 P and 974 P, xanthan gums, alginic acid (alginate), guar gums, locust bean gum, chitosan, pectins and other gelling agents well known to experts in the art.

[0141] In preferred embodiments the nonionic surfactant is polyoxyl 40 stearate at a concentration from about 1 to about 15% w/v, more preferably at about 5.5% w/v.

[0142] In such preferred embodiment, polyoxyl 40 stearate is found to enhance the redness reduction effect preferentially over aqueous solutions and other nonionic surfactants such as poloxamer 407, particularly in the presence of an α-2 agonist.

[0143] In other preferred embodiments, the nonionic surfactant is polysorbate 80 at a concentration from about 0.5% to about 10% w/v, more preferably from about 1% to about 7% w/v and even more preferably from about 2% to about 5% w/v, yet more preferably from about 2.5% to about 4% w/v and most preferably at about 2.5% or 2.75% or 3% or 4% or 5% w/v.

[0144] Viscosity agents suitable for the present invention include, but are not limited to gums such as guar gum, hydroxypropyl-guar ("hp-guar"), and xanthan gum, alginate, chitosan, gelrite, hyauluronic acid, dextran, Carbopol® (polyacrylic acid or carbomer) including Carbopol® 900 series including Carbopol® 940 (carbomer 940), Carbopol® 910 (carbomer 910) and Carbopol® 934 (carbomer 934), cellulose derivatives such as carboxymethyl cellulose ("CMC"), methylcellulose, methyl cellulose 4000, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxyl propyl methyl cellulose 2906, carboxypropylmethyl cellulose, hydroxypropylethyl cellulose, and hydroxyethyl cellulose, polyethylene glycol, polyvinyl alcohol, polyvinyl pyrrolidone, gellan, carrageenan, alignic acid, carboxyvinyl polymer or combinations thereof.

[0145] In a preferred embodiment the viscosity agent will have an equilibration viscosity less than 100 cps, preferably from about 15 to about 35 cps, and most preferably at about 30 cps. In a preferred embodiment the viscosity agent is Carbopol® 940 (carbomer 940) at a concentration from about 0.05% to about 1.5% w/v, preferably from about 0.09% to about 1.0% w/v, more preferably at 0.09%, 0.25%, 0.5%, 0.75%, 0.9% or 1.0% w/v. In certain combinations it has been surprisingly discovered nonionic surfactant / viscosity combinations may result in phase separation over time with precipitate formation. In such situations, particularly for polyoxyls, in a preferred embodiment polyoxyl 40 stearate, and cellulose derivatives, particularly hydroxypropylmethyl cellulose, use of a nonpolysaccharide derivative for viscosity enhancement, such as polyacrylic acid derivatives (carbomers, carbomer 934 or 940 in preferred embodiments) may prevent such separation; or alternatively use of a non polyoxyl nonionic surfactant, such as polysorbate 80 with either a cellulose derivative or noncellulose derivative viscosity agent may be substituted.

[0146] In another preferred embodiment, the viscosity agent is carboxymethyl cellulose at a concentration from about 1% to about 2% w/v, more preferably from 1.35% to about 1.45% w/v and most preferably 1.42% w/v or 1.40% w/v.

[0147] In another preferred embodiment, the viscosity agent is hydroxypropylmethyl cellulose at a concentration from about 0.5% to about 1.75%, and more preferably about 0.75% or 1.5%, still more preferably from about 1.0% to about 1.5%, and most preferably at about 1.25%.

[0148] Not wishing to be held to particularly theory, it appears the quinuclidine nucleus of the heterocyclic nitrogen on aceclidine is so electron rich it easily attacks surrounding compounds as well as itself.

[0149] It is a discovery of the present invention that several modifications may singly or in combination be used to enhance cold chain stability storage, including in addition to in a preferred embodiment aceclidine 1.40% - 1.75%, tropicamide 0.025% - 0.10% and optionally a nonioinic surfactant such as polyoxyl 40 stearate 0.5%-10%, preferably 5.5% one or more of (See Table 1):

[0150] Acidic pH, preferably less than 5.5, preferably less than 5.0 and most preferably at a pH of about 4.75;

[0151] Viscosity agent, preferably at 25C viscosity of about 15-50 cps, and more preferably 20-45 cps, where a preferred embodiment is carbomer 940 0.09% - 1.5%;

[0152] Addition of a cryoprotectant, in a preferred embodiment a polyol, preferably Mannitol 2.5% - 4.0%;

[0153] Addition of a buffer, where acetate or phosphate buffers are preferred, 2-100 mmole range with 3-5 mmole is preferred; and

[0154] Addition of a preservative, where BAK 0.015% is preferred.

[0155] The selective α-2 agonist may be included within the composition of the present invention or applied topically preferably just minutes before or less preferably just minutes afterward if additional means to reduce nasal congestion or redness is desired for sensitive subjects. Selective α-2 agonists suitable for the present invention have minimal α-1 agonist activity at low concentrations. For example, for brimonidine or fadolmidine, 1% to 2% w/v is considered extremely high, 0.5% to 1.0% w/v still highly inductive of α-1 receptors and toxic for purposes of the present invention. Further, 0.10% to 0.5% w/v is still too high and even 0.070% to 0.10% w/v is associated with a higher than preferred incidence of rebound hyperemia

(however, for dexmedetomidine, its greater lipophilicity and intraocular penetration reduces rebound risk in this range). Only 0.065% w/v or below is potentially acceptable, where for most α-2 agonists, depending on degree of selectivity 0.050% w/v or even more preferably 0.035% w/v or less is desired. On the other hand some degree of useful activity may occur at one or more orders of magnitude further reduction of concentration. The preferred embodiments, brimonidine, fadolmidine and guanfacine, of the present invention preferentially stimulate α-2 adrenergic receptors, and even more preferably α-2b adrenergic receptors so that α-1 adrenergic receptors are not stimulated sufficiently enough to cause excessive large vessel arteriolar constriction and vasoconstrictive ischemia. In addition, it has been discovered that preventing or reducing redness for drugs that otherwise directly induce redness, such as the acetylcholine agonist, aceclidine, enhances compliance for sensitive subjects that may have induced redness or nasal congestion even with formulations of the present invention that do not include an α-2 agonist. However, because α-2 agonists are shifted to their ionized equilibrium an acidic pH is somewhat offset by the fact such agonists exert greater affect at neutral or alkaline pH. Therefore each α-2 agonist has a preferred pH range depending on its lipophilicity and pKa value when added to the inventive compositions with aceclidine. For the present invention while pH range of 5.0 to 8.0 is tolerated, preferred embodiments are at pH 5.5 to 7.5 and more preferably 6.5 to 7.0. Further, it has been discovered that cyclodextrins and/or polyoxyl 40 stearate as a nonionic surfactant component or as the sole nonionic surfactant, result in a greater whitening effect when the α-2 agonist is included in the composition rather than poloxamer 407. The α-2 agonist may optionally be applied separately or in certain preferred embodiments with formulations of the present invention that do not include an α-2 agonist, such as those formulas with polyoxyl 40 stearate 5.5% w/v as the non-ionic surfactant, although the α-2 agonist is not required except for occasional sensitive subjects. Fadolmidine represents the α-2 agonist with highest hydrophilicity and therefore high surface retention for the present invention. Guanfacine is also highly selective and hydrophilic. Brimonidine is highly selective with moderate lipophilicity. Finally, dexmedetomidine has high selectivity with high lipophilicity that may be used with less efficacy for reducing redness for the purposes of the present invention (although possibly inducing fatigue as a side effect in some patients). In a preferred embodiment using polyoxyl 40 stearate 5.5% w/v; CMC 0.80% w/v; NaCl 0.037% w/v; ethylenediaminetetraacetic acid ("EDTA")

0.015% w/v, borate buffer 5 mM and BAK 0.007% w/v results in redness of about 1.0 to 1.5 out of 4 which is transient lasting about ten minutes, and by 30 minutes returns to about baseline.

[0156] In one embodiment, the selective α-2 adrenergic receptor agonist is a compound which has binding affinity of about 900 fold or greater, even more preferably about 1000 fold or greater, and most preferably, about 1500 fold or greater.

[0157] The selective α-2 adrenergic receptor agonist may be present at a concentration from between about 0.0001% to about 0.065% w/v; more preferably, from about 0.001% to about 0.035% w/v; even more preferably, from about 0.01% to about 0.035% w/v; and even more preferably, from about 0.020% to about 0.035% w/v.

[0158] In one embodiment, the selective α-2 adrenergic receptor is selected from the group consisting of brimonidine, guanfacine, fadolmidine, dexmedetomidine, (+)-(S)-4-[1-(2,3-dimethyl-phenyl)-ethyl]-1,3-dihydro-imidazole-2-thione, 1-[(imidazolidin-2-yl)imino]indazole, and mixtures of these compounds. Analogues of these compounds that function as highly selective α-2 agonists may also be used in compositions and methods of the present invention.

[0159] In a more preferred embodiment, the selective α-2 agonist is selected from the group consisting of fadolmidine, guanfacine and brimonidine. In a yet more preferred embodiment the selective α-2 agonist is brimonidine in the form of a salt at a concentration of 0.025% to 0.065% w/v, more preferably from 0.03% to 0.035% w/v. In a preferred embodiment, the salt is a tartrate salt.

[0160] In another yet more preferred embodiment, the selective α-2 agonist is fadolmidine at a concentration from about 0.005% to about 0.05% w/v, more preferably from 0.02% to about 0.035% w/v in the form of a hydrochloride ("HCl") salt.

[0161] In another yet more preferred embodiment, the selective α-2 agonist is guanfacine at a concentration from about 0.005% to about 0.05% w/v, more preferably from 0.02% to about 0.035% w/v in the form of an HCl salt.

[0162] In another yet more preferred embodiment, the selective α-2 agonist is dexmedetomidine at a concentration from about 0.005% to about 0.05% w/v, more preferably from 0.04% to about 0.05% w/v in the form of an HCl salt.

[0163] In another preferred embodiment a pH less than physiologic pH is found to enhance the whitening effect for brimonidine, preferably pH 4.5 to 6.5, and more preferably pH 5.5 to 6.0. However, redness reduction is achieved at all pHs, and enhancement of aceclidine absorption

occurs at alkaline pH, such that more effect occurs from a given concentration, and therefore while effective at pH ranges from 4.5 to 8.0, pH range of 6.5 to 7.5 is preferred for the present invention, and 7.0 to 7.5 most preferred.

[0164] The present invention is further directed to an ophthalmological composition further comprising a cycloplegic agent. It is a surprising and totally unexpected discovery of the present invention that certain cycloplegic agents can be combined with miotic agents, particularly for the present invention, aceclidine, without reducing miotic onset, magnitude, or duration; and further blunt the normally attendant spike in miotic effect coinciding with time of peak absorption in aqueous formulations to provide a constant miosis versus time after onset from 15 to 30 minutes to 6 to 10 hours depending on the desired formulation. The addition of the cycloplegic agent also reduces any residual associated discomfort that may otherwise occur soon after topical instillation, which presumably is a result of ciliary spasms or excessive pupillary miosis.

[0165] Cycloplegic agents suitable for the present invention include, but are not limited to, atropine, Cyclogyl® (cyclopentolate hydrochloride), hyoscine, pirenzepine, tropicamide, atropine, 4-diphenylacetoxy-N-methylpiperidine methobromide (4-DAMP), AF-DX 384, methoctramine, tripitramine, darifenacin, solifenacin (Vesicare), tolterodine, oxybutynin, ipratropium, oxitropium, tiotropium (Spriva), and otenzepad (a.k.a. AF-DX 116 or 11-{[2-(diethylamino)methyl]-1-piperidinyl}acetyl]-5,11-dihydro-6H-pyrido[2,3b][1,4]benzodiazepine-6-one). In a preferred embodiment the cycloplegic agent is tropicamide at a concentration from about 0.004% to about 0. 025% w/v, more preferably from about 0.005% to about 0.015% w/v and still more preferably from about 0.005% to about 0.011% w/v, from about 0.005% to about 0.007% w/v and from about 0.005% to about 0.006% w/v. In another preferred embodiment the cycloplegic agent is a mixture of tropicamide at a concentration from about 0.04% to about 0.07% w/v or pirenzepine or otenzepad at a concentration from about 0.002% to about 0.05% w/v.

[0166] In a preferred embodiment, tropicamide 0.01% w/v was found to slightly reduce brow ache, 0.030% w/v to further reduce brow ache and from 0.04% to about 0.07% w/v to completely eliminate brow ache without reduction of the average pupillary miosis diameter over duration of effect. Tropicamide in preferred embodiments has demonstrated completely unexpected sensitivity of effect, where at about 0.04% w/v unexpectedly and very effectively reduces or eliminates brow ache and ciliary spasm pain, becoming very noticeably further reduced at

0.042% w/v and absent at 0.044% w/v in a preferred embodiment with no cycloplegia (surprising due to its common use as a pupil dilating agent). Yet, tropicamide did not reduce the mean degree of pupil miosis, the time of onset of pupil miosis or the subsequent visual benefits. On the contrary, tropicamide blunted the peak miosis seen in aqueous formulations to create a smooth consistent miotic effect over time. It allowed modulation of peak pupil miosis to achieve a more even effect over time with no dilation as has been found with its prior use. Specifically, tropicamide is useful to prevent transient constriction below 1.50 mm at 30 to 60 minutes following aceclidine in some embodiments and to reduce transient excessive and undesirable dimming of vision that may otherwise occur at peak onset of about 30 minutes. As an example, an ophthalmological composition comprising 1.53% w/v aceclidine, 5% w/v HPβCD, 0.75% w/v CMC, 0.25% w/v NaCl , 0.01% w/v BAK and a phosphate buffer at pH 7.0; or 1.45% w/v aceclidine; 5.5% w/v polyoxyl 40 stearate; 0.80% w/v CMC; 0.037% w/v NaCl; 0.015% w/v EDTA; 0.007% w/v BAK and 5mM phosphate buffer at a pH 7.0; was varied from 0.040% w/v tropicamide, where moderate dimming was noted, to 0.044% w/v tropicamide where dimming became almost undetectable other than in extremely dim light conditions. This additional pupil size modulation with a cycloplegic agent allows aceclidine concentrations sufficient for prolonged effect while blunting the attendant peak excessive constriction that is undesirable as well as any uncomfortable brow ache. Surprisingly and due to its short-acting nature, tropicamide achieves this blunting effect without causing mydriasis. Further, in a preferred embodiment, tropicamide 0.014% w/v was found to reduce brow ache, 0.021% w/v to further reduce brow ache and from 0.028% to 0.060% w/v and in some embodiments up to 0.09% w/v to completely eliminate brow ache without cycloplegia (i.e. paralysis of ciliary muscle of the eye).

