HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION

Cross-Reference to Related Application

The present application claims priority based on U.S. Provisional Patent Application Serial No. 61/487,789 filed May 19, 2011 and U.S. Provisional Patent Application Serial No. 61/548,957 filed October 19, 2011.

Technical Field of the Invention

The present invention relates to an ophthalmic composition containing a relatively high concentration of olopatadine. More particularly, the present invention relates to an ophthalmic aqueous solution containing a relatively high concentration of solubilized olopatadine wherein the solution is capable of providing enhanced relief from symptoms of ocular allergic disorders (e.g., conjunctivitis) in the early phase, the late phase or preferably both phases.

Background of the Invention

Individuals suffering from allergic conjunctivitis experience symptoms such as ocular irritation, itchiness, redness and the like. It has been found that these symptoms are significantly reduced using topical ophthalmic solutions containing olopatadine. Such solutions are sold under the tradenames PATANOL® and PATADAY®, which are both commercially available from Alcon Laboratories, Inc., Fort Worth, TX.

These marketed solutions were generally believed to be the most efficacious products known for addressing symptoms of allergic conjunctivitis. Surprisingly, and as discussed further below, it has been discovered that relatively high concentration solutions of olopatadine provide significantly improved reduction of late phase ocular allergic conjunctivitis symptoms in addition to relief from early phase symptoms. Even more surprising, it has been discovered that such high concentrations of olopatadine also provide significantly improved reduction of redness in the early phase. Further, it has been discovered that enhanced relief from these early and late phase symptoms can be achieved through once a day

dosing of relatively high concentration olopatadine solution as opposed to greater dosing frequencies.

The discovery of improved reduction of early and late phase symptoms is quite significant and desirable for individuals suffering from allergic conjunctivitis. Generally, these discoveries can provide patients greater relief from itching and provide better aesthetic appearance to the eye. Further, avoiding more frequent dosing is more convenient for patients and helps assure better compliance. Further yet, improved early prevention and/or reduction of redness is particularly desirable since patients generally have a desire to keep as much redness out of their eyes as possible.

The discovery that relatively high concentration solutions of olopatadine can relieve late phase ocular allergic conjunctivitis symptoms provides hope to sufferers of ocular allergic conjunctivitis that a single dose of olopatadine per day could provide a substantial degree of full day relief from their symptoms. However, the development of a multi-dose ophthalmic solution that includes high concentrations of olopatadine necessary to achieve desired levels of efficacy is extremely difficult and complex.

Solubilizing high concentrations of olopatadine in a stable manner has proven difficult by itself. Olopatadine, by itself, is only soluble in water (pH about 7.0) at room temperature up to a concentration of about 0.18 w/v%. However, it is desirable to achieve solubilization of much higher concentrations of olopatadine in an effort to treat late phase allergic conjunctivitis.

Solubilizing such higher concentrations of olopatadine has proven difficult. As one example, excipients such as polyethylene glycol (PEG) 400 and polyvinylpyrrolidone (PVP), when used at reasonably desirable concentrations, have proven incapable, alone or in combination, of solubizing sufficient concentrations of olopatadine in compositions having approximately neutral pH. Thus, innovation is required to solubilize a sufficient concentration of olopatadine.

In the process of such innovation, is has been discovered that higher molecular weight PEGs such as PEG 6000 can significantly enhance solubility of olopatadine. However, such PEGs cause risk of discomfort when administered to humans. It has also been discovered that cyclodextrins, such as hydroxypropyl-γ-

cyclodextrin, hydroxypropyl-β-cyclodextrin and sulfoalkyl ether-β-cyclodextrin, have the ability to solubilize significantly higher concentrations of olopatadine. However, use of undesirably high concentrations of cyclodextrins has been found to reduce olopatadine efficacy and/or preservation efficacy of solutions. As such, still further innovation was needed to create a desirable olopatadine formulation that not only solubilized sufficient amounts of olopatadine, but also allowed the formulation to achieve other desirable pharmaceutical characteristics.

Thus, the present invention is directed at an ophthalmic composition that can provide high concentrations of olopatadine topically to the eye. Further, the present invention is directed to such a composition wherein the olopatadine is solubilized in solution in a stable manner, the composition exhibits consistent efficacy against late phase symptoms of allergic conjunctivitis, the composition exhibits sufficient antimicrobial activity to provide desired levels of preservation efficacy or any combination thereof.

Summary of the Invention

The present invention is directed to an ophthalmic composition for treatment of allergic conjunctivitis. The composition will include a relatively high concentration of olopatadine, preferably at least 0.67 w/v % olopatadine, preferably dissolved in solution. The composition will typically include a cyclodextrin, and more particularly, a γ-cyclodextrin derivative and/or a β-cyclodextrin derivative to aid in solubilizing the olopatadine. The cyclodextrin derivative is preferably hydroxypropyl-γ-cyclodextrin (HP-γ-CD), hydroxypropyl- β-cyclodextrin (HP- β-CD), sulfoalkyl ether β-cyclodextrin (SAE- β-CD)(e.g., sulfobutyl ether β-cyclodextrin (SBE-β-CD)), or a combination thereof. The composition will typically include a lactam polymer (e.g., polyvinylpyrrolidone (PVP)) to aid in the solubilization of the olopatadine. The composition will also typically include a polyether (e.g., polyethylene glycol (PEG)) for enhancing solubility and/or aiding in achieving the desired tonicity. It is generally desirable for the composition to be disposed in an eyedropper, have a pH of 5.5 to 8.0, to have an osmolality of 200 to 450, to have a viscosity of 10 to 200 cps or any combination thereof. The composition will also typically include a preservative to allow the composition to achieve United States and/or European Pharmacopeia preservation standards. Preferred preservatives include a polymeric quaternary ammonium compound, such

as polyquaternium-1, and benzalkonium chloride. The composition also typically includes borate and/or polyol to aid in achieving desired preservation.

The present invention also contemplates a method of treating ocular allergy symptoms. The method will include topically applying a composition having a defined combination of the characteristics described above to an eye of a human. This step of topically applying the composition preferably includes dispensing an eyedrop from an eyedropper.

Brief Description of the Drawings

FIG. 1 is a graph of mean conjunctival redness determined by a conjunctival allergen challenge (CAC) at 27 minutes.

FIG. 2 is a graph of mean conjunctival redness determined by a conjunctival allergen challenge (CAC) at16 hours.

FIG. 3 is a graph of mean total redness determined by a conjunctival allergen challenge (CAC) at 24 hours.

FIG. 4 is a graph of mean ocular itching determined by a conjunctival allergen challenge (CAC) at 24 hours.

FIG. 5 is a graph of mean conjunctival redness determine by a conjunctival allergen challenge (CAC) at 24 hours.

Detailed Description of the Invention

The present invention is predicated upon the provision of an ophthalmic composition for treatment of allergic conjunctivitis. The ophthalmic composition is preferably an aqueous solution. The ophthalmic composition includes a relatively high concentration of olopatadine solubilized in aqueous solution. The ophthalmic composition also includes a unique set of excipients for solubilizing the olopatadine while maintaining comfort of the composition and/or efficacy of the composition in treating symptoms associate with allergic conjunctivitis, particularly symptoms associated with late phase allergic conjunctivitis. Preferably, the composition

exhibits improved late phase efficacy in reducing ocular itching, ocular redness or both. The composition also preferably exhibits improved early phase efficacy in reducing ocular redness relative to vehicle and/or relative to lower concentrations of olopatadine. In a preferred embodiment, the ophthalmic composition is a multi-dose ophthalmic composition that also exhibits a required degree of preservation efficacy.

Unless indicated otherwise, all component amounts (i.e., concentrations) are presented on a weight volume percent (w/v%) basis and all references to concentrations of olopatadine are to olopatadine free base.

Olopatadine is a known compound that can be obtained by the methods disclosed in U.S. Pat. No. 5,116,863, the entire contents of which are hereby incorporated by reference in the present specification for all purposes. The formulation of the present invention contains at least 0.50%, more typically at least 0.55%, more typically at least 0.6% or 0.65%, even more typically at least 0.67% or 0.68%, still more typically at least 0.7%, possibly at least 0.75% and even possibly at least 0.85% but typically no greater than 1.5% more typically no greater than 1.0%, still more typically no greater than 0.8%, possibly no greater than 0.75% and even possibly no greater than 0.72% of olopatadine where concentrations of olopatadine typically represent concentrations of olopatadine in free base form if the olopatadine is added to the composition as a salt. These lower limits of concentrations of olopatadine are particularly important since it has been found that efficacy of olopatadine in aqueous ophthalmic solutions in reducing late phase allergy symptoms and enhanced reduction of early phase redness begins to show improvement at concentrations greater than 0.5 w/v% of olopatadine and begins to show statistically significant improvements in reducing late phase allergy symptoms at concentrations of about 0.7 w/v% olopatadine and above (e.g., at least 0.65 w/v%, at least 0.67 w/v% or at least 0.68 w/v%). Most preferably, the concentration of the olopatadine in the composition is 0.7 w/v%.

Generally, olopatadine will be added in the form of a pharmaceutically acceptable salt. Examples of the pharmaceutically acceptable salts of olopatadine include inorganic acid salts such as hydrochloride, hydrobromide, sulfate and phosphate; organic acid salts such as acetate, maleate, fumarate, tartrate and citrate; alkali metal salts such as sodium salt and potassium salt; alkaline earth metal salts such as magnesium salt and calcium salt; metal salts such as aluminum salt and

zinc salt; and organic amine addition salts such as triethylamine addition salt (also known as tromethamine), morpholine addition salt and piperidine addition salt. The most preferred form of olopatadine for use in the solution compositions of the present invention is the hydrochloride salt of (Z)-11-(3-dimethylaminopropylidene)-6,11-dihydro-dibenz-[b,e]oxepin-2-acetic acid. When olopatadine is added to the compositions of the present invention in this salt form, 0.77% olopatadine hydrochloride is equivalent to 0.7% olopatadine free base, 0.88% olopatadine hydrochloride is equivalent to 0.8% olopatadine free base, and 0.99% olopatadine hydrochloride is equivalent to 0.9% olopatadine free base.

Generally, it is preferred that the entire concentration of olopatadine is dissolved in the composition as a water based or aqueous solution. However, it is contemplated that olopatadine could be only partially dissolved. For example, a portion of the olopatadine could be in solution with the remainder being in suspension.

The composition of the present invention also preferably includes cyclodextrin derivative and more preferably β-cyclodextrin derivative, γ-cyclodextrin derivative or both to aid in solubilizing the olopatadine (i.e., as a solubilizer). The β-cyclodextrin derivative, γ-cyclodextrin derivative or combination thereof is typically present in the composition at a concentration that is at least 0.5% w/v, more typically at least 1.0% w/v and even possibly at least 1.3% w/v, but is typically no greater than 4.0% w/v, typically no greater than 3.2% w/v and even possibly no greater than 2.8% w/v. Preferably, the total concentration of cyclodextrin is from 0.9 w/v% to 3.2 w/v%.

The specific amount of β-cyclodextrin derivative, γ-cyclodextrin derivative or combination thereof in a particular composition will typically depend upon the type or combination of types of derivatives used. One particularly desirable β-cyclodextrin derivative is a hydroxy alkyl-β-cyclodextrin such as hydroxypropyl-β-cyclodextrin (HP-β-CD). One particularly desirable γ-cyclodextrin derivative is a hydroxy alkyl-γ-cyclodextrin such as hydroxypropyl-γ-cyclodextrin (HP-γ-CD). Another particularly desirable β-cyclodextrin derivative is sulfoalkyl ether-β-cyclodextrin (SAE-β-CD), particularly sulfobutyl ether-β-cyclodextrin (SBE-β-CD). It is contemplated that a combination of hydroxypropyl-β-cyclodextrin, hydroxypropyl- γ -cyclodextrin and/or sulfoalkyl ether-β-cyclodextrin derivative may be employed in a single composition, but it is typically desirable to use only

one of the three as the sole or substantially the sole (i.e., at least 90% by weight of the cyclodextrin component) cyclodextrin derivative.

When HP-β-CD is employed as the sole or substantially sole β-cyclodextrin derivative, it is typically present in the composition at a concentration that is at least 0.5% w/v, more typically at least 1.0% w/v and even more typically at least 1.3% w/v, but is typically no greater than 3.0% w/v, typically no greater than 2.2% w/v and is typically no greater than 1.7% w/v. When HP-γ-CD is employed as the sole or substantially sole γ-cyclodextrin derivative, it is typically present in the composition at a concentration that is at least 0.5% w/v, more typically at least 1.0% w/v and even more typically at least 1.3% w/v, but is typically no greater than 3.0% w/v, typically no greater than 2.2% w/v and is typically no greater than 1.7% w/v. When SAE-β-CD is employed as the sole or substantially sole β-cyclodextrin derivative, it is typically present in the composition at a concentration that is at least 0.3% w/v, more typically at least 0.7% w/v and even more typically at least 0.9% w/v, but is typically no greater than 2.4% w/v, typically no greater than 1.5% w/v and is typically no greater than 1.1% w/v.

HP-β-CD is a commodity product and pharmaceutical grades of HP-β-CD can be purchased from a variety of sources, for example, from SIGMA ALDRICH, which has its corporate headquarters in St. Louis, Missouri or ASHLAND SPECIALTY INGREDIENTS, headquartered in Wayne, New Jersey. HP-γ-CD is a commodity product and pharmaceutical grades of HP-γ-CD can be purchased from a variety of sources, for example, from SIGMA ALDRICH, which has its corporate headquarters in St. Louis, Missouri or ASHLAND SPECIALTY INGREDIENTS, headquartered in Wayne, New Jersey. SAE-β-CD can be formed based upon the teachings of U.S. Patent Nos. 5,134,127 and 5,376,645, which are incorporated herein by reference for all purposes. It is generally preferred, however, to use purified SAE-β-CD. Purified SAE-β-CD is preferably formed in accordance with the teachings of U.S. Patent Nos. 6,153,746 and 7,635,773. Purified SAE-β-CD is commercially available under the tradename CAPTISOL® from CyDex Pharmaceuticals, Inc., Lenexa, KS.

With regard to γ-cyclodextrin derivative and β-cyclodextrin derivative in the composition of the present invention, it has been found that undesirably high concentrations of γ-cyclodextrin derivative and/or β-cyclodextrin derivative can significantly interfere with preservation efficacy of the compositions, particularly

when benzalkonium chloride and/or polymeric quaternary ammonium compound are employed as preservation agents. Thus, lower concentrations of γ-cyclodextrin derivative and/or β-cyclodextrin derivative are typically preferred. Advantageously, it has also been found, however, that the ability of the γ-cyclodextrin derivative and β-cyclodextrin derivatives in solubilizing olopatadine is very strong and relatively low concentrations of γ-cyclodextrin derivative and/or β-cyclodextrin derivative can solubilize significant concentrations of olopatadine in aqueous solution. As such, more desirable and reasonable concentrations of additional solubilizing agent can be used to aid in solubilizing the desired amounts of olopatadine.

Further, it has been found that a composition formed using a combination of solubilizing agents such as polyvinylpyrrolidone, tyloxapol, polyethylene glycol and others to solubilize relatively high concentrations of olopatadine in the absence of γ-cyclodextrin derivative and/or β-cyclodextrin derivative will typically lack long term stability or shelf life. It has been found that such a composition will typically begin to precipitate after undesirably short periods of time. Thus, it is important to employ the γ-cyclodextrin derivative and/or β-cyclodextrin derivative in combination with one or more additional solubilizers.

As such, the ophthalmic composition of the present invention includes at least one solubilizing agent (i.e., solubilizer), but possibly two or more solubilizing agents, in addition to cyclodextrin. The additional solubilizing agents can include surfactants such as castor oil, polysorbate or others. Preferably, the additional solubilizing agent[s] includes one or more polymers. One preferred polymer for aiding in solubilizing the olopatadine is lactam polymer. Another preferred polymer for aiding in solubilizing the olopatadine is polyether.

As used herein, the phrase "lactam polymer" refers to any polymer formed from more than one lactam monomer. The lactam polymer is typically present in the composition at a concentration that is at least 1.0% w/v, more typically at least 3.0% w/v and even more typically at least 3.7 % w/v, but is typically no greater than 8.0% w/v, typically no greater than 5.0% w/v and is typically no greater than 4.3% w/v. Polyvinylpyrrolidone (PVP) is the most preferred lactam polymer and can be the only or substantially the only lactam polymer. Thus, in a preferred embodiment, the lactam polymer consists or consists essentially of only PVP. The average molecular weight of the lactam polymer, particularly when it is PVP, is at

least 20,000, more typically at least 46,000 and even more typically at least 54,000 but is typically no greater than 90,000, more typically no greater than 70,000 and still more typically no greater than 62,000. One preferred PVP is sold under the tradenames PLASDONE® K29/32 or K30, which have an average molecular weight of approximately 50,000 and are commercially available from ASHLAND SPECIALTY INGREDIENTS, headquartered in Wayne, NJ, USA.

The polyether can aid in the solubility of olopatadine in the composition and/or can provide tonicity to the composition (i.e., act as a tonicity agent). The polyether is typically present in the composition at a concentration that is at least 1.0% w/v, more typically at least 3.0% w/v and even more typically at least 3.7 % w/v, but is typically no greater than 8.0% w/v, typically no greater than 5.0% w/v and is typically no greater than 4.3% w/v. Polyethylene glycol (PEG) is the most preferred polyether and can be the only or substantially the only polyether polymer. Thus in a preferred embodiment, the polyether consists or consist essentially of only PEG. The average molecular weight of the PEG will typically depend upon the particular solubility and particular tonicity desired for the composition. In a preferred embodiment, the average molecular weight of the polyether, particularly when it is PEG, is at least 200, more typically at least 320 and even more typically at least 380 but is typically no greater than 800, more typically no greater than 580 and still more typically no greater than 420. One preferred PEG is PEG400.

It may also be desirable for the ophthalmic composition of the present invention to include a viscosity enhancing agent in order to enhance residence time of the composition upon the cornea when the composition is topically administered. Examples of potentially suitable viscosity enhancing agent include, without limitation, carboxyvinyl polymer, galactomannan, hyaluronic acid, cellulosic polymer, any combination thereof or the like. In a preferred embodiment, the ophthalmic composition includes hydroxyethyl cellulose (HEC), hydroxylpropylmethyl cellulose (HPMC) or both. One preferred HEC is sold under the tradename NASTROSOL® 250HX, which is commercially available from Hercules Incorporated, Aqualon Division, Argyle, TX. One preferred HPMC is sold under the tradename E4M 2910 and is commercially available from Dow Chemical, Midland, MI.

The amounts and molecular weights of HPMC and/or HEC used in the composition will depend upon the viscosity, osmolality and other attributes to be

achieved for the composition. As used herein, viscosity is measured by a Brookfield viscometer (LVDVI+, CP-42, 12 RPM and a temperature of 25 °C). In a preferred embodiment, the viscosity of the composition is at least 2.0 centipoise (cps), more typically at least 15 cps, even more typically at least 21 cps and even possibly at least 27 cps, but is typically no greater than 65 cps, typically no greater than 40 cps, more typically nor greater than 33 cps and even possibly no greater than 30 cps. Advantageously, and as further discussed below, viscosity within these ranges has been discovered to be more desirable for producing desired droplet sizes when the composition of the present invention is topically delivered from an eye dropper.

The preferred average molecular weight of HEC, when used, is typically in the range of 90,000 to 1,300,000 (e.g., approximately 1,000,000). The preferred average molecular weight of HPMC is typically in the range of 10,000 to 1,500,000 and more typically in the range of 189,000 to 688,000).

When HPMC is used alone, it is typically present in composition at a concentration that is at least 0.15% w/v, more typically at least 0.3% w/v and even more typically at least 0.5% w/v, but is typically no greater than 1.5% w/v, typically no greater than 1.0% w/v and is typically no greater than 0.7% w/v. When HEC is used alone, it is typically present in the composition at a concentration that is at least 0.1% w/v, more typically at least 0.25% w/v and even more typically at least 0.45% w/v, but is typically no greater than 1.4% w/v, typically no greater than 0.9% w/v and is typically no greater than 0.65% w/v. Advantageously, when HPMC and HEC are used to together, they may produce a synergistic viscosity effect which allows the use of low concentrations of these excipients to produce the desired viscosity of the compositions. When HPMC and HEC are used in combination, HPMC is typically present in composition at a concentration that is at least 0.05% w/v, more typically at least 0.1% w/v and even more typically at least 0.2% w/v, but is typically no greater than 1.0% w/v, typically no greater than 0.55% w/v and is typically no greater than 0.4% w/v. When HPMC and HEC are used in combination, HEC is typically present in composition at a concentration that is at least 0.02% w/v, more typically at least 0.06% w/v and even more typically at least 0.09% w/v, but is typically no greater than 0.6% w/v, typically no greater than 0.3% w/v and is typically no greater than 0.17% w/v. Notably, in at least some embodiments of the present invention,

HPMC is a preferred viscosity enhancing agent since, as the data present below shows, it can also aid in solubilizing the olopatadine.

The composition can also include buffering agents and/or tonicity agents. Suitable tonicity-adjusting agents and/or buffering agents include, but are not limited to, mannitol, sodium chloride, glycerin, sorbitol, phosphates, borates, acetates and the like.

Borate is a highly preferred buffering agent and will typically be included in the composition of the present invention. As used herein, the term "borate" shall refer to boric acid, salts of boric acid, borate derivatives and other pharmaceutically acceptable borates, or combinations thereof. Most suitable are: boric acid, sodium borate, potassium borate, calcium borate, magnesium borate, manganese borate, and other such borate salts. Typically, when used, the borate is at least about 0.05 w/v %, more typically at least about 0.18 w/v % and even possibly at least about 0.27 w/v % of the ophthalmic composition and is typically less than about 1.0 w/v %, more typically less than about 0.75 w/v % and still more typically less than about 0.4 w/v %, and even possibly less than about 0.35 w/v % of the ophthalmic composition.

The composition of the present invention can also include polyol. As used herein, the term "polyol" includes any compound having at least one hydroxyl group on each of two adjacent carbon atoms that are not in *trans* configuration relative to each other. The polyol can be linear or cyclic, substituted or unsubstituted, or mixtures thereof, so long as the resultant complex is water soluble and pharmaceutically acceptable. Examples of such compounds include: sugars, sugar alcohols, sugar acids and uronic acids. Preferred polyols are sugars, sugar alcohols and sugar acids, including, but not limited to: mannitol, glycerin, xylitol, sorbitol and propylene glycol. It is contemplated that the polyol may be comprised of two or more different polyols.

When both borate and polyol are present in the composition, borate typically interacts with polyol, such as glycerol, propylene glycol, sorbitol and mannitol, or any combination thereof to form borate polyol complexes. The type and ratio of such complexes depends on the number of OH groups of a polyol on adjacent carbon atoms that are not in trans configuration relative to each other. It shall be understood that weight/volume percentages of the ingredients polyol and borate

include those amounts whether as part of a complex or not. Advantageously, the borate and polyol can act as buffers and/or tonicity agents and can also aid in enhancing preservation efficacy of the composition.

In a preferred embodiment of the invention, the composition includes propylene glycol, glycerine or both. It has been found that γ-cyclodextrin derivatives and/or β-cyclodextrin derivatives tend to inhibit preservation efficacy within the formulations of the present invention, however, propylene glycol in the presence of borate appears to significantly limit this inhibition. Moreover, it has been found that glycerine often acts in a manner very similar to propylene glycol when used for aiding preservation. When used, propylene glycol, glycerine or a combination thereof is typically present in the composition at a concentration that is at least 0.4 w/v%, more typically at least 0.65 w/v% and even possibly at least 0.85 w/v% but is typically no greater than 5.0 w/v%, more typically no greater than 2.2 w/v% and even more typically no greater than 1.7 w/v%.

In a same or alternative preferred embodiment of the invention, the composition includes mannitol, sorbitol or both. Mannitol may also aid preservation of the composition of the present invention when used in the presence of borate. Moreover, it has been found that sorbitol often acts in a manner very similar to mannitol when used for aiding preservation. When used, mannitol, sorbitol or a combination thereof is typically present in the composition at a concentration that is at least 0.05 w/v%, more typically at least 0.2 w/v% and even possibly at least 0.4 w/v% but is typically no greater than 3.0w/v%, more typically no greater than 1.0 w/v% and even more typically no greater than 0.5 w/v%.

The composition of the present invention typically includes a preservative. Potential preservatives include, without limitation, hydrogen peroxide, benzalkonium chloride (BAK), polymeric quaternary ammonium compound (PQAM), biquanides, sorbic acid, chlorohexidine or others. Of these, benzalkonium chloride and polymeric quaternary ammonium compound such as polyquaternium-1 have proven quite desirable.

The polymeric quaternary ammonium compounds useful in the compositions of the present invention are those which have an antimicrobial effect and which are ophthalmically acceptable. Preferred compounds of this type are described in U.S. Pat. Nos. 3,931,319; 4,027,020; 4,407,791; 4,525,346; 4,836,986; 5,037,647 and

5,300,287; and PCT application WO 91/09523 (Dziabo et al.). The most preferred polymeric ammonium compound is polyquaternium-1, otherwise known as POLYQUAD® with a number average molecular weight between 2,000 to 30,000. Preferably, the number average molecular weight is between 3,000 to 14,000.

When used, the polymeric quaternary ammonium compound is generally used in the composition of the present invention in an amount that is greater than about 0.00001 w/v %, more typically greater than about 0.0003 w/v % and even more typically greater than about 0.0007 w/v % of the ophthalmic composition. Moreover, the polymeric quaternary ammonium compound is generally used in the composition of the present invention in an amount that is less than about 0.01 w/v %, more typically less than about 0.007 w/v %, even more typically less than 0.003 w/v%, still more typically less than 0.0022 w/v% and even possibly less than about 0.0015 w/v % of the ophthalmic composition.

BAK is generally used in the composition of the present invention in an amount that is greater than about 0.001 w/v %, more typically greater than about 0.003 w/v % and even more typically greater than about 0.007 w/v % of the ophthalmic composition. Moreover, BAK is generally used in the composition of the present invention in an amount that is less than about 0.1 w/v %, more typically less than about 0.03 w/v % and even more typically less than about0.020 or 0.015 w/v % of the ophthalmic composition.

It is also contemplated that the composition of the present invention may benefit from the use of two different polyols, borate and a preservative (e.g., BAK or polymeric quaternary ammonium compound) to provide enhanced preservations efficacy. Examples of such systems are disclosed in U.S. Patent Publication Nos. 2009/0232763 and 2010/0324031, which are expressly incorporated herein in their entirety for all purposes.

Notably, it has been found that polymeric ammonium compound is particularly desirable for preserving compositions containing SAE-β-CD while BAK is particularly desirable for preserving compositions containing hydroxypropyl beta or gamma cyclodextrin derivatives. It has also been found that filtration (e.g., micron filtration) of the preservative followed by aseptic addition of the preservative to the sterile composition can aid preservation efficacy.

It is contemplated that the composition of the present invention can include a variety of additional ingredients. Such ingredients include, without limitation, additional therapeutic agents, additional or alternative antimicrobial agents, suspension agents, surfactants, additional or alternative tonicity agents, additional or alternative buffering agents, anti-oxidants, additional or alternative viscosity-modifying agents, chelating agents any combinations thereof or the like.

The compositions of the present invention will generally be formulated as sterile aqueous solutions. The compositions of the present invention are also formulated so as to be compatible with the eye and/or other tissues to be treated with the compositions. The ophthalmic compositions intended for direct application to the eye will be formulated so as to have a pH and tonicity that are compatible with the eye. It is also contemplated that the compositions can be suspensions or other types of solutions.

The composition of the present invention will typically have a pH in the range of 4 to 9, preferably 5.5 to 8.5, and most preferably 5.5 to 8.0. Particularly desired pH ranges are 6.0 to 7.8 and more specifically 6.4 to 7.2. The compositions will have an osmolality of 200 to 400 or 450 milliosmoles per kilogram (mOsm/kg), more preferably 240 to 360 mOsm/kg.

It is generally preferred that the composition of the present invention be provided in an eye dropper that is configured to dispense the composition as eyedrops topically to the cornea of the eye. However, desired size of a single eyedrop (i.e., droplet size) for the ophthalmic composition can be difficult to accomplish. It has been discovered that the cyclodextrin in the composition imparts a relatively high surface energy to the composition. In turn, droplet size tends to be relatively high. It has been discovered, however, that by dispensing droplets through a relatively small orifice and/or by maintaining the viscosity of the composition within the ranges discussed above, desired droplet size can be achieved. Desired droplet size is typically at least 10 µl, more typically at least 18 µl and even more typically at least 23 µl, but is typically no greater than 60 µl, typically no greater than 45 µl and is typically no greater than 33 µl. Advantageously, this droplet size for the composition with the concentrations of olopatadine specified herein allows an individual to dispense one droplet per eye once a day and receive relief from symptoms of ocular allergic conjunctivitis

generally, but particularly receive relief from late phase symptoms ocular allergic conjunctivitis.

In a preferred embodiment, the composition of the present invention is a multi-dose ophthalmic compositions that have sufficient antimicrobial activity to allow the compositions to satisfy the USP preservative efficacy requirements, as well as other preservative efficacy standards for aqueous pharmaceutical compositions.

The preservative efficacy standards for multi-dose ophthalmic solutions in the U.S. and other countries/regions are set forth in the following table:

Preservative Efficacy Test ("PET") Criteria
(Log Order Reduction of Microbial Inoculum Over Time

	Bacteria	Fungi
USP 27	A reduction of 1 log (90%), by day 7; 3 logs (99.9%) by day 14; and no increase after day 14	The compositions must demonstrate over the entire test period, which means no increases of 0.5 logs or greater, relative to the initial inoculum
Japan	3 logs by 14 days; and no increase from day 14 through day 28	No increase from initial count at 14 and 28 days
Ph. Eur. A[1]	A reduction of 2 logs (99%) by 6 hours; 3 logs by 24 hours; and no recovery after 28 days	A reduction of 2 logs (99%) by 7 days, and no increase thereafter
Ph. Eur. B	A reduction of 1 log at 24 hours; 3 logs by day 7; and no increase thereafter	A reduction of 1 log (90%) by day 14, and no increase thereafter
FDA/ISO 14730	A reduction of 3 logs from initial challenge at day 14; and a reduction of 3 logs from rechallenge	No increase higher than the initial value at day 14, and no increase higher than the day 14 rechallenge count through day 28

[1]There are two preservative efficacy standards in the European Pharmacopoeia ' "A" and "B".

The standards identified above for the USP 27 are substantially identical to the requirements set forth in prior editions of the USP, particularly USP 24, USP 25 and USP 26.

Advantages and Problems Overcome

The olopatadine ophthalmic composition of the present invention can provide multiple advantages over the olopatadine compositions that came before it. The composition disclosed herein provides an aqueous ophthalmic composition having a relatively high concentration of olopatadine that provides enhanced relief from late phase allergic conjunctivitis and early phase allergic conjuctivitis. Surprisingly and advantageously, preferred compositions of the present invention, as shown in FIGs. 1 through 5 and tables K through O, showed improved reduction in early phase redness, in late phase redness and in late phase itching. It is surprising that the enhanced concentration of olopatadine showed such significant reduction in late phase symptoms. It is even more surprising that the enhanced concentration of olopatadine showed enhanced reduction of early phase redness since it was generally believed that itching and redness would show similar responses to different concentrations of olopatadine.

Further, the composition can solubilize the relatively high concentration of olopatadine in solution form suitable as an eyedrop where other formulations have failed. Further yet, the composition can solubilize the higher concentrations of olopatadine while maintaining efficacy in treatment of the symptoms of allergic conjunctivitis where other efforts to develop such a solution have failed. Still further, the compositions can, when in multi-dose form, pass preservation efficacy standards where other compositions have failed.

As an additional advantage, it has been discovered that, for the particular composition of the present invention, composition containing HP-γ-CD have unexpectedly been found to be more susceptible to preservation. It has also unexpectedly been found to have solubility characteristics similar to the other beta cyclodextrin derivative discussed herein. This discovery has been particularly advantageous in providing a composition that is capable of solubilizing relatively high concentrations of olopatadine, capable of being stable for extended time periods and capable of robust preservation relative to both European and United States preservation efficacy standards.

It is still further advantageous that the cyclodextrin does not appear to interfere with the efficacy of the olopatadine. In particular, cyclodextrins have been found to entrap other drugs in a manner that does not allow those drugs to later release and show efficacy. However, this was not the case for olopatadine and was particularly not the case for HP-γ-CD.

Applicants specifically incorporate the entire contents of all cited references in this disclosure. Further, when an amount, concentration, or other value or parameter is given as either a range, preferred range, or a list of upper preferable values and lower preferable values, this is to be understood as specifically disclosing all ranges formed from any pair of any upper range limit or preferred value and any lower range limit or preferred value, regardless of whether ranges are separately disclosed. Where a range of numerical values is recited herein, unless otherwise stated, the range is intended to include the endpoints thereof, and all integers and fractions within the range. It is not intended that the scope of the invention be limited to the specific values recited when defining a range.

Other embodiments of the present invention will be apparent to those skilled in the art from consideration of the present specification and practice of the present invention disclosed herein. It is intended that the present specification and examples be considered as exemplary only with a true scope and spirit of the invention being indicated by the following claims and equivalents thereof.

Table A below provides a listing of exemplary ingredients suitable for an exemplary preferred formulation of the ophthalmic composition of the present invention and a desired weight/volume percentage for those ingredients. It shall be understood that the following Table A is exemplary and that certain ingredients may be added or removed from the Table and concentrations of certain ingredients may be changed while the formulation can remain within the scope of the present invention, unless otherwise specifically stated.

TABLE A

Ingredient	w/v percent
Olopatadine (Olopatadine HCl)	0.7
Polyether (PEG)	4.0
Lactam Polymer (PVP)	4.0
Viscosity Agent (HEC)	0.1 (if used w/ HPMC or other viscosity agent) 0.3 (if used w/o HPMC or other viscosity agent)
Viscosity Agent (HPMC)	0.15 (if used w/ HEC or other viscosity agent) 0.35 (if used w/o HEC or other viscosity agent)
Chelating agent (Disodium EDTA)	0.005
Borate (Boric Acid)	0.3
γ-cyclodextrin derivative and or β-cyclodextrin derivative	1.0 for SAE-β-CD or 1.5 HP-β-CD or 1.5 HP-γ-CD
Polyol (Mannitol)	0.3
Polyol (Propylene Glycol)	1.0
Tonicity Agent (Sodium Chloride)	0.35
Preservative	0.01 for BAK or 0.0015 PQAM
pH adjusting agents (NaOH or HCl)	sufficient to achieve pH = 7.0
purified water	Q.S. 100

The following examples are presented to further illustrate selected embodiments of the present invention. The formulations shown in the examples were prepared using procedures that are well-known to persons of ordinary skill in the field of ophthalmic pharmaceutical compositions.

EXAMPLES

Preparatory Example 1

Ingredients	Composition (w/w)
Olopatadine hydrochloride	0.77 g
Hydroxypropyl-β-Cyclodextrin(HP-β-CD)	1.5 g
PEG400(Polyethylene glycol 400)	4.0 g
PVP(Polyvinylpyrrolidone K30)	4.0 g
HPMC (Methocel E4m Premium)	0.6 g
HEC(Natrosol 250HX)	0.3 g
Disodium EDTA	0.01 g
Mannitol	0.6 g
Boric Acid	0.3 g
Benzalkonium Chloride	0.01 g
HCl / NaOH	q.s. to pH 7.0
Purified water	q.s. to 100 g

In a clean suitable and tared glass bottle, add and dissolve HPMC with an amount of purified water at 90-95°C equivalent to about 15% of the required batch size. Mix by stirring until homogenization. Bring to the 35% of the final weight with purified water and mix by stirring with propeller until complete dispersion. Add HEC and mix by stirring until homogenization. Steam sterilize the solution (122°C/20 min) and cool afterwards (Part A).In a separate vessel with a stir bar, add an amount of purified water equivalent to about 40% of the required batch size. Add and dissolve batch quantities of weighed PEG400, PVP, HP-β-CD, Olopatadine HCl, Boric Acid, Mannitol, EDTA and BAC, allowing each component to dissolve before adding the next component. Check the pH and adjust to 7.0 ± 0.1 with the required amount of NaOH 2N (Part B). In a laminar flow hood (sterile conditions), filter the solution Part B into the glass bottle containing the autoclaved fraction (Part A), using GV PVDF membrane, 0.22 μm filter unit and stir until homogenization. Mix by stirring with propeller for 15 min. Check

the pH and adjust to 7.0 ± 0.1 with the required amount of NaOH 1N/HCl 1N, if necessary. Bring to final weight with sterile purified water and stir until homogenization.

Preparatory Example 2

Ingredients	Composition (w/w)
Olopatadine hydrochloride	0.77 g
Hydroxypropyl-β-Cyclodextrin (HP-β-CD)	1.5 g
PVP(Polyvinylpyrrolidone K30)	4.0 g
PEG400(Polyethylene glycol 400)	4.0 g
HPMC (Methocel E4m Premium)	0.2 g
HEC(Natrosol 250HX)	0.125 g
Disodium EDTA	0.01 g
Boric Acid	0.3 g
Benzalkonium Chloride	0.01 or 0.015 g
NaOH 1N	0.83 ml
HCl 1N	0.58 ml
HCl / NaOH	q.s. to pH 7.0
Purified water	q.s. to 100 g

In a clean suitable and tared glass bottle, add and dissolve HPMC with an amount of purified water at 90-95°C equivalent to about 15% of the required batch size. Mix by stirring until homogenization. Bring to the 30% of the final weight with purified water and mix by stirring with propeller until complete dispersion. Add HEC and mix by stirring until homogenization (Part A). In a clean beaker with stir bar, weigh an amount of purified water equivalent to about 40% of the required batch size. Heat and maintain this water around 70-75°C. Add NaOH 1N and mix by moderate stirring. Add PVP and dissolve under agitation during 20 minutes. Add HCl 1N, mix and quickly cool down to 30-40°C. Add and dissolve batch quantities of PEG400, HP-β-CD, Olopatadine HCl, Boric Acid, EDTA and BAC, allowing each component to dissolve before adding the next component. Check the pH of the solution and adjust to 6.8 ± 0.1 with the required amount of

NaOH 2N (Part B). Transfer Part B to Part A and stir the batch until it is homogenous. Bring to the 85% of the final weight with purified water and stir until homogenization. Steam sterilize the solution (122°C/20 min) and cool afterwards. In a laminar flow hood (sterile conditions), check the pH and adjust to 7.0 ± 0.1 with the required amount of NaOH 1N/HCl 1N, if necessary. Bring to final weight with sterile purified water and stir until homogenization.

Formulary Examples A through I in Table B below

Formulary Examples A through I show the solubility of olopatadine in different formulations.

Ingredients	A	B	C	D	E
PEG 400	4	4	4	4	3.8
Dibasic Sodium Phosphate, anhydrous	0.15	-	-	-	0.5
Hydroxypropyl-β-Cyclodextrin	-	1.5	1.5	1.5	1
Sulfobutyl ether β Cyclodextrin	2	-	-	-	-
PVP K29/32	5	5	3	4	1.5
Polysorbate 80	0.1	-	-	-	-
Tyloxapol	-	-	-	-	-
Natrosol 250HX	0.3	0.3	0.3	0.3	-
HPMC 2910	0.6	0.6	0.6	0.6	-
Boric Acid	-	0.3	0.3	0.3	-
Sodium Chloride	0.15	-	-	-	-
Mannitol	-	0.6	0.6	0.6	-
Benzalkonium Chloride	0.01	0.01	0.01	0.01	0.01
Disodium EDTA	0.01	0.01	0.01	0.01	0.01
Sodium Hydroxide/ Hydrochloric Acid quantity sufficient to achieve pH of 7.4					
Purified water quantity sufficient to 100%					
Olopatadine Solubility (%)	1.064	0.901	0.725	0.811	0.461

Ingredients	F	G	H	I
PEG 400	6	6	6	6
Dibasic Sodium Phosphate, anhydrous	0.5	0.5	0.5	0.5
Hydroxypropyl-β-Cyclodextrin	-	1	1	1
Sulfobutyl ether β Cyclodextrin	-	-	-	-
PVP K29/32	1.5	-	1.5	1.5
Polysorbate 80	-	-	-	-
Tyloxapol	-	-	-	0.05
Natrosol 250HX	-	-	-	-
HPMC 2910	-	-	-	-
Boric Acid	-	-	-	-
Sodium Chloride	-	-	-	-
Mannitol	-	-	-	-
Benzalkonium Chloride	0.01	0.01	0.01	0.01
Disodium EDTA	0.01	0.01	0.01	0.01
Sodium Hydroxide/ Hydrochloric Acid quantity sufficient to achieve pH of 7.4				
Purified water quantity sufficient to 100%				
Olopatadine Solubility (%)	0.352	0.450	0.513	0.494

As can be seen, cyclodextrin can significantly enhance the solubility of olopatadine in aqueous solution. Moreover, it will be understood that the formulations of lower solubility, particularly those without cyclodextrin, will also typically exhibit worse solubility characteristics over time and tend to form precipitates.

Formulary Example J through M in Table C below

Formulary Examples J through M show the preservation efficacy of olopatadine containing formulations both with and without β-cyclodextrin.

Ingredients	J	K	L	M
Olopatadine HCL	0.77	0.77	0.77	0.77
PEG 400	-	4	-	-
Sodium Pyruvate	-		-	-
Dibasic Sodium Phosphate, anhydrous	0.15	0.15	0.15	0.1
Purified Guar	-	-	-	0.17
Hydroxypropyl-β-Cyclodextrin	1.5	-	-	5
PVP K30	2	3	3	-
Tyloxapol	-	-	0.2	-
Polysorbate 80	-	0.1	-	-
Natrosol 250HX		0.3	0.3	-
HPMC 2910	-	0.6	0.6	-
Boric Acid	-	-	-	0.17
Sodium Borate, decahydrate	-	-	-	0.5
Propylene Glycol	-	-	-	-
Sodium Chloride	-	0.15	0.55	0.1
Mannitol	2.5	-	-	-
Sorbitol	-	-	-	1
Sodium Citrate, dihydrate	-	-	-	0.35
Benzalkonium Chloride	0.01	0.01	0.01	0.01
Polyquaternium-1	-	-	-	-
Disodium EDTA	0.01	0.01	0.01	-
Sodium Hydroxide/ Hydrochloric Acid	q.s. to pH 7.0	q.s. to pH 7.0	q.s. to pH 7.0	q.s. to pH 7.0
Purified water	q.s. to 100%	q.s. to 100%	q.s. to 100%	q.s. to 100%
PET	Log_{10} Unit Reduction			
S. aureus 6 h/24h/7 d/14d/28d	0.1/1.9 /5.0/5. 0/5.0	5.0/5.0/ 5.0/5.0/ 5.0	1.5/5.0/ 5.0/5.0/ 5.0	0.0/0.0/ 0.9/3.3/ 5.0
P. aerugin 6 h/24h/7 d/14d/28d	4.9/4.9 /4.9/4. 9/4.9	4.9/4.9/ 4.9/4.9/ 4.9	4.9/4.9/ 4.9/4.9/ 4.9	0.3/0.5/ 0.0/0.0/ 0.5
E. coli 6 h/24h/7 d/14d/28d	2.8/4.9 /4.9/4. 9/4.9	4.9/4.9/ 4.9/4.9/ 4.9	4.9/4.9/ 4.9/4.9/ 4.9	0.1/0.2/ 1.4/3.3/ 5.0

C. albican 7 d/14d/28d	4.3/5.1 /5.1/4. 1/4.1	5.1/5.1/ 5.1/5.1/ 5.1	2.5/5.1/ 5.1	0.7/2.7/ 3.2
A. niger 7 d/14d/28d	0.8/0.9 /1.3	2.1/4.2/ 4.9	0.7/1.7/ 2.3	1.2/1.1/ 1.5

As can be seen, cyclodextrin derivatives can significantly inhibit the ability of a preservative to provide desired preservation to an aqueous formulation.

As an added advantage, it has also been discovered that HPMC can aid in solubilizing olopatadine. This effect is shown in Table D below.

TABLE D

% PVP K29/32	% SBE-CD	% PEG 400	% HPMC	Concentration (mg/mL)	Final pH
4	1.5	4	-	6.13	6.97
4	2.0	4	-	6.74	6.97
4	2.2	4	-	6.97	7.01
4	2.3	4	-	7.16	7.02
4	2.5	4	-	7.34	6.98
4	1.5	4	0.6	7.46	6.96
4	2.0	4	0.6	8.11	7.06
4	2.2	4	0.6	8.62	7.02
4	2.3	4	0.6	8.66	7.01
4	2.5	4	0.6	9.04	7.04

Table E below presents several formulations (N through Q) that can solubilize a high concentration of olopatadine using PVP in combination with a relatively low amount of HP-β-CD and that show desirable preservation using a combination of BAK and Boric Acid. Notably, PEG and HPMC are also believed to be aiding in the solubility of olopatadine.

TABLE E

Ingredients	N	O	P	Q
Olopatadine HCL	0.77	0.77	0.77	0.77
PEG 400	4	4	4	4
Hydroxypropyl-β-Cyclodextrin	1.5	1.5	1.5	1.5
PVP K29/32	4	4	4	4
Natrosol 250HX	0.3	0.3	0.3	0.125
HPMC 2910	0.6	0.6	0.6	0.2
Boric Acid	0.3	0.3	0.3	0.3
Disodium EDTA	0.01	0.01	0.01	0.01
Benzalkonium Chloride	0.01	0.01	0.01	0.01
Polyquaternium-1	-	-	-	-
Sodium Hydroxide/ Hydrochloric Acid	q.s. to pH 7	q.s. to pH 7	q.s. to pH 7	q.s. to pH 7
Purified water	q.s. to 100%	q.s. to 100%	q.s. to 100%	q.s. to 100%
PET Result	Log $_{10}$ Unit Reduction			
S. aureus 6 h/24h/7 d/14d/28d	0.4/3.6/4.9/4.9/4.9	0.2/1.4/5.0/5.0/5.0	0.3/2.9/4.9/4.9/4.9	0.4/3.2/5.0/5.0/5.0
P. aerugin 6 h/24h/7 d/14d/28d	5.0/5.0/5.0/5.0/5.0	5.1/5.1/5.1/5.1/5.1	5.0/5.0/5.0/5.0/5.0	5.2/5.2/5.2/5.2/5.2
E. coli 6 h/24h/7 d/14d/28d	4.9/4.9/4.9/4.9/4.9	2.7/5.1/5.1/5.1/5.1	2.1/5.1/5.1/5.1/5.1	2.3/5.1/5.1/5.1/5.1
C. albican 7 d/14d/28d	4.9/4.9/4.9	2.5/4.8/4.8	1.6/4.1/5.0	2.4/4.6/4.6
A. niger 7 d/14d/28d	3.8/5.2/5.2	3.6/5.1/5.1	4.3/5.2/5.2	3.9/4.7/5.2

Tables F and G below show the difficulty associated with preservation of formulations (R through X) containing SBE-β-CD.

TABLE F

Ingredient	R	S	T	U
Olopatadine HCl	0.77	0.77	0.77	0.77
Sulfobutylether-β-Cyclodextrin	0.75	0.75	0.75	0.75
PVP K29/32	4	4	4	4
PEG 400	2	2	2	2
Natrosol 250HX	-	-	-	-
HPMC 2910	0.6	0.6	0.6	0.6
Boric Acid	0.6	0.3	0.3	0.3
Mannitol	-	-	**0.2**	-
Disodium EDTA	-	0.01	0.01	0.01
Polyquaternium-1	**0.001**	-	-	-
BAC	-	**0.02**	**0.02**	-
Benzododecinium Bromide	-	-	-	-
Sorbic Acid	-	-	-	**0.2**
Thimerosal	-	-	-	-
Chlorhexidine Digluconate	-	-	-	-
NaOH/HCl	q.s. to pH 7.0	q.s. to pH 7.0	q.s. to pH 7.0	q.s. to pH 6.0
Purified water	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100
PET RESULTS				
S. aureus 6 h/24h/7 d/14d/28d	1.8/2.8/5.0/5.4/	0.0/0.5/4.7/	0.0/0.4/4.7/	0.1/0.1/4.7/
P. aerugin 6 h/24h/7 d/14d/28d	0.6/0.8/5.4/5.4/	5.0/5.0/5.0/	5.0/5.0/5.0/	5.0/5.0/5.0/
E. coli 6 h/24h/7 d/14d/28d	1.2/3.2/5.4/5.4/	1.4/3.1/5.1/	1.7/3.2/5.1/	0.2/0.3/5.1/
C. albicans 7 d/14d/28d	0.3/1.5/	0.7/	0.6	0.1/
A. Niger 7 d/14d/28d	0.7/0.7/	2.1/	1.2	1.1/

5

TABLE G

Ingredients	V	W	X
Olopatadine HCl	0.77	0.77	0.77
Sulfobutylether-β-Cyclodextrin	0.75	0.75	0.75
PVP K29/32	4	4	4
PEG 400	2	2	2
Natrosol 250HX	-	-	-
HPMC 2910	0.6	0.6	0.6
Boric Acid	0.3	0.3	0.3
Mannitol	-	-	-
Disodium EDTA	0.01	0.01	0.01
Polyquaternium-1	-	-	-
BAC	-	-	-
Benzododecinium Bromide	**0.02**	-	-
Sorbic Acid	-	-	-
Thimerosal	-	**0.01**	-
Chlorhexidine Digluconate	-	-	**0.01**
NaOH/HCl	q.s. to pH 7.0	q.s. to pH 7.0	q.s. to pH 7.0
Purified water	q.s. to 100	q.s. to 100	q.s. to 100
	PET RESULTS		
S. aureus 6 h/24h/7 d/14d/28d	0.0/0.1/4.7/	0.0/0.0/4.7/	0.0/0.4/4.7/
P. aerugin 6 h/24h/7 d/14d/28d	5.0/5.0/5.0/	5.0/5.0/5.0/	5.0/5.0/5.0/
E. coli 6 h/24h/7 d/14d/28d	0.6/1.3/5.1/	1.1/5.0/5.0/	1.0/3.9/5.0/
C. albicans 7 d/14d/28d	0.5/	5.8/	3.9/
A. Niger 7 d/14d/28d	1.2/	5.0/	1.4

Tables H and I show the achievement of significantly improved preservation of formulations (Y through II), which also contain SBE-β-CD.

TABLE H

Ingredients	Y	Z	AA	BB	CC	DD
			+ + +	+ + -	+-+	-+-
Olopatadine HCl	0.77	0.77	0.77	0.77	0.77	0.77
Sulfobutylether-β-Cyclodextrin	1.5	1.5	1	1	1	0.75
PVP K29/32	4	4	4	4	4	4
PEG 400	4	4	2	2	2	2
Natrosol 250HX	0.3	0.3	-	-	-	-
HPMC 2910	0.6	0.6	0.6	0.6	0.6	0.6
Boric Acid	0.3	0.3	0.3	0.3	0.3	0.3
Mannitol	0.6	-	-	-	-	-
Propylene glycol	-	1	1	0.5	1	0.5
Polyquaternium-1	0.001	0.001	0.002	0.002	0.001	0.002
Sodium Hydroxide and/or Hydrochloric acid Qs to pH 7.2						
Purified Water Qs to 100						
PET DATA						
S. aureus 6 h/24h/7 d/14d/28d	0.9/1.7/4.9/ 4.9/4.9	1.2/1.6/4.9/ 4.9/4.9	1.6/2.2/4.7/ 4.7/4.7	1.6/2.4/4.7/ 4.7/4.7	1.8/2.0/4.7/ 4.7/4.7	2.1/2.9/5.05 .0/
P. aerugin 6 h/24h/7 d/14d/28d	3.4/4.9/4.9/ 4.9/4.9	0.3/1.4/5.2/ 5.2/5.2	0.0/1.0/4.6/ 5.1/5.1	0.2/1.2/5.1/ 5.1/5.1	0.1/1.0/5.1/ 5.1/5.1	0.6/1.5/5.45 .4/
E. coli 6 h/24h/7 d/14d/28d	1.9/4.2/4.9/ 4.9/4.9	1.0/2.7/5.2/ 5.2/5.2	0.3/1.6/4.8/ 4.8/4.8	1.7/4.8/4.8/ 4.8/4.8	0.3/1.2/4.8/ 4.8/4.8	2.2/4.9/5.45 .4/
C. albican 7 d/14d/28d	0.1/0.4/0.4	0.9/1.1/2.1	1.2/2.5/	1.0/2.2/	0.8/2.3/	0.9/2.7/
A. niger 7 d/14d/28d	3.6/3.6/3.1	1.0/1.0/1.0	0.6/0.7/	0.2/0.8/	0.2/0.8/	0.6/0.8/

TABLE I

FID	EE	FF	GG	HH	II
	-++	---	+--	--+	NA
Olopatadine HCl	0.77	0.77	0.77	0.77	0.77
Sulfobutylether-β-Cyclodextrin	0.75	0.75	1	0.75	0.75
PVP K29/32	4	4	4	4	4
PEG 400	2	2	2	2	2
Natrosol 250HX	-	-	-	-	-
HPMC 2910	0.6	0.6	0.6	0.6	0.6
Boric Acid	0.3	0.3	0.3	0.3	0.6
Mannitol	-	-	-	-	-
Propylene glycol	1	0.5	0.5	1	-
Polyquaternium-1	0.002	0.001	0.001	0.001	0.001
Sodium Hydroxide and/or Hydrochloric acid Qs to pH 7.2					
Purified Water Qs to 100					
PET DATA					
S. aureus 6 h/24h/7 d/14d/28d	2.0/3.1/4.7/ 4.7/4.7	0.7/1.2/4.7/ 4.7/4.7	1.5/1.8/4.7/ 4.7/4.7	2.0/2.9/5.05 .0/	1.8/2.8/5.05 .4/
P. aerugin 6 h/24h/7 d/14d/28d	0.5/1.4/5.1/ 5.1/5.1	0.0/0.4/2.0/ 1.2/0.2	0.4/1.1/5.1/ 5.1/5.1	0.6/6.3/5.45 .4/	0.6/0.8/5.45 .4/
E. coli 6 h/24h/7 d/14d/28d	1.6/4.6/4.8/ 4.8/4.8	0.0/0.0/0.00 .0/2.6	0.2/0.8/4.8/ 4.8/4.8	2.4/5.2/5.45 .4/	1.2/3.2/5.45 .4/
C. albican 7 d/14d/28d	1.1/2.7/	0.6/1.9/	0.7/1.9/	0.3/2.4/	0.3/1.5/
A. niger 7 d/14d/28d	0.7/0.8/	0.7/0.9/	0.7/0.8/	0.7/0.8/	0.7/0.7/

Table J illustrates that formula preservation can best be achieved using HP-γ-CD. In particular, formulas JJ through TT in Table J exhibit robust preservation

relative to both European and United States preservation standards. This is particularly surprising when the data in Table J is compared with the data in Tables A, B and E since there is no readily identifiable reason that the formulations containing HP-γ-CD should exhibit greater preservation efficacy relative to the formulations containing HP-β-CD.

TABLE J

Formula	**JJ**	**KK**	**LL**	**MM**	**NN**	**OO**
Batch #	11-63920	11-63921	11-63900	11-63901	11-63902	11-63922
Component						
Olopatadine Hydrochloride	0.77	0.77	0.77	0.77	0.77	0.77
HP-γ-CD	1.5	1.5	1.5	1.5	1.5	1.5
Povidone K29/32	4	4	4	4	4	4
PEG 400	4	4	4	4	4	4
HPMC 2910 E4M	0.4	0.4	0.4	0.4	0.4	0.4
Boric acid	0.3	0.3	0.3	0.3	0.3	0.3
Mannitol	0.2	0.2	0.2	0.2	0.2	0.2
Disodium EDTA	-	-	-	-	-	0.005
Benzalkonium Chloride	0.015	0.0125	0.01	0.0075	0.005	0.015
Sodium Hydroxide and/or Hydrochloric acid Qs to pH 7.2						
Purified Water Qs to 100						
PET DATA						
S.aureus 6h/24h/7d/14d/28d	4.9/4.9/4.9/4.9/4.9	4.9/4.9/4.9/4.9/4.9	4.8/4.8/4.8/4.8/4.8	4.8/4.8/4.8/ 4.8/4.8	4.8/4.8/4.8/ 4.8/4.8	4.9/4.9/4.9/ 4.9/4.9
P.aeruginosa 6h/24h/7d/14d/28d	4.9/4.9/4.9/4.9/4.9	4.9/4.9/4.9/4.9/4.9	4.9/4.8/4.9/4.9/4.9	4.9/4.9/4.9/ 4.9/4.9	4.9/4.9/4.9/ 4.9/4.9	4.9/4.9/4.9/ 4.9/4.9
E.coli 6h/24h/7d/14d/28d	5.0/5.0/5.0/5.0/5.0	2.6/5.0/5.0/5.0/5.0	1.1/3.0/4.9/4.9/4.9	0.9/1.8/4.9/ 4.9/4.9	0.4/1.2/4.9/ 4.9/4.9	5.0/5.0/5.0/ 5.0/5.0
C.albican 6h/24h/7d/14d/28d	4.8/4.8/4.8	4.8/4.8/4.8	4.9/4.9/4.9	4.9/4.9/4.9	4.9/4.9/4.9	4.8/4.8/4.8
A.niger 6h/24h/7d/14d/28d	5.1/5.1/5.1	5.1/5.1/5.1	5.1/5.1/5.1	5.1/5.1/5.1	5.1/5.1/5.1	5.1/5.1/5.1
Test Results						
pH Initial	**7.31**	**7.25**	**7.25**	**7.20**	**7.29**	**7.25**

TABLE J CONTINUED

FID	PP	QQ	RR	SS	TT
Batch #	11-63923	11-63899	11-63905	11-63908	11-64011
Component					
Olopatadine Hydrochloride	0.77	0.77	0.77	0.77	0.77
HP-γ-CD	1.5	1.5	1.5	1.5	1.5
Povidone K29/32	4	4	4	4	4
PEG 400	4	4	4	4	4
HPMC 2910 E4M	0.4	0.4	0.4	0.4	0.4
Boric acid	0.3	0.3	0.3	0.3	0.3
Mannitol	0.2	0.2	0.2	0.2	0.2
Disodium EDTA	0.005	0.005	0.005	0.005	0.005
Benzalkonium Chloride	0.0125	0.01	0.0075	0.005	0.01
Sodium Hydroxide and/or Hydrochloric acid Qs to pH 7.2					
Purified Water Qs to 100					
PET DATA					
S.aureus 6h/24h/7d/14d/28d	4.9/4.9/4.9/ 4.9/4.9	4.8/4.8/4.8/ 4.8/4.8	4.8/4.8/4.8/ 4.8/4.8	4.9/4.9/4.9/ 4.9/4.9	5.0/5.0/5.0/5 .0/5.0
P.aeruginosa 6h/24h/7d/14d/28d	4.9/4.9/4.9/ 4.9/4.9	4.9/4.9/4.9/4 .9/4.9	4.9/4.9/4.9/ 4.9/4.9	4.9/4.9/4.9/ 4.9/4.9	5.0/5.0/5.0/5 .0/5.0
E.coli 6h/24h/7d/14d/28d	5.0/5.0/5.0/5 .0/5.0	4.9/4.9/4.9/ 4.9/4.9	4.9/4.9/4.9/ 4.9/4.9	5.0/5.0/5.0/ 5.0/5.0	5.1/5.1/5.1/5 .1/5.1
C.albican 6h/24h/7d/14d/28d	4.8/4.8/4.8	4.9/4.9/4.9	4.9/4.9/4.9	4.8/4.8/4.8	4.9/4.9/4.9
A.niger 6h/24h/7d/14d/28d	4.4/5.1/5.1	5.1/5.1/4.9	5.1/5.1/5.1	4.4/5.1/5.1	5.3/5.3/5.3
Test Results					
pH Initial	**7.24**	**7.24**	**7.23**	**7.28**	**7.29**

5

Tables K through O below corresponding to graphs in FIGS. 1 through 5, provide results from a conjunctival allergen challenge (CAC) study of a high concentration olopatadine composition as compared to a marketed lower concentration olopatadine composition (marketed as PATADAY® by Alcon Laboratories, Inc., a Novartis Company). The CAC study was performed according to a standard CAC model that instills allergen in the eye (the challenge) and then makes determinations of ocular redness and ocular itching at time points (determination times) after the challenge. The CAC study was performed by ORA, Inc., Andover, Massachusetts, United States, 01810, which uses a model accepted by the food and drug administration (FDA). It is noted that in tables K through O and FIGs. 1 through 5, the references to 0.77% olopatadine are references to olopatadine HCL and actually represent 0.7% olopatadine as base and the references to 0.2% olopatadine are references to 0.22% olopatadine HCL and 0.2% olopatadine as base.

In the CAC model, each patient is dosed with drug or vehicle and exposed to allergen at specific challenge times. The challenge times for the study were 27 minutes, 16 hours and 24 hours after dosing. Thereafter, itching is determined at determination times of 3, 5 and 7 minutes after challenge times and redness is determined at determination times of 7, 15 and 20 minutes after the challenge times. Therefore, patients received three doses of drug or vehicle and each dose was followed by an allergen challenge and then the itching and redness determination are made as discussed. Results from the determination times are provided in Tables K through O and the graphs of FIGS. 1 through 5.

Redness scores are determined on a scale of 0 to 4 by visual observation and the patient is asked to rate their ocular itching on a scale of 0 to 4 to attain itching scores and in each score 0 is the least and 4 is greatest. The results of those determinations at those time points are provided in Tables K through O and the graphs of FIGS. 1 through 5. Each of Tables K through O provide a mean score (Mean), a standard deviation (Std) to that score, a number (N) of patients, a minimum (Min) score determined for any of the patients, a maximum (Max) score determined for any of the patients and p-values for indications of statistical significance with a p-value of less than 0.05 indicating statistical significance.

Table K below provides data relative to mean conjunctival redness as determined by the conjunctival allergen challenge (CAC) study 27 minutes after challenge and that data is provided as a graph in FIG 1.

TABLE K

Conjunctival Redness (Onset-of-Action CAC)

		Mean	Std	N	Min	Max	By Time p-value	Overall p-value
7min	**Olopatadine 0.77%**	0.8	0.7	63	0	3		
	Olopatadine 0.2%	1.3	0.8	63	0	3	<.0001	<.0001
	Vehicle	2.1	0.7	60	0	3	<.0001	<.0001
15min	**Olopatadine 0.77%**	1.1	0.9	63	0	3		
	Olopatadine 0.2%	1.9	0.8	63	0	3	<.0001	
	Vehicle	2.3	0.6	60	1	4	<.0001	
20min	**Olopatadine 0.77%**	1.1	0.8	63	0	3		
	Olopatadine 0.2%	1.9	0.8	63	0	3	<.0001	
	Vehicle	2.3	0.7	60	0	4	<.0001	

Main Effect of Treatment p-value=<.0001
Treatment by Time Interaction p-value=0.0036

As can be seen in Table K and FIG. 1, olopatadine at a concentration of 0.7% (note that the 0.77% above is for olopatadine HCl and represents 0.7% olopatadine) provides statistically significant (i.e., $p < 0.05$) relief of redness at onset-of-action relative to both vehicle and olopatadine 0.2%. Further, olopatadine at a concentration of 0.7% provides more that a 1.0 unit difference relative to vehicle in relief of redness. Olopatadine at this concentration is believed to be the first antihistamine/mast cell stabilizer to provide such a difference. This data is particularly surprising since, prior to this CAC study, there was no indication that a high concentrations olopatadine composition would provide any additional reduction in redness at onset-of-action.

Olopatadine's IC_{50} value or half maximal inhibitory concentration (IC_{50}) for inhibition of human conjunctival mast cell degranulation is in the 500 to 600 μM range. Olopatadine's binding affinity (Ki) value for histamine binding to the H1 receptor is in the 30 to 50 nM range. The molar concentration of olopatadine in a 0.1% solution of olopatadine is approximately 2.5 mM. These values suggest that a

0.1% solution of olopatadine should have more than a sufficient quantity of olopatadine to provide maximal inhibition of human conjunctival mast cell degranulation and maximal fully histamine binding.

In particular, for inhibition of mast cell degranulation, these values indicate that when a 0.1% solution of olopatadine is dosed onto the eye, there is exposure to 5 times the IC_{50} value for mast cell degranulation (500 μM vs 2.5 mM). When a 0.2% olopatadine solution is dosed to the eye, the exposure increases from approximately 2.5 mM (for a 0.1% solution) to 5 mM or about 10 times excess drug for inhibition of mast cell degranulation. Because olopatadine does not have any vasoconstrictive effect, which would typically reduce redness, this inhibition of redness is believed to result from inhibition of the release of the mast cell mediators brought about by the mast cell degranulation. As such, a 0.1% or 0.2% solution of olopatadine should provide full inhibition of redness at onset of action since both of these solutions provide excess olopatadine for inhibiting mast cell degranulation.

Surprisingly, however, the data in Table K and FIG. 1 show that a 0.7% solution of olopatadine prevents redness even better than a 0.2% solution of olopatadine at onset of action. Even more surprising, it provides a statistically significant difference in redness inhibition relative the 0.2% solution at onset of action.

In contrast to this surprising discovery relative to redness, a similar finding was not made for itching (see Table KK below), which is believed to be avoided through histamine binding.

TABLE KK

Ocular Itching
(Onset-of-Action CAC)

		Mean	Std	N	Min	Max	By Time p-value	Overall p-value
3min	**Olopatadine 0.77%**	0.4	0.7	63	0	3		
	Olopatadine 0.2%	0.4	0.6	63	0	3	0.8434	
	Vehicle	1.9	1.1	60	0	4	<.0001	
5min	**Olopatadine 0.77%**	0.6	0.8	63	0	3		
	Olopatadine 0.2%	0.7	0.7	63	0	3	0.5341	
	Vehicle	2.1	1.1	60	0	4	<.0001	
7min	**Olopatadine 0.77%**	0.5	0.7	63	0	3		
	Olopatadine 0.2%	0.7	0.8	63	0	4	0.3667	0.5441
	Vehicle	2.0	1.1	60	0	4	<.0001	<.0001

Main Effect of Treatment p-value=<.0001
Treatment by Time Interaction p-value=0.4025

The similarity in itching values for olopatadine 0.7% and olopatadine 0.2% for itching at onset of action are to be expected since 0.2% olopatadine and 0.7% olopatadine both provide enough olopatadine to provide maximal inhibition of itching at onset of action. Thus, the above discussed finding relative to redness at onset of action is quite unique.