[0167] It has been found for a racemic 50:50 mixture of (+) and (-) aceclidine optical isomers (where in some studies (+) is more potent and in others it is felt (-) may be more potent) tropicamide effects may vary depending on the ratio of aceclidine to tropicamide. For example, in an ophthalmological composition of the present invention comprising 1.55% w/v aceclidine, 5.5% w/v HPβCD or in a preferred embodiment polyoxyl 40 stearate, 0.75% w/v CMC (1% = 2,500 centipoise), 0.25% w/v NaCl, and 0.01% w/v BAK and at pH 7.5, 0.042% w/v tropicamide can be differentiated from even 0.035% w/v, with the former demonstrating normal indoor night vision and the latter slight dimming that becomes more noticeable at still lower concentrations. At higher concentrations, such as from about 0.075% to about 0.090% w/v tropicamide, loss of

optimal range pupil constriction 1.50 mm to 1.80 mm range begins, and frank mydriasis at higher concentrations begins to occur. As isomer ratio may alter the effective concentration, this must be factored into the clinical efficacy anticipated using aceclidine; for preferred embodiments of the present invention a polarimeter was used to determine an exact 50:50 isomer ratio was used (personal communication Toronto Research Chemicals).

[0168] FIG. 1 shows the effect of a miotic agent with or without a cycloplegic agent and with or without a carrier. Subject is an emmetrope over the age of 45 with a baseline near vision of 20.100 and baseline distance vision of 20.20. Topical administration to the eye of 1% w/v pilocarpine in saline solution results in an improvement of near vision to 20.40 (8a), however this improvement comes at the expense of a reduction in distance vision to 20.100 (8b). The addition of 0.015% w/v tropicamide results in an improvement of near vision to 20.25 (9a) and a lessening of the reduction of distance vision to 20.55 (9b), though in certain instances with some induced irregular astigmatism (mildly blotched areas in reading field of vision). Topical administration of 1.55% w/v aceclidine in saline solution results in an improvement of near vision to 20.40 for an extended time period of 6 hrs (10a) without any effect on the baseline distance vision (10b). 10c and 10d show the effects of administering aceclidine in a carrier composed of 5.5% w/v 2-hydroxypropyl beta cyclodextrin, 0.75% w/v CMC (1% = 2,500 centipoise), 0.25% w/v NaCl, and 0.01% w/v BAK. As seen in 10c the carrier increases the beneficial effect of aceclidine resulting in better than 20.20 near vision. As seen in 10d a similar increase in distance vision occurs. 10e and 10f show the effects of adding 0.042% w/v tropicamide to the aceclidine in the carrier. As seen in 10e near vision is improved to 20.15 with a quicker onset of maximum visual acuity. As seen in 10f a similar improvement is seen in distance vision. Taken together, FIG. 1 shows that aceclidine is capable of temporarily correcting near vision in a presbyopic subject without affecting the baseline distance vision. Similar results can be achieved with a different miotic agent, pilocarpine, with the addition of a cycloplegic agent such as tropicamide. A proper drug carrier can also have a beneficial effect.

[0169] The present invention is further directed to an ophthalmological composition further comprising a tonicity adjustor and a preservative.

[0170] A tonicity adjustor can be, without limitation, a salt such as sodium chloride (“NaCl”), potassium chloride, mannitol or glycerin, or another pharmaceutically or ophthalmologically acceptable tonicity adjustor. In certain embodiments the tonicity adjustor is 0.037% w/v NaCl,

[0171] Preservatives that can be used with the present invention include, but are not limited to, benzalkonium chloride ("BAK"), sorbic acid, oxychloro complex, citric acid, chlorobutanol, thimerosal, phenylmercuric acetate, disodium ethylenediaminetetraacetic acid, phenylmercuric nitrate, perborate or benzyl alcohol. In a preferred embodiment the preservative is BAK, sorbic acid, oxychloro complex or a combination thereof. In a yet more preferred embodiment BAK is at a concentration of about 0.001% to about 1.0% w/v, more preferably at a concentration of about 0.007%, 0.01% or 0.02% w/v. In another preferred embodiment the preservative is perborate at a concentration of 0.01% to about 1.0% w/v, more preferably at a concentration of about 0.02% w/v.

[0172] Various buffers and means for adjusting pH can be used to prepare ophthalmological compositions of the invention. Such buffers include, but are not limited to, acetate buffers, citrate buffers, phosphate buffers and borate buffers. It is understood that acids or bases can be used to adjust the pH of the composition as needed, preferably of 1 to 10 mM concentration, and more preferably about 3 mM or 5 mM. In a preferred embodiment the pH is from about 4.0 to about 8.0, in a more preferred embodiment the pH is from about 5.0 to about 7.0.

[0173] The present invention is further directed to an ophthalmological composition further comprising an antioxidant. Antioxidants that can be used with the present invention include but are not limited to disodium ethylenediaminetetraacetic acid at a concentration from about 0.005% to about 0.50% w/v, citrate at a concentration from about 0.01% to about 0.3% w/w, dicalcium diethylenetriamine pentaacetic acid ("Ca2DTPA") at a concentration from about 0.001% to about 0.2% w/v, preferably about 0.01% w/v Ca2DTPA which can be formulated by adding 0.0084% w/v $Ca(OH)_2$ and 0.0032% w/v pentetic acid to the formulation and mixing slowly. Further combinations of antioxidants can be used. Other antioxidants that can be used with the present invention include those well known to experts in the art such as ethylenediaminetetraacetic acid at a concentration from about 0.0001% to about 0.015% w/v.

[0174] It is a surprising and unexpected discovery that topical formulations of the present invention, particularly one of the preferred embodiments comprising aceclidine 1.35% to 1.55% w/v; 5.5% w/v polyoxyl 40 stearate; 0.80% w/v CMC; 0.037% w/v NaCl; 0.015% w/v EDTA; 0.007% w/v BAK; and 5mM phosphate buffer at pH 7.0 result in considerably prolonged contact lens wear and comfort after a single topical instillation daily. The single daily use of the preferred embodiments allowed a subject with dry eye to sleep in his lenses for one week periods

where previously even after a single night vision would be blurred and contact lenses coated with film requiring removal and cleaning or replacement (see Example 7).

[0175] In preferred embodiments, an ophthalmological composition of the present invention comprises aceclidine, a cryoprotectant, optionally a cycloplegic agent, a nonionic surfactant at a concentration from about 1% to about 5% w/v and a viscosity agent at a concentration of about 0.75% to about 1.6% w/v, preferably about 1.25% to about 1.5% w/v.

[0176] The following representative embodiments are provided solely for illustrative purposes and are not meant to limit the invention in any way.

REPRESENTATIVE EMBODIMENTS

[0177] In one embodiment, the ophthalmological composition comprises:

aceclidine at a concentration of about 1.75%w/v; and

mannitol at a concentration of about 2.5% w/v.

[0178] In another embodiment, the ophthalmological composition comprises:

aceclidine at a concentration of about 1.75%w/v;

mannitol at a concentration of about 2.5% w/v; and

tropicamide at a concentration of about 0.02% w/v.

[0179] In another embodiment, the ophthalmological composition comprises:

aceclidine at a concentration of about 1.75%w/v;

mannitol at a concentration of about 2.5% w/v;

polysorbate 80 at a concentration of about 5.0% w/v;

carboxymethyl cellulose at a concentration of about 1.4% w/v;

BAK at a concentration of about 0.015% w/v; and

phosphate buffer at a concentration of about 3 mM,

wherein the pH is about 5.

[0180] In another embodiment, the ophthalmological composition comprises:

aceclidine at a concentration of about 1.75%w/v;

mannitol at a concentration of about 2.5% w/v;

polysorbate 80 at a concentration of about 0.5% w/v;

NaCl at a concentration from about 0.10% to about 0.50% w/v;

Carbopol® 940 at a concentration of about 0.95% w/v;

BAK at a concentration of about 0.01% w/v; and

phosphate buffer at a concentration of about 3 mM,

wherein the pH is about 5.

[0181] In another embodiment, the ophthalmological composition comprises:

aceclidine at a concentration of about 1.75%w/v;

mannitol at a concentration of about 2.5% w/v;

polysorbate 80 at a concentration of about 2.0% w/v;

NaCl at a concentration of about 0.50% w/v

Carbopol® 940 at a concentration of about 1.5% w/v;

BAK at a concentration of about 0.015% w/v; and

phosphate buffer at a concentration of about 3 mM,

wherein the pH is about 5.25.

[0182] In another embodiment, the ophthalmological composition comprises:

aceclidine at a concentration of about 1.75%w/v;

mannitol at a concentration of about 2.5% w/v;

polysorbate 80 at a concentration of about 0.25% w/v;

NaCl at a concentration of about 0.1% w/v;

boric acid at a concentration of about 0.12% w/v;

Carbopol® 940 at a concentration of about 0.95% w/v; and

BAK at a concentration of about 0.015% w/v;

wherein the pH is about 5.

[0183] In another embodiment, the ophthalmological composition comprises:

aceclidine at a concentration of about 1.75%w/v;

mannitol at a concentration of about 2.5% w/v;

polysorbate 80 at a concentration of about 0.50% w/v;

NaCl at a concentration of about 0.05% w/v;

boric acid at a concentration of about 0.2% w/v;

Carbopol® 940 at a concentration of about 0.95% w/v;

BAK at a concentration of about 0.01% w/v; and

phosphate buffer at a concentration of about 3 mM,

wherein the pH is about 5.

[0184] In another embodiment, the ophthalmological composition comprises:

aceclidine at a concentration of about 1.75%w/v;
mannitol at a concentration of about 2.5% w/v;
polysorbate 80 at a concentration of about 0.1% w/v;
boric acid at a concentration of about 0.2% w/v;
Carbopol® 940 at a concentration of about 0.9% w/v;
BAK at a concentration of about 0.05% w/v; and
phosphate buffer at a concentration of about 3 mM,
wherein the pH is about 5.

[0185] In another embodiment, the ophthalmological composition comprises:
aceclidine at a concentration of about 1.75%w/v;
mannitol at a concentration of about 2.5% w/v;
polysorbate 80 at a concentration of about 0.1% w/v;
NaCl at a concentration of about 0.1% w/v;
boric acid at a concentration of about 0.12% w/v;
Carbopol® 940 at a concentration of about 0.95% w/v;
BAK at a concentration of about 0.01% w/v; and
phosphate buffer at a concentration of about 3 mM,
wherein the pH is about 5.

[0186] In another embodiment, the ophthalmological composition comprises:
aceclidine at a concentration of about 1.75% w/v;
tropicamide at a concentration of about 0.01% w/v;
mannitol at a concentration of about 2.5% w/v;
polysorbate 80 at a concentration of about 5.0% w/v;
CMC at a concentration of about 1.4% w/v;
BAK at a concentration of about 0.015% w/v; and
phosphate buffer at a concentration of about 3 mM,
wherein the pH is about 5.

[0187] In another embodiment, the ophthalmological composition comprises:
aceclidine at a concentration of about 1.75%w/v;
tropicamide at a concentration of about 0.02% w/v;
mannitol at a concentration of about 2.5% w/v;

polysorbate 80 at a concentration of about 0.25% w/v;
NaCl at a concentration of about 0.1% w/v;
boric acid at a concentration of about 0.12% w/v;
Carbopol® 940 at a concentration of about 0.95% w/v; and
BAK at a concentration of about 0.01% w/v.
wherein the pH is about 5.

[0188] In another embodiment, the ophthalmological composition comprises:
aceclidine at a concentration of about 1.75%w/v;
tropicamide at a concentration of about 0.015% w/v;
mannitol at a concentration of about 2.5% w/v;
polysorbate 80 at a concentration of about 0.75% w/v;
NaCl at a concentration of about 0.05% w/v;
boric acid at a concentration of about 0.2% w/v;
Carbopol® 940 at a concentration of about 0.95% w/v;
BAK at a concentration of about 0.01% w/v; and
phosphate buffer at a concentration of about 3 mM.
wherein the pH is about 5.

[0189] In another embodiment, the ophthalmological composition comprises:
aceclidine at a concentration of about 1.75%w/v;
tropicamide at a concentration of about 0.025% w/v;
mannitol at a concentration of about 2.5% w/v;
polysorbate 80 at a concentration of about 0.1% w/v;
boric acid at a concentration of about 0.2% w/v;
Carbopol® 940 at a concentration of about 0.9% w/v;
BAK at a concentration of about 0.05% w/v; and
phosphate buffer at a concentration of about 3 mM.
wherein the pH is about 5.

[0190] In another embodiment, the ophthalmological composition comprises:
aceclidine at a concentration of about 1.75%w/v;
tropicamide at a concentration of about 0.02% w/v;
mannitol at a concentration of about 2.5% w/v;

polysorbate 80 at a concentration of about 0.1% w/v;
NaCl at a concentration of about 0.1% w/v;
boric acid at a concentration of about 0.12% w/v;
Carbopol® 940 at a concentration of about 0.95% w/v;
BAK at a concentration of about 0.01% w/v; and
phosphate buffer at a concentration of about 3 mM.
wherein the pH is about 5.

[0191] In another embodiment, the ophthalmological composition comprises:
aceclidine at a concentration of about 1.75% w/v;
tropicamide at a concentration of about 0.040% w/v;
polyoxyl 40 stearate at a concentration of about 5.0% w/v;
mannitol at a concentration of about 2.5% w/v;
acetate or phosphate buffer at a concentration of about 3.0 mM; and
BAK at a concentration of about 0.01% w/v,
wherein said composition has a pH of about 4.75.

[0192] In another embodiment, the ophthalmological composition comprises:
aceclidine at a concentration of about 1.55% w/v;
tropicamide at a concentration of about 0.040% w/v;
polyoxyl 40 stearate at a concentration of about 5.0% w/v;
citric acid monohydrate at a concentration of about 0.1% w/v;
mannitol at a concentration of about 4.0% w/v;
Carbopol® 940 at a concentration of 0.09% w/v; and
acetate or phosphate buffer at a concentration of about 3.0 mM;
wherein said composition has a pH of about 5.0.

[0193] In another embodiment, the ophthalmological composition comprises:
aceclidine at a concentration of about 1.50% w/v;
tropicamide at a concentration of about 0.042% w/v;
polyoxyl 40 stearate at a concentration of about 5.5% w/v;
mannitol at a concentration of about 2.5% w/v;
phosphate buffer at a concentration of about 3.0 mM;
Carbopol® 940 at a concentration of about 0.85% w/v; and

BAK at a concentration of about 0.01% w/v,

wherein said composition has a pH of about 4.75.

[0194] In another embodiment, the ophthalmological composition comprises:

aceclidine at a concentration of about 1.45% w/v;

tropicamide at a concentration of about 0.042% w/v;

polyoxyl 40 stearate at a concentration of about 5.5% w/v;

citric acid monohydrate at a concentration of about 0.1% w/v;

acetate buffer at a concentration of about 3.0 mM; and

Carbopol® 940 at a concentration of about 0.75% w/v,

wherein said composition has a pH of about 4.75.

[0195] In another embodiment, the ophthalmological composition comprises:

aceclidine at a concentration of about 1.45% w/v;

tropicamide at a concentration of about 0.042% w/v;

polyoxyl 40 stearate at a concentration of about 5.5% w/v;

mannitol at a concentration of about 2.0% w/v;

citric acid monohydrate at a concentration of about 0.1% w/v;

phosphate buffer at a concentration of about 3.0 mM; and

Carbopol® 940 at a concentration of about 1.0% w/v,

wherein said composition has a pH of about 4.75.

[0196] In another embodiment, the ophthalmological composition comprises:

about 1.75% w/v aceclidine;

about 2.5% w/v mannitol;

about 2.75% w/v polysorbate 80; and

about 1.25%; 1.0% - 1.80% w/v hydroxypropylmethyl cellulose (depending on its molecular weight).

[0197] In another embodiment, the ophthalmological composition comprises:

about 1.75% w/v aceclidine;

about 0.005% to about 0.011% tropicamide;

about 2.5% w/v mannitol;

about 2.75% w/v polysorbate 80; and

about 1.25%; 1.0% - 1.80% w/v hydroxypropylmethyl cellulose (depending on its molecular weight).

[0198] In another embodiment, the ophthalmological composition comprises:

about 1.75% w/v aceclidine;

about 0.010% w/v tropicamide;

about 2.5% w/v mannitol;

about 5.0% w/v polysorbate 80;

about 1.40% w/v carboxymethyl cellulose high viscosity;

about 3 mM phosphate buffer; and

about 0.010% BAK = as preservative,

with a pH of about 5.0.

[0199] In another embodiment, the ophthalmological composition comprises:

about 1.75% w/v aceclidine;

about 0.006% w/v tropicamide;

about 2.5% w/v mannitol;

about 2.5% w/v polysorbate 80;

about 1.25%; 1.0% - 1.80% w/v hydroxypropylmethyl cellulose (depending on its molecular weight);

about 3 mM phosphate buffer; and

about 0.020% BAK = as preservative,

with a pH of about 5.0.

[0200] In another embodiment, the ophthalmological composition comprises:

about 1.75% w/v aceclidine;

about 0.006% w/v tropicamide;

about 2.5% w/v mannitol;

about 2.5% w/v polysorbate 80;

about 1.25%; 1.0% - 1.80% w/v hydroxypropylmethyl cellulose (depending on its molecular weight);

about 3 mM phosphate buffer;

about 0.50% w/v NaCl; and

about 0.020% BAK = as preservative,

with a pH of about 5.0.

[0201] In another embodiment, the ophthalmological composition comprises:

about 1.75% w/v aceclidine;

about 2.5% w/v mannitol;

about 3.5% w/v polysorbate 80;

about 1.25%; 1.0% - 1.80% w/v hydroxypropylmethyl cellulose (depending on its molecular weight);

about 3 mM phosphate buffer;

about 0.50% w/v NaCl; and

about 0.020% BAK or 0.15% sorbic acid as preservative,

with a pH of about 5.0.

[0202] In another embodiment, the ophthalmological composition comprises:

about 1.75% w/v aceclidine;

about 2.5% w/v mannitol;

about 3.5% w/v polysorbate 80; and

about 1.25%; 1.0% - 1.80% w/v hydroxypropylmethyl cellulose (depending on its molecular weight);

In another embodiment, the ophthalmological composition comprises:

about 1.75% w/v aceclidine;

about 2.5% w/v mannitol;

about 3.5% w/v polysorbate 80;

about 1.25%; 1.0% - 1.80% w/v hydroxypropylmethyl cellulose (depending on its molecular weight); and

one or more excipient selected from the group consisting of about 0.50 % w/v sodium chloride, about 0.02% w/v benzalkonium chloride, about 0.10% w/v sorbate, about 0.01% w/v ethylenediaminetetraacetic acid (EDTA) and 0.10% w/v citric acid.

[0203] In another embodiment, the ophthalmological composition comprises:

about 1.75% w/v aceclidine;

about 2.5% w/v mannitol;

about 0.01% w/v tropicamide;

about 0.1% w/v sodium citrate, anhydrous;

about 0.02% w/v benzalkonium chloride;
about 0.12% w/v sorbic acid;
about 0.1% w/v disodium edetate dihydrate;
about 4.0% w/v polysorbate 80; and
about 1.25% w/v hydroxypropylmethyl cellulose,
wherein the pH is about 5.0.

[0204] In another embodiment, the ophthalmological composition comprises:
about 1.75% w/v aceclidine;
about 2.5% w/v mannitol;
about 0.01% w/v tropicamide;
about 0.1% w/v sodium citrate, anhydrous;
about 0.02% w/v benzalkonium chloride;
about 0.1% w/v sorbic acid;
about 0.1% w/v EDTA;
about 3.5% w/v polysorbate 80; and
about 1.25%; 1.0% - 2.25% w/v hydroxypropylmethyl cellulose (depending on its molecular weight),
wherein the pH is about 5.0.

[0205] In another embodiment, the ophthalmological composition comprises:
about 1.75% w/v aceclidine;
about 2.5% w/v mannitol;
about 0.01% w/v tropicamide;
about 3mM phosphate buffer;
about 0.02% w/v benzalkonium chloride;
about 0.1% w/v sorbic acid;
about 0.1% w/v citrate;
about 3.5% w/v polysorbate 80; and
about 1.25%; 0.25% - 2.25% w/v hydroxypropylmethyl cellulose (depending on its molecular weight);
wherein the pH is about 5.0.

[0206] In another embodiment, the ophthalmological composition comprises:

aceclidine at a concentration of 1.5% w/v, mannitol at a concentration of 2.5% w/v.

[0207] In another embodiment, the ophthalmological composition comprises:
aceclidine at a concentration of 1.55% w/v, mannitol at a concentration of 2.5% w/v.

[0208] In another embodiment, the ophthalmological composition comprises:
aceclidine at a concentration of 1.6% w/v, mannitol at a concentration of 2.5% w/v.

[0209] In another embodiment, the ophthalmological composition comprises:
aceclidine at a concentration of 1.65% w/v, mannitol at a concentration of 2.5% w/v.

[0210] In another embodiment, the ophthalmological composition comprises:
aceclidine at a concentration of 1.7% w/v, mannitol at a concentration of 2.5% w/v.

[0211] In another embodiment, the ophthalmological composition comprises:
aceclidine at a concentration of 1.75% w/v, mannitol at a concentration of 2.5% w/v.

[0212] In another embodiment, the ophthalmological composition comprises:
aceclidine at a concentration of 1.80% w/v, mannitol at a concentration of 2.75% w/v and Carbopol® 940 at a concentration of 0.09% w/v.

[0213] In another embodiment, the ophthalmological composition comprises:
aceclidine at a concentration of 1.48% w/v, mannitol at a concentration of 1.5% w/v and Carbopol® 940 at a concentration of 0.50% w/v.

[0214] In another embodiment, the ophthalmological composition comprises:
aceclidine at a concentration of 1.80% w/v, mannitol at a concentration of 2.5% w/v and Carbopol® 940 at a concentration of 0.9% w/v.

[0215] The following Examples are provided solely for illustrative purposes and are not meant to limit the invention in any way.

EXAMPLES

Example 1 Effect of aceclidine on vision of subjects aged 47 to 67 years

[0216] Table 1 demonstrates the effect on the near focus ability of presbyopic subjects before and after ophthalmological administration of a composition containing aceclidine. Each composition included aceclidine in the concentrations indicated and 5.5% w/v HPβCD, 0.75% w/v CMC, 0.25% w/v NaCl and 0.01% w/v BAK. Additionally compositions administered to subjects 4 and 5 included 0.125% w/v tropicamide. As aceclidine is an enantiomer, the clinical effectiveness may vary with different ratios. For the present studies a nearly exact 50:50 ratio of stereoisomers was measured as best determined by polarimetry.

Table 1. Effects of aceclidine on vision of presbyopic patients.

Date	#	Age	Aceclidine	Vision Baseline				Post Gtt 15"				Effect (h)
			%	R Pre Dist	L Pre Dist	R Pre Near	L Pre Near	R Post Dist	L Post Dist	R Post Near	L Post Near	
8/21/2013	1	67	1.5	20.20	20.30	20.60	20.60	20.20	20.20	20.15	20.15	9.00
8/22/2013	2	52	1.5	20.30	20.30	20.50	20.50	20.25	20.25	20.25	20.20	8.00
8/23/2013	3	61	1.5	20.40	20.30	20.60	20.50	20.20	20.25	20.15	20.15	8.00
8/23/2013	4	61	1.1	20.20	20.25	20.80	20.50	20.15	20.15	20.20	20.15	12.00
8/23/2013	5	53	1.1	20.20	20.20	20.60	20.60	20.20	20.20	20.25	20.25	7.00
8/24/2013	6	47	1.5	20.25	20.25	20.100	20.100	20.20	20.20	20.15	20.15	8.00
8/25/2013	7	58	1.5	20.30	20.200	20.100	20.30	20.25	20.30	20.20	20.30	8.00

[0217] As seen in Table 1 all subjects had less than perfect near vision (20.20) in both the left and right eye (object at 15 inches from the eye) and most subjects had less than perfect distance vision before administration of the composition. After administration of the composition all subjects experienced an improvement in their near vision that lasted from 7 to 12 hours. Surprisingly, the majority of subjects also experienced improvement of their distance vision for the same time period. Still more surprisingly the improvement in near point was much closer than 16" typically required for comfortable reading, in some cases to about 8.5" more commonly seen in individuals 30 or less. The addition of tropicamide, a cycloplegic agent, had no additive or deleterious effect on vision correction.

Example 2 Effect of concentration of concentration of aceclidine and tropicamide

Table 2: Effect of concentration of concentration of aceclidine and tropicamide.

	#1	#2	#3	#4	#5 (OD)	#5 (OS)	#6	#7
Brimonidine	0.03%	0.03%	0.03%	0.03%	0.03%	0.03%	0.03%	
Poloxamer 407	5.5%							
HPBCD		5.5%	5.5%	5.5%	5.5%	5.5%	5.5%	5.5%
Aceclidine	1.5%	1.5%	0.75%	1.1%	1.1%	1.1%	1.1%	1.1%
Tropicamide				0.014%	0.021%	0.028%	0.042%	0.062%
NaCl	0.25%	0.25%	0.25%	0.25%	0.25%	0.25%	0.25%	0.25%
CMC	0.75%	0.75%	0.75%	0.75%	0.75%	0.75%	0.75%	0.75%
BAK	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
Redness (15 m)	3+	1	0.5	0.5	0	0	0	0
Redness (30 m)	1.5	0.5	0.25	0.25	0	0	0	0
Brow Ache (60 m)	2+	2+	2	0.5	0.5	0.0	0.0	0.0
Stinging (10 m)	2	2	0.5	0	0	0	0	0
BD-OD	20.20	20.20	20.20	20.20	20.20	20.20	20.20	20.20
BD-OS	20.25	20.25	20.25	20.25	20.25	20.25	20.25	20.25
BN-OD	8 pt	8 pt	8 pt	8 pt	8 pt	8 pt	8 pt	8 pt
BN-OS	7 pt	7 pt	7 pt	7 pt	7 pt	7 pt	7 pt	7 pt
BP-photopic	3 mm	3 mm	3 mm	3 mm	3 mm	3 mm	3 mm	3 mm
BP-mesopic	5 mm	5 mm	5 mm	5 mm	5 mm	5 mm	5 mm	5 mm
Miosis start (m)	15	15	15	15	15	15	15	15
Miosis (OU) (1 hr)	1.63 mm	1.63 mm	2.0-2.5 mm	1.63 mm	1.63 mm	1.63 mm	1.63 mm	1.70 mm
Distance (OU) (20 m)	20.20	20.20	20.20	20.20	20.20	20.20	20.20	20.20
Distance (OD) (1hr)	20.15+2	20.15+2	20.20	20.15+2	20.15+2	20.15+2	20.15+2	20.15+2
Distance (OS) (1hr)	20.15+2	20.15+2	20.20	20.15+2	20.15+2	20.15+2	20.15+2	20.15+2
Disance (OU) (1hr)	20.10-3	20.10-3	20.15	20.10-3	20.10-3	20.10-3	20.10-3	20.10-3
Near (OU) (20 m)	4 pt	4 pt	4pt	4 pt	4 pt	4 pt	4 pt	4 pt
Time (hr)	12.5	12.5	6.5	11	10	10		

[0218] Abbreviations: (C) indicates corrected vision, (m) indicates minutes, (hr) indicates hour, mm indicates millimeters, BD indicates baseline distance vision; BN indicates baseline near vision, BP indicates baseline pupil size, OD indicates right eye; OS indicates left eye and OU indicates both eyes.

[0219] All percentages are w/v. "pt" reflects size of print materials, 4 being equivalent to 20/20 vision and 3 to 20/15 vision.

[0220] "Time" refers to duration of the effect.