Table L below provides data relative to mean conjunctival redness determined by the CAC study 16 hours after challenge and that data is provided as a graph in FIG 2.

TABLE L

Conjunctival Redness (16hrs Duration CAC)

		Mean	Std	N	Min	Max	By Time p-value	Overall p-value
7min	**Olopatadine 0.77%**	1.3	0.8	65	0	3		
	Olopatadine 0.2%	1.6	0.7	65	1	3	0.0123	0.0056
	Vehicle	1.8	0.8	65	1	3	<.0001	0.0001
15min	**Olopatadine 0.77%**	1.5	0.8	65	0	4		
	Olopatadine 0.2%	1.9	0.7	65	1	4	0.0061	
	Vehicle	1.9	0.8	65	1	4	0.0013	
20min	**Olopatadine 0.77%**	1.5	0.8	65	0	4		
	Olopatadine 0.2%	1.9	0.7	65	1	4	0.0061	
	Vehicle	1.9	0.9	65	1	4	0.0015	

Main Effect of Treatment p-value=0.0004
Treatment by Time Interaction p-value=0.0077

As can be seen in Table L and FIG. 2, olopatadine at a concentration of 0.7% provides statistically significant relief of redness at 16 hours relative to both vehicle and olopatadine 2%.

Table M below provides data relative to mean total redness determined by the CAC study 24 hours after challenge and that data is provided as a graph in FIG 3. Mean total redness is a summation three redness determinations: i) conjunctival; ii) episcleral; and iii) ciliary, each taken on a scale of 1 through 4.

TABLE M

Total Redness
(24hrs Duration CAC)

		Mean	Std	N	Min	Max	By Time p-value	Overall p-value
7min	**Olopatadine 0.77%**	4.1	2.6	66	0	10		
	Olopatadine 0.2%	5.4	2.4	66	1	11	0.0022	0.0073
	Vehicle	6.1	2.3	68	1	10	<.0001	<.0001
15min	**Olopatadine 0.77%**	5.0	2.9	66	0	10		
	Olopatadine 0.2%	6.2	2.3	66	1	11	0.0086	
	Vehicle	6.7	2.3	68	1	11	<.0001	
20min	**Olopatadine 0.77%**	5.4	2.9	66	1	11		
	Olopatadine 0.2%	6.3	2.3	66	2	11	0.0383	
	Vehicle	6.6	2.6	68	1	11	0.0040	

Main Effect of Treatment p-value=0.0003
Treatment by Time Interaction p-value=0.0136

As can be seen in Table M and FIG. 3, olopatadine at a concentration of 0.7% provides statistically significant relief of total redness at 24 hours relative to both vehicle and olopatadine 2%.

Table N below provides data relative to ocular itching determined by the CAC study 24 hours after challenge and that data is provided as a graph in FIG 4.

TABLE N

Ocular Itching
(24hrs Duration CAC)

		Mean	Std	N	Min	Max	By Time p-value	Overall p-value
3min	**Olopatadine 0.77%**	0.9	0.8	66	0	3		
	Olopatadine 0.2%	1.4	0.8	66	0	3	0.0010	
	Vehicle	2.5	0.8	68	1	4	<.0001	
5min	**Olopatadine 0.77%**	1.1	0.9	66	0	3		
	Olopatadine 0.2%	1.5	0.9	66	0	4	0.0107	
	Vehicle	2.6	0.8	68	0	4	<.0001	
7min	**Olopatadine 0.77%**	1.1	0.9	66	0	3		
	Olopatadine 0.2%	1.5	1.0	66	0	4	0.0149	0.0034
	Vehicle	2.5	0.9	68	0	4	<.0001	<.0001

Main Effect of Treatment p-value=<.0001
Treatment by Time Interaction p-value=0.3221

As can be seen in Table N and FIG. 4, olopatadine at a concentration of 0.7% provides statistically significant relief of ocular itching at 24 hours relative to both vehicle and olopatadine 2%.

Table O below provides data relative to ocular itching determined by the CAC study 24 hours after challenge and that data is provided as a graph in FIG 5.

TABLE O

Conjunctival Redness
(24hrs Duration CAC)

		Mean	Std	N	Min	Max	By Time p-value	Overall p-value
7min	**Olopatadine 0.77%**	1.5	0.8	66	0	3		
	Olopatadine 0.2%	1.9	0.8	66	0	4	0.0016	0.0075
	Vehicle	2.1	0.8	68	1	4	<.0001	<.0001
15min	**Olopatadine 0.77%**	1.8	0.9	66	0	4		
	Olopatadine 0.2%	2.1	0.7	66	0	4	0.0131	
	Vehicle	2.3	0.7	68	1	4	<.0001	
20min	**Olopatadine 0.77%**	1.8	0.9	66	0	4		
	Olopatadine 0.2%	2.1	0.7	66	1	4	0.0402	
	Vehicle	2.3	0.9	68	1	4	0.0024	

Main Effect of Treatment p-value=0.0002
Treatment by Time Interaction p-value=0.1540

As can be seen in Table O and FIG. %, olopatadine at a concentration of 0.7% provides statistically significant relief of conjunctival redness at 24 hours relative to both vehicle and olopatadine 2%.

We Claim:

1. An ophthalmic composition for treatment of ocular allergic conjunctivitis, the composition comprising:
at least 0.67 w/v % olopatadine; and
water.

2. A composition as in claim 1 wherein the concentration of olopatadine is at least 0.7 w/v% and is dissolved in solution.

3. A composition as in claim 1 further comprising a γ-cyclodextrin derivative, a β-cyclodextrin derivative or both to aid in the solubility of the olopatadine.

4. A composition as in claim 1 further comprising a lactam polymer to aid in the solubility of the olopatadine.

5. A composition as in claim 4 wherein the lactam polymer is polyvinylpyrrolidone.

6. A composition as in claims 1 further comprising a polyether.

7. A composition as in claim 6 wherein the polyether is polyethylene glycol.

8. A composition as in claim 1 wherein the composition is disposed in an eyedropper, has a pH of 5.5 to 8.0 and an osmolality of 200 to 450.

9. An ophthalmic composition for treatment of ocular allergic conjunctivitis, the composition comprising:
at least 0.67 w/v % olopatadine dissolved in solution;
PEG having a molecular weight of 300 to 500;
polyvinylpyrrolidone; and
cyclodextrin derivative selected from β-cyclodextrin derivative, γ-cyclodextrin or both.

10. A composition as in claim 9 further comprising a preservative selected from a polymeric quaternary ammonium compound and benzalkonium chloride.

11. A composition as in claim 10 wherein the cyclodextrin derivative is hydroxypropyl- β-cyclodextrin or sulfoalkyl ether β-cyclodextrin.

12. A composition as in claim 11 wherein the β-cyclodextrin derivative is hydroxypropyl- β-cyclodextrin when the preservative is the benzalkonium chloride and the β-cyclodextrin derivative is sulfoalkyl ether β-cyclodextrin when the preservative is the polymeric quaternary ammonium compound.

13. A composition as in claim 10 wherein the preservative is benzalkonium chloride and the cyclodextrin derivative is hydroxypropyl-γ-cyclodextrin.

14. A composition as in claim 9 further comprising borate.

15. A composition as in claim 14 further comprising polyol.

16. An ophthalmic composition for treatment of ocular allergic conjunctivitis, the composition comprising:

at least 0.67 w/v % but no greater than 1.0 w/v% olopatadine dissolved in solution;

PEG having a molecular weight of 300 to 500 wherein the concentration of the PEG in solution is from about 2.0 w/v % to about 6.0 w/v%;

a lactam polymer wherein the lactam polymer is polyvinylpyrrolidone and the concentration of the polyvinylpyrrolidone in solution is from about 2.0 w/v % to about 6.0 w/v%; and

a β-cyclodextrin derivative or a γ-cyclodextrin derivative selected from SAE-β-cyclodextrin, HP-γ-cyclodextrin and HP-β-cyclodextrin wherein the concentration of the β-cyclodextrin derivative or the γ-cyclodextrin derivative is at least 0.5 w/v% but no greater than 2.0 w/v%.

17. A composition as in claims 16 further comprising borate at a concentration of at least about 0.18 w/v % but less than about 0.5 w/v%.

18. A composition as in claim 17 further comprising polyol.

19. A composition as in claim 18 wherein the polyol include polyethylene glycol at a concentration of at least 0.4 w/v% but no greater than 2.2 w/v%.

20. An ophthalmic composition for treatment of ocular allergic conjunctivitis, the composition comprising:

at least 0.67 w/v % but no greater than 1.0 w/v% olopatadine dissolved in solution;

PEG having a molecular weight of 300 to 500 wherein the concentration of the PEG in solution is from about 2.0 w/v % to about 6.0 w/v%;

a lactam polymer wherein the lactam polymer is polyvinylpyrrolidone and the concentration of the polyvinylpyrrolidone in solution is from about 2.0 w/v % to about 6.0 w/v%; and

hydroxypropyl-γ-cyclodextrin in the composition at a concentration of at least 0.5 w/v% but no greater than 2.0 w/v%.

21. A composition as in claims 20 further comprising borate at a concentration of at least about 0.18 w/v % but less than about 0.5 w/v%.

22. A composition as in claim 21 further comprising polyol.

23. A composition as in claim 22 wherein the polyol include polyethylene glycol at a concentration of at least 0.4 w/v% but no greater than 2.2 w/v%.

24. A method of treating ocular allergy symptoms, the method comprising:

topically applying the composition of claim 20 to an eye of a human.

25 A method as in claim 24 wherein the step of topically applying the composition includes dispensing an eyedrop from an eyedropper.

Abstract

The present invention is an ophthalmic composition containing a relatively high concentration of olopatadine. The composition is typically an ophthalmic aqueous solution containing relatively high concentrations of olopatadine solubilized within the solution. The composition is preferably capable of providing enhanced relief from symptoms of ocular allergic conjunctivitis, particularly late phase symptoms of ocular allergic conjunctivitis.

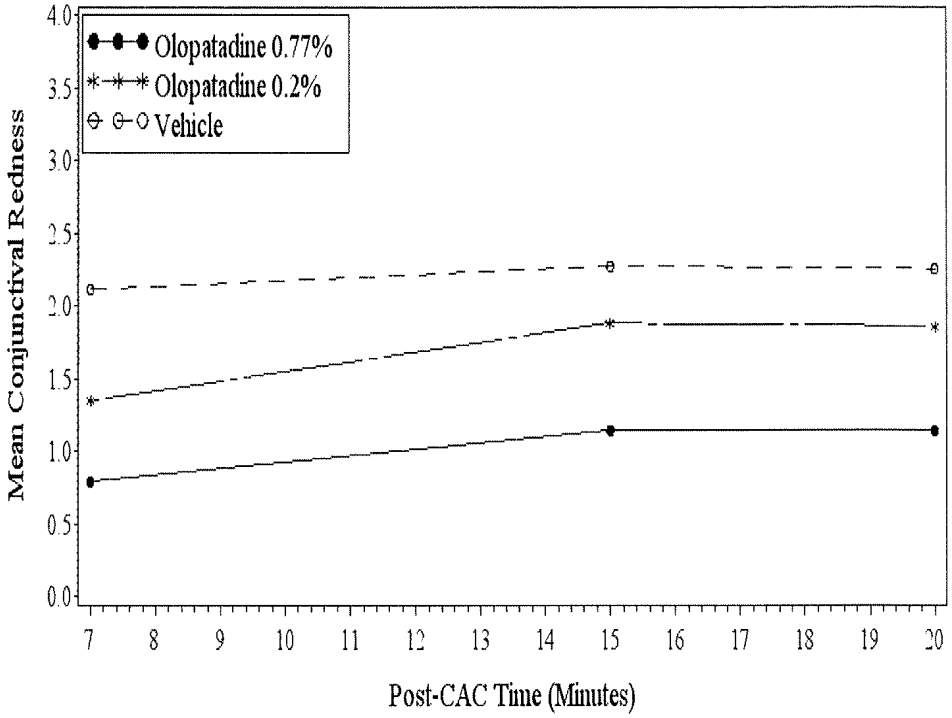
Olopatadine 0.77%
Olopatadine 0.2%
Vehicle
Mean Conjunctival Redness
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
7
8
9
10
11
12
13
14
15
16
17
18
19
20
Post-CAC Time (Minutes)

FIG. 1

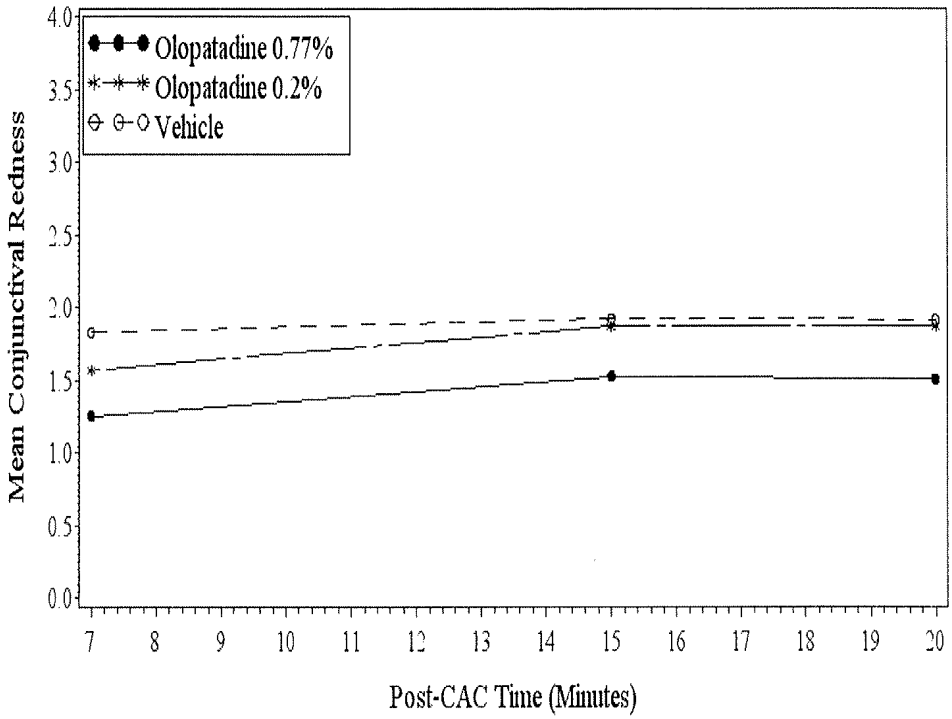
Olopatadine 0.77%
Olopatadine 0.2%
Vehicle
Mean Conjunctival Redness
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
7
8
9
10
11
12
13
14
15
16
17
18
19
20
Post-CAC Time (Minutes)

FIG. 2

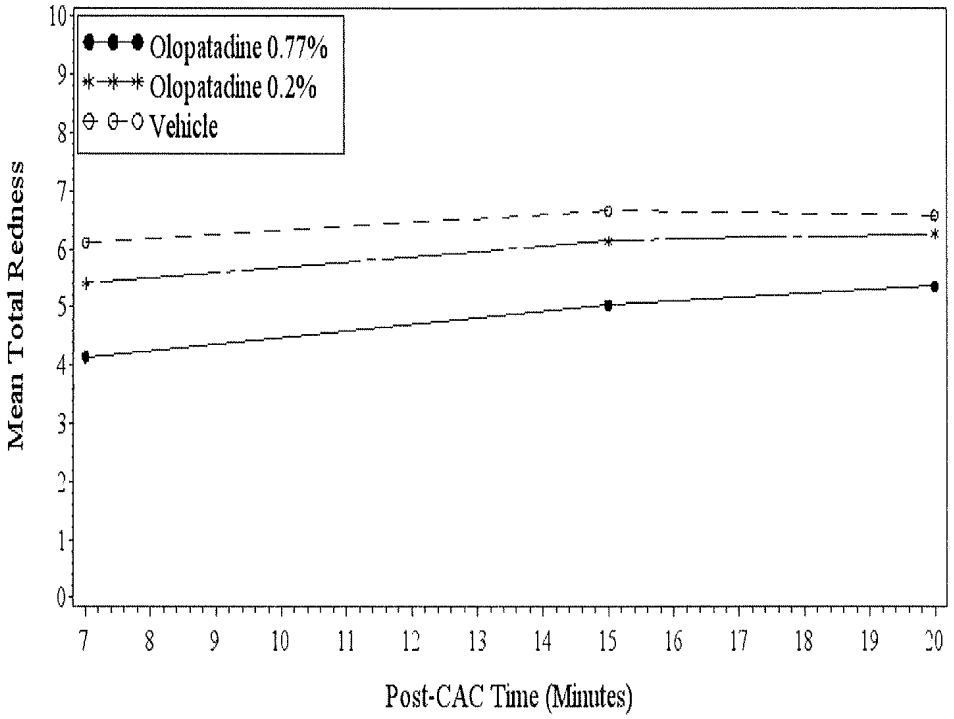
Olopatadine 0.77%
Olopatadine 0.2%
Vehicle
Mean Total Redness
0
1
2
3
4
5
6
7
8
9
10
7
8
9
10
11
12
13
14
15
16
17
18
19
20
Post-CAC Time (Minutes)

FIG. 3

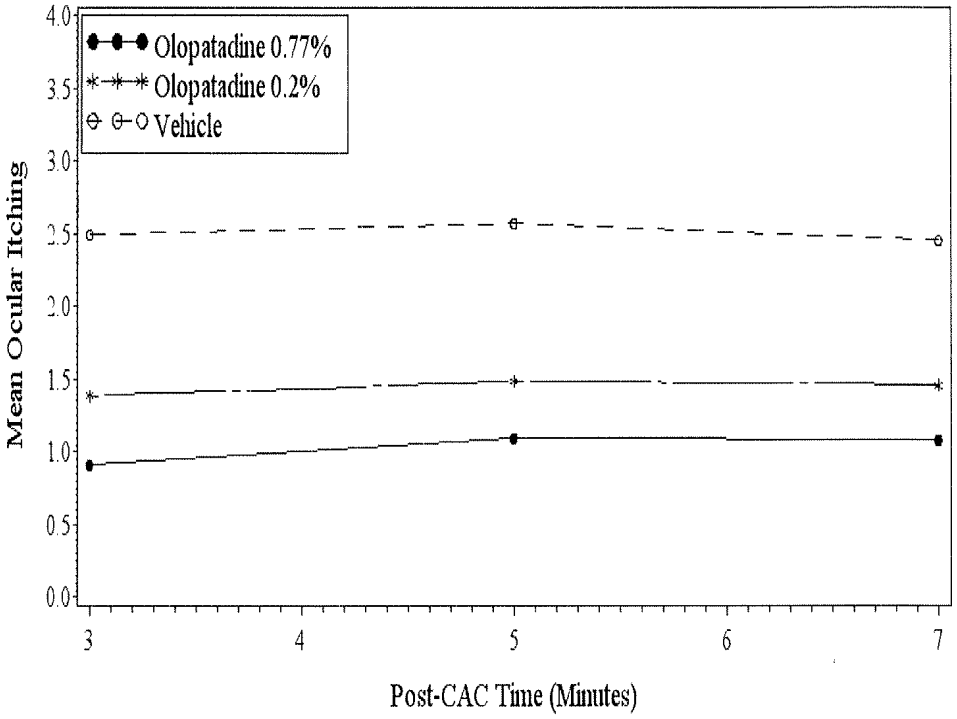
Olopatadine 0.77%
Olopatadine 0.2%
Vehicle
Mean Ocular Itching
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
3
4
5
6
7
Post-CAC Time (Minutes)

FIG. 4

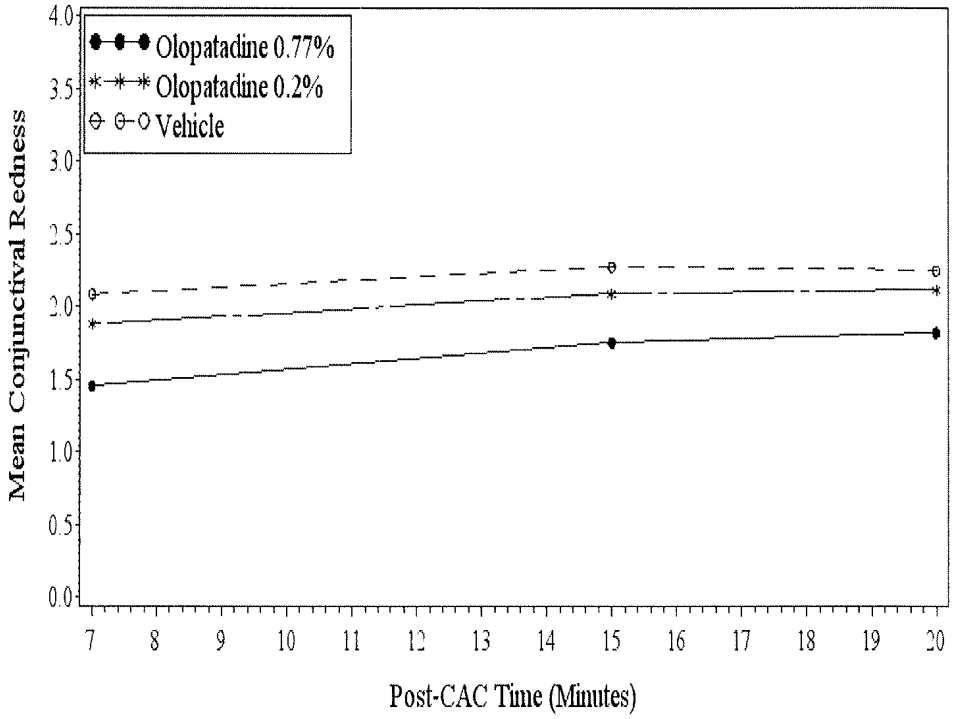
Olopatadine 0.77%
Olopatadine 0.2%
Vehicle
Mean Conjunctival Redness
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
7
8
9
10
11
12
13
14
15
16
17
18
19
20
Post-CAC Time (Minutes)

FIG. 5

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, we hereby declare that:

Our residence, post office address and citizenship are as stated below next to our names.

We believe we are the original, first and joint inventors of the subject matter which is claimed and for which a patent is sought on the invention entitled:

HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION

described and claimed herewith and further identified as Attorney Docket No. 3988 US the specification of which (check one)

(X) is attached hereto.

( ) was filed by an authorized person on my behalf on _____, as Application Serial No. _____ and was amended on _____ (if applicable)

We hereby state that we have reviewed and understand the contents of the above-identified specification, including the claims as amended by any amendment referred to above.

We acknowledge the duty to disclose information which is known to me to be material to patentability as defined in Section 1.56.

We hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT international application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s):			Priority Claimed	
Application Number	**Country**	**Filed (Month/Day/Year)**	**Yes**	**No**

We hereby claim the benefit under 35 USC §119(e) of any United States provisional application(s) listed below.

Prior Provisional Application(s):		Priority Claimed	
Application Number	Filed (Month/Day/Year)	Yes	No
61/487,789	05/19/2011	X	
61/548,957	10/19/2011	X	

We hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s), or Section 365(c) of any PCT international application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of Title 35, United States Code, Section 112. We acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Prior U.S. Application(s):		Status: Patent, Pending, Abandoned
Application Number	Filed (Month/Day/Year)	

We hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

We hereby appoint those patent practitioners associated with Customer No. **26356** as my attorneys, with full power of substitution and revocation, to prosecute this application and to transact all business in the United States Patent and Trademark Office connected therewith.

Full name of Inventor:	Daniel A. Gamache
Address:	5610 Hunterwood Lane Arlington, Texas 76017
Inventor's Signature:	_____
Date:	_____
Citizenship:	United States of America

Full name of Inventor:	Laman Alani
Address:	6809 Shadow Creek Court Fort Worth, Texas 76132
Inventor's Signature:	_____
Date:	_____
Citizenship:	United States of America

Full name of Inventor:	Malay Ghosh
Address:	4221 Kirkland Court Fort Worth, Texas 76109
Inventor's Signature:	_____
Date:	_____
Citizenship:	United States of America

Full name of Inventor:	Francisco Javier Galán
Address:	c/ Dels Pins, 19 08329 Teià Barcelona (Spain)
Inventor's Signature:	_____
Date:	_____
Citizenship:	Spain
Full name of Inventor:	Núria Carreras Perdiguer
Address:	Ametller, 9 08140 Calades de Montbui Barcelona (Spain)
Inventor's Signature:	_____
Date:	_____
Citizenship:	Spain
Full name of Inventor:	Onkar N. Singh
Address:	5606 Rachel Court Arlington, Texas 76017
Inventor's Signature:	_____
Date:	_____
Citizenship:	United States of America

Address for Correspondence:
Alcon Research, Ltd.
Scott A. Chapple, IP Legal
6201 South Freeway, TB4-8
Fort Worth, Texas 76134
Phone: 817-615-5288
Docket No.: 3988 US

Customer No.: 26356

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION
First Named Inventor/Applicant Name:	Daniel A. Gamache
Filer:	Scott Chapple/Barbara McKenzie
Attorney Docket Number:	3988 US

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility application filing	1011	1	380	380
Utility Search Fee	1111	1	620	620
Utility Examination Fee	1311	1	250	250
Pages:				
Claims:				
Claims in excess of 20	1202	5	60	300
Independent claims in excess of 3	1201	2	250	500
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**2050**

Electronic Acknowledgement Receipt

EFS ID:	12817309
Application Number:	13475607
International Application Number:	
Confirmation Number:	4130
Title of Invention:	HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION
First Named Inventor/Applicant Name:	Daniel A. Gamache
Customer Number:	26356
Filer:	Scott Chapple/Barbara McKenzie
Filer Authorized By:	Scott Chapple
Attorney Docket Number:	3988 US
Receipt Date:	18-MAY-2012
Filing Date:	
Time Stamp:	17:22:49
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$2050
RAM confirmation Number	4272
Deposit Account	010682
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		3988_US_Appln-final_051812.pdf	2386476 6302957ccd2bc296e3b1cd51b6842ee8900c1240	yes	48

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	39
Claims	40	42
Abstract	43	43
Drawings-only black and white line drawings	44	48

Warnings:

Information:

2	Oath or Declaration filed	3988_US_Decl-POA_unsigned.pdf	170512 e6e84d8fa5bba27214192e17f4e8bdc8c23a1fe8	no	5

Warnings:

Information:

3	Fee Worksheet (SB06)	fee-info.pdf	37950 42cd26414a4f264df67a668515899b39e626387f	no	2

Warnings:

Information:

Total Files Size (in bytes):	2594938

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Electronic Acknowledgement Receipt

EFS ID:	12817309
Application Number:	13475607
International Application Number:	
Confirmation Number:	4130
Title of Invention:	HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION
First Named Inventor/Applicant Name:	Daniel A. Gamache
Customer Number:	26356
Filer:	Scott Chapple/Barbara McKenzie
Filer Authorized By:	Scott Chapple
Attorney Docket Number:	3988 US
Receipt Date:	18-MAY-2012
Filing Date:	
Time Stamp:	17:22:49
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$2050
RAM confirmation Number	4272
Deposit Account	010682
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		3988_US_Appln-final_051812.pdf	2386476 6302957ccd2bc296e3b1cd51b6842ee8900c1240	yes	48

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	39
Claims	40	42
Abstract	43	43
Drawings-only black and white line drawings	44	48

Warnings:

Information:

2	Oath or Declaration filed	3988_US_Decl-POA_unsigned.pdf	170512 e6e84d8fa5bba27214192e17f4e8bdc8c23a1fe8	no	5

Warnings:

Information:

3	Fee Worksheet (SB06)	fee-info.pdf	37950 42cd26414a4f264df67a668515899b39e626387f	no	2

Warnings:

Information:

Total Files Size (in bytes):	2594938

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

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New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Electronic Acknowledgement Receipt

EFS ID:	12817309
Application Number:	13475607
International Application Number:	
Confirmation Number:	4130
Title of Invention:	HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION
First Named Inventor/Applicant Name:	Daniel A. Gamache
Customer Number:	26356
Filer:	Scott Chapple/Barbara McKenzie
Filer Authorized By:	Scott Chapple
Attorney Docket Number:	3988 US
Receipt Date:	18-MAY-2012
Filing Date:	
Time Stamp:	17:22:49
Application Type:	Utility under 35 USC 111(a)

Electronic Acknowledgement Receipt

Adjustment date: 06/01/2012 MNGUYEN
05/21/2012 INTEFSW 00004272 010682 13475607
05 FC:1201 500.00 CR

06/01/2012 MNGUYEN 00000018 010682 13475607

01 FC:1201 250.00 DR

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$2050
RAM confirmation Number	4272
Deposit Account	010682
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/475,607

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	380
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	620
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	250
TOTAL CLAIMS (37 CFR 1.16(i))	25 minus 20 =	* 5			OR	x 60 =	300
INDEPENDENT CLAIMS (37 CFR 1.16(h))	4 minus 3 =	* 1				x 250 =	250
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1800

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/475,607	05/18/2012	1629	1800	3988 US	25	4

CONFIRMATION NO. 4130

26356
ALCON
IP LEGAL, TB4-8
6201 SOUTH FREEWAY
FORT WORTH, TX 76134

FILING RECEIPT

OC000000054601503

Date Mailed: 06/04/2012

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

Daniel A. Gamache, Arlington, TX;
Laman Alani, Fort Worth, TX;
Malay Ghosh, Fort Worth, TX;
Francisco Javier Galán, Barcelona, SPAIN;
Núria Carreras Perdiguer, Barcelona, SPAIN;
Onkar N. Singh, Arlington, TX;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This appln claims benefit of 61/487,789 05/19/2011
and claims benefit of 61/548,957 10/19/2011

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)

If Required, Foreign Filing License Granted: 06/01/2012

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/475,607**

Projected Publication Date: To Be Determined - pending completion of Missing Parts

Non-Publication Request: No

Early Publication Request: No

Title

HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as

set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/475,607	05/18/2012	Daniel A. Gamache	3988 US

CONFIRMATION NO. 4130

26356
ALCON
IP LEGAL, TB4-8
6201 SOUTH FREEWAY
FORT WORTH, TX 76134

FORMALITIES LETTER

OC000000054601504

Date Mailed: 06/04/2012

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The oath or declaration is unsigned.

The applicant needs to satisfy supplemental fees problems indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- A surcharge (for late submission of filing fee, search fee, examination fee or oath or declaration) as set forth in 37 CFR 1.16(f) of $**130** for a non-small entity, must be submitted.

SUMMARY OF FEES DUE:

Total fee(s) required within **TWO MONTHS** from the date of this Notice is $**130** for a non-small entity
- $**130** Surcharge.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

/kung/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Daniel A. Gamache et al.

U.S. Serial No.: 13/475,607

Confirmation No.: 4130

Filed: May 18, 2012

Examiner:

Group Art Unit: 11629

CERTIFICATE OF FILING VIA EFS-WEB

I hereby certify that this correspondence is being submitted to the Mail Stop Missing Parts; Commissioner for Patents, P.O. Box 1450, Alexandria, VA. 22313-1450 via EFS-Web on this date:

26 June 2012.

By: /Barbara McKenzie/
Barbara McKenzie

For: HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION

RESPONSE TO NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

Mail Stop Missing Parts
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This paper is submitted in response to the Notice To File Missing Parts of Nonprovisional Application – Filing Date Granted mailed June 4, 2012. Applicants submit herewith a fully executed Declaration And Power Of Attorney. Applicants respectfully submit that no additional parts are required to be filed in the above-referenced application, and, therefore, the application should be processed accordingly.

The Commissioner is hereby authorized to charge payment of the following fee and any additional fees which may be required associated with this communication to **Deposit Account No. 010682** of Alcon Research, Ltd.

1. The fee amount of $130.00 for late submission of an executed Oath or Declaration under 37 CFR 1.16(f).

Respectfully submitted,

Alcon Research, Ltd.

June 26, 2012

Scott A. Chapple
Reg. No. 46,287

Address for Correspondence:
Alcon Research, Ltd.
Scott A. Chapple, IP Legal
6201 S. Freeway, TB4-8
Fort Worth, TX 76134-2099
Phone: 817-615-5288

Attorney Docket: 3988 US

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, we hereby declare that:

Our residence, post office address and citizenship are as stated below next to our names.

We believe we are the original, first and joint inventors of the subject matter which is claimed and for which a patent is sought on the invention entitled:

HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION

described and claimed herewith and further identified as Attorney Docket No. 3988 US the specification of which (check one)

(X) is attached hereto.

( ) was filed by an authorized person on my behalf on _____, as Application Serial No. _____ and was amended on _____ (if applicable)

We hereby state that we have reviewed and understand the contents of the above-identified specification, including the claims as amended by any amendment referred to above.

We acknowledge the duty to disclose information which is known to me to be material to patentability as defined in Section 1.56.

We hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT international application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s):			**Priority Claimed**	
Application Number	**Country**	**Filed (Month/Day/Year)**	**Yes**	**No**

We hereby claim the benefit under 35 USC §119(e) of any United States provisional application(s) listed below.

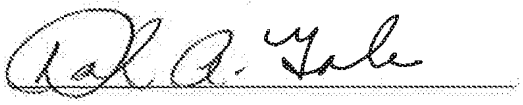
Prior Provisional Application(s):		Priority Claimed	
Application Number	Filed (Month/Day/Year)	Yes	No
61/487,789	05/19/2011	X	
61/548,957	10/19/2011	X	

We hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s), or Section 365(c) of any PCT international application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of Title 35, United States Code, Section 112. We acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

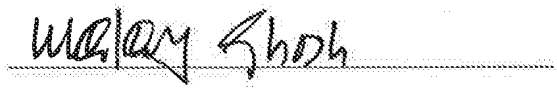
Prior U.S. Application(s):		Status: Patent, Pending, Abandoned
Application Number	Filed (Month/Day/Year)	

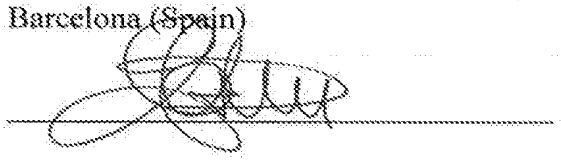
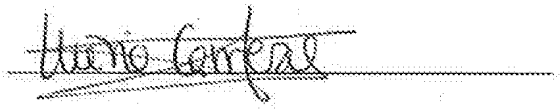
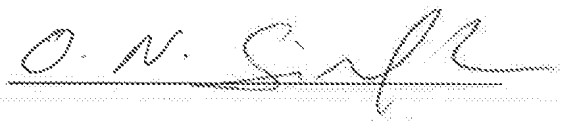
We hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

We hereby appoint those patent practitioners associated with Customer No. **26356** as my attorneys, with full power of substitution and revocation, to prosecute this application and to transact all business in the United States Patent and Trademark Office connected therewith.

Full name of Inventor:	Daniel A. Gamache
Address:	5610 Hunterwood Lane Arlington, Texas 76017
Inventor's Signature:	
Date:	6-20-2012
Citizenship:	United States of America

Full name of Inventor:	Laman Alani
Address:	6809 Shadow Creek Court Fort Worth, Texas 76132
Inventor's Signature:	
Date:	6/19/2012
Citizenship:	United States of America

Full name of Inventor:	Malay Ghosh
Address:	4221 Kirkland Court Fort Worth, Texas 76109
Inventor's Signature:	
Date:	6/19/2012
Citizenship:	United States of America

Full name of Inventor:	Francisco Javier Galán
Address:	c/ Dels Pins, 19 08329 Teià Barcelona (Spain)
Inventor's Signature:	
Date:	22 MAY 2012
Citizenship:	Spain
Full name of Inventor:	Núria Carreras Perdiguer
Address:	Ametller, 9 08140 Calades de Montbui Barcelona (Spain)
Inventor's Signature:	
Date:	11.MAY 12
Citizenship:	Spain
Full name of Inventor:	Onkar N. Singh
Address:	5606 Rachel Court Arlington, Texas 76017
Inventor's Signature:	
Date:	06-04-2012
Citizenship:	United States of America

Address for Correspondence:
Alcon Research, Ltd.
Scott A. Chapple, IP Legal
6201 South Freeway, TB4-8
Fort Worth, Texas 76134
Phone: 817-615-5288
Docket No.: 3988 US

Customer No.: 26356

Electronic Patent Application Fee Transmittal

Application Number:	13475607
Filing Date:	18-May-2012
Title of Invention:	HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION
First Named Inventor/Applicant Name:	Daniel A. Gamache
Filer:	Scott Chapple/Barbara McKenzie
Attorney Docket Number:	3988 US

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Late filing fee for oath or declaration	1051	1	130	130
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**130**

Electronic Acknowledgement Receipt

EFS ID:	13106589
Application Number:	13475607
International Application Number:	
Confirmation Number:	4130
Title of Invention:	HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION
First Named Inventor/Applicant Name:	Daniel A. Gamache
Customer Number:	26356
Filer:	Scott Chapple/Barbara McKenzie
Filer Authorized By:	Scott Chapple
Attorney Docket Number:	3988 US
Receipt Date:	26-JUN-2012
Filing Date:	18-MAY-2012
Time Stamp:	14:11:22
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$130
RAM confirmation Number	384
Deposit Account	010682
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Applicant Response to Pre-Exam Formalities Notice	3988_US_MissingPartsResponse_062612.pdf	67454 bccb6ee4fef3e3127d88a0d3b77e84c119a39e8a	no	2
Warnings:					
Information:					
2	Oath or Declaration filed	3988_US_Decl-POA_signed.pdf	299206 79b623effb9a5451439410d96b2c5b944d167291	no	6
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30372 551f9acef6a7aec0abc1858c953e24d9e68cfd92	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	397032		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/475,607	05/18/2012	1629	1930	3988 US	25	4

CONFIRMATION NO. 4130

UPDATED FILING RECEIPT

26356
ALCON
IP LEGAL, TB4-8
6201 SOUTH FREEWAY
FORT WORTH, TX 76134

OC000000055125577

Date Mailed: 07/05/2012

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

Daniel A. Gamache, Arlington, TX;
Laman Alani, Fort Worth, TX;
Malay Ghosh, Fort Worth, TX;
Francisco Javier Galán, Barcelona, SPAIN;
Núria Carreras Perdiguer, Barcelona, SPAIN;
Onkar N. Singh, Arlington, TX;

Power of Attorney: The patent practitioners associated with Customer Number 26356

Domestic Priority data as claimed by applicant

This appln claims benefit of 61/487,789 05/19/2011
and claims benefit of 61/548,957 10/19/2011

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)

If Required, Foreign Filing License Granted: 06/01/2012

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/475,607**

Projected Publication Date: 11/22/2012

Non-Publication Request: No

Early Publication Request: No

Title

HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as

set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/475,607

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	380
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	620
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	250
TOTAL CLAIMS (37 CFR 1.16(i))	25 minus 20 =	* 5			OR	x 60 =	300
INDEPENDENT CLAIMS (37 CFR 1.16(h))	4 minus 3 =	* 1				x 250 =	250
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1800

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	13475607
Filing Date	2012-05-18
First Named Inventor	Daniel A. Gamache
Art Unit	1629
Examiner Name	
Attorney Docket Number	3988 US

U.S.PATENTS						Remove
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	3767788		1973-10-23	Rankin	
	2	3843782		1974-10-22	Krezanoski et al.	
	3	3856919		1974-12-24	Rankin	
	4	3931319		1976-01-06	Green et al.	
	5	3947573		1976-03-30	Rankin	
	6	4027020		1977-05-31	Green et al.	
	7	4120949		1978-10-17	Bapatla et al.	
	8	4283393		1981-08-11	Field et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13475607
	Filing Date	2012-05-18
	First Named Inventor	Daniel A. Gamache
	Art Unit	1629
	Examiner Name	
	Attorney Docket Number	3988 US

	9	4407791		1983-10-04	Stark	
	10	4470965		1984-09-11	Wolf et al.	
	11	4525346		1985-06-25	Stark	
	12	4836986		1989-06-06	Ogunbiyi et al.	
	13	4923693		1990-05-08	Michalos	
	14	5037647		1991-08-06	Chowhan et al.	
	15	5068225		1991-11-26	Pennell et al.	
	16	5116863		1992-05-26	Oshima et al.	
	17	5134127		1992-07-28	Stella et al.	
	18	5141961		1992-08-25	Coapman	
	19	5300287		1994-04-05	Park	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13475607
	Filing Date	2012-05-18
	First Named Inventor	Daniel A. Gamache
	Art Unit	1629
	Examiner Name	
	Attorney Docket Number	3988 US

	20	5376645		1994-12-27	Stella et al.	
	21	5472954		1995-12-05	Loftsson	
	22	5591426		1997-01-07	Dabrowski et al.	
	23	5597559		1997-01-28	Olejnik et al.	
	24	5624962		1997-04-29	Takeuchi et al.	
	25	5888493		1999-03-30	Sawaya	
	26	6153746		2000-11-28	Shah et al.	
	27	6511949		2003-01-28	Nitta et al.	
	28	6828356		2004-12-07	Su et al.	
	29	7074424		2006-07-11	Avila et al.	
	30	7147844		2006-12-12	Hamano et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13475607
	Filing Date	2012-05-18
	First Named Inventor	Daniel A. Gamache
	Art Unit	1629
	Examiner Name	
	Attorney Docket Number	3988 US

	31	7429602		2008-09-30	Trach et al.	
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	Application Number	13475607
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	First Named Inventor	Daniel A. Gamache
	Art Unit	1629
	Examiner Name	
	Attorney Docket Number	3988 US

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	1	0862414	EP		2001-12-05	Novartis AG		☐

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(54) OPHTHALMIC COMPOSITIONS CONTAINING CYCLODEXTRINS AND QUATERNARY AMMONIUM COMPOUNDS

OPHTALMISCHE ZUSAMMENSETZUNGEN DIE CYCLODEXTRINEN UND QUATERNÄREN AMMONIUMVERBINDUNGEN ENTHALTEN

COMPOSITIONS OPHTALMIQUES CONTENANT DES CYCLODEXTRINES AINSI QUE DES COMPOSES D'AMMONIUM QUATERNAIRE

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Description

[0001] The present invention describes a pharmaceutical composition, in particular a preserved ophthalmic composition, comprising a cyclodextrin, a quaternary ammonium salt, an alkylene glycol and a pharmaceutically active compound.

[0002] Numerous ophthalmic compositions have been described in prior art. The majority of the prior art ophthalmic compositions are dealing with those properties which characterize the human tears and which are e.g. the osmolality, the viscosity or the pH. Other publications related to such compositions are directed towards the preservation of ophthalmic compositions. The addressed topics can be approached with different solutions. A few of these proposed solutions are shortly reviewed infra.

[0003] EP 349 487 describes an antimicrobial ophthalmic solution comprising a quaternary ammonium salt, namely Bradosol®, as the microbicide and methods of using the same.

[0004] Ophthalmic solutions containing hydroxyethyl cellulose are described in GB 2 169 508, which solutions may serve as artificial tears.

[0005] EP 76 136 describes an aqueous disinfecting solution for contact lenses, which solutions contain certain polymeric quaternary ammonium compounds, such as e.g. Onamer M™.

[0006] DE 2 839 752 (Toko) discloses an ophthalmological gel, which is a homogenous mixture of an aqueous solution of a carboxy vinyl polymer with a polymer content of 0.05 to 5 % by weight, a water-soluble basic compound, a therapeutically effective amount of a common ophthalmological drug, having a pH in the range of 5 to 8 and a viscosity of 1000 to 100'000 mPas at 20°C, characterized in that it comprises 0.001 to 0.5 % weight NaCl.

[0007] GB 2 196 265 (Resdevco) discloses eye drops consisting of an essentially isotonic solution of a physiologically acceptable organic humectant in combination with required adjuvants or auxiliaries, containing less than 1.5 millimol/liter inorganic salt.

[0008] EP 37 043 (Wellcome) describes an isotonic liquid pharmaceutical formulation comprising trimethoprim and polymyxin, a vehicle therefor, a mercury containing preservative and an isotonic agent, characterized in that the isotonic agent comprises a non-ionic polyhydroxy compound.

[0009] Cyclodextrins have been proposed in several applications which are dealing with ophthalmic compositions. WO 94/15582 (Javitt et al.) describes e.g. an ophthalmic composition comprising an effective amount of a carbonic anhydrase inhibitor and an amount of an amorphous (β-cyclodextrin effective in increasing the bioavailability of the carbonic anhydrase inhibitor when coadministered topically.

[0010] β- and γ-cyclodextrins, in particular partially etherified derivatives thereof, have been proposed in EP 149 197 and EP 197 571 (both to Janssen) for pharmaceutical preparations comprising inclusion complexes of medicinal substances which are sparingly soluble in water or instable in water.

[0011] It is also known to preserve eye medicaments by means of quaternary ammonium salts (see, for example, EP-A-306,984). Only a very few quaternary ammonium salts have found practical application for the preservation of eye medicaments - evidently because of the multifarious requirements which must be fulfilled - these are, in particular, the three substances mentioned explicitly in EP-A-306,984, cetyltrimethylammonium bromide, cetylpyridinium chloride and benzalkonium chloride (cf. also EP-A-242,328). A preferred preservative for eye medicaments at the present time is typically benzalkonium chloride (see, for example, EP-A-306,984, page 2, lines 31-33), which has the following structure: N-benzyl-N-(C_8-C_{18}alkyl)-N,N-dimethylammonium chloride.

[0012] In another publication ophthalmic solutions are reviewed, which solutions comprise cyclodextrins and preservatives such as benzalkonium chloride (see Karl-Heinz Frömming and Josef Szejtli in Cyclodextrins in Pharmacy, 1994 Kluwer Academic Publishers, page 181, lines 10 - 21). The authors point out that the cyclodextrins may have a positive impact e.g. on the drug solubility or on the improvement of drug bioavailability. In contrast to this the same authors teach, that the cyclodextrins may also have a negative impact on such ophthalmic compositions, namely a decrease of the bioavailability of a drug, if the stability constant of the drug/cyclodextrin complex is very large, and in particular a loss of the preservative efficacy for certain preservatives such as e.g. benzalkonium chloride.

[0013] Therefore the problem to be solved consists of providing a preserved aqueous ophthalmic solution with good ocular tolerability, further comprising a pharmaceutically active compound having a high bioavailability when administered topically to the eye. In other words the problem to be solved consists of (1) maintaining the positive effects of both a cyclodextrin and of an ophthalmically acceptable quaternary ammonium salt within an ophthalmic composition designated for topical administration, and of (2) eliminating the negative impact of a cyclodextrin in particular with respect to a quaternary ammonium salt preservative.

[0014] Surprisingly it has been found, that a carefully balanced composition fulfills in fact all the criteria mentioned above for ophthalmic preparations. Accordingly a first aspect of the present invention is a preserved ophthalmic composition, comprising a cyclodextrin, a quaternary ammonium salt, an alkylene glycol and a pharmaceutically active compound.

[0015] In more detail, it has been found, that an alkylene glycol in accordance with the present invention exhibits a

particular function which is different from ist known tonicity enhancing property. While an alkylene glycol may still act as tonicity and/or solubility enhancing agent, it has been found, that an alkylene glycol may enhance (or at least maintain) both the efficacy of a quaternary ammonium salt in its function as a preservative as well as the bioavailability enhancing efficacy of a cyclodextrin on a pharmaceutically active compound. In other words, all the effects known from a cyclodextrin itself on a pharmaceutically active compound or from a quaternary ammonium salt itself are typically enhanced in a synergistic fashion. An ophthalmic composition manufactured in accordance with the present invention will usually contain much lower concentrations of a preservative or of an ophthalmic drug as compared to a prior art composition. Accordingly such an ophthalmic composition will typically exhibit an excellent ophthalmic tolerability. In addition to this, an ophthalmic composition in accordance to the present invention will typically impart improved stability to a pharmaceutically active drug used.

[0016] Another aspect is a preserved ophthalmic composition, comprising a cyclodextrin, a quaternary ammonium salt, an alkylene glycol, a pharmaceutically active compound and a carrier.

[0017] The present invention also relates to a preserved ophthalmic composition, comprising a cyclodextrin, a quaternary ammonium salt, an alkylene glycol, a pharmaceutically active compound, a carrier and one or more of an excipient selected from the group consisting of buffers, solubilizers, complexing agents, stabilizers, preservatives different from quaternary ammonium salts, tonicity enhancing agents and fillers.

[0018] Another aspect is a preserved ophthalmic composition, comprising a cyclodextrin, a quaternary ammonium salt, an alkylene glycol, a pharmaceutically active compound, a carrier and a solubilizer.

[0019] Still another aspect is a preserved ophthalmic composition, comprising a cyclodextrin, a quaternary ammonium salt, an alkylene glycol, a pharmaceutically active compound, a carrier, a solubilizer and a complexing agent.

[0020] According to the invention an ophthalmic composition is advantageously applied topically to the eye, especially in the form of a solution, a suspension, an ointment, a gel or a solid insert. Such compositions comprise a pharmaceutically active ingredient, for example, in a range of from approximately 0.000001 to approximately 10.0% by weight, preferably from approximately 0.001 to approximately 1.0% by weight, or more preferably in the range of from approximately 0.01 to approximately 0.5% by weight and most preferably in the range of from 0.025 to 0.1% by weight. The dose of the active ingredient may depend on various factors, such as mode of administration, requirement, age and/or individual condition.

[0021] There are used for a corresponding ophthalmic composition other customary pharmaceutically acceptable excipients and additives known to the person skilled in the art, for example those of the type mentioned below, especially carriers, stabilizers, solubilizers, tonicity enhancing agents, buffer substances, preservatives different from quaternary ammonium salts, thickeners, complexing agents and other excipients. Examples of such additives and excipients can be found in U.S. Patents Nos. 5134124 and 4906613. Such compositions are prepared in a manner known per se, for example by mixing an active ingredient with the corresponding excipients and/or additives to form corresponding ophthalmic compositions.

[0022] Carriers used in accordance to the present invention are typically suitable for topical or general administration, and are for example water, mixtures of water and water-miscible solvents, such as C_1- to C_7-alkanols, vegetable oils or mineral oils comprising from 0.5 to 5% by weight hydroxyethylcellulose, ethyl oleate, carboxymethyl-cellulose, polyvinylpyrrolidone and other non-toxic water-soluble polymers for ophthalmic uses, such as, for example, cellulose derivatives, such as methylcellulose, alkali metal salts of carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, methylhydroxypropylcellulose and hydroxypropylcellulose, acrylates or methacrylates, such as salts of polyacrylic acid or ethyl acrylate, polyacrylamides, natural products, such as gelatin, alginates, pectins, tragacanth, karaya gum, xanthan gum, carrageenin, agar and acacia, starch derivatives, such as starch acetate and hydroxypropyl starch, and also other synthetic products, such as polyvinyl alcohol, polyvinylpyrrolidone, polyvinyl methyl ether, polyethylene oxide, preferably cross-linked polyacrylic acid, such as neutral Carbopol, or mixtures of those polymers. Preferred carriers are water, cellulose derivatives, such as methylcellulose, alkali metal salts of carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, methylhydroxypropylcellulose and hydroxypropylcellulose, neutral Carbopol, or mixtures thereof. The concentration of the carrier is, for example, from 1 to 100000 times the concentration of the active ingredient.

[0023] The solubilizers used for an ophthalmic composition of the present invention are, for example, tyloxapol, fatty acid glycerol polyethylene glycol esters, fatty acid polyethylene glycol esters, polyethylene glycols, glycerol ethers or mixtures of those compounds. A specific example of an especially preferred solubilizer is a reaction product of castor oil and ethylene oxide, for example the commercial products Cremophor EL® or Cremophor RH 40® . Reaction products of castor oil and ethylene oxide have proved to be particularly good solubilizers that are tolerated extremely well by the eye. Another preferred solubilizer is tyloxapol. The concentration used depends especially on the concentration of the active ingredient. The amount added is typically sufficient to solubilize the active ingredient. For example, the concentration of the solubilizer is from 0.1 to 5000 times the concentration of the active ingredient.

[0024] Buffers, tonicity enhancing agents and preservatives different from quaternary ammonium salts may be used in an ophthalmic composition of the present invention as well.

[0025] Examples of buffer substances are acetate, ascorbate, borate, hydrogen carbonate /carbonate, citrate, gluconate, lactate, phosphate, propionate and TRIS (tromethamine) buffers. Tromethamine and borate buffer are preferred buffers. The amount of buffer substance added is, for example, that necessary to ensure and maintain a physiologically tolerable pH range. The pH range is typically in the range of from 5 to 9, preferably from 6 to 8.5 and more preferably from 6.5 to 8.2.

[0026] Tonicity enhancing agents are, for example, ionic compounds, such as alkali metal or alkaline earth metal halides, such as, for example, $CaCl_2$, KBr, KCl, LiCl, NaI, NaBr or NaCl, or boric acid. Non-ionic tonicity enhancing agents are, for example, urea, glycerol, sorbitol, mannitol, propylene glycol, or dextrose. For example, sufficient tonicity enhancing agent is added to impart to the ready-for-use ophthalmic composition an osmolality of approximately from 50 to 1000 mOsmol, preferred from 100 to 400 mOsmol, more preferred from 200 to 400 mOsmol and even more preferred from 250 to 350 mOsmol.

[0027] Examples of preservatives different from quaternary ammonium salts are alkyl-mercury salts of thiosalicylic acid, such as, for example, thiomersal, phenylmercuric nitrate, phenylmercuric acetate or phenylmercuric borate, parabens, such as, for example, methylparaben or propylparaben, alcohols, such as, for example, chlorobutanol, benzyl alcohol or phenyl ethanol, guanidine derivatives, such as, for example, chlorohexidine or polyhexamethylene biguanide, or sorbic acid. Preferred preservatives are alkyl-mercury salts and parabens. Where appropriate, a sufficient amount of preservative is added to the ophthalmic composition to ensure protection against secondary contaminations during use caused by bacteria and fungi.

[0028] The ophthalmic compositions may comprise further non-toxic excipients, such as, for example, emulsifiers, wetting agents or fillers, such as, for example, the polyethylene glycols designated 200, 300, 400 and 600, or Carbowax designated 1000, 1500, 4000, 6000 and 10000. Other excipients that may be used if desired are listed below but they are not intended to limit in any way the scope of the possible excipients. They are especially complexing agents, such as disodium-EDTA or EDTA, antioxidants, such as ascorbic acid, acetylcysteine, cysteine, sodium hydrogen sulfite, butyl-hydroxyanisole, butylhydroxytoluene or alpha-tocopherol acetate; stabilizers, such thiourea, thiosorbitol, sodium dioctyl sulfosuccinate or monothioglycerol; or other excipients, such as, for example, lauric acid sorbitol ester, triethanol amine oleate or palmitic acid ester. Preferred exipients are complexing agents, such as disodium-EDTA. The amount and type of excipient added is in accordance with the particular requirements and is generally in the range of from approximately 0.0001 to approximately 90% by weight.

[0029] The pharmaceutically active compounds useful in accordance with the present invention may be selected from a wide variety of especially ophthalmically acceptable agents, including beneficial pharmaceutical agents, diagnostic agents, vitamins, nutrients, lubricants, and the like. The pharmaceutically active compounds may include, without limitation thereto, 3H-thymidine, acetylcholine chloride, acyclovir, adrenaline, amethocaine, aminocaproic acid, antazoline phosphate, arachidonic acid, atropine, benoxinate hydrochloride, betaxolol hydrochloride, bupivacaine, carbachol, carteolol, chloramphenicol, chlortetracycline hydrochloride, chymatrypsin, clonidine, cocaine, corynanthine, cromolyn sodium, cyclopentolate, demecarium bromide, dexamethasone, dibutoline, dichlorphenamide, diclofenac, dipivefrin hydrochloride, echodtiophate iodide, ephedrine, epinephrine bitartrate, erythromycin, ethambutol, etidocaine, eucatropine, fluoromethalone, fluorometholone, gentamycin sulfate, gramicidine, H-thymidine, homatropine hydrobromide, hyaluronic acid, hydrocortisone, idoxuridine, indomethacin, inositol triphosphate, inositol phosphates, isoflurophate, isosorbide, lachesine, levobunolol, levocabastine, lidocaine, lignocaine, medrysone, mepivacaine, methacholine, methazolamide, naphazoline hydrochloride, natamycin, neomycin sulfate, neostigmine, noradrenaline, ofloxacin, oxybuprocaine, oxymetazolin, oxyphenonium, pheniramine maleate, phenylephrine hydrochloride, phosphatidylinositol phosphates, physostigmine, pilocarpine hydrochloride, polymyxin B sulfates, prednisolone sodium phosphate, proparacaine hydrochloride, proxymethacaine, pyrilamine maleate, scopolamine hydrobromide, sorbinil, sulfacetamide, sulfisoxazole disolamine, tamoxifen, tetracaine hydrochloride, tetracycline, tetrahydrozoline hydrochloride, timolol maleate and hemihydrate, trifluridine, tropicamide, vidarabine, and salts and other ophthalmically acceptable salts, and mixtures thereof.

[0030] Preferred pharmaceutically active compounds are selected from the group of betaxolol hydrochloride, chloramphenicol, diclofenac, dipivefrin hydrochloride, ephedrine, epinephrine bitartrate, erythromycin, gentamycin sulfate, indomethacin, levobunolol, levocabastine, ofloxacin, pilocarpine hydrochloride, polymyxin B sulfates, prednisolone sodium phosphate, tetracycline and other ophthalmically acceptable salts thereof.

[0031] More preferred pharmaceutically active compounds are selected from the group of, betaxolol hydrochloride, chloramphenicol, diclofenac, dipivefrin hydrochloride, levobunolol, levocabastine, pilocarpine hydrochloride and other ophthalmically acceptable salts thereof.

[0032] A cyclodextrin as is referred to within the present invention is either an α-, β- or γ-cyclodextrin itself, a derivative thereof, e.g. a partially etherified derivative as e.g. a hydroxyalkyl ether or a mixture thereof. A random cyclodextrin does not automatically form an inclusion complex with any random pharmaceutical compound. Therefore the present invention relates preferably to such a cyclodextrin that meets the cavity needs of a pharmaceutical compound used. This may typically be accomplished by using either an α-, β- or γ-cyclodextrin itself or an appropriately substituted, α-,

β- or γ- cyclodextrin or a mixture of the aforementioned cyclodextrins.

[0033] Appropriately substituted α-, β- or γ-cyclodextrins are e.g. alkylated, hydroxyalkylated, carboxyalkylated or alkyloxycarbonyl-alkylated derivatives. Other typical examples are carbohydrate derivatives of cyclodextrins such as mono- or diglycosyl-α-, β- or γ-cyclodextrin, mono- or dimaltosyl-α-, β- or γ- cyclodextrin or panosyl-cyclodextrin. Another parameter which describes the substitution pattern of a cyclodextrin is the degree of substitution (d.s.). The d.s. is another parameter in the determination of the cavity size of a cyclodextrin. A cyclodextrin is composed of several glucose units which have three free hydroxy groups per glucose. Accordingly the d.s. may vary from 0.125 up to 3. In the latter case all free (γ-cyclodextrin has 24) hydroxy groups may be substituted, while in the former case only 1 may be substituted. A minimal d.s. is preferred when γ-cyclodextrin is used as a solubilizer of a pharmaceutically active drug (see EP 197 571). A higher d.s. is e.g. preferred in technical applications and e.g. enzymes. In the latter instance, the higher d.s. causes that also those hydroxy groups are functionalized which are located in the cavity of the γ-cyclodextrin. Consequently the diameter of the cavity is decreased. By selecting the appropriate d.s. and the appropriate substituents the size of the cavity can be adapted in order to obtain the optimum space required for a certain molecule to appropriately fit into the cavity of the cyclodextrin. Preferably the d.s. may vary from 0.125 to 1.5 and more preferably from 0.125 to 0.5.

[0034] Preferred cyclodextrins are α-, β- and γ-cyclodextrin, derivatives and mixtures thereof.

[0035] Other preferred cyclodextrins are mono-, diglycosyl-β- cyclodextrin, mono- and dimaltosyl-β-cyclodextrin.

[0036] Strongly preferred cyclodextrins are hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, dimethyl-β-cyclodextrin and dimethyl-γ-cyclodextrin.

[0037] The amount of a cyclodextrin used in accordance with the present invention may range from 0.01 - 20 % by weight, preferably from 0.1 - 15 % by weight and more preferably from 1 - 10 % by weight.

[0038] The very small number of quaternary ammonium salts useful in eye medicaments for preservation is in contrast with the large number of known quaternary ammonium salts ("quats") which are employed for preservation in other fields. This is clearly restricted by the ocular tolerability of an addressed preservative. Accordingly in the present invention quaternary ammonium salts with excellent ocular tolerability are highly preferred.

[0039] The quaternary ammonium salts useful in accordance with the present invention may be selected from a wide variety of especially ophthalmically acceptable salts and are in particular selected from sepazonium chloride, cetyltrimethylammonium bromide (cetrimide), cetylpyridinium chloride, benzoxonium chloride, benzethonium chloride, domiphen bromide (Bradosol®) and benzalkonium chloride

[0040] A preferred preservative useful in accordance with the present invention is benzalkonium chloride which has the following structure: N-benzyl-N-(C_8-C_{18}alkyl)-N,N-dimethylammonium chloride.

[0041] The amount of a quaternary ammonium salt used in accordance with the present invention may range from 0.00001 % by weight to 0.5 % by weight, preferably from 0.0001 % by weight to 0.1 % by weight and more preferably from 0.001 % weight to 0.05 % by weight.

[0042] Alkylene glycol useful in accordance with the present invention may be selected from a wide variety of alkylene glycols wherein alkylene has up to and including 18 C-atoms and is linear, cyclic or branched.

[0043] Examples of linear alkylene are methylene, 1,2-ethylene, 1,3-propylene, 1,4-butylene, 1,5-pentylene, 1,6-hexylene, 1,7-heptylene or 1,11-undecylene.

[0044] Examples of cyclic alkylene groups are 1,2-cis or trans cyclopropylene, 1,2- or 1,3- cis or trans cyclobutylene, the regio- and stereo-isomers of cyclopentylene, cyclohexylene or cycloheptylene.

[0045] Branched alkylene groups are for example 2-methyl-1,3-propylene, 2,2-dimethyl-1,4-butylene, 3-ethyl-2,4-butylene, 2, 3, 4-trimethyl-1,5-pentylene, 3-isopropy-1,6-hexylene or 3-methyl-1,7-heptylene.

[0046] A preferred alkylene glycol in accordance with the present invention is selected from an alkylene glycol with up to and including 7 C-atoms and is either linear, branched or cyclic. A more preferred alkylene glycol is selected from linear, branched and cyclic alkylene glycol having 3 to 7 C-atoms.

[0047] Highly preferred alkylene glycols are for example 1,2- or 1,3-propylene glycol, 1,2-, 1,3-, 2,3- or 1,4-butylene glycol or all isomers of pentylene, hexylene and heptylene glycol. Most preferred is propylene glycol.

[0048] The amount of an alkylene glycol used in accordance with the present invention may range from 0.01 - 20 % by weight, preferably from 0.1- 15 % by weight and more preferably from 1 - 10 % by weight.

[0049] Alkyl means throughout this invention an alkyl group having up to and including 18, more preferably 12 and even more preferably 7 C-atoms, and is either a linear or a branched alkyl group.

[0050] Examples for alkyl are methyl, ethyl, propyl, butyl, iso-propyl, t-butyl, neo-pentyl, octyl or dodecyl.

[0051] The term weight % used herein refers to the weight % of the total weight of an addressed composition or object.

[0052] The expression propylene glycol as used herein refers to 1,2-propylene glycol, unless specified differently.

[0053] Typical experimental procedures which illustrate the present invention, are described below.