[0221] As seen in Table 2 aceclidine at a concentration of at least 1.1% w/v was able to reduce the size of the pupil to 1.63 mm 1 hour after topical instillation resulting in corrected near and distance vision for at least 10 hours. Lowering of the concentration of aceclidine to 0.75% w/v (formula #3) reduced the miotic effect to 2.0-2.5 mm after 1 hour and vision correction lasted only 6.5 hours. The addition of 0.03% w/v brimonidine reduced redness of the eye (4 out of 4

without brimonidine, not shown) to 1.5 out of 4 within 30 minutes after topical instillation which was maintained for the entire time vision was corrected. Switching the nonionic surfactant to HPβCD (formulas #2-6) further reduced the redness of the eye. Lowering of the concentration of aceclidine to 0.75% w/v (formula #3) further reduced eye redness but as mention above also reduced the vision correction duration of the formula.

[0222] A brow ache and stinging in the eye were noticeable in formulas #1-3 with a 2 out of 4 level of pain which was also associated with feelings of slight nausea, upset stomach and fatigue. Surprisingly, the addition of a cycloplegic agent, tropicamide, reduced brow ache and stinging to 0.5 out of 4 and 0 out of 4 respectively with brow ache dissipating after 60 minutes (formula # 4). Further, the raising of the concentration of aceclidine to 1.1% w/v restored the longer duration of corrected vision seen in formulas #1-2 without increasing eye redness. However, upon re-topical instillation of formula #4 at the end of the 10 hours noticeable brow ache occurred. Topical instillation of formula #5 (OD) and (OS), with increased tropicamide concentrations, following formula #4 relieved the brow ache experienced with re-installation of formula #4. Upon a 3rd topical instillation, at the end of the effective duration of formula #5, re-topical instillation of formula #5 again led to considerable brow ache. Once again, in formula #6, raising the concentration of tropicamide was able to overcome the brow ache. Additionally and unexpectedly, tropicamide, despite being a cycloplegic agent, had no effect on pupil miosis or vision correction. Surprisingly, the addition of tropicamide resulted in a prolonged duration of optimal pupil size constriction.

[0223] To determine the effect of brimonidine on pupil miosis, formula #7, was administered. Administration of formula #7 resulted in only a slight decrease in pupil miosis to 1.70 mm with identical distance and near vision improvement to that of formula #5. A 2-3+ conjunctival injection was noted.

[0224] All baseline vision data was based on vision corrected with distance contact lenses. Near vision was noted by subject as outstanding from 8 inches to the horizon at 1.5 hours after installation. A Marco Autorefractor with infrared camera and superimposed pupil calibration scale was used for all pupil size measurements. Once an image was selected it remained on screen allowing accurate calibration.

Example 3 Effect of concentration of aceclidine, brimonidine, guanfacine, fadolmidine, tropicamide and additives

Table 3: Effect of concentration of aceclidine, brimonidine, guanfacine, fadolmidine, tropicamide and additives.

	AB2T	AB4T	AB6T	AB11T	AB12T	PROPH13
Aceclidine	1.55	1.55	1.55	1.55	1.85	1.55
Brimonidine	0.037	0.037	0.037	0.037		
Fadolmidine						0.037
Guanfacine					0.037	
HPBCD	5.5	5.5	5.5	5.5	5.5	5
Tropicamide	0.043	0.043	0.043	0.043	0.042	0.043
CMC*	0.075	0.075	0.075	0.075	0.075	0.075
NaCl	0.025	0.025	0.025	0.025	0.025	0.025
BAK	0.01	0.01	0.01	0.01	0.01	0.01
Glycerin	0.1		0.1			0.1
Poloxamer 188	0.1	0.05				
Polyoxyl 40 stearate		0.05				
pH	6.5	7.5	7.5	7.5	7.0	7.5
nasal congestion	0	0	0	0	0	0
stinging initial	0.75	0	1.5	3.5	0	1.5
stinging, 3 min	0.5	0	0	wash out	0	0
redness initial	0	0	1	D/C	1	1
redness 15 min	0	0	0	D/C	0	0
whitening	0	0	0	D/C	1.5	1.5
pain	0	0	0	D/C	0	0
vision near	20.30	20.15	20.15	D/C	20.15	20.15
vision distance	20.20	20.20	20.20	D/C	20.20	20.20
onset (min)	20	12	16	D/C	12	16
duration (hrs)	5.5	7.5	7.5	D/C	7.5	7.5
color	clear	yellow	yellow	yellow	yellow	yellow
OVERALL	2.5	3.9	3.8	0	4	3.9

[0225] *1% = 2,500 cps

[0226] All percentages are w/v. Scores for nasal congestion, stinging initial, stinging, 3 min, redness initial, redness 15 min, whitening, pain and overall are out of 4.

[0227] "pt" reflects size of print materials, 4 being equivalent to 20/20 vision and 3 to 20/15 vision.

[0228] Baseline vision was 20.20 both eyes for distance; 20.70 right eye unaided for near; 20.80 left eye for near (best @ 16").

[0229] D/C stands for discontinued after eye washing due to intolerable stinging.

[0230] Aceclidine at a concentration of 1.55% w/v was able to reduce the size of the pupil to about 1.63 mm 30 minutes after topical instillation resulting in corrected near and distance vision to 20.20 or better for at least 6 hours, with noticeable affect lasting about 7.5 hours as seen in Table 3. Lowering of the concentration of aceclidine to 1.25% w/v (not shown) resulted in useful near vision improvement to about 20.25 – 20.30, but not as effective as at the higher dose range alkaline pH resulted in quicker onset, longer duration, and greater effect. The addition of 0.037% w/v brimonidine reduced redness of the eye (4 out of 4 without brimonidine, not shown) to baseline within 15 minutes after topical instillation which was maintained for the about the entire time vision was corrected. Adding glycerin 0.10% w/v noticeably reduced stinging. Adding instead poloxamer 188 0.05% w/v and polyoxyl 40 stearate 0.05% w/v however reduced initial stinging further but was more viscous. The combination of glycerin 0.1% w/v, poloxamer 188 0.1% w/v at a pH of 6.5 was noticeably reduced in onset, duration, comfort and effectiveness. AB11T did not include glycerin, poloxamer 188, or polyoxyl 40 stearate, which resulted in substantial stinging and discontinuation of the experiment with eye flush irrigation immediately after topical instillation. Substitution of guanfacine 0.037% w/v in AB12T for brimonidine resulted in minimal initial redness with prolonged redness reduction and some degree of whitening, and appeared to provide overall the best cosmesis though requiring slightly higher aceclidine concentration for optimal effect.

[0231] All baseline vision data was based on vision corrected with distance contact lenses. Near vision was noted by subject as outstanding from 8 to 10 inches to the horizon at 30 minutes after installation for AB4T and AB6T.

[0232] AB4T and AB6T were repeated both monocularly and binocularly. Substantial improvement in depth perception, near point acuity to 3 pt (20.15), and near point distance (8", 20.20) was noted when both eyes were treated vs. monocular treatment. Monocular treatment resulted in worsening of vision with both eyes open versus testing only the treated eye.

Example 4 Effect of concentration of aceclidine, brimonidine, tropicamide, and additives

Table 4: Effect of concentration of aceclidine, brimonidine, tropicamide, and additives.

	#8	#9	#10	#11	#12	#13	#14	#15	#16	#17	#18	#19	#20	#21
Aceclidine	1.61%	1.61%	1.61%	1.61%	1.61%	1.53%	1.53%	1.53%	1.53%	1.53%	1.53%	**1.45%**	1.65%	1.75%
Tropicamide	0.042%	0.042%	0.042%	0.042%	0.042%	0.044%	0.044%	0.044%	0.044%	0.044%	0.044%	0.042%	0.044%	0.035%
Brimonidine	0.042%	0.042%	0.042%	0.042%			0.042%	0.042%	0.042%		0.042%	0.042%	0.042%	0.042%
CMC	0.75%	0.75%	0.80%	0.87%	0.75%	0.75%	0.75%	0.80%	0.80%	0.80%	0.80%	0.75%	0.75%	0.75%
NaCl	0.25%	0.25%	0.50%	0.50%	0.25%	0.50%	0.50%	0.50%	0.75%	0.75%	1.00%	0.25%	0.25%	0.25%
BAK	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%
pH	7.00	7.00	7.00	7.00	8.00	7.00	7.00	7.00	7.00	8.00	7.00	7.00	7.00	8.00
phosphate buffer	5 mM		5 mM	5 mM	6 mM	5 mM	5 mM	5 mM	5 mM	5 mM	5 mM	5 mM	5 mM	6 mM
borate buffer		5 mM												
Onset (min)	15	15	15	15	15	15	15	15	15	15	15	15	15	15
Duration (hrs)	7	7	10-12	10-12	7	9	7	10-12	9	9	7	7	7	7
Pupil range (mm)	1.5-1.7	1.5-1.7	1.5-1.7	1.5-1.7	1.5-1.7	1.8-2.0	1.8-2.0	1.8-2.0	1.8-2.0	1.8-2.0	1.8-2.0	1.8-2.1	1.8-2.1	1.8-2.2
Dimming 0-4	1.5	1.5	1.5	1.5	1.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Sting 0-4	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Ache 0-4	0.25	0.25	0.25	0.25	0.25	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.25	0.00
Redness 0-4	0.5	0.5	0.5	0.5	1.5	1.0	0.5	0.5	0.5	1.0	0.5	0.5	0.5	0.5
Other	watery	watery	sl thicker	sl residue	watery	watery	watery	sl thicker	sl thicker	sl thicker	thicker	watery	watery	watery
Overall 0-5	3.5	3.5	4	4	2.5	4.5	4.75	5	5	5	4	4	4	4

[0233] As seen in Table 4, formulas #8-9, an increase in brimonidine to 0.42% w/v resulted in redness reduction to 0.5, while 0.75% w/v CMC resulted in a watery consistency. Unexpectedly, increasing CMC from 0.75% w/v to a range of 0.80% w/v to 0.87% w/v and increasing NaCl from 0.25% w/v to 0.75% w/v in formulas #10-11 resulted in a thicker consistency and an increased residence time from 7 hours to 10-12 hours and decreased the amount of drug that drained into the nasolacrimal duct. This decreased drug delivery to the nasal passages results in less nasal congestion.

[0234] In formulas #13-18 a decrease in the amount of aceclidine from 1.61% to 1.53% w/v resulted in a pupil size range from 1.8-2.0 mm. Dimming as a result of the restriction of the pupil decreased linearly from 1.5 to 0.5 with the decreased amount of aceclidine. Specifically, the 1.8 to 2.0 mm pupil created 41% more light than the 1.5 to 1.7 mm pupil. Surprisingly, the 1.8 to 2.0 mm pupil had a near depth increase of 1.75 D. This is only a 0.25 D loss from the beneficial 2.00 D seen with the 1.5-1.7 mm range. Thus, the 1.80 to 2.0 mm range produces 41% more light while still allowing the full benefit of increased near vision in individuals under 60 years of age; whereas, individuals 60 years of age and over still experience total computer benefit and some increased near benefit.

[0235] The increase in tropicamide concentration from 0.042% w/v (formulas #8-#11) to 0.044% w/v (formulas #13-#18) resulted in a decrease in ache to negligible amounts. The amount of ache may also be correlated with the age of the individual. For those individuals under the age of 45, an increase of tropicamide concentration to a range from 0.046% to 0.060% w/v may be preferred.

[0236] Further, Table 4 shows an unexpected result seen in formulas #13 and #17 where the increase of NaCl from 0.25% w/v to a range of 0.50 to 0.75% w/v resulted in an acceptable redness score of only 1.0 even without the addition of the redness reducing agent brimonidine.

[0237] Formulas #15, #16 and #17 each result in an overall maximum rating of 5 by combining the benefits of: (1) reduced aceclidine concentrations to improve the amount of light produced without significantly affecting the near vision benefits seen in formulas #8 - #12; (2) increased NaCl concentrations resulting in a further reduction in redness even in the absence of brimonidine; and (3) increased CMC concentrations resulting in longer residency time on the eye.

[0238] Formula #19 is an excellent alternative for the minority of individuals that are high responders to formulas #15- #17 and get noticeable dimming with 1.53% w/v aceclidine. Formula #20 is an excellent alternative for the minority of individuals that are low responders to formula #19. Lastly, Formula #21 is an excellent alternative for the minority of individuals that are low responders and get poor pupil response with Formula #20.

Example 5 Comparison of Effects of Polyoxyl 40 Stearate, HPβCD and Poloxamer 407

Table 5. Comparison of Effects of Polyoxyl 40 Stearate, HPβCD and Poloxamer 407.

	#22	#23	#24
Aceclidine	1.45%	1.45%	1.45%
Tropicamide	0.044%	0.044%	0.044%
Brimonidine	0.040%	0.040%	0.040%
Polyoxyl 40 Stearate	5.5%		
HPβCD		5.5%	
Poloxamer 407			5.5%
CMC	0.80%	0.80%	0.80%
NaCl	0.037%	0.037%	0.037%
EDTA	0.015%	0.015%	0.015%
BAK	0.007%	0.007%	0.007%
pH	7.00	7.00	7.00
phosphate buffer	5 mM	5 mM	5 mM
Nasal Congestion	0.00	0.50	1.50
Stinging	0.25	0.25	0.25
Wetting	4.00	4.00	4.00
Redness	0.25	0.50	0.50
Visual Blur (< 15 sec)	0.50	0.50	1.50
Duration	6-8 hrs	6-8 hrs	6-8 hrs
Overall 0-4	4.00	4.00	4.00

Clinical Protocol

[0239] 20 presbyopic patients with full distance correction were each given one of the above formulas (#22 - #23). All patients received pre- and post-drop distance and near acuity measurement, Zeiss Visante® (Visante is a registered trademark of Carl Zeiss Meditec AG) optical adherence tomography, axial length and contrast acuity testing (i.e. Colenbrander-Michelson 10% Lum target) with the following results:

all patient achieved a miotic pupil of 1.5 to 2.20 mm;

no patient experienced ciliary ache, ciliary spasm, or induced accommodation;

all patients achieved 20/30+ visual acuity or better at 14" and were very satisfied with their high contrast near vision results and there was no significant complaint of burning or aching;

the duration of effect lasted 6 -8 hrs in all cases;

binocular vision afforded all patients 1 – 1.5 additional lines of near acuity over monocular testing;

the last 10 patients were tested at 20" (i.e. computer distance, cell phone distance) and all achieved 20/25 or better near visual acuity;

moderately hyperopic (approx. +2.25 sphere) uncorrected presbyopes were very satisfied with distance visual acuity that improved to a 20/25 or better level at distance and near vision in the 20/30 range; and

uncorrected distance acuity was often improved for those patients who chose not to routinely correct a small refractive error.