Example 1, eve drop formulations				
diclofenac potassium	1.00 mg	0.5 mg	-	-
diclofenac sodium	-	-	1.00 mg	0.5 mg
tyloxapol USP	1.00 mg	1.00 mg	1.00 mg	1.00 mg
tromethamine	1.00 mg	1.00 mg	1.00 mg	1.00 mg
propylene glycol	19.0 mg	19.0 mg	19.0 mg	19.0 mg
hydroxypropyl-γ-cyclodextrin	20.0 mg	20.0 mg	20.0 mg	20.0 mg
disodium edetate	1.00 mg	1.00 mg	1.00 mg	1.00 mg
benzalkonium chloride	0.05 mg	0.05 mg	0.05 mg	0.05 mg
hydrochloric acid 1N	qs	qs	qs	qs
water for injections ad	1.00 ml	1.00 ml	1.00 ml	1.00 ml
pH	7.96	7.98	7.96	7.98
osmolality (mOsmol)	305	303	305	303

Example 2, eye gel formulations		
diclofenac potassium	1.00 mg	-
diclofenac sodium	-	1.00 mg
tyloxapol USP	1.00 mg	1.00 mg
tromethamine	6.50 mg	6.50 mg
propylene glycol	19.0 mg	19.0 mg
hydroxypropyl-γ-cyclodextrin	20.0 mg	20.0 mg
disodium edetate	1.00 mg	1.00 mg
benzalkonium chloride	0.05 mg	0.05 mg
carbopol 980	3.50 mg	3.50 mg
water for injections ad	1.00 ml	1.00 ml
pH	8.00	8.00
osmolality (mOsmol)	308	308
viscosity (mPa s)	380	380

Example 3, eye drop formulations				
diclofenac potassium	1.00 mg	0.5 mg	-	-
diclofenac sodium	-	-	1.00 mg	0.5 mg
tromethamine	1.00 mg	1.00 mg	1.00 mg	1.00 mg
propylene glycol	20.5 mg	20.5 mg	20.5 mg	20.5 mg
hydroxypropyl-γ-cyclodextrin	20.0 mg	20.0 mg	20.0 mg	20.0 mg
disodium edetate	1.00 mg	1.00 mg	1.00 mg	1.00 mg
benzalkonium chloride	0.06 mg	0.06 mg	0.06 mg	0.06 mg
hydrochloric acid 1 N	qs	qs	qs	qs

(continued)

Example 3, eye drop formulations				
water for injections ad	1.00 ml	1.00 ml	1.00 ml	1.00 ml
pH	7.90	7.90	7.90	7.90
osmolality (mOsmol)	296	296	296	296

Example 4; comparison of eye drop compositions with respect to their preservative efficacy according to the recommendations of the European Pharmacopoeia (Ph. Eur.).					
propylene glycol	20.0 mg	20.0 mg			20.0 mg
tromethamine	0.5 mg	0.5 mg	0.5 mg	0.5 mg	
NaH_2PO_4 2 H_2O					0.6 mg
Na_2HPO_4 12 H_2O					6.0 mg
hydroxypropyl-β-cyclodextrin	20.0 mg	20.0 mg	20.0 mg		20.0 mg
disodium edetate	1.00 mg	1.00 mg	1.00 mg	1.00 mg	1.00 mg
benzalkonium chloride	0.1 mg		0.1 mg	0.1 mg	0.1 mg
sodium chloride			8.5 mg	8.7 mg	
hydrochloric acid 10%	0.6 mg	0.2 mg	0.3 mg	0.1 mg	
water for injections ad	1.00 ml	1.00 ml	1.00 ml	1.00 ml	1.00 ml
pH	7.49	7.32	7.38	7.36	7.30
osmolality (mOsmol)	308	306	302	305	348
preservative efficacy Ph. Eur.	B	r.n.m.	r.n.m.	A	B

A: Meets the criteria A recommended in the European Pharmacopoeia

B: Meets the criteria B recommended in the European Pharmacopoeia

r.n.m.: Recommendations of the European Pharmacopoeia not met.

[0054] The European Pharmacopoeia (Ph. Eur.) describes an efficacy test for antimicrobial preservation. Accordingly a preserved solution is inoculated with micro-organisms, characterized in that 10^5 to 10^6 micro-organisms are contained in one milliliter of the challenged preparation. The inoculum used does not exceed 1% of the total volume of said preparation. Five micro-organisms are used for the challenge, each separately namely, pseudomonas aeruginosa, staphylococcus aureus, candida albicans and aspergillus niger. The challenged solutions are kept at room temperature and protected from light. At regular time intervals samples are removed and the number of viable micro-organisms is determined either by plate count or by membrane filtration. For ophthalmic preparations the European Pharmacopoeia recommends criteria "A", which require e.g. that the bacterial micro-organisms are reduced by a factor of 1000, 24 hours after the challenge. Criteria "B" are still acceptable according to the recommendations of the European Pharmacopoeia, and require e.g. that the bacterial micro-organisms are reduced by a factor of 10, 24 hours after the challenge (for details refer to the European Pharmacopoeia, 1994). Accordingly, whenever the preservative efficacy rec-

ommendations of the European Pharmacopoeia are referred to herein, this relates to the 1994 version.

Example 5, eye drop formulations containing a pharmaceutically active compound. Preservative efficacy is determined as in example 4.					
diclofenac potassium	1.00 mg	1.00 mg	1.00 mg	1.00 mg	1.00 mg
propylene glycol	20.0 mg	20.0 mg	20.0 mg	20.0 mg	20.0 mg
tromethamine	0.5 mg	0.5 mg	0.5 mg	0.5 mg	0.5 mg
hydroxypropyl-β-cyclodextrin	20.0 mg				
hydroxypropyl-γ-cyclodextrin		20.0 mg			
α-cyclodextrin			20.0 mg		
β-cyclodextrin				15.0 mg	
γ-cyclodextrin					20.0 mg
disodium edetate	1.00 mg	1.00 mg	1.00 mg	1.00 mg	1.00 mg
benzalkonium chloride	0.1 mg	0.1 mg	0.1 mg	0.1 mg	0.1 mg
hydrochloric acid 10 %	0.4 mg	0.5 mg		0.4 mg	0.3 mg
water for injections ad	1.00 ml	1.00 ml	1.00 ml	1.00 ml	1.00 ml
pH	7.40	7.41	7.44	7.41	7.34
osmolality (mOsmol)	307	315	307	302	330
preservative efficacy Ph. Eur	B	A	B	B	A

Example 6, eye drop formulation	
diclofenac sodium	1.00 mg
propylene glycol	20.0 mg
tromethamine	0.5 mg
hydroxypropyl-β-cyclodextrin	20.0 mg
disodium edetate	1.00 mg
benzalkonium chloride	0.1 mg
hydrochloric acid 10 %	0.3 mg
water for injections ad	1.00 ml
pH	7.45
osmolality (mOsmol)	312
preservative efficacy Ph. Eur	B

Example 7; eye drop formulations, not meeting the criteria as recommended in the European Pharmacopoeia. Preservative efficacy is determined as in example 4.					
diclofenac potassium	1.00 mg	1.00 mg	1.00 mg	1.00 mg	1.00 mg
Cremophor EL	20.0 mg	20.0 mg	20.0 mg	20.0 mg	20.0 mg
tromethamine	0.5 mg	0.5 mg	0.5 mg	0.5 mg	0.5 mg

(continued)

Example 7; eye drop formulations, not meeting the criteria as recommended in the European Pharmacopoeia. Preservative efficacy is determined as in example 4.					
hydroxypropyl-β-cyclodextrin	20.0 mg				
hydroxypropyl-γ-cyclodextrin		20.0 mg			
α-cyclodextrin			20.0 mg		
β-cyclodextrin				15.0 mg	
γ-cyclodextrin					20.0 mg
disodium edetate	1.00 mg	1.00 mg	1.00 mg	1.00 mg	1.00 mg
benzalkonium chloride	0.1 mg	0.1 mg	0.1 mg	0.1 mg	0.1 mg
sodium chloride	8.00 mg	8.00 mg	8.00 mg	8.00 mg	8.00 mg
hydrochloric acid 10 %	0.4 mg	0.4 mg		0.3 mg	0.2 mg
water for injections ad	1.00 ml	1.00 ml	1.00 ml	1.00 ml	1.00 ml
pH	7.44	7.44	7.49	7.47	7.44
osmolality (mOsmol)	308	309	301	311	296
preservative efficacy Ph. Eur	r.n.m.	r.n.m.	r.n.m.	r.n.m.	r.n.m.

Claims

1. A preserved ophthalmic composition, comprising a cyclodextrin, a quaternary ammonium salt, an alkylene glycol and a pharmaceutically active compound.

2. A preserved ophthalmic composition according to claim 1, further comprising a carrier.

3. A preserved ophthalmic composition according to claim 1, further comprising one or more of an excipient selected from the group consisting of buffers, solubilizers, complexing agents, stabilizers, preservatives different from quaternary ammonium salts, tonicity enhancing agents and fillers.

4. A preserved ophthalmic composition according to claim 1, further comprising a carrier and a solubilizer.

5. A preserved ophthalmic composition according to claim 1, further comprising a carrier, a solubilizer and a complexing agent.

6. A preserved ophthalmic composition according to claims 1 to 5, wherein the composition meets the preservative efficacy recommendations of the European Pharmacopoeia (1994 version).

7. A preserved ophthalmic composition according to claims 1 to 5, wherein the quaternary ammonium salt is selected from sepazonium chloride, cetyltrimethylammonium bromide (cetrimide), cetylpyridinium chloride, benzoxonium chloride, benzethonium chloride, domiphen bromide (Bradosol®) and benzalkonium chloride.

8. A preserved ophthalmic composition according to claims 1 to 5, wherein the cyclodextrin is selected from α-, β- and γ-cyclodextrin, derivatives and mixtures thereof.

9. A composition according to claim 8, wherein the cyclodextrin is selected from mono-, diglycosyl-β- cyclodextrin, mono-, dimaltosyl-β-cyclodextrin, hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, dimethyl-β- cyclodextrin and dimethyl-γ-cyclodextrin.

10. A preserved ophthalmic composition according to claims 1 to 5, wherein the alkylene glykol is selected from linear, branched and cyclic alkylene glycol having up to 7 C-atoms.

11. A composition according to claim 10, wherein the alkylene glykol is selected from linear, branched and cyclic alkylene glycol having 3 to 7 C-atoms.

12. A preserved ophthalmic composition according to claim 2, wherein the carrier is selected from water, cellulose derivatives, such as methylcellulose, alkali metal salts of carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, methylhydroxypropylcellulose and hydroxypropylcellulose, neutral Carbopol and mixtures thereof.

13. A preserved ophthalmic composition according to claims 3 or 4, wherein the solubilizer is selected from tyloxapol, fatty acid glycerol polyethylene glycol esters, fatty acid polyethylene glycol esters, polyethylene glycols, glycerol ethers and mixtures of those compounds.

14. A preserved ophthalmic composition according to claims 3 or 5, wherein the complexing agent is EDTA or disodium EDTA.

15. A preserved ophthalmic composition according to claim 1, wherein the pharmaceutically active compound is selected from the group of betaxolol hydrochloride, chloramphenicol, diclofenac, dipivefrin hydrochloride, levobunolol, levocabastine, pilocarpine hydrochloride and salts or other ophthalmically acceptable salts thereof.

Patentansprüche

1. Konservierte ophthalmische Zusammensetzung, die ein Cyclodextrin, ein quarternäres Ammoniumsalz, ein Alkylenglykol und eine pharmazeutisch wirksame Verbindung umfasst.

2. Konservierte ophthalmische Zusammensetzung nach Anspruch 1, die zusätzlich einen Träger umfasst.

3. Konservierte ophthalmische Zusammensetzung nach Anspruch 1, die einen oder mehrere Zuschlagstoffe umfasst, ausgewählt aus Puffern, Lösevermittlern, Komplexbildnern, Stabilisatoren, anderen Konservierungsmitteln als quarternäre Ammoniumsalze, tonizitätserhöhenden Mitteln und Füllstoffen.

4. Konservierte ophthalmische Zusammensetzung nach Anspruch 1, die zusätzlich einen Träger und einen Lösevermittler umfasst.

5. Konservierte ophthalmische Zusammensetzung nach Anspruch 1, die zusätzlich einen Träger, einen Lösevermittler und einen Komplexbildner umfasst.

6. Konservierte ophthalmische Zusammensetzung nach Anspruch 1 bis 5, deren Zusammensetzung den Empfehlungen über die Konservierungswirkung der Europäischen Pharmacopoeia (Version 1994) entspricht.

7. Konservierte ophthalmische Zusammensetzung nach Anspruch 1 bis 5, in der das quarternäre Ammoniumsalz aus Sepazoniumchlorid, Cetyltrimethylammoniumbromid, (Cetrimid), Cetylpyridiniumchlorid, Benzoxoniumchlorid, Benzethoniumchlorid, Domiphenbromid (Bradosol®) und Benzalkoniumchlorid ausgewählt ist.

8. Konservierte ophthalmische Zusammensetzung nach Anspruch 1 bis 5, in der das Cyclodextrin aus α-, β- und γ-Cyclodextrin, Derivaten und Gemischen davon, ausgewählt ist.

9. Zusammensetzung nach Anspruch 8, in der das Cyclodextrin aus Mono-, Diglycosyl-β-cyclodextrin, Mono-, Dimaltosyl-β-cyclodextrin, Hydroxypropyl-β-cyclodextrin, Hydroxypropyl-γ-cylodextrin, Dimethyl-β-cyclodextrin und

Dimethyl-y-cyclodextrin ausgewählt ist.

10. Konservierte ophthalmische Zusammensetzung nach Anspruch 1 bis 5, in der das Alkylenglykol aus linearen, verzweigten und zyklischen Alkylenglykolen mit bis zu 7 C-Atomen ausgewählt ist.

11. Zusammensetzung nach Anspruch 10, in der das Alkylenglykol aus linearen, verzweigten und zyklischen Alkylenglykolen mit 3 bis 7 C-Atomen ausgewählt ist.

12. Konservierte ophthalmische Zusammensetzung nach Anspruch 2, in welcher der Träger aus Wasser, Cellulosederivaten, wie Methylcellulose; Alkalimetallsalzen von Carboxymethylcellulose; Hydroxymethylcellulose, Hydroxyethylcellulose, Methylhydroxypropylcellulose und Hydroxypropylcellulose; neutralem Carbopol und Gemischen dieser Verbindungen ausgewählt ist.

13. Konservierte ophthalmische Zusammensetzung nach Anspruch 3 oder 4, in welcher der Lösevermittler aus Tyloxapol, Fettsäure-Glycerin-Polyethylenglykolester, Fettsäure-Polyethylengylkolester, Polyethylenglykolen, Glycerinethern und Gemischen dieser Verbindungen ausgewählt ist.

14. Konservierte ophthalmische Zusammensetzung nach Anspruch 3 oder 5, in welcher der Komplexbildner EDTA oder Dinatrium-EDTA ist.

15. Konservierte ophthalmische Zusammensetzung nach Anspruch 1, in der die pharmazeutisch wirksame Verbindung aus Betaxololhydrochlorid, Chloramphenicol, Diclofenac, Dipivefrinhydrochlorid, Levobunolol, Levocabastin, Pilocarpinhydrochlorid und Salzen oder anderen ophthalmisch verträglichen Salzen davon ausgewählt ist.

Revendications

1. Une composition ophtalmique conservée, comprenant une cyclodextrine, un sel d'ammonium quaternaire, un alkylèneglycol et un composé pharmaceutiquement actif.

2. Une composition ophtalmique conservée selon la revendication 1, comprenant en outre un véhicule.

3. Une composition ophtalmique conservée selon la revendication 1, comprenant en outre un ou plusieurs excipients choisis parmi le groupe comprenant des tampons, des solubilisants, des agents complexants, des stabilisants, des conservateurs différents des sels d'ammonium quaternaires, des agents augmentant la tonicité et des charges.

4. Une composition ophtalmique conservée selon la revendication 1, comprenant en outre un véhicule et un solubilisant.

5. Une composition ophtalmique conservée selon la revendication 1, comprenant en outre un véhicule, un solubilisant et un agent complexant.

6. Une composition ophtalmique conservée selon les revendications 1 à 5, où la composition est conforme aux recommandations d'efficacité de conservation de la Pharmacopée européenne (version de 1994).

7. Une composition ophtalmique conservée selon les revendications 1 à 5, où le sel d'ammonium quaternaire est choisi parmi le chlorure de sépazonium, le bromure de cétyltriméthylammonium (cétrimide), le chlorure de cétylpyridinium, le chlorure de benzoxonium, le chlorure de benzéthonium, le bromure de domiphène (Bradosol®) et le chlorure de benzalkonium.

8. Une composition ophtalmique conservée selon les revendications 1 à 5, où la cyclodextrine est choisie parmi l'α-, la β- et la γ-cyclodextrine, leurs dérivés et leurs mélanges.

9. Une composition selon la revendication 8, où la cyclodextrine est choisie parmi la mono-, diglycosyl-β-cyclodextrine, la mono-, dimaltosyl-β-cyclodextrine, l'hydroxypropyl-β-cyclodextrine, l'hydroxypropyl-γ-cyclodextrine, la diméthyl-β-cyclodextrine et la diméthyl-γ-cyclodextrine.

10. Une composition ophtalmique conservée selon les revendications 1 à 5, où l'alkylèneglycol est choisi parmi un

alkylèneglycol linéaire, ramifié et cyclique ayant jusqu'à 7 atomes de carbone.

11. Une composition selon la revendication 10, où l'alkylèneglycol est choisi parmi un alkylèneglycol linéaire, ramifié et cyclique ayant de 3 à 7 atomes de carbone.

12. Une composition ophtalmique conservée selon la revendication 2, où le véhicule est choisi parmi l'eau, les dérivés de la cellulose tels que la méthylcellulose, les sels de métaux alcalins de la carboxyméthylcellulose, de l'hydroxyméthylcellulose, de l'hydroxyéthylcellulose, de la méthylhydroxypropylcellulose et de l'hydroxypropylcellulose, le Carbopol neutre et leurs mélanges.

13. Une composition ophtalmique conservée selon les revendications 3 ou 4, où le solubilisant est choisi parmi le tyloxapol, les esters d'acides gras du glycérol et du polyéthylèneglycol, les esters d'acides gras du polyéthylèneglycol, les polyéthylèneglycols, les éthers du glycérol et les mélanges de ces composés.

14. Une composition ophtalmique conservée selon les revendications 3 ou 5, où l'agent complexant est l'EDTA ou l'EDTA disodique.

15. Une composition ophtalmique conservée selon la revendication 1, où le composé pharmaceutiquement actif est choisi parmi le groupe du chlorhydrate de bétaxolol, le chloramphénicol, le diclofénac, le chlorhydrate de dipivéfrine, le lévobunolol, la lévocabastine, le chlorhydrate de pilocarpine et leurs sels ou d'autres de leurs sels ophtalmiquement acceptables.

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(54) **PHARMACEUTICAL COMPOSITIONS COMPRISING A BASIC DRUG, A CYCLODEXTRIN, A POLYMER AND AN ACID**

ARZNEIMITTEL ENTHALTEND EINEN BASISCHEN WIRKSTOFF, EIN CYCLODEXTRIN, EIN POLYMER UND EINE SAURE

COMPOSITIONS PHARMACEUTIQUES COMPRENANT UN MEDICAMENT BASIQUE, UNE CYCLODEXTRINE, UN POLYMERE ET UN ACIDE

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Description

[0001] This invention relates to pharmaceutical compositions and dosage forms providing improved drug release and uptake on administration into externally voiding body cavities (e.g. the gi tract) or on topical administration, for acid solubilized basic drug compounds.

[0002] Many drug compounds, while possessing desired therapeutic properties, are used inefficiently due to their poor water solubilities. Thus for example where such compounds are administered orally, only a small fraction of the drug is taken up into the blood during transit of the gi tract. As a result, to achieve adequate drug uptake it may be necessary to administer high doses of the drug compound, to prolong the period of drug administration or to make frequent administrations of the drug compound. Indeed, the poor solubility and hence poor bioavailability of a drug may cause an alternative drug, perhaps one with undesired side effects or one which requires invasive administration (e.g. by injection or infusion), to be used in place of the poorly soluble drug.

[0003] One approach to poor solubility is to derivatise the drug molecule to introduce water solubilizing groups, e.g. ionic groups such as carboxyl groups or non-ionic groups such as polyhydroxyalkyl groups, so as to produce a more soluble derivative. This approach however is not always successful as it may not be possible to maintain adequately high therapeutic efficacy and adequately low toxicity or other side effects. Thus one example of a poorly water soluble drug which has not been superseded by a solubilized derivative is the antifungal agent itraconazole.

Attempts have therefore been made to enhance the uptake of drugs such as itraconazole by increasing the surface area of the drug compound exposed to saliva or gastric fluid, and hence promote dissolution of the drug compound, by thinly coating the drug compound onto essentially inert carrier particles, e.g. sugar beads. This however has the drawback that the volume of solid composition required to administer a given quantity of the drug compound is quite high since the carrier contributes significantly to the overall administration volume. Since administration of large volume capsules or tablets, or of large quantities of smaller volume capsules or tablets, provides difficulties for the patient, the drawbacks of this approach are obvious.

[0004] Yet another approach has been to administer the drug compound in the form of a solution of the drug compound and a drug complexing agent such as a cyclodextrin. This approach has limitations also in that the dosage volume is constrained by the solubilizing power of the complexing agent, readily unitized solid dosage forms can not be used, and there is no gradual release of the drug compound for biological uptake.

[0005] EP-A-0,689,844 describes complexes of vinpocetine formed with cyclodextrin and pharmaceutical compositions containing them.

[0006] WO 94/12217 relates to pharmaceutical compositions comprising a therapeutic agent, a carboxy-containing polymer and cyclodextrin in an aqueous medium.

[0007] However, we have now found that by combining such drug compounds with a cyclodextrin, a water-soluble acid from 35 to 95 % by weight and a water-soluble organic polymer, an administration form may be produced which surprisingly improves the biological uptake of the drug compound, in particular a form which can surprisingly improve the time profile for the drug content of the plasma of the patient (*i.e.* the pharmacokinetic profile defined by such parameters as AUC, t_{max}, C_{max}, etc.).

[0008] Thus viewed from one aspect the invention provides a pharmaceutical composition comprising a no more than sparingly water-soluble basic drug compound, a cyclodextrin, a physiologically tolerable water-soluble acid, and a physiologically tolerable water-soluble organic polymer characterized in that it comprises from 35 to 95 % by weight of acid relative to the total weight of cyclodextrin, drug compound, organic polymer and acid.

Viewed from a further aspect the invention provides the use of a no more than sparingly water-soluble basic drug compound, a cyclodextrin, a physiologically tolerable water-soluble acid from 35 to 95 % by weight (relative to the total weight of cyclodextrin, drug compound, organic polymer and acid), and a physiologically tolerable water-soluble organic polymer for the manufacture of a pharmaceutical composition according to the invention for use in a method of therapy or diagnosis of the human or non-human animal (e.g. mammalian, reptilian or avian) body.

[0009] The compositions of the invention may if desired be aqueous, but in general will preferably be substantially water-free, e.g. containing up to 3% by weight, preferably less than 1% by weight water, and most preferably less than 0.5% water, but may be mixed with water immediately before administration or may be coated and dispersed in an aqueous medium whereby the coating is only broken down after administration. Such aqueous compositions are deemed to fall within the scope of the invention.

[0010] Depending on the selection of components, the compositions of the invention may be liquid, solid or semi-solid - e.g. gel-like. Preferably the compositions are non-freeflowing at ambient temperature (e.g. 21°C), other than as free flowing particulates. Thus the compositions at ambient temperature are preferably solids or semi-solids or, less preferably, highly viscous fluids.

[0011] In the compositions of the invention the drug compound, acid, cyclodextrin and organic polymer are intimately admixed.

[0012] Thus where the composition is particulate, the acid, drug compound, cyclodextrin and organic polymer are

mixed together within the particles (e.g. at the molecular level following solvent removal from a solution of these components). Granulate mixtures where individual particles do not contain all four components, or have cores of one or more components coated with other components are not preferred. This intimate admixture is important since the effects of the components are complimentary at the microscopic level during dissolution of the compositions of the invention.

[0013] Preferably, all components are dispersed so as to form a system that is chemically and physically uniform or homogenous throughout, or consists of one phase as defined in thermodynamics ; such a dispersion will be called a glass thermoplastic phase or system hereinafter. The components of the glass thermoplastic system are readily bioavalaible to the organisms to which they are administered. This advantage can probably be explained by the ease with which said glass thermoplastic system can form liquid solutions when contacted with a body liquid such as gastric juice. The case of dissolution may be attributed at least in part to the fact that the energy required for dissolution of the components from a glass thermoplastic system is less than that required for the dissolution of components from a crystalline or microcrystalline solid phase.

[0014] As the cyclodextrin in the compositions of the invention, there may be used any of the physiologically tolerable water-soluble substituted or unsubstituted cyclodextrins or physiologically tolerable derivatives thereof, e.g. α-, β- or γ-cyclodextrins or derivatives thereof, in particular derivatives wherein one or more of the hydroxy groups are substituted, e.g. by alkyl, hydroxyalkyl, carboxyalkyl, alkylcarbonyl, carboxyalkoxyalkyl, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl or hydroxy-(mono or polyalkoxy)alkyl groups, wherein each alkyl or alkylene moiety preferably contains up to six carbons.

[0015] Substituted cyclodextrins which can be used in the invention include polyethers, e.g. as described in US Patent 3,459,731. In general, to produce these, unstibstituted cyclodextrins are reacted with an alkylene oxide, preferably under superatmospheric pressure and at an elevated temperature, in the presence of an alkaline catalyst. Since a hydroxy moiety of the cyclodextrin can be substituted by an alkylene oxide which itself can react with yet another molecule of alkylene oxide, the average molar substitution (MS) is used as a measure of the average number of moles of the substituting agent per glucose unit. The MS can be greater than 3 and theoretically has no limit. In the cyclodextrin derivatives for use in the compositions according to the present invention the M.S. is conveniently in the range of 0.125 to 10, in particular of 0.3 to 3, or from 0.3 to 1.5. Preferably the M.S. ranges from about 0.3 to about 0.8, in particular from about 0.35 to about 0.5 and most particularly it is about 0.4. M.S. values determined by NMR or IR preferably range from 0.3 to 1, in particular from 0.55 to 0.75.

[0016] Further examples of substituted cyclodextrins include ethers wherein the hydrogen of one or more cyclodextrin hydroxy groups is replaced by C_{1-6}alkyl, hydroxyC_{1-6}-alkyl, carboxy-C_{1-6}alkyl or C_{1-6}alkyloxycarbonyl-C_{1-6}alkyl groups or mixed ethers thereof. In particular such substituted cyclodextrins are ethers wherein the hydrogen of one or more cyclodextrin hydroxy groups is replaced by C_{1-3}alkyl, hydroxy-C_{2-4}alkyl or carboxy-C_{1-2}alkyl or more particularly by methyl, ethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, carboxymethyl or carboxyethyl.

[0017] In the foregoing definitions, the term "C_{1-6}alkyl" is meant to include straight and branched saturated hydrocarbon radicals, having from 1 to 6 carbon atoms, such as methyl, ethyl 1-methylethyl, 1,1-dimethylethyl, propyl, 2-methylpropyl, butyl, pentyl, hexyl and the like.

[0018] Such ethers can be prepared by reacting a cyclodextrin with an appropriate O-alkylating agent or a mixture of such agents in a concentration selected such that the desired cyclodextrin ether is obtained. The reaction is preferably conducted in a solvent in the presence of a base. With such ethers, the degree on substitution (DS) is the average number of substituted hydroxy functions per glucose unit, the DS being thus 3 or less.

[0019] In the cyclodextrin derivatives for use in the compositions according to the present invention, the DS preferably is in the range of 0.125 to 3, in particular 0.3 to 2, more particularly 0.3 to 1, and the MS is in the range of 0.125 to 10, in particular 0.3 to 3 and more particularly 0.3 to 1.5.

[0020] Of particular utility in the present invention are the β-cyclodextrin ethers, e.g. dimethyl-β-cyclodextrin as described in Drugs of the Future, Vol. 9, No. 8, p. 577-578 by M. Nogradi (1984) and polyethers, e.g. hydroxypropyl-β-cyclodextrin and hydroxyethyl-β-cyclodextrin. Such alkyl ethers may for example be methyl ethers with a degree of substitution of about 0.125 to 3, e.g. about 0.3 to 2. Such a hydroxypropyl cyclodextrin may for example he formed from the reaction between β-cyclodextrin and propylene oxide and may have a MS value of about 0.125 to 10, e.g. about 0.3 to 3.

[0021] Especially suitable cyclodextrins are β-CD, 2,6-dimethyl-β-CD, 2-hydroxyethyl-β-CD. 2-hydroxyethyl-γ-CD, 2-hydroxypropyl-γ-CD and (2-carboxymethoxy)propyl-β-CD, and in particular 2-hydroxypropyl-β-CD.

[0022] Besides simple cyclodextrins, branched cyclodextrins and cyclodextrin polymers may also be used.

[0023] Other cyclodextrins are described for example in Chemical and Pharmaceutical Bulletin 28: 1552-1558 (1980), Yakugyo Jiho No. 6452 (28 March 1983), Angew. Chem. Int. Ed. Engl. 19: 344-362 (1980), US-3,459,731, EP-A-0,149,197. EP-A-0,197,571, US-4,535,152, WO-90/12035 and GB-2,189,245. Other references describing cyclodextrins for use in the compositions according to the present invention, and which provide a guide for the preparation, purification and analysis of cyclodextrins include the following: "Cyclodextrin Technology" by József Szejtli, Kluwer

Academic Publishers (1988) in the chapter Cyclodextrins in Pharmaceuticals; "Cyclodextrin Chemistry" by M.L. Bender et al., Springer-Verlag, Berlin (1978); "Advances in Carbohydrate Chemistry", Vol. 12, Ed. by M.L. Wolfrom. Academic Press, New York in the chapter The Schardinger Dextrins by Dexter French at p. 189-260: "Cyclodextrins and their Inclusion Complexes" by J. Szejtli, Akademiai Kiado, Budapest, Hungary (1982): I. Tabushi in Acc. Chem. Research, 1982, 15, p. 66-72; W. Sanger, Angewandte Chemie, 92, p. 343-361 (1981): A.P. Croft and R.A. Bartsch in Tetrahedron, 39. p. 1417-1474 (1983); Irie et al. Pharmaceutical Research, 5, p. 713-716, (1988): Pitha et al. Int. J. Pharm. 29, 73, (1986); DE 3,118.218; DE-3,317,064: EP-A-94,157; US-4,659,696; and US-4,383,992.

[0024] More recent examples of substituted cyclodextrins include sulfobutylcyclodextrins (US-5,134,127-A). Their use is also envisaged in the present invention.

[0025] The cyclodextrin used is preferably a β-cyclodextrin, in particular hydroxypropyl-β-cyclodextrin. The most preferred cyclodextrin derivative for use in the compositions of the present invention is hydroxypropyl-β-cyclodextrin having a M.S. in the range of from 0.35 to 0.50 and containing less than 1.5% unsubstituted β-cyclodextrin. M.S. values determined by NMR or IR preferably range from 0.55 to 0.75.

[0026] Nevertheless, the choice of cyclodextrin may be directed by the ability of the selected drug compound to be complexed by a particular cyclodextrin - thus the cyclodextrins with greater affinity for the particular drug compound may be preferred.

[0027] In the compositions of the invention, the cyclodextrin is preferably present at 5 to 70% by weight, more preferably 8 to 55%, most preferably 10 to 45% by weight (relative to the total weight of cyclodextrin, acid, organic polymer and drug). The quantity of cyclodextrin used however will generally be dependent on the quantity of drug and the molar ratio of cyclodextrin to drug will preferably lie in the range 100:1 to 1:5, especially 50:1 to 1:2, more especially 10:1 to 1:1.

[0028] The acid used in the compositions of the invention may be any of the water-soluble physiologically tolerable acids, in particular any of the inorganic or, more preferably, organic acids conventionally used in the preparation of acid salts of drug compounds, e.g. citric, fumaric, tartaric, maleic, malic, succinic, oxalic, malonic, benzoic, mandelic and ascorbic acids.

[0029] Tartaric acid and more especially citric acid are preferred since the salts they form with drug compounds usually have a reduced tendency to precipitate from aqueous solutions. In general however, any acid which is not so strong as to cause degradation of the cyclodextrin and yet which is capable, on the addition of water, of generating a low pH environment, preferably lower than pH 4 and ideally about pH 2, may be used. The acid may be in liquid (e.g. solution) or solid form; however acids which are solid at ambient conditions in their anhydrous or hydrate forms will generally be preferred.

[0030] In the compositions of the invention, the acid is present from 35 to 95% by weight, preferably 35 to 60% by weight (relative to the total weight of cyclodextrin, drug compound, organic polymer and acid). The amount of acid used will be dependent upon the selected acid and drug compound, but in general an increase in the relative proportion of acid will result in an acceleration of drug dissolution on contact with water. The amount of acid used will normally be at least the amount necessary to form a 1:1 salt with the drug compound.

[0031] In general, the acid will form a significant proportion of dosage forms that dissolve rapidly in body fluids. Typically, they will comprise from 50 to 95% by weight of acid, preferably 50 to 90% by weight, more preferably 55 to 60% by weight. Thus viewed from a further aspect the invention provides a pharmaceutical composition comprising an organic drug compound, a water-soluble physiologically tolerable acid, a water-soluble physiologically tolerable cyclodextrin and a water-soluble physiologically tolerable organic polymer, characterised in that the weight ratios of drug compound to acid and of drug compound to cyclodextrin are no more than 2:1, preferably no more than 1.5:1, especially preferably no more than 1:1, and particularly preferably no more than 0.9:1, especially no more than 0.5:1.

[0032] The organic polymer used in the compositions of the invention may be any of the physiologically tolerable water soluble synthetic, semi-synthetic or non-synthetic organic polymers.

[0033] Thus for example the polymer may be a natural polymer such as a polysaccharide or polypeptide or a derivative thereof, or a synthetic polymer such as a polyalkylene oxide (e.g. PEG), polyacrylate, polyvinylpyrrolidone, etc. Mixed polymers, e.g. block copolymers and glycopeptides may of course be used.

[0034] It is believed that the effect of the organic polymer arises from an enhancement in viscosity which serves to stabilize supersaturated solutions of the drug compound on dissolution of the composition of the invention. Thus the polymer conveniently has a molecular weight in the range 500D to 2 MD, and conveniently has an apparent viscosity of 1 to 100 mPa.s when in a 2% aqueous solution at 20°C. For example, the water-soluble polymer can be selected from the group comprising

- alkylcelluloses such as methylcellulose,
- hydroxyakylcelluloses such as hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxybutylcellulose,
- hydroxyalkyl alkylcelluloses such as hydroxyethyl methylcellulose and hydroxypropyl methylcellulose,
- carboxyalkylcelluloses such as carboxymethylcellulose,

- alkali metal salts of carboxyalkylcelluloses such as sodium carboxymethylcellulose,
- carboxyalkylalkylcelluloses such as carboxymethylethylcellulose,
- carboxyalkylcellulose esters,
- starches,
- pectins such as sodium carboxymethylamylopectin,
- chitin derivates such as chitosan,
- heparin and heparinoids,
- polysaccharides such as alginic acid, alkali metal and ammonium salts thereof, carrageenans, galactomannans, tragacanth, agar-agar, gum arabic, guargum and xanthan gum,
- polyacrylic acids and the salts thereof,
- polymethacrylic acids and the salts thereof, methacrylate copolymers,
- polyvinylalcohol,
- polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone with vinyl acetate,
- polyalkylene oxides such as polyethylene oxide and polypropylene oxide and copolymers of ethylene oxide and propylene oxide, e.g. poloxamers and poloxamines.

[0035] Non-enumerated polymers which are pharmaceutically acceptable and have appropriate physico-chemical properties as defined hereinbefore are equally suited for preparing compositions according to the present invention.

[0036] Particularly preferably the organic polymer is a cellulose ether, e.g. methyl cellulose, hydroxyethylmethylcellulose, or hydroxypropylmethylcellulose (HPMC), for example a Methocel® (available from Colorcon, England) such as Methocel A, Methocel E, Methocel F, Methocel K, Methocel J or Methocel HB or a Metolose® such as Metolose SM, Metolose SH or Metolose SE. Especially preferably the organic polymer is a hydroxypropylmethylcellulose, e.g. from 5 cps Methocel E to 15000 cps Methocel K15M.

[0037] Even very small quantities of the organic polymer serve to achieve a beneficial effect in the compositions of the invention. Thus in the compositions of the invention the organic polymer is conveniently present at 0.05 to 35% by weight, preferably 0.1 to 20%, more preferably 0.5 to 15%, and most preferably 2 to 11% by weight (relative to the total weight of drug compound, acid, cyclodextrin and organic polymer). The content and viscosity grade of the organic polymer both affect the dissolution profile for the drug compound in the compositions of the invention, with increased organic polymer content and/or increased viscosity grade (e.g. 15000 mPa.s in place of 5 mPa.s (mPa.s values being at 2% aqueous solution at 20°)) both tending to decelerate drug compound dissolution). Accordingly the selection of the identity and quantity of the organic polymer will generally depend upon the dissolution profile that is desired. For example, a composition that provides sustained release of the drug, will comprise a water soluble polymer having an apparent viscosity of more than 1,000 mPa.s when dissolved in a 2% aqueous solution at 20°C.

[0038] The drug compound used in the compositions of the invention may be any organic or inorganic basic material which is no more than sparingly soluble, *i.e.* which is sparingly soluble, slightly soluble, very slightly soluble, or practically insoluble in pure water at 21°C (ie. requiring from 30, from 100, from 1000 or from 10000 parts water to put 1 part by weight drug compound into solution).

[0039] Examples of such poorly water-soluble compounds that may be used in the compositions of the invention include nifedipine, itraconazole (described in EP-A-6711), saperconazole (see US-A-4916134), (-)-[2S-[2α,4α(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl]-2-[[(4-methyl-4*H*-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one (Compound 40 in WO96/13499), cisapride (described in EP-A-76530), (B)-N-[4-[2-ethyl-1-(1H-1,2,4-triazol-1-yl)butyl]phenyl]-2-benzothiazolamine (described in WO-97/49704); methyl 6,11-dihydro-11-[1-[2-[4-(2-quinolinylmethoxy)phenyl]ethyl]-4-piperidinylidene]-5*H*-imidazo[2,1-b][3]benzazepine-3-carboxylate (described in WO-97/34897);
4-[[4-amino-6-[(2,6-dichlorophenyl)methyl]-1,3,5-triazin-2-yl]amino]benzonitrile (described in EP-0,834,507);
(B-cis)-1-[4-[4-[4-[[4-(2,4-difluorophenyl)-4-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-3-(1-methylethyl)-2-imidazolidinone;
(2S-cis)-1-[4-[4-[4-[[4-(2,4-difluorophenyl)-4-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-3-(1-methylethyl)-2-imidazolidinone;
3-[2-[3,4-dihydrobenzofuro[3,2-c]pyridin-2(1*H*)-yl]ethyl]-2-methyl-4*H*-pyrido-[1,2-a]pyrimidin-4-one;
N-[2-[4-(4-chlorophenyl)-1-piperazinyl]ethyl]-2-benzothiazolamine;
(B1)-*N*-[4-[2-(dimethylamino)-1-(1*H*-imidazol-1-yl)propyl]phenyl]-2-benzo-thiazolamine (described in WO-97/49704)
(B)-6-[amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone;
(B)-*N*-[4-[2-ethyl-1-(1*H*-1,2,4-triazol-1-yl)butyl]phenyl]-2-benzothiazolamine; 3-[6-(dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-*N,N*-dipropylpyrazolo-[2,3-a]pyrimidin-7-amine monohydrochloride;
(S)-[1-[2-[3-[(2,3-dihydro-1*H*-inden-2-yl)oxy]-4-methoxyphenyl]propyl]-1*H*-imidazol-2-yl]cyanamide; and
(+)-(B-trans)-4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinyl]-*N*-(2,6-dimethylphenyl)-1-piperazineacetamide (S)-hydroxybutanedioate (1:1).

[0040] Further suitable basic active ingredients are those which exert a local physiological effect, as well as those which exert a systemic effect, either after penetrating the mucosa or - in the case of oral administration - alter transport to the gastro-intestinal tract with saliva. The dosage forms prepared from the compositions according to the present invention are particularly suitable for active ingredients which exert their activity during an extended period of time, i. e. drugs having a half-life of at least several hours. Examples thereof include those of the following active agents that have basic character:

analgesic and anti-inflammatory drugs (celecoxib, MK966, L-745,337, NSAIDs, fentanyl, indomethacin, ketoprofen, nabumetone, oxyphenbutazone, paracetamol. phenylbutazone, piroxicam, tramadol) ; anti-arrhythmic drugs (gallopamil, procainamide, quinidine, verapamil) ; antibacterial and antiprotozoal agents (amoxicillin, ampicillin, benzathine penicillin, benzylpenicillin, cefaclor, cefadroxil, cefprozil, cefuroxime axetil, cephalexin, chloramphenicol, chloroquine, ciprofloxacin, clarithromycin, clavulanic acid, clindamycin, doxyxycline, erythromycin, flucloxacillin, halofantrine, isoniazid, kanamycin, lincomycin, mefloquine, minocycline, nafcillin, neomycin, norfloxacin, ofloxacin, oxacillin, phenoxymethyl-penicillin, pyrimethamine-sulfadoxime, quinine, streptomycin); anti-coagulants (warfarin) ; antidepressants (amitriptyline, amoxapine, butriptyline, clomipramine, desipramine, dothiepin, doxepin, fluoxetine, fluvoxamine, gepirone, imipramine, lithium carbonate, mianserin, milnacipran, nortriptyline, paroxetine, sertraline ; 3-[2-[3,4-dihydrobenzofuro [3,2-c]pyridin-2(1*H*)-yl]ethyl]-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one) ; anti-diabetic drugs (glibenclamide, metformin) : antiepileptic drugs (carbamazepine, clonazepam, ethosuximide, phenobarbitone, phenytoin, primidone, topiramate, valpromide) ; antifungal agents (amphotericin, clotrimazole, econazole, fluconazole, flucytosine, griseofulvin, itraconazole, ketoconazole, miconazole nitrate, nystatin, terbinafine, voriconazole) ; antigout (benzbromarone, probenecid) ; antihistamines (astemizole, cinnarizine, cyproheptadine, decarboethoxyloratadine, fexofenadine, flunarizine, levocabastine, loratadine, norastemizole, oxatomide, promethazine, terfenadine) : anti-hypertensive drugs (captopril, clonidine, cyclizine, diazoxide, dihydralazine, enalapril, fosinopril, guanethidine, ketanserin, lisinopril, minoxidil, prazosin, ramipril, rescinnamine, reserpine, terazosin) ; anti-muscarinic agents (atropine sulphate, hyoscine) ; antivirals (acyclovir, AZT, ddC, ddI, ganciclovir, loviride, tivirapine, 3TC, delavirdine, indinavir, nelfinavir, ritonavir, saquinavir) ; antineoplastic agents and antimetabolites (adriamycine, cladrihine, dactinomycin, daunorubicin, doxorubicin, etoposide, mitomycin, mitoxantrone, paclitaxel, taxol, taxotere, trimetrexate, vincristine, vinblasline) ; anti-migraine drugs (alniditan, naratriptan, sumatriptan) ; anti-Parkinsonian drugs (bromocryptine mesylate, carbidopa, levodopa, selegiline) : antipsychotic, hypnotic, anxiolylic and sedating agents (alprazolam, buspirone, chlordiazepoxide, chlorpromazine, chlorprothixene, clozapine, diazepam, flupenthixol, fluphenazine, flurazepam, haloperidol, 9-hydroxyrisperidonc, lorazepam, mazapertine, melperone, methaqualone, olanzapine, oxazepam, pimozide, pipamperone, piracetam, promazine, risperidone, selfotel, seroquel, sertindole, sulphide, temazepam, thioridazine, thiothixene, triazolam, trifluoperazine, trifluperidol, triflupromazine, ziprasidone, zolpidem) ; anti-stroke agents (lubeluzole, lubeluzole oxide, riluzole, aptiganel, eliprodil, remacemide) ; antitussive (dextromethorphan, laevodropropizine, noscapine) ; beta-adrenoceptor blocking agents (atenolol, bupranolol, carvedilol, labetalol, metipranolol, metoprolol, nebivolol, oxprenolol, propanolol) ; cardiac inotropic agents (amrinone, digitoxin, digoxin, milrinone) ; corticosteroids (beclomethasone dipropionate, betamethasone, budesonide, cortisone, dexamethasone, fludrocortisone, hydrocortisone, methylprednisolone, paramethasone, prednisolone, prednisone, triamcinolone) ; disinfectants (chlorhexidine) ; diuretics (acetazolamide, amiloride, benzthiazide, chlorothiazide, chlorthalidone, dichlorphenamide, ethacrynic acid, ethoxzolamide, frusemide, hydrochlorothiazide, hydroflumethiazide, isosorbide, polythiazide, spironolactone, triamterene, trichloromethiazide) ; enzymes ; ergot alkaloids (codergocrine, ergotamine, nicergolin) ; essential oils (anethole, anise oil, caraway, cardamom, cassia oil, cineole, cinnamon oil. clove oil, coriander oil, dementholised mint oil, dill oil, eucalyptus oil, eugenol, ginger, lemon oil, mustard oil, neroli oil, nutmeg oil, orange oil, peppermint, sage, spearmint, terpineol, thyme) ; gastro-intestinal agents (bromopride, cimetidine, cisapride, elebopride, diphenoxylate, domperidone, famotidine, lansoprazole, loperamide, loperamide oxide, mesalazine, metoclopramide, mosapride, nizatidine, norcisapride, olsalazine, omeprazole, pantoprazole, perprazole, pirenzepine, prucalopride, ranitidine, rabeprazole, ridogrel, sulphasalazine) ; haemostatics (aminocaproic acid) ; immunosuppressants (cyclosporin A, tacrolimus) ; lipid regulating agents (atorvastatin, lovastatin, pravastatin, probucol, simvastalin) ; local anaesthetics (benzocaine, lignocaine) ; opioid analgesics (buprenorphine, codeine, dextromoramide, dextropropoxyphene, dihydrocodeine, hydrocodone, oxycodone, morphine, papaverine, pentazoeine, pethidine) ; parasympathomimetics (eptastigmine, galanthamine, metrifonate, neostigmine, physostigmine, tacrine, donepezil, rivastigmine, milameline, sabcomeline, talsaclidine, xanomcline, memantine, lazabemide) ; sex hormones (androgens : methyltestosterone, oxymetholone, stanozolol ; oestrogens : conjugated oestrogens, ethinyloestradiol, mestranol, oestradiol, oestriol, oestrone ; progestogens ; chlormadinone acetate, cyproterone acetate, 17-deacetyl norgestimate, desogestrel, dienogest, dydrogesterone, ethynodiol diacetate, gestodene, 3-keto desogestrel, levonorgestrel, lynestrenol, medroxy-progesterone acetate, megestrol, norethindrone, norethindrone acetate, norethisterone, norethisterone acetate, norethynodrel, norgestimale, norgestrel, norgestrienone, progesterone, quingestanol acetate) ; stimulating agents (sildenafil) ; sympathomimetics (ephedrine, clenbuterol, fenoterol, norfenefrine, pseudoephedrine) ; vasodilators (amlodipine, amyl nitrite, buflomedil, buphenine, carbocromen, diltiazem, dipyridamole, glyceryl trinitrate, isosorbide dinitrate, lidoflazine, molsidomine, nicardipine,

nifedipine, nimodipine, oxpentifylline, pentaerythritol tetranitrate).

[0041] Other examples include those of the following active agents that have basic character:

alpha-Lipoic acid	lactose	methylxanthine
8-Methoxypsoralen	lithium salts	phytomenadione
Allopurinol	magnesium salts	propylthiouracil
alpha.-Tocopherol	menadione	
iron salts	methylthiouracil	

[0042] Basic drug compounds suitable for use in the compositions of the invention include drugs of all types conventionally administered topically (e.g. in a gel patch) or into an externally voiding body duct, e.g. orally, nasally, aurally, rectally or vaginally. Such drugs include in particular antifungals, calcium channel blockers, antibacterials, antihypertensives, antivirals, analgesics, apolipoprotein B synthesis inhibitors, and drugs which modify transit of gi tract contents (e.g. antidiarrhoea agents or motility promoters). Indeed, the invention is particularly applicable to poorly water-soluble imidazole, triazole, imidazo-benzazepines, nitrophenyl-pyridine, *N,N'*-bisphenyl-piperazine, and *N*-phenoxyalkyl-piperidine derivatives, e.g. the compounds mentioned above and compounds as described in EP-A-6711, WO96/13499 and EP-A-76530.

[0043] The compositions of the invention may conveniently contain the drug compound at 0.001 to 50% by weight, preferably 0.1 to 35%, more preferably 0.5 to 30%, especially 8 to 25% and most especially 10 to 15% by weight (relative to the total weight of acid, cyclodextrin, organic polymer and drug compound). The quantity of drug will of course depend upon the desired dissolution profile, the intrinsic solubility of the drug compound and the drug dosage required where the drug is to be delivered in dosage units (e.g. capsules, coated tablets, etc).

[0044] Thus the present invention also provides pharmaceutical dosage forms comprising a therapeutically effective amount of a composition as described hereinbefore.

[0045] For example if the drug is to be delivered in a standard capsule (e.g. with a 900 mg capacity for a glass thermoplastic system as described in the Examples hereto, and the desired drug dose is 100 mg/capsule) then the quantities and natures of the other composition components may be selected to give the desired drug dissolution profile - in general only a small quantity of organic polymer, e.g. 20 to 50 mg, may be necessary, and the balance may be made up from acid and cyclodextrin with the ratio of acid to cyclodextrin being set according to the required dissolution profile, e.g. with 200 to 400 mg cyclodextrin and 450 to 650 mg acid.

[0046] Besides the drug compound, the organic polymer, the acid and the cyclodextrin, the compositions of the invention may contain other conventional pharmaceutical excipients, e.g. flavours, colouring agents, antioxidants, bulking agents, fats, waxes, coating agents, dispersants, suspension fluids (e.g. where the composition coated with a gastric juice resistant coating and dispersed as particles in a suspension fluid such as water or a syrup), etc. Preferably such components when in intimate admixture with the drug compound will make up only a minor proportion of the composition, e.g. 0.01 to 10% by weight (relative to the total weight of acid, organic polymer, cyclodextrin and drug compound). However where the composition of the invention is encapsulated or disposed in a carrier (e.g. a fluid or a solid or semi-solid matrix), the further components not in intimate admixture with the drug compound (e.g. coating or encapsulating materials, dispersion media, etc.) may of course make up a minor or major proportion, e.g. 5 to 95% by weight, of the overall composition.

[0047] The compositions of the invention may be prepared by making an intimate admixture of the drug compound, cyclodextrin, acid and organic polymer. This may be effected most straightforwardly by dissolving these components in a liquid solvent therefor and subsequently removing the solvent. Thus viewed from a further aspect the invention provides a process for the preparation of a pharmaceutical composition, said process comprising: dissolving a drug compound, a water-soluble cyclodextrin, a physiologically tolerable water-soluble acid and a physiologically tolerable water-soluble organic polymer in a solvent; removing solvent from the resultant solution: optionally forming the resultant product into desired shapes; and optionally coating the resulting product with a physiologically tolerable coating material.

[0048] The solvent used in the process of the invention is preferably a physiologically tolerable material. suitably an organic solvent such as a C_{1-6} alkanol (e.g. ethanol), acetone, DMF, a linear or cyclic ether (e.g. diethyl ether, dimethyl ether, or THF), cyclohexane, DMSO, etc. or a solvent mixture that also may comprise water. For an acid with a high melting point, solvents or solvent mixtures which have high boiling points may conveniently be used; generally however the boiling point of the solvent or solvent system will be no more than about 100°C. Such solvents may be used efficiently in the production of the compositions of the invention and the level of residual solvent will be minimal. The solvent may conveniently be removed by evaporation, e.g. under reduced pressure, and as this may leave some solvent residue (e.g. up to 3% by weight) it is particularly desirable to use a solvent such as ethanol (or an ethanol-water mixture) which is a permitted pharmaceutical excipient.

[0049] If the drug compound is insoluble or poorly soluble in the solvent of choice, the process of the invention may involve dispersion of microparticles (e.g. nanoparticles having a particle size of 1 to 100 nm) of the drug compound in the solvent rather than full dissolution of the drug compound. If this is done, it is desirable that the drug compound particles be as small as possible. Nanoparticles of insoluble compounds may be prepared for example by various precipitation techniques or by milling with physiologically tolerable inorganic beads, e.g. of zirconia (EP-0,499.299).

[0050] The solvent removal may be essentially complete or it may he incomplete, in the former case to produce a solid or a gel-like solid or semi-solid, and in the latter case to produce a viscous fluid which can for example be filled into capsules.

[0051] In general, essentially complete solvent removal will he preferred as the resultant product can then readily be shaped. Shaping may be effected by spray-drying the solution (to provide the product in particulate form), by evaporation of Solvent from solution disposed in molds, by molding (e.g. injection molding), by extrusion and the like. In general the product can be formed when hot and allowed to solidify on cooling. The shaped product may likewise be produced in film or sheet form by evaporation or by pouring a heated mass onto a plate and evaporating off the solvent.

[0052] In one preferred embodiment the product is shaped by filling into (e.g. by pouring or by extrusion) capsule shells, e.g. of gelatin.

[0053] The product may be hygroscopic, and thus may be "tacky" if touched by hand due to its absorption of moisture from the skin. Accordingly it is particularly preferred for the product to be provided with a protective coating to prevent moisture uptake during handling. Such coatings may for example take the form of capsule casings (as described above), tablet coatings, protective film or web coatings, and moisture-proof removable wrappings. Tablet coatings may be applied in conventional manner and may he such as to dissolve in the mouth or stomach (e.g. sugar or sugar/beeswax coatings), or alternatively may be gastric juice resistant polymers (such as the gastric juice resistant Eudragit® coatings produced by Röhm GmbH) where it is desired that drug uptake should occur in the intestines. Protective films or webs may for example be used where the product is to be applied topically, e.g. for uptake across the skin or a toe or finger nail. In this event a pad of the composition will generally be disposed between an adhesive upper protective layer and a lower removable layer. An example of a topical application form for application on nails and adjoining tissue, e.g. for the treatment of fungal infection, is shown in US-A-5181914.

[0054] Where the product is produced in particulate form, e.g. by spray-drying, the particles can be loaded into water-tight administration devices (e.g. spray devices or powder dosing devices such as inhalers) for oral, nasal or topical administration of the particulate. Alternatively particulates may be loaded into capsules or mixed with hulking agents such as lactose, starch, microcrystalline cellulose and mixtures thereof, and compressed to form tablets. In any event, the particles may additionally be provided with one or more coatings, e.g. to provide a delayed or prolonged release administration forms.

[0055] Generally however it will he preferred to shape the product into individual doses and to provide these with a protective coat, e.g. to produce a capsule, coated tablet or film covered pad single dosage unit.

[0056] While not wishing to be bound by theory it is thought that the advantageous drug compound dissolution profile for the compositions of the invention is achieved as a result of a combination of the effects of the components of the composition on exposure to water or aqueous body fluids. The water and the acid provide a highly acidic microenvironment in which the solubility of the basic drug compound is increased. This acidic microenvironment contains the cyclodextrin which is capable of complexing the solubilized drug causing the production of a supersaturated solution of the drug compound and this supersaturated solution is stabilized by the viscosity enhancing effects of the organic polymer which hinders precipitation of the drug as the pH increases as the microenvironment becomes more dilute as more water enters.

[0057] As has been mentioned above, the compositions according to the invention can be produced with particularly favourable drug dissolution profiles. Thus dissolution may be sufficiently rapid to ensure substantially complete availability of the drug compound for biological uptake (e.g. from the mouth, nose, stomach or vagina) yet sufficiently slow to provide a more prolonged plasma uptake profile (see for example Figure 1 of the accompanying drawings) e.g. by avoidance of drug reprecipitation before the composition reaches the stomach.

[0058] Such a dissolution profile is thus advantageous in its own right and viewed from a further aspect the pharmaceutical composition according to the invention may comprise at least one water-soluble physiologically tolerable excipient, so that at 5, 15 and 45 minutes after addition of a quantity of said composition containing 100 mg of a basic drug compound to 600 mL of 0.1N hydrochloric acid at 37°C, from 7 to 25 (preferably 10 to 20, especially 12 to 18) %, 45 to 70 (preferably 50 to 65, especially 54 to 63) % and at least 96 (preferably at least 97, especially at least 98) % respectively of said drug compound is in solution in said hydrochloric acid. These figures relate to *in vitro* dissolution studies conducted in accordance with the monograph USP 23, <711> Dissolution, pp. 1791-1793.

[0059] For example, in determining the dissolution profiles set out above, the composition is placed without a coating or with a rapidly soluble coating (e.g. a gelatin capsule shell) in 0.1 N HCl (or an other appropriate medium) and the mixture is stirred using the USP-method with a paddle, apparatus 2, at a speed of 50 or 100 rpm.

[0060] The compositions according to the invention may be in any form convenient for topical administration or ad-

ministration into an externally voiding body cavity (e.g. nose, lungs, mouth, ear, stomach, rectum or vagina). Typical administration forms include patches, tablets, buccal tablets, lozenges, can-plugs, nose plugs, coated tablets, capsules, suppositories, chewing gum, gels, powders, granules, syrups and dispersions, although patches and powders and more especially capsules and coated tablets are preferred. The drug dosage will depend upon the drug compound as well as the species and size of the subject being treated. Typically, dosages will be 0.5 to 1.2, preferably 0.8 to 1.05 times the conventional dosages for the selected drug compound administered by the same route.

[0061] Further, this invention comprioses a pharmaceutical composition or a pharmaceutical dosage form as described hereinbefore for use in a method of therapy or diagnosis of the human or non-human animal body.

[0062] This invention also relates to a pharmaceutical composition for use in the manufacture of a pharmaceutical dosage form for oral administration to a mammal in need of treatment, characterized in that said dosage form can be administered at any time of the day independently of the food taken in by said mammal.

[0063] Or, in other words, the present invention also concerns the se of a pharmaceutical composition as described hereinbefore for the manufacture of a pharmaceutical dosage form for oral administration to a mammal in need of treatment, characterized in that said dosage form can be administered at any time of the day independently of the food taken in by said mammal.

[0064] This invention also relates to a pharmaceutical package suitable for commercial sale comprising a container, an oral dosage form as claimed in any one of claims 12 to 16, and associated with said package written matter non-limited as to whether the dosage form can be administered with or without food.

[0065] The invention will now be described further with reference to the following nonlimiting Examples and the accompanying drawings, in which:

Figures 1 and 2 are graphs showing plasma concentrations of the drug (-)-[2S-[2α,4α(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl]-2-[[(4-methyl-4*H*-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one administered in a composition according to the invention and in a conventional administration form (sugar particles coated with the drug and loaded in a gelatin capsule) [see Example 6 for further details]; and

Figure 3 is a dissolution profile for the three itraconazole compositions of Example 2.

Example 1

Glass thermoplastic system composition preparation

[0066] The following ingredients are mixed in a 250 mL glass flask:

Drug compound (e.g. itraconazole)	20 g
Citric acid monohydrate	100 g

Anhydrous ethanol (100 mL) is added. The glass flask is placed on a steam bath (bain mane) and stirred at 70°C until the drug and acid are completely dissolved (about 10 minutes). Thereafter the following ingredients are added:

Hydroxypropyl-β-cyclodextrin	50 g
Hydroxypropylmethylcellulose (2910.5 mPa.s)	10 g

The flask is placed on the steam bath and stirred at 70°C until dissolution is complete (about 70 minutes). The solution is then poured onto cleaned stainless steel plates which are then placed in a drying oven for 2 hours at 80°C under vacuum and subsequently for 40°C under vacuum overnight. The plates are then heated to 80°C and the gel residue is scraped off and filled into 900 mg capacity gelatin capsules (size no. 0).

Example 2

Composition preparation

[0067] Analogously to Example 1, gelatin capsules having the following relative weights of components are prepared:

(A)	100 mg	Itraconazole
	500 mg	citric acid monohydrate
	275 mg	hydroxypropyl-β-cyclodextrin
	25 mg	Methocel E5
(B)	100 mg	Itraconazole
	500 mg	citric acid monohydrate
	250 mg	hydroxypropyl-β-cyclodextrin
	50 mg	Methocel E5
(C)	100 mg	Itraconazole
	500 mg	citric acid monohydrate
	225 mg	hydroxypropyl-β-cyclodextrin
	75 mg	Methocel E5
(D)*	200 mg	Methyl 6,11-dihydro-11-[1-[2-[4-(2-quinolinylmethoxy)phenyl]ethyl]-4-piperidinylidene]-5*H*-imidazo[2,1-b]-[3]benzazepine 3-carboxylate
	650 mg	citric acid monohydrate
	250 mg	hydroxypropyl-β-cyclodextrin
(E)	100 mg	(-)-[2S-[2α,4α(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl]-2-[[(4-methyl-4*H*-1,2,4-triazol-3-yl)thio [methyl]-1,3-dioxolan-4-yl]methoxy]-phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one
	500 mg	citric acid monohydrate
	250 mg	hydroxypropyl-β-cyclodextrin
	50 mg	Methocel E5

* For example 2(D) the composition is loaded into 1100 mg gelatin capsules.

[0068] The dissolution profiles of the gels of Example 2(A), (B) and (C) are shown in Figure 3 of the accompanying drawings. These were determined by placing one capsule containing 100 mg of itraconazole in 300 mL of stirred 0.1 N HCl at 37°C and observing the percentage of dissolved drug compound at times 0, 5, 15, 30, 45 and 60 minutes (stirring was effected using the USP-method with paddle, apparatus 2, 100 rpm). For Example 2(E), with 100 mg drug compound added to 600 mL of 0.1 N HCl at 37°C, the mean percentages of drug compound in solution at 5, 15, 30 and 45 minutes were 17.22, 61.18, 92.73 and 98.67 respectively (stirring was effected using the USP-method with paddle, apparatus 2, 100 rpm).

[0069] The dissolution profile of Example 2(E) was compared with that of a conventional capsule dosage form in which the gelatin capsule is loaded with sugar particles coated with 100 mg of (-)-[2S-[2α,4α(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl]-2-[[(4-methyl-4*H*-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]-phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one. The capsules were placed in 10 ml of 0.1 N HCl at 37°C in glass vials and shaken in a mechanical shaker (100 strokes per minute) and the percentage of drug compound in solution after 0, 30 and 60 minutes was determined. The results are set out in Table 1 below.

Table 1

Percentage of drug compound in solution		
Time	Example 2(E)	Conventional Capsule
0	0	0
30	91.26	15.54
60	101.90	18.39

This clearly shows how much more readily the drug compound is made bioavailable by the compositions of the invention.

Example 3

Effect of organic polymer on supersaturation stability

[0070] Aqueous solutions of hydroxypropyl-β-cyclodextrin (HPβCD) anti Methocel E5 in 300 ml 0.1 N HCl at 37"C were prepared having the concentrations set out in Table 2. The solutions were stirred using the USP-method with paddle, apparatus 2, 150 rpm.

Sample	HPβCD (mg)	Methocel E5 (mg)
1	250	250
2	500	0
3	250	00
4	500	500
5	0	250
6	500	250
7	0	0
8	250	0
9	0	500

[0071] To these solutions, with stirring, a concentrated solution of itraconazole in DMF (50 mg/mL) was added drop-wise until precipitation was observed. Subsequently the concentration of dissolved itraconazole expressed in mg% (ie. the number of mg dissolved in 100 mL) was observed at 0, 30, 60 and 120 minutes. The results are set out in Table 3 below:

Table 3

Percentage of drug compound in solution									
Sample Time (minutes)	1	2	3	4	5	6	7	8	9
0	59.52	72.10	58.95	75.47	42.65	75.27	42.60	60.95	42.95
30	62.02	74.40	62.05	78.12	44.85	80.17	44.10	62.92	45.20
60	62.52	70.37	62.50	79.47	45.40	80.40	44.97	64.07	46.00
120	62.79	45.82	63.90	80.77	46.55	81.25	31.32	33.65	47.05
HPBCD:	1:1	2:0	1:2	2:2	0:1	2:1	0:0	1:0	0:2
Methocel ratio									

[0072] These results clearly demonstrate (i) the solubilizing effect of the cyclodextrin (Samples 2, 6 and 4 show the highest initial itraconazole concentrations, followed by Samples 8, 1 and 3, with Samples 7, 5 and 9 showing the lowest initial concentrations) and (ii) the stabilizing effect of the organic polymer (Samples 2, 8 and 7 show the greatest drop in itraconazole concentrations over 120 minutes, etc).

Example 4

Extended release formulation

[0073] Analogously to Example 1, gelatin capsules were prepared containing the following:

41.55 mg	Cisapride
508.45 mg	citric acid monohydrate
250 mg	hydroxypropyl-β-cyclodextrin
100 mg	Methocel K15M

This formulation has a much slower dissolution rate than the compositions of Example 2. However the rate of dissolution is much more close to linear with time and shows much less dependence on the pH of the dissolution medium.

Example 5

Nail gel

[0074] A gel for application to nails or hooves to effect antifungal treatment is made with the following composition:

Itraconazole	250 mg
Citric acid monohydrate	2083 mg
Hydroxypropyl-β-cyclodextrin	333 mg
Hydroxypropylmethylcellulose (Methocel E5)	83 mg
Anhydrous ethanol	2 ml

Example 6

Body uptake

[0075] The plasma concentrations of R 103757 were determined in healthy humans at 0, ½, 1, 1½, 2, 3, 4, 6, 8 and 12 hours after oral administration of 100 mg (-)-[2S-[2α,4α(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl]-2-[[(4-methyl-4*H*-1,2,4-triazol-3-yl)-thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one as (i) a 5 mg/mL oral solution containing 25% hydroxypropyl-β-cyclodextrin solution administered under fasting conditions, (ii) a conventional capsule containing (-)-[2S-[2α,4α(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl]-2-[[(4-methyl-4*H*-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one coated onto sugar particles administered under fasting conditions, (iii) a conventional capsule containing (-)-[2S-[2α,4α(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl]-2-[[(4-methyl-4*H*-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]-phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one coated onto sugar particles administered after a standard breakfast, (iv) a capsule according to Example 2(E) administered under fasting conditions and (v) a capsule according to Example 2(E) administered after a standard breakfast.

[0076] The "standard breakfast" comprised four slices of bread, one slice of ham, one slice of cheese, butter, jelly and two cups of coffee or tea with milk and/or sugar if desired. The 100 mg dose of (-)-[2S-[2α,4α(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl]-2-[[(4-methyl-4*H*-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one was administered just after such a breakfast.

[0077] Blood samples of 10 mL were taken to obtain 5 mL plasma. The blood samples were taken, collected in heparinized tubes, and centrifuged at 1000g for 10 minutes within 2 hours of collection. Plasma was transferred into plastic tubes, which were sealed and stored at -70°C until assayed.

[0078] The results are shown in Figures 1 and 2 which presents drug concentrations as a function of time. As can be seen, the conventional capsule performs significantly worse than the solution even with fasting. However the capsule according to the invention outperforms the solution after 3 hours whether or not the recipient has fasted and, most surprisingly, completely outperforms the solution where the recipient has not fasted.