[0240] As seen in Table 5, the use of polyoxyl 40 stearate provides the most comfortable aceclidine formulation with the least amount of visual blur and redness. To achieve similar results to that of formula #22, formula #23 requires 10-15% higher concentrations of the non-ionic surfactant and formula #24 requires 15-20% higher concentrations of the non-ionic surfactant. HPβCD induced a color change over time, possibly indicative of oxidation. Captisol® (sulfobutylether β-cyclodextrin) was substituted with similar findings.

Example 6 Modulation of Aceclidine Concentrations in a Preferred Embodiment.

[0241] Preferred embodiment:

Aceclidine 1.35% - 1.55% w/v;

Polyoxyl 40 stearate 5.5% w/v;

NaCl 0.037% w/v;

a viscosity agent, preferably CMC 0.80% w/v or an amount of Carbopol® 934 or 940 sufficient to achieve a viscosity of from about 5 to about 35 cps upon topical instillation, such as Carbopol® 940 at a concentration from about 0.09% to about 1.0% w/v;

BAK 0.015% w/v; and

a phosphate, citrate, citrophosphate, or acetate buffer from about 3 to about 10 mM,

wherein the pH is from about 4.75 to about 6.0.

[0242] For 1.35% w/v aceclidine –

[0243] Stinging on topical instillation 0.25 / 4.0 (lasting about 2-5 seconds);

[0244] Induced redness at 10 minutes: 1.0 to 1.5 / 4.0;

[0245] Induced redness at 30 minutes: 0.0 to 0.25 / 4.0;

[0246] Comfort: very high.

[0247] Wetting: very high, the eye maintaining sensation of improved wetting for most of a 24 hour period after a single topical instillation.

[0248] Depth of Focus distance: excellent.

[0249] Depth of Focus near: excellent.

[0250] In testing the above formulations on several subjects it was discovered that there is a slight range in clinical effect depending on the concentration of aceclidine, where 1.35% - 1.55% w/v aceclidine is preferred, but for which 1.35% w/v and 1.45% w/v confer the desired benefits on most subjects.

[0251] Further, it is discovered that the clinical effect of 1.35% w/v aceclidine can be improved when instilled as follows:

1) baseline effect: 1 drop to each eye.

2) enhanced effect: 2 drops to each eye.

3) greater effect: after 2) above repeat 1) above.

4) maximum effect: after 2) above repeat 2) above.

Example 7 Use of a preferred embodiment to prolong contact lens wear.

[0252] Preferred embodiment:

Aceclidine 1.45% w/v;

Polyoxyl 40 stearate 5.5% w/v;

NaCl 0.037% w/v;

a viscosity agent, preferably CMC 0.80% w/v or an amount of Carbopol® 934 or 940 sufficient to achieve a viscosity of from about 5 to about 35 cps upon topical instillation, such as Carbopol® 940 at a concentration from about 0.09% to about 1.0% w/v;

BAK 0.02% w/v; and

a phosphate, citrate, citrophosphate, or acetate buffer from about 3 to about 10 mM,

wherein the pH is from about 4.75 to about 6.0.

[0253] As a baseline, the subject, who normally wore extended wear lenses (Air Optix®; Air Optix is a registered trademark of Novartis AG) for daily wear only, slept in these lenses overnight. On arising each morning the subject's vision was blurred and the contact lenses required removal and cleaning of film and deposits that had formed overnight. Average vision on arising at distance: 20.60; average vision at near on a Michelson contrast acuity chart: 20.80.

[0254] Then, for seven consecutive days the above formulation was instilled between 7 am and 10 am each day as a single dose. Subject wore the Air Optix® lenses throughout each day and slept in the lenses overnight. Upon arising each morning the subject's vision at distance: 20.20+; vision at near 20.40 unaided (consistent with subject's baseline presbyopia when the subject did not wear the lenses overnight and instead inserted the lenses upon arising).

Example 8 Comparison of Effects of Polyoxyl 40 Stearate and Captisol® (sulfobutylether β-cyclodextrin

Table 6. Comparison of Effects of Polyoxyl 40 Stearate and Captisol® (sulfobutylether β-cyclodextrin).

	#25	#26	#27	#28	#29	#30	#31	**#32**	**#33**
Aceclidine	1.35%	1.35%	1.35%	1.35%	1.35%	1.35%	1.35%	1.35%	1.35%
Tropicamide	0.044%	0.044%	0.044%	0.044%	0.044%	0.044%	0.044%	0.044%	0.044%
Polyoxyl 40 stearate	5.5%	5.5%	5.5%	5.5%	5.5%	5.5%	5.5%		
Captisol®								5.5%	5.5%
Cocamidopropyl betaine							0.10%		
EDTA			0.015%	0.015%	0.005%	0.005%	0.005%	0.005%	0.015%
CMC 1%=2,500 cps	0.80%	0.80%	0.80%	0.80%	0.80%	0.80%	0.80%	0.80%	0.80%
NaCl	0.037%	0.037%	0.037%	0.037%	0.037%	0.037%	0.037%	0.037%	0.037%
Mannitol								4%	4%
BAK	0.007%	0.007%	0.007%	0.007%	0.007%	0.007%	0.007%	0.007%	0.007%
Borate buffer (mM)	4		4		4	4	4	4	4
Phosphate buffer (mM)		4		4					
pH	7	7	7	7	7	7	7	7	7
Redness, 10 min	1.25	1.25	2	2	1.75	1.75	0	0	0
Redness, 30 min	0	0	1.5	1.5	1.25	1.25	0	0	0
Pupil, 30 min (mm)	<2	<2	<2	<2	<2	<2	<2	<2	<3
Blur on instill (sec)	10	10	10	10	10	10	10	10	10
Ache	0	0	0	0	0	0	1	0	0
Rating	4.00	4.00	2.00	2.00	2.50	2.50	1.00	5.00	TBD

[0255] As seen in Table 6, when using polyoxyl 40 stearate as the surfactant the exclusion of EDTA results in reduced redness and best overall rating among polyoxyl 40 stearate compositions (Formulas #25 and #26). The addition of cocamidopropyl betaine ("CAPB") further reduces redness however results in significant ache (Formula #31). Replacing polyoxyl 40 stearate with Captisol® (sulfobutylether β-cyclodextrin) and adding mannitol achieves similar results in redness reduction as the addition of CAPB to polyoxyl 40 stearate but without the attendant ache resulting in the highest overall rating among aceclidine compositions (Formula #32). After several weeks formulations with Captisol® (sulfobutylether β-cyclodextrin) had an orange hue, possibly indicative of oxidation.

Example 9 Preferred Cold Chain Composition

[0256] Composition

aceclidine at a concentration of about 1.40%-1.80% w/v; and

tropicamide at about 0.42% w/v;

polyoxyl 40 stearate at about 5.5% w/v;

mannitol at a concentration of about 2.5% to 4.5% w/v;

carbomer 940 at a concentration of about 0.09% to about 2.0% w/v;

optionally, a preservative such as BAK at a concentration of about 0.2% w/v;

optionally citrate at a concentration of about 0.1%;

optionally with acetate or phosphate buffer at 2-100 mM, more preferably 3-5 mM

wherein said composition has a pH of about 4.50 to about 5.0; and preferably, about 4.75 to about 5.0; and

wherein w/v denotes weight by volume

[0257] A composition as described above was administered to a 62 year old subject. It resulted in pupils of 1.8-1.9 mm ou, 20.20 + reading vision, and 20.20 + distance vision; whereas without carbomer 940 reduced effectiveness resulted at 2.5% mannitol, and no near vision effect resulted at 4.0% mannitol. No ciliary spasm or loss of distance vision resulted. Onset was within about 15 minutes. Transient redness of about 1+ /out of 4 was noted for about 20 minutes without alpha agonist vasoconstrictor. The presence or absence of BAK had no clinical effect, and was used to provide an optional preservative.

Example 10 Stabile Aceclidine Formulations

Composition Tested:

aceclidine at a concentration of about 1.50% w/v;

tropicamide at a concentration of about 0.042% w/v;

polyoxyl 40 stearate at a concentration of about 5.5% w/v;

mannitol at a concentration of about 2.5% w/v;

citrate at a concentration of about 3 mM;

wherein said composition has a pH of about 4.75.

[0258] 20 samples of the above composition were divided evenly and stored at 25 ºC and 4 ºC. Prior to storage, initial concentrations of aceclidine were measured using high-pass liquid chromatography ("HPLC"). The amount of aceclidine in each solution was calculated by the area under the principal peak compared to a reference solution of aceclidine. Samples were then subject to storage for 3 months. Aceclidine measurements were taken at 1, 2 and 3 months. Results of the stability test are shown in Table 7.

Table 7. Stability of Aceclidine in Cold Chain Storage

	25 °C	4 °C
Initial	100%	100%
1 month	92%	93%
2 months	75%	92%
3 months	50%	88%

[0259] As seen in Table 7 “cold chain storage” or storage of the aceclidine composition at from 2 ºC to 8 ºC resulted in a significant increase in stability of aceclidine at all 3 time points.

Example 11 Use of compositions containing little or no cycloplegic agent

[0260] Aceclidine alone causes incidence migraine-like severe ciliary spasm (brow ache) and myopic blur. These effects are inversely correlated to age with subjects age 40 reporting the highest incidence and subject age 60+ reporting the lowest incidence. The addition of a cycloplegic agent reduces ciliary spasms and attendant brow ache, migranious headache, squeezing pressure around eyes or other symptoms of ciliary spasms. The addition of the cycloplegic agent, surprisingly, does not reduce the myopic effect of aceclidine. The addition of 2.5% w/v mannitol however does reduce the myopic effect of aceclidine. Increasing the aceclidine concentration overcomes this reduction in myopic effect seen with the addition of mannitol. Surprisingly, however, the increase in aceclidine is not coincident with an increase in ciliary spasm. Even more surprising, the concentration of the cycloplegic agent can be reduced or even eliminated in the presence of mannitol without an increase in ciliary spasm. Thus, combining a higher concentration of aceclidine with little to no cycloplegic agent in the presence of mannitol results in an improvement of near vision acuity without attendant side effects on par with lower concentrations of aceclidine and higher concentrations of the cycloplegic agent in the absence of a cycloplegic agent.

[0261] Further and unexpectedly, the addition of a nonionic surfactant increases both the quantitative measure of near vision improvement and the duration. This effect is concentration sensitive. In a preferred embodiment the non-ionic surfactant is at least 1%, preferably at least 2%, more preferably from about 1% to about 5%, and most preferably about 5%. For example, polysorbate 80 or polyoxyl 40 stearate at a concentration from about 1% to about 5% w/v results in about 1.5 to about 2.0 lines of improvement and a duration from about 4 to about 5 hours.

[0262] Not to be held to particular theory, the increase in concentration of a surfactant may crowd the surface of the cornea, and at an optimal concentration this crowding result in small and probably nanometer diameters, which given the dual polarity of surfactants, where nonionic are most preferred, enhances corneal absorption of the entrapped highly polar aceclidine molecules.

[0263] The further addition of a viscosity agent by itself does not enhance duration. Surprisingly, the addition of a viscosity agent in a formulation with optimal ratios of aceclidine,

tropicamide and a non-ionic surfactant dramatically improves duration. For example, a formulation of the present invention comprising 1.75% aceclidine, 2.5% mannitol, 0.01% tropicamide, 5% polysorbate 80 improves near vision in a presbyopic patient by up to 3 lines of vision acuity for about 4 to about 5 hours. The addition of 1.4% CMC further increases the near vision improvement to from about 7 to about 10 hours. Not to be held to a particular theory, a threshold above the critical micellar threshold greatly enhances permeation through the cornea by reducing micelle size from micrometers to nanometers. See Figure 2.

[0264] Examples of compositions containing little or no cycloplegic agent are shown in Table 8 below.

Table 8. Compositions containing little or no cycloplegic agent

	#L1	#L2	#L3	#L4	#L5	#L6	#L7	#L8	#L9	#L10
Aceclidine	1.75%	1.75%	1.75%	1.75%	1.75%	1.75%	1.75%	1.75%	1.75%	1.75%
Tropicamide	0.02%	0.02%	0.02%	0.02%	0.02%	—	—	—	—	—
Mannitol	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%
Polysorbate 80	0.75%	0.25%	0.25%	0.1%	0.1%	0.5%#	0.25%	0.25%	0.1%	0.1%
Carbopol® 940 or CMC	0.95%	0.95%	0.95%	0.9%	0.95%	0.95%*	0.95%*	0.95%*	0.9%*	0.95%*
Glycerine										
Phosphate buffer	3mM	—	3mM	3mM	3mM	3mM	—	3mM	3mM	3mM
NaCl	0.5%	0.1%	0.05%	—	0.1%	0.5%#	0.1%	0.05%	—	0.1%
Boric acid	—	0.12%	0.2%	0.2%	0.12%	—	0.12%	0.2%	0.2%	0.12%
BAK	0.015%	0.01%	0.01%	0.05%	0.01%	0.015%	0.01%	0.01%	0.05%	0.01%
pH	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0

Table 8. (continued)

	#L11	#L12	#L13	#L14	#L15	#L16	#L17	#L18	#L19	#L20	#L21
Aceclidine	1.65%	1.65%	1.75%	1.75%	1.65%	1.75%	1.75%	1.75%	1.75%	1.75%	1.75%
Tropicamide	0.01%	—	—	0.025%	0.025%	0.025%	0.025%	0.025%	0.025%	0.015%	0.015%
Mannitol	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%
Polysorbate 80	2%	2%	1%	0.10%	2.50%	2.50%	3.00%	2.50%	2.50%	2.50%	2.50%
Carbopol® 940 or CMC	0.75%	0.75%	0.75%	0.75%	0.75%	0.75%	0.75%	1.50%	0.75%	0.75%	0.75%
Glycerine	0.10%	0.10%	0.10%	0.10%	0.10%	0.10%	0.10%	0.10%	0.20%	0.20%	0.20%
Phosphate buffer	3 mM	3 mM	3 mM	3 mM	3 mM	3 mM	3 mM	3 mM	3 mM	3 mM	3 mM
NaCl	—	—	—	—	—	—	—	—	—	—	—
Boric acid	—	—	—	—	—	—	—	—	—	—	—
BAK	0.01%	0.01%	0.01%	0.01%	0.015%	0.015%	0.015%	0.015%	0.015%	0.015%	0.015%
pH	5.0	5.0	5.0	5.0	5.25	5.25	5.25	5.25	5.25	5.25	5.25