Example 7

Effect of pH on dissolution rate

[0079] Following the procedure of Example 1, a placebo capsule comprising methylene blue (2,63 mg), citric acid (600 mg), hydroxypropyl-β-cyclodextrin (250 mg) and hydroxypropylmethylcellulose (Methocel E5, 50 mg) was prepared. The dissolution of these capsules was determinated at various pH values according to the USP method (600 ml medium, 37°C, Apparatus 2 with paddle, 100 rpm). The six media tested were : 0.1N HCl (pH 1.55), 0.01N HCl (pH 2.25), 0.001N HCl (pH 2.75), USP pH 4.5 (pH 4.40), USP pH 6.5 (pH 5.80) and USP pH 7.5 (pH 7.0).

[0080] The results are set out in table 4 below :

Time (min.)	0.1N HCl	0.01N HCl	0.001N HCl	USP pH 4.5	USP pH 6.5	USP pH 7.5
0	0.00	0.00	0.00	0.00	0.00	0.00
5	16.62	21.85	16.62	21.40	15.48	16.62
15	60.77	73.75	74.43	71.93	60.55	62.59
30	95.60	104.25	104.93	100.15	102.20	100.83
45	100.83	104.93	105.39	104.48	103.57	104.25
60	102.43	104.70	104.93	105.16	104.48	104.02
pH	1.55	2.25	2.75	4.40	5.80	7.00

Example 8

[0081] Following the procedure of Example 1, various drug containing capsules were made having the following relative weights of components :

A.	100 mg	itraconazole
	500 mg	citric acid
	250 mg	hydroxypropyl-β-cyclodextrin
	50 mg	HPMC E5
B.	200 mg	methyl 6,11-dihydro-11-[1-[2-[4-(2-quinolinylmethoxy)phenyl]ethyl]-4-piperidinylidene]-5*H*-imidazo[2,1-b][3]benzazepine-3-carboxylate
	650 mg	citric acid
	250 mg	hydroxypropyl-β-cyclodextrin
C.	100 mg	(-)-[2S-[2α,4α(S*)]]-4-[4-[4-[4-[[2-(4-methyl-4*H*-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one
	500 mg	citric acid
	250 mg	hydroxypropyl-β-cyclodextrin
	50 mg	HPMC E5
D.	100 mg	4-[[4-amino-6-[(2,6-dichlorophenyl)methyl]-1,3,5-triazin-2-yl]amino]-benzonitrile
	500 mg	citric acid
	250 mg	hydroxypropyl-β-cyclodextrin
	50 mg	HPMC E5
E.	5 mg	(B)-N-[4-[2-ethyl-1-(1H-1,2,4-triazol-1-yl)butyl]phenyl]-2-benzothiazolamine
	500 mg	citric acid
	395 mg	hydroxypropyl-β-cyclodextrin
F.	100 mg	(B-cis)-1-[4-[4-[4-[[4-(2,4-difluorophenyl)-4-(1*H*-1,2,4-triazol-1-yl-methyl)-1,3-dioxolan-2-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-3-(1-methylethyl)-2-imidazolidinone
	500 mg	citric acid
	250 mg	hydroxypropyl-β-cyclodextrin
	50 mg	HPMC E5

[0082] The dissolution of these compositions was determined according to the USP method (600 ml 0.1 N HCl, 37°C, Apparatus 2 with paddle, 100 ppm), except formulation (A) where only 300 ml medium was used. The results are set

out in the following tables 5-10 :

Table 5 :

Formulation (A)			
Time (min)	sample 1	sample 2	sample 3
0	0.00	0.00	0.00
5	10.75	9.99	10.69
15	56.61	57.18	59.61
30	85.89	88.98	90.24
45	95.46	99.84	96.87
60	101.94	102.06	102.87

Table 6 :

Formulation (B)			
Time (min)	0.1N HCl	0.01N HCl	0.001N HCl
0	0.00	0.00	0.00
5	27.00	25.17	21.39
15	92.13	86.94	84.75
30	97.11	96.63	93.09
45	98.64	99.45	94.83
60	100.29	100.08	95.28

Table 7 : Formulation (C)

	Calculated concentration in % of the active dose						
Time (min)	sample 1	sample 2	sample 3	sample 4	sample 5	sample 6	average
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5	13.81	17.28	17.67	19.79	18.56	16.19	17.22
15	58.44	59.10	66.60	63.42	62.46	57.06	61.18
30	92.34	92.94	93.36	92.46	92.52	92.76	92.73
45	98.28	98.94	98.82	99.30	98.52	98.16	98.67
60	100.08	99.54	99.66	100.20	100.02	99.96	99.91

Table 8 : Formulation (D)

	Calculated concentration in % of the active dose
Time (min)	Sample 1
5	0.00
5	7.41
15	49.49
30	86.92
45	99.57
60	99.84
90	101.77
120	103.52
150	103.70

Table 9 : Formulation (E)

	Calculated concentration in % of the active dose		
Time (min)	0.1N HCl	0.01N HCl	0.001 N HCl
0	0.00	0.00	0.00
5	48.72	26.16	24.96
15	100.92	96.36	94.20
30	102.48	98.76	95.76
45	103.08	102.24	96.96
60	102.00	102.00	97.80

Table 10 : Formulation (F)

	Calculated concentration in % of the active dose						
Time (min)	sample 1	sample 2	sample 3	sample 4	sample 5	sample 6	average
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5	12.66	14.76	12.66	12.66	15.36	17.34	14.24
15	54.36	56.82	61.98	64.80	54.78	63.78	59.42
30	94.26	93.96	97.50	98.40	95.58	97.20	96.15
45	100.98	101.28	100.50	101.16	100.68	101.34	100.99
60	101.22	101.34	101.16	101.52	100.86	101.58	101.28

Example 9

Stability testing of formulation 8 (C)

[0083] Capsules of formulation 8(C) were stored for 1 month and 3 months at 40°C, and for 1 year at room temperature. Dissolution measurements were made according to the USP method (600 ml 0.1N HCl, 37°C, paddle apparatus 2.100 rpm). The following results were obtained :

Table 11 : after 1 month at 40°C

	Calculated concentration in % of the active dose						
Time (min)	sample 1	sample 2	sample 3	sample 4	sample 5	sample 6	average
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5	10.11	10.79	9.94	9.59	14.35	10.33	10.85
15	59.72	55.02	48.97	54.36	66.54	52.38	56.17
30	93.00	90.06	89.70	92.70	95.46	89.16	91.68
45	100.14	98.22	98.94	99.84	99.48	99.18	99.30
60	100.50	100.92	99.36	99.54	100.56	100.26	100.19

Table 12 : after 3 months at 40°C

	Calculated concentration in % of the active dose						
Time (min)	sample 1	sample 2	sample 3	sample 4	sample 5	sample 6	average
	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	5.74	5.90	13.93	11.49	7.56	7.78	8.73
	43.62	45.00	56.76	48.30	43.14	47.76	47.43
	88.80	89.10	89.70	87.96	84.54	84.42	87.42
	99.36	99.96	99.54	99.78	99.18	100.08	99.65
	100.32	100.14	100.92	100.44	101.70	100.50	100.67

Table 13 : after 1 year at room temperature

	Calculated concentration in % of the active dose			
Time (min)	sample 1	sample 2	sample 3	average
0	0.00	0.00	0.00	0.00
5	14.94	16.14	15.48	15.52
15	61.98	66.12	67.32	65.14
30	92.52	91.86	96.12	93.50
45	99.72	99.60	98.70	99.34
60	101.10	100.80	99.36	100.42

Example 10

Variability in bioavailability of Formulation (D)

[0084] The variability in the bioavailability of Formulation (D) in beagle dogs was evaluated as follows. First, two beagle dogs received as single oral administration of a PEG-400 solution comprising 4-[[4-amino-6-[(2,6-dichlorophenyl)methyl]-1,3,5-triazin-2-yl]amino]benzonitrile at a dose of 10 mg/kg. Plasm levels were measured for 32 hours. After 7 days, the same dogs were now treated with a single oral capsule comprising the formula (D) at 10 mg/kg. Plasm levels were again determined for up to 32 hours after administration. The individual results are as follows.

			Plasma levels (ng/ml)	
Formulation	Day	Time	Dog 1	Dog 2
PEG-400 solution	0	0 h	5.8	NQ
		0.5 h	141	63.2
		1 h	247	158
		2 h	291	141
		4 h	534	200
		6 h	368	171
		8 h	246	141
	1	24 h	95.2	47.4
		32 h	36.1	20.9

			Plasma levels (ng/ml)	
Formulation	Day	Time	Dog 1	Dog 2
GTS capsule	7	0 h	NQ	NA
		0.5 h	24.2	68.5
		1 h	567	600
		2 h	850	859
		4 h	461	492
		6 h	288	343
		8 h	237	207
	8	24 h	74.0	32.9
		32 h	32.7	10.1

NQ : not quantifiable by the HPLC method (< 5.0 ng/ml).

[0085] Surprisingly, the plasm levels obtained after administration of the capsules comprising formula (D) are very much more similar to one another in the two test animals than those obtained after administration of the PEG 400 solution.

Example 11

Permeation and accumulation of itraconazole through and in human skin

[0086] A Franz cell was fitted with fresh whole human skin and its receptor filled with a 20% (w/v) solution of hydroxypropyl-β-cyclodextrin in water. A Finn Chambers patch was filled with Formulation 8(A) and was then placed on the skin wetted with a small amount of phosphate buffered saline. Samples of the receptor solution were withdrawn at regular intervals and the presence of itraconazole in the solution was measured using high performance liquid chro-

matography. At no time point could any trace of itraconazole be detected, indicating that this compound did not penetrate whole human skin. At the end of the experiment the skin was thoroughly washed and then extracted in order to determine the amount of itraconazole accumulated in the skin. A mean value of 12.2 $\mu g/cm^2$ could be calculated from the results of 8 independent experiments.

Claims

1. A pharmaceutical composition comprising a no more than sparingly water-soluble basic drug compound, a cyclodextrin, a physiologically tolerable water-soluble acid, and a physiologically tolerable water-soluble organic polymer, **characterized in that** it comprises from 35 to 95 % by weight of acid relative to the total weight of cyclodextrin, drug compound, organic polymer and acid.

2. The composition of claim 1 **characterised in that** the weight ratios of drug compound to acid and of drug compound to cyclodextrin are no more than 2:1.

3. The composition of claim 1 or 2 **characterized in that** the components of the composition are so dispersed as to form a chemically and physically uniform or homogeneous system or to consist of one phase.

4. The composition of claim 3 wherein the cyclodextrin is 2-hydroxypropyl-β-cyclodextrin.

5. The composition of claim 3 wherein the acid is selected from the group comprising citric, fumaric, tartaric, maleic, malic, succinic, oxalic, malonic, benzoic, mandelic and ascorbic acid.

6. The composition of claim 5 wherein the acid is citric acid.

7. The composition of claim 3 wherein the polymer is selected from the group comprising

   - alkylcelluloses such as methylcellulose,
   - hydroxyakylcelluloses such as hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxybutylcellulose,
   - hydroxyalkyl alkylcelluloses such as hydroxyethyl methylcellulose and hydroxypropyl methylcellulose,
   - carboxyalkylcelluloses such as carboxymethylcellulose,
   - alkali metal salts of carboxyalkylcelluloses such as sodium carboxymethylcellulose,
   - carboxyalkylalkylcelluloses such as carboxymethylethylcellulose,
   - carboxyalkylcellulose esters,
   - starches,
   - pectins such as sodium carboxymethylamylopectin,
   - chitin derivates such as chitosan,
   - heparin and heparinoids,
   - polysaccharides such as alginic acid, alkali metal and ammonium salts thereof, carrageenans, galactomannans, tragacanth, agar-agar, gum arabic, guargum and xanthan gum,
   - polyacrylic acids and the salts thereof,
   - polymethacrylic acids and the salts thereof, methacrylate copolymers,
   - polyvinylalcohol,
   - polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone with vinyl acetate,
   - polyalkylene oxides such as polyethylene oxide and polypropylene oxide and copolymers of ethylene oxide and propylene oxide, e.g. poloxamers and poloxamines.

8. The composition of claim 7 wherein the polymer has an apparent viscosity of 1 - 100 mPa.s when dissolved in a 2% aqueous solution at 20°C.

9. The composition of claim 8 wherein the polymer is hydroxypropylmethylcellulose.

10. A composition according to any one of the preceding claims that dissolves rapidly in body fluids, **characterized in that** it comprises from 50 to 95 % by weight of acid.

11. A composition according to any one of the preceding claims that provides sustained release of the drug, **charac-**

terized in that it comprises a water soluble polymer having an apparent viscosity of more than 1,000 mPa.s when dissolved in a 2% aqueous solution at 20°C.

12. A pharmaceutical dosage form comprising a therapeutically effective amount of a pharmaceutical composition as defined in any one of the preceding claims.

13. The dosage form of claim 12 adapted for topical administration or administration into an externally voiding body cavity such as the nose, lungs, mouth, ear, stomach, rectum and vagina.

14. The dosage form of claim 12 wherein said composition is filled into a standard capsule, or alternatively is mixed with bulking agents and compressed into tablets.

15. The dosage form of claim 12, **characterised in that** at 5, 15 and 45 minutes after addition of said dosage form to 0.1N hydrochloric acid at 37°C in the dissolution test set forth in USP test <711> in a USP-2 dissolution apparatus equiped with a paddle, from 7 to 25%, 45 to 70% and at least 96% respectively of drug is dissolved in said 0.1 N hydrochloric acid.

16. A pharmaceutical composition according to any one of claims 1 to 11 or a pharmaceutical dosage form according to any one of claims 12 to 15 for use in a method of therapy or diagnosis of the human or non-human animal body.

17. A pharmaceutical composition according to any one of claims 1 to 11 for use in the manufacture of a pharmaceutical dosage form for oral administration to a mammal in need of treatment, **characterized in that** said dosage form can be administered at any time of the day independently of the food taken in by said mammal.

18. Use of a pharmaceutical composition according to any one of claims 1 to 11 for the manufacture of a pharmaceutical dosage form for oral administration to a mammal in need of treatment, **characterized in that** said dosage form can be administered at any time of the day independently of the food taken in by said mammal.

19. Use of pharmaceutical composition according to any one of claims 1 to 11 for the manufacture of a medicament for use in a method of therapy or diagnosis of the human or non-human body.

20. A pharmaceutical package suitable for commercial sale comprising a container, an oral dosage form as claimed in any one of claims 12 to 16, and associated with said package written matter non-limited as to whether the dosage form can be administered with or without food.

Patentansprüche

1. Pharmazeutische Zusammensetzung, enthaltend eine höchstens geringfügig wasserlösliche, basische Arzneimittelverbindung, ein Cyclodextrin, eine physiologisch unbedenkliche wasserlösliche Säure und ein physiologisch unbedenkliches wasserlösliches organisches Polymer, **dadurch gekennzeichnet, daß** sie von 35 bis 95 Gew.-% Säure, bezogen auf das Gesamtgewicht an Cyclodextrin, Arzneimittelverbindung, organischem Polymer und Säure, enthält.

2. Zusammensetzung nach Anspruch 1, **dadurch gekennzeichnet, daß** das Gewichtsverhältnis von Arzneimittelverbindung zu Säure und von Arzneimittelverbindung zu Cyclodextrin nicht mehr als 2:1 beträgt.

3. Zusammensetzung nach Anspruch 1 oder 2, **dadurch gekennzeichnet, daß** die Komponenten der Zusammensetzung so dispergiert sind, daß sie ein chemisch und physikalisch einheitliches oder homogenes System bilden oder aus einer Phase bestehen.

4. Zusammensetzung nach Anspruch 3, wobei es sich bei dem Cyclodextrin um 2-Hydroxypropyl-β-cyclodextrin handelt.

5. Zusammensetzung nach Anspruch 3, wobei die Säure aus der aus Citronensäure, Fumarsäure, Weinsäure, Maleinsäure, Äpfelsäure, Bernsteinsäure, Oxalsäure, Benzoesäure, Mandelsäure und Ascorbinsäure bestehenden Gruppe ausgewählt ist.

6. Zusammensetzung nach Anspruch 5, wobei es sich bei der Säure um Citronensäure handelt.

7. Zusammensetzung nach Anspruch 3, wobei das Polymer aus der aus

- Alkylcellulosen wie Methylcellulose,
- Hydroxyalkylcellulosen wie Hydroxymethylcellulose, Hydroxyethylcellulose, Hydroxypropylcellulose und Hydroxybutylcellulose,
- Hydroxyalkylalkylcellulosen wie Hydroxyethylmethylcellulose und Hydroxypropylmethylcellulose,
- Carboxyalkylcellulosen wie Carboxymethylcellulose,
- Alkalisalzen von Carboxyalkylcellulosen wie Natriumcarboxymethylcellulose,
- Carboxyalkylalkylcellulosen wie Carboxymethylethylcellulose,
- Carboxyalkylcelluloseestern,
- Stärken,
- Pektinen wie Natriumcarboxymethylamylopektin,
- Chitinderivaten wie Chitosan,
- Heparin und Heparinoiden,
- Polysacchariden wie Alginsäure und deren Alkali- und Ammoniumsalze, Carrageenanen, Galactomannanen, Tragacanthgummi, Agar-Agar, Gummi arabicum, Guargummi und Xanthangummi,
- Polyacrylsäuren und deren Salzen,
- Polymethacrylsäuren und deren Salzen, Methacrylatcopolymeren,
- Polyvinylalkohol,
- Polyvinylpyrrolidon, Copolymeren von Polyvinylpyrrolidon mit Vinylacetat,
- Polyalkylenoxiden wie Polyethylenoxid und Polypropylenoxid und Copolymeren von Ethylenoxid und Propylenoxid, z.B. Poloxameren und Poloxaminen,

bestehenden Gruppe ausgewählt ist.

8. Zusammensetzung nach Anspruch 7, wobei das Polymer eine scheinbare Viskosität von 1 - 100 mPa.s aufweist, wenn es bei 20°C in einer 2%igen wäßrigen Lösung gelöst wird.

9. Zusammensetzung nach Anspruch 8, wobei es sich bei dem Polymer um Hydroxypropylmethylcellulose handelt.

10. Zusammensetzung nach einem der vorhergehenden Ansprüche, die sich schnell in Körperflüssigkeiten löst, **dadurch gekennzeichnet, daß** sie von 50 bis 95 Gew.-% Säure enthält.

11. Zusammensetzung nach einem der vorhergehenden Ansprüche, die für eine retardierte Freisetzung des Arzneimittels sorgt, **dadurch gekennzeichnet, daß** sie ein wasserlösliches Polymer enthält, das, wenn es bei 20°C in einer 2%igen wäßrigen Lösung gelöst wird, eine scheinbare Viskosität von über 1000 mPa.s aufweist.

12. Pharmazeutische Dosierungsform, enthaltend eine therapeutisch wirksame Menge einer nach einem der vorhergehenden Ansprüche definierten pharmazeutischen Zusammensetzung.

13. Dosierungsform nach Anspruch 12, die für eine topische Verabreichung oder eine Verabreichung in eine mit der Umgebung in Kontakt stehende Körperhöhle wie der Nase, den Lungen, dem Mund, dem Ohr, dem Magen, dem Rektum und der Vagina ausgelegt ist.

14. Dosierungsform nach Anspruch 12, wobei die Zusammensetzung in eine Standardkapsel abgefüllt wird oder alternativ mit Füllstoffen gemischt und zu Tabletten verpreßt wird.

15. Dosierungsform nach Anspruch 12, **dadurch gekennzeichnet, daß** 5, 15 und 45 Minuten nach Zugabe der Dosierungsform zu 0,1 N Salzsäure bei 37°C in dem im USP-Test <711> beschriebenen Auflösungstest in einem mit einem Rührer ausgestatteten USP-2-Auflösungsapparat von 7 bis 25%, von 45 bis 70% bzw. wenigstens 96% des Arzneimittels in der 0,1 N Salzsäure gelöst ist.

16. Pharmazeutische Zusammensetzung nach einem der Ansprüche 1 bis 11 oder pharmazeutische Dosierungsform nach einem der Ansprüche 12 bis 15 zur Verwendung in einem Therapie- oder Diagnoseverfahren am menschlichen Körper oder nichtmenschlichen Tierkörper.

17. Pharmazeutische Zusammensetzung nach einem der Ansprüche 1 bis 11 zur Verwendung bei der Herstellung einer pharmazeutischen Dosierungsform zur oralen Verabreichung an ein einer Behandlung bedürftiges Säugetier, **dadurch gekennzeichnet, daß** die Dosierungsform dem Säugetier zu jeder Tageszeit unabhängig von der Nahrungsmittelaufnahme verabreicht werden kann.

18. Verwendung einer pharmazeutischen Zusammensetzung nach einem der Ansprüche 1 bis 11 zur Herstellung einer pharmazeutischen Dosierungsform zur oralen Verabreichung an ein einer Behandlung bedürftiges Säugetier, **dadurch gekennzeichnet, daß** die Dosierungsform dem Säugetier zu jeder Tageszeit unabhängig von der Nahrungsmittelaufnahme verabreicht werden kann.

19. Verwendung einer pharmazeutischen Zusammensetzung nach einem der Ansprüche 1 bis 11 zur Herstellung eines Medikaments zur Verwendung in einem Therapie- oder Diagnoseverfahren am menschlichen oder nichtmenschlichen Körper.

20. Pharmazeutische Packung, geeignet für den kommerziellen Verkauf, enthaltend ein Behältnis, eine orale Dosierungsform nach einem der Ansprüche 12 bis 16 und eine gedruckte Packungsbeilage, wobei nicht eingeschränkt wird, ob die Dosierungsform mit oder ohne Nahrungsmittel verabreicht werden kann.

Revendications

1. Composition pharmaceutique comprenant un composé médicinal basique pas plus que peu hydrosoluble, une cyclodextrine, un acide hydrosoluble physiologiquement tolérable, et un polymère organique hydrosoluble physiologiquement tolérable, **caractérisée en ce qu'**elle comprend de 35 à 95 % en poids d'acide par rapport au poids total de cyclodextrine, de composé médicinal, de polymère organique et d'acide.

2. Composition selon la revendication 1, **caractérisée en ce que** les rapports en poids du composé médicinal à l'acide et du composé médicinal à la cyclodextrine ne sont pas plus que 2:1.

3. Composition selon la revendication 1 ou 2,
caractérisée en ce que les composants de la composition sont dispersés de manière à former un système chimiquement et physiquement uniforme ou homogène ou à constituer une phase.

4. Composition selon la revendication 3, **caractérisée en ce que** la cyclodextrine est la 2-hydroxypropyl-β-cyclodextrine.

5. Composition selon la revendication 3, **caractérisée en ce que** l'acide est choisi dans le groupe comprenant l'acide citrique, fumarique, tartrique, maléique, malique, succinique, oxalique, malonique, benzoïque, mandélique et ascorbique.

6. Composition selon la revendication 5, **caractérisée en ce que** l'acide est l'acide citrique.

7. Composition selon la revendication 3, **caractérisée en ce que** le polymère est choisi dans le groupe comprenant

- les alkylcelluloses telles que la méthylcellulose,
- les hydroxyalkylcelluloses telles que l'hydroxyméthylcellulose, l'hydroxyéthylcellulose, l'hydroxypropylcellulose et l'hydroxybutyl-cellulose,
- les hydroxyalkylalkylcelluloses telles que l'hydroxyéthylméthylcellulose et l'hydroxypropyl-méthylcellulose,
- les carboxyalkylcelluloses telles que la carboxyméthylcellulose,
- les sels alcalins des carboxyalkylcelluloses telles que la carboxyméthylcellulose sodique,
- les carboxyalkylalkylcelluloses telles que la carboxyméthyléthylcellulose,
- les esters de carboxyalkylcellulose,
- les amidons,
- les pectines telles que la carboxyméthylamylo-pectine sodique,
- les dérivés de chitine tels que le chitosane,
- l'héparine et les héparinoïdes,
- les polysaccharides tels que l'acide alginique, les sels alcalins et d'ammonium de ceux-ci, les carraghénanes, les galactomannanes, la gomme tragacanthe, la gélose, la gomme arabique, la gomme guar et la gomme

xanthane,

- les acides polyacryliques et leurs sels,
- les acides polyméthacryliques et leurs sels, les copolymères méthacrylates,
- l'alcool polyvinylique,
- la polyvinylpyrrolidone, les copolymères de polyvinylpyrrolidone avec l'acétate de vinyle,
- les polyoxydes d'alkylène tels que le polyoxyde d'éthylène et le polyoxyde de propylène et les copolymères d'oxyde d'éthylène et d'oxyde de propylène, par ex. les poloxamères et les poloxamines.

8. Composition selon la revendication 7, **caractérisée en ce que** le polymère a une viscosité apparente de 1 - 100 mPa.s lorsqu'il est dissous dans une solution aqueuse à 2 % à 20°C.

9. Composition selon la revendication 8, **caractérisée en ce que** le polymère est l'hydroxypropyl-méthylcellulose.

10. Composition selon l'une quelconque des revendications précédentes qui se dissout rapidement dans les liquides corporels, **caractérisée en ce qu'**elle comprend de 50 à 95 % en poids d'acide.

11. Composition selon l'une quelconque des revendications précédentes qui donne une libération prolongée du médicament, **caractérisée en ce qu'**elle comprend un polymère hydrosoluble ayant une viscosité apparente supérieure à 1 000 mPa.s lorsqu'il est dissous dans une solution aqueuse à 2 % à 20°C.

12. Forme pharmaceutique comprenant une quantité thérapeutiquement efficace d'une composition pharmaceutique telle que définie dans l'une quelconque des revendications précédentes.

13. Forme pharmaceutique selon la revendication 12, adaptée à l'administration par voie topique ou à l'administration dans une cavité corporelle à évacuation externe telle que le nez, les poumons, la bouche, l'oreille, l'estomac, le rectum et le vagin.

14. Forme pharmaceutique selon la revendication 12, **caractérisée en ce que** ladite composition est mise dans une capsule standard, ou de manière alternative est mélangée avec des agents de masse et mise en comprimés.

15. Forme pharmaceutique selon la revendication 12, **caractérisée en ce qu'**à 5, 15 et 45 minutes après l'addition de ladite forme pharmaceutique à de l'acide chlorhydrique 0,1 N à 37°C dans le test de dissolution énoncé dans le test USP <711> dans un appareil de dissolution USP-2 muni de pale, on dissout respectivement de 7 à 25 %, de 45 à 70 % et d'au moins 96 % de médicament dans ledit acide chlorhydrique 0,1 N.

16. Composition pharmaceutique selon l'une quelconque des revendications 1 à 11, ou forme pharmaceutique selon l'une quelconque des revendications 12 à 15, destinée à être utilisée dans une méthode de thérapie ou de diagnostic du corps animal humain ou non humain.

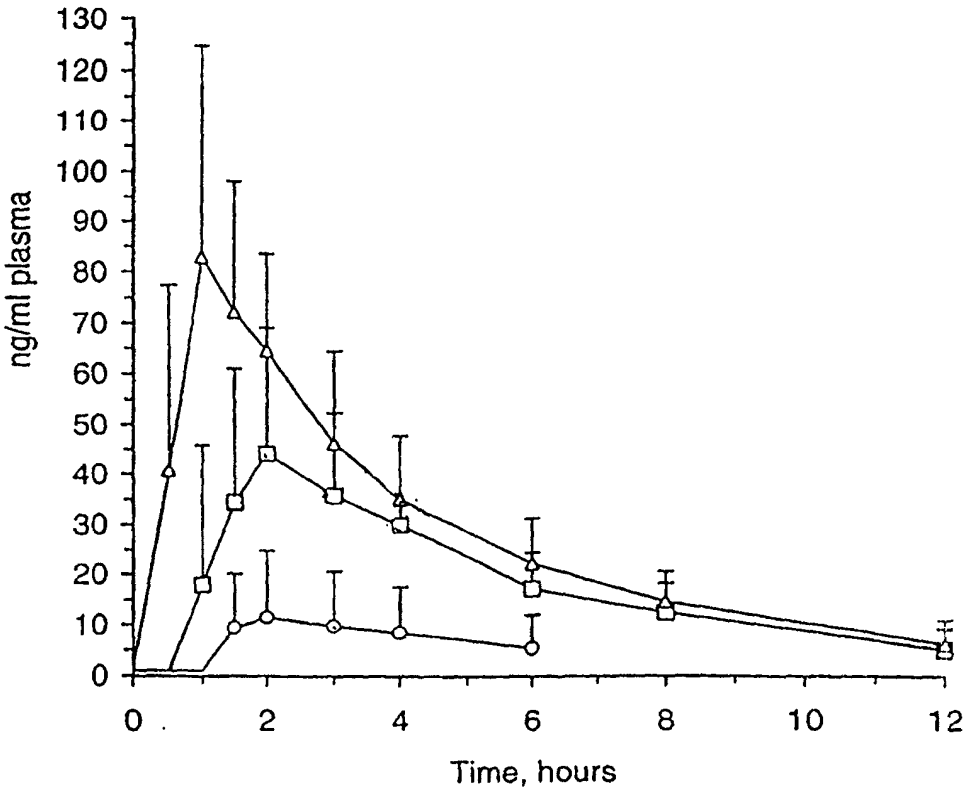
17. Composition pharmaceutique selon l'une quelconque des revendications 1 à 11, destinée à être utilisée dans la fabrication d'une forme pharmaceutique à administrer par voie orale à un mammifère nécessitant le traitement, **caractérisée en ce que** ladite forme pharmaceutique peut être administrée à tout moment de la journée indépendamment de la prise de nourriture par ledit mammifère.

18. Utilisation d'une composition pharmaceutique selon l'une quelconque des revendications 1 à 11, pour la fabrication d'une forme pharmaceutique à administrer par voie orale à un mammifère nécessitant le traitement, **caractérisée en ce que** ladite forme pharmaceutique peut être administrée à tout moment de la journée indépendamment de la prise de nourriture par ledit mammifère.

19. Utilisation de la composition pharmaceutique selon l'une quelconque des revendications 1 à 11, pour la fabrication d'un médicament destiné à être utilisé dans une méthode de thérapie ou de diagnostic du corps humain ou non humain.

20. Trousse pharmaceutique convenant à la commercialisation, comprenant un récipient, une forme pharmaceutique à administrer par voie orale selon l'une quelconque des revendications 12 à 16, et, associé à ladite trousse, un document écrit non limité en ce qui est de savoir si la forme pharmaceutique peut être administrée avec ou sans la nourriture.

Figure 1



—Δ— treatment (i)
—o— treatment (ii)
—□— treatment (iii)

Figure 2

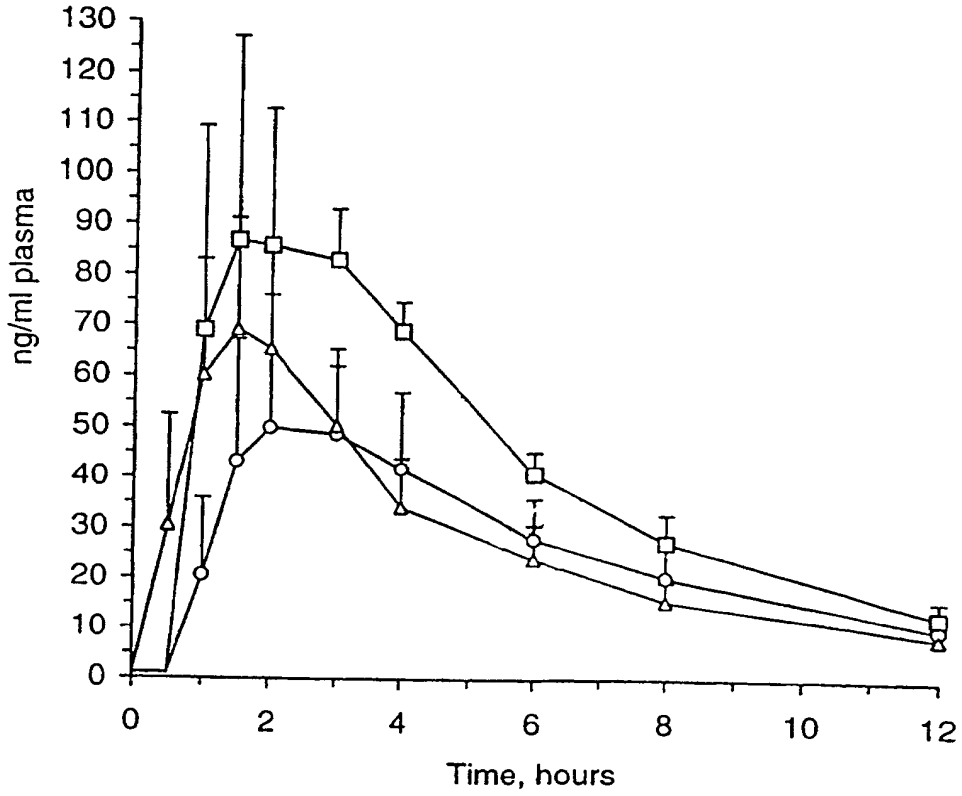
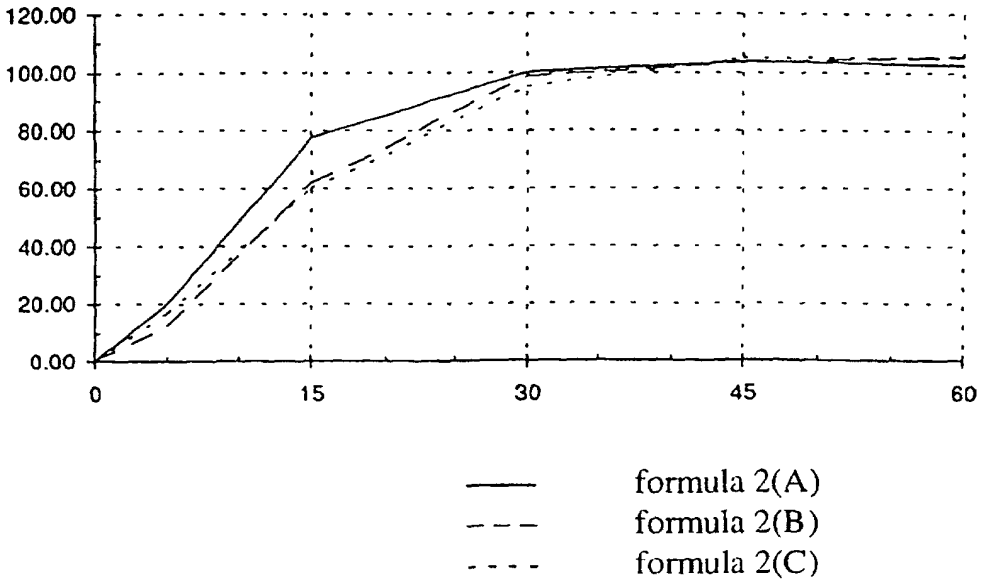


Figure 3



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(54) Ophthalmic solutions containing hydroxyethyl cellulose

(57) A sterile aqueous solution suitable for topical application to the eye as an artificial tear in the treatment of 'dry-eye' syndrome and as a comfort drop for wearers of contact lenses is described. The solution contains a hydroxyethyl cellulose together with sufficient of an ionic tonicity adjusting agent (e.g. an inorganic salt) to give the solution a tonicity value equivalent to that of a solution containing from 0.3 to 1.1% of sodium chloride. Preferred solutions are hypotonic and additionally contain a buffering agent to buffer the solution to a pH value of about 8.0.

GB 2 169 508 A

SPECIFICATION

Ophthalmic Compositions and Use

The present invention relates to an ophthalmic composition suitable for topical administration to the eye and to the use of that composition in the treatment of "dry-eye".

Some people suffer from discontinuous lachrymal films and in certain cases the lachrymal film can be almost completely deficient. Such "dry-eye" conditions can lead to discomfort, inflammation, profound damage to the cornea and even to loss of vision in extreme cases. Clearly there is a requirement to provide a remedy for dry-eye and a number of compositions have been described which offer some relief to the sufferer. Generally these known compositions have employed polymers to provide a synthetic lachrymal film as may be observed in the disclosures of United States Patent Specifications Nos. 3767788, 3767789, 3856919, 3907985, 3920810, 3937573, 4039662, 4120949 and 4131651. A variety of solutions for the remedy of dry eye are commercially available. However, most of these commercially available artificial tear solutions have been either very viscous, making them difficult to use, and their use can result in the build-up of sticky or even powdery residues on the eyelids and eyelashes thereby causing discomfort, or their viscosity is so low that a tear film is formed only for an unacceptably short time. It has now been found that an aqueous solution of hydroxyethyl cellulose and an ionic tonicity adjusting agent provides an artificial tear composition which provides a satisfactory tear film life time, also known as tear film break up time, without being excessively viscous.

Accordingly the present invention provides a sterile aqueous solution suitable for topical administration to the eye for the treatment of dry-eye which contains an effective amount of a hydroxyethyl cellulose together with sufficient of an ionic tonicity adjusting agent to give the solution a tonicity value equivalent to that of a solution containing from 0.3 to 1.1% of sodium chloride.

The present invention does not include solutions which contain a medicament and in particular they do not contain a medicament which is pharmacologically active in the eye.

The effective amount of hydroxyethyl cellulose required will depend upon its molecular weight and the effect that molecular weight has upon the viscosity of its aqueous solution. Clearly to provide an aqueous solution of suitable viscosity as hereinafter defined more hydroxyethyl cellulose will be required of a material having a low molecular weight than is required of a high molecular weight to give the same viscosity. In general, however, an effective amount of hydroxyethyl cellulose will be between 0.1 and 10%.

Hydroxyethyl celluloses are available commercially for example as Natrosols (Registered trade mark of Hercules Inc.), and Cellosizes (Registered trade mark of Union Carbide Chemical Co.). Suitable hydroxyethyl celluloses are those for which a 2% aqueous solution has a viscosity of between 4500 and 6500 cps at 25°C using a Brookfield LVF viscometer with a No. 4 spindle at a spindle speed of 60 rpm. A particularly favoured hydroxyethyl cellulose is available commercially as Natrosol 250M.

Suitably this hydroxyethyl cellulose will be present in an amount from 0.1 to 1.5%, more suitably from 0.25% to 0.75% and preferably 0.3 to 0.6% for example 0.4% or 0.5%. (When used herein % refers to percentage weight/volume).

It is particularly surprising that a solution containing simply 0.1 to 1.5% of hydroxyethyl cellulose together with an ionic tonicity agent will give suitable values for tear film break up time in the absence of film forming agents such as polyvinyl alcohol which are present in prior art formulations.

In order to obtain satisfactory tear film break up time without making the solution excessively viscous it is desirable that the tonicity of the solution is adjusted using an ionic tonicity agent. It has been found surprisingly that if an equivalent amount of a non-ionic tonicity agent is used the resulting tear film break up time is significantly lower than that of a solution containing an ionic tonicity agent. Suitable ionic tonicity adjusting agents include sodium chloride, potassium chloride, sodium borate with boric acid, mixtures of sodium and potassium salts of phosphoric acid or mixtures of any of these components, for example, a mixture of sodium chloride, sodium dihydrogen phosphate and disodium hydrogen phosphate. Particularly apt ionic tonicity agents are sodium chloride and sodium chloride mixed with sodium salt of boric acid. Preferred ionic tonicity adjusting agent is a mixture of sodium chloride, sodium dihydrogen phosphate and disodium hydrogen phosphate.

Suitably the solutions of the present invention will have a tonicity which is equivalent to that of an aqueous solution which contains from 0.3 to 1.1% of sodium chloride. More aptly the tonicity will be equivalent to a 0.45 to 0.75% sodium chloride solution. It is preferred that the solutions are hypotonic that is have a tonicity less than that of a 0.9% solution of sodium chloride. This has been found to provide a comfortable solution when applied to the eye and a satisfactory tear film break up time for the artificial tear film.

It is desirable that solutions of the present invention should contain buffering agent. Suitably the pH value of the solution will lie in the range from 6.0 to 9.0 and preferably from 7.0 to 8.5 and most preferably will be between 8.0 and 8.5. The pH of the natural tear film is approximately 7.4 and it is believed by some authorities that an artificial tear solution having a pH higher than 7.4 has a soothing effect on the eye in people suffering from dry eye. It is an advantage of solutions of the present invention that at such pHs the viscosity of the solution is not deleteriously raised or lowered thereby adversely affecting tear film break up time.

Suitable buffering agents include those based on mixtures of alkali metal salts of phosphoric acid, mixtures of sodium borate and boric acid and mixtures of potassium chloride, boric acid and sodium hydroxide which give suitable pH values.

From the foregoing the skilled man will appreciate that the use of such buffering agents will contribute to the tonicity of the solution and he will be aware of tables which provide formulations of suitable isotonic buffered aqueous solutions (see for example United States National Formulary 1980).

Suitably the aqueous solutions of the present invention will also contain a polyalkylene glycol. The presence of a polyalkylene glycol is believed to aid retention of the artificial tear film on the eye, thereby contributing to the satisfactory film life found with these solutions. Suitably the polyalkylene glycol is a polyethylene glycol having a molecular weight of between 200 and 8000. Such polyethylene glycols are known as the Carbowaxes (Registered trade mark of Carbide and Carbon Chemicals Company). A preferred polyethylene glycol is one having a molecular weight of 300, as exemplified by Carbowax 300. The amount of polyalkylene glycol present in the composition is suitably from 0.1 to 2.5%, and is more suitably 0.5 to 2.0% and is preferably 0.75 to 1.25%, for example 1%.

Most aptly the aqueous solution of this invention will be preserved with an ophthalmically acceptable preservative such as benzalkonium chloride, thiomersal, chlorbutanol and phenylethanol, phenylmercuric salts such as the nitrate or acetate. The preservative should be chosen to be compatible with the other components of the solution and not to effect unduly the tonicity. Each preservative has a concentration at which it is an effective bacteriostat without causing irritation to the eye. Thus suitably benzalkonium chloride will be present in an amount of 0.001 to 0.05% of the composition, preferably 0.005 to 0.02%. Thiomersal will be present at 0.001 to 0.05% of the composition and more suitably 0.002 to 0.01% and preferably 0.003 to 0.006%. Phenylmercuric salts such as the nitrate and acetate will be present at 0.001 to 0.01%, more suitably 0.0015 to 0.006% and preferably 0.002 to 0.004% of the composition. Most suitably the preservative used will be phenylmercuric nitrate.

Generally the viscosity of compositions of this invention will suitably lie between 10 and 100 centipoise and more suitably between 15 and 60 centipoise and preferably 20 to 50 centipoise. Viscosities are measured on a Brookfield LVF Viscometer using a UL adaptor at 12 rpm and at a temperature of 22°C.

Generally the tear film break up time of compositions of this invention will be above 250 seconds, more suitably will be above 300 seconds and preferably will be above 500 seconds. The tear film break up times are measured using an in vitro technique similar to that described in "The break-up time of artificial pre-ocular films on the rabbit cornea" J. W. Lamble, D. Gilbert, J. J. Ashford in J. Pharm. Pharmac. 1976 *28* 450—451.

Favourably the present invention provides a sterile aqueous solution suitable for topical administration to the eye for the treatment of dry eye which contains from 0.1 to 1.5% of hydroxyethyl cellulose, sufficient of an ionic tonicity adjusting agent to give the solution a tonicity value equivalent to that of a solution containing from 0.4 to 0.8% of sodium chloride, 0.001 to 0.05% of an ophthalmically acceptable preservative, the solution being buffered at pH 7.0 to 8.5.

Preferably the present invention provides a sterile aqueous solution suitable for topical administration to the eye for the treatment of dry eye which contains from 0.25 to 0.75% of hydroxyethyl cellulose, 0.3 to 0.5% sodium chloride, 0.002 to 0.004% phenylmercuric nitrate, the solution being buffered at a pH of 8.0 to 8.5 using a mixture of sodium borate and boric acid, the solution having a tonicity equivalent to an aqueous solution containing 0.45 to 0.75% sodium chloride.

In a second preferred embodiment the present invention provides a sterile aqueous solution suitable for topical administration to the eye for the treatment of dry eye which contains from 0.25 to 0.75% of hydroxyethyl cellulose, 0.1 to 1.5% of polyethylene glycol 0.3 to 0.5% sodium chloride, 0.002 to 0.004% phenylmercuric nitrate, the solution being buffered at a pH of 7.5 to 8.0 using a mixture of sodium dihydrogen phosphate and disodium hydrogen phosphate, the solution having a tonicity equivalent to an aqueous solution containing 0.45 to 0.75% sodium chloride.

The aqueous solutions of the present invention are sterile. Sterilisation may be carried out prior to preparation of the solution by sterilising the components separately, for example by sterilising hydroxyethyl cellulose aqueous solution by heat for example by autoclaving and then sterilising the aqueous solution containing the other components by filtration. The two sterile components are then brought together in appropriate amounts under aseptic conditions and filled into pre-sterilised eye-dropper bottles by conventional means. In a second method the solutions may be prepared by mixing the components in appropriate quantities. The resultant solution may be filled into eye-dropper bottles and the bottles and contents sterilised by heat, for example by autoclaving at 116°C for 30 minutes at 10 psi. In a third manner, the solution may be sterilised in bulk by heat, for example by autoclaving and the sterilised solution filled into pre-sterilised eye-dropper bottles under aseptic conditions.

Further the present invention provides a unit dose of the solution of the present invention having a volume of from 0.01 to 0.08 ml (that is a drop of 10 to 80 microlitres) and more usually 0.02 to 0.05 ml.

The aqueous solutions of this invention are aptly provided in a multidose container from which drops may be dispensed into the eye. Such containers are well known in the art for dispensing liquid drops into the eye and such conventional containers may be employed. Aptly such containers are adapted to hold 1 to 20 mls, more usually 2 to 12 mls and preferably 3 to 10 mls.

The solutions of the present invention may be prepared by dissolving appropriate amounts of the components in water. Most suitably the water is distilled water.

The invention further provides a method of treating dry eye by administering topically to the

eye a sterile aqueous solution containing hydroxyethyl cellulose together with an ionic tonicity adjusting agent. Suitable compositions containing hydroxyethyl cellulose and ionic tonicity agent are described herein.

EXAMPLE 1
Artificial Tear Solution

An aqueous solution suitable for use as an artificial tear was formulated as follows:

Hydroxyethylcellulose	0.44%
Sodium chloride	0.34%
Disodium hydrogen phosphate	0.54%
Phenylmercuric nitrate	0.002%
Sodium hydroxide solution to adjust pH to	8.5
Distilled water to	100 ml

The aqueous solution was prepared by dissolving the hydroxyethylene cellulose, sodium chloride, disodium hydrogen phosphate and phenyl mercuric nitrate in water (90 ml). The pH value of this solution was adjusted to 8.5 by the addition of 0.1M sodium hydroxide. Finally the volume of the solution was adjusted to 100 ml by the addition of distilled water. The solution may be filled into eye-dropper bottles and the bottle and its contents subsequently sterilised by heat for example by autoclaving at 116°C for 30 minutes at 10 psi pressure.

The solution had a viscosity of 30 cps when measured using a Brookfield LVF Viscometer using a UL adaptor at 12 rpm and at a temperature of 22°C. The solution had a tear film break up time when tested on the rabbit cornea as hereinbefore referred to of 555 seconds. The solution had a tonicity equivalent to a 0.7% solution of sodium chloride.

EXAMPLE 2
Artificial Tear Solution

An aqueous solution suitable for use as an artificial tear was formulated as follows:

Hydroxyethylcellulose	0.44%
Sodium chloride	0.34%
Boric acid	0.50%
Phenylmercuric nitrate	0.002%
Sodium hydroxide solution to adjust pH to	8.5
Distilled water to	100 ml

The aqueous solution was prepared in a similar manner to that described in Example 1. The solution may be packaged and sterilised as described in Example 1.

This solution had a viscosity of 30 cps and had a tonicity equivalent to a 0.7% solution of sodium chloride. The solution had a tear film break up time of 500 seconds.

EXAMPLE 3
Artificial Tear Solution

An aqueous solution suitable for use as an artificial tear was formulated as follows:

Hydroxyethyl cellulose	0.44%
Disodium hydrogen phosphate	0.57%
Sodium dihydrogen phosphate	0.12%
Sodium chloride	0.34%
Distilled water to	100 ml

The aqueous solution was prepared in a similar manner to that described in Example 1. The solution may be packaged and sterilised as described in Example 1.

This solution had a viscosity of 33.5 cps and was substantially isotonic, having a pH of 7.4. This solution had a tear film break up time of 573 seconds.

EXAMPLE 4
Artificial Tear Solution

An aqueous solution suitable for use in an artificial tear was formulated as follows:

Hydroxyethyl cellulose	0.4%
Sodium chloride	0.44%
Disodium hydrogen phosphate	0.57%
Sodium dihydrogen phosphate	0.12%
Polyethylene glycol (molecular weight 300)	1.0%
Phenylmercuric nitrate	0.002%
Distilled water to	100 ml

This aqueous solution was prepared in a similar manner to that described in Example 1. The solution may be packaged and sterilised as described in Example 1.

This solution had a viscosity of 30 cps and was isotonic at a pH of 7.4. The solution had a tear film break up time of 780 seconds.

EXAMPLE 5

Artificial Tear Solution

An aqueous solution suitable for use in an artificial tear is formulated as follows:

Hydroxyethyl cellulose	0.5%
Sodium chloride	0.44%
Disodium hydrogen phosphate	0.57%
Sodium dihydrogen phosphate	0.12%
Phenylmercuric nitrate	0.002%
Distilled water to	100 ml

The hydroxyethyl cellulose is dissolved in water (50 ml). The resultant solution is sterilised by heat, for example autoclaving at 116°C for 30 minutes at 10 psi pressure and is then stored under aseptic conditions. The sodium chloride, phosphate salts and phenylmercuric nitrate are dissolved in water (40 ml) and the resultant solution is sterilised by filtration through a 0.22 micron cellulose ester membrane filter.

The two sterile solutions thus prepared are combined under aseptic conditions and the volume is made up to 100 ml with sterile distilled water. The solution is then filled into pre-sterilised eye-dropper bottles.

CLAIMS

1. A sterile aqueous solution suitable for topical administration to the eye which contains an effective amount of a hydroxyethyl cellulose together with sufficient of an ionic tonicity adjusting agent to give the solution a tonicity value equivalent to that of a solution containing from 0.3 to 1.1% of sodium chloride.

2. A sterile aqueous solution as claimed in claim 1 which contains from 0.1 to 10% of hydroxyethyl cellulose.

3. A sterile aqueous solution as claimed in either of claims 1 or 2 which contains from 0.25 to 0.75% of hydroxyethyl cellulose.

4. A sterile aqueous solution as claimed in any one of claims 1 to 3 in which the tonicity value of the solution is equivalent to that of a solution containing from 0.45 to 0.75% of sodium chloride.

5. A sterile aqueous solution as claimed in any one of claims 1 to 4 in which the pH value of the solution lies in the range 7.0 to 8.5.

6. A sterile aqueous solution as claimed in any one of claims 1 to 5 which additionally contains a buffering agent.

7. A sterile aqueous solution as claimed in claim 6 in which the buffering agent is a mixture of disodium hydrogen phosphate and sodium-dehydrogen phosphate.

8. A sterile aqueous solution as claimed in claim 6 in which the buffering agent is a mixture of sodium borate and boric acid.

9. A sterile aqueous solution as claimed in any one of claims 1 to 8 which additionally contains from 0.1 to 2.5% of polyalkylene glycol.

10. A sterile aqueous solution as claimed in claim 9 in which the polyalkylene glycol is a polyethylene glycol having a molecular weight of between 200 and 8000.

11. A sterile aqueous solution as claimed in any one of claims 1 to 10 which additionally contains an ophthalmically acceptable preservative.

12. A sterile aqueous solution as claimed in claim 11 in which the preservative comprises from 0.001 to 0.01% of a phenylmercuric salt.

13. A sterile aqueous solution as claimed in any one of claims 1 to 12 in which the viscosity of the solution lies between 10 and 100 centipoise when measured on a Brookfield LVF Viscometer using a UL adaptor at 12 rpm and at a temperature of 22°C.

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最終頁に続く

(54)【発明の名称】　眼科用組成物及び抗アレルギー薬の持続性向上方法

(57)【要約】
【解決手段】　抗アレルギー薬を含有し、更に、高分子化合物及び／又は非イオン性界面活性剤を含有するソフトコンタクトレンズ用の眼科用組成物及び抗アレルギー薬を有効成分として含有するソフトコンタクトレンズ用の眼科用組成物に、高分子化合物及び／又は非イオン性界面活性剤を配合することを特徴とするソフトコンタクトレンズ装用時の眼への抗アレルギー薬の持続性向上方法。
【効果】　本発明によれば、ソフトコンタクトレンズ装用によって生じる眼のアレルギー症状を長時間に亘って改善する効果の高いソフトコンタクト用の眼科用組成物が得られ、また、ソフトコンタクトレンズ装用時の眼に対するアレルギー薬による改善効果の持続性を向上させることができる。

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【特許請求の範囲】

【請求項１】　抗アレルギー薬を含有してなることを特徴とするソフトコンタクトレンズ用の眼科用組成物。

【請求項２】　更に、高分子化合物及び／又は非イオン性界面活性剤を含有してなる請求項１記載のソフトコンタクトレンズ用の眼科用組成物。

【請求項３】　抗アレルギー薬を有効成分として含有するソフトコンタクトレンズ用の眼科用組成物に、高分子化合物及び／又は非イオン性界面活性剤を配合することを特徴とする抗アレルギー薬の持続性向上方法。

【発明の詳細な説明】

【０００１】

【発明の属する技術分野】本発明は、ソフトコンタクトレンズ用の眼科用組成物に関し、より詳しくは、抗アレルギー薬を含有することによって、ソフトコンタクトレンズ装用時における眼のアレルギー症状を改善することができ、更に、高分子化合物及び／又は非イオン性界面活性剤を配合することによって、ソフトコンタクトレンズ装用によって生じる眼のアレルギー症状を長時間に亘って改善する効果の高いソフトコンタクト用の眼科用組成物に関する。更に、本発明は、抗アレルギー薬による上記アレルギー症状の改善効果の持続性を向上させる抗アレルギー薬の持続性向上方法に関する。

【０００２】

【従来の技術】コンタクトレンズは、一般にハードコンタクトレンズとソフトコンタクトレンズとに大別することができる。これらコンタクトレンズの装用によって、かゆみ、炎症、充血、乾き目、疲れ目などの様々なトラブルが眼に生ずる。特にソフトコンタクトレンズの場合は、装用性が良好であるために、長時間の装用が可能であり、レンズ表面が乾燥して外界からの花粉等の異物や汚染物質が付着しやすくなる。このような外界からの花粉等の異物は、アレルギー反応を引き起こし、アレルギーの症状であるかゆみ、炎症、充血を誘えることが多い。

【０００３】しかしながら、ソフトコンタクトレンズ装用時に、これらのかゆみや炎症、充血を緩めてアレルギー症状を改善する組成物はこれまでにはなく、このようなソフトコンタクトレンズ用の眼科用組成物の出現が望まれていた。また、このような眼科用組成物としては、ソフトコンタクトレンズ装用時に有効成分が眼に長時間滞留して、アレルギー症状を長時間に亘って改善できることが望ましい。

【０００４】

【発明が解決しようとする課題】本発明は、上記事情に鑑みなされたもので、ソフトコンタクトレンズ装用によって生じる眼のアレルギー症状を改善するソフトコンタクトレンズ用の眼科用組成物及び抗アレルギー薬による

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【０００５】

【課題を解決するための手段及び発明の実施の形態】本発明者らは、上記課題を解決するために鋭意検討を行った結果、ソフトコンタクトレンズ用の眼科用組成物に抗アレルギー薬を配合することにより、ソフトコンタクトレンズ装用時に起こる特有のかゆみなどのアレルギー症状が改善されることを見い出した。更に、高分子化合物及び／又は非イオン性界面活性剤を配合すると、ソフトコンタクトレンズの濡れ性が高まり、違和感がないなどの使用性が向上すると共に、眼への抗アレルギー薬の滞留性が向上して、ソフトコンタクトレンズ装用時のアレルギー症状を長時間に亘って改善させることが可能となることを知見し、本発明をなすに至った。

【０００６】即ち、本発明は、（１）抗アレルギー薬を含有してなることを特徴とするソフトコンタクトレンズ用の眼科用組成物、より好ましくは、更に、高分子化合物及び／又は非イオン性界面活性剤を含有してなるソフトコンタクトレンズ用の眼科用組成物、（２）抗アレルギー薬を有効成分として含有するソフトコンタクトレンズ用の眼科用組成物に、高分子化合物及び／又は非イオン性界面活性剤を配合することを特徴とする抗アレルギー薬の持続性向上方法を提供する。

【０００７】以下、本発明につき、更に記述すると、本発明の眼科用組成物は、抗アレルギー薬を必須成分として含有するものである。

【０００８】ここで、本発明の抗アレルギー薬としては、例えばクロモグリク酸ナトリウム、クロモグリク酸カリウムなどのクロモグリク酸又はその塩、グリチルリチン酸二カリウム、グリチルリチン酸アンモニウムなどのグリチルリチン酸又はその塩、アンレキサノクス、トラニラスト、ペミロラストカリウム、フマル酸ケトチフェン等が挙げられ、これらは１種単独で又は２種以上を適宜組み合わせて使用することができる。本発明の場合、これらの中でも、特に好ましくはクロモグリク酸ナトリウム、グリチルリチン酸二カリウム等が挙げられる。

【０００９】本発明の眼科用組成物における上記抗アレルギー薬の配合量は、その種類などによって適宜選定され、例えばクロモグリク酸又その塩であれば、通常、組成物中に０．０５～１０ｗ／ｖ％（質量／容量％、以下同様）配合すると好適であり、より好ましくは０．１～５ｗ／ｖ％の範囲である。また、例えばグリチルリチン酸又はその塩であれば、通常、組成物中に０．０５～３ｗ／ｖ％配合すると好適であり、より好ましくは０．１～２ｗ／ｖ％である。配合量が少なすぎると、配合の効果を充分に得ることが困難な場合があり、多すぎると、製剤設計上の制約が生じる場合がある。

【００１０】本発明のソフトコンタクトレンズ用の眼科

フトコンタクトレンズ用のアレルギー用点眼剤等として使用される。

【００１１】ここで、本発明の眼科用組成物は、更に、高分子化合物及び／又は非イオン性界面活性剤を配合すると、より好適であり、本発明の抗アレルギー薬の持続性向上方法は、このように上記抗アレルギー薬を有効成分として含有するソフトコンタクトレンズ用の眼科用組成物に、更に上記高分子化合物及び／又は非イオン性界面活性剤を配合することによって、ソフトコンタクトレンズ装用時の眼への抗アレルギー薬の滞留性を向上させて、その改善効果を持続させるものである。

【００１２】本発明における高分子化合物としては、例えばポリビニルアルコール、ポリビニルピロリドン、ヒドロキシエチルセルロース、ヒドロキシプロピルメチルセルロース、メチルセルロース、シクロデキストリン等が挙げられ、これらは１種単独で又は２種以上を適宜組み合わせて使用することができる。これらの中でも、特に好ましくはメチルセルロース、シクロデキストリン等である。

【００１３】本発明の眼科用組成物における上記高分子化合物の配合量は、その種類などによって適宜選定され、例えばメチルセルロース、ヒドロキシエチルセルロース、ヒドロキシプロピルメチルセルロースであれば、通常、組成物中に好ましくは０．０１～５ｗ／ｖ％、より好ましくは０．０５～１ｗ／ｖ％、シクロデキストリンであれば、通常、組成物中に好ましくは０．００１～５ｗ／ｖ％、より好ましくは０．００５～２ｗ／ｖ％、ポリビニルアルコール、ポリビニルピロリドンであれば、通常、組成物中に好ましくは０．０１～１０ｗ／ｖ％、より好ましくは０．１～５ｗ／ｖ％の範囲で配合すると好適である。上記高分子化合物の配合量が少なすぎると、レンズの濡れ性が不十分となるため、抗アレルギー薬の眼への滞留性向上を達成することが困難となり、十分な持続性が得られ難い場合があり、上記高分子化合物の配合量が多すぎると、粘度が高すぎて点眼時に違和感を感じる場合がある。

【００１４】本発明における非イオン性界面活性剤としては、水溶性のポリオキシエチレン硬化ヒマシ油等のポリオキシエチレン高級脂肪酸エステル、ポリオキシエチレンソルビタン高級脂肪酸エステル等が挙げられ、より具体的には、例えば、ポリオキシエチレン（ｐ＝６０）硬化ヒマシ油、ポリオキシエチレン（ｐ＝２０）ソルビタンモノオレエート等がある。ここで、ｐはエチレンオキシドの平均付加モル数を示す。これらは１種単独で又は２種以上を適宜組み合わせて使用することができる。

【００１５】本発明の眼科用組成物における非イオン性界面活性剤の配合量は、特に制限されるものではなく、通常、組成物中に０．０１～１ｗ／ｖ％配合すると好適

／ｖ％未満であるとレンズの濡れ性が不十分となるため、抗アレルギー薬の眼への滞留性向上を達成して、優れた持続性を得ることが困難となる場合があり、また１ｗ／ｖ％を超えると眼への刺激性が強くなる等の問題を生じる場合がある。

【００１６】本発明のソフトコンタクトレンズ用の眼科用組成物の形状としては、例えば点眼剤、眼軟膏剤、ゲル剤、用時溶解により液状となる固形製剤等が挙げられるが、好ましくは点眼剤の形態である。

【００１７】本発明においては、本発明の効果を妨げない範囲で前記した必須成分の他に前記した点眼剤、眼軟膏剤、ゲル剤等の製剤の調製に通常使用する全ての緩衝剤、溶解補助剤、等張化剤、安定化剤、粘稠剤、キレート剤、ｐＨ調整剤、清涼化剤等の各種の添加剤及びその他の薬学的有効成分などを通常使用量において配合することができる。

【００１８】より具体的には、緩衝剤としては、例えばホウ酸又はその塩（ホウ砂等）、クエン酸又はその塩（クエン酸ナトリウム等）、リン酸又はその塩（リン酸一水素ナトリウム等）、酒石酸又はその塩（酒石酸ナトリウム等）、グルコン酸又はその塩（グルコン酸ナトリウム等）、酢酸又はその塩（酢酸ナトリウム等）、各種アミノ酸等又はそれらの組み合わせなどが挙げられる。

【００１９】溶解補助剤としては、例えばポリエチレングリコール、プロピレングリコール等が挙げられる。等張化剤としては、例えば塩化ナトリウム、塩化カリウム、マンニトール、プロピレングリコール等が挙げられる。

【００２０】安定化剤としては、例えばエデト酸ナトリウム、シクロデキストリン、亜硫酸塩、クエン酸又はその塩等が挙げられる。粘稠剤としては、例えばポリエチレングリコール、ポリビニルアルコール、ポリビニルピロリドン、ヒドロキシエチルセルロース、ヒドロキシプロピルメチルセルロース、メチルセルロース、コンドロイチン硫酸ナトリウム等が挙げられる。

【００２１】キレート剤としては、例えばエデト酸ナトリウム、クエン酸ナトリウム等が挙げられる。ｐＨ調整剤としては、例えば塩酸、クエン酸又はその塩、ホウ酸又その塩、リン酸又はその塩、酢酸又はその塩、酒石酸又はその塩、水酸化ナトリウム、水酸化カリウム、炭酸ナトリウム、炭酸水素ナトリウム等が挙げられる。清涼化剤としては、例えばメントール、ボルネオール、カンフル、グラニオール、リモネン、オイゲノール、ハッカ油、ユーカリ油等が挙げられる。

【００２２】薬学的有効成分としては、例えば充血除去剤（塩酸ナファゾリン、塩酸テトラヒドロゾリン、塩酸フェニレフリン等）、消炎・収斂剤（メチル硫酸ネオスチグミン、イプシロン－アミノカプロン酸、アラントイ

ベンジル、マレイン酸クロルフェニラミン等）、ビタミン類［ビタミンA及びそのエステル（例えば酢酸エステル、パルミチン酸エステル）、活性型ビタミンB_2、ビタミンB_6、ビタミンB_{12}、ビタミンE及びそのエステル（例えば酢酸エステル）等］、アミノ酸類（L－アスパラギン酸カリウム、L－アスパラギン酸マグネシウム、アミノエチルスルホン酸、コンドロイチン硫酸ナトリウム等）、サルファ剤、殺菌剤（イオウ、イソプロピルメチルフェノール、ヒノキチオール等）、局所麻酔剤（リドカイン、塩酸リドカイン、塩酸プロカイン、塩酸ジブカイン等）などを適宜配合することができる。

【００２３】本発明の眼科用組成物のｐＨは、眼科的に許容される範囲であれば特に制限はなく、通常ｐＨ４～９の範囲であり、好ましくは５～８．５である。

【００２４】本発明の眼科用組成物の調製方法は特に問わないが、例えば、点眼剤の場合は、各配合成分を順次滅菌精製水に加えて溶解し、ｐＨを調整することにより得られる。

【００２５】本発明のソフトコンタクトレンズ用眼科用組成物の投与量は、眼科的に許容される範囲であれば特に制限はないが、例えば点眼剤として用いる場合、１回量１～３滴を１日４～６回投与することが好ましい。

【００２６】

【実施例】以下に実施例及び比較例を挙げて本発明を更に詳細に説明するが、本発明は、下記実施例によって何ら限定されるものではない。

【００２７】［実施例１～３及び比較例１，２］表１に＊示す組成に従って点眼剤を常法により調製した。アレルギー既往歴のあるソフトコンタクトレンズ装用者６名をパネラーとし、アレルギー（かゆみ）発症時に各点眼剤を投与したときのかゆみの改善度合いとその持続時間及び使用感（違和感の程度）を調べた。得られた結果を以下の評価基準にしたがって評価した。結果を表２に示す。