Table 8. (continued)

	#L22	#L23	#L24	#L25	#L26	#L27	#L28	#L29	#L30	#L31	#L32
Aceclidine	1.65%	1.75%	1.75%	1.75%	1.75%	1.65%	1.75%	1.75%	1.75%	1.75%	1.75%
Tropicamide	0.025%	0.275%	0.020%	0.015%	0.027%	0.0275%	0.0275%	0.0275%	0.025%	0.022%	0.0175%
Mannitol	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%
Polysorbate 80	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%
Carbopol® 940 or CMC	1.25%	1.45%	1.45%	1.45%	1.45%	1.25%	1.40%	1.40%	1.50%	1.40%	1.50%
Glycerine											
Phosphate buffer	3 mM	3 mM	3 mM	3 mM	3 mM	3 mM	3 mM	3 mM	3 mM	3 mM	3 mM
NaCl	–	–	–	–	–	–	–	–	–	–	–
Boric acid	–	–	–	–	–	–	–	–	–	–	–
BAK	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%
pH	5.0	5.0	5.0	5.0	6.0	5.0	5.0	5.0	5.0	5.0	6.0
Pupil Size (mm)											
Reading vs. Baseline 40 cm	3+	3+	3+	3+	3+	3+	3+	3+			3+
Duration (hours)	7	10+	10+	10+	10+	7.0	10+	10+			10+
Ciliary Spasms	0.0	tr	0.5	1.0	1.0	0.0	tr	0.5		1.0	1.0
Stinging	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5			0.5
Blur (min)	1	1	1	1	1	1	1	1			1
Distance Blur											
Onset (min)	20	20	20	20	20	20	20	20			20
Redness 1hr (0-4)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5			0.5
Redness 4hr (0-4)											
Overall Comfort	sl sticky	sl sticky	sl sticky	sl sticky	sl sticky	sl sticky	sl sticky	sl sticky			sl sticky
Osmolarity											
Efficacy index: read*dur											
OVERALL (1-5)	best	best	best	best	best	best	best	best			best

Table 8. (continued)

	#L33	#L34	#L35	#L36	#L37	#L38	#L47	#L48	#L49	#L50	#L51
Aceclidine	1.75%	1.40%	1.40%	1.25%	1.45%	1.45%	1.45%	1.55%	1.65%	1.75%	1.65%
Tropicamide	-	-	-	-	-	0.0200%	-	0.0200%	0.0300%	0.0300%	0.0200%
Brimonidine	-	-	-	-	-	-	-	-	-	-	-
Mannitol	-	-	-	-	-	-	2.5%	4.0%	2.5%	2.5%	2.5%
Polysorbate 80	-	-	-	-	-	-	-	-	-	5.00%	-
Polyoxyl 40 Stearate	-	-	-	-	5.5%	5.5%	5.5%	5.5%	5.5%	-	5.5%
Citrate	0.10%	0.10%	0.10%	0.10%	0.10%	0.10%	0.10%	0.10%	0.10%	-	0.10%
Glycerine	-	0.10%	0.10%	0.10%	0.10%	0.10%	0.10%	0.10%	0.10%	0.10%	0.10%
CMC	-	1.45%	0.75%	-	0.85%	0.75%	0.75%	0.75%	0.75%	0.75%	0.75%
HPMC	-	-	-	-	-	-	-	-	-	-	-
Carbopol® 940	-	-	-	-	-	-	-	-	-	-	-
NaCl	0.75%	0.75%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.00%
Boric Acid	-	-	-	-	-	-	-	-	-	-	-
Postassium Borate	-	-	-	-	-	-	-	-	-	-	-
Phosphate buffer	3	3	3	3	3	3	3	3	3	3	3
Acetate	-	-	-	-	-	-	-	-	-	-	-
pH	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.25	5.0	5.0
BAK	0.015%	0.015%	0.015%	0.015%	0.015%	0.015%	0.015%	0.015%	0.015%	0.015%	0.015%
Pupil Size (mm)											
Reading vs. Baseline 40 cm	3	3.25	3	2	3	2.5	1.5	0.5	1.5	1.5	1
Duration (hours)	4	7	4.5		6.5	6	3	2	4	4	2
Ciliary Spasms	4	4	3	2	3	2	0.5	0.5	0.5	0.5	0.5
Stinging	1.0		1.0		1.0	1.0	1	1	0.5	1	1
Blur (min)											
Distance blur	none	none	none	none	none	none	none	none	none	none	none
Onset (min)	20-11	20-12	20-13	20-14	20-15	20-16	20-25	20-25	20-25	20-25	20-25
Redness 1hr (0-4)	2.0		1.5		0.5	0.5	0.5	0.5	0.5	0.5	0.5
Redness 4hr (0-4)											
Overall comfort	poor	poor	poor	fair	poor	poor	good	good	good	good	good
Osmolarity	hi	hi	hi	hi	hi	hi	hi	hi	hi	hi	hi
Efficacy index: read*dur	12	23	14	0	20	15	5	1	6	6	2
OVERALL (1-5)	*	** 1/2	*	-	*	**	***	*	*	*	*

Table 8. (continued)

	#L52	#L53	#L54	#L55	#L56	#L57	#L58	#L59	#L60	#L61	#L62
Aceclidine	1.65%	1.65%	1.65%	1.75%	1.75%	1.65%	1.65%	1.65%	1.65%	1.65%	1.75%
Tropicamide	0.0100%	0.0250%	0.0000%	0.0000%	0.0250%	0.0250%	0.0250%	0.0150%	0.0400%	0.0250%	0.0300%
Brimonidine	-	-	-	-	-	-	-	-	-	-	-
Mannitol	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%
Polysorbate 80	2.00%	2.50%	2.00%	1.00%	0.10%	2.00%	2.50%	2.50%	3.50%	2.50%	3.50%
Polyoxyl 40 Stearate	-	-	-	-	-	-	-	-	-	-	-
Citrate	-	0.10%	-	-	-	-	-	-	-	-	-
Glycerine	0.10%	0.10%	0.10%	0.10%	0.10%	0.10%	0.10%	0.10%	0.10%	0.10%	0.10%
CMC	0.75%	0.85%	0.85%	0.85%	0.85%	0.85%	0.85%	0.75%	0.60%	1.60%	0.60%
HPMC	-	-	-	-	-	-	-	-	-	-	-
Carbopol® 940	-	-	-	-	-	-	-	0.75%	0.60%		0.60%
NaCl	0.50%	0.50%	-	-	-	-	-	-	-	-	-
Boric Acid	-	-	-	-	-	-	-	-	-	-	-
Postassium Borate	-	-	-	-	-	-	-	-	-	-	-
Phosphate buffer	3	3	3	3	3	3	3	3	3	3	3
Acetate	-	-	-	-	-	-	-	-	-	-	-
pH	5.0	5.0	5.0	5.3	5.3	5.3	5.00	5.00	5.00	5.00	5.00
BAK	0.015%	0.015%	0.015%	0.015%	0.015%	0.015%	0.015%	0.015%	0.015%	0.015%	0.015%
Pupil Size (mm)											
Reading vs. Baseline 40 cm	2.5	3	3	2	1.5	2.5	3	2	1.5	2.5	2.5
Duration (hours)	6	5	6	4	4	6	5.5	7	3	7	7
Ciliary Spasms	0.5	0.5	2	2	0	0	0	0.5	0	0.5	0.5
Stinging	1	0.5	1	0.5	0.5	0.5	0.5	0.5	0.25	0.25	0.25
Blur (min)									1.5	1	2
Distance blur	none	none	none	none	none	none	none	none	none	none	none
Onset (min)	20-25	20-25	20-25	20-25	20-25	20-25	20-25	20-25	20-25	20-25	20-25
Redness 1hr (0-4)	0.5	0.5	0.5	0.5	1.0	0.5	0.5	0.5		0.5	0.5
Redness 4hr (0-4)											
Overall comfort	poor	poor	poor	poor	good	good	good	good	good	good	good
Osmolarity	hi	hi	nl	nl	nl	nl	nl	nl	nl	nl	nl
Efficacy index: read*dur	15	15	18	8	6	15	17	14	5	18	18
OVERALL (1-5)	**									****	****

Table 8. (continued)

	#L63	#L64	#L65	#L66	#L67	#L68	#L69	#L70	#L71	#L72	#L73
Aceclidine	1.65%	1.75%	1.65%	1.75%	1.75%	1.75%	1.75%	1.75%	1.75%	1.75%	1.75%
Tropicamide	0.0250%	0.0250%	0.0250%	0.0275%	0.0275%	0.0275%	0.0250%	0.0180%	0.0160%	0.0160%	0.0150%
Brimonidine	-	-	-	-	-	-	-	-	-	-	-
Mannitol	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%
Polysorbate 80	2.50%	3.50%	4.00%	5.00%	5.00%	2.00%	2.00%	2.00%	2.25%	4.00%	4.00%
Polyoxyl 40 Stearate	-	-	-	-	-	-	-	-	-	-	-
Citrate	-	-	-	-	-	-	-	-	-	-	-
Glycerine	0.10%	0.10%	0.10%	-	-	-	-	-	-	-	-
CMC	0.75%	0.50%	0.75%	-	1.35%		1.35%	1.45%	1.45%	1.45%	1.45%
HPMC	-	-	-	-	-	-	-	-	-	-	-
Carbopol® 940		0.50%		1.35%	-	1.45%	-	-	-	-	-
NaCl	-	-	-	-	-	-	-	-	-	-	-
Boric Acid	-	-	-	-	-	-	-	-	-	-	-
Postassium Borate	-	-	-	-	-	-	-	-	-	-	-
Phosphate buffer	3	3	3	3	3	3	3	3	3	3	3
Acetate				-	-	-	-	-	-	-	-
pH	5.00	5.00	5.00	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
BAK	0.015%	0.015%	0.015%	0.015%	0.015%	0.015%	0.015%	0.015%	0.01%	0.01%	0.01%
Pupil Size (mm)											
Reading vs. Baseline 40 cm	2	2.5	2	2.75	2.75	2.75	2.75	2.75	2.75	2.75	3
Duration (hours)	4		5	7	7	5.5	6	7	7	7	7.5
Ciliary Spasms	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Stinging	0.5	0.5	0.5	0.5	0.5	0.5					
Blur (min)										1	
Distance blur	none	none	none	none	none	none	none	none	none	none	none
Onset (min)	20-25	20-25	20-25	20-25	20-25	20-25	20-25	20-25	20-25	20-25	20-25
Redness 1hr (0-4)	0.5	0.5	0.5	0.5	0.5	0.5					
Redness 4hr (0-4)											
Overall comfort	good	good	good	good	good	good	good	good	good	good	good
Osmolarity	nl	nl	nl	nl	nl	nl	nl	nl	nl	nl	nl
Efficacy index: read*dur	8	0	10	19	19	15	17	19	19	19	23
OVERALL (1-5)	poor		?	** 1/2		**				****	**** ½

Table 8. (continued)

	#L74	#L75	#L76	#L77	#L78	#L79	#L80	#L81	#L82	#L83	#L84
Aceclidine	1.75%	1.75%	1.75%	1.75%	1.75%	1.75%	1.75%	1.75%	1.75%	1.65%	1.40%
Tropicamide	0.0150%	0.0150%	0.0120%	0.0110%	0.0100%	0.0000%	-	0.0100%	0.0150%	0.0000%	0.0000%
Brimonidine	-	-	-	-	-	0.015%	-	-	-	-	-
Mannitol	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%
Polysorbate 80	5.00%	5.00%	5.00%	5.00%	5.00%	5.00%	-	6.00%	7.00%	0.00%	0.00%
Polyoxyl 40 Stearate	-	-	-	-	-	-	-	-	-	-	5.5%
Citrate	-	-	-	-	-	-	-	-	-	-	-
Glycerine	-	-	-	-	-	-	-	-	-	-	-
CMC	1.45%	1.43%	1.43%	1.40%	1.40%	1.40%	1.40%	1.40%	1.40%	0.00%	0.75%
HPMC	-	-	-	-	-	-	-	-	-	-	-
Carbopol® 940	-	-	-	-	-	-	-	-	-	-	-
NaCl	-	-	-	-	-	-	-	-	0.50%	-	-
Boric Acid	-	-	-	-	-	-	-	-	-	-	-
Postassium Borate	-	-	-	-	-	-	-	-	-	-	-
Phosphate buffer	3	3	3	3	3	3	3	3	3	3	3
Acetate	-	-	-	-	-	-	-	-	-	-	-
pH	5.0	5.0	5.0	5.0	5.0	5.0		5.0	5.0	5.0	5.0
BAK	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	-	0.01%	0.01%	0.010%	0.010%
Pupil Size (mm)											
Reading vs. Baseline 40 cm	3.25	3.25	3.5	3.5	3.75	2.5	2.5	2.75	2.5	1	1.5
Duration (hours)	7.5	7.5	7	8	9	8	7	5.5	5	3	3.5
Ciliary Spasms	0.5	0.5	1	1	1	2	2	0.5	0.5	1	1
Stinging											1.0
Blur (min)	1.5	1.5	1.5								
Distance blur	none	none	none	none	none	none	none	none	none	none	none
Onset (min)	20-25	20-25	20-25	20-25	20-25	20-25	20-25	20-25	20-25	20-25	20-25
Redness 1hr (0-4)											2.0
Redness 4hr (0-4)											
Overall comfort	good-exc	good-exc	good-exc	exc	exc	fair	fair	good	good		fair
Osmolarity	nl	nl	nl	nl	nl	nl	nl	nl	hi	nl	nl
Efficacy index: read*dur	24	24	25	28	34	20	18	15	13	3	5
OVERALL (1-5)	*****	*****	*****!	*****!!	*****!!	****	****	***	***		*

Table 8. (continued)