【００２８】かゆみの改善度合いの評価基準

５点：かゆみが軽減された

４点：かゆみがやや軽減された

３点：かゆみが変わらない

２点：かゆみがややひどくなった

１点：かゆみがひどくなった

【００２９】かゆみ改善の持続の度合いの評価基準

◎：６０分以上持続した

○：３０分以上６０分未満の持続

△：１０分以上３０分未満の持続

×：１０分未満の持続

－：かゆみの改善なし、またはひどくなった

【００３０】使用感（違和感の程度）の評価基準

◎：全く違和感がない

○：ほとんど違和感がない

△：違和感が感じられた

×：違和感が強く感じられた

【００３１】

【表１】

成分(g/100ml)	実施例1	実施例2	実施例3	比較例1	比較例2
ｸﾛﾓｸﾞﾘｶﾝ酸ナトリウム	1.0	1.0	1.0	—	—
ｼﾞｸｴﾄｷｼﾝ酸二ﾅﾄﾘｳﾑ	—	—	—	—	—
ﾒﾁﾙｾﾙﾛｰｽ	—	0.35	—	—	0.35
ﾎﾟﾘｵｷｼｴﾁﾚﾝ硬化ﾋﾏｼ油60	—	—	0.25	—	0.25
塩化ﾅﾄﾘｳﾑ	0.5	0.5	0.5	0.5	0.5
塩化ｶﾘｳﾑ	0.15	0.15	0.15	0.15	0.15
砂糖	1.0	1.0	1.0	1.0	1.0
和砂	0.1	0.1	0.1	0.1	0.1
ﾒﾁﾙﾊﾟﾗﾍﾞﾝ	0.01	0.01	0.01	0.01	0.01
塩化ﾍﾞﾝｻﾞﾙｺﾆｳﾑ	0.005	0.005	0.005	0.005	0.005
滅菌精製水	適量	適量	適量	適量	適量
全量	100ml	100ml	100ml	100ml	100ml
ｐＨ	7.0	7.0	7.0	7.0	7.0

【００３２】

【表２】

評価項目	パネラー	実施例1	実施例2	実施例3	比較例1	比較例2
かゆみの改善度合い	A	4点	5点	6点	2点	2点
	B	4点	5点	6点	2点	2点
	C	4点	5点	5点	2点	2点
	D	4点	5点	4点	2点	2点
	E	4点	5点	5点	3点	3点
	F	5点	5点	5点	3点	3点
かゆみ改善の持続時間の度合い	A	○	◎	◎	－	－
	B	○	◎	◎	－	－
	C	△	◎	○	－	－
	D	○	◎	◎	－	－
	E	◎	◎	◎	－	－
	F	○	◎	◎	－	－
使用感（違和感の程度）	A	○	◎	○	△	×
	B	○	◎	◎	△	／
	C	◎	◎	◎	○	○
	D	◎	◎	◎	△	△
	E	◎	◎	◎	○	△
	F	○	○	◎	△	△

【００３３】表２の結果から明らかなように、抗アレルギー薬の配合によりかゆみが改善され、更に高分子化合物を配合した実施例２及び非イオン性界面活性剤を含有した実施例３を点眼した眼はかゆみの改善度合いが高まり、またかゆみ改善の持続時間が長く、更に使用感についても向上した。これに対して、抗アレルギー薬を含まない比較例１、高分子化合物及び非イオン性界面活性剤のみを含有した比較例２を点眼した眼では、かゆみの改善度合いにほとんど変化がなく、使用感も悪かった。

【００３４】このことより、抗アレルギー薬の配合により、コンタクトレンズ装用時に起こるかゆみなどのアレルギー症状が改善されることが確認された。更に、抗アレルギー薬に高分子化合物及び／又は非イオン性界面活性剤を併用することによって、コンタクトレンズ装用時のかゆみなどのアレルギー症状が長時間に亘って改善されると共に、点眼時の使用感が高まることが確認された。

【００３５】〔実施例４～２７〕表３～５に示す組成に従って常法により点眼剤を調製し、ソフトコンタクトレンズ装用者８名に上記実施例及び比較例と同様の評価基準で眼のかゆみの改善度合い、持続時間、使用感（違和感の程度）を評価させた。８人中最も多かった評点を評価点とした。結果を表３～５に併記する。

【００３６】

【表３】

成分(g/100ml)	実施例							
	4	5	6	7	8	9	10	11
ﾄﾗﾆﾗｽﾄ	0.05	0.1	0.5	1.0	1.0	2.0	3.9	5.0
ﾒﾁﾙｾﾙﾛｰｽ	－	0.05	1.0	0.35	－	－	－	－
α-ｼｸﾛﾃﾞｷｽﾄﾘﾝ	0.005	－	－	－	0.5	－	－	2.0
β-ｼｸﾛﾃﾞｷｽﾄﾘﾝ	－	－	1.0	－	－	－	－	－
γ-ｼｸﾛﾃﾞｷｽﾄﾘﾝ	－	0.1	－	－	－	－	－	－
ﾋﾄﾞﾛｷｼﾌﾟﾛﾋﾟﾙﾒﾁﾙｾﾙﾛｰｽ	0.25	－	－	－	－	－	－	－
ﾋﾄﾞﾛｷｼｴﾁﾙｾﾙﾛｰｽ	－	－	－	－	－	0.7	－	－
ｶﾞﾚﾋﾞﾆｺｰﾙ	－	－	－	－	－	－	－	0.6
ｶﾞﾚﾋﾞﾆﾙｱﾙｺｰﾙ	－	－	－	－	－	－	0.25	－
ﾎﾟﾘｵｷｼｴﾁﾚﾝ硬化ﾋﾏｼ油60	0.15	0.15	0.2	－	0.3	0.3	0.3	－
ﾎﾟﾘｿﾙﾍﾞｰﾄ80	－	－	－	0.25	－	－	－	0.3
塩化ﾅﾄﾘｳﾑ	0.5	0.5	0.5	0.4	0.4	0.45	0.45	0.45
塩化ｶﾘｳﾑ	0.15	0.15	0.1	0.15	0.1	0.1	0.1	0.1
ﾎｳ酸	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
ﾎｳ砂	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07
ｴﾃﾞﾄ酸ﾅﾄﾘｳﾑ	0.01	0.005	0.01	0.002	0.01	0.01	0.01	0.005
塩化ﾍﾞﾝｻﾞﾙｺﾆｳﾑ	0.003	0.005	0.005	0.003	0.005	0.01	0.005	0.005
精製水	適量	適量	適量	適量	適量	適量	適量	適量
結果 かゆみの改善	4点	4点	5点	5点	5点	5点	5点	5点
結果 持続時間	△	○	◎	◎	◎	◎	◎	◎
結果 使用感	◎	◎	◎	◎	◎	◎	◎	△

成分(g/100ml)	実施例							
	12	13	14	15	16	17	18	19
ﾀﾞｲﾔｽﾀﾃﾝ酸二ﾅﾄﾘｳﾑ	0.05	0.1	0.25	0.5	0.8	1.0	2.0	3.0
ﾒﾁﾙｾﾙﾛｰｽ	—	0.05	1.0	2.0	—	—	—	—
α-ｼｸﾛﾃﾞｷｽﾄﾘﾝ	0.001	—	—	—	0.5	—	—	3.0
β-ｼｸﾛﾃﾞｷｽﾄﾘﾝ	—	—	1.0	—	—	—	—	—
γ-ｼｸﾛﾃﾞｷｽﾄﾘﾝ	—	0.1	—	—	—	—	—	—
ﾋﾄﾞﾛｷｼｴﾁﾙｾﾙﾛｰｽ	0.25	—	—	—	—	—	—	—
ﾋﾄﾞﾛｷｼﾌﾟﾛﾋﾟﾙﾒﾁﾙｾﾙﾛｰｽ	—	—	—	—	—	0.5	—	—
ﾎﾟﾘｵｷｼｴﾁﾚﾝｿﾙﾋﾞﾄﾝ	—	—	—	—	—	—	—	0.005
ﾎﾟﾘｵｷｼｴﾁﾚﾝｾﾁﾙｴｰﾃﾙ	—	—	—	—	—	—	1.0	—
ﾎﾟﾘｵｷｼｴﾁﾚﾝ硬化ﾋﾏｼ油60	0.05	0.15	0.2	—	—	0.3	0.45	—
ﾎﾟﾘｿﾙﾍﾞｰﾄ80	—	—	—	0.15	0.25	—	—	0.5
塩化ﾅﾄﾘｳﾑ	0.5	0.5	0.5	0.45	0.4	0.4	0.45	0.45
塩化ｶﾘｳﾑ	0.15	0.15	0.1	0.1	0.15	0.1	0.1	0.1
ﾎｳ酸	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
ﾎｳ砂	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07
ｴﾃﾞﾄ酸ﾅﾄﾘｳﾑ	0.01	0.005	0.01	0.005	0.002	0.01	0.01	0.005
塩化ﾍﾞﾝｻﾞﾙｺﾆｳﾑ	0.002	0.005	0.005	0.005	0.003	0.005	0.01	0.005
殺菌精製水	適量	適量	適量	適量	適量	適量	適量	適量
結果 かゆみの改善	4点	4点	5点	5点	5点	5点	5点	5点
結果 持続時間	△	○	◎	◎	◎	◎	◎	◎
結果 使用感	◎	◎	◎	◎	◎	◎	◎	△

【００３８】

＊20＊【表５】

成分(g/100ml)	実施例							
	20	21	22	23	24	25	26	27
ﾄﾏｰﾗｽﾀﾝ	0.1	0.5	1.0	—	—	—	—	—
ｱﾝﾚｷｻﾉｰﾙｽ	—	—	—	—	—	0.25	—	—
ﾍﾐﾛﾗｽﾄﾅﾄﾘｳﾑ	—	—	—	0.05	0.2	—	—	—
ﾌﾙﾙﾋﾞﾌﾟﾛﾌｪﾝ	—	—	—	—	—	—	0.01	0.05
ﾒﾁﾙｾﾙﾛｰｽ	—	0.5	2.0	0.05	—	—	—	—
α-ｼｸﾛﾃﾞｷｽﾄﾘﾝ	0.005	—	—	—	0.7	—	—	0.01
β-ｼｸﾛﾃﾞｷｽﾄﾘﾝ	—	—	0.005	—	—	—	—	—
γ-ｼｸﾛﾃﾞｷｽﾄﾘﾝ	—	0.2	—	—	—	—	—	—
ﾋﾄﾞﾛｷｼｴﾁﾙｾﾙﾛｰｽ	0.5	—	—	—	—	—	—	—
ﾋﾄﾞﾛｷｼﾌﾟﾛﾋﾟﾙﾒﾁﾙｾﾙﾛｰｽ	—	—	—	—	—	0.7	—	—
ﾎﾟﾘｵｷｼｴﾁﾚﾝｿﾙﾋﾞﾄﾝ	—	—	—	—	—	—	—	2.0
ﾎﾟﾘｵｷｼｴﾁﾚﾝｾﾁﾙｴｰﾃﾙ	—	—	—	—	0.05	—	5.0	—
ﾎﾟﾘｵｷｼｴﾁﾚﾝ硬化ﾋﾏｼ油60	0.05	0.15	0.2	—	—	0.3	0.45	—
ﾎﾟﾘｿﾙﾍﾞｰﾄ80	—	—	—	0.15	0.25	—	—	0.5
塩化ﾅﾄﾘｳﾑ	0.5	0.55	0.5	0.5	0.4	0.4	0.45	0.45
塩化ｶﾘｳﾑ	0.15	0.15	0.15	0.1	0.15	0.1	0.1	0.1
ﾎｳ酸	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
ﾎｳ砂	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07
ｴﾃﾞﾄ酸ﾅﾄﾘｳﾑ	0.01	0.005	0.005	0.01	0.002	0.01	0.01	0.005
塩化ﾍﾞﾝｻﾞﾙｺﾆｳﾑ	0.003	0.005	0.005	0.005	0.003	0.005	0.01	0.005
殺菌精製水	適量	適量	適量	適量	適量	適量	適量	適量
結果 かゆみの改善	4点	5点	5点	4点	5点	5点	4点	5点
結果 持続時間	○	◎	◎	○	◎	◎	○	◎
結果 使用感	◎	◎	◎	◎	◎	◎	◎	◎

【００３９】

【発明の効果】本発明によれば、ソフトコンタクトレンズ装用によって生じる眼のアレルギー症状を長時間に亘って改善する効果の高いソフトコンタクトレンズ用の眼科用組成物が得られ、また、ソフトコンタクトレンズ装用時の眼に対するアレルギー薬による改善効果の持続性を向上させることができる。

フロントページの続き

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(54) METHOD FOR IMPROVING SUSTAINABILITY OF OPHTHALMIC COMPOSITION AND ANTI-ALLERGIC MEDICINE

(57)Abstract:

PROBLEM TO BE SOLVED: To obtain an ophthalmic composition having a high potency for improving the allergic symptoms of eyes generated by wearing soft contact lenses, for a long period of time, and also capable of improving the sustainability of the improving effect by the anti-allergic medicine for the eyes on wearing the soft contact lenses.

SOLUTION: This ophthalmic composition for the soft contact lenses contains the anti-allergic medicine and further a polymeric compound and/or nonionic surfactant, and the method for improving the sustainability of an anti-allergic medicine for eyes on wearing soft contact lenses is characterized by blending the ophthalmic composition for soft lenses, containing the anti-allergic medicine as an active ingredient with the polymeric compound and/or nonionic surfactant.

* NOTICES *

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3.In the drawings, any words are not translated.

CLAIMS

[Claim(s)]
[Claim 1]A constituent for ophthalmology for soft contact lenses which contains an antiallergic drug and is characterized by things.
[Claim 2]A constituent for ophthalmology containing a high molecular compound and/or a nonionic surfactant for the soft contact lenses according to claim 1.
[Claim 3]An upper part method for durability of an antiallergic drug blending a high molecular compound and/or a nonionic surfactant with a constituent for ophthalmology for soft contact lenses which contains an antiallergic drug as an active principle.

[Translation done.]

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DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention]The present invention about the constituent for ophthalmology for soft contact lenses in more detail, By containing an antiallergic drug, can improve the allergies of the eye at the time of soft contact lens wearing, and by blending a high molecular compound and/or a nonionic surfactant further, It is related with the high constituent for ophthalmology of the effect of covering a long time and improving the allergies of the eye produced by soft contact lens wearing for soft contact. The present invention relates to the upper part method for durability of the antiallergic drug which improves the durability of the improvement effect of the above-mentioned allergies by an antiallergic drug.
[0002]
[Description of the Prior Art]Generally a contact lens can be divided roughly into a hard lens and a soft contact lens. By wearing of these contact lenses, various troubles, such as itching, inflammation, congestion, a dryness eye, and eye strain, arise in an eye. Since wearing nature is good especially in the case of a soft contact lens, prolonged wearing is possible, a lens surface dries and the foreign matters and pollutants from the external world, such as pollen, adhere easily. Foreign matters, such as pollen from such the external world, trigger an allergic reaction, and appeal against the itching, inflammation, and congestion which are the condition of allergy in many cases.

[0003]However, at the time of soft contact lens wearing, such itching or inflammation, and the constituent which calms congestion and improves allergies are not in the former, and an appearance of such a constituent for ophthalmology for soft contact lenses was desired. It is desirable to stagnate in an eye for a long time, and for an active principle to cover a long time and to be able to improve allergies as such a constituent for ophthalmology, at the time of soft contact lens wearing.

[0004]

[Problem to be solved by the invention]The present invention was made in view of the above-mentioned situation, and an object of the present invention is to provide the upper part method for durability of an antiallergic drug make the improvement effect by the constituent for ophthalmology and antiallergic drug for soft contact lenses which improve the allergies of the eye produced by soft contact lens wearing maintain.

[0005]

[The means for solving a technical problem and an embodiment of the invention] The inventors found out that allergies, such as characteristic itching which happens at the time of soft contact lens wearing, were improved by blending an antiallergic drug with the constituent for ophthalmology for soft contact lenses, as a result of inquiring intensively, in order to solve an aforementioned problem. If a high molecular compound and/or a nonionic surfactant are blended, usability, like the wettability of a soft contact lens increases and it is comfortable will improve, and. The retentivity of the antiallergic drug to an eye improves, the knowledge of it becoming possible to cover a long time and to make the allergies at the time of soft contact lens wearing improve is carried out, and it came to make the present invention.

[0006]namely, the constituent for ophthalmology for soft contact lenses which the present invention contains (1) antiallergic drug and is characterized by things -- more preferably, The constituent for ophthalmology containing a high molecular compound and/or a nonionic surfactant for soft contact lenses, (2) Provide the upper part method for durability of the antiallergic drug blending a high molecular compound and/or a nonionic surfactant with the constituent for ophthalmology for soft contact lenses which contains an antiallergic drug as an active principle.

[0007]Hereafter, if it describes about the present invention, the constituent for ophthalmology of the present invention contains an antiallergic drug as an essential

ingredient.

[0008]As an antiallergic drug of the present invention, here, for example Cromoglycic acid or its salts, such as disodium cromoglycate and the cromoglycic acid potassium, Glycyrrhizic acid, such as glycyrrhizinate dipotassium and glycyrrhizic acid ammonium, or the salt of those, amlexanox, tranilast, pemirolast potassium, ketotifen fumarate, etc. are mentioned, and these can be used, combining suitably a 1 type independent or 2 type or more. In the case of the present invention, disodium cromoglycate, glycyrrhizinate dipotassium, etc. are especially mentioned preferably also in these.

[0009]The compounding amount of the above-mentioned antiallergic drug in the constituent for ophthalmology of the present invention, if it is suitably selected by the kind, for example, it is cromoglycic acid and its salt, when 0.05-10 w/v% (mass / capacity %, and the following -- the same) combination will usually be carried out into a constituent, it is preferable and is 0.1 - 5 w/v% of range more preferably. If it is glycyrrhizic acid or its salt, for example, when 0.05-3 w/v% combination is carried out into a constituent, it is preferable and is usually 0.1 - 2 w/v% more preferably. If it may be difficult to acquire the effect of combination sufficiently if there is too little compounding amount and there are, the restrictions on a dosage form design may arise. [too many]

[0010]The constituent for ophthalmology for the soft contact lenses of the present invention can be used for the constituent of all the ophthalmology uses for soft contact lenses. Specifically, it is used as ophthalmic solutions for allergy for soft contact lenses, etc.

[0011]When a high molecular compound and/or a nonionic surfactant are blended, more, the constituent for ophthalmology of the present invention is still more nearly preferable here, and the upper part method for durability of the antiallergic drug of the present invention, Thus, to the constituent for ophthalmology for soft contact lenses contained as an active principle, the above-mentioned antiallergic drug by blending the above-mentioned high molecular compound and/or a nonionic surfactant, The retentivity of the antiallergic drug to the eye at the time of soft contact lens wearing is improved, and the improvement effect is made to maintain.

[0012]As a high molecular compound in the present invention, for example Polyvinyl alcohol, A polyvinyl pyrrolidone, hydroxyethyl cellulose, hydroxypropylmethylcellulose,

methyl cellulose, cyclodextrin, etc. are mentioned, and these can be used, combining suitably a 1 type independent or 2 type or more. Also in these, they are methyl cellulose, cyclodextrin, etc. especially preferably.

[0013]The compounding amount of the above-mentioned high molecular compound in the constituent for ophthalmology of the present invention, Are suitably selected by the kind, for example, if it is methyl cellulose, hydroxyethyl cellulose, and hydroxypropylmethylcellulose, usually, the inside of a constituent -- preferable -- 0.01-5 -- w/v%, if it is 0.05 - 1 w/v% and cyclodextrin more preferably, usually, the inside of a constituent -- preferable -- 0.001-5 -- w/v%, if it is 0.005 - 2 w/v%, polyvinyl alcohol, and a polyvinyl pyrrolidone more preferably, usually, the inside of a constituent -- preferable -- 0.01-10 -- w/v%, if it blends in 0.1 - 5 w/v% of range more preferably, it is preferable. Since the wettability of a lens will become insufficient if there is too little compounding amount of the above-mentioned high molecular compound, It becomes difficult to attain the improvement in retentivity to the eye of an antiallergic drug, sufficient durability may be hard to be acquired, if there is too much compounding amount of the above-mentioned high molecular compound, viscosity is too high and sense of incongruity may be sensed at the time of instillation.

[0014]As a nonionic surfactant in the present invention, They are mentioned by polyoxyethylene higher-fatty-acid ester, such as water-soluble polyoxyethylene hydrogenated castor oil, polyoxyethylene sorbitan higher-fatty-acid ester, etc., and more specifically, For example, there are polyoxyethylene (p= 60) hydrogenated castor oil, polyoxyethylene (p= 20) sorbitan monooleate, etc. Here, p shows the number of average addition mols of ethylene oxide. These can be used combining suitably a 1 type independent or 2 type or more.

[0015]When the compounding amount in particular of the nonionic surfactant in the constituent for ophthalmology of the present invention is not restricted and usually carries out 0.01-1 w/v% combination into a constituent, it is preferable and is 0.05 - 0.5 w/v% of range more preferably. Since the wettability of a lens becomes that the compounding amount of a nonionic surfactant is less than [0.01 w/v%] insufficient, If it may become difficult to attain the improvement in retentivity to the eye of an antiallergic drug, and to acquire the outstanding durability and 1 w/v% is exceeded, the stimulativeness to an eye may produce problems, such as becoming strong.

[0016]as the form of the constituent for ophthalmology for the soft contact lenses of the present invention -- ophthalmic solutions, ophthalmic ointments, gel, and business -- the time -- the dissolution -- being liquefied -- becoming -- solid preparations -- etc. -- mentioning -- having -- although -- preferable -- the form of ophthalmic solutions -- it is .

[0017]The ophthalmic solutions described above besides the essential ingredient described above in the present invention in the range which does not bar the effect of the present invention, Various kinds of additive agents, such as all the buffers which carry out normal use, a solubilizing agent, an isotonizing agent, a stabilizing agent, a viscous agent, a chelating agent, a pH adjuster, and a cool-ized agent, other pharmacological active principles, etc. can be blended with preparation of pharmaceutical preparation, such as ophthalmic ointments and gel, in the amount of normal use.

[0018]As a buffer, more specifically, for example Boric acid or its salt (borax etc.), Citrate or its salts (sodium acid citrate etc.), phosphoric acid, or its salt (phosphoric acid 1 hydrogen sodium etc.), Those combination, such as tartaric acid or its salts (sodium tartrate etc.), gluconic acid or its salts (sodium gluconate etc.), acetic acid or its salt, and various amino acid (sodium acetate etc.), is mentioned.

[0019]As a solubilizing agent, a polyethylene glycol, propylene glycol, etc. are mentioned, for example. As an isotonizing agent, sodium chloride, potassium chloride, mannitol, propylene glycol, etc. are mentioned, for example.

[0020]As a stabilizing agent, disodium edetate, cyclodextrin, sulfite salt, citrate, or its salt is mentioned, for example. As a viscous agent, a polyethylene glycol, polyvinyl alcohol, a polyvinyl pyrrolidone, hydroxyethyl cellulose, hydroxypropylmethylcellulose, methyl cellulose, sodium chondroitin sulfate, etc. are mentioned, for example.

[0021]As a chelating agent, disodium edetate, sodium acid citrate, etc. are mentioned, for example. As a pH adjuster, chloride, citrate or its salt, boric acid and its salt, phosphoric acid or its salt, acetic acid or its salt, tartaric acid or its salt, sodium hydroxide, a potassium hydrate, sodium carbonate, sodium bicarbonate, etc. are mentioned, for example. As a cool-ized agent, menthol, borneol, camphor, geraniol, limonene, eugenol, mentha oil, eucalyptus oil, etc. are mentioned, for example.

[0022]as a pharmacological active principle -- for example, a congestion remover

(naphazoline hydrochloride and the tetracaine hydrochloride --) resolution and astringents (neostigmine methylsulfate --), such as phenylephrine hydrochloride Epsilon-aminocaproic acid, allantoin, berberine chloride, sulfate of zinc, antihistamines (diphenhydramine hydrochloride and isothipendyl hydrochloride --), such as lysozyme chloride vitamin [vitamin A, such as chlorpheniramine maleate, and ester (for example, acetate ester --) of those Pulmitic acid ester and active vitamin B_2, vitamin B_6,], such as vitamin B_{12}, vitamin E, and its ester (for example, acetate ester), amino acid (potassium L-aspartate and L-aspartic acid magnesium --) Aminoethylsulfonic acid, sodium chondroitin sulfate, etc. can blend suitably sulfa drugs, germicides (sulfur, isopropylmethyl phenol, hinokitiol, etc.), local anesthetic (lidocaine, lidocaine hydrochloride, procaine hydrochloride, dibucaine hydrochloride, etc.), etc.

[0023]If pH of the constituent for ophthalmology of the present invention is a range permitted ophthalmologically, there will be no restriction in particular, and it is usually the range of pH 4-9, and is 5-8.5 preferably.

[0024]Although the preparing method in particular of the constituent for ophthalmology of the present invention is not asked, when it is ophthalmic solutions, each combination component is sequentially added to sterile purified water, and it dissolves, and is obtained by adjusting pH, for example.

[0025]If the dose of the constituent for ophthalmology of the present invention for soft contact lenses is a range permitted ophthalmologically, there will be no restriction in particular, but when using, for example as ophthalmic solutions, it is preferable to prescribe 1-3 drops of single doses for the patient 4 to 6 times per day.

[0026]

[Working example]Although an working example and a comparative example are given to below and the present invention is described still in detail, the present invention is not limited at all by the following working example.

[0027][The working examples 1-3 and comparative examples 1 and 2] According to the composition shown in Table 1, ophthalmic solutions were prepared with the conventional method. Six soft contact lens wearing persons with an allergy anamnesis were made into the panelist, and the improvement degree, its temporal duration, and the using feeling (degree of sense of incongruity) of the itching when each point eye

agent was prescribed for the patient at the time of the onset of allergy (itching) were investigated. The obtained result was evaluated in accordance with the following valuation bases. A result is shown in Table 2.

[0028]Five valuation bases of the improvement degree of the itching: The 1 point:itching to which the 2 point:itching which does not change the 3 point:itching by which the 4 point:itching by which the itching was reduced was reduced a little became a little severe became severe. [0029]Continuation - below self-sustaining x:10 minute below self-sustaining **:10 minute [more than] 30 minute below O:30 minute [more than] 60 minute which the degree of continuation of an itching improvement maintained valuation-basis O:60 minutes or more: It became improvement nothing [of the itching], or severe. [0030]valuation-basis O: of a using feeling (degree of sense of incongruity) -- O: which is completely comfortable -- almost comfortable **: -- x:sense of incongruity as which sense of incongruity was sensed was sensed strong [0031]

[Table 1]

成分(g/100ml)	実施例1	実施例2	実施例3	比較例1	比較例2
クロモグリク酸ナトリウム	1.0	1.0	1.0	---	---
ダリテルヒドン酸二ナトリウム	---	---	---	---	---
メチルセルロース	---	0.35	---	---	0.35
ポリオキシエチレン硬化ヒマシ油60	---	---	0.25	---	0.25
塩化ナトリウム	0.5	0.5	0.5	0.5	0.5
塩化カリウム	0.15	0.15	0.15	0.15	0.15
ホウ酸	1.0	1.0	1.0	1.0	1.0
ホウ砂	0.1	0.1	0.1	0.1	0.1
エデト酸ナトリウム	0.01	0.01	0.01	0.01	0.01
塩化ベンザルコニウム	0.005	0.005	0.005	0.005	0.005
滅菌精製水	適量	適量	適量	適量	適量
全量	100ml	100ml	100ml	100ml	100ml
pH	7.0	7.0	7.0	7.0	7.0

[0032]

[Table 2]

評価項目	パネラー	実施例1	実施例2	実施例3	比較例1	比較例2
かゆみの改善度合い	A	4点	5点	5点	3点	3点
	B	4点	5点	5点	3点	3点
	C	4点	5点	5点	2点	2点
	D	4点	5点	4点	3点	3点
	E	4点	5点	5点	3点	3点
	F	5点	5点	5点	3点	3点
かゆみ改善の持続時間の度合い	A	○	◎	◎	—	—
	B	○	◎	◎	—	—
	C	△	◎	○	—	—
	D	○	◎	◎	—	—
	E	◎	◎	◎	—	—
	F	○	◎	◎	—	—
使用感（違和感の程度）	A	○	◎	○	△	×
	B	○	◎	◎	△	×
	C	◎	◎	◎	○	○
	D	◎	◎	◎	△	△
	E	◎	◎	◎	○	△
	F	○	○	◎	×	△

[0033]The itching is improved by combination of an antiallergic drug so that clearly from the result of Table 2, The improvement degree of the itching increased, and the eye which applied eyewash in the working example 3 containing the working example 2 and nonionic surfactant which blended the high molecular compound had the long temporal duration of the itching improvement, and also it improved also about the using feeling. On the other hand, in the eye which applied eyewash in the comparative example 2 only containing the comparative example 1, high molecular compound, and nonionic surfactant which do not contain an antiallergic drug, there was almost no change in the improvement degree of the itching, and the using feeling was also bad.

[0034]From this, it was checked that allergies, such as itching which happens at the time of contact lens wearing, are improved by combination of an antiallergic drug. By using together a high molecular compound and/or a nonionic surfactant to an antiallergic drug, allergies, such as itching at the time of contact lens wearing, covered the long time, and have been improved, and it was checked that the using feeling at the time of instillation increases.

[0035][Working examples 4-27] According to the composition shown in Tables 3-5, ophthalmic solutions were prepared with the conventional method, and eight soft contact lens wearing persons were made to evaluate the improvement degree of the itching of an eye, temporal duration, and a using feeling (degree of sense of incongruity) by the same valuation basis as the above-mentioned working example and

a comparative example. The marks which were were made into evaluation items among eight persons. A result is written together to Tables 3-5.

[0036]

[Table 3]

成分(g/100ml)		実施例							
		4	5	6	7	8	9	10	11
クロモグリク酸ナトリウム		0.05	0.1	0.5	1.0	1.0	2.0	3.0	5.0
メチルセルロース		—	0.05	1.0	0.35	—	—	—	—
α-シクロデキストリン		0.005	—	—	—	0.5	—	—	2.0
β-シクロデキストリン		—	—	1.0	—	—	—	—	—
γ-シクロデキストリン		—	0.1	—	—	—	—	—	—
ヒドロキシエチルセルロース		0.25	—	—	—	—	—	—	—
ヒドロキシプロピルメチルセルロース		—	—	—	—	—	0.7	—	—
ポリビニルピロリドン		—	—	—	—	—	—	—	0.6
ポリビニルアルコール		—	—	—	—	—	—	0.25	—
ポリオキシエチレン硬化ヒマシ油60		0.15	0.15	0.2	—	0.3	0.3	0.3	—
ポリソルベート80		—	—	—	0.25	—	—	—	0.3
塩化ナトリウム		0.5	0.5	0.5	0.4	0.4	0.45	0.45	0.45
塩化カリウム		0.15	0.15	0.1	0.15	0.1	0.1	0.1	0.1
ホウ酸		0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
ホウ砂		0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07
エデト酸ナトリウム		0.01	0.005	0.01	0.002	0.01	0.01	0.01	0.005
塩化ベンザルコニウム		0.003	0.005	0.005	0.005	0.005	0.01	0.005	0.005
滅菌精製水		適量	適量	適量	適量	適量	適量	適量	適量
結果	かゆみの改善	4点	4点	5点	5点	5点	5点	5点	5点
	持続時間	△	○	◎	◎	◎	◎	◎	◎
	使用感	◎	◎	◎	◎	◎	◎	◎	△

[0037]

[Table 4]

成分(g/100ml)		実施例							
		12	13	14	15	16	17	18	19
グリチルリチン酸二カリウム		0.05	0.1	0.25	0.5	0.5	1.0	2.0	3.0
メチルセルロース		—	0.05	1.0	2.0	—	—	—	—
α-シクロデキストリン		0.001	—	—	—	0.5	—	—	3.0
β-シクロデキストリン		—	—	1.0	—	—	—	—	—
γ-シクロデキストリン		—	0.1	—	—	—	—	—	—
ヒドロキシエチルセルロース		0.25	—	—	—	—	—	—	—
ヒドロキシプロピルメチルセルロース		—	—	—	—	—	0.5	—	—
ポリビニルピロリドン		—	—	—	—	—	—	—	0.005
ポリビニルアルコール		—	—	—	—	—	—	1.0	—
ポリオキシエチレン硬化ヒマシ油60		0.05	0.15	0.2	—	—	0.3	0.45	—
ポリソルベート80		—	—	—	0.15	0.25	—	—	0.5
塩化ナトリウム		0.5	0.5	0.5	0.45	0.4	0.4	0.45	0.45
塩化カリウム		0.15	0.15	0.1	0.1	0.15	0.1	0.1	0.1
枸酸		0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
枸砂		0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07
エデト酸ナトリウム		0.01	0.005	0.01	0.005	0.002	0.01	0.01	0.005
塩化ベンザルコニウム		0.003	0.005	0.005	0.005	0.003	0.005	0.01	0.005
滅菌精製水		適量	適量	適量	適量	適量	適量	適量	適量
結果	かゆみの改善	4点	4点	5点	5点	5点	5点	5点	5点
	持続時間	△	○	◎	◎	◎	◎	◎	◎
	使用感	◎	◎	◎	◎	◎	◎	◎	△

[0038]

[Table 5]

成分(g/100ml)		実施例							
		20	21	22	23	24	25	26	27
トラネキスト		0.1	0.5	1.0	—	—	—	—	—
アンキサンクス		—	—	—	—	—	0.25	—	—
ペミロラストカリウム		—	—	—	0.05	0.2	—	—	—
ヒト型組換えインターフェロン		—	—	—	—	—	—	0.01	0.05
メチルセルロース		—	0.5	2.0	0.05	—	—	—	—
α-シクロデキストリン		0.005	—	—	—	0.7	—	—	0.01
β-シクロデキストリン		—	—	0.005	—	—	—	—	—
γ-シクロデキストリン		—	0.2	—	—	—	—	—	—
ヒドロキシエチルセルロース		0.5	—	—	—	—	—	—	—
ヒドロキシプロピルメチルセルロース		—	—	—	—	—	0.7	—	—
ポリビニルピロリドン		—	—	—	—	—	—	—	2.0
ポリビニルアルコール		—	—	—	—	0.05	—	5.0	—
ポリオキシエチレン硬化ヒマシ油60		0.05	0.15	0.2	—	—	0.3	0.45	—
ポリソルベート80		—	—	—	0.15	0.25	—	—	0.5
塩化ナトリウム		0.5	0.55	0.5	0.5	0.4	0.4	0.45	0.45
塩化カリウム		0.15	0.15	0.15	0.1	0.15	0.1	0.1	0.1
枸酸		0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
枸砂		0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07
エデト酸ナトリウム		0.01	0.005	0.005	0.01	0.002	0.01	0.01	0.005
塩化ベンザルコニウム		0.003	0.005	0.005	0.005	0.003	0.005	0.01	0.005
滅菌精製水		適量	適量	適量	適量	適量	適量	適量	適量
結果	かゆみの改善	4点	5点	5点	4点	5点	5点	4点	5点
	持続時間	○	◎	◎	○	◎	◎	○	◎
	使用感	◎	◎	◎	◎	◎	◎	◎	◎

[0039]

[Effect of the Invention]According to the present invention, the constituent for ophthalmology for soft contact lenses with a high effect of covering a long time and improving the allergies of the eye produced by soft contact lens wearing is obtained, The durability of the improvement effect by the allergy medicine to the eye at the time of soft contact lens wearing can be improved.

[Translation done.]

TECHNICAL FIELD

[Field of the Invention]The present invention about the constituent for ophthalmology for soft contact lenses in more detail, By containing an antiallergic drug, can improve the allergies of the eye at the time of soft contact lens wearing, and by blending a high molecular compound and/or a nonionic surfactant further, It is related with the high constituent for ophthalmology of the effect of covering a long time and improving the allergies of the eye produced by soft contact lens wearing for soft contact. The present invention relates to the upper part method for durability of the antiallergic drug which improves the durability of the improvement effect of the above-mentioned allergies by an antiallergic drug.

[Translation done.]

PRIOR ART

[Description of the Prior Art]Generally a contact lens can be divided roughly into a hard lens and a soft contact lens. By wearing of these contact lenses, various troubles, such as itching, inflammation, congestion, a dryness eye, and eye strain, arise in an eye. Since wearing nature is good especially in the case of a soft contact lens, prolonged wearing is possible, a lens surface dries and the foreign matters and pollutants from the external world, such as pollen, adhere easily. Foreign matters, such as pollen from such the external world, trigger an allergic reaction, and appeal against the itching, inflammation, and congestion which are the condition of allergy in many cases.
[0003]However, at the time of soft contact lens wearing, such itching or inflammation, and the constituent which calms congestion and improves allergies are not in the former, and an appearance of such a constituent for ophthalmology for soft contact lenses was desired. It is desirable to stagnate in an eye for a long time, and for an active principle to cover a long time and to be able to improve allergies as such a constituent for ophthalmology, at the time of soft contact lens wearing.

[Translation done.]

EFFECT OF THE INVENTION

[Effect of the Invention]According to the present invention, the constituent for ophthalmology for soft contact lenses with a high effect of covering a long time and improving the allergies of the eye produced by soft contact lens wearing is obtained, The durability of the improvement effect by the allergy medicine to the eye at the time of soft contact lens wearing can be improved.

[Translation done.]

TECHNICAL PROBLEM

[Problem to be solved by the invention]The present invention was made in view of the above-mentioned situation, and an object of the present invention is to provide the upper part method for durability of an antiallergic drug make the improvement effect by the constituent for ophthalmology and antiallergic drug for soft contact lenses which improve the allergies of the eye produced by soft contact lens wearing maintain.

[0005]

[The means for solving a technical problem and an embodiment of the invention] The inventors found out that allergies, such as characteristic itching which happens at the time of soft contact lens wearing, were improved by blending an antiallergic drug with the constituent for ophthalmology for soft contact lenses, as a result of inquiring intensively, in order to solve an aforementioned problem. If a high molecular compound and/or a nonionic surfactant are blended, usability, like the wettability of a soft contact lens increases and it is comfortable will improve, and. The retentivity of the antiallergic drug to an eye improves, the knowledge of it becoming possible to cover a long time and to make the allergies at the time of soft contact lens wearing improve is carried out, and it came to make the present invention.

[0006]namely, the constituent for ophthalmology for soft contact lenses which the present invention contains (1) antiallergic drug and is characterized by things -- more preferably, The constituent for ophthalmology containing a high molecular compound and/or a nonionic surfactant for soft contact lenses, (2) Provide the upper part method for durability of the antiallergic drug blending a high molecular compound and/or a nonionic surfactant with the constituent for ophthalmology for soft contact lenses which contains an antiallergic drug as an active principle.

[0007]Hereafter, if it describes about the present invention, the constituent for ophthalmology of the present invention contains an antiallergic drug as an essential ingredient.

[0008]As an antiallergic drug of the present invention, here, for example Cromoglycic acid or its salts, such as disodium cromoglycate and the cromoglycic acid potassium, Glycyrrhizic acid, such as glycyrrhizinate dipotassium and glycyrrhizic acid ammonium, or the salt of those, amlexanox, tranilast, pemirolast potassium, ketotifen fumarate, etc.

are mentioned, and these can be used, combining suitably a 1 type independent or 2 type or more. In the case of the present invention, disodium cromoglycate, glycyrrhizinate dipotassium, etc. are especially mentioned preferably also in these.

[0009]The compounding amount of the above-mentioned antiallergic drug in the constituent for ophthalmology of the present invention, if it is suitably selected by the kind, for example, it is cromoglycic acid and its salt, when 0.05-10 w/v% (mass / capacity %, and the following -- the same) combination will usually be carried out into a constituent, it is preferable and is 0.1 - 5 w/v% of range more preferably. If it is glycyrrhizic acid or its salt, for example, when 0.05-3 w/v% combination is carried out into a constituent, it is preferable and is usually 0.1 - 2 w/v% more preferably. If it may be difficult to acquire the effect of combination sufficiently if there is too little compounding amount and there are, the restrictions on a dosage form design may arise. [too many]

[0010]The constituent for ophthalmology for the soft contact lenses of the present invention can be used for the constituent of all the ophthalmology uses for soft contact lenses. Specifically, it is used as ophthalmic solutions for allergy for soft contact lenses, etc.

[0011]When a high molecular compound and/or a nonionic surfactant are blended, more, the constituent for ophthalmology of the present invention is still more nearly preferable here, and the upper part method for durability of the antiallergic drug of the present invention, Thus, to the constituent for ophthalmology for soft contact lenses contained as an active principle, the above-mentioned antiallergic drug by blending the above-mentioned high molecular compound and/or a nonionic surfactant, The retentivity of the antiallergic drug to the eye at the time of soft contact lens wearing is improved, and the improvement effect is made to maintain.

[0012]As a high molecular compound in the present invention, for example Polyvinyl alcohol, A polyvinyl pyrrolidone, hydroxyethyl cellulose, hydroxypropylmethylcellulose, methyl cellulose, cyclodextrin, etc. are mentioned, and these can be used, combining suitably a 1 type independent or 2 type or more. Also in these, they are methyl cellulose, cyclodextrin, etc. especially preferably.

[0013]The compounding amount of the above-mentioned high molecular compound in the constituent for ophthalmology of the present invention, Are suitably selected by the

kind, for example, if it is methyl cellulose, hydroxyethyl cellulose, and hydroxypropylmethylcellulose, usually, the inside of a constituent -- preferable -- 0.01-5 -- w/v%, if it is 0.05 - 1 w/v% and cyclodextrin more preferably, usually, the inside of a constituent -- preferable -- 0.001-5 -- w/v%, if it is 0.005 - 2 w/v%, polyvinyl alcohol, and a polyvinyl pyrrolidone more preferably, usually, the inside of a constituent -- preferable -- 0.01-10 -- w/v%, if it blends in 0.1 - 5 w/v% of range more preferably, it is preferable. Since the wettability of a lens will become insufficient if there is too little compounding amount of the above-mentioned high molecular compound, It becomes difficult to attain the improvement in retentivity to the eye of an antiallergic drug, sufficient durability may be hard to be acquired, if there is too much compounding amount of the above-mentioned high molecular compound, viscosity is too high and sense of incongruity may be sensed at the time of instillation.

[0014]As a nonionic surfactant in the present invention, They are mentioned by polyoxyethylene higher-fatty-acid ester, such as water-soluble polyoxyethylene hydrogenated castor oil, polyoxyethylene sorbitan higher-fatty-acid ester, etc., and more specifically, For example, there are polyoxyethylene (p= 60) hydrogenated castor oil, polyoxyethylene (p= 20) sorbitan monooleate, etc. Here, p shows the number of average addition mols of ethylene oxide. These can be used combining suitably a 1 type independent or 2 type or more.

[0015]When the compounding amount in particular of the nonionic surfactant in the constituent for ophthalmology of the present invention is not restricted and usually carries out 0.01-1 w/v% combination into a constituent, it is preferable and is 0.05 - 0.5 w/v% of range more preferably. Since the wettability of a lens becomes that the compounding amount of a nonionic surfactant is less than [0.01 w/v%] insufficient, If it may become difficult to attain the improvement in retentivity to the eye of an antiallergic drug, and to acquire the outstanding durability and 1 w/v% is exceeded, the stimulativeness to an eye may produce problems, such as becoming strong.

[0016]as the form of the constituent for ophthalmology for the soft contact lenses of the present invention -- ophthalmic solutions, ophthalmic ointments, gel, and business -- the time -- the dissolution -- being liquefied -- becoming -- solid preparations -- etc. -- mentioning -- having -- although -- preferable -- the form of ophthalmic solutions -- it is .

[0017]The ophthalmic solutions described above besides the essential ingredient described above in the present invention in the range which does not bar the effect of the present invention, Various kinds of additive agents, such as all the buffers which carry out normal use, a solubilizing agent, an isotonizing agent, a stabilizing agent, a viscous agent, a chelating agent, a pH adjuster, and a cool-ized agent, other pharmacological active principles, etc. can be blended with preparation of pharmaceutical preparation, such as ophthalmic ointments and gel, in the amount of normal use.

[0018]As a buffer, more specifically, for example Boric acid or its salt (borax etc.), Citrate or its salts (sodium acid citrate etc.), phosphoric acid, or its salt (phosphoric acid 1 hydrogen sodium etc.), Those combination, such as tartaric acid or its salts (sodium tartrate etc.), gluconic acid or its salts (sodium gluconate etc.), acetic acid or its salt, and various amino acid (sodium acetate etc.), is mentioned.

[0019]As a solubilizing agent, a polyethylene glycol, propylene glycol, etc. are mentioned, for example. As an isotonizing agent, sodium chloride, potassium chloride, mannitol, propylene glycol, etc. are mentioned, for example.

[0020]As a stabilizing agent, disodium edetate, cyclodextrin, sulfite salt, citrate, or its salt is mentioned, for example. As a viscous agent, a polyethylene glycol, polyvinyl alcohol, a polyvinyl pyrrolidone, hydroxyethyl cellulose, hydroxypropylmethylcellulose, methyl cellulose, sodium chondroitin sulfate, etc. are mentioned, for example.

[0021]As a chelating agent, disodium edetate, sodium acid citrate, etc. are mentioned, for example. As a pH adjuster, chloride, citrate or its salt, boric acid and its salt, phosphoric acid or its salt, acetic acid or its salt, tartaric acid or its salt, sodium hydroxide, a potassium hydrate, sodium carbonate, sodium bicarbonate, etc. are mentioned, for example. As a cool-ized agent, menthol, borneol, camphor, geraniol, limonene, eugenol, mentha oil, eucalyptus oil, etc. are mentioned, for example.

[0022]as a pharmacological active principle -- for example, a congestion remover (naphazoline hydrochloride and the tetracaine hydrochloride --) resolution and astringents (neostigmine methylsulfate --), such as phenylephrine hydrochloride Epsilon-aminocaproic acid, allantoin, berberine chloride, sulfate of zinc, antihistamines (diphenhydramine hydrochloride and isothipendyl hydrochloride --), such as lysozyme chloride vitamin [vitamin A, such as chlorpheniramine maleate, and ester (for example,

acetate ester --) of those Pulmitic acid ester and active vitamin B_2, vitamin B_6,], such as vitamin B_{12}, vitamin E, and its ester (for example, acetate ester), amino acid (potassium L-aspartate and L-aspartic acid magnesium --) Aminoethylsulfonic acid, sodium chondroitin sulfate, etc. can blend suitably sulfa drugs, germicides (sulfur, isopropylmethyl phenol, hinokitiol, etc.), local anesthetic (lidocaine, lidocaine hydrochloride, procaine hydrochloride, dibucaine hydrochloride, etc.), etc.

[0023]If pH of the constituent for ophthalmology of the present invention is a range permitted ophthalmologically, there will be no restriction in particular, and it is usually the range of pH 4-9, and is 5-8.5 preferably.

[0024]Although the preparing method in particular of the constituent for ophthalmology of the present invention is not asked, when it is ophthalmic solutions, each combination component is sequentially added to sterile purified water, and it dissolves, and is obtained by adjusting pH, for example.

[0025]If the dose of the constituent for ophthalmology of the present invention for soft contact lenses is a range permitted ophthalmologically, there will be no restriction in particular, but when using, for example as ophthalmic solutions, it is preferable to prescribe 1-3 drops of single doses for the patient 4 to 6 times per day.

[Translation done.]

EXAMPLE

[Working example]Although an working example and a comparative example are given to below and the present invention is described still in detail, the present invention is not limited at all by the following working example.

[0027][The working examples 1-3 and comparative examples 1 and 2] According to the composition shown in Table 1, ophthalmic solutions were prepared with the conventional method. Six soft contact lens wearing persons with an allergy anamnesis were made into the panelist, and the improvement degree, its temporal duration, and the using feeling (degree of sense of incongruity) of the itching when each point eye agent was prescribed for the patient at the time of the onset of allergy (itching) were investigated. The obtained result was evaluated in accordance with the following valuation bases. A result is shown in Table 2.

[0028]Five valuation bases of the improvement degree of the itching: The 1 point:itching to which the 2 point:itching which does not change the 3 point:itching by which the 4 point:itching by which the itching was reduced was reduced a little became a little severe became severe. [0029]Continuation - below self-sustaining x:10 minute below self-sustaining **:10 minute [more than] 30 minute below O:30 minute [more than] 60 minute which the degree of continuation of an itching improvement maintained valuation-basis O:60 minutes or more: It became improvement nothing [of the itching], or severe. [0030]valuation-basis O: of a using feeling (degree of sense of incongruity) -- O: which is completely comfortable -- almost comfortable **: -- x:sense of incongruity as which sense of incongruity was sensed was sensed strong [0031]

[Table 1]

成分(g/100ml)	実施例1	実施例2	実施例3	比較例1	比較例2
クロモグリク酸ナトリウム	1.0	1.0	1.0	—	—
ダリチルリチン酸二ナトリウム	—	—	—	—	—
メチルセルロース	—	0.35	—	—	0.35
ポリオキシエチレン硬化ヒマシ油60	—	—	0.25	—	0.25
塩化ナトリウム	0.5	0.5	0.5	0.5	0.5
塩化カリウム	0.15	0.15	0.15	0.15	0.15
ホウ酸	1.0	1.0	1.0	1.0	1.0
ホウ砂	0.1	0.1	0.1	0.1	0.1
エデト酸ナトリウム	0.01	0.01	0.01	0.01	0.01
塩化ベンザルコニウム	0.005	0.005	0.005	0.005	0.005
滅菌精製水	適量	適量	適量	適量	適量
全量	100ml	100ml	100ml	100ml	100ml
pH	7.0	7.0	7.0	7.0	7.0

[0032]

[Table 2]

評価項目	パネラー	実施例1	実施例2	実施例3	比較例1	比較例2
かゆみの改善度合い	A	4点	5点	5点	3点	3点
	B	4点	5点	5点	3点	3点
	C	4点	5点	5点	2点	2点
	D	4点	5点	4点	3点	3点
	E	4点	5点	5点	3点	3点
	F	5点	5点	5点	3点	3点
かゆみ改善の持続時間の度合い	A	○	◎	◎	—	—
	B	○	◎	◎	—	—
	C	△	◎	○	—	—
	D	○	◎	◎	—	—
	E	◎	◎	◎	—	—
	F	○	◎	◎	—	—
使用感(違和感の程度)	A	○	◎	○	△	×
	B	○	◎	◎	△	×
	C	◎	◎	◎	○	○
	D	◎	◎	◎	△	△
	E	◎	◎	◎	○	△
	F	○	○	◎	×	△

[0033]The itching is improved by combination of an antiallergic drug so that clearly from the result of Table 2, The improvement degree of the itching increased, and the eye which applied eyewash in the working example 3 containing the working example 2 and nonionic surfactant which blended the high molecular compound had the long temporal duration of the itching improvement, and also it improved also about the using feeling. On the other hand, in the eye which applied eyewash in the comparative example 2 only containing the comparative example 1, high molecular compound, and nonionic surfactant which do not contain an antiallergic drug, there was almost no change in the improvement degree of the itching, and the using feeling was also bad.

[0034]From this, it was checked that allergies, such as itching which happens at the

time of contact lens wearing, are improved by combination of an antiallergic drug. By using together a high molecular compound and/or a nonionic surfactant to an antiallergic drug, allergies, such as itching at the time of contact lens wearing, covered the long time, and have been improved, and it was checked that the using feeling at the time of instillation increases.

[0035][Working examples 4-27] According to the composition shown in Tables 3-5, ophthalmic solutions were prepared with the conventional method, and eight soft contact lens wearing persons were made to evaluate the improvement degree of the itching of an eye, temporal duration, and a using feeling (degree of sense of incongruity) by the same valuation basis as the above-mentioned working example and a comparative example. The marks which were were made into evaluation items among eight persons. A result is written together to Tables 3-5.

[0036]

[Table 3]

成分(g/100ml)		実施例							
		4	5	6	7	8	9	10	11
クロモグリク酸ナトリウム		0.05	0.1	0.5	1.0	1.0	2.0	3.0	5.0
メチルセルロース		—	0.05	1.0	0.35	—	—	—	—
α-シクロデキストリン		0.005	—	—	—	0.5	—	—	2.0
β-シクロデキストリン		—	—	1.0	—	—	—	—	—
γ-シクロデキストリン		—	0.1	—	—	—	—	—	—
ヒドロキシエチルセルロース		0.25	—	—	—	—	—	—	—
ヒドロキシプロピルメチルセルロース		—	—	—	—	—	0.7	—	—
ポリビニルピロリドン		—	—	—	—	—	—	—	0.6
ポリビニルアルコール		—	—	—	—	—	—	0.25	—
ポリオキシエチレン硬化ヒマシ油60		0.15	0.15	0.2	—	0.3	0.3	0.3	—
ポリソルベート80		—	—	—	0.25	—	—	—	0.3
塩化ナトリウム		0.5	0.5	0.5	0.4	0.4	0.45	0.45	0.45
塩化カリウム		0.15	0.15	0.1	0.15	0.1	0.1	0.1	0.1
約酸		0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
ホウ砂		0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07
エデト酸ナトリウム		0.01	0.005	0.01	0.002	0.01	0.01	0.01	0.005
塩化ベンザルコニウム		0.003	0.005	0.005	0.003	0.005	0.01	0.005	0.005
滅菌精製水		適量	適量	適量	適量	適量	適量	適量	適量
結果	かゆみの改善	4点	4点	5点	5点	5点	5点	5点	5点
	持続時間	△	○	◎	◎	◎	◎	◎	◎
	使用感	◎	◎	◎	◎	◎	◎	◎	△

[0037]

[Table 4]

成分(g/100ml)		実施例							
		12	13	14	15	16	17	18	19
グリチルリチン酸二カリウム		0.05	0.1	0.25	0.5	0.5	1.0	2.0	3.0
メチルセルロース		—	0.05	1.0	2.0	—	—	—	—
α-シクロデキストリン		0.001	—	—	—	0.5	—	—	3.0
β-シクロデキストリン		—	—	1.0	—	—	—	—	—
γ-シクロデキストリン		—	0.1	—	—	—	—	—	—
ヒドロキシエチルセルロース		0.25	—	—	—	—	—	—	—
ヒドロキシプロピルメチルセルロース		—	—	—	—	—	0.5	—	—
ポリビニルピロリドン		—	—	—	—	—	—	—	0.005
ポリビニルアルコール		—	—	—	—	—	—	1.0	—
ポリオキシエチレン硬化ヒマシ油60		0.05	0.15	0.2	—	—	0.3	0.45	—
ポリソルベート80		—	—	—	0.15	0.25	—	—	0.5
塩化ナトリウム		0.5	0.5	0.5	0.45	0.4	0.4	0.45	0.45
塩化カリウム		0.15	0.15	0.1	0.1	0.15	0.1	0.1	0.1
乳酸		0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
白砂糖		0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07
エデト酸ナトリウム		0.01	0.005	0.01	0.005	0.002	0.01	0.01	0.005
塩化ベンザルコニウム		0.003	0.005	0.005	0.005	0.003	0.005	0.01	0.005
滅菌精製水		適量	適量	適量	適量	適量	適量	適量	適量
結果	かゆみの改善	4点	4点	5点	5点	5点	5点	5点	5点
	持続時間	△	○	◎	◎	◎	◎	◎	◎
	使用感	◎	◎	◎	◎	◎	◎	◎	△

[0038]

[Table 5]

成分(g/100ml)		実施例							
		20	21	22	23	24	25	26	27
トラネキスト		0.1	0.5	1.0	—	—	—	—	—
アルキサノクス		—	—	—	—	—	0.25	—	—
ペミロラストカリウム		—	—	—	0.05	0.2	—	—	—
フマル酸ケトチフェン		—	—	—	—	—	—	0.01	0.05
メチルセルロース		—	0.5	2.0	0.05	—	—	—	—
α-シクロデキストリン		0.005	—	—	—	0.7	—	—	0.01
β-シクロデキストリン		—	—	0.005	—	—	—	—	—
γ-シクロデキストリン		—	0.2	—	—	—	—	—	—
ヒドロキシエチルセルロース		0.5	—	—	—	—	—	—	—
ヒドロキシプロピルメチルセルロース		—	—	—	—	—	0.7	—	—
ポリビニルピロリドン		—	—	—	—	—	—	—	2.0
ポリビニルアルコール		—	—	—	—	0.05	—	5.0	—
ポリオキシエチレン硬化ヒマシ油60		0.05	0.15	0.2	—	—	0.3	0.45	—
ポリソルベート80		—	—	—	0.15	0.25	—	—	0.5
塩化ナトリウム		0.5	0.55	0.5	0.5	0.4	0.4	0.45	0.45
塩化カリウム		0.15	0.15	0.15	0.1	0.15	0.1	0.1	0.1
乳酸		0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
白砂糖		0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07
エデト酸ナトリウム		0.01	0.005	0.005	0.01	0.002	0.01	0.01	0.005
塩化ベンザルコニウム		0.003	0.005	0.005	0.005	0.003	0.005	0.01	0.005
滅菌精製水		適量	適量	適量	適量	適量	適量	適量	適量
結果	かゆみの改善	4点	5点	5点	4点	5点	5点	4点	5点
	持続時間	○	◎	◎	○	◎	◎	○	◎
	使用感	◎	◎	◎	◎	◎	◎	◎	◎

[Translation done.]

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(54) Title: IMPROVED VISCOELASTIC FLUID FOR OPHTHALMIC SURGERY AND METHOD OF USING SAME

(57) Abstract

This invention relates to an improved viscoelastic vitreous substitute for use in ophthalmic surgery which consists of a mixture of hydroxypropylmethyl cellulose and polyethylene oxide in selected concentrations not to exceed approximately 2 % and 200 ppm, respectively, contained in a physiologic balanced salt solution. It also encompasses the novel method of protecting and lubricating the corneal tissues during surgery with uses of different concentrations of the same solution introduced simultaneously to protect the inner cornea while periodically irrigating the outer cornea, all without obscuring the surgeon's view of the site.

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IMPROVED VISCOELASTIC FLUID FOR OPHTHALMIC SURGERY AND METHOD OF USING SAME

BACKGROUND OF THE INVENTION

There are a number of surgical procedures performed on the eyes by skilled ophthalmic surgeons. Among these are cataract surgery, vitreo-retinal surgery and radial keratotomy to reduce myopia. In all of these surgical procedures except for radial keratotomy in which the corneal tissue is not penetrated, the recommended practice is to use an intraocular viscoelastic fluid for protecting the inner endothelial corneal surface and the delicate inner eye structures.

In addition, the outer epithelial surface of the cornea must be lubricated continuously with some type of moisturizing agent to keep it from drying out under the heat generated by the operating microscope light.

Methylcellulose has a long history of safe and effective use for ophthalmic applications. In 1945, Dr. Kenneth C. Swan studied the effects of methylcellulose on the ocular tissues of rabbit eyes. He suggested its use as a vehicle for ophthalmic drugs, to treat

keratoconjunctivitis sicca and as an emollient. Then in 1959, Flemming, Merrill and Girard reported on further studies of methylcellulose in relation to irritation, hypersensitivity and its outflow from the anterior chamber of the rabbit eye.

The first reported use of methylcellulose as an intraocular lens coating serving to protect the corneal endothelium in rabbits was made by Drs. Kaufman and Katz in 1976. In the following year Dr. Paul Fechner reported upon the first human clinical use of methylcellulose to coat an intraocular lens prior to implantation.

Then in November of 1982, Dr. Danielle Aron-Rosa reported using methylcellulose in extracapsular surgery instead of high molecular weight sodium hyaluronate extracted from rooster combs which is very expensive. Shortly thereafter, Dr. Fechner amplified upon his earlier findings describing the use of methylcellulose as a viscous cushioning material in ophthalmic surgery.

Additional work confirming these earlier results has been conducted by Dr. Scott M. MacRae who compared the efficacy and toxicity of sodium hyaluronate, methylcellulose and chrondroitin sulfate, all three of which are used as protective substances suitable for use in ophthalmic surgery. Finally Drs. Smith and Lindstrom evaluated the safety and efficacy of 2% methylcellulose in cat and monkey implant surgery with favorable results.

Despite the high cost of viscoelastic products based upon sodium hyaluronate, all

commercially available ones in common use have it as the sole or at least principal ingredient. Some manufacturers of viscoelastic materials are believed to be engaged in experimentation with a bioengineered form of sodium hyaluronate but so far it appears that efforts at producing it with a sufficiently high molecular weight have been only marginally successful. A polyacrylamide material is evidently being tested as a material having hydroxypropyl methylcellulose as its basic ingredient.

On the other hand, as far as topical solutions for use in surgery to lubricate the corneal epithelium and protect them from the heat generated by the operating microscope, to applicants knowledge the only product used at the present time is a balanced salt solution which must be administered as often as every 30 to 45 seconds by an assisting surgeon or scrub nurse.

FIELD OF THE INVENTION

The present invention relates to an improved viscoelastic formulation which when used in dilute form as a topical solution in place of balanced salt solution to keep the corneal surfaces moist lasts up to ten times as long in the eye before having to be renewed. The same unique formulation when used in a different concentration has proven to be equally as good if not better than sodium hyaluronate for use as a protective agent for the inner endothelial corneal surface and other delicate inner eye structures during ophthalmic surgery and considerably less expensive. The invention also encompasses the

novel method of using the two different yet compatible solutions together during ophthalmic surgery so as to simultaneously protect the cornea and irrigate it without obscuring the surgeon's view of the site in any way.

DESCRIPTION OF THE RELATED ART

As already noted, the use of methylcellulose derivatives as protective cushioning materials to protect the inner eye structures during ophthalmic surgery is old and well known. On the other hand, use of methylcellulose as one ingredient of a topical surgical solution which, in a more dilute form, is used to keep the corneal tissues moist as an adjunct to surgery is, once again, so far as applicant is aware, heretofore unknown in the art although it is, of course, used as an ingredient in so-called "artifical tears" for treating dry eyes and as a component of contact lens solutions.

The closest and most pertinent prior art known to applicant is contained in two U.S. Patents, specifically, Patent No. 4,500,538 issued February 19, 1985 to Otto W. Woltersdorf under the title of "Benzothiazolesulfonamide Derivatives for the Topical Treatment of Elevated Intraocular Pressure" and Irving Katz Patent No. 4,287,175 issued September 1, 1981 for "Contact Lens Wetting Agents", both of the aforementioned patents being assigned to Merck & Co., Inc. The earlier Katz patent teaches the use of hydroxypropylmethyl cellulose or polyethylene oxide among other polymeric viscosity building agents as a solid water soluble insert as a wetting agent for

contact lens wearers or so-called "artificial tears". These wetting agents are, however, used in solid form and, as such, are totally unsuitable for use in protecting the delicate epithelial cells in ophalmic surgery. Moreover, there is no suggestion that they be used together or that any useful result whatsoever would be achieved by so doing. As a matter of fact, the elastic properties of the two in combination or, for that matter either one alone, is not a factor in their use as wetting agents.

The Woltersdorf patent also mentions the use of hydroxypropylmethyl cellulose and polyethylene oxide as solid water soluble carriers for the active medicament of the invention, namely, the carbonates of 6 or 5-hydroxy-2-benzothiazolesulfonamide for use in the reduction of elevated intraocular pressure of the type often associated with glaucoma. Here again, these high molecular weight substances are used merely as a base for the active ingredient when used as a solid insert as opposed to a solution administered in the form of drops. There is no mention of them being used together nor is their elastic property of any consequence in this application. Most significant, however, is that the formulation of the Woltersdorf patent would be unsuitable for use as a viscoelastic coating to protect the delicate inner eye surfaces during opthalmic surgery or, for that matter, as a topical moisturizing agent to be used during such surgery as a long-lasting moisturizing agent.

SUMMARY OF THE INVENTION

This invention encompasses a novel fluid viscoelastic formulation of variable viscosity for use in ophthalmic surgery containing as its active ingredients a mixture of both hydroxypropylmethyl cellulose and polyethylene oxide together with a physiologic buffered saline solution. Hydroxypropylmethyl cellulose is clear, non-toxic and quite viscous, however, it is also essentially non-elastic. It has now been found in accordance with the teaching of the present invention that, quite unexpectedly, the addition of polyethylene oxide which is a thixotropic material having a nominal molecular weight of 4 million, greatly improves the elasticity of the mixture and makes it comparable, if not superior, to sodium hyaluronate for use as a viscoelastic material in ophthalmic surgery. In addition, different relative concentrations of the two active ingredients in the aforesaid composition have proven to be far superior to balanced salt solution for topical application to keep the tissues moist during surgery by maintaining a smooth, hydrated cornea under the heat of the operating room microscope light. Moreover, since the two solutions contain the same active ingredients, they are fully compatible and can be used simultaneously to both protect and irrigate the delicate corneal tissues.

It is, therefore, the principal object of the present invention to provide an improved viscoelastic solution for use in ophthalmic surgery which is made up in two different

concentrations and administered simultaneously to both protect and irrigate the corneal tissues.

A second object is to provide a solution of the type aforementioned which is susceptible of being made up in selected viscosities by changing the relative concentrations of the active ingredients to adapt it for use as either a topical moisturizing agent or a protective shield for the delicate corneal surfaces and epithelial cells within the inner eye.

Another objective of the invention herein disclosed and claimed is that of providing a topical moisturizing agent which remains effective many times longer than the conventional balanced salt solution while, at the same time, doing a better job.

Still another objective of the within-described invention is to provide a protective solution for intracorneal use in eye surgery which has excellent clarity and transparency but, more importantly, much improved elasticity when compared with hydroxypropylmethyl cellulose alone.

An additional object is to provide a high-molecular weight viscoelastic mixture which is equally effective if not, in fact, superior to sodium hyaluronate-based products at a fraction of the cost.

Further objects are to provide a solution for use in ophthalmic surgery which is safe, non-toxic, readily absorbed, easy to administer, versatile in its application, requires no refrigeration and has a long shelf life.

Other objects will be in part apparent and in part pointed out specifically hereinafter in connection with the detailed description of the preferred embodiments which follow.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The anterior chamber of the eye is filled with circulating aqueous, whereas its posterior chamber with vitreous. The endothelial cell layer of the cornea is easily damaged and, once lost, these cells do not regenerate. The surgical procedures used in cataract surgery, corneal transplants and other types of ophthalmic surgery are likely to result in damage to these delicate cells unless measures are taken to protect them in the manner in which aqueous does naturally.

Of the several prior art substances that have been developed as substitutes for aqueous and vitreous both as a protective layer covering the endothelial cells and as a coating on the surgical instruments and implanted material, undoubtedly the most widely used is sodium hyaluronate extracted from rooster combs, mixtures thereof or bioengineered forms of the naturally-occurring substance. Once the surgical procedure is completed, the remaining vitreous/aqueous substitute is aspirated from the site using a syringe while what is left over is merely resorbed by the body in time without ill effect.

The main problem with hyaluronate-based products is their cost which at the present time runs around $70 or so for less than a cubic centimeter of material. While attempts have been

made to use various methylcellulose derivatives as less expensive viscoelastic substitutes, they have not been well accepted nor do they work as well as hyaluronate.

It has now been found that a vastly improved material having greatly improved elasticity at least equivalent to sodium hyaluronate, but at a fraction of its cost, can be made by the simple, yet unobvious, expedient of combining the relatively non-elastic hydroxypropylmethyl cellulose with a high viscosity thixotropic elasticizer, specifically polyethylene oxide, both in a carrier comprising physiologic buffered saline solution.

The other problem encountered in ophthalmic surgery is that of keeping the external tissues of the eye moist under the drying effect of the operating microscope. As previously noted, this is generally handled on a more-or-less continuous basis by irrigating the external corneal tissues with a balanced salt solution, sometimes as often as twice a minute. Unexpectedly, applicant has discovered that a carefully modified mixture used as the intraocular viscoelastic material for the internal tissues can be advantageously used as a topical solution to keep the external corneal tissues moist many times longer than the balanced salt solution by merely varying the relative concentrations and, therefore, the resulting viscosity of the previously-mentioned intraocular viscoelastic solution that acts as a supplement and substitute for the naturally-occurring vitreous.

Specifically, the topical solution will contain approximately 1% hydroxypropylmethyl cellulose and 20 ppm polyethylene oxide carried in a physiologic saline solution. By way of contrast, the intraocular viscoelastic composition will have the concentration of the hydroxypropylmethyl cellulose increased to 2% while the concentration of the polyethylene oxide is reduced to only 10 ppm. In accordance with the teaching found herein, a unique method of simultaneously irrigating and protecting the delicate corneal tissues is taught using two fully compatible solutions containing the same active ingredients but in different concentrations. When this is done, the stroma and entire cornea is hydrated while the fluid loss through the incision is minimized. It also acts as a tamponade on the scleral flap area.

Since these fluids are aspirated from the eye upon completion of the surgery in order to minimize the incidence of intraocular pressure increases, a non-toxic and physiologically inert tinting material may be added so that the surgeon can be surer that he or she has removed most of the fluid added during the surgery. The resulting compositions, with or without the dye, have proven to be every bit as effective as hyaluronate-based preparations while being far less expensive and, at the same time, lowering operating room costs due to the more efficient use of personnel that results from the less frequent need for irrigation of the corneal tissues.

CLAIMS

What is is claimed is:

1. The viscoelastic aqueous/vitreous substitute for ophthalmic surgery which comprises: a solution containing at least approximately 1% hydroxypropylmethyl cellulose and at least approximately 100 ppm polyethylene oxide in a physiologic balanced salt solution.

2. The viscoelastic aqueous/vitreous substitute as set forth in claim 1 in which: the concentration of the hydroxypropylmethyl cellulose is approximately 2%.

3. The viscoelastic aqueous/vitreous substitute as set forth in claim 1 in which: the concentration of the polyethylene oxide is approximately 200 ppm.

4. The method of irrigating and protecting the corneal tissues during ophthalmic surgery which comprises: covering the inner cornea with a physiologic saline solution containing approximately 2% hydroxypropylmethyl cellulose and approximately 10 ppm polyethylene oxide while simultaneously periodically wetting the outer cornea with a compatible physiologic saline solution containing approximately half the hydroxypropylmethyl cellulose and approximately twice the polyethylene oxide.

INTERNATIONAL SEARCH REPORT

International Application No. pct/ PCT/US88/01389

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(4): A61K 31/715; A61K 47/00; A61K 31/74

U.S.Cl.: 424/78; 514/57,781,912,915

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	424/78 514/57,781,912,915

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

Computer Search on CAS-ON-LINE and APS:
hydroxypropylmethyl(w)cellulose; polyethylene(w)oxide:eye, ocular, ophthal?, surger?

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	US, A, 3,856,919 (RANKIN) 24 December 1974. See column 1, lines 16-17; column 1, line 57 through column 2, line 4; column 7, line 25 and claims 10 and 12.	1-4
X	US, A, 3,947,573 (RANKIN) 30 March 1976. See claims 1 and 10.	1-4
A	US, A, 4,343,787 (KATZ) 10 August 1982. See entire document.	1-4
A	US, A, 4,629,623 (BALAZS) 16 December 1986. See entire document.	1-4
A	International Ophthal. Clin., Volume 13, issued 1973, M. Lemp, "Tear Substituents in the Treatment of Dry Eyes. See entire document.	1-4

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
20 JULY 1988.	08 AUG 1988
International Searching Authority	**Signature of Authorized Officer**
ISA/US	DOUGLAS W. ROBINSON

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(54) Title: IMPROVED VISCOELASTIC FLUID FOR USE IN SURGERY AND OTHER THERAPIES AND METHOD OF USING SAME

(57) Abstract

This invention relates to an improved viscoelastic fluid or gel for use in surgery and other therapies which consists of polyethylene oxide in selected concentrations not to exceed approximately 15 % (15,000 ppm), contained in a physiologic balanced salt solution. The PEO may also be used in conjunction with viscosity enhancers which also act as heat stabilizers, such as methyl cellulose and its derivatives, polyvinyl pyrrolidone or polyvinyl alcohol or in conjunction with elasticizers such as low molecular weight polyethylene glycols or polypropylene glycols or in conjunction with gelation modifiers. These mixtures may be modified to increase retention time in the body by crosslinking with the use of materials like dimethyl urea. The invention encompasses the novel method of protecting and lubricating the corneal tissues during surgery with uses of different concentrations of the same solution introduced simultaneously to protect the inner cornea while periodically irrigating the outer cornea, all without obscuring the surgeon's view of the site. This invention also prevents the development of wound adhesion and has many utilizations in orthopedics.

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Title

IMPROVED VISCOELASTIC FLUID FOR USE IN SURGERY AND OTHER THERAPIES AND METHOD OF USING SAME

CROSS-REFERENCE

This application is a Continuation-In-Part of co-pending application Serial No. 07/045,326; Filed May 4, 1987.

BACKGROUND OF THE INVENTION

There are a number of ophthalmic musculoskeletal and nerve surgical procedures performed by skilled surgeons which require or are facilitated by the use of a viscoelastic medium. Among these are cataract surgery, vitreo-retinal surgery, radial keratotomy to reduce myopia, arthroscopic surgery, urologic surgery, joint surgery, plastic surgery, and wound adhesion prevention.

In all of the ophthalmic surgical procedures except for radial keratotomy in which the corneal tissue is not fully penetrated, the recommended practice is to use an intraocular viscoelastic fluid for protecting the inner endothelial corneal surface and the delicate inner eye structures.

In addition, the outer epithelial surface of the cornea must be lubricated continuously with some type of hydrating agent to

keep it from drying out under the heat generated by the operating microscope light.

Methylcellulose has a long history of safe and effective use for ophthalmic applications. In 1945, Dr. Kenneth C. Swan studied the effects of methylcellulose on the ocular tissues of rabbit eyes. He suggested its use as a vehicle for ophthalmic drugs, to treat keratoconjunctivitis sicca and as an emollient. Then in 1959, Flemming, Merrill and Girard reported on further studies of methylcellulose in relation to irritation, hypersensitivity and its outflow from the anterior chamber of the rabbit eye.

The first reported use of methylcellulose as an intraocular lens coating serving to protect the corneal endothelium in rabbits was made by Drs. Kaufman and Katz in 1976. In the following year Dr. Paul Fechner reported upon the first human clinical use of methylcellulose to coat an intraocular lens prior to implantation.

Then in November of 1982, Dr. Danielle Aron-Rosa reported using methylcellulose in extracapsular surgery instead of high molecular weight sodium hyaluronate extracted from rooster combs which is very expensive. Shortly thereafter, Dr. Fechner amplified upon his earlier findings describing the use of methylcellulose as an intraocular viscous cushioning material in ophthalmic surgery.

Additional work confirming these earlier results has been conducted by Dr. Scott M. MacRae who compared the efficacy and toxicity of sodium

hyaluronate, methylcellulose and chondroitin sulfate, all three of which are used as protective substances suitable for use in ophthalmic surgery. Finally Drs. Smith and Lindstrom evaluated the safety and efficacy of 2% methylcellulose in cat and monkey implant surgery with favorable results.

As already noted, the use of methylcellulose derivatives as protective cushioning materials to protect the inner eye structures during ophthalmic surgery is old and well known. On the other hand, use of methylcellulose as one ingredient of a topical surgical solution which, in a more dilute form, is used to keep the corneal tissues moist as an adjunct to surgery is, once again, so far as applicant is aware, heretofore unknown in the art although it is, of course, used as an ingredient in so-called "artificial tears" for treating dry eyes and as a component of contact lens solutions.

The closest and most pertinent prior art known to applicant is contained in two U.S. Patents, specifically, Patent No. 4,500,538 issued February 19, 1985, to Otto W. Woltersdorf under the title of "Benzothiazolesulfonamide Derivatives for the Topical Treatment of Elevated Intraocular Pressure" and Irving Katz Patent No. 4,287,175 issued September 1, 1981, for "Contact Lens Wetting Agents," both of the aforementioned patents being assigned to Merck & Co., Inc. The earlier Katz patent teaches the use of hydroxypropylmethyl cellulose or polyethylene oxide among other polymeric viscosity building agents as a solid

water soluble insert as a wetting agent for contact lens wearers or so-called "artificial tears". These wetting agents are, however, used in solid form and, as such, are totally unsuitable for use in hydrating and protecting the delicate epithelial cells in ophthalmic surgery. Moreover, there is no suggestion that they be used together or that any useful result whatsoever would be achieved by so doing. As a matter of fact, the elastic properties of the two in combination or, for that matter, either one alone is not a factor in their use as wetting agents.

The Woltersdorf patent also mentions the use of hydroxypropylmethyl cellulose and polyethylene oxide as solid water soluble carriers for the active medicament of the invention, namely, the carbonates of 6 or 5-hydroxy-2-benzothiazolesulfonamide for use in the reduction of elevated intraocular pressure of the type often associated with glaucoma. Here again, these high molecular weight substances are used merely as a base for the active ingredient when used as a solid insert as opposed to a solution administered in the form of drops. There is no mention of them being used together nor is their elastic property of any consequence in this application. Most significant, however, is that the formulation of the Woltersdorf patent would be unsuitable for use as a viscoelastic coating to protect the delicate inner eye surfaces during ophthalmic surgery or, for that matter, as a topical moisturizing agent to be used during such surgery as a long-lasting moisturizing agent.

In arthroscopy the surgeon visualizes

the inside of a joint through a small diameter endoscope inserted into the joint through a 2 mm incision. The joint may be operated upon through similar incisions using fiber-optic light systems along with miniaturized hand and motorized instruments.

Diagnostic arthroscopy is currently being used in temporomandibular, shoulder, elbow, wrist, finger, hip and ankle joints. Surgical arthroscopic procedures include synovectomy, chondroplasty, removal of loose bodies and resection of scar tissue.

During the surgical procedures a copious flow of saline solution is used to maintain a clear surgical field. Intense, magnified light is directed into the surgical area through fiber-optic light bundles. During surgery the surgeon is assisted by a well trained technician. The technician helps to position the extremity, controls the irrigation system and hands instruments to the surgeon. Up to six liters of saline solution may be used during the procedure. The joint area is vacuumed to remove loose bodies and bloody synovial debris. Copious fluid flow and contact by the instruments to the bone may contribute to tissue damage and post surgical inflammation.

Modifications of sodium hyaluronate or hyaluronic acid are being developed to be used in arthroscopic surgery to enhance visualization, and control bleeding; to be used as a post surgical joint lubricant to replace synovial fluid; and to be injected into joints to treat pain caused by arthritis. (Private Placement Memorandum for

Biomatrix, Inc. by BNE Associates, June 14, 1988.)

Spinal laminectomies are performed when disc material extrudes from the spinal column, putting pressure on nerves, causing low back pain. The remedy is to remove the offending disc material. However, in nearly 70% of all spine surgery, while the surgery is successful, the pain is not eliminated and the patient suffers from "failed back syndrome". The cause for this failure is postulated to be scar tissue formation around the dura and nerve roots. Adhesions cause pressure and friction resulting in pain.

Methyl cellulose and methyl cellulose derivatives are known to reduce the formation of adhesions and scarring that may develop following surgery. (Thomas E. Elkins M.D., et al., "Potential for In-Vitro Growth Bacteria in Solutions of 32% Dextran 70 to 10% Sodium Carboxymethylcellulose" Fertility and Sterility, Vol. 43, #3, Mar. 1985; Thomas E. Elkins M.D., et al., "Adhesion Prevention by Solutions of Sodium Carboxymethylcellulose in The Rat, Part I", Fertility and Sterility, Vol. 41, #6, June 1984; Thomas E. Elkins M.D., et al., "Adhesion Prevention by Solutions of Sodium Carboxymethylcellulose in The Rat, Part II", Fertility and Sterility, Vol. 41, #6, June 1984; C. M. Federicks Ph.D., et al., "Adhesion Prevention in The Rabbit with Sodium Carboxymethylcellulose Solutions", American Journal of Obstetrics and Gynecology, 1986; 1ss; 667.70).

Indwelling urinary catheters can be

difficult to remove and the process painful to the patient. Mucous membranes tend to dry around the hydrophobic catheter. A dry coating which becomes slippery and stays hydrated would facilitate removal of catheters.

Urologic surgery is similar to arthroscopic surgery in the use of endoscopic instruments, lights and large amounts of sterile saline operating fluids. Indeed, many of the techniques and devices of arthroscopy were derived from urologic procedures.

Implantable silicone prostheses are commonly used in plastic surgery. The silicone implants now on the market are filled with silicone gel or a saline solution. Saline solutions lack viscosity and in the event of implant rupture, they quickly lose their volume and shape. Silicone gel has been shown to permeate the silicone shell membrane with the result that the silicone fluid collects within the body. Silicone fluids are not broken down and excreted by the body and many cause adverse effects such as scleroderma. Post surgically, the body forms a scar around all silicone implants in a process known as capsular contracture. In mammary augmentation, this process results in firm, hard upraised breasts. The scar must be broken to restore a "natural" breast line. Adhesion formation is common with all types of silicone implants.

U.S. patent 4,042,978 to Jones et al. discloses the use of polyethylene oxide in a rigid plastic implantable prosthetic device.

Despite the high cost of viscoelastic

products based upon sodium hyaluronate, all commercially available ones in common use have it as the sole or at least principal ingredient. Some manufacturers of viscoelastic materials have developed a bioengineered form of sodium hyaluronate but so far it appears that efforts at producing it with a sufficiently high molecular weight have been only marginally successful. A polyacrylamide based viscoelastic material is evidently being tested.

FIELD OF THE INVENTION

The present invention relates to an improved viscoelastic composition for use in surgery and other therapies as a lubricant, cushioning material, cellular protectant, visualization enhancer, bleeding controller, and an implantable prosthesis. The invention, when used in various concentrations, has proven to be equally as good as, if not better than, sodium hyaluronate for use as a protective agent for the inner endothelial corneal surface and other delicate inner eye structures during ophthalmic surgery and considerably less expensive. Similar results have also been obtained with respect to orthopedics, urology, plastic, spinal and neurosurgery. The invention is also effective in the prevention of wound adhesion and scarring. The invention also encompasses the novel method of using the two different, yet compatible, solutions together during ophthalmic surgery so as to simultaneously protect the cornea and irrigate it without obscuring the surgeon's view of the site in any way.

SUMMARY OF THE INVENTION

The present invention is directed to the use of polyethylene oxide (PEO) containing viscoelastic fluids and/or gels primarily for use within extracellular normally sterile areas of the body of a patient. A normally sterile area means a part of the body that does not usually contain microorganisms.

The fluids or gels can contain up to 1.5% by weight of PEO (15000 ppm) and can be modified by the addition of any one or all of the following: viscosity enhancers which also serve as stabilizers to permit heat sterilization of fluids, elasticizers to increase the elasticity of the fluids and gelation modifiers which act as surface modifiers or surfactants.

The mixture is carried in an isotonic balanced salt solution resulting in a final pH of 7 ± .2 and a final osmolality of 320 ± 40.

The viscosity enhancers and stabilizers can include hydroxypropyl methylcellulose (HPMC), carboxymethyl cellulose (CMC), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), methyl cellulose (MC), or mixtures thereof. These polymers may make up from 0.5 to 3 weight percent of the final solution. Other viscosity enhancers can include polyvinyl pyrrolidone (0.5 to 3 weight percent) or polyvinyl alcohol (0.5 to 10 weight percent).

The elasticizers, which can be added to the above mixtures or combinations thereof to increase elasticity, include the lower molecular weight polyethylene glycols (up to 10,000 mw) and

the lower molecular weight polypropylene glycols and trimethyol propane.

The gelation modifiers, which can be added as surfactants to any of the above mixtures or combinations thereof, include the Pluronic polyols F-127 and F-68.

The entire system can be modified to increase retention time in the body (that is, to prolong the absorption rate) by crosslinking with the use of materials like dimethyl urea, formaldehyde urea, formaldehyde or epichlorhydrin or other common crosslinking agents. The effect of this crosslinking is to bind OH radicals in a random manner between and among the materials.

This invention encompasses a novel fluid viscoelastic formulation of variable viscosity for use in ophthalmic surgery containing, as its active ingredients, a mixture of both hydroxypropylmethyl cellulose and polyethylene oxide together with a physiologic buffered saline solution. Other celluloses such as CMC, MC, HEC or HPC may also be used but HPMC is preferred. Hydroxypropylmethyl cellulose is clear, non-toxic and quite viscous, however, it is also essentially non-elastic. It has now been found in accordance with the teaching of the present invention that, quite unexpectedly, the addition of polyethylene oxide in small quantities (less than 500 ppm) which is a thixotropic material having a nominal molecular weight of 4 million, greatly improves the elasticity of the mixture and makes it comparable, if not superior, to sodium hyaluronate for use as a viscoelastic material in ophthalmic surgery. In addition, different relative concentrations of the

two active ingredients in the aforesaid composition have proven to be far superior to balanced salt solution for topical application to keep the tissues moist during surgery by maintaining a smooth, hydrated cornea under the heat of the operating room microscope light. Moreover, since the two solutions contain the same active ingredients, they are fully compatible and can be used simultaneously to both protect and irrigate the delicate corneal tissues.

It is therefore the principal object of the present invention to provide a viscoelastic composition for use in extracellular normally sterile parts of a mammal's body comprising about 10 ppm to 15000 ppm PEO.

A second aspect is to provide a composition of the type of aforementioned composition further comprising by weight .005% to 3% of a methyl cellulose.

Still another aspect of the invention herein disclosed is to provide compositions of the type aforementioned further comprising an elasticity modifier.

A still further aspect on the present invention is to provide a gelation modifier to the compositions of the type aforementioned.

Still yet another principal aspect of the present invention is to provide methods of treating patients using the aforementioned compositions.

It is also another aspect of the present invention to provide an improved viscoelastic solution for use in ophthalmic surgery which is made up in two different concentrations and

administered simultaneously to both protect and irrigate the corneal tissues.

A further aspect is to provide a solution of the type aforementioned which is susceptible of being made up in selected viscosities by changing the relative concentrations of the active ingredients to adapt it for use as either a topical moisturizing agent or a protective shield for the delicate corneal surfaces and epithelial cells within the inner eye.

Still another objective of the invention herein disclosed and claimed is that of providing a topical moisturizing agent which remains effective many times longer than the conventional balanced salt solution while, at the same time, doing a better job.

Still yet another aspect of the within-described invention is to provide a protective solution for intracorneal use in eye surgery which has excellent clarity and transparency but, more importantly, much improved elasticity when compared with hydroxypropylmethyl cellulose alone.

An additional aspect is to provide a high-molecular weight viscoelastic mixture which is equally effective if not, in fact, superior to sodium hyaluronate-based products at a fraction of the cost.

Further aspects are to provide a solution for use in ophthalmic surgery which is safe, non-toxic, readily absorbed, easy to administer, versatile in its application, requires no refrigeration and has a long shelf life.

Other aspects will be in part apparent

and in part pointed out specifically hereinafter in connection with the detailed description of the preferred embodiments which follow.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Ophthalmology

The anterior chamber of the eye is filled with circulating aqueous, whereas its posterior chamber with vitreous. The endothelial cell layer of the cornea is easily damaged and, once lost, these cells do not regenerate. The surgical procedures used in cataract surgery, corneal transplants and other types of ophthalmic surgery are likely to result in damage to these delicate cells unless measures are taken to protect them in the manner in which aqueous does naturally.

Of the several prior art substances that have been developed as substitutes for aqueous and vitreous, both as a protective layer covering the endothelial cells and as a coating on the surgical instruments and implanted material, undoubtedly the most widely used is sodium hyaluronate extracted from rooster combs, mixtures thereof or bioengineered forms of the naturally-occurring substance. Once the surgical procedure is completed, the remaining vitreous/aqueous substitute is aspirated from the site using a syringe, while what is left over is merely resorbed by the body in time without ill effect.

The main problem with hyaluronate-based products is their cost which, at the present time, runs around $70 or so for less than one half of one cubic centimeter of material. While attempts

have been made to use various methylcellulose derivatives as less expensive viscoelastic substitutes, they have not been well accepted nor do they work as well as hyaluronate.

It has now been found that a vastly improved material having greatly improved elasticity at least equivalent to sodium hyaluronate, but at a fraction of its cost, can be made by the simple, yet unobvious, expedient of combining the relatively non-elastic hydroxypropylmethyl cellulose with a high viscosity thixotropic elasticizer, specifically polyethylene oxide, both in a carrier comprising physiologic buffered saline solution.

The other problem encountered in ophthalmic surgery is that of keeping the external tissues of the eye moist under the drying effect of the operating microscope. As previously noted, this is generally handled on a more-or-less continuous basis by irrigating the external corneal tissues with a balanced salt solution, sometimes as often as twice a minute. Unexpectedly, applicant has discovered that a carefully modified mixture used as the intraocular viscoelastic material for the internal tissues can be advantageously used as a topical solution to keep the external corneal tissues moist many times longer than the balanced salt solution by merely varying the relative concentrations and, therefore, the resulting viscosity of the previously-mentioned intraocular viscoelastic solution that acts as a supplement and substitute for the naturally occurring aqueous fluid.

Specifically, the topical-solution will

contain approximately up to 1% hydroxypropylmethyl cellulose based on weight and from about 10 up to 40 ppm polyethylene oxide carried in the isotonic salt solution described above. This solution is used to hydrate the cornea for a prolonged period of time during surgery. By way of contrast, the intraocular viscoelastic composition will have the concentration of the hydroxypropylmethyl cellulose increased from about 2 to 2½% based on weight, while the concentration of the polyethylene oxide remains the same. This solution is used as a surgical aid to increase visualization and to protect the sensitive internal eye structures during surgery. An alternative formulation is 2 weight percent CMC and 40 ppm PEO. An even more elastic intraocular fluid has high PEO (from about 50 to 500 ppm). This fluid is used to protect the corneal endothelial layer from high ultrasonic energy used during phacoemulsification of the nucleus in cataract surgery. In accordance with the teaching found herein, a unique method of simultaneously irrigating and protecting the delicate corneal tissues is taught using two fully compatible solutions containing the same active ingredients but in different concentrations. When this is done, the stroma and entire cornea are hydrated while the fluid loss through the incision is minimized. It also acts as a tamponade on the scleral flap area.

Since these fluids are aspirated from the eye upon completion of the surgery in order to minimize the incidence of intraocular pressure increases, a non-toxic and physiologically inert tinting material may be added so that the surgeon

can be surer that he or she has removed most of the fluid added during the surgery. The resulting compositions, with or without the dye, have proven to be every bit as effective as hyaluronate-based preparations while being far less expensive and, at the same time, lowering operating room costs due to the more efficient use of personnel that results from the less frequent need for irrigation of the corneal tissues.

Orthopedics

The viscoelastic fluids of the invention may comprise a system of fluids which contain an operating fluid which facilitates the surgical process (a third pair of hands) and a cushioning fluid which enhances the patients recovery from surgery.

The operating fluid is used as a surgical aid. The fluid is injected into the joint and enhances visualization by the surgeon, the fluid coats and protects sensitive tissues from contact with the operating instruments and acts as a tamponade to control and direct bleeding. The fluid manipulates tissue during surgery and distends the joint capsule during surgery thereby reducing the amount of saline solution circulating through the joint during surgery. Copious fluid flow may contribute to tissue damage and post surgical inflammation.

In diagnostic and surgical arthroscopy the operating fluid can have from 20 to 1000 ppm of PEO (0.1/10 of 1 weight percent) in a 2 weight percent solution of HPMC.

Arthroscopic examination is made on two

of the knees of the 10 dogs.

The knee joints of half of these dogs are injected with 1.0 ml of a 1000 ppm PEO and 2 weight percent HPMC solution during the surgery. The joints of the other half of the dogs are injected with 1.0 ml of a physiological saline solution as a control. Better visibility, and less bleeding and debris are observed in the animals receiving the viscoelastic fluid than the control. The viscoelastic inflates the joint capsule during surgery. Minimal post operative inflammation is observed.

The viscoelastic cushioning fluid acts as a cushioning barrier between hard joint surfaces during the immediate post-surgical period before the synovial fluid has had a chance to be replaced naturally as well as to act as a replacement synovial fluid for a short period of time. It reduces postsurgical inflammation by creating less friction within the joint and acts as a joint lubricant. It also reduces postsurgical scarring by acting as a barrier to prevent blood from reaching tissue surfaces and forming adhesions. Postoperative joint swelling is reduced, eliminating the inflammation which causes the joint to fill with fluids and the recovery process is shortened by eliminating or minimizing postsurgical complications.

In joint replacement surgery the operating fluid contains up to 5000 ppm (one half of one weight percent) of PEO and up to 2½% weight percent of HPMC. The fluid is elastic and viscous to provide for good joint lubrication and acts as a cushioning agent between the bone and new

artificial joint surfaces postsurgically until the natural synovial fluid has had a chance to replenish.

Synovial fluid is drained from two of the knee joints of 10 dogs. The knee joints of half of these dogs are injected with 3 mls. of a 5000 ppm PEO and 2½ weight percent HPMC solution. The joints of the other half of the dogs are injected with 3 mls of a saline solution as a control. The dogs are observed postoperatively at 12 hour intervals for two weeks. The dogs receiving the viscoelastic PEO HPMC solution have less swelling and heal faster than the control group.

Osteo arthritis is a degenerative bone disease characterized by the progressive loss of cartilage within the affected joint which allows hard bone surfaces to come in contact with one another and be worn away. Inflammation is caused by the underlying disease which leads to loss of joint lubrication which results in friction and more inflammation. Inflammation impedes normal tissue function and the cycle continues.

The viscoelastic composition of the invention acts as a cushioning agent to break the destructive cycle of inflammation and deterioration of tissue function with more inflammation and eventual cartilage destruction. The fluid acts as a cushion which allows the body to heal itself to eliminate the inflammation which probably initiated the destructive process. It is important that an effective cushioning agent does not cause post application swelling or joint blowout with a possible rupture of the joint

capsule.

The fluid is injected into the joint at six to nine month intervals.

Cortisone treatments have been used to treat inflamed joints but, because they mask the underlying etiology, they simply serve to hasten the destructive process.

In osteo arthritis, the fluid must be more gelatinous. The fluid can contain from about 10 up to 5000, ppm PEO, from about 2 up to 2½ weight percent HPMC and from 5 up to 13 weight percent Pluronic F-127. This fluid provides excellent lubrication and cushioning for a prolonged period of time in order to reduce the joint inflammation and allow the body to begin a natural healing process. None of the animals receiving applications of the fluid in their joints exhibit an allergic reaction. An allergic reaction is frequently typified by the accumulation of water within the joint capsule postsurgically. The viscoelastic operating and cushioning fluids are also used to impregnate artificial ligaments and tendons to prevent tissue ingrowth postoperatively.

The viscoelastic fluid has also been used to treat degenerative joint disease in horses. A 100 ppm PEO and 2½ percent by weight of HPMC mixture in a physiological saline solution (4 to 6 mls) was injected into the knee joints of horses. Lameness disappeared and the animals had symptomatic relief for up to nine months.

Spine and Neurosurgery

The viscoelastic medium of the invention may reduce or prevent any adhesions or scar tissue formation around the dura and nerve roots following laminectomy surgery. The viscoelastic medium acts as a barrier preventing blood from reaching the area which was operated on. The theory is that, with no blood there can be no scar tissue formation and no adhesion. The viscoelastic material stays at the wound site long enough to allow healing to occur before allowing natural body fluids into the area.

In spine surgery, specifically a laminectomy, and in nerve surgery, the solution may contain from about 20 up to 5000 ppm PEO, from about 1 to 2½ weight percent carboxymethyl cellulose and from about 5 up to 13 weight percent Pluronic F-127. The purpose of the fluid is to act as a barrier to prevent blood from entering or accumulating in the wound area and to act as a lubricant preventing the formation of wound adhesions or scar tissue between the exposed nerves and surrounding tissue in the wound area. Retention time is controlled by crosslinking.

Crosslinking may be accomplished using the following method:

1. Using the ingredients and weight percentages listed in Table 1, below, the carboxymethyl cellulose, polyethylene oxide and Pluronic F-127 are mixed into the buffered physiological saline solution. When thoroughly mixed, the dimethyl urea crosslinking agent is added, and the ammonium chloride, which acts as a catalyst, is added

to initiate the crosslinking reaction. The mixture is heated to 90°C and held at this temperature for one hour. The resulting composition prevents or minimizes wound adhesion.

TABLE 1

Ingredient	Weight %
Polyethylene oxide	0.5
Carboxymethyl cellulose	2.5
Pluronic F-127	13.0
Dimethyl urea	0.25
Ammonium chloride NH_4Cl	0.025
Buffered physiological saline	83.725

The following animal trials in rabbits have established that scar formation is reduced with these solutions.

Surgical Procedures:

This study was performed in 60 adult, female New Zealand rabbits. However, because of post-surgical complications only 54 rabbits were used in data representation. After undergoing general anesthesia, each animal underwent the following procedure: (1) a medial incision was made along the spinous process to the lumbosacral region. After cutting through the skin and subcutaneous tissue, the fascia of the muscle was opened from the right of the spinous process. The muscles were pulled aside laterally to expose the spinous processes and vertebral arches. A small retractor was inserted into the wound and an oval defect of approximately 3 X 10 mm was drilled into the lamina with a dentist drill. A second similar laminectomy was made with one intact vertebra

between the laminectomies. This second laminectomy served as a control site. Bone wax or Gelfoam was used to control excessive bleeding from the bone when required. One laminectomy site was coated with a standardized amount of one of the following agents: (1) 2% hydroxypropyl methylcellulose (10 ppm PEO); (2) 2% hydroxypropyl methylcellulose (20 ppm PEO); (3) Dextran 70(Hyskon); (4) 2% sodium carboxymethylcellulose; (5) 1% sodium carboxymethylcellulose; and (6) sodium hyaluronate (Hylatin V). The other site received no treatment and thus served as a control. The wounds were then closed using a continuous 3-0 chromium catgut suture of 3-0 mercelene. For the sake of later orientation, a metal suture of 3-0 steel wire was placed in the muscle near the middle of the intact vertebra between the hemilaminectomies.

The animals were allowed to recover from surgery and returned to their individual cages. At four weeks and eight weeks following surgery one-half of the rabbits were sacrificed, the spinal column cut at both ends of the operative area to include the excised vertebra in their entirety and the entire specimen immersed in 10% neutral buffered formalin.

Histological Analysis:

Histological analysis was performed on decalcified specimens. After decalcification in 10% formic acid, formalin solution for two weeks, specimens were cut in the middle of the intact vertebra between laminectomies. The specimens (both control and test) were reduced in size and

left to decalcify for two more weeks. Specimens were then embedded in paraffin and four 10um sections were cut so that the plane of the surface included the graft material with the spinal cord in the microscopical section. Staining was accomplished with hematoxylin-eosin for all groups. All sections for each specimen were examined. However, the qualitative assessment was performed on what was considered to be the best cut section from the group. This assessment consisted of a microscopic examination of the surgical site. Particular attention was paid to how much scar tissue was present on the dura and whether the scar tissue extended into the surgical site. Another parameter that was evaluated was the size of the laminal defect and whether the surgical gap had reduced in size. The number and type of cellular detail at the surgical site (i.e. osteoblast (bone), fibroblasts and lymphocytes (scar tissue) and chondrocytes (collegen synthesis)) were also noted.

Results:

Only the data for the four week specimens are summarized. This was done since the eight week specimens, which healed more completely than the four week specimens, invariably demonstrated no significant change from the four week specimens with respect to whether the control or treated site demonstrated the least amount of scar tissue. Therefore, based on visual observation, a value of 0 was assigned to each animal if the treated site appeared comparable in healing to the control site, - if the control site

appeared better healed than the treated site, and a + if the treated site appeared best.

Utilizing this grading scale, it is apparent from Table 1 that both 1% and 2% CMC appeared to afford the best prevention of extensive scar formation. It should be noted that in no specimens was there any histological evidence of healing totally devoid of scar tissue. This assessment therefore, more accurately reflects the degree to which scar tissue was present relative to all the other specimens.

Summary for Four Week Evaluation

Table 1

Rabbit #	Group	Evaluation	Notes
N112	Hyskon	+	
N113	Hyskon	-	
N114	Hyskon	+	
N129	Hyskon	+	
N200	87094-V*	-	macrophages present @ treated site
N201	87094-V	-	
N202	87094-V	+	
N203	87094-V	+	
N256	87093-I0**	+	
N257	87093-I0	-	
N255	87093-I0	+	
N258	87093-I0	-	
N259	87093-I0	0	
* 2% HPMC, 10 ppm PEO			
** 2% HPMC, 20 ppm PEO			
Q139	2% CMC	-	
Q140	2% CMC	+	
Q135	2% CMC	++	1 week specimen
Q136	2% CMC	+	
Q127	2% CMC	-	
Q133	1% CMC	+	
Q134	1% CMC	+	numerous chondrocytes present
P668	1% CMC	++	same as Q134
P669	1% CMC	+	possible soft tissue inflammation response
P743	1% CMC	0	
P751	Hylartin	0	numerous chondrocytes

Q374	Hylartin	-	
Q375	Hylartin	-	
Q378	Hylartin		numerous chondrocytes
Q377	Hylartin	0	same as Q378

Neurosurgical applications of the fluids are similar to the spinal applications. Namely, the elimination or reduction of scar tissue formation in and around the brain post-operatively. The "barrier" effect is the mode of operation by which the fluid achieves its purpose.

The anti-adhesion properties of these fluids are useful in several other areas of surgery where it is important to reduce scar formation. These surgical areas include abdominal surgery, thortic and cardiovascular surgery and ob/gyn.

Urology

In connection with urology the viscoelastic fluid includes an operating fluid and a postsurgical cushioning fluid. The operating fluid facilitates the introduction of instruments into the urethra, bladder and ureters, and enhances the surgeon's visualization, while it protects sensitive tissue from damage and instrument contact. The viscoelastic operating fluid also expands the diameter of narrow passageways and acts as a tamponade against unwanted accumulation of blood. In addition, the viscoelastic fluid of the invention facilitates the passage of urinary

stones and fragments through the ureters because of the lubricating properties of the fluid. The urology operating fluid is composed of up to 500 ppm PEO and 1 to 2 weight percent of HPMC. A composition of 3 mls of a physiological solution having 500 ppm of PEO and 2 weight percent of HPMC is injected into the ureter of five cats having kidney stones (urinary calculi) and facilitate passage of urinary calculi. It also acts as a lubricant and inflates the diameter of the ureter. The fluid may be used alone or with lithotrophsy (ultrasonic fragmentation of the stone). The solution has been shown to dissolve the calculi and reduce reoccurrence in cats.

The urological cushioning fluid reduces postoperative inflammation pain and speeds patient recovery. About 2 mls of 1000 ppm PEO and 2 weight percent HPMC in physiological saline solution was applied to the postoperative area following urological surgery. Minimal scar and adhesion formation were observed. The same results are observed following transurethral resection and no inflammation occurred.

About 0.5 mls of 40 ppm PEO and 2 weight percent HPMC in a physiological solution was injected into the ureter of five cats having urinary calculi. The calculi passed spontaneously. No reoccurrence of stones were found 12 months after treatment.

Plastic surgery:

A viscoelastic gel fluid of the present invention is used to replace the silicone gel fluids in all silicone implants. Such implants

include mammary implants for cosmetic or reconstruction purposes, testicular implants, penile implants, small "pillow" implants and so on. The viscoelastic fluid is used separately as an anti-adhesion agent to act as a slippery barrier to prevent contact between the implant and healing tissue. The implantable fluid is composed of from about 2 up to 3 weight percent HPMC for high viscosity and from about 10 up to 50 ppm of PEO for moderate elasticity. This fluid is placed in a silicone shell and is implanted within the body. The shell is also coated with the fluid. Following implantation, no inflammation or adhesion is observed. Crosslinking in a manner similar to that described for the wound adhesion prevention preparation is used to increase the cohesiveness of the fluid.

Crosslinking may be performed as follows:

1. Using the ingredients and weight percentages listed in Table 2 below, the hydroxylpropyl methylcellulose and polyethylene oxide are mixed into the buffered saline solution. When thoroughly mixed, the formaldehyde urea crosslinking agent is added. Then the ammonium chloride, which sets as catalyst, is added to initiate the crosslinking reaction. The mixture is heated for one hour at 90°C. The resulting composition is an inert gel fill which will not bleed through a prosthetic shell.

TABLE 2

Ingredients	Weight%
Polyethylene oxide	.005
Hydroxypropylmethylcellulose	3.0
Formaldehyde urea	0.2
Ammonium chloride	0.02
Buffered physiological saline	96.775

Variations and modifications can, of course, be made without departing from the spirit and scope of the invention.

CLAIMS

What is claimed is:

1. A viscoelastic composition for use in extracellular normally sterile parts of a mammal's body comprising: about 10 ppm to 15,000 ppm polyethylene oxide (PEO) in a physiologically compatible formulation.

2. A composition according to claim 1 and further comprising by weight about .0001% to 3% of a methyl cellulose.

3. A composition according to claim 2 wherein the methyl cellulose is selected from methyl cellulose (MC), hydroxypropylmethyl cellulose (HPMC) and carboxymethyl cellulose (CMC).

4. A composition according to claim 1 and further comprising by weight about .0001% to 3% of a selected one of hydroxypropyl cellulose (HPC) and hydroxyethyl cellulose (HEC).

5. A composition according to claim 1 and further comprising by weight about .05% to 3% polyvinyl pyrollidone (PVP).

6. A composition according to claim 1 and further comprising by weight about .05% to 10% of polyvinyl alcohol (PVA).

7. A composition according to claim 1 and further comprising an elasticity modifier.

8. A composition according to claim 7 wherein the elasticity modifier is a polyethylene glycol.

9. A composition according to claim 8 wherein the elasticity modifier is PPG.

10. A composition according to claim 2 and further comprising an elasticity modifier.

11. A composition according to claim 1 and further comprising a gelation modifier.

12. A composition according to claim 11 wherein the gelation modifier is a pluronic polyol.

13. A viscoelastic composition for use in normally sterile parts of the body comprising a crosslinked preparation of a methyl cellulose and PEO in a physiological compatible formulation.

14. In an orthopedic surgical method which includes operating in the area of a bone, the improvement comprising delivering a quantity of the composition of claim 2 to the bone area being operated on thereby coating the bone and preventing injury from surgical instruments.

15. In a method for replacing synovial fluid in a specific joint area, the improvement comprising delivering a quantity of the composition of claim 2 to said joint area and

allowing the composition to act as a cushioning agent in the joint area.

16. A method for treating osteoarthritis comprising obtaining access to the area of the arthritis, delivering a composition, including about 20 to 15,000 ppm polyethylene oxide, about 2 to 2½ weight percent hydroxypropylmethyl cellulose and about 5 to 13 weight percent of a pluronic polyol to that area, and reducing inflammation in that area.

17. A method for preventing wound adhesion during and following surgery comprising delivering a composition having about 20 to 15,000 ppm polyethylene oxide, about 2 to 3 weight percent carboxymethyl cellulose and about 5 to 13 weight percent of a pluronic polyol to the wound area and allowing the composition to be absorbed in the wound area.

18. In a surgical method using an implantable prosthesis containing a composition, the improvement comprising implanting into the body of a patient a prosthesis filled with a viscoelastic composition including about 2 to 3 percent by weight of hydroxypropylmethyl cellulose and about 50 to 5000 ppm of PEO in a physiologically acceptable mixture.

19. In a method for treating urinary calculi, the improvement comprising delivering a quantity of a composition including about 50 to 500 ppm of polyethylene oxide and about 1 to 2

percent by weight of hydroxypropylmethyl cellulose to the urinary calculi of a patient and coating the calculi with the composition.

20. In a method for treating urinary calculi, the improvement comprising delivering a quantity of a composition including about 50 to 500 ppm of polyethylene oxide and about 1 to 2 percent by weight of hydroxypropylmethyl cellulose to the urinary calculi of a patient facilitating passage of calculi in the urine.

21. In urological surgery involving manipulation of the ureter, the improvement comprising injecting a composition including about 50 to 500 ppm polyethylene oxide and about 1 to 2 percent by weight of hydroxypropylmethyl cellulose into the ureter, and lubricating and inflating the ureter with the composition.

22. The viscoelastic aqueous/vitreous substitute for ophthalmic surgery which comprises: a solution containing at least approximately 1% of a cellulose derivative and, about 10 ppm to 100 ppm polyethylene oxide in a physiologically compatible solution.

23. The viscoelastic aqueous/vitreous substitute as set forth in claim 22 in which: the derivative is hydroxypropylmethyl cellulose and the concentration of hydroxypropylmethyl cellulose is about 2% to 2 1/2%.

24. The viscoelastic aqueous/vitreous substitute as set forth in claim 22 in which: the concentration of the polyethylene oxide is about 10 to 100 ppm.

25. The method of irrigating and protecting the corneal tissues during ophthalmic surgery which comprises: covering the inner cornea with a physiologic saline solution containing approximately 2% hydroxypropylmethyl cellulose and approximately 10 ppm polyethylene oxide while simultaneously periodically wetting the outer cornea with a compatible physiologic saline solution containing approximately half the hydroxypropylmethyl cellulose and approximately twice the polyethylene oxide.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US89/04842

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) 6

According to International Patent Classification (IPC) or to both National Classification and IPC

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U.S.D. 424/631,80 514/57,781,912,915

II. FIELDS SEARCHED

Minimum Documentation Searched 7

Classification System	Classification Symbols
U.S.	424/631 514/57,781,912,915

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched 8

III. DOCUMENTS CONSIDERED TO BE RELEVANT 9

Category *	Citation of Document, 11 with indication, where appropriate, of the relevant passages 12	Relevant to Claim No. 13
"Y"	US,A, 3,856,919 (RANKIN) 24 DECEMBER 1974 See column 1. lines 16-17, column 1 line 57 through column 2, line 5 and column 7 line 25.	22-25
"Y"	US,A, 3,947,573 (RANKIN) 30 MARCH 1976 See claims 1 and 10.	22-25

* Special categories of cited documents: 10

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
28 FEBRUARY 1990	26 MAR 1990
International Searching Authority	**Signature of Authorized Officer**
ISA/US	Zohreh A. Fay ZOHREH FAY

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(54) Title: NON OXIDATIVE OPHTHALMIC COMPOSITIONS AND METHODS FOR PRESERVING AND USING SAME

(57) Abstract

Ophthalmic compositions, such as those used to care for contact lenses, methods of preserving such compositions, and methods for disinfecting contact lenses using such compositions are disclosed. The compositions may comprise an ophthalmically acceptable, liquid aqueous medium and, included therein, an effective preserving or disinfecting amount of certain oxygen-containing ionene polymers.

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NON OXIDATIVE OPHTHALMIC COMPOSITIONS AND METHODS FOR PRESERVING AND USING SAME

Background of the Invention

This invention relates to ophthalmic compositions and methods for preserving and using such compositions. More particularly, the present invention relates to ophthalmic compositions, e.g., useful in caring for contact lenses, which include one or more of certain ionene polymers as preservatives or disinfectants, and to methods for disinfecting and/or preserving using such compositions.

Various compositions, e.g., solutions, are used in association with contact lenses to ensure that the lenses may be safely, comfortably and conveniently worn. Contact lens care compositions, for example, disinfecting compositions, preserving compositions, cleaning compositions, wetting compositions, conditioning compositions and the like, often utilize at least one disinfectant or preservative, depending on the type of composition, for disinfecting or preserving contact lenses after wear or preserving the lens care composition itself. A contact lens disinfecting composition generally has sufficient antimicrobial activity so that when the composition is contacted with a lens to be disinfected, microorganisms associated with the lens are killed or otherwise removed and the contact lens is effectively disinfected within a reasonable time, e.g., in the range of about 0.1 hour to about 12 hours. A contact lens disinfecting composition may be termed a microbio-cidal composition. In contrast, a contact lens preserving composition has sufficient antimicrobial activity, often less of such activity than is present in a contact lens disinfecting composition,so that when the composition is contacted with a contact lens substantially no increase in the microorganism population on the lens or in the composition is obtained. A contact lens

preserving composition may be termed a microbio-static composition. Other contact lens care compositions are preserved to prevent any substantial increase in the population of contaminating microorganisms in the compositions and, thereby, to extend their shelf life. Such preserved contact lens care compositions may be termed microbio-static compositions. Some preservatives used in lens preserving compositions or in preserved compositions may also be used as disinfecting agents in lens disinfecting compositions.

Various compounds are known for use as preserving agents in contacts lens preserving compositions and preserved contact lens care compositions. Examples include thimerosal, benzalkonium chloride and chlorhexidine. However, these preserving agents are known to exhibit ocular toxicity which may result in irritation or sensitivity to the eye. The degree of ocular toxicity increases when these agents are utilized as disinfecting agents. Further, a soft contact lens, a rigid gas permeable contact lens (RGP) or a hard contact lens can absorb or adsorb these compounds. This causes the contact lens to retain the irritating compound and contributes to the eye irritation and sensitivity which may result.

Stark U.S. Patent No. 4,525,346 discloses a contact lens disinfecting solution and preserved contact lens care compositions containing 1-tris (2-hydroxyethyl) ammonium-2-butenyl-4-poly [1-dimethyl ammonium-2-butenyl]-w-tris (2-hydroxyethyl-) ammonium the salt of which has a pharmaceutically acceptable anion. The quaternary ammonium polymer disclosed in this Stark patent is capable of causing irritation and sensitivity to some contact lens wearers.

Japanese Patent Publication 63131124 discloses a liquid composition for contact lens care including as an antimicrobial component a polymeric condensate of a diamine, such as N, N, N', N' - tetramethyl 1,2-diaminoethane, and a

dihalogen compound, such as 1,2-dichloroethane. Such polymeric condensates include no oxygen. Further, there is no suggestion that other polymeric condensates are useful as antimicrobial agents in the contact lens care context.

Other conventional methods of contact lens chemical disinfection utilize one or more active disinfecting agents in an aqueous medium, for example a chlorhexidine/thimerosal solution or a relatively mild solution of hydrogen peroxide. Some of these disinfecting solutions, such as those named above, are cytotoxic and are known to be adsorbed or absorbed onto or into a contact lens and cause the lens to elicit a cytotoxic response after disinfection. For example, contact lenses which have been soaked in a disinfecting hydrogen peroxide solution are to be treated to remove residual hydrogen peroxide, e.g., by soaking in a catalase solution, before they may be comfortably and safely worn again. If residual hydrogen peroxide remains on the lenses, then irritation or injury to the eye may result. A lens disinfecting system employing a substantially non-oxidative disinfectant composition is particularly useful since the risk of introducing active oxidizing agents into the eye is substantially eliminated.

Ellis et al U.S. Patent 4,168,112 discloses treating an ionically charged contact lens with a lens solution containing an oppositely charged ionic polymer to form a hydrophilic polyelectrolyte complex on the lens surface. This complex forms a hydrogel and acts as a cushion which provides comfort to the eye. Ionene polymers are among the many ionic polymers disclosed by Ellis et al. In addition, Ellis et al discloses that other additives, such as preservatives, e.g., benzalkonium chloride, ethylenediaminetetraacetic acid, mercurials and chlorobutanol, can be included in the lens treating solutions. Ellis et al does not distinguish between ionene polymers, nor is there any suggestion than any ionene

polymers are useful as preservatives or disinfectants in the contact lens care context.

Stockel et al U.S. Patent 4,499,077 discloses oxidative contact lens disinfecting compositions including stabilized chlorine dioxide and a quaternary ammonium compound which is a copolymer of at least one mono-or di-tertiary amine and a dihalo organic compound. Stockel U.S. Patent 4,654,208 discloses oxidative contact lens disinfecting compositions including one or more of the quaternary ammonium copolymers noted above in this paragraph plus a potentiating amount of an oxidizing agent. Neither of the Stockel et al patents disclose non-oxidation contact lens care compositions using such quaternary ammonium copolymers.

Thus, it is readily apparent that a continuing need exists for safe and efficacious compositions that can be used as contact lens disinfecting and preserving compositions and as preserved contact lens care compositions.

Summary of the Invention

New disinfecting and preserving compositions and methods, particularly such compositions and methods directed to contact lens care, have been discovered. The present compositions are substantially non-oxidative and include effective disinfectants and/or preservatives. Thus, for example, a contact lens can be effectively disinfected in a reasonable length of time. Also, contact lens care products can be effectively preserved against growth of contaminating microorganisms. Importantly, such disinfecting and preserving activities are achieved and the contact lenses disinfected, preserved or otherwise cared for using the present compositions can be safely and comfortably worn with little or no risk of eye irritation or sensitivity, e.g., from the presence of residual oxidizing agent.

In one broad aspect of the invention, a substantially non-oxidative composition useful for disinfecting, or preserving, a contact lens is provided. This composition includes an ophthalmically acceptable, preferably sterile, medium, preferably a liquid aqueous medium. Included within this medium is an effective disinfecting, or preserving, amount of an ophthalmically acceptable quaternary ammonium polymer selected from ionene polymers containing an oxygen atom covalently bonded to two carbon atoms and mixtures thereof. Methods of disinfecting, or preserving, a contact lens include contacting the lens to be disinfected, or preserved, with an appropriate composition, as described herein. Such ionene polymers are effective disinfectants and preservatives in the contact lens care context without the need for oxidizing agents. Contact lenses which are disinfected, preserved or otherwise treated using the present compositions can be safely and comfortably worn with little or no risk of eye irritation or sensitivity.

Preserved compositions, e.g., contact lens care compositions, which include an ophthalmically acceptable medium, preferably containing one or more components effective to beneficially affect a contact lens and/or the wearing of a contact lens, are included within the scope of the present invention. Such preserved compositions are preferably substantially non-oxidative, and include an effective preserving amount of an ophthalmically acceptable quaternary ammonium polymer, as described herein.

Detailed Description of the Invention

The present invention is applicable to disinfecting all types of lenses, e.g., contact lenses, which are benefited by such disinfecting. Such lenses, e.g., conventional soft contact lenses, RGPs and hard contact lenses, may be made of any suitable material or combination of materials and may have any suitable configuration. The invention is also applicable

to preserving compositions, such as contact lens care compositions, and other eye care products which are benefited by being preserved.

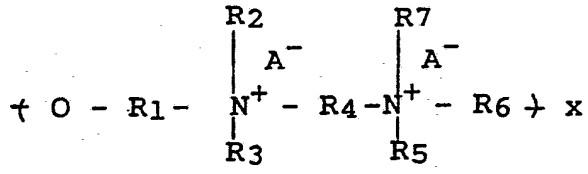
One important feature of the substantially non-oxidative compositions of the present invention is the inclusion of an effective, e.g., for disinfecting and/or preserving, amount of at least one ophthalmically acceptable quaternary ammonium polymer selected from the group consisting of ionene polymers containing an oxygen atom covalently bonded to two carbon atoms, hereinafter referred to as "(C-O-C) ionene polymers", and mixtures thereof. Without wishing to limit the invention to any particular theory of operation, it is believed that the quaternary ammonium polymers useful in the present invention are sufficiently active to provide the desired degree of disinfecting or preserving without causing substantial eye irritation or sensitivity.

The presently useful quaternary ammonium polymers are distinguished from the quaternary ammonium polymer described in Stark U.S. Patent 4,525,346 and the polymeric condensate described in Japanese Patent Publication 63131124. In the Stark patent and the Japanese Publication, the quaternary ammonium polymer and the polymeric condensate are not (C-O-C) ionene polymers. The presently useful quaternary ammonium polymers provide the desired antimicrobial activity without causing substantial eye irritation and sensitivity.

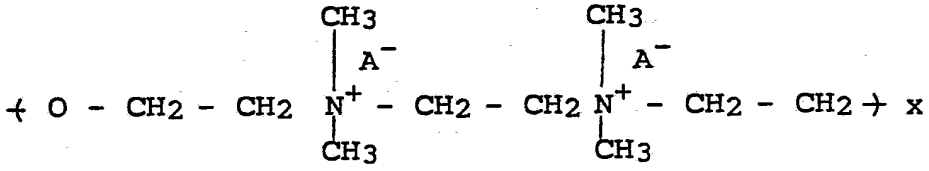
The presently useful quaternary ammonium polymers are preferably dispersible or soluble in the ophthalmically acceptable medium. Since contact lens disinfecting, preserving and other care compositions are most often solutions, the quaternary ammonium polymers are more preferably soluble in the medium. The amount of quaternary ammonium polymer employed in the present compositions is that sufficient to effect the desired result. Care should be taken to avoid excessive amounts of quaternary ammonium polymer.

Not only are such materials quite expensive, but the use of large excesses of quaternary ammonium polymer may result in some degree of eye irritation and/or sensitivity. The presently useful quaternary ammonium polymers are preferably present in an amount in the range of about 0.00001% to about 1%, more preferably about 0.0001% to about 0.5%, by weight per volume of ophthalmically acceptable medium.

The presently useful quaternary ammonium polymers preferably have the following repeating unit



wherein R_1, R_4 and R_6 are each independently selected from alkylene radicals containing 1 to about 6 carbon atoms, R_2, R_3, R_5 and R_7 are each independently selected from alkyl radicals containing 1 to about 6 carbon atoms, each A^- is independently selected from ophthalmically acceptable anions, and x is the number of repeating units in the polymer and is an integer in the range of about 5 to about 30. A particularly useful quaternary ammonium polymer has the following repeating unit



The number of repeating units per polymer molecule, represented by x, is more preferably about 8 to about 30, especially about 14.

Examples of ophthalmically acceptable anions include chloride (Cl^-), bromide, iodide, bisulfate, phosphate, acid

phosphate, nitrate, acetate, maleate, fumarate, oxalate, lactate, tartrate, citrate, gluconate, saccharate, p-toluene sulfonate and the like. The preferred ophthalmically acceptable anion is Cl^-.

In one particularly useful embodiment, the quaternary ammonium polymer has a molecular weight in the range of about 500 to about 5000.

Methods for producing the presently useful quaternary ammonium polymers are described in Buckman et al U.S. Patent 4,250,269, which patent is hereby incorporated in its entirety herein by reference. A specific example of a quaternary ammonium polymer useful in the present invention is poly (oxyethylene (dimethyliminio) ethylene-(dimethyliminio) ethylene dichloride), such as that sold by Buckman Laboratories, Inc. under the trademark WSCP.

The present compositions may include other, e.g., complementary and/or potentiating, antimicrobial agents. Examples of such other antimicrobial agents include, but are not limited to, thimerosal, sorbic acid, 1.5-pentanedial, alkyl triethanolamines, boric acid, ophthalmically acceptable salts of any of the above, 3-chloroallyl-3, 5, 7, triaza-1-azonia adamantine chloride, phenylmercuric salts and mixtures thereof. Ophthalmically acceptable salts may include one or more ophthalmically acceptable anions, e.g., as noted above, or ophthalmically acceptable cations, in particular alkali and alkali metal cations. Materials which provide more than one beneficial or desired property to the present compositions may also be included. For example, certain combinations of quaternary ammonium compounds which possess both antimicrobial activity and wetting properties may be included. Examples of such combinations of quaternary ammonium compounds include, but are not limited to, balanced mixtures of N-alkyl dimethyl benzyl ammonium chlorides and N-alkyl dimethyl ethylbenzyl ammonium chlorides. Each of these agents/materials may be

included in the present compositions in an amount effective to provide the beneficial or desired property or properties.

The compositions of the present invention include an ophthalmically acceptable medium, preferably an ophthalmically acceptable liquid aqueous medium. This medium often acts as a carrier, e.g., as a solvent, for the other components in the composition. A material is "ophthalmically acceptable" if the material can be placed into a mammalian eye without causing any substantial damage or harm to the eye. One particularly useful ophthalmically acceptable medium is water. Preferably, the medium, and in fact the entire composition, is sterile.

One or more additional components can be included in the present compositions based on the particular application for which the compositions are formulated. Thus, the present compositions can be formulated as disinfecting compositions, cleaning compositions, wetting compositions, conditioning compositions, soaking compositions and the like. Also, the present compositions can be formulated to be useful in performing two or more contact lens caring operations. For example, a disinfecting/cleaning composition, or a cleaning/conditioning composition or even an all purpose lens care composition can be formulated and such multi-functional compositions are included within the scope of the present invention.

The additional component or components included in the present compositions are chosen to impart or provide at least one beneficial or desired property to the compositions. Such additional components may be selected from components which are conventionally used in one or more contact lens care compositions. Examples of such additional components include buffering agents, cleaning agents, wetting agents, nutrient agents, sequestering agents, viscosity builders, tonicity agents, contact lens conditioning agents, antioxidants, pH

adjustors, and the like. These additional components are each included in the present compositions in an amount effective to impart or provide the beneficial or desired property to the compositions. For example, such additional components may be included in the present compositions in amounts similar to the amounts of such components used in other, e.g., conventional, contact lens care products.

Useful buffering agents include, but not limited to, acetate buffers, citrate buffers, phosphate buffers and borate buffers. Acids and bases may be used to adjust the pH of the present compositions as needed.

Useful wetting agents include, but are not limited to, polyvinyl alcohol, poloxamers, polyvinyl pyrrollidone, hydroxypropyl methyl cellulose and mixtures thereof.

Useful sequestering agents include, but are not limited to, disodium ethylene diamine tetraacetate, alkali metal hexametaphosphate, citric acid, sodium citrate and mixtures thereof.

Useful tonicity adjustors include, but are not limited to, sodium chloride, potassium chloride, mannitol, dextrose, glycerin, propylene glycol and mixtures thereof.

Useful viscosity builders include, but are not limited to, hydroxyethyl cellulose, hydroxy methyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol and mixtures thereof.

Useful antioxidants include, but are not limited to, sodium metabisulfite, sodium thiosulfate, N-acetylcysteine, butylated hydroxyanisole, butylated hydroxytoluene and mixtures thereof.

In a particularly useful embodiment, the quaternary ammonium polymer-containing composition further includes at least one enzyme effective to remove debris from a contact lens. Among the types of debris that form on a contact lens during normal use are protein-based debris, mucin-based debris, lipid-based debris and carbohydrate-based debris. One

or more types of debris may be present on a single contact lens.

The enzyme employed may be selected from enzymes which are conventionally employed in the enzymatic cleaning of contact lenses. For example, many of the enzymes disclosed in Huth et al U.S. Patent RE 32,672 and Karageozian et al U.S. Patent 3,910,296 are useful in the present invention. Each of these patents is incorporated in its entirety by reference herein. Among the useful enzymes are those selected from proteolytic enzymes, lipases and mixtures thereof.

Preferred proteolytic enzymes are those which are substantially free of sulfhydryl groups or disulfide bonds. Metallo-proteases, those enzymes which contain a divalent metal ion such as calcium, magnesium or zinc bound to the protein, may also be used.

A more preferred group of proteolytic enzymes are the serine proteases, particularly those derived from Bacillus and Streptomyces bacteria and Asperigillus molds. Within this grouping, the still more preferred enzymes are the derived alkaline proteases generically called subtilisin enzymes. Reference is made to Deayl, L., Moser, P.W. and Wildi. B.S., "Proteases of the Genus Bacillus, II Alkaline Proteases", Biotechnology and Bioengineering, Vol. XII, pp 213-249 (1970) and Keay, L. and Moser, P.W., "Differentiation of Alkaline Proteases form Bacillus Species" Biochemical and Biophysical Research Comm., Vol 34, No. 5, pp 600-604, (1969).

The subtilisin enzymes are broken down onto two sub-classes, subtilisin A and subtilisin B. In the subtilisin A grouping are enzymes derived from such species as B. subtilis, B. licheniformis and B. pumilis. Organisms in this sub-class produce little or no neutral protease or amylase. The subtilisin B sub-class is made up of enzymes from such organisms as B. subtilis, B. subtilis var. amylosacchariticus, B. amyloliquefaciens and B. subtilis NRRL B3411. These

organisms produce neutral proteases and amylases on a level about comparable to their alkaline protease production. One or more enzymes from the subtilisin A sub-class are particularly useful.

In addition other preferred enzymes are, for example, pancreatin, trypsin, collaginase, keratinase, carboxylase, aminopeptidase, elastase, and aspergillo-peptidase A and B, pronase E (from S. griseus) and dispase (from B. polymyxa).

An effective amount of enzyme is to be used in the practice of this invention. Such amount will be that amount which effects removal in a reasonable time (for example overnight) of substantially all of at least one type of debris from a lens due to normal wear. This standard is stated with reference to contact lens wearers with a history of normal pattern of lens debris accretion, not the very small group who may at one time or another have a significantly increased rate of debris accretion such that cleaning is recommended every day, or every two or three days.

The amount of enzyme required to make an effective cleaner will depend on several factors, including the inherent activity of the enzyme, and the excipient it contains.

As a basic yardstick, the working solution should contain sufficient enzyme to provide about 0.001 to about 3 Anson units of activity, preferably about 0.01 to about 1 Anson units, per single lens treatment. Higher or lower amounts may be used.

Enzyme activity is pH dependent. Thus, for any given enzyme, there is a particular pH range in which that enzyme will function best. The determination of such range can readily be done by known techniques.

The present compositions may be used in the care of a contact lens, e.g., to disinfect the lens, to preserve the

lens, to otherwise treat the lens and/or to make wearing the lens safe and comfortable. The present compositions, formulated appropriately, may be used in conventional contact lens care regimens by using the present compositions in place of prior conventional compositions. In many instances, these contact lens care regimens involve contacting the lens with the present composition in an amount, and at conditions, effective to obtain the beneficial or desired contact lens care result. For example, a contact lens to be disinfected may be contacted with a disinfecting composition, e.g., aqueous solution, according to the present invention, preferably at a temperature in the range of about 0°C to about 100°C, more preferably in the range of about 10°C to about 60°C and still more preferably in the range of about 15°C to about 30°C. Contacting at or about ambient temperature is very convenient and useful. The contacting preferably occurs at or about atmospheric pressure. The contacting preferably occurs for a time to substantially disinfect the lens being treated. Such contacting times can be in the range of about 1 minute to about 12 hours or more.

After this contacting, the disinfected contact lens can be taken from the composition and placed directly in an eye, e.g., a human eye, for safe and comfortable wear. Alternately, after being disinfected, the contact lens can be contacted with a second medium, e.g., a liquid aqueous medium such as a preserved isotonic saline solution, prior to being placed in the eye of the wearer of the disinfected contact lens.

The contact lens care compositions disclosed herein are adaptable for use in most types of contact lens care equipment, such as ultrasonic cleaners and the like.

The following examples are set out to illustrate, but not limit, the scope of this invention.

EXAMPLES 1 TO 4

A series of four (4) compositions were prepared by blending the constituents together. These compositions were as follows:

CONSTITUENT	COMPOSITION (3) (4)			
	1	2	3	4
Ionene polymer (1) concentrate, wt.%	0.05	0.01	0.01	0.01
Disodium ethylene diamine tetraacetate, wt.%			0.10	0.10
Sodium chloride, wt%	0.67	0.67	0.60	0.55
Boric acid, wt.%	0.39	0.39	0.39	0.39
Sodium Borate Decahydrate NF, Wt.%	0.20	0.20	0.20	0.20
Nonionic surfactant(2) wt.%			0.10	
Hydroxyethyl cellulose NF, wt.%				0.40
Purified water, USP	QS	QS	QS	QS

(1) A concentrate containing 60% by weight of poly (oxyethylene (dimethyliminio)-ethylene (dimethyliminio) ethylene dichloride) sold under the trademark WSCP by Buckman Laboratories, Inc.

(2) A nonionic surfactant containing polyoxyethylene-polyoxypropylene block copolymer and sold under the trademark Pluronic F 127 by BASF Wyandotte Corporation.

(3) Hydrochloric acid and sodium hydroxide were added to give a pH within the range of 7.3 to 7.5.

(4) Compositions 1 and 2 were formulated as borate buffered saline solutions. Composition 3 was formulated as a soft contact lens disinfecting solution. Composition 4 was formulated as an eye rewetting solution.

Each of these compositions was tested for preservative efficacy and passed the USP preservative efficacy criteria.

These results demonstrate that certain quaternary ammonium polymers, as described herein, at concentrations ranging from 60 ppm to 300 ppm by weight are effective antimicrobial preservatives for contact lens care products. Composition 3 is quite effective as a contact lens disinfecting solution in a standard contact lens care regimen, with or without simultaneous or sequential enzymatic lens cleaning as part of the regimen.