	#L85	#L86	#L87	#L88	#L89	#L90	#L91	#L92	#L93	#L94
Aceclidine	1.75%	1.75%	1.75%	1.75%	1.75%	1.75%	1.75%	1.75%	1.75%	1.75%
Tropicamide	0.0000%	0.0100%	0.0900%	0.0060%	0.0060%	0.0100%	0.0060%	0.0060%	0.0060%	0.0060%
Brimonidine	-	-	-	-	-	-	-	-	-	-
Mannitol	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	-	2.5%
Polysorbate 80	5.00%	2.5%	2.5%	2.5%	2.5%	2.50%	2.50%	2.75%	2.75%	3.50%
Polyoxyl 40 Stearate	-	-	-	-	-	-	-	-	-	-
Citrate	-	-	-	-	-	-	-	-	-	-
Glycerine	-	-	-	-	-	-	-	-	-	-
CMC	1.40%	-	-	-	-	-	-	-	-	-
HPMC	-	1.75%	1.75%	1.75%	1.75%	-	-	-	-	-
Carbopol® 940	-	-	-	-	-	1.75%	1.75%	1.80%	1.80%	1.80%
NaCl	0.00%	0.50%	-	0.50%	-	0.50%	0.50%	0.50%	0.50%	0.50%
Boric Acid	-	-	0.35%	-	-	-	-	-	0.25%	-
Postassium Borate	-	-	0.47%	-	-	-	-	-	0.37%	-
Phosphate buffer	3	3	3	3	4	3	3	3	3	3
Acetate	-	-	-	-	-	-	-			
pH	5.0	5.0	5.0	5.0	6.0	5.0	5.0	5.0	5.0	5.0
BAK	0.010%	0.020%	0.020%	0.020%	0.020%	0.02%	0.02%	0.02%	0.02%	0.02%
Pupil Size (mm)										
Reading vs. Baseline 40 cm	3.5	3.5	3.5	3.75	3.75	3.5	3.75	3.75	3.75	3.75
Duration (hours)	7	8	7	9	9	7	7	8	8	8.5
Ciliary Spasms	2	0.5	0.5	0.5	0.5	0.5	0.5	0	0	0
Stinging	0.5									
Blur (min)										
Distance blur	2.0	none	none	none	none	none	none	none	none	none
Onset (min)	20-25	20-25	20-25	20-25	20-25	20-25	20-25	20-25	20-25	20-25
Redness 1hr (0-4)	1.0	1.0	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Redness 4hr (0-4)										
Overall comfort	good	good	good	good	good					
Osmolarity	nl	nl	nl	nl	lo					
Efficacy index: read*dur	25	28	25	34	34	25	26	30	30	32
OVERALL (1-5)	****					*****	*****	*****	*****	*****

All concentration in weight by volume.

mm denotes millimeters.

cm denotes centimeters.

min denotes minutes.

%* denotes amount can optionally vary from about 0.01% to about 1% w/v.

# denotes formulation can include polysorbate 80 or not include polysorbate 80.
Ciliary spasms scores correspond to the following: 0=no discomfort; 0.5=slight sting; 1=noticeable squeeze/discomfort; 2=pain for less than 30 minutes; 3=pain for 1 hour or more; and 4=severe to intolerable pain.

[0265] The efficacy index is demonstrated in Figure 3. In brief, the score is calculated by multiplying the lines of improvement in near visual acuity by the number of hours the improvement lasts. For example a score of: 5 is equal to +1 lines of improvement in near visual acuity for 5 hours; 10 is equal to +1.5 lines of improvement for 6.7 hours; 15 is equal to 2 lines of improvement for 7.5 hours; 20 is equal to 2.5 lines of improvement for 8 hours; 25 is equal to 3+ lines of improvement for 8.3 hours and 35 is equal to 3.75+ lines of improvement for 9 hours.

[0266] As demonstrated by comparing the Reading vs. Baseline at 40 cm and Efficacy Indexes of formulas #L33-#L37, formulas containing 1.40% or more aceclidine are better at correcting presbyopia than those formulas containing 1.25% aceclidine. Inversely, the lower concentration of aceclidine results in better overall comfort to the user. The addition of 2.5% mannitol to formulas with 1.45% aceclidine improves overall comfort but at the expense of reducing the presbyopic correcting effect (compare #L37 with #L47.) This reduction in near vision improvement is exacerbated with the addition of 4.0% mannitol (compare #L47 with #L48.) Increasing aceclidine concentrations to 1.65% or 1.75% overcome the reduction in near vision improvement seen with the addition of mannitol (compare #L47 with #L49 and #L50.)

[0267] Further, formulas containing 1.75% aceclidine and 2.5% mannitol have an increased efficacy and duration in treating presbyopia that is correlated with an increase in polysorbate 80 up to 5.0% and then inversely correlated with a decrease in CMC from 1.45% to 1.40% (compare formulas #L66 to #L78.) Optimal formulations are demonstrated by #L77, #L78 and #L85-#L94, which each have the highest improve reading at 40 cm at between 3.5 and 3.75 visual acuity lines and the highest Efficacy Index scores of 25 to 34, and the longest duration from 7 to 9 hours. The increase in effectiveness and duration of formulas from #L66 to #L78 are also inversely correlated with a decrease in tropicamide from 0.0275% to 0.01%. This same trend is demonstrated by the increase in effectiveness (i.e. Reading vs. Baseline 40 cm) when comparing #L85 through #L94.

[0268] This data demonstrates that mannitol can effectively reduce ciliary spasms caused by aceclidine, thus reducing the need for a cycloplegic agent such as tropicamide. Further, this data

demonstrates that the addition of a non-ionic surfactant and viscosity agent can further enhance the efficacy and duration of compositions containing aceclidine, mannitol and low tropicamide. This data also demonstrates that the use of a cycloplegic agent in aceclidine compositions containing polysorbate 80 and CMC is most beneficial to presbyopic correction when the cycloplegic agent is closer to 0.006% than 0.025%. Finally, this data demonstrates that compositions comprising aceclidine and mannitol are sufficient to correct presbyopia with tolerable pain.

Example 12 Use of further high tropicamide formulations

[0269] The following examples are of aceclidine formulations containing more than 0.03% tropicamide.

Table 9. High tropicamide formulations

	#L39	#L40	#L41	#L42	#L43	#L44	#L45	#L46
Aceclidine	1.45%	1.45%	1.40%	1.40%	1.40%	1.40%	1.40%	1.40%
Tropicamide	0.035%	0.037%	0.040%	0.050%	0.055%	0.06%	0.08%	0.04%
Polyoxyl 40 Stearate	5.5%	5.5%	5.5%	5.5%	5.5%	5.5%	5.5%	5.5%
Citrate	0.10%	0.10%	0.10%	0.10%	0.10%	0.10%	0.10%	0.10%
Glycerine	0.10%	0.10%	0.10%	0.10%	0.10%	0.10%	0.10%	0.10%
CMC	0.75%	0.75%	0.75%	0.75%	0.75%	0.75%	0.75%	0.75%
NaCl	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%
Phosphate buffer	3	3	3	3	3	3	3	3
pH	5.0	5.0	5.0	5.25	5.5	5.25	5.0	5.0
BAK	0.015%	0.015%	0.015%	0.015%	0.015%	0.015%	0.015%	0.015%
Reading vs. Baseline 40 cm	3.5	3.5	3.5	2	1	1	1	3
Duration (hours)	6	6	6	2	2	1	1	6
Ciliary Spasm	1	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Stinging	1.0	1.0	1.0	0.5	0.25	0.5	1	1
Distance blur	none	none	none	none	none	none	none	none
Onset (min)	20-17	20-18	20-19	20-20	20-21	20-22	20-23	20-24
Redness 1hr (0-4)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Overall comfort	fair	good	good	good	good	good	good	good
Osmolarity	hi	hi	hi	hi	hi	hi	hi	hi
Efficacy index: read*dur	21	21	21	4	2	1	1	18
OVERALL (1-5)	**	***	***	*	½*	¼*	¼*	***

Ciliary spasms scores correspond to the following: 0=no discomfort; 0.5=slight sting; 1=noticeable squeeze/discomfort; 2=pain for less than 30 minutes; 3=pain for 1 hour or more; and 4=severe to intolerable pain.

[0270] As demonstrated by formulas #L39-#L41 and compared to formulas #L74-#L78 in Table 8, formulas containing about 1.40% to about 1.45% aceclidine, about 0.035% to about 0.04% tropicamide, about 5.5% polyoxyl 40 stearate and about 0.75% CMC are almost, but not quite as effective at treating presbyopia as formulas containing about 1.65% to about 1.75% aceclidine, about 2.5% mannitol, about 5% polysorbate 80, about 1.40% CMC formulas. This effectiveness decreases dramatically when tropicamide is increased to about 0.05% to about 0.08% tropicamide.

Example 13. Use of a compound containing mannitol

Formulation:

aceclidine 1.75% w/v

tropicamide 0.006% w/v

mannitol 2.5% w/v

polysorbate 80 2.75% w/v

NaCl 0.5% w/v

hydroxypropylmethyl cellulose 0.5% -1.80% w/v

phosphate buffer 3 mM

pH 5.0, and

BAK 0.020% as preservative.

Method:

[0271] The subject instilled 2 drops of the above formulation in each eye and the excess wiped from lids and lashes.

Results:

[0272] Within 20 minutes, near vision improvement of about 3 lines of visual acuity was noted with very slight dimming. Throughout the day near vision remained enhanced with no loss of distance vision. Further, if the subject previously suffered from any mild refractive errors distance vision was improved. Over a 5-8 hour period the pupil begins to slightly recover, and after a few hours the minimal dimming was no longer noted. Both excellent near vision near

onset, and possibly still slightly improved near vision continued as the pupil slightly begins to increase from its minimal size earlier in the day.

Example 14. Use of a preferred embodiment optimizing tropicamide and hydroxypropyl methyl cellulose

[0273] Composition

Aceclidine	1.75% w/v
Tropicamide	0.010% w/v
Mannitol	2.50% w/v
Polysorbate 80	3.50% w/v
NaCl	0.50% w/v
HPMC	1.25% w/v
BAK	0.02% w/v
Phosphate buffer	3 mM
pH	5.00

Method

[0274] The subject instilled 2 drops of the above formulation in each eye as 1 single drop each eye and a second drop after 5 minutes.

Results:

[0275] Comfort, duration and efficacy were assessed. Stinging upon instillation and over the first hour was minimal with a score of 0.25 out of 4. Redness over the first hour was also minimal with a score of 0.5 out of 4 assessed at 20 minutes. Onset of vision improvement occurred with the first 20 to 25 minutes after instillation. Baseline near vision (i.e. 40 centimeters) was improved by 3.5 lines of visual acuity. Improvement in near vision lasted for 8.5 hours. Comparing this formula to those in Table 8, the Efficacy Index score was 29.75. Substituting HPMC 1.80% w/v with HPMC 1.65% w/v resulted in a slight reduction in near vision improvement to 3.25 lines of visual acuity and a slight reduction in duration to just over about 6 hour. Comparing this formula to those in Table 8, the Efficacy Index score was 19.5.

Example 15. Use of a compound containing mannitol with various nonionic surfactants

Compositions

[0276] Table 10 lists the active ingredients, excipients and their concentrations for compositions with both tested and prophetic examples of nonionic surfactants.

Methods

[0277] The subject independently instilled 2 drops of the above compositions in each eye and the excess wiped from lids and lashes.

Results

[0278] All nonionic surfactants tested demonstrate substantial near vision improvement. Of those tested only Brij® 35 was marginal due to the significant corneal irritation, hyperemia and reduced duration that resulted. Polysorbate 80 and poly 35 castor oil were most preferred, polyoxyl 40 stearate and poloxamer 407 excellent as well. However, polyoxyl 40 stearate caused a precipitate reaction with cellulose viscosity agents and added other stability issues.

[0279] Comfort and duration for each non-ionic surfactant were also tested and are noted in Table 10. Stinging and Redness are based on a scale of 0 to 4 with 0 being none and 4 being the most severe. Other than Brij® 35 stinging and redness were mild to nearly absent. Duration was excellent for each nonionic surfactant tested.

Table 10. Comparing efficacy and comfort of various nonionic surfactants

% w/v	Polysorbate 80	Polyoxyl 35 castor oil	Polyoxyl 40 stearate	Poloxamer 407	Brij® 35	Tyloxapol (prophetic)	Polysorbate 20 (prophetic)	Poloxamer 188 (prophetic)	Solulan C-24 (prophetic)
Aceclidine	1.75%	1.75%	1.75%	1.75%	1.75%	1.75%	1.75%	1.75%	1.75%
Tropicamide	0.006%	0.006%	0.005%	0.005%	0.005%	0.006%	0.006%	0.006%	0.006%
Mannitol	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%
Nonionic surfactant	3.5%	3.5%	3.5%	3.5%	3.5%	3.5%	3.5%	3.5%	3.5%
NaCl	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%
HPMC	1.80%	1.80%	1.80%	1.80%	1.80%	1.80%	1.80%	1.80%	1.80%
BAK	0.02%	0.02%	0.02%	0.02%	0.02%	0.02%	0.02%	0.02%	0.02%
Phosphate buffer	3 mM	3 mM	3 mM	3 mM	3 mM	3 mM	3 mM	3 mM	3 mM
pH	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
Stinging	0.25	0	0.5	0.5	2	0-2	0-2	0-2	0-2
Redness 1hr	0.5	0.25	0.75	1	2.5	0.25-2.5	0.25-2.5	0.25-2.5	0.25-2.5
Reading vs. Baseline (40 cm)	3.75	3.5	3	3	2	2-3.5	2-3.5	2-3.5	2-3.5
Duration (hours)	10	9	7	7	4	4-8	4-8	4-8	4-8
Efficacy Index read*dur	37.5	31.5	21	21	8	8-37.5	8-37.5	8-37.5	8-37.5
Onset (min)	20-25	20-25	20-25	20-25	30-40	20-40	20-40	20-40	20-40

Example 16. Use of a compound containing optimizing nonionic surfactant and antioxidant additives and concentrations

Compositions

Aceclidine	1.75% w/v
Tropicamide	0.010% w/v
Mannitol	2.50% w/v
Polysorbate 80	4.00% w/v
NaCl	0.00% w/v
HPMC	1.25% w/v (high MW equaling viscosity of about 400 cps units)
BAK	0.02% w/v

Sorbate	0.12% w/v
BAK	0.02% w/v
EDTA	0.01%
Citrate buffer	3 mM
pH	5.00

Method

[0280] 2 subjects instilled 2 drops each of the above formulation in each eye about 5 minutes apart.

Results:

Comfort, duration and efficacy were assessed. Stinging upon instillation and over the first hour was minimal for each subject with a score of 0.50 out of 4 for about 15 seconds. Redness over the first hour was also minimal for each subject with a score of 0.25 out of 4 assessed at 20 minutes. Onset of vision improvement occurred with the first 20 to 25 minutes after instillation. For subject 1 baseline near vision (i.e. 40 centimeters) was improved by 4.0 – 4.25 lines of visual acuity and lasted for 11.5 hours. For subject 2 baseline near vision was improved by 3.5 lines of visual acuity and lasted for 9.5 hours. The Efficacy Index score was 47.38 and 33.25, among the highest achieved for any formulation.

Example 17. Aceclidine compositions for Cold Chain Storage (prophetic)

Table 11. Cold Chain Storage Compositions

Composition	CS#1	CS#2	CS#3	CS#4	CS#5	CS#6	CS#7	CS#8
Aceclidine	1.75%	1.75%	2.50%	4.00%	2.00%	1.65%	1.75%	1.75%
Mannitol	2.50%	2.50%	2.50%	2.50%	2.50%	-	2.50%	2.50%
Polysorbate 80	4.00%	4.00%	4.00%	4.00%	4.00%	-	4.00%	4.00%
HPMC	1.25%	1.25%	1.25%	1.25%	1.25%	0.75%	1.10%	1.10%
Sodium Citrate	0.10%	0.10%	0.10%	0.10%	0.10%	-	0.10%	0.10%
BAK	0.02%	0.02%	0.02%	0.02%	-	-	0.02%	0.02%
Sorbic Acid	0.12%	0.12%	0.10%	0.12%	0.12%	0.12%	0.12%	0.12%
Disodium Edetate Dihydrate	0.10%	0.10%	0.10%	0.10%	-	-	0.10%	0.10%

Sodium Ascorbate	-	-	0.10%	-	-	-	-	-
Sodium bisulfate	-	-	-	0.10%	-	-	-	-
Sodium metabisulfite	-	-	-	-	0.10%	-	-	-
pH	5.0	6.0	6.0	6.5	6.5	7.0	5.0	6.0
N2 fill/purge	Yes	Yes	Yes	Yes	Yes	No	No	No

Table 11. Cold Chain Storage Compositions (cont'd)

Composition	CS#9	CS#10	CS#11	CS#12	CS#13	CS#14	CS#15	CS#16
Aceclidine	4.00%	0.50%	2.50%	3.00%	4.00%	4.00%	4.00%	4.00%
Mannitol	-	-	-	-	-	-	-	-
Polysorbate 80	-	-	-	-	-	-	-	-
HPMC	-	-	-	0.75%	1.25%	1.25%	1.25%	1.25%
Sodium Citrate	-	-	-	-	-	0.10%	-	-
BAK	-	-	-	-	-	-	-	-
Sorbic Acid	-	-	-	-	-	-	-	-
Disodium Edetate Dihydrate	-	-	-	-	-	-	-	-
Sodium Ascorbate	-	-	-	-	-	-	-	-
Sodium bisulfate	-	-	-	-	-	-	0.10%	-
Sodium metabisulfite	-	-	-	-	-	-	-	0.10%
pH	5.0	7.0	6.0	6.0	6.0	6.0	6.0	6.0
N2 fill/purge	No	No	Yes	Yes	Yes	Yes	Yes	Yes

Table 11. Cold Chain Storage Compositions (cont'd)

Composition	CS#17	CS#18	CS#19	CS#20
Aceclidine	4.00%	4.00%	4.00%	4.00%
Mannitol	2.50%	2.50%	2.50%	2.50%
Polysorbate 80	4.00%	4.00%	4.00%	4.00%
HPMC	1.25%	1.25%	1.25%	1.25%
Sodium Citrate	0.10%	-	-	0.25%
BAK	0.02%	0.02%	0.02%	0.02%
Sorbic Acid	0.12%	0.12%	0.12%	0.12%
Disodium Edetate Dihydrate	-	-	-	-
Sodium Ascorbate	-	-	-	-
Sodium bisulfate	-	0.10%	-	-
Sodium metabisulfite	-	-	0.10%	-
pH	6.0	6.0	6.0	6.0
N2 fill/purge	Yes	Yes	Yes	Yes

Methods

[0281] Aceclidine cold chain storage compositions CS#1-5 and 11-20 were filled into vials each under a nitrogen overlay followed by a nitrogen purge of remaining headspace. CS#6-10 were filled into vials each under ambient air and headspace. 1 vial of each composition was stored at 25 degrees Celsius and the other was stored at 5 degrees Celsius.

Results

Table 12. Aceclidine Cold Chain Storage Composition Stability

Composition	CS#9	CS#10	CS#11	CS#12	CS#13	CS#14
25 Celsius 90% Stability	4	5	-	-	-	-

(weeks)						
5 Celsius 90% Stability (months)	7	8	12	12.5	15	18

Table 12. Aceclidine Cold Chain Storage Composition Stability (cont'd)

Composition	CS#15	CS#16	CS#17	CS#18	CS#19	CS#20
25 Celsius 90% Stability (weeks)	-	-	-	-	-	-
5 Celsius 90% Stability (months)	18	18	20	20	20	22

[0282] As seen in Figure 4, CS#3-5 contaiing 0.10% sodium ascorbate, 0.10% sodium bisulfate or 0.10% sodium metabisulifite were stable for about 2 months at 25 degrees Celsisus and for about 26 months at 5 degrees Celsius.

[0283] As seen in Table 12, filling vials under a nitrogen overlay and nitrogen purge of the headspace resulted in a cold storage stability increase of 4-5 months. The addition of HPMC further increased stability another 3 months; sodium citrate, sodium bisulate or sodium metabisulifite another 3 months; and the further addition of sorbic acid and BAK another 2 months further increased the length of stability. CS#20 increased stability up to 22 months.

Example 18. Stability in Mylar® lined Pouches

[0284] Aceclidine formulations of the present invention were placed in containers that were subsequently placed in biaxially-oriented polyethylene terephthalate lined pouches at -20, 5 and 25 C for up to 3 months. Aceclidine total related substances was recorded at 1, 2, 3 and 6 months. Results of this study can be seen in Table 13, below.

[0285] Mylar® was used as the source of biaxially-oriented polyethylene terephthalate. Mylar is a registered trademark of and available from DuPont Teijin Films US Limited.

Table 13. Aceclidine Total Related Substances after Storage

Conditions	Initial Result	One Month Result	Two Month Result	Three Month Result	Six Month Result	Total % Change
Unpouched (5C)	0.41%	0.55%	0.51%	0.05%	0.49%	0.08%
Unpouched (25C)		0.58%	1.45%	1.39%	4.87%	4.46%
Pouched (5C)		0.54%		0.35%	0.47%	0.06%
Pouched (25C)		0.55%		1.26%	0.36%	-0.05%
Pouched (-20C)		0.74%		0.25%	0.00%	-0.41%
Pouched (5C)		0.50%		0.18%	0.00%	-0.41%
Pouched (25C)		0.74%		0.31%	0.00%	-0.41%

[0286] As seen in Table 13, the use of a Mylar® lined pouches helped maintain aceclidine potency by reducing degradation rate. Specifically, compare Unpouched at room temperature (25 C) total % change of 4.46% to the -0.05% and 0.041% total % change of Pouched at room temperature (25 C).

[0287] It will be appreciated that many further modifications and permutations of various aspects of the described embodiments are possible. Accordingly, the described aspects are intended to embrace all such alterations, modifications, and variations that fall within the spirit and scope of the appended claims.

[0288] The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

WHAT IS CLAIMED IS:

1. A method of stabilizing a composition comprising aceclidine comprising storing the composition in a container having a headspace at a temperature from about 2 degrees Celsius to about 8 degrees Celsius, wherein the term "about" is defined as ± 10% of each particular value.

2. The method of claim 1, wherein the composition is filled into the container under an inert gas overlay.

3. The method of claim 2, wherein the headspace is purged with an inert gas.

4. The method of claim 1, wherein the container comprises a closure and a vessel wherein a portion of the closure and a portion of the vessel are sealed with an anti-leaching material selected from the group consisting of biaxially-oriented polyethylene terephthalate, polytetrafluorethylene and aluminum foil.

5. The method of claim 1, wherein the container is disposed in a second container that is formed with or lined with an anti-leaching material selected from the group consisting of biaxially-oriented polyethylene terephthalate, polytetrafluorethylene and aluminum foil.

6. The method of claim 1, wherein aceclidine is at a concentration from about 0.25% to about 4.0% w/v aceclidine, wherein w/v denotes weight by total volume of the composition.

7. The method of claim 1, wherein the method provides at least 90% stability of aceclidine for at least 7 months.

8. The method of claim 5, wherein the method provides at least 90% stability of aceclidine for at least 12 months.

9. The method of claim 1, wherein the composition further comprises a viscosity agent, a polysorbate, a cryoprotectant and a preservative.

10. The method of claim 9, wherein the method provides at least 90% stability of aceclidine for at least 18 months.

11. The method of claim 9, wherein the viscosity agent provides a viscosity of at least 50 centipoise.

12. The method of claim 9, wherein the cryoprotectant is selected from the group consisting of a ~~a~~ polyol, a sugar, an alcohol, a lower alkanol, a lipophilic solvent, a hydrophilic solvent, a bulking agent, a solubilizer, a surfactant, an antioxidant, a cyclodextrin, a maltodextrin, colloidal silicon dioxide, polyvinyl alcohol, 2-methyl-2,4-pentanediol, cellobiose, gelatin, polyethylene

glycol (PEG), dimethyl sulfoxide (DMSO), formamide, antifreeze protein 752 or a combination thereof.

13. The method of claim 9, wherein the preservative is selected from the group consisting of benzalkonium chloride, sorbate, an antioxidant and a combination thereof.

14. The method of claim 11, wherein the antioxidant is selected from the group consisting of sodium ascorbate, sodium bisulfate, sodium metabisulfite, n-acetyl cysteine and a combination thereof.

15. A method of stabilizing a composition comprising aceclidine, a viscosity agent, and a nonionic surfactant comprising storing the composition in a container having a headspace at a temperature from about 2 degrees Celsius to about 8 degrees Celsius, wherein the composition is filled into the container under a nitrogen overlay and the headspace is purged with nitrogen and wherein the composition provides a low shear (1/sec) viscosity from about 50 to about 1000 centipoise and a high shear (1:1000/sec) of about 0.5 or less centipoise, wherein the term "about" is defined as ± 10% of each particular value.

16. A method of stabilizing a composition comprising aceclidine, hydroxypropylmethyl cellulose, polysorbate 80, mannitol, sorbate and an antioxidant selected from the group consisting of sodium ascorbate, sodium bisulfate, sodium metabisulfite, n-acetyl cysteine or a combination thereof comprising storing the composition in a container having a headspace at a temperature from about 2 degrees Celsius to about 8 degrees Celsius, wherein the composition is filled into the container under a nitrogen overlay and the headspace is purged with nitrogen, wherein the term "about" is defined as ± 10% of each particular value.

17. The method of claim 16, wherein the aceclidine is at a concentration from about 0.25% to about 4.00% w/v, the hydroxypropylmethyl cellulose is at a concentration from about 0.75% to about 1.25% w/v, polysorbate 80 is at a concentration from about 2% to about 4% w/v, mannitol is at a concentration from about 2% to about 4% w/v, sorbate is at a concentration from about 0.10% to about 0.12% w/v and the antioxidant is at a concentration from about 0.10% to about 0.25% w/v, wherein w/v denotes weight by total volume of the composition.

18. The method of claim 17, wherein the method provides at least 90% stability of aceclidine for at least 20 months.

19. The method of claim 18, wherein the method provides at least 90% stability of aceclidine for at least 22 months.

20. A container comprising aceclidine prepared by the process comprising the steps of:

a) providing a container;

b) filling the container with a composition comprising aceclidine under an inert gas overlay;

c) purging a headspace created during the filling step b) with an inert gas;

d) capping the container.

21. The container of claim 20, wherein the process further comprises the step of storing the container at a temperature from about 2 to about 8 degrees Celsius, wherein the term "about" is defined as ± 10% of each particular value.

22. The container of claim 20, wherein the composition further comprises a preservative selected from the group consisting of sorbate, benzalkoniumbenzalkonim chloride, sodium ascorbate, sodium bisulfate, soidium metabisulfite, n-acetyl cysteine and a combination thereof.

23. The container of claim 20, wherein the composition has a viscosity of at least 50 centipoise.

24. A composition comprising from about 0.25% to about 4.0% w/v aceclidine and one or more means of stabilizing the composition selected from the group consisting of filling the composition into a container under an inert gas overlay and purging a headspace created during filling with an inert gas, having a total viscosity of the composition of at least 50 centipoise or more, adding a preservative to the composition selected from the group consisting of sorbate, benzalkoniumbenzalkonim chloride, sodium ascorbate, sodium bisulfate, soidium metabisulfite, n-acetyl cysteine and a combination thereof,

wherein the composition is stored at a temperature from about 2 to about 8 degrees Celsisus and wherein w/v denotes weight by total volume of the composition and wherein the term "about" is defined as ± 10% of each particular value.

25. A method of stabilizing a composition comprising aceclidine comprising storing the composition in a container having a headspace at a temperature from about 22 degrees Celsius to about 25 degrees Celsius, wherein the container comprises a closure and a vessel wherein a portion of the closure and a portion of the vessel are sealed with an anti-leaching material selected from the group consisting of biaxially-oriented polyethylene terephthalate, polytetrafluorethylene and aluminum foil and/or the container is disposed in a second container that is formed with or lined with biaxially-oriented polyethylene terephthalate, polytetrafluorethylene and aluminum foil, wherein the term "about" is defined as ± 10% of each particular value.

26. The method of claim 25, wherein the second container comprises a second closure, wherein the second closure provides an airtight seal.

27. The method of claim 26, wherein the airtight seal is resealable.