EXAMPLE 5

Composition 3, described above, is used to disinfect a conventional soft contact lens as follows. 7.5 ml of the composition is provided at room temperature. The contact lens to be disinfected is placed in the composition. Four hours after the contact lens is first introduced into the composition, it is removed from the composition and placed directly into the wearer's eye. It is found that after four hours, the contact lens is effectively disinfected. Also, the lens wearer experiences no discomfort or eye irritation form wearing the disinfected contact lens. Alternately, after the contacting for four hours noted above, the disinfected contact lens is rinsed with preserved or non-preserved sterile isotonic saline solution prior to placing the disinfected lens in the wearer's eye. The lens wearer experiences no discomfort or eye irritation from wearing the disinfected contact lens.

EXAMPLE 6

Example 5 is repeated except that about 50 ppm by weight of subtilisin A, based on the total weight of the Composition 3 used, is added at the same time the contact lens to be disinfected is added to the composition. Four hours after the contact lens is first introduced into the

composition, it is removed from the composition, rinsed with Composition 3, or with preserved or non-preserved sterile isotonic saline solution, and placed directly into the wearer's eye. It is found that after four hours, the contact lens is effectively disinfected and cleaned of protein-based debris. Also, the lens wearer experiences no discomfort or eye irritation from wearing the disinfected and cleaned contact lens.

While this invention has been described with respect to various specific examples and embodiments, it is to be understood that the invention is not limited thereto and that it can be variously practiced within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A method for disinfecting a contact lens comprising:

contacting a contact lens to be disinfected with a substantially non-oxidative composition including an effective disinfecting amount of an ophthalmically acceptable, quaternary ammonium polymer selected from the group consisting of ionene polymers containing an oxygen atom covalently bonded to two carbon atoms and mixtures thereof, at conditions to effectively disinfect said contact lens to be disinfected.

2. The method of claim 1 wherein said composition includes a liquid aqueous medium.

3. The method of claim 2 wherein said quaternary ammonium polymer is present during said contacting in an amount in the range of about 0.00001% to about 1% by weight per volume of said liquid aqueous medium.

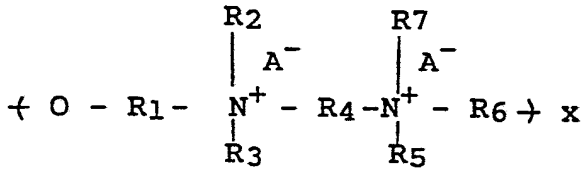
4. The method of claim 2 wherein said contact lens after being disinfected is contacted with a second liquid aqueous medium prior to being placed in the eye of the wearer of said contact lens.

5. The method of claim 1 which further comprises contacting said contact lens to be disinfected or the disinfected contact lens in a liquid medium with at least one enzyme capable of removing debris from a contact lens in an amount effective to remove debris from said contact lens to be disinfected or the disinfected contact lens.

6. The method of claim 5 wherein said contact lens-quaternary ammonium polymer contacting and said contact lens-enzyme contacting occur at substantially the same time.

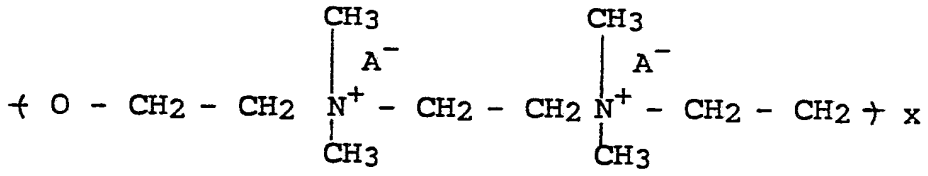
7. The method of claim 1 where said quaternary ammonium polymer has a molecular weight in the range of about 500 to about 5000.

8. The method of claim 1 wherein said quaternary ammonium polymer has a repeating unit



wherein R_1, R_4 and R_6 are each independently selected from the group consisting of alkylene radicals containing 1 to about 6 carbon atoms, R_2, R_3, R_5 and R_7 are each independently selected from alkyl radicals containing 1 to about 6 carbon atoms, each A^- is independently selected from the group consisting of ophthalmically acceptable anions, and x is the number of said repeating units in said quaternary ammonium polymer and is an integer in the range of about 5 to about 30.

9. The method of claim 1 wherein said quaternary ammonium polymer has a repeating unit



wherein each A^- is independently selected from the group consisting of ophthalmically acceptable anions, and x is the number of said repeating units in said quaternary ammonium polymer and is a integer in the range of about 8 to about 30.

10. The method of claim 9 wherein each A^- is Cl^- and x is about 14.

11. The method of claim 1 wherein said quaternary ammonium polymer is poly (oxyethylene (dimethyliminio) ethylene dimethyliminio) ethylene dichloride.

12. A method for preserving an ophthalmically acceptable medium comprising:

contacting a substantially non-oxidative ophthalmically acceptable medium with an effective preserving amount of an ophthalmically acceptable, quaternary ammonium polymer selected for the group consisting of ionene polymers containing an oxygen atom covalently bonded to two carbon atoms and mixtures thereof, at conditions to effectively preserve said substantially non-oxidative, ophthalmically acceptable medium.

13. The method of claim 12 wherein said substantially non-oxidative, ophthalmically acceptable medium is useful in caring for a contact lens.

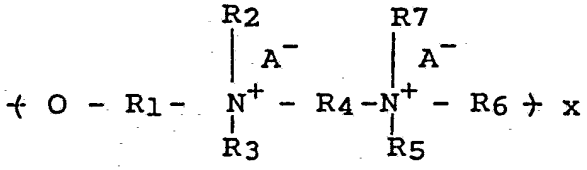
14. The method of claim 13 wherein said ophthalmically acceptable medium is sterile.

15. The method of claim 12 wherein said ophthalmically acceptable medium is a liquid aqueous medium.

16. The method of claim 12 wherein said quaternary ammonium polymer is present during said contacting in an amount in the range of about 0.00001% to about 1% by weight per volume of said ophthalmically acceptable medium.

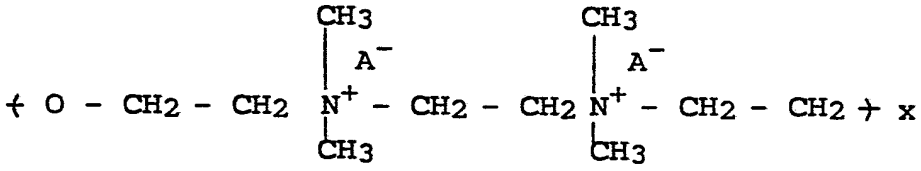
17. The method of claim 12 where said quaternary ammonium polymer has a molecular weight in the range of about 500 to about 5000.

18. The method of claim 12 wherein said quaternary ammonium polymer has a repeating unit



wherein R_1, R_4 and R_6 are each independently selected from the group consisting of alkylene radicals containing 1 to about 6 carbon atoms, R_2, R_3, R_5 and R_7 are each independently selected from alkyl radicals containing 1 to about 6 carbon atoms, each A^- is independently selected from the group consisting of ophthalmically acceptable anions, and x is the number of said repeating units in said quaternary ammonium polymer and is an integer in the range of about 5 to about 30.

19. The method of claim 12 wherein said quaternary ammonium polymer has a repeating unit



wherein each A^- is independently selected from the group consisting of ophthalmically acceptable anions, and x is the number of said repeating units in said quaternary ammonium polymer and is a integer in the range of about 8 to about 30.

20. The method of claim 19 wherein each A^- is Cl^- and x is about 14.

21. The method of claim 12 wherein said quaternary ammonium polymer is poly (oxyethylene (dimethyliminio) ethylene dimethyliminio) ethylene dichloride.

22. A composition useful for disinfecting a contact lens comprising an ophthalmically acceptable, liquid aqueous medium and, included therein, an effective disinfecting amount of an ophthalmically acceptable, quaternary ammonium polymer selected from the group consisting of ionene polymers containing an oxygen atom covalently bonded to two carbon atoms and mixtures thereof, said composition being substantially non-oxidative.

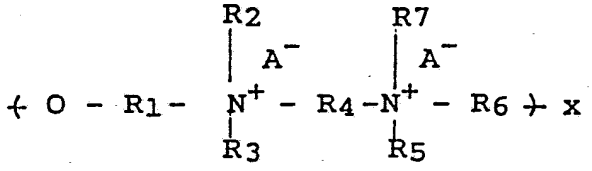
23. The composition of claim 22 wherein said composition is sterile.

24. The composition of claim 22 wherein said quaternary ammonium polymer is present in an amount in the range of about 0.00001% to about 1% by weight per volume of said ophthalmically acceptable liquid aqueous medium.

25. The composition of claim 22 which further comprises at least one enzyme capable of removing debris from a contact lens in an amount effective to remove debris from a debris laden contact lens.

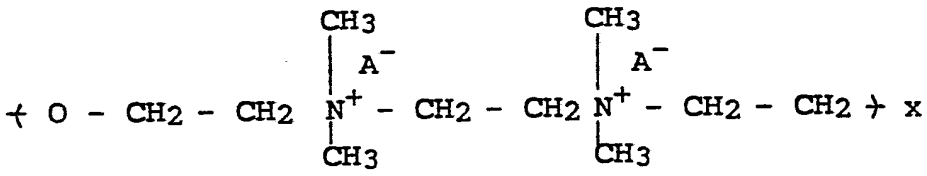
26. The composition of claim 22 where said quaternary ammonium polymer has a molecular weight in the range of about 500 to about 5000.

27. The composition of claim 22 wherein said polymer quaternary ammonium polymer has a repeating unit



wherein R_1, R_4 and R_6 are each independently selected from the group consisting of alkylene radicals containing 1 to about 6 carbon atoms, R_2, R_3, R_5 and R_7 are each independently selected from alkyl radicals containing 1 to about 6 carbon atoms, each A^- is independently selected from the group consisting of ophthalmically acceptable anions, and x is the number of said repeating units in said quaternary ammonium polymer and is an integer in the range of about 5 to about 30.

28. The composition of claim 22 wherein said quaternary ammonium polymer has a repeating unit



wherein each A^- is independently selected from the group consisting of ophthalmically acceptable anions, and x is the number of said repeating units in said quaternary ammonium polymer and is a integer in the range of about 8 to about 30.

29. The composition of claim 28 wherein each A^- is Cl^- and x is about 14.

30. The composition of claim 22 wherein said quaternary ammonium polymer is poly (oxyethylene (dimethyliminio) ethylene dimethyliminio) ethylene dichloride.

31. A preserved composition comprising an ophthalmically acceptable medium and, included therein, an effective preserving amount of an ophthalmically acceptable, quaternary ammonium polymer selected from the group consisting of ionene polymers containing an oxygen atom covalently bonded to two carbon atoms and mixtures thereof, said composition being substantially non-oxidative.

32. The composition of claim 31 wherein said composition is sterile.

33. The composition of claim 31 wherein said ophthalmically acceptable medium is useful in caring for a contact lens.

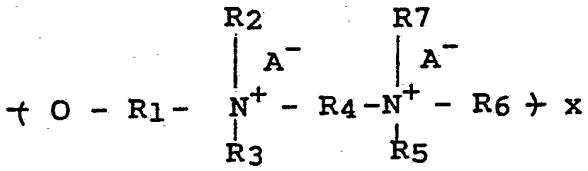
34. The composition of claim 31 wherein said ophthalmically acceptable medium is a liquid aqueous medium.

35. The composition of claim 31 wherein said quaternary ammonium polymer is present during said contacting

in an amount in the range of about 0.00001% to about 1% by weight per volume of said ophthalmically acceptable medium.

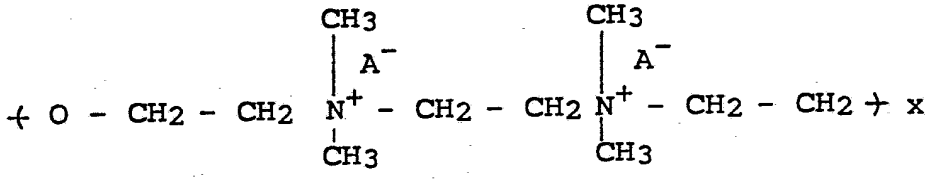
36. The composition of claim 31 wherein said quaternary ammonium polymer has a molecular weight in the range of about 500 to about 5000.

37. The composition of claim 31 wherein said polymer quaternary ammonium polymer has a repeating unit



wherein R_1, R_4 and R_6 are each independently selected from the group consisting of alkylene radicals containing 1 to about 6 carbon atoms, R_2, R_3, R_5 and R_7 are each independently selected from alkyl radicals containing 1 to about 6 carbon atoms, each A^- is independently selected from the group consisting of ophthalmically acceptable anions, and x is the number of said repeating units in said quaternary ammonium polymer and is an integer in the range of about 8 to about 30.

38. The composition of claim 31 wherein said quaternary ammonium polymer has a repeating unit



wherein each A^- is independently selected from the group consisting of ophthalmically acceptable anions, and x is the number of said repeating units in said oxygen-containing ionene polymer and is a integer in the range of about 8 to about 30.

39. The composition of claim 38 wherein each A^- is Cl^- and x is about 14.

40. The composition of claim 31 wherein said quaternary ammonium polymer is poly (oxyethylene (dimethyliminio) ethylene dimethyliminio) ethylene dichloride.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US90/07479

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

Accerding to International Patent Classification (IPC) or to both National Classification and IPC

IPC: A01N 33/12;A61L 2/18;U.S. Cl: 422/28; 514/642; 424/78

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S. Cl.	422/28,32; 514/642; 424/78

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

APS, DIALOG

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
y	US, A, 4,525,346 (Stark) 25 JUNE 1985. See Abstract.	33
y	US, A, 4,168,112 (Ellis et al.) 18 September 1979, See entire document.	1-40
y	US, A, 3,910,296 (Karageozian et al.) 07 October 1975. See col. 2, lines 14-21.	5-6
y	US, A, 3,771,989 (Pera et al.) 13 November 1973, See entire document.	1-40
A	US, A, 4,499,077 (Stockel et al.) 12 February 1985. See col. 6, lines 6-14.	1-40

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IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
08 MARCH 1991	22 APR 1991
International Searching Authority [1]	**Signature of Authorized Officer** [20]
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(54) Title: TOPICAL OPHTHALMIC FORMULATIONS CONTAINING DOXEPIN DERIVATIVES FOR TREATING ALLERGIC EYE DISEASES

(57) Abstract

Topical ophthalmic formulations of the invention contain as an active ingredient 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid or a pharmaceutically acceptable salt thereof. The formulations are useful for treating allergic eye diseases such as allergic conjunctivitis, vernal conjunctivitis, vernal keratoconjunctivitis, and giant papillary conjunctivitis.

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TOPICAL OPHTHALMIC FORMULATIONS CONTAINING DOXEPIN DERIVATIVES FOR TREATING ALLERGIC EYE DISEASES

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to topical ophthalmic formulations used for treating allergic eye diseases, such as allergic conjunctivitis, vernal conjunctivitis, vernal keratoconjunctivitis, and giant papillary conjunctivitis. More particularly, the present invention relates to therapeutic and prophylactic topical use of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid for treating and/or preventing allergic eye diseases.

Description of the Related Art

As taught in U.S. Patent Nos. 4,871,865 and 4,923,892, both assigned to Burroughs Wellcome Co. ("the Burroughs Wellcome Patents"), certain carboxylic acid derivatives of doxepin, including 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepine-2-carboxylic acid and 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepine-2(E)-acrylic acid, have antihistamine and antiasthmatic activity. These two patents classify the carboxylic acid derivatives of doxepin as mast cell stabilizers with antihistaminic action because they are believed to inhibit the release of autacoids (i.e., histamine, serotonin, and the like) from mast cells and to inhibit directly histamine's effects on target tissues. The Burroughs Wellcome Patents teach various pharmaceutical formulations containing the carboxylic acid derivatives of doxepin; Example 8 (I) in both of the patents discloses an ophthalmic solution formulation.

Although both of the Burroughs Wellcome Patents claim that the variety of pharmaceutical formulations disclosed are effective both for veterinary and for human medical use, neither patent contains an example demonstrating that the carboxylic acid derivatives of doxepin have activity in humans. Example 7 in the Burroughs Wellcome Patents demonstrates antihistamine activity in male guinea pigs and Example G demonstrates anaphylactoid activity in Wistar rats.

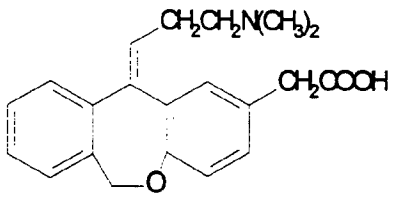
It is now well established, however, that the types of mast cells which exist in rodents are different from those in humans. See, for example, THE LUNG: Scientific Foundations, Raven Press, Ltd., New York, Ch. 3.4.11 (1991). Moreover, mast cell populations exist within the same species that differ in phenotype, biochemical properties, functional and pharmacological responses and ontogeny. These recognized differences in mast cells both between and within species are referred to as mast cell heterogeneity. See for example, Irani et al., "Mast Cell Heterogeneity," *Clinical and Experimental Allergy*, Vol. 19, pp. 143-155 (1989). Because different mast cells exhibit different responses to pharmacological agents, it is not obvious that compounds claimed to be anti-allergic ("mast cell stabilizers") will have clinical utility in specific mast cell populations. The assumption that mast cells are a homogeneous population and that therefore the effects of anti-allergic drugs observed in experiments in rat mast cells would be predictive of those in human cells is known to be incorrect. Church, "Is Inhibition of Mast Cell Mediator Release Relevant to the Clinical Activity of Anti-Allergic Drugs?," *Agents and Actions*, Vol. 18, 3/4, 288-293, at 291 (1986).

Examples exist in the art in which mast cell stabilizing drugs inhibit only select populations of mast cells. Disodium cromoglycate is an anti-allergic drug whose local effects are believed to be due to inhibition of mast cell degranulation (Church, *Agents and Actions*, at 288). This drug was shown to inhibit rodent mast cell degranulation. In human trials, 100 μM of the drug inhibited mast cells obtained from bronchoalveolar lavage fluid. In dispersed human lung mast cell preparations,

1000 μM of the drug was required to inhibit only 25% to 33% of histamine release. Finally, histamine release from human skin mast cells was not inhibited at all by disodium cromoglycate. Pearce et al., "Effect of Disodium Cromoglycate on Antigen Evoked Histamine Release in Human Skin," *Clinical Exp. Immunol.*, Vol. 17, 437-440 (1974); and Clegg et al., "Histamine Secretion from Human Skin Slices Induced by Anti-IgE and Artificial Secretagogues and the Effects of Sodium Cromoglycate and Salbutanol," *Clin. Allergy*, Vol. 15, 321-328 (1985). These data clearly indicate that classification of a drug as an anti-allergic does not predict that the drug possess inhibitory effects on all mast cell populations.

Topical ophthalmic formulations which contain drugs having conjunctival mast cell activity may only need to be applied once every 12-24 hours instead of once every 2-4 hours. One disadvantage to the ophthalmic use of reported anti-allergic drugs which in fact have no human conjunctival mast cell stabilizing activity is an increased dosage frequency. Because the effectiveness of ophthalmic formulations containing drugs which do not have conjunctival mast cell activity stems primarily from a placebo effect, more frequent doses are typically required than for drugs which do exhibit conjunctival mast cell activity.

U.S. Patent 5,116,863, assigned to Kyowa Hakko Kogyo Co., Ltd., ("the Kyowa patent"), teaches that acetic acid derivatives of doxepin and, in particular, the *cis* form of the compound having the formula



(i.e., Z-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid), have anti-allergic and anti-inflammatory activity.

The Kyowa patent demonstrates anti-allergic activity and anti-inflammatory activity in Wistar male rats. Medicament forms taught by the Kyowa patent for the acetic acid derivatives of doxepin include a wide range of acceptable carriers; however, only oral and injection administration forms are mentioned. In the treatment of allergic eye disease, such as allergic conjunctivitis, such administration methods require large doses of medicine.

What is needed are topically administrable drug compounds which have demonstrated stabilizing activity on mast cells obtained from human conjunctiva, the target cells for treating allergic eye diseases. What is also needed are local administration methods for the treatment of allergic eye disease.

Summary of the Invention

The present invention provides a method for treating an allergic eye disease characterized by administering to the eye a topical ophthalmic formulation which contains a therapeutically effective amount of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid (referred to as "Compound A" hereinafter) or a pharmaceutically acceptable salt thereof. The formulation may contain the *cis* isomer of Compound A (Z-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid), the *trans* isomer of Compound A (E-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid), or a combination of both the *cis* and the *trans* isomers of Compound A, and unless specified otherwise,"11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid" or "Compound A" means the *cis* isomer, the *trans* isomer or a mixture of both. "*Cis* isomer" means the *cis* isomer substantially free of the *trans* isomer; "*trans* isomer" means the *trans* isomer substantially free of

the *cis* isomer. One isomer is "substantially free" of the other isomer if less than about two percent of the unwanted isomer is present.

Compound A has human conjunctival mast cell stabilizing activity, and may be applied as infrequently as once or twice a day in some cases. In addition to its mast cell stabilizing activity, Compound A also possesses significant antihistaminic activity. Thus, in addition to a prophylactic effect, Compound A will also have a therapeutic effect.

Detailed Description of the Invention

Compound A is a known compound and both the *cis* and the *trans* isomers of Compound A can be obtained by the methods disclosed in U.S. Patent No. 5,116,863, the entire contents of which are hereby incorporated by reference in the present specification.

Examples of the pharmaceutically acceptable salts of Compound A include inorganic acid salts such as hydrochloride, hydrobromide, sulfate and phosphate; organic acid salts such as acetate, maleate, fumarate, tartrate and citrate; alkali metal salts such as sodium salt and potassium salt; alkaline earth metal salts such as magnesium salt and calcium salt; metal salts such as aluminum salt and zinc salt; and organic amine addition salts such as triethylamine addition salt (also known as tromethamine), morpholine addition salt and piperidine addition salt.

The inhibitory effects of reported anti-allergic, mast cell stabilizing drugs on mast cells obtained from human conjunctiva (the target cells for topical ophthalmic drug preparations claimed useful in treating allergic conjunctivitis) were tested according to the following experimental method. Human conjunctival tissues obtained from organ/tissue donors were weighed and transferred to petri dishes

containing RPMI 1640 culture medium supplemented with heat inactivated fetal bovine serum (20%, v/v), L-glutamine (2mM), penicillin (100 units/ml), streptomycin (100 μg/ml), amphotericin B (2.5μg/ml) and HEPES (10mM) and equilibrated overnight at 37°C (5% CO_2).

Post equilibration, tissues were placed in Tyrode's buffer (in mM: 137 NaCl, 2.7 KCl, 0.35 Na H_2PO_4, 1.8 $CaCl_2$, 0.98 $MgCl_2$, 11.9 Na HCO_3, 5.5 glucose) containing 0.1% gelatin (TGCM) and incubated with 200U each of collagenase (Type IV) and hyaluronidase (Type I-S) per gram of tissue for 30 minutes at 37°C. Following enzyme digestion, tissues were washed with an equal volume of TGCM over Nitex® filter cloth (Tetko, Briarcliff Manor, NY). Intact tissues were placed in TGCM for further enzymatic digestions.

The filtrate obtained from each digestion was centrifuged (825 g, 7 minutes) and pelleted cells were resuspended in calcium/magnesium free Tyrode's buffer (TG). Pooled cells from all digestions were centrifuged (825 g, 30 minutes) over a 1.058 g/L Percoll® cushion. Mast cell enriched cell pellets were resuspended and washed in TG buffer. Viability and number of mast cells were determined by vital dye exclusion and toluidine blue 0 staining of the harvested cell suspensions. Mast cell containing preparations were placed in supplemented RPMI 1640 culture medium and allowed to equilibrate at 37°C prior to challenge with anti-human IgE (goat derived IgG antibody).

Cell suspensions containing 5000 mast cells were added to TGCM containing tubes and challenged with anti-human IgE. The final volume of each reaction tube was 1.0 mL. Tubes were incubated at 37°C for 15 minutes post challenge. The release reaction was terminated by centrifugation (500 g, 7 minutes). Supernatants were collected and stored (-20°C) until mediator analyses.

Initially, supernatants were analyzed for histamine content by both the automated fluorimetric method described by Siraganian, "An Automated Continuous Flow System for the Extraction and Fluorometric Analysis of Histamine," Anal.

Biochem., Vol. 57, 383-94 (1974), and a commercially available radioimmunoassay (RIA) system (AMAC, Inc., Westbrook, ME). Results from these assays were positively correlated (r = 0.999): therefore, the remainder of histamine analyses were performed by RIA.

Each experiment included an anti-human IgE (plus vehicle) positive release control, a spontaneous/vehicle release and a total histamine release control. Total histamine release was determined by treatment with Triton X-100® (0.1%). The experiments also included a non-specific goat IgG control. Test compounds are administered to the mast cell cultures either 1 or 15 minutes before stimulation with anti-human IgE. Inhibition of histamine release resulting from challenge of drug treated mast cells was determined by direct comparison with histamine release from vehicle treated, anti-IgE challenged mast cells using Dunnett's t-test (Dunnett, "A multiple comparison procedure for comparing treatments with a control, "*J. Amer. Stat Assoc.*, Vol. 50, 1096-1121 (1955)). The results are reported in Table 1, below.

As Table 1 clearly shows, the anti-allergic drugs disodium cromoglycate and nedocromil failed to significantly inhibit human conjunctival mast cell degranulation. In contrast, Compound A (*cis* isomer) produced concentration-dependent inhibition of mast cell degranulation.

Table 1

Compound Effect on Histamine Release from Human Conjunctival Tissue Mast Cells upon anti-Human IgE Challenge.

Compound	Dose (μM)	Treatment (min)	Inhibition (%)
Cromolyn sodium	1000	15	-15.4
	300	15	-6.9
	100	15	-1.2
	30	15	1.8
	10	15	10.6
Cromolyn sodium	1000	1	-9.4
	300	1	-1.8
	100	1	1.2
	30	1	0.1
	10	1	-0.9
Nedocromil sodium	1000	15	7.2
	300	15	11.3
	100	15	28.2*
	30	15	15.2
	10	15	9.2
	3	15	13.2
	1	15	10.7
	0.3	15	3.7
	0.1	15	8.7
Nedocromil sodium	1000	1	-1.1
	300	1	4.0
	100	1	6.7
	30	1	-0.9
	10	1	-6.5
	3	1	0.8
	1	1	4.8
	0.3	1	8.8
	0.1	1	17.4
Compound A	2000	15	92.6*
	1000	15	66.7*
	600	15	47.5*
	300	15	29.6*
	100	15	13.0
	30	15	-3.9

*p<0.05, Dunnett's t-test

Dunnett's t-test, is a statistical test which compares multiple treatment groups with one control group. In the assay described above, histamine released from drug treated mast cells are compared to histamine released from the anti-human IgE plus vehicle treated mast cells which serve as the positive control. Statistically significant inhibition is determined using this procedure. The probability level of 0.05 is accepted as the level of significance in biomedical research. Data indicated as significant have a low probability (0.05) of occurring by chance, indicating that the inhibition observed is an effect of the drug treatment.

The effects of the *cis* and *trans* isomers of Compound A on histamine release from human conjunctival tissue mast cells upon anti-human IgE challenge are compared in Table 2. The same experimental method used in Table 1 was used in Table 2. The results in Table 2 indicate that there is no statistically significant difference between the conjunctival mast cell activity of the two isomers at the indicated dose level.

Table 2

Isomeric Effect of Compound A on In-Vitro Histamine Release from Human Conjunctival Tissue Mast Cells upon anti-Human IgE Challenge.

Compound	Dose (μM)	Treatment (min)	Inhibition (%)
Compound A(*cis*)	500	15	29.7*_
Compound A (*trans*)	500	15	26.2*_

*p< 0.05, Dunnett's t-test compared to anti-IgE positive control.
_ not significantly different; p > 0.05 Studentized Range comparison of indicated doses

The topical activity of Compound A was tested in a passive anaphylaxis assay performed in rat conjunctiva. This assay indicates whether a topically applied compound effectively prevents or decreases the local allergic response in the

conjunctiva. This assay allows an assessment of bioavailability following topical dosing. Briefly, male Sprague Dawley rats (6/group) were passively sensitized by subconjunctival injection of a rat serum containing IgE specific for ovalbumin (OA). Twenty-four hours post sensitization, test compound prepared in saline (0.9% NaCl) or saline vehicle was applied topically onto the sensitized eye. Twenty (20) minutes after dosing, rats were challenged intravenously via the lateral tail vein with 1.0 ml of a solution containing OA (1.0 mg/ml) and Evans Blue dye (2.5 mg/ml). Thirty (30) minutes post antigen challenge, animals were killed, skin was reflected, and the size of the resulting wheal and the intensity of the extravasated dye were determined. The wheal area multiplied by the dye intensity produced the individual response score. Scores for each group of animals were compared with the scores of the saline treated group using Dunnett's test and are listed in Table 3.

TABLE 3

In-Vivo Effects of Compound A on Passive Conjunctival Anaphylaxis in Rats

Compound	Conc. (%, w/v)	Permeability Score (x ± S.D.)	% Change
NaCl	0.9	239 ± 22	—
Compound B	0.1	133 ± 53*	-55
Compound C	0.1	139 ± 36*	-53
Compound A (*cis*)	0.1	55 ± 56*@	-86
Compound A (*trans*)	0.1	43 ± 34*@	-81

* p <0.01, Dunnett's test
@ p <0.05, Studentized Range Comparison Procedure, significantly different from Compounds B and C.

Compound B = (Z)-11-(3-Dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid
Compound C = (Z)-11-(3-Dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acrylic acid

Compound A may be administered to the eye by means of conventional topical ophthalmic formulations, such as solutions, suspensions or gels. The

preferred formulation for topical ophthalmic administration of Compound A is a solution. The solution is administered as eye drops. The preferred form of Compound A in the topical ophthalmic formulations of the present invention is the *cis* isomer. A general method of preparing the eye drops of the present invention is described below.

Compound A and an isotonic agent are added to sterilized purified water, and if required, a preservative, a buffering agent, a stabilizer, a viscous vehicle and the like are added to the solution and dissolved therein. The concentration of Compound A is 0.0001 to 5 w/v %, preferably 0.001 to 0.2 w/v %, and most preferably about 0.1 w/v %, based on the sterilized purified water. After dissolution, the pH is adjusted with a pH controller to be within a range which allows the use as an ophthalmologic medicine, preferably within the range of 4.5 to 8.

Sodium chloride, glycerin or the like may be used as the isotonic agent; p-hydroxybenzoic acid ester, benzalkonium chloride or the like as the preservative; sodium hydrogenphosphate, sodium dihydrogenphosphate, boric acid or the like as the buffering agent; sodium edetate or the like as the stabilizer; polyvinyl alcohol, polyvinyl pyrrolidone, polyacrylic acid or the like as the viscous vehicle; and sodium hydroxide, hydrochloric acid or the like as the pH controller.

If required, other ophthalmologic chemicals such as epinephrine, naphazoline hydrochloride, berberine chloride, sodium azulenesulfonate, lysozyme chloride, glycyrrhizate and the like may be added.

The eye drops produced by the above method typically need only be applied to the eyes a few times a day in an amount of one to several drops at a time, though in more severe cases the drops may be applied several times a day. A typical drop is about 30 μl.

Certain embodiments of the invention are illustrated in the following examples.

Example 1: Preferred Topical Ophthalmic Solution Formulation

Ingredient	Concentration (W/V%)
Compound A•HCl	0.111*
Dibasic Sodium Phosphate (Anhydrous), USP	0.5
Sodium Chloride, USP	0.65
Benzalkonium Chloride	0.01
Sodium Hydroxide, NF	q.s. pH = 7.0
Hydrochloric Acid, NF	q.s. pH = 7.0
Purified Water	q.s. 100

* 0.111% Compound A•HCl is equivalent to 0.1% Compound A

Example 2: Topical Ophthalmic Gel Formulation

Ingredient	Concentration (W/V%)
Compound A•HCl	0.11*
Carbopol 974 P	0.8
Disodium EDTA	0.01
Polysorbate 80	0.05
Benzalkonium Chloride, Solution	0.01+5 xs
Sodium Hydroxide	q.s. pH 7.2
Hydrochloric acid	q.s. pH 7.2
Water for Injection	q.s. 100

* 0.11% Compound A•HCl is equivalent to 0.1% Compound A

WHAT IS CLAIMED IS:

1. A method for treating allergic eye diseases comprising topically administering to the eye a composition comprising a therapeutically effective amount of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid or a pharmaceutically acceptable salt thereof.

2. The method of Claim 1 wherein the composition is a solution and the amount of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid is from about 0.0001 w/v.% to about 5% (w/v).

3. The method of Claim 2 wherein the amount of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid is from about 0.001 to about 0.2% (w/v).

4. The method of Claim 3 wherein the amount of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid is about 0.1% (w/v).

5. The method of Claim 1 wherein the 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid is (Z)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid, substantially free of (E)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid.

6. The method of Claim 5 wherein the amount of (Z)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid is from about 0.0001 to about 5% (w/v).

7. The method of Claim 6 wherein the amount of (Z)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid is from about 0.001 to about 0.2% (w/v).

8. The method of Claim 7 wherein the amount of (Z)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid is 0.1% (w/v).

9. The method of Claim 1 wherein the 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid is (E)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid, substantially free of (Z)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid.

10. The method of Claim 9 wherein the amount of (E)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid is from about 0.0001 to about 5% (w/v).

11. The method of Claim 10 wherein the amount of (E)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid is from about 0.001 to about 0.2% (w/v).

12. The method of Claim 11 wherein the amount of (E)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid is about 0.1% (w/v).

13. A topically administrable ophthalmic composition for treating allergic eye diseases comprising a therapeutically effective amount of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid, or a pharmaceutically acceptable salt thereof.

14. The composition of Claim 13 wherein the amount of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid is from about 0.0001 to about 5% (w/v).

15. The composition of Claim 14 wherein the amount of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid is from about 0.001 to about 0.2% (w/v).

16. The composition of Claim 15 wherein the amount of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid is about 0.1% (w/v).

17. The composition of Claim 13 wherein the 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid is (Z)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid, substantially free of (E)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid.

18. The composition of Claim 17 wherein the amount of (Z)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid is from about 0.0001 to about 5% (w/v).

19. The composition of Claim 18 wherein the amount of (Z)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid is from about 0.001 to about 0.2% (w/v).

20. The composition of Claim 19 wherein the amount of (Z)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid is about 0.1% (w/v).

21. The composition of Claim 13 wherein the 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid os (E)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid, substantially free of (Z)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid.

22. The composition of Claim 21 wherein the amount of (E)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid is from about 0.0001 to about 5% (w/v).

23. The composition of Claim 22 wherein the amount of (E)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid is from about 0.001 to about 0.2% (w/v).

24. The composition of Claim 23 wherein the amount of (E)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid is about 0.1% (w/v).

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(54) Title: OPHTHALMIC ANTI-ALLERGY COMPOSITIONS SUITABLE FOR USE WITH CONTACT LENSES

(57) Abstract: Topically administrable anti-allergy compositions comprising olopatadine and a polymeric quaternary ammonium preservative are suitable for use by patients wearing contact lenses.

OPHTHALMIC ANTI-ALLERGY COMPOSITIONS SUITABLE FOR USE WITH CONTACT LENSES

BACKGROUND OF THE INVENTION

The present invention relates generally to ophthalmic anti-allergy compositions. In particular, the present invention relates to topical anti-allergy compositions that can be safely applied by a patient wearing contact lenses.

Ophthalmic formulations generally contain one or more active compounds along with excipients such as surfactants, comforting agents, complexing agents, stabilizers, buffering systems, chelating agents, viscosity agents or gelling polymers and anti-oxidants. Ophthalmic formulations which are intended for multidose use require a preservative. Benzalkonium chloride ("BAC") is the most widely used ophthalmic preservative.

Topically administrable multidose ophthalmic products are generally not suitable for use with contact lenses because the active or the preservative may bind to or accumulate in the contact lenses, causing irritation or toxic effects.

Olopatadine is a known anti-allergy drug. See U.S. Patent No. 5,641,805 (Yanni, et al.). PATANOL® brand of olopatadine hydrochloride ophthalmic solution is marketed as a topical anti-allergy composition. Emedastine is a known anti-histamine drug. EMADINE® brand of emedastine difumarate solution is marketed as a topical anti-allergy composition. Like other topically administrable anti-allergy products, these compositions are preserved with BAC. BAC is known to bind to or accumulate in contact lenses. Thus, like other topically administrable ophthalmic pharmaceutical products containing BAC, PATANOL® brand of olopatadine hydrochloride ophthalmic solution and EMADINE® brand of emedastine difumarate ophthalmic solution contain in their labelling information precautionary

instructions to remove contact lenses before use and to wait ten minutes after administering the product before replacing the lenses. The dosing regimen for anti-allergy products typically calls for two to four applications a day, making it inconvenient for contact lens wearers to treat ophthalmic allergy symptoms.

Polyquaternium-1, which is used under the trade name Polyquad®, is one preservative known to be compatible with contact lenses. Polyquaternium-1 and other polymeric quaternary ammonium compounds are used as disinfectants and preservatives in contact lens care and artificial tear solutions. See, for example, U.S. Patent Nos. 5,037,647; 4,525,346; and 4,407, 791. The currently marketed Opti-Free® brand of contact lens care products, including multi-purpose solutions and cleaning solutions, contains polyquaternium-1 as a disinfectant and preservative.

In addition to contact lens care products, polyquaternium-1 can also be used as a preservative in certain topically administrable ophthalmic drug products. U.S. Patent No. 5,603,929 discloses the use of polyquaternium-1 in combination with boric acid to preserve topically administrable ophthalmic compositions of acidic drugs, such as non-steroidal anti-inflammatory drugs. Although the '929 patent defines suitable ophthalmic drug compounds for use with the polyquaternium-1 and boric acid preservative system to include ophthalmically acceptable salts, amides, esters and prodrugs of the many types of acidic drugs, it does not mention anti- allergy drugs or olopatadine in particular. See Col. 3, lines 12 -30 of the '929 patent.

SUMMARY OF THE INVENTION

It has now been discovered that compositions of olopatadine and emedastine that comprise polyquaternium-1 as a preservative are suitable for use with contact lenses. The present invention relates to multi-dose, topically administrable compositions of olopatadine and emedastine containing a polymeric quaternary ammonium compound, such as polyquaternium-1, as a preservative. The compositions of the present invention do not contain BAC.

The present invention also relates to a method for treating or controlling ocular allergies in patients wearing contact lenses which comprises topically administering a composition comprising olopatadine or emedastine and a polymeric quaternary ammonium compound as a preservative, where the composition is applied without removing the contact lenses.

DETAILED DESCRIPTION OF THE INVENTION

Olopatadine is (Z)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]- oxepin-2-acetic acid. Olopatadine can be made using the methods disclosed in U.S. Patent No. 5, 116,863, the entire contents of which are hereby incorporated by reference. The concentration of olopatadine in the compositions of the present invention will range from about 0.0001 to 5 %(w/v), preferably from about 0.001 to 0.25 %(w/v), and most preferably from about 0.1 to 0.25 %(w/v), based on the sterilized purified water. The olopatadine ingredient may be present in the form of a pharmaceutically acceptable salt. Unless indicated otherwise, "olopatadine" as used herein refers to both olopatadine and its pharmaceutically acceptable salts. The most preferred form of olopatadine is olopatadine hydrochloride. The most preferred concentration of olopatadine hydrochloride is from about 0.111 to 0.222 %(w/v), which is equivalent to 0.1 to 0.2 %(w/v) olopatadine.

Emedastine's chemical name is 1-(2-ethoxyethyl)-2-(4-methyl-1-homopiper-azinyl)-benzimidazole. The ophthalmic use of emedastine is

disclosed in U.S. Patent No. 5,441,958. Emedastine can be made using the methods disclosed in U.S. Patent No. 4,430,343, the entire contents of which are hereby incorporated by reference. The concentration of emedastine in the compositions of the present invention will range from about 0.0001 to 1 %(w/v), preferably from about 0.005 to 0.1 %(w/v), and most preferably about 0.05 %(w/v). The emedastine ingredient may be present in the form of a pharmaceutically acceptable salt. Unless indicated otherwise, "emedastine" as used herein refers to both emedastine and its pharmaceutically acceptable salts. The most preferred form of emedastine is emedastine difumarate. The most preferred concentration of emedastine difumarate is about 0.0884 %(w/v), which is equivalent to 0.05 %(w/v) emedastine.

In addition to olopatadine or emedastine, or a pharmaceutically acceptable salt thereof, the compositions of the present invention contain a polymeric quaternary ammonium compound as a preservative. The polymeric quaternary ammonium compounds useful in the compositions of the present invention are those which have an antimicrobial effect and which are ophthalmically acceptable. Preferred compounds of this type are described in US Patents Nos. 3,931,319; 4,027,020; 4,407,791; 4,525,346; 4,836,986; 5,037,647 and 5,300,287; and PCT application WO 91/09523 (Dziabo et al.). The most preferred polymeric ammonium compound is polyquaternium-1 , otherwise known as Polyquad® or Onamer M®, with a number average molecular weight between 2,000 to 30,000. Preferably, the number average molecular weight is between 3,000 to 14,000.

The polymeric quaternary ammonium compounds are generally used in the compositions of the present invention in an amount from about 0.00001 to about 3 %(w/v), preferably from about 0.001 to about 0.1 %(w/v). Most preferably, the compositions of the present invention contain from about 0.001 to about 0.05 %(w/v) of polymeric quaternary ammonium compounds.

It may be necessary or desirable to add boric acid to the compositions to achieve desired levels of preservative efficacy. See U.S. Patent No.

5,603,929, the entire contents of which are hereby incorporated by reference. The boric acid suitable for use in the compositions of the present invention includes not only boric acid, but also its ophthalmically acceptable acid addition salts, as well as borate-polyol complexes of the type described in US Patent No. 5,342,620 (Chowhan). If present, the amount of boric acid will generally range from about 0.3 to about 5.0 %(w/v).

The compositions of the present invention should have an ophthalmically acceptable tonicity, such as 260- 320 mOsm/kg, and an ophthalmically acceptable pH, such as pH 5 -8, and preferably pH 6.8 -7.6. The topically administrable, multi-dose compositions of the present invention optionally comprise other excipients, such as tonicity adjusting agents, buffering agents, chelating agents, and pH adjusting agents. For example, sodium chloride, mannitol, or the like may be used as the isotonic agent; sodium hydrogenphosphate, sodium dihydrogenphosphate, p-hydroxybenzoic acid ester, boric acid or the like as the buffering agent; sodium edetate or the like as the chelating agent or stabilizer; and sodium hydroxide, hydrochloric acid or the like as the pH adjusting agent.

The compositions of the present invention may also include viscosity modifying agents such as: cellulosic ethers, such as, hydroxypropyl methyl cellulose (HPMC), hydroxyethyl cellulose (HEC), ethyl hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose, and carboxymethyl cellulose; carbomers (e.g. Carbopol®; polyvinyl alcohol; polyvinyl pyrrolidone; alginates; carrageenans; and guar, karaya, agarose, locust bean, and xanthan gums.

The following examples are presented to illustrate further various aspects of the present invention, but are not intended to limit the scope of the invention in any respect.

EXAMPLE 1

	Formulation (%w/v)	
Ingredient	A	B
Olopatadine Hydrochloride	0.111 or 0.222	0.111 or 0.222
NaCl	q.s. to 260 – 320 mOsm/kg	0.3
Polyethylene Glycol (400)	2.0	2.0
Polyquaternium-1	0.001-0.15	0.005
Dibasic sodium phosphate (anhydrous)	0.5	0.5
HCl/NaOH	q.s. to pH 6.8 – 7.2	q.s. to pH 7
Purified Water	q.s. to 100%	q.s. to 100%

EXAMPLE 2

	Formulation (%w/v)	
Ingredient	C	D
Emedastine difumarate	0.0884	0.0884
NaCl	q.s. to 260-320 mOsm/kg	0.68
Hydroxypropyl methylcellulose (2910)	0.25	0.25
Tromethamine	0.5	0.5
Polyquaternium-1	0.001 – 0.15	0.005
Dibasic Sodium Phosphate (Anhydrous)	0.5	0.5
HCl/NaOH	q.s. to pH 7.2 – 7.6	q.s. to pH 7.4
Purified Water	q.s. to 100%	q.s. to 100%

The invention has been described by reference to certain preferred embodiments; however, it should be understood that it may be embodied in other specific forms or variations thereof without departing from its spirit or essential characteristics. The embodiments described above are therefore considered to be illustrative in all respects and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description.

WHAT IS CLAIMED IS:

1. A topically administrable, multi-dose anti-allergy composition suitable for use by patients wearing contact lenses, wherein the composition comprising an anti-allergy effective amount of a drug selected from the group consisting of olopatadine and emedastine; and an ophthalmically acceptable polymeric quaternary ammonium compound as a preservative, provided that the composition does not contain benzalkonium chloride.

2. The composition of Claim 1 wherein the drug is olopatadine and the anti-allergy effective amount of olopatadine is from about 0.0001 to 5 %(w/v).

3. The composition of Claim 2 wherein the anti-allergy effective amount of olopatadine is from about 0.001 to 0.25 %(w/v).

4. The composition of Claim 3 wherein the olopatadine is olopatadine hydrochloride and the anti-allergy effective amount of olopatadine is from about 0.1 - 0.25 %(w/v).

5. The composition of Claim 1 wherein the drug is emedastine and the anti-allergy effective amount of emedastine is from about 0.0001 to 1 %(w/v).

6. The composition of Claim 5 wherein the anti-allergy effective amount of emedastine is from about 0.005 to 0.1 %(w/v).

7. The composition of Claim 5 wherein the emedastine is emedastine difumarate and the anti-allergy effective amount of emedastine is about 0.0884 %(w/v).

8. The composition of Claim 1 wherein the polymeric quaternary ammonium compound is polyquaternium-1.

9. The composition of Claim 8 wherein the polymeric quaternary ammonium compound is present in an amount from about 0.00001 to about 3 %(w/v).

10. The composition of Claim 9 wherein the polymeric quaternary ammonium compound is present in an amount from about 0.001 to about 0.1 %(w/v).

11. The composition of Claim 1 wherein the composition further comprises one or more ingredients selected from the group consisting of tonicity adjusting agents; buffering agents; chelating agents; pH adjusting agents; and viscosity modifying agents.

12. A method for treating or controlling ocular allergies in patients wearing contact lenses which comprises topically administering a composition comprising an anti-allergy effective amount of a drug selected from the group consisting of olopatadine and emedastine; and a polymeric quaternary ammonium compound as a preservative, wherein the composition is applied without removing the contact lenses and the composition does not contain benzalkonium chloride.

13. The method of Claim 12 wherein the drug is olopatadine and the anti-allergy effective amount of olopatadine is from about 0.0001 to 5 %(w/v).

14. The method of Claim 13 wherein the olopatadine is olopatadine hydrochloride and the anti-allergy effective amount of olopatadine is from about 0.1 to 0.25 %(w/v).

15. The method of Claim 12 wherein the drug is emedastine and the anti-allergy effective amount of emedastine is from about 0.005 to 0.1 %(w/v).

16. The method of Claim 15 wherein the emedastine is emedastine difumarate and the anti-allergy effective amount of emedastine is about 0.0884 %(w/v).

17. The method of Claim 12 wherein the polymeric quaternary ammonium compound is polyquaternium-1.

18. The method of Claim 17 wherein the polymeric quaternary ammonium compound is present in an amount from about 0.00001 to about 3 %(w/v).

19. The method of Claim 12 wherein the composition further comprises one or more ingredients selected from the group consisting of tonicity adjusting agents; buffering agents; chelating agents; pH adjusting agents; and viscosity modifying agents.

INTERNATIONAL SEARCH REPORT

Interna Application No
PCT/US 01/02418

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/335 A61K31/551 A61P27/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, EPO-Internal, PAJ, CHEM ABS Data, BIOSIS, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 192 780 A (ALCON LABORATORIES, INC.) 9 March 1993 (1993-03-09) column 2, line 9 - line 19 column 3, line 5 - line 6 column 4, line 12 claims 1-4 ---	1-19
X	US 5 037 647 A (ALCON LABORATORIES, INC.) 6 August 1991 (1991-08-06) cited in the application column 1, line 64 -column 2, line 34 ---	1-19
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 603 929 A (ALCON LABORATORIES, INC.) 18 February 1997 (1997-02-18) cited in the application column 2, line 18 - line 30 column 2, line 61 -column 3, line 30 claims 1-20 -----	1-19

INTERNATIONAL SEARCH REPORT

Information on patent family members

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(54) Title: THE PROCESS OF MANUFACTURING PHARMACEUTICAL COMPOSITION WITH INCREASED CONTENT OF POORLY SOLUBLE PHARMACEUTICAL INGREDIENTS

(57) Abstract: The present invention relates to a process for solubilizing poorly soluble active pharmaceutical ingredients in a mixture of low molecular and high molecular polyethylene glycol and polyvinyl pyrolidine. The resulting compositions can be encapsulated in a gelatin shell and their capsules provide an effective means for oral delivery of a wide variety of poorly soluble pharmaceutical actives.

WO 03/013481 A1

THE PROCESS OF MANUFACTURING PHARMACEUTICAL COMPOSITION WITH INCREASED CONTENT OF POORLY SOLUBLE PHARMACEUTICAL INGREDIENTS

Technical Field

The present invention relates to process for manufacturing pharmaceutical composition with increased content of poorly soluble active pharmaceutical ingredients. Poorly soluble active pharmaceutical ingredients needs larger amount of inactives to prepare a clear liquid preparation for encapsulation into a soft gelatin capsule. This necessitates increase in size of a capsule and/or increase in number of capsules to be consumed for a therapeutic effect. The present invention relates to improving the content of poorly soluble active pharmaceutical ingredients in a clear liquid solution.

According to present invention use of two or polyethelene glycol of different molecular weight along with a dispersing agent like vinyl pyrolidone. The resulting solution are clear and remains clear even after encapsulation in a soft gelatin capsule for its self life and beyond.

BACKGROUND OF THE INVENTION

Liquid, and especially concentrated liquid pharmaceutical compositions offer many advantages over solid compositions. Liquids are easy to swallow and provide an excellent vehicle for the uniform delivery of pharmaceutical actives. Liquids provide a rapid onset of pharmacologic action, since the composition does not first have to disintegrate and dissolve in the gastrointestinal tract. Concentrated liquid compositions are ideally suited for encapsulation within a soft gelatin shell, to provide a portable and easy-to-swallow soft, flexible capsule. Encapsulation would also permit the accurate and uniform delivery of a unit dose of a pharmaceutical active, an advantage which becomes especially important when relatively small amounts of an active are to be delivered. Additionally, soft gelatin capsules are aesthetically appealed (especially when filled with a transparent liquid) and can be manufactured in a wide variety of sizes, shapes, and colors.

However, despite these advantages of liquid compositions, it is not always possible to prepare a liquid composition of the desired pharmaceutical active. Many pharmaceutical actives are poorly soluble and therefore require relatively large volumes of solvent for dissolution. Also, the choice of solvents available for use in liquid compositions is limited by safety, compatibility, stability, and economic concerns. Furthermore, the use of large volumes of solvents for solubilizing pharmaceutical actives is undesirable because the resulting solutions would be so dilute as to require impractically large dosages for delivering a therapeutically

effective amount of active. It would thus be difficult, if not impossible, to encapsulate such large volumes into only one or two gelatin capsules and yet have them be of a reasonable size for easy swallowing.

One approach to overcoming these solubility problems has been to incorporate water, water-miscible co-solvents, and surfactants into the compositions. See, U.S. Pat. No. 4,794,117, to Corbiere, issued Dec. 27, 1988 which discloses the solubiliazation of hydrophobic pharmaceuticals in aqueous solutions of polyethylene glycol at controlled pH; U.S. Pat. No. 4,690,823, to Lohner at al, issued Sep. 1, 1987 which discloses the solubilization of ibuprofen in a mixture of polyethylene glycol and a surfactant; U.S. Pat. No. 3,784,684, to Bossert et al., issued Jan. 8, 1974 which discloses the solubilization of a pharmaceutical active in a mixture of polyethylene glycol and an alcohol having 2-8 carbons and 1-3 hydroxy groups; It is desirable to have poorly soluble drugs like acetaminophen solubilised into a clear solution in as high concentration as possible. It typically involves use of organic solvents.

US patent 5484606 describes the process for reducing the precipitation of difficult to solublize pharmaceutical actives. It used propylene glycol to achieve this purpose along with polyethylene glycol and polyvinyl pyrolidine to achieve this. US patent 5505961 deals with gelatin capsules containing a highly concentrated acetaminophen solution. The invention, involves use of alkali metal acetate to improve solubility of acetaminophen in a solution containing polyethylene glycol, polypropylene glycon and water. US patent 5510389 deals with concentrated acetaminophen solution compositions. Use of propylene glycol along with polyethylene glycol and polyvinyl pyrolidine improves solubility. Patent no. 5071643 is for solvent system enhancing the solubility of pharmaceuticals for encapsulation. It involves use of gelling agents like sodium stearate, sodium palmitate and calcium acetate to improve solubility of pharmaceutical ingredients into polyethylene glycol.

US patent 6287594 discloses oral liquid compositions with improved Bioavailability. They are designed to provide drugs with minimal gastric irritability wherein ratio of active drug to polymer based dispersing agent is from about 3:1 to 1:50 w/w. The resulting solution is found to be hazy. Polyvinyl pyrolidone is dispersing agent described. The purpose of invention is not to provide a clear solution.

US patent 6383515 provides a medicament in concentration of 49% to 70 % wherein solvent system comprises of low molecular weight polymer and organic acid. It involves heating as a part of process. The process may, may not result in a clear solution as disclosed in examples.

US patent 6387400 discloses a process for improving concentration of a pharmaceutically active ingredient relative to fill composition. It comprises of two step addition process. In step one a suspension of part of a drug is made in polyethelene glycol with a molecular weight of 200 daltons to 100,000 daltons and solubilizing it subsequently with hydroxide ion. In step two remaining drug is added and resulting suspension is solubilized by adding remaining part of hydroxide ion. The ratio of a drug to fill material by weight is 1:2 and/or 5:9.

US patent 5919, 481 discloses fill material for soft gelatin capsule which is translucent, semisolid in nature. It uses poly alkylene glycol with average molecular weight of about 600 or less along with cellulose ether.

The US patent 5141961 discloses a process for solubilizing difficulty soluble pharmaceutical actives. It uses polyethelene glycol, polyvinyl pyrolidine and monohydric alcohols. The ratio of polyethylene glycol to polyvinyl pyrolidine is about 2.5 to 1. It does not involve use of heat. It does not require use of solvent and surfactants.

PCT Application No. W088/02625, to Yu et al., published Apr. 21, 1988 which discloses the solubilization of an ionized or partly-ionized pharmaceutical active in a mixture of water.

The present invention provides a process by which clear solution of poorly soluble pharmaceutical substances is obtained wherein the amount of pharmaceutical substance is increased compared to conventional pharmaceutical compositions available.

In many instances it may not be possible or desirable to incorporate, water-miscible co-solvents, or surfactants into a pharmaceutical composition. For example, water-miscible co-solvents, such as ethanol, have the disadvantage of being relatively volatile, thereby resulting in concentration changes in the actives over time. Also, these co-solvents may not be compatible with the desired pharmaceutical actives. A more important disadvantage of volatile water-miscible co-solvents is that they are incompatible with soft gelatin capsules. Even though it may be possible to prepare soft gelatin capsules containing these solvents, over time the capsules gradually soften and deform, and develop leaks as these solvents dissolve the soft gelatin shell. Thus, it would be highly desirable to develop a solubilization process water-miscible co-solvents are used, it would be highly desirable to develop a process in which the water-miscible solvents are ultimately removed from the final compositions.

The present invention uses a combination of polyethylene glycol with different molecular weight with polymer and water. Polyethylene glycol(PEG) used as per the present invention is a mixture of PEG with different molecular weights. Polymer is any polymer, including polyvinyl pyrolidone.

The process as per the present invention does not use any alkalizing substance, surfactant to increase content of poorly soluble pharmaceutical ingredients as a clear liquid solution for encapsulation in a soft gelatin capsule.

As per the present invention it is possible to obtain a stable clear liquid solution of acetaminophen using PEG and PVP alone, wherein the concentration of acetaminophen is more than 30%.

It is not possible to make a clear solution of acetaminophen to a concentration more than 27% without using hydroxide, alkalizing substance, surfactant or propylene glycol.
It is therefore an object of the present invention to provide a process for solubilizing poorly soluble pharmaceutical actives. Another object of the present invention is to provide a solubilization process which does not require hydroxide, alkalizing agent, or surfactants. A further object of the present invention is to provide pharmaceutical compositions containing increased poorly soluble pharmaceutical actives.

These and other objects of this invention will become apparent in light of the following disclosure.

SUMMARY OF THE INVENTION

The invention herein provides for a process whereby the concentration of pharmaceutically active ingredients is improved in clear solution which can be used for encapsulation in a soft gelatin capsule. This permits the use of reduced overall fill volumes or alternatively, higher concentrations of the active ingredient per dosage unit or form.
The process according to the present invention increases the achievable concentration of pharmaceutically active ingredient in a clear liquid solution which can be used for encapsulation of soft gelatin capsule comprises use of two or more polyethelene glycol with different molecular weight and polyvinyl pyrolidone.

Thus there is disclosed process of increasing concentration of pharmaceutically cative ingredient in a clear liquid solution comprising the steps of

a. Mixing polyethylene glycol of different molecular weights in the range of about 40% to about 60% of the total weight.
b. Addition of water while stirring to step a.
c. Addition of dispersing agents like polyvinyl pyrrolidine while stirring in a range of about 4% to about 8% to the liquid obtained from step b.
d. Addition of poorly soluble active pharmaceutical ingredients while stirring to the liquid obtained from step c.
e. Heating of a resultant mixture obtained from step d while stirring at temperature not exceeding 90 ^{0}C.

Pharmaceutical active ingredients suitable for use invention including but not limited to acetaminophen, acetylsalicylic acid, ibuprofen, fenbrprofen, flurbiprofen, indomethacin, naproxen, and mixture thereof.

Polyethelene glycols which can be used in accordance with present invention include those having molecular weight range from about 200 daltons to about 100000 daltons. Preferable two polyethelene glycol as per present invention are those having average molecular weight of 400 daltons and 1000 daltons.

Polyvinyl pyrolidone is used in present invention can also have a wide ranging molecular weight most preferred poly vinyl pyrolidone has molecular weight of about 30,000(k 30)

The heating is required to achieve a clear liquid solution. Heating should not exceed 90^0c. It is preferable done between 60^0c to 80^0c.

The invention provides clear liquid solution with increased content of active pharmaceutical ingredient comprising:

a. from about 15% to about 40% of at least one poorly soluble pharmaceutical active;
b. from about 40% to about 60% of a polyethylene glycol;
c. from about 4% to about 8% of a polyvinyl pyrolidine; and
d. from about 5% to about 10% water, wherein the ratio of poltethylene glycol to polyvinyl pyrolidine is from 4:1 to 15:1.

The pharmaceutical composition and soft gelatin capsule made as per present invention are stable for more than two years under standard stability conditions and self life

DETAILED DESCRIPTION OF THE INVENTION

The polyethylene glycols useful herein are those which are liquids at room temperature or have a melting point slightly there above. Preferred are the polyethylene glycols having a molecular weight range from about 300 to about 1000. More preferred are the polyethylene glycols having a molecular weight range from about 400 to about 1000. Most preferred is a polyethylene glycol having a molecular weight of about 600 and 1000.
If only a low molecular weight. PEG is used, the poorly soluble drug are either become turbid or precipitate. I a high molecular weight PEG, with poorly soluble drugs are not formed a clear liquid. To get clear concentrated liquid preparation, a mixture of low and high molecular height PEG are better, therefore, mixtures of two or more polyethylene glycols of different average molecular weight range can also be employed in the present invention.

The process for preparing the highly concentrated liquid compositions of the present invention comprises adding from about 40% to about 60% polyethylene glycol.

An essential component of the present compositions is polyvinylpyrrolidone ("PVP"), which is a polymer of N-vinyl-2-pyrrolidone

The soluble forms of polyvinylpyrrolidone are preferred for use in the present invention. Preferred are soluble polyvinylpyrrolidones having an average molecular weight in the range from about 2900 to about 1,100,000; more preferred are those having an average molecular weight in the range from about 9000 to about 45,000; and most preferred are those having an average molecular weight of about 30,000 (k-30). Moreover, mixtures of two or more soluble polyvinylpyrrolidones of different average molecular weight can be employed.

The process disclosed in the present invention for preparing the highly concentrated liquid compositions of the instant invention comprises adding from about 4% to about 8% of a soluble polyvinylpyrrolidone.

With the use of PVP in combination with PEGs there is a definite increase the solubility of poorly soluble drugs. If heating is given to the mixture of poorly soluble drugs along with PVP and PEG, the solubility of poorly soluble drugs can be further increased.

EXAMPLE I

Ingredients	Quantity per capsule (mg)	Quantity for a batch of 0.2 Lac capsule (Kg)
1. Acetaminophen	325.00	6.500
2. Pseudoephedrine hydrochloride	32.25	0.645
3. Chlorpheniramine Maleate	2.15	0.043
4. Polyethylene glycol 400	510.60	10.212
5. Polyethylene glycol 1000	30.00	0.600
6. Purified water	75.00	1.500
7. Poly vinyl pyrolidine 1.100	55.00	
Total Weight	1030 mg	20.600 Kg

Process :

Take 10.212 Kg of polyethylene glycol 400 (PEG 400) and filter through 80 mesh stainless steel sieve in to a stainless steel jacketed tank with impeller type stirrer. Take 1.500 Kg purified water and add to the PEG 400 after filtering through 80 mesh stainless steel sieve. To the mixture of PEG 400 and purified water, slowly add 0.600 Kg of polyethylene glycol 1000 with stirring. The resultant mixture is subjected to heating up to 70 ^{0}C and mix for 10 minutes. Take 1.100 Kg Poly vinyl pyrolidine and pass through 40 mesh stainless steel sieve and add slowly to the above mixture with constant stirring till clear liquid obtains. Take 6.500 Kg of Acetaminophen, 0.645 Kg of Pseudoephedrine hydrochloride and 0.043 Kg of Chlorpheniramine Maleate and separately pass through a 60 mesh stainless steel sieve with the help of mechanical vibratory shifter. Add Acetaminophen, Pseudoephedrine hydrochloride and Chlorpheniramine Maleate one after another to the clear liquid obtained above with constant stirring. After addition of all the ingredients, heat the mixture slowly up to a maximum of 90 ^{0}C with constant stirring till clear liquid obtained. Filter the clear liquid through 200 mesh stainless steel sieve and allow the liquid to cool up to 25 ^{0}C. After cooling, the liquid is subjected to de aerate under a vacuum pressure between 630 mm hg to 670 mm Hg. This liquid is ready for encapsulation in a soft gelatine shell. All blending and mixing operations are carried out at relative humidity from 25% to 35%.

EXAMPLE II

Ingredients	Quantity per capsule (mg)	Quantity for a batch of 0.2 Lac capsule (Kg)
1. Acetaminophen	325.00	6.500
2. Pseudoephedrine hydrochloride	32.25	0.645
3. Dextromethorphan Hydrobromide	10.75	0.215
4. Doxylamine Succinate	6.72	0.1344
5. Polyethylene glycol 400	515.28	10.306
6. Polyethylene glycol 1000	30.00	0.600
7. Purified water	75.00	1.500
8. Poly vinyl pyrolidine 1.100	55.00	
Total Weight	1050 mg	21.000 Kg

Process :

Take 10.306 Kg of polyethylene glycol 400 (PEG 400) and filter through 80 mesh stainless steel sieve in to a stainless steel jacketed tank with impeller type stirrer. Take 1.500 Kg purified water and add to the PEG 400 after filtering through 80 mesh stainless steel sieve. To the mixture of PEG 400 and purified water, slowly add 0.600 Kg of polyethylene glycol 1000 with stirring. The resultant mixture is subjected to heating up to 70 ^{0}C and mix for 10 minutes. Take 1.100 Kg Poly vinyl pyrolidine and pass through 40 mesh stainless steel sieve and add slowly to the above mixture with constant stirring till clear liquid obtains. Take 6.500 Kg of Acetaminophen, 0.645 Kg of Pseudoephedrine hydrochloride, 0.215 Kg of Dextromethorphan Hydrobromide and 0.1344 Kg of Doxylamine Succinate and separately pass through a 60 mesh stainless steel sieve with the help of mechanical vibratory shifter. Add Acetaminophen, Pseudoephedrine hydrochloride, Dextromethorphan Hydrobromide and Doxylamine Succinate one after another to the clear liquid obtained above with constant stirring. After addition of all the ingredients, heat the mixture slowly up to a maximum of 90 ^{0}C with constant stirring till clear liquid obtained. Filter the clear liquid through 200 mesh stainless steel sieve and allow the liquid to cool up to 25 ^{0}C. After cooling, the liquid is subjected to de aerate under a vacuum pressure between 630 mm hg to 670 mm Hg. This liquid is ready for encapsulation in a soft gelatine shell. All blending and mixing operations are carried out at relative humidity from 25% to 35%.

EXAMPLE III

Ingredients	Quantity per capsule (mg)	Quantity for a batch of 0.2 Lac capsule (Kg)
1. Acetaminophen	325.00	6.500
2. Pseudoephedrine hydrochloride	32.25	0.645
3. Dextromethorphan Hydrobromide	10.75	0.215
4. Polyethylene glycol 400	512.75	10.240
5. Polyethylene glycol 1000	30.00	0.600
6. Purified water	75.00	1.500

7. Poly vinyl pyrolidine 1.100		55.00	
Total Weight	1040 mg		20.800 Kg

Process :

Take 10.240 Kg of polyethylene glycol 400 (PEG 400) and filter through 80 mesh stainless steel sieve in to a stainless steel jacketed tank with impeller type stirrer. Take 1.500 Kg purified water and add to the PEG 400 after filtering through 80 mesh stainless steel sieve. To the mixture of PEG 400 and purified water, slowly add 0.600 Kg of polyethylene glycol 1000 with stirring. The resultant mixture is subjected to heating up to 70 ^{0}C and mix for 10 minutes. Take 1.100 Kg Poly vinyl pyrolidine and pass through 40 mesh stainless steel sieve and add slowly to the above mixture with constant stirring till clear liquid obtains. Take 6.500 Kg of Acetaminophen, 0.645 Kg of Pseudoephedrine hydrochloride and 0.215 Kg of Dextromethorphan Hydrobromide and separately pass through a 60 mesh stainless steel sieve with the help of mechanical vibratory shifter. Add Acetaminophen, Pseudoephedrine hydrochlorlde and Dextromethorphan Hydrobromide one after another to the clear liquid obtained above with constant stirring. After addition of all the ingredients, heat the mixture slowly up to a maximum of 90 ^{0}C with constant stirring till clear liquid obtained. Filter the clear liquid through 200 mesh stainless steel sieve and allow the liquid to cool up to 25 ^{0}C. After cooling, the liquid is subjected to de aerate under a vacuum pressure between 630 mm hg to 670 mm Hg. This liquid is ready for encapsulation in a soft gelatine shell. All blending and mixing operations are carried out at relative humidity from 25% to 35%.

EXAMPLE IV

Ingredients	Quantity per capsule (mg)		Quantity for a batch of 0.2 Lac capsule (Kg)
1. Acetaminophen	325.00		6.500
2. Pseudoephedrine hydrochloride	32.25		0.645
3. Polyethylene glycol 400	512.75		10.255
4. Polyethylene glycol 1000	30.00		0.600
5. Purified water	75.00		1.500
6. Poly vinyl pyrolidine 1.100		55.00	
Total Weight	1040 mg		20.600 Kg

Process :

Take 10.255 Kg of polyethylene glycol 400 (PEG 400) and filter through 80 mesh stainless steel sieve in to a stainless steel jacketed tank with impeller type stirrer. Take 1.500 Kg purified water and add to the PEG 400 after filtering through 80 mesh stainless steel sieve. To the mixture of PEG 400 and purified water, slowly add 0.600 Kg of polyethylene glycol 1000 with stirring. The resultant mixture is subjected to heating up to 70 ^{0}C and mix for 10 minutes. Take 1.100 Kg Poly vinyl pyrolidine and

pass through 40 mesh stainless steel sieve and add slowly to the above mixture with constant stirring till clear liquid obtains. Take 6.500 Kg of Acetaminophen, 0.645 Kg of Pseudoephedrine hydrochloride and separately pass through a 60 mesh stainless steel sieve with the help of mechanical vibratory shifter. Add Acetaminophen, Pseudoephedrine hydrochloride one after another to the clear liquid obtained above with constant stirring. After addition of all the ingredients, heat the mixture slowly up to a maximum of 90 ^{0}C with constant stirring till clear liquid obtained. Filter the clear liquid through 200 mesh stainless steel sieve and allow the liquid to cool up to 25 ^{0}C. After cooling, the liquid is subjected to de aerate under a vacuum pressure between 630 mm hg to 670 mm Hg. This liquid is ready for encapsulation in a soft gelatine shell. All blending and mixing operations are carried out at relative humidity from 25% to 35%.

EXAMPLE V

Ingredients	Quantity per capsule (mg)	Quantity for a batch of 0.2 Lac capsule (Kg)
1. Acetaminophen	325.00	6.500
2. Pseudoephedrine hydrochloride	32.25	0.645
3. Dextromethorphan Hydrobromide	10.75	0.215
4. Chlorpheniramine maleate	2.15	0.043
4. Polyethylene glycol 400	519.85	10.397
5. Polyethylene glycol 1000	30.00	0.600
6. Purified water	75.00	1.500
7. Poly vinyl pyrolidine 1.100	55.00	
Total Weight	1050 mg	21.000 Kg

Process :

Take 10.397 Kg of polyethylene glycol 400 (PEG 400) and filter through 80 mesh stainless steel sieve in to a stainless steel jacketed tank with impeller type stirrer. Take 1.500 Kg purified water and add to the PEG 400 after filtering through 80 mesh stainless steel sieve. To the mixture of PEG 400 and purified water, slowly add 0.600 Kg of polyethylene glycol 1000 with stirring. The resultant mixture is subjected to heating up to 70 ^{0}C and mix for 10 minutes. Take 1.100 Kg Poly vinyl pyrolidine and pass through 40 mesh stainless steel sieve and add slowly to the above mixture with constant stirring till clear liquid obtains. Take 6.500 Kg of Acetaminophen, 0.645 Kg of Pseudoephedrine hydrochloride and 0.215 Kg of Dextromethorphan Hydrobromide and0.043 kg of Chlorpheniramine maleate separately pass through a 60 mesh stainless steel sieve with the help of mechanical vibratory shifter. Add Acetaminophen, Pseudoephedrine hydrochloride and Dextromethorphan Hydrobromide and Chlorpheniramine maleate one after another to the clear liquid obtained above with constant stirring. After addition of all the ingredients, heat the mixture slowly up to a maximum of 90 ^{0}C with constant stirring till clear liquid obtained. Filter the clear liquid through 200 mesh stainless steel sieve and allow the liquid to cool up to 25 ^{0}C. After cooling, the liquid is subjected to de aerate under a vacuum pressure between 630 mm hg to 670 mm Hg. This liquid is ready for encapsulation in a soft gelatine shell. All blending and mixing operations are carried out at relative humidity from 25% to 35%.

Propylene glycol may be used in above process. However its amount should not increase more than 2%. Otherwise solution looses its clarity.

As per present invention substitution of polyvinyl pyrolidone by surfactants like Tween-80, Tween 40, Hydrogenated castor oil derivatives like cremaphor RH-40, Cremaphor EL results in loss of clarity of a solution.

Following examples demonstrates the limitation of present process in obtaining concentrated clear liquid pharmaceutical composition of poorly soluble

pharmaceutical active ingredients. All of below mentioned compositions are either no clear or loose their clarity during there self life.

EXAMPLE I

Ingredients	Quantity per capsule (mg)	Quantity for a batch of 0.2 Lac capsule (Kg)
1. Acetaminophen	400.00	8.000
2. Polyethylene glycol 400	530.00	10.600
3. Polyethylene glycol 1000	30.00	0.600
4.PVP(k 30)	55	1.100
6. Purified water	75.00	1.500
Total Weight	1090 mg	21.800 Kg

EXAMPLE II

Ingredients	Quantity per capsule (mg)	Quantity for a batch of 0.2 Lac capsule (Kg)
1. Acetaminophen	400.00	8.000
2. Polyethylene glycol 400	530.00	10.600
3. Polyethylene glycol 1000	35.00	0.700
4.PVP(k 30 + k90)	57.5 + 27.5	1.100
6. Purified water	75.00	1.500
Total Weight	1125 mg	21.8 Kg

EXAMPLE III

Ingredients	Quantity per capsule (mg)	Quantity for a batch of 0.2 Lac capsule (Kg)
1. Acetaminophen	400.00	8.000
2. Polyethylene glycol 400	530.00	10.600
3. Polyethylene glycol 1000	30.00	0.600
4.PVP(k 90)	55	1.100
6. Purified water	80.00	1.600
Total Weight	1095 mg	21.900 Kg

EXAMPLE IV

Ingredients	Quantity per capsule (mg)	Quantity for a batch of 0.2 Lac capsule (Kg)
1. Acetaminophen	450.00	9.000
2. Polyethylene glycol 400	550.00	11.000
3. Polyethylene glycol 1000	30.00	0.600
4.PVP(k 90)	60	1.200
5. Purified water	85.00	1.700
Total Weight	1175 mg	23.500 Kg

EXAMPLE V

Ingredients	Quantity per capsule (mg)	Quantity for a batch of 0.2 Lac capsule (Kg)
1. Acetaminophen	400.00	8.000
2. Polyethylene glycol 400(495)	45%	10.600
3. Polyethylene glycol 1000(66)	6%	0.600
4.PVP(k 30)	55	1.100
5. Purified water	75.00	1.500
Total Weight	1100 mg	21.8 Kg

EXAMPLE VI

Ingredients	Quantity per capsule (mg)	Quantity for a batch of 0.2 Lac capsule (Kg)
1. Acetaminophen	400.00	8.000
2. Polyethylene glycol 400(522)	47.5%	10.600
3. Polyethylene glycol 1000(29.2)	2.7%	0.600
4.PVP(k 30)	55	1.100
5. Purified water	75.00	1.500

EXAMPLE VII

Ingredients	Quantity per capsule (mg)	Quantity for a batch of 0.2 Lac capsule (Kg)

1. Acetaminophen	400.00	8.000
2. Polyethylene glycol 400(495)	45%	10.600
3. Polyethylene glycol 1450(44)	4%	0.600
4.PVP(k 30)	55	1.100
5. Purified water	75.00	1.500

EXAMPLE VIII

Ingredients	Quantity per capsule (mg)	Quantity for a batch of 0.2 Lac capsule (Kg)
1. Acetaminophen	400.00	8.000
2. Polyethylene glycol 400	520	10.400
3. Polyethylene glycol 1000	30	0.600
4.PVP(k 30)	90	1.800
5. Purified water	75.00	1.500
6. Potassium Acetate	6	0.120
Total Weight	1121 mg	22.420Kg

EXAMPLE IX

Ingredients	Quantity per capsule (mg)	Quantity for a batch of 0.2 Lac capsule (Kg)
1. Acetaminophen	450.00	8.000
2. Polyethylene glycol 400	400	10.600
3. Polyethylene glycol 200	120	
4. Polyethylene glycol 1450	44	0.600
5.PVP(k 30)	90	1.100
6. Purified water	75.00	1.500
Total Weight	1179 mg	21.8Kg

EXAMPLE XI

Ingredients	Quantity per capsule (mg)	Quantity for a batch of 0.2 Lac capsule (Kg)
1. Acetaminophen	400.00	8.000
2. Polyethylene glycol 400	483.00	0.966
3. Polyethylene glycol 1500	29.00	0.580
4. PVP(k 90)	63	1.260
5. Purified water	175.00	3.500
Total Weight	1217mg	14.306Kg

EXAMPLE XII

Ingredients	Quantity per capsule (mg)	Quantity for a batch of 0.2 Lac capsule (Kg)
1. Acetaminophen	500.00	10.000
2. Polyethylene glycol 400	483.00	0.966
3. Polyethylene glycol 1500	29.00	0.580
4. PVP(k 90)	63	1.260
5. Purified water	175.00	3.500
Total Weight	1250mg	16.306Kg

EXAMPLE XIII

Ingredients	Quantity per capsule (mg)	Quantity for a batch of 0.2 Lac capsule (Kg)
1. Acetaminophen	400.00	10.000
2. Polyethylene glycol 400	483.00	0.966
3. Polyethylene glycol 1500	29.00	0.580
4. PVP(k 90)	63	1.260
5. Purified water	175.00	3.500
Total Weight	1250mg	16.306Kg

We Claim

1. The process of manufacturing pharmaceutical composition with increased content of poorly soluble pharmaceutical ingredients in a clear liquid solution comprising the steps of:
   a. Preparing a solvent system comprising of at least two from polyethylene glycol of different molecular weights in the range of about 40% to about 60% of the total weight, water, and dispersing agents like polyvinyl pyrrolidine in a range of about 4% to about 8%.
   b. Addition of poorly soluble active pharmaceutical ingredients while stirring to the liquid obtained from step a.
   c. Heating of a resultant mixture obtained from step b while stirring at temperature not excceding 90 ^{0}C.
2. The process according to claim 1 wherein the pharmaceutically active ingredient ranges from about 15% to about 40%.
3. The process according to claim 2 wherein the pharmaceutical active ingredient ranges from about 25% to about 33%.
4. The process according to claim 1 wherein at least one of the polyethylene glycol have average molecular weight below 600.
5. The process according to claim 1 wherein one of the polyethylene glycol have average molecular weight is 400.
6. The process according to claim 1 wherein at least another polyethylene glycol should have molecular weight of 800 or above.
7. The process according to claim 4 wherein at least another polyethylene glycol should have molecular weight of 1000 or above.
8. Polyethylene glycol with molecular weight lower than 600 as claimed in claim 4 should be 85% or above of total polyethylene glycol.
9. The process according to claim 8 wherein polyethylene glycol with molecular weight lower than 600 should be 88% or above of total polyethylene glycol.
10. The process according to claim 8 wherein polyethylene glycol with molecular weight lower than 600 should be 92% or above of total polyethylene glycol.
11. The process according to claim 1 wherein polyethylene glycol with high molecular weight should be 15% or less of total polyethylene glycol.
12. The process according to claim 11 wherein polyethylene glycol with high molecular weight should be at least 3% of total polyethylene glycol.
13. The process according to claim 11 wherein polyethylene glycol with high molecular weight should be at least 5% of total polyethylene glycol.
14. The process according to claim 1 wherein the ratio of polyethylene glycol to polyvinyl pyrolidine is about 4:1 to 15:1.
15. The process according to claim 14 wherein the ratio of polyethylene glycol to polyvinyl pyrolidine is about 4:1 or above.
16. The process according to claim 14 wherein the ratio of polyethylene glycol to polyvinyl pyrolidine is about 5:1 or above.
17. The process according to claim 14 wherein the ratio of polyethylene glycol to polyvinyl pyrolidine is about 6:1 or above.
18. A process according to claim 1 wherein poorly soluble active pharmaceutical ingredients is selected from the group consisting of acetaminophen, acetylsalicylic acid, ibuprofen, fenbrprofen, flurbiprofen, indomethacin, naproxen, and mixture thereof.
19. A process according to claim 18 wherein the poorly soluble active pharmaceutical ingredient is acetaminophen.

20. A process according to claim 1 which further comprises combining in step (b) form about 0.5% to 20% of a second pharmaceutical active ingredient selected from the group consisting of dextromethorphan hydrobromide, doxyllamine succinate, pseudoephedrine hydrochloride, chlorpheniramine maleate, guaifenesin, tripolidine hydrochloride, diphenhydramine hydrochloride, and mixture thereof.
21. A process of manufacturing pharmaceutical composition with increased content of poorly soluble pharmaceutical ingredients in a clear liquid solution comprising the steps of:
    a. Preparing a solvent system comprising of at least two from polyethylene glycol of different molecular weights in the range of about 40% to about 60% of the total weight, water, and dispersing agents like polyvinyl pyrrolidine in a range of about 4% to about 8%.
    b. Addition of poorly soluble active pharmaceutical ingredients while stirring to the liquid obtained from step a.
    c. Heating of a resultant mixture obtained from step b while stirring at temperature not excceding 90 ^{0}C.
    d. Encapsulating the clear liquid composition in a soft gelatin shell.
22. A process according to claim 21 wherein poorly soluble active pharmaceutical ingredients is selected from the group consisting of acetaminophen, acetylsalicylic acid, ibuprofen, fenbrprofen, flurbiprofen, indomethacin, naproxen, and mixture thereof.
23. A process according to claim 21 which further comprises combining in step (b) form about 0.5% to 20% of a second pharmaceutical active ingredient selected from the group consisting of dextromethorphan hydrobromide, doxyllamine succinate, pseudoephedrine hydrochloride, chlorpheniramine maleate, guaifenesin, tripolidine hydrochloride, diphenhydramine hydrochloride, and mixture thereof.
24. A concentrated clear liquid , pharmaceutical composition prepared in accordance with the process of claim 1.
25. A concentrated clear liquid , pharmaceutical composition prepared in accordance with the process of claim 18.
26. A concentrated clear liquid , pharmaceutical composition prepared in accordance with the process of claim 20.
27. A soft gelatin capsule prepared in accordance with the process of claim 21.
28. A soft gelatin capsule prepared in accordance with the process of claim 22.
29. A soft gelatin capsule prepared in accordance with the process of claim 23.
30. A concentrated clear liquid, pharmaceutical composition which is comprising,
    a. from about 15% to about 40% of at least one poorly soluble pharmaceutical active;
    b. from about 40% to about 60% of a polyethylene glycol;
    c. from about 4% to about 8% of a polyvinyl pyrolidine; and
    d. from about 5% to about 10% water, wherein the ratio of poltethylene glycol to polyvinyl pyrolidine is from 4:1 to 15:1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 02/03015

CLASSIFICATION OF SUBJECT MATTER

IPC[7]: A61K 9/66, 47/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[7]: A61K

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

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

WPI, EPODOC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	EP 0719549 A1 (McNEIL-PPC, INC.) 3 July 1996 (03.07.96) *page 3, lines 7-13,29-32; page 3, line 57-page 4, line 3.*	1-5,14-19,21,22,24,25,27,28,30
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Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
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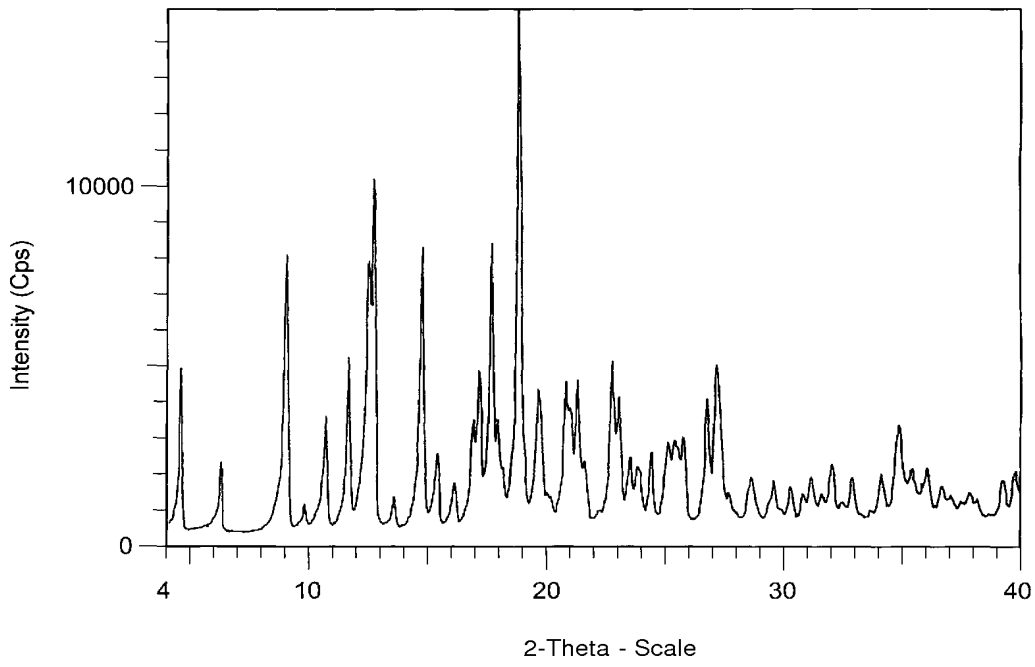
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: AMORPHOUS CYCLODEXTRIN COMPOSITIONS



(57) Abstract: Compositions comprising a plurality of particles are disclosed. The particles comprise a cyclodextrin and a water-soluble polymer. The cyclodextrin is in intimate contact with the water-soluble polymer in the particles. At least a major portion of the cyclodextrin in the particles is amorphous.

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AMORPHOUS CYCLODESTRIN COMPOSITIONS

BACKGROUND OF THE INVENTION

The present invention relates to compositions comprising amorphous cyclodexthn and a water-soluble polymer.

Cyclodextrins are cyclic multicyclopyranose units connected by alpha-(1 ,4) linkages. The most widely known cyclodextrins are alpha, beta and gamma-cyclodextrins. Derivatives of these cyclodextrins are also known and used in the pharmaceutical field. The cyclic nature of the cyclodextrins, the hydrophobic properties of their cavities as well as the hydrophilic character of their outer surfaces, enables them to interact with other chemicals and to produce inclusion compounds.

Numerous reviews and patents related to the use of cyclodextrins and their derivatives to prepare inclusion complexes of active agents are found in the literature, for example, D. Duchene, *Cyclodextrins and their Industrial Uses,* Editions de Sante, Paris, 1987, Chapter 6 (21 1-257), Chapter 8 (297-350), Chapter 10 (393-439); D. Duchene et al, Acta Pharma Technol. 36(1)6, 1-6, 1990; D. Duchene et al, Drug Dev. Ind. Pharm., 16(17), 2487-2499, 1990; C. Hunter et al, European Patent Publication No. EP 0346006, December 1988. See also U.S. Pat. Nos. 4,024,223; 4,228,160; 4,232,009; 4,351,846; 4,352,793; 4,383,992; 4,407,795; 4,424,209; 4,425,336; 4,438,106; 4,474,811; 4,478,995; 4,479,944; 4,479,966; 4,497,803; 4,499,085; 4,524,068; 4,555,504; 4,565,807; 4,575,548; 4,598,070; 4,603,123; 4,608,366; 4,623,641; 4,659,696; 4,663,316; 4,675,395; 4,728,509; 4,728,510; and 4,751,095.

Inclusion complexes prepared to specifically improve water solubility and hence bioavailability of poorly soluble drugs have been reported by workers such as D. D. Chow et al, Int. J. Pharm., 28, 95-101, 1986; F. A. Menard et al, Drug Dev. Ind. Pharm., 14(11), 1529-1547, 1988; F. J. Otera-Espinar et al, Int. J. Pharm., 75, 37-44, 1991; and Berand M. Markahan et al, European Patent Publication No. EP 0274444, July 1988. Chemical modifications of cyclodextrins to prepare derivatives that further improve solubility of water insoluble drugs have been described, for example, by J. Pitha, U.S. Pat. No. 4,727,064, February 1988; N. S. Bodor, U.S. Pat. No. 5,024,998, July 1991.

It is known that some types of cyclodextrins are capable of crystallizing *in vivo,* significantly limiting the effectiveness of cyclodextrins for solubilizing poorly soluble drugs. To overcome this limitation, researchers have chemically modified the cyclodextrins to prevent crystallization. See for example, U.S. Patent Application Publication No. 2003-0 148996A1 , U.S. Patent Nos. 6,407,061 , 6,407,061 , 6,342,478, 6,313,093, 6,180,603, 5,624,898, 5,296,472, 5,180,716, 4,596,795, J. Pitha, *J. Contr. Rel.,* 6:309-313 (1987), J. Pitha et al., *Life Sciences,* 43:493-502 (1988), T. Irie, *Pharm. Res.,* 5(1 1):713-717 (1988), J. Pitha, *Neurotransmissions,* V(1):1-4 (1989). These chemically modified cyclodextrins are typically a mixture of modified products with varying degrees and types of substituents, which prevents crystallization.

Nevertheless, there is still a need to provide amorphous forms of cyclodextrin that do not require chemical modification of the cyclodextrin, and that overcomes other drawbacks of the prior art. These needs are met by the present invention, which is summarized and described in detail below.

BRIEF SUMMARY OF THE INVENTION

In a first aspect, a composition comprises a solid composition comprising a plurality of particles. Each of the particles comprises a cyclodextrin and a water-soluble polymer. The cyclodextrin is in intimate contact with the water-soluble polymer in the particles. At least a major portion of the cyclodextrin in the particles is amorphous.

In a second aspect, a composition comprises an active and a plurality of particles, each of the particles comprising a cyclodextrin and a water-soluble polymer, wherein the cyclodextrin is in intimate contact with the water-soluble polymer, and wherein at least a major portion of the cyclodextrin is amorphous.

In a third aspect, a process is provided for making a plurality of particles, each of the particles comprising a cyclodextrin and a water-soluble polymer, the process comprising: (a) forming a solution comprising cyclodextrin, a water-soluble polymer, and a solvent, (b) rapidly removing the solvent from the solution to form a solid, and (c) forming particles from the so-formed solid, wherein at least a major portion of the cyclodextrin is amorphous. In one embodiment, steps (b) and (c) are preformed simultaneously by spray-drying the solution into a chamber.

The present invention overcomes the drawbacks of the prior art in that the cyclodextrin is present in an amorphous form without needing to chemically modify the cyclodextrin. The water-soluble polymer is present in a sufficient amount to retard crystallization of the cyclodextrin in the particles, effectively stabilizing the amorphous form of the cyclodextrin. The compositions of the present invention comprising amorphous cyclodextrins have an advantage of resulting in faster dissolution and/or dispersing of the cyclodextrin when administered to an aqueous use environment. This can lead to more rapid formation of inclusion complexes with actives. When the active has a low aqueous solubility, this more rapid formation of an inclusion complex can lead to improved solubilization of the active in the aqueous use environment.

As used herein, an "active" is meant a compound that can form an inclusion complex or otherwise associate with a cyclodextrin. Examples of such materials include pharmaceuticals, vitamins, nutriceuticals, agrochemical compounds, nutrients, fertilizers, pesticides, fungicides, botanical extracts, flavoring agents, fruit extracts, spices, cosmetics, coloring agents, pigments, and the like.

As used herein, an "aqueous use environment" refers to any environment that contains water in which it may be desirable to deliver, use, or otherwise contain the active. For example, when the active is a pharmaceutical, the aqueous use environment may be *in vivo* fluids, such as present in the buccal space or the GI tract of an animal, such as a mammal, and particularly a human. When the active is an agrochemical compound, the aqueous use environment may be the mass of the vegetation or the soil in which the vegetation is planted. Alternatively, the aqueous use environment may be an *in vitro* environment of a test solution, such as unbuffered water, a simulated mouth buffer (MB) or a simulated gastric buffer (GB). An appropriate simulated MB test solution is 0.05M KH_2PO_4 buffer adjusted to pH 7.3 with 10M KOH. Appropriate GB test solutions include 0.01 N HCl and 0.1 N HCl. "Administration" to a use environment means, where the *in vivo* use environment is the mouth or GI tract, ingestion or other such means to deliver the composition. Where the use environment is *in vitro,* "administration" refers to placement or delivery of the composition or dosage form containing the composition to the *in vitro* test medium.

The foregoing and other objectives, features, and advantages of the invention will be more readily understood upon consideration of the following detailed description of the invention.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

FIG. 1 is an X-ray diffraction pattern of the crystalline β-cyclodextrin used to form the particles in Example 1.

FIG. 2 is an X-ray diffraction pattern of particles of β-cyclodextrin and HPMC formed in Example 1 showing no crystalline cyclodexthn in the particles.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention relates to solid compositions of a cyclodextrin and a water-soluble polymer. At least a major portion of the cyclodextrin in the particles is amorphous. The nature of the solid compositions, suitable cyclodextrins and water-soluble polymers, and methods for making the compositions are discussed in more detail below.

CYCLODEXTRINS

The solid compositions of the present invention comprise a cyclodextrin. Cyclodextrins useful in the present invention include *a-,* β- and γ-cyclodextrins and alkyl and hydroxyalkyl derivatives thereof, with β-cyclodextrins and derivatives of β-cyclodextrin being the most preferred from the standpoint of availability and cost. Exemplary derivatives of cyclodextrin include mono- or polyalkylated β-cyclodextrin, mono- or polyhydroxyalkylated β-cyclodextrin, mono, tetra or hepta-substituted β-cyclodextrin, and sulfoalkyl ether cyclodextrin (SAE-CD). Specific cyclodextrin derivatives for use herein include hydroxypropyl- β-cyclodextrin, hydroxyethyl- β-cyclodextrin, hydroxypropyl- γ-cyclodextrin, hydroxyethyl- γ-cyclodextrin, dihydroxypropyl- β-cyclodextrin, glucosyl- α-cyclodextrin, glucosyl- β-cyclodexthn, diglucosyl- β-cyclodextrin, maltosyl- α-cyclodextrin, maltosyl- β-cyclodextrin, maltosyl-γ-cyclodextrin, maltotriosyl- β-cyclodextrin, maltotriosyl- γ-cyclodextrin, dimaltosyl- β-cyclodextrin, methyl- β-cyclodexthn, and mixtures thereof such as maltosyl- β-cyclodextrin/dimaltosyl- β-cyclodextrin. A preferred cyclodextrin is β-cyclodextrin.

WATER-SOLUBLE POLYMERS

The solid compositions of the present invention also comprise a water-soluble polymer. As used herein, the term "polymer," which can be a mixture of polymers, is used conventionally, meaning a compound that is made of monomers connected together to form a larger molecule. A polymeric component generally consists of at least about 20 monomers. Thus, the molecular weight of a polymeric component will generally be about 2000 daltons or more. The term "water-soluble" means the polymer has an aqueous solubility of at least about 0.1 mg/mL over at least a portion of the pH range of 1 to 8. Preferably, the polymer has an aqueous solubility of at least about 0.5 mg/mL, and more preferably at least about 1 mg/mL.

In general, polymers useful in the compositions of the present invention may be neutral or ionizable cellulosic or non-cellulosic polymers. Examples of neutral non-cellulosic polymers include vinyl polymers and copolymers, polyvinyl alcohols, polyvinyl alcohol/polyvinyl acetate copolymers, polyvinyl

pyrrolidone polyethylene glycol/polypropylene glycol copolymers, polyvinyl pyrrolidone, polyethylene/polyvinyl alcohol copolymers, and polyoxyethylene/polyoxypropylene block copolymers (also known as poloxamers). Examples of ionizable non-cellulosic polymers include carboxylic acid functionalized polymethacrylates and carboxylic acid functionalized polyacrylates, amine-functionalized polyacrylates and polymethacrylates, high molecular weight proteins such as gelatin and albumin, and carboxylic acid functionalized starches such as starch glycolate. Examples of neutral cellulosic polymers are hydroxypropyl methyl cellulose (HPMC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), methyl cellulose, hydroxyethyl methyl cellulose, and hydroxyethyl ethyl cellulose. Examples of ionizable cellulosic polymers are hydroxypropyl methyl cellulose acetate succinate (HPMCAS), hydroxypropyl methyl cellulose phthalate (HPMCP), carboxymethyl ethyl cellulose (CMEC), carboxyethyl cellulose, carboxymethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose acetate phthalate, and cellulose acetate trimellitate. Neutralized forms of ionizable polymers may also be useful, such as sodium carboxymethyl cellulose (sodium CMC). Preferred water-soluble polymers include polyvinyl alcohols, polyvinyl pyrrolidone, poloxamers, polymethacrylates and polyacrylates, gelatin, HPMC, HEC, HPC, HPMCAS, HPMCP, CMEC, and sodium CMC.

SOLID PARTICLES OF CYCLODEXTRIN AND POLYMER

The compositions of the present invention comprise a plurality of particles. Each of these particles comprises both a cyclodextrin and a water-soluble polymer. The amount of polymer to the amount of cyclodextrin in each of the particles depends on the characteristics of the polymer and cyclodextrin and may vary widely from a cyclodextrin-to-polymer weight ratio of from about 0.01 (1 part cyclodextrin to 100 parts polymer) to about 100 (e.g., 1 wt% cyclodextrin to 99 wt% cyclodextrin). In order to keep the total mass of the composition small, it is preferred that the particles comprise higher amounts of cyclodextrin. Thus, the cyclodextrin-to-polymer weight ratio preferably is at least about 0.05 (about 5 wt% cyclodextrin), more preferably at least about 0.1 (about 10 wt% cyclodextrin), even more preferably at least about 0.2 (about 17 wt% cyclodextrin), and even more preferably at least about 0.33 (about 25 wt% cyclodextrin).

The particles should also contain a sufficient amount of water-soluble polymer to stabilize the amorphous form of the cyclodextrin in the particles, retarding crystallization of the cyclodextrin. Thus, the cyclodextrin-to-polymer weight ratio is preferably less than about 49 (about 98 wt% cyclodextrin), more preferably less than about 19 (about 95 wt% cyclodextrin), more preferably less than about 9 (about 90 wt% cyclodextrin), and even more preferably less than about 3 (about 75 wt% cyclodextrin).

At least a major portion of the cyclodextrin in the particles is amorphous. By "amorphous" is meant that the cyclodextrin is in a non-crystalline state. As used herein, the term "a major portion" of the cyclodextrin means that at least 60 wt% of the cyclodextrin in the particles is in the amorphous form, rather than the crystalline form. Preferably "a substantial portion" of the cyclodextrin in the particles is amorphous, meaning that at least 75 wt% of the cyclodextrin in the particles is in the amorphous form. More preferably the cyclodextrin is "almost completely amorphous," meaning that the amount of drug in the crystalline form does not exceed 10 wt%. Amounts of crystalline cyclodextrin may be measured by powder X-ray diffraction, Scanning Electron Microscope (SEM) analysis, differential scanning calorimetry (DSC), or any other standard quantitative measurement. Most preferably the particles are substantially free of crystalline cyclodextrin.

The amorphous cyclodextrin in the particles is in intimate contact with the water-soluble polymer. The amorphous cyclodextrin in the particle can exist as a pure phase, as a solid solution of cyclodextrin homogeneously distributed throughout the water-soluble polymer, or any combination of these states or those states that lie intermediate between them. In cases where cyclodextrin-rich amorphous domains exist, these domains are generally quite small; that is, less than about 1 μm in size. Preferably, such domains are less than about 100 nm in size. The particles may have a single glass-transition temperature, indicating that the cyclodextrin is homogeneously dispersed throughout the water-soluble polymer, or may have two glass-transition temperatures, corresponding to a cyclodextrin-rich amorphous phase and a cyclodextrin-poor amorphous phase.

The primary constituents of the particles are the cyclodextrin and the water-soluble polymer. The cyclodextrin and water-soluble polymer together constitute at least 50 wt% of the particles. The cyclodextrin and water-soluble polymer may constitute even greater amounts of the composition, and may constitute at least 60 wt%, at least 70 wt%, at least 80 wt%, or even at least 90 wt% of the particles. In one embodiment, the particles consist essentially of the cyclodextrin and water-soluble polymer.

METHODS FOR MAKING PARTICLES OF CYCLODEXTRIN AND POLYMER

The particles of cyclodextrin and water-soluble polymer of the present invention may be made according to any known process that results in at least a major portion (that is, at least 60 wt%) of the cyclodextrin being in the amorphous state. One preferred technique is solvent processing. In solvent processing, the cyclodextrin and water-soluble polymer are dissolved in a common solvent and the solvent subsequently removed by evaporation or by mixing with a non-solvent. "Common" here means that the solvent, which can be a mixture of compounds, will dissolve both the cyclodextrin and the polymer. After both the cyclodextrin and the polymer have been dissolved, the solvent is removed by evaporation or by mixing with a non-solvent. Exemplary processes are spray-drying, spray-coating (pan-coating, fluidized bed coating, etc.), evaporation, lyophilization, and precipitation by rapid mixing of the polymer and cyclodextrin solution with CO_2, or some other non-solvent.

Solvents suitable for solvent processing are preferably volatile with a boiling point of 150°C or less. In addition, the solvent should have relatively low toxicity and be removed from the particles to a level that is acceptable according to The International Committee on Harmonization (ICH) guidelines. Removal of solvent to this level may require a subsequent processing step such as tray drying. Preferred solvents include water; alcohols such as methanol, and ethanol; ketones such as acetone, methyl ethyl ketone and methyl iso-butyl ketone; and various other solvents such as acetonitrile, methylene chloride, and tetrahydrofuran. Lower volatility solvents such as dimethyl acetamide or dimethylsulfoxide can also be used in small amounts in mixtures with a volatile solvent. Mixtures of solvents, such as 50% methanol and 50% acetone, can also be used, as can mixtures with water, so long as the polymer and cyclodextrin are sufficiently soluble to make the process practicable.

The solvent may be removed by spray-drying. The term "spray-drying" is used conventionally and broadly refers to processes involving breaking up liquid mixtures into small droplets (atomization) and rapidly removing solvent from the mixture in a spray-drying apparatus where there is a strong driving force for

evaporation of solvent from the droplets. Spray-drying processes and spray-drying equipment are described generally in Perry's *Chemical Engineers' Handbook,* pages 20-54 to 20-57 (Sixth Edition 1984). More details on spray-drying processes and equipment are reviewed by Marshall, "Atomization and Spray-Drying," 50 *Chem. Eng. Prog. Monogr. Series 2* (1954), and Masters, *Spray Drying Handbook* (Fourth Edition 1985). The strong driving force for solvent evaporation is generally provided by maintaining the partial pressure of solvent in the spray-drying apparatus well below the vapor pressure of the solvent at the temperature of the drying droplets. This is accomplished by (1) maintaining the pressure in the spray-drying apparatus at a partial vacuum (e.g., 0.01 to 0.50 atm); or (2) mixing the liquid droplets with a warm drying gas; or (3) both (1) and (2). In addition, at least a portion of the heat required for evaporation of solvent may be provided by heating the spray solution.

The solvent-bearing feed, comprising the cyclodextrin and the water-soluble polymer, can be spray-dried under a wide variety of conditions and yet still yield particles with acceptable properties. For example, various types of nozzles can be used to atomize the spray solution, thereby introducing the spray solution into the spray-dry chamber as a collection of small droplets. Essentially any type of nozzle may be used to spray the solution as long as the droplets that are formed are sufficiently small that they dry sufficiently (due to evaporation of solvent) that they do not stick to or coat the spray-drying chamber wall.

Although the maximum droplet size varies widely as a function of the size, shape and flow pattern within the spray-dryer, generally droplets should be less than about 500 μm in diameter when they exit the nozzle. Examples of types of nozzles that may be used to form the solid particles include the two-fluid nozzle, the fountain-type nozzle, the flat fan-type nozzle, the pressure nozzle and the rotary atomizer.

The spray solution can be delivered to the spray nozzle or nozzles at a wide range of temperatures and flow rates. Generally, the spray solution temperature can range anywhere from just above the solvent's freezing point to about 20^{0}C above its ambient pressure boiling point (by pressurizing the solution) and in some cases even higher. Spray solution flow rates to the spray nozzle can vary over a wide range depending on the type of nozzle, spray-dryer size and spray-dry conditions such as the inlet temperature and flow rate of the drying gas. Generally, the energy for evaporation of solvent from the spray solution in a spray-drying process comes primarily from the drying gas.

The drying gas can, in principle, be essentially any gas, but for safety reasons and to minimize undesirable oxidation of the cyclodextrin or other materials in the solid composition, an inert gas such as nitrogen, nitrogen-enriched air or argon is utilized. The drying gas is typically introduced into the drying chamber at a temperature between about 60° and about 300^{0}C and preferably between about 80° and about 240^{0}C.

The large surface-to-volume ratio of the droplets and the large driving force for evaporation of solvent leads to rapid solidification times for the droplets. Solidification times should be less than about 20 seconds, preferably less than about 10 seconds, and more preferably less than 1 second. This rapid solidification is often critical to the particles maintaining a major portion of amorphous cyclodextrin.

Following solidification, the solid powder typically stays in the spray-drying chamber for about 5 to 60 seconds, further evaporating solvent from the solid powder. The final solvent content of the particles as they exit the dryer should be low, since this reduces the mobility of the cyclodextrin molecules in the

particles, thereby improving its stability. Generally, the solvent content of the particles as they leave the spray-drying chamber should be less than 10 wt% and preferably less than 2 wt%. Following formation, the particles can be dried to remove residual solvent using suitable drying processes, such as tray drying, fluid bed drying, microwave drying, belt drying, rotary drying, vacuum drying, and other drying processes known in the art.

In another embodiment, the particles are formed by an evaporation process. In this process the cyclodextrin and water-soluble polymer are dissolved in a common solvent as described above. The solvent is then removed by evaporation to form the solid composition. Examples of evaporation processes include rotoevaporation, multiple-effect evaporation, flash evaporation, and film evaporation. The resulting solids are preferably formed into small particles, such as by using a mortar and pestle or other milling processes known in the art. The particles may be sieved and dried as necessary to obtain a material with the desired properties.

In another embodiment, the particles are formed by spraying a coating solution of the cyclodextrin and water-soluble polymer onto seed cores. The seed cores can be made from any suitable material such as starch, microcrystalline cellulose, sugar or wax, by any known method, such as melt- or spray-congealing, extrusion/spheronization, granulation, spray-drying and the like.

The coating solution can be sprayed onto such seed cores using coating equipment known in the pharmaceutical arts, such as pan coaters (e.g., Hi-Coater available from Freund Corp. of Tokyo, Japan, Accela-Cota available from Manesty of Liverpool, U.K.), fluidized bed coaters (e.g., Würster coaters or top-sprayers available from Glatt Air Technologies of Ramsey, New Jersey and from Niro Pharma Systems of Bubendorf, Switzerland) and rotary granulators (e.g., CF-Granulator, available from Freund Corp).

The particles may also be made by a lyophilization process. In lyophilization processes, also known in the art as freeze-drying processes, a solution of the cyclodextrin and polymer in a solvent is frozen into a solid state. The solvent is then removed from the solid by sublimation using a vacuum. After the solvent has been removed, the solids are preferably formed into small particles, such as by using a mortar and pestle or other milling processes known in the art.

Once the particles comprising the cyclodextrin and water-soluble polymer have been formed, several processing operations can be used to facilitate incorporation of the particles into compositions. These processing operations include drying, granulation, and milling.

The particles may be granulated to increase their size and improve handling of the particles while forming a suitable composition. Preferably, the average size of the granules will range from 50 to 1000 μm. Dry or wet granulation processes can be used for this purpose. An example of a dry granulation process is roller compaction. Wet granulation processes can include so-called low shear and high shear granulation, as well as fluid bed granulation. In these processes, a granulation fluid is mixed with the composition after the dry components have been blended to aid in the formation of the granulated composition. Examples of granulation fluids include water, ethanol, isopropyl alcohol, n-propanol, the various isomers of butanol, and mixtures thereof. A polymer may be added with the granulation fluid to aid in granulating the particles. Examples of suitable polymers include poloxamers, hydroxypropyl cellulose, hydroxyethyl cellulose, and hydroxypropyl methylcellulose.

If a wet granulation process is used, the granulated composition is often dried prior to further processing. Examples of suitable drying processes to be used in connection with wet granulation are the same as those described above. Where the particles are made by a solvent process, the composition can be granulated prior to removal of residual solvent. During the drying process, residual solvent and granulation fluid are concurrently removed from the composition.

Once the particles have been granulated, they may then be milled to achieve the desired particle size. Examples of suitable processes for milling the granules include hammer milling, ball milling, fluid-energy milling, roller milling, cutting milling, and other milling processes known in the art.

ACTIVES

In one embodiment, a composition of the present invention comprises an active. The active can be any compound that can form an inclusion complex or otherwise associate with a cyclodextrin. Examples of suitable actives include pharmaceuticals, vitamins, nutriceuticals, agrochemical compounds, nutrients, fertilizers, pesticides, fungicides, botanical extracts, flavoring agents, fruit extracts, spices, cosmetics, coloring agents, pigments, and the like.

One particular class of actives that may benefit from the compositions of the present invention is pharmaceuticals, and in particular, unpleasant tasting drugs. The term "drug" is conventional, denoting a compound having beneficial prophylactic and/or therapeutic properties when administered to an animal, especially humans. Cyclodextrins can be used to taste mask unpleasant tasting drugs. Cyclodextrins form complexes with the drug in an aqueous environment that prevents contact of drug with the taste buds; often these complexes have improved taste over the uncomplexed drug. The compositions of the present invention comprising particles of amorphous cyclodextrin and a water-soluble polymer can be mixed with unpleasant tasting drugs to effectively taste-mask the drug. Tastemasking unpleasant drugs with the compositions of the present invention are disclosed in detail in co-pending U.S. Patent Application, Serial No. _____ (Attorney Docket No. PC25840), incorporated herein by reference.

Exemplary drugs that may be used with the current invention include, without limitation, inorganic and organic compounds that act on the peripheral nerves, adrenergic receptors, cholinergic receptors, nervous system, skeletal muscles, cardiovascular smooth muscles, blood circulatory system, synaptic sites, neuroeffector junctional sites, endocrine and hormone systems, immunological system, reproductive system, autocoid systems, alimentary and excretary systems, inhibitors of autocoids and histamine systems. Preferred classes of drugs include, but are not limited to, antacids, analgesics, anti¬anginals, anti-anxiety agents, antiarrhythmics, anti-bacterials, antibiotics, anti-diarrheals, anti-depressants, anti-epileptics, anti-fungals, anti-histamines, anti-hypertensives, anti-inflammatory agents, anti-virals, cardiac agents, contraceptives, cough suppressants, cytotoxics, decongestants, diuretics, drugs for genito-urinary disorders, drugs for use in parkinsonism and related disorders, drugs for use in rheumatic disorders, hypnotics, minerals and vitamins, lipid lowering drugs and sex hormones. Veterinary drugs may also be suitable for use with the present invention.

Each named drug should be understood to include the neutral form of the drug and pharmaceutically acceptable forms thereof. By "pharmaceutically acceptable forms" thereof is meant any

pharmaceutically acceptable derivative or variation, including stereoisomers, stereoisomer mixtures, enantiomers, solvates, hydrates, isomorphs, polymorphs, pseudomorphs, salt forms and prodrugs.

Specific examples of unpleasant-tasting drugs include acetaminophen, albuterol, aminoguanidine hydrochloride, aminophylline, amitriptyline, amoxicillin trihydrate, ampicillin, amlodipine besylate, aspirin, azithromycin, barbiturates, berberine chloride, caffeine, calcium carbonate, calcium pantothenate, cephalosporins, cetirizine, chloramphenicol, chlordiazepoxide, chloroquine, chlorpheniramine, chlorpromazine, cimetidine, ciprofloxacin, clarithromycin, codeine, demerol, dextromethorphan, digitoxin, digoxin, diltiazem hydrochloride, diphenhydramine, diphenylhydantoin, doxazosin mesylate, doxylamine succinate , eletriptan, enoxacin, epinephrine, erythromycin, ethylefrine hydrochloride, etinidine, famotidine, fluconazole, glipizide, guaifenesin, ibuprofen, indeloxazine hydrochloride, lidocaine, lomotil, loratadine, lupitidine, magnesium oxide, meclizine, methacholine, morphine, neostigmine, nifentidine, niperotidine, nizatidine, ofloxacin, paracetamol, pefloxacin, penicillin, phenobarbital, phenothiazine, phenylbutazone, phenylpropanolamine, pipemidic acid, pirbuterol hydrochloride , piroxicam , prednisolone, propranolol hydrochloride, pseudoephedrine, pyridonecarboxylic acid antibacterials, ranitidine, roxatidine, salicylic acid, sertaraline hydrochloride, sildenafil, spironolactone, sulbactam sodium, sulfonamides, sulfotidine, sulpyrine, sultamicillin tosylate , tenidap, terfenadine, theophylline, trimethoprim, tuvatidine, valdecoxib, zaltidine, and zonisamide.

Another class of actives that may benefit from the compositions of the present invention is "low solubility" drugs, meaning that the drug has a minimum aqueous solubility at physiologically relevant pH (e.g., pH 1-8) of about 0.5 mg/mL or less. Cyclodexthns can solubilize low-solubility drugs, enhancing the concentration of dissolved drug when administered to an aqueous environment of use. The, compositions of the present invention are preferred for low-solubility drugs having an aqueous solubility of less than about 0.1 mg/mL, more preferred for low-solubility drugs having an aqueous solubility of less than about 0.05 mg/mL, and even more preferred for low-solubility drugs having an aqueous solubility of less than about 0.01 mg/mL. In general, it may be said that the drug has a dose-to-aqueous solubility ratio greater than about 10 mL, and more typically greater than about 100 mL, where the aqueous solubility (mg/mL) is the minimum value observed in any physiologically relevant aqueous solution (e.g., those with pH values between 1 and 8) including USP simulated gastric and intestinal buffers, and dose is in mg. Thus, a dose-to-aqueous solubility ratio may be calculated by dividing the dose (in mg) by the aqueous solubility (in mg/mL).

Preferred classes of low-solubility drugs include, but are not limited to, antihypertensives, antianxiety agents, anticlotting agents, anticonvulsants, blood glucose-lowering agents, decongestants, antihistamines, antitussives, antineoplastics, beta blockers, anti-inflammatories, antipsychotic agents, cognitive enhancers, cholesterol-reducing agents, anti-atherosclerotic agents, antiobesity agents, autoimmune disorder agents, anti-impotence agents, antibacterial and antifungal agents, hypnotic agents, anti-Parkinsonism agents, anti-Alzheimer's disease agents, antibiotics, anti-depressants, antiviral agents, glycogen phosphorylase inhibitors, and cholesteryl ester transfer protein inhibitors.

Each named drug should be understood to include any pharmaceutically acceptable forms of the drug. Specific examples of antihypertensives include prazosin, nifedipine, amlodipine besylate, trimazosin and doxazosin; specific examples of a blood glucose-lowering agent are glipizide and chlorpropamide; a

specific example of an anti-impotence agent is sildenafil and sildenafil citrate; specific examples of antineoplastics include chlorambucil, lomustine and echinomycin; a specific example of an imidazole-type antineoplastic is tubulazole; a specific example of an anti-hypercholesterolemic is atorvastatin calcium; specific examples of anxiolytics include hydroxyzine hydrochloride and doxepin hydrochloride; specific examples of anti-inflammatory agents include betamethasone, prednisolone, aspirin, piroxicam, valdecoxib, carprofen, celecoxib, flurbiprofen and (+)-N-{4-[3-(4-fluorophenoxy)phenoxy]-2-cyclopenten-1-yl}-N-hyroxyurea; a specific example of a barbiturate is phenobarbital; specific examples of antivirals include acyclovir, nelfinavir, and virazole; specific examples of vitamins/nutritional agents include retinol and vitamin E; specific examples of beta blockers include timolol and nadolol; a specific example of an emetic is apomorphine; specific examples of a diuretic include chlorthalidone and spironolactone; a specific example of an anticoagulant is dicumarol; specific examples of cardiotonics include digoxin and digitoxin; specific examples of androgens include 17-methyltestosterone and testosterone; a specific example of a mineral corticoid is desoxycorticosterone; a specific example of a steroidal hypnotic/anesthetic is alfaxalone; specific examples of anabolic agents include fluoxymesterone and methanstenolone; specific examples of antidepression agents include sulpiride, [3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-(1-ethylpropyl)-amine, 3,5-dimethyl-4-(3'-pentoxy)-2-(2',4',6'-trimethylphenoxy)pyridine, pyroxidine, fluoxetine, paroxetine, venlafaxine and sertraline; specific examples of antibiotics include carbenicillin indanylsodium, bacampicillin hydrochloride, troleandomycin, doxycyline hyclate, ampicillin and penicillin G; specific examples of anti-infectives include benzalkonium chloride and chlorhexidine; specific examples of coronary vasodilators include nitroglycerin and mioflazine; a specific example of a hypnotic is etomidate; specific examples of carbonic anhydrase inhibitors include acetazolamide and chlorzolamide; specific examples of antifungals include econazole, terconazole, fluconazole, voriconazole, and griseofulvin; a specific example of an antiprotozoal is metronidazole; specific examples of anthelmintic agents include thiabendazole and oxfendazole and morantel; specific examples of antihistamines include astemizole, levocabastine, cetirizine, decarboethoxyloratadine and cinnarizine; specific examples of antipsychotics include ziprasidone, olanzepine, thiothixene hydrochloride, fluspirilene, risperidone and penfluridole; specific examples of gastrointestinal agents include loperamide and cisapride; specific examples of serotonin antagonists include ketanserin and mianserin; a specific example of an anesthetic is lidocaine; a specific example of a hypoglycemic agent is acetohexamide; a specific example of an anti-emetic is dimenhydrinate; a specific example of an antibacterial is cotrimoxazole; a specific example of a dopaminergic agent is L-DOPA; specific examples of anti-Alzheimer's Disease agents are THA and donepezil; a specific example of an anti-ulcer agent/H2 antagonist is famotidine; specific examples of sedative/hypnotic agents include chlordiazepoxide and triazolam; a specific example of a vasodilator is alprostadil; a specific example of a platelet inhibitor is prostacyclin; specific examples of ACE inhibitor/antihypertensive agents include enalaprilic acid and lisinopril; specific examples of tetracycline antibiotics include oxytetracycline and minocycline; specific examples of macrolide antibiotics include erythromycin, clarithromycin, and spiramycin; a specific example of an azalide antibiotic is azithromycin; specific examples of glycogen phosphorylase inhibitors include [R-(R*S*)]-5-chloro-N-[2-hydroxy-3-{methoxymethylamino}-3-oxo-1-(phenylmethyl)propyl-1H-indole-2-carboxamide and 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-(2R)-hydroxy-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl-)-3-oxypropyl]amide;

and specific examples of cholesteryl ester transfer protein (CETP) inhibitors include [2R.4S] 4-[(3,5-bis-trifluoromethyl-benzyO-methoxycarbonyl-arninol- 2-ethyl-β-trifluoromethyl-a^-dihydro^H-quinoline-i-carboxylic acid ethyl ester, [2R.4S] 4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester, [2R, 4S] 4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1 -carboxylic acid isopropyl ester, (2R)-3-[[3-(4-chloro-3-ethylphenoxy)phenyl][[3-(1 ,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1 ,1,1-trifluoro-2-propanol, the drugs disclosed in commonly owned U.S. Patent Application Serial Nos. 09/918,127 and 10/066,091, both of which are incorporated herein by reference in their entireties for all purposes, and the drugs disclosed in the following patents and published applications: DE 19741400 A1; DE 19741399 A1; WO 9914215 A1; WO 9914174; DE 19709125 A1; DE 19704244 A1; DE 19704243 A1; EP 818448 A1; WO 9804528 A2; DE 19627431 A1; DE 19627430 A1; DE 19627419 A1; EP 796846 A1; DE 19832159; DE 818197; DE 19741051; WO 9941237 A1; WO 9914204 A1; WO 9835937 A1; JP 11049743; WO 200018721; WO 200018723; WO 200018724; WO 200017164; WO 200017165; WO 200017166; EP 992496; and EP 987251 , all of which are hereby incorporated by reference in their entireties for all purposes.

Compositions of the present invention comprising a low-solubility drug and a plurality of particles, the particles comprising cyclodextrin and a water-soluble polymer, can enhance the concentration of the drug in an aqueous use environment. The term "enhance the concentration" means that the particles comprising cyclodextrin and a water-soluble polymer are present in a sufficient amount in the composition so as to improve the concentration of dissolved drug in an aqueous use environment relative to a control composition free from the particles. As used herein, a "use environment" can be either the *in vivo* environment of the GI tract, subdermal, intranasal, buccal, intrathecal, ocular, intraaural, subcutaneous spaces, vaginal tract, arterial and venous blood vessels, pulmonary tract or intramuscular tissue of an animal, such as a mammal and particularly a human, or the *in vitro* environment of a test solution, such as phosphate buffered saline (PBS), simulated intestinal buffer without enzymes (SIN), a Model Fasted Duodenal (MFD) solution, or a solution to model the fed state. Concentration enhancement may be determined through either *in vitro* dissolution tests or through *in vivo* tests. It has been determined that enhanced drug concentration in *in vitro* dissolution tests in such *in vitro* test solutions provide good indicators of *in vivo* performance and bioavailability. An appropriate PBS solution is an aqueous solution comprising 20 mM sodium phosphate (Na_2HPO_4), 47 mM potassium phosphate (KH_2PO_4), 87 mM NaCl, and 0.2 mM KCl, adjusted to pH 6.5 with NaOH. An appropriate SIN solution is 50 mM KH_2PO_4 adjusted to pH 7.4. An appropriate MFD solution is the same PBS solution wherein additionally is present 7.3 mM sodium taurocholic acid and 1.4 mM of 1-palmitoyl-2-oleyl-sn-glycero-3-phosphocholine. An appropriate solution to model the fed state is the same PBS solution wherein additionally is present 29.2 mM sodium taurocholic acid and 5.6 mM of 1-palmitoyl-2-oleyl-sn-glycero-3-phosphocholine. In particular, a composition of the present invention may be dissolution-tested by adding it to an *in vitro* test solution and agitating to promote dissolution.

In one aspect, a composition of the present invention, when dosed to an aqueous use environment, provides a maximum drug concentration (MDC) that is at least 1.25-fold the MDC provided by a control composition. In other words, if the MDC provided by the control composition is 100 mg/mL, then a composition of the present invention containing particles comprising cyclodextrin and a water-soluble polymer

provides an MDC of at least 125 mg/mL More preferably, the MDC of drug achieved with the compositions of the present invention are at least 2-fold, even more preferably at least 3-fold, and most preferably at least 5-fold that of the control composition.

The control composition is conventionally drug alone (e.g., typically, the crystalline drug alone in its most thermodynamically stable crystalline form, or in cases where a crystalline form of the drug is unknown, the control may be the amorphous drug alone) or the drug plus a weight of inert diluent equivalent to the weight of the particles used in the test composition. By inert is meant that the diluent is not concentration enhancing.

Alternatively, the compositions of the present invention provide in an aqueous use environment a concentration versus time Area Under the Curve (AUC), for any period of at least 90 minutes between the time of introduction into the use environment and about 270 minutes following introduction to the use environment that is at least 1.25-fold that of the control composition. More preferably, the AUC in the aqueous use environment achieved with the compositions of the present invention are at least 2-fold, more preferably at least 3-fold, and most preferably at least 5-fold that of a control composition.

Alternatively, the compositions of the present invention, when dosed orally to a human or other animal, provide an AUC in drug concentration in the blood plasma or serum that is at least 1.25-fold that observed when an appropriate control composition is dosed. Preferably, the blood AUC is at least about 2-fold, preferably at least about 3-fold, preferably at least about 4-fold, preferably at least about 6-fold, preferably at least about 10-fold, and even more preferably at least about 20-fold that of the control composition. It is noted that such compositions can also be said to have a relative bioavailability of from about 1.25-fold to about 20-fold that of the control composition. Thus, the compositions that, when evaluated, meet either the *in vitro* or the *in vivo,* or both, performance criteria are a part of this invention.

Alternatively, the compositions of the present invention, when dosed orally to a human or other animal, provide maximum drug concentration in the blood plasma or serum (C_{max}) that is at least 1.25-fold that observed when an appropriate control composition is dosed. Preferably, the blood C_{max} is at least about 2-fold, preferably at least about 3-fold, preferably at least about 4-fold, preferably at least about 6-fold, preferably at least about 10-fold, and even more preferably at least about 20-fold that of the control composition.

A typical *in vitro* test to evaluate enhanced drug concentration can be conducted by (1) administering with agitation a sufficient quantity of test composition (that is, the low solubility drug and a plurality of particles, the particles comprising cyclodextrin and a water-soluble polymer) in a test medium, such that if all of the drug dissolved, the theoretical concentration of drug would exceed the equilibrium concentration of the drug by a factor of at least 2; (2) in a separate test, adding an appropriate amount of control composition to an equivalent amount of test medium; and (3) determining whether the measured MDC and/or AUC of the test composition in the test medium is at least 1.25-fold that provided by the control composition. In conducting such a dissolution test, the amount of test composition or control composition used is an amount such that if all of the drug dissolved, the drug concentration would be at least 2-fold, preferably at least 10-fold, and most preferably at least 100-fold that of the aqueous solubility (that is, the equilibrium concentration) of the drug.

The concentration of dissolved drug is typically measured as a function of time by sampling the test medium and plotting drug concentration in the test medium vs. time so that the MDC and/or AUC can be ascertained. The MDC is taken to be the maximum value of dissolved drug measured over the duration of the test. The aqueous AUC is calculated by integrating the concentration versus time curve over any 90-minute time period between the time of introduction of the composition into the aqueous use environment (when time equals zero) and 270 minutes following introduction to the use environment (when time equals 270 minutes). Typically, when the composition reaches its MDC rapidly, in say less than about 30 minutes, the time interval used to calculate AUC is from time equals zero to time equals 90 minutes. However, if the AUC of a composition over any 90-minute time period described above meets the criterion of this invention, then the composition formed is considered to be within the scope of this invention.

To avoid drug particulates that would give an erroneous determination, the test solution is either filtered or centrifuged. "Dissolved drug" is typically taken as that material that either passes a 0.45 μm syringe filter or, alternatively, the material that remains in the supernatant following centrifugation. Filtration can be conducted using a 13 mm, 0.45 μm polyvinylidine difluoride syringe filter sold by Scientific Resources under the trademark TITAN®. Centrifugation is typically carried out in a polypropylene microcentrifuge tube by centrifuging at 13,000 G for 60 seconds. Other similar filtration or centrifugation methods can be employed and useful results obtained. For example, using other types of microfilters may yield values somewhat higher or lower (±10-40%) than that obtained with the filter specified above but will still allow identification of preferred dispersions. It is recognized that this definition of "dissolved drug" encompasses not only monomeric solvated drug molecules but also a wide range of species such as drug/cyclodextrin complexes, and other such drug-containing species that are present in the filtrate or supernatant in the specified dissolution test.

Alternatively, the compositions of the present invention, when dosed orally to a human or other animal, results in improved bioavailability or C_{max}. Relative bioavailability and C_{max} of drugs in the compositions can be tested *in vivo* in animals or humans using conventional methods for making such a determination. An *in vivo* test, such as a crossover study, may be used to determine whether a composition of the present invention provides an enhanced relative bioavailability or C_{max} compared with a control composition as described above. In an *in vivo* crossover study a test composition comprising a low-solubility drug and particles, the particles comprising cyclodextrin and a water-soluble polymer, is dosed to half a group of test subjects and, after an appropriate washout period (e.g., one week) the same subjects are dosed with a control composition that consists of an equivalent quantity of crystalline drug as the test composition (but with no cyclodextrin-containing particles present). The other half of the group is dosed with the control composition first, followed by the test composition. The relative bioavailability is measured as the concentration of drug in the blood (serum or plasma) versus time area under the curve (AUC) determined for the test group divided by the AUC in the blood provided by the control composition. Preferably, this test/control ratio is determined for each subject, and then the ratios are averaged over all subjects in the study. *In vivo* determinations of AUC and C_{max} can be made by plotting the serum or plasma concentration of drug along the ordinate (y-axis) against time along the abscissa (x-axis). The determination of AUCs and

C_{max} is a well-known procedure and is described, for example, in Welling, "Pharmacokinetics Processes and Mathematics," ACS Monograph 185 (1986).

FORMATION OF COMPOSITIONS

In one embodiment, the invention provides a composition comprising an active and a plurality of particles, the particles comprising cyclodextrin and a water-soluble polymer. The particles are substantially free of the active. The compositions of the present invention may be prepared by first forming the particles comprising the cyclodextrin and polymer and then dry- or wet-mixing the particles with the active. Mixing processes include physical processing as well as wet-granulation and coating processes.

For example, mixing methods include convective mixing, shear mixing, or diffusive mixing. Convective mixing involves moving a relatively large mass of material from one part of a powder bed to another, by means of blades or paddles, revolving screw, or an inversion of the powder bed. Shear mixing occurs when slip planes are formed in the material to be mixed. Diffusive mixing involves an exchange of position by single particles. These mixing processes can be performed using equipment in batch or continuous mode. Tumbling mixers (e.g., twin-shell) are commonly used equipment for batch processing. Continuous mixing can be used to improve composition uniformity.

Milling may also be employed to prepare the compositions of the present invention. Milling conditions are generally chosen that do not alter the physical form of the particles. Conventional mixing and milling processes suitable for use in the present invention are discussed more fully in Lachman, et al., *The Theory and Practice of Industrial Pharmacy* (3d Ed. 1986).

In addition to the physical mixtures described above, the compositions of the present invention may constitute any device or collection of devices that accomplishes the objective of delivering to the aqueous use environment both the particles and the active. For example, when the active is a pharmaceutical, the composition may be in the form of a dosage form in which the particles and active occupy separate regions within the dosage form. Thus, in the case of oral administration to a mammal, the dosage form may constitute a layered tablet wherein one or more layers comprise the particles and one or more other layers comprise the active.

Although the key ingredients present in the compositions of the present invention are simply the active and the cyclodextrin-containing particles, the inclusion of other excipients in the composition may be useful. These excipients may be included in the particles comprising the cyclodextrin and water-soluble polymer, or may be combined in the compositions with the active.

When the active is a pharmaceutical, conventional formulation excipients may be employed in the compositions of this invention, including those excipients well known in the art (e.g., as described in Remington's Pharmaceutical Sciences (20th ed. 2000)). Generally, excipients such as fillers, disintegrating agents, pigments, binders, lubricants, glidants, flavorants, and so forth may be used for customary purposes and in typical amounts without adversely affecting the properties of the compositions. Chewable tablets may be formulated using conventional tableting excipients such as diluents, swelling agents, anti-tack agents, binders, lubricants, flavorings and sweeteners.

In one embodiment the composition further comprises one or more tastemasking agents. Examples of taste masking agents include sweeteners such as aspartame, compressible sugar, dextrates, lactose, mannitol, maltose, sodium saccharin, sorbitol, and xylitol, and flavors such as banana, grape, vanilla, cherry, eucalyptus oil, menthol, orange, peppermint oil, raspberry, strawberry, and watermelon.

Examples of fillers or diluents include lactose, mannitol, xylitol, dextrose, sucrose, sorbitol, compressible sugar, microcrystalline cellulose, powdered cellulose, starch, pregelatinized starch, dextrates, dextran, dextrin, dextrose, maltodextrin, calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, magnesium carbonate, magnesium oxide, poloxamers, polyethylene oxide, and hydroxypropyl methyl cellulose.

Examples of surface active agents include sodium lauryl sulfate and polysorbate 80.

Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone (polyvinylpyrrolidone), methyl cellulose, microcrystalline cellulose, powdered cellulose, starch, pregelatinized starch, and sodium alginate.

Examples of tablet binders include acacia, alginic acid, carbomer, carboxymethyl cellulose sodium, dextrin, ethylcellulose, gelatin, guar gum, hydrogenatetd vegetable oil, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, liquid glucose, maltodextrin, polymethacrylates, povidone, pregelatinized starch, sodium alginate, starch, sucrose, tragacanth, and zein.

Examples of lubricants include calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc, and zinc stearate.

Examples of glidants include silicon dioxide, talc and cornstarch.

The composition may be incorporated into a pharmaceutical formulation that may be tasted, including sublingual tablets, chewable tablets, capsules, or unit dose packets, sometimes referred to in the art as "sachets" or "oral powders for constitution" (OPC); syrups; and suspensions. Solid dosage forms, such as chewable tablets for oral administration, are preferred.

One exemplary chewable tablet may be made as follows. First, a pharmaceutical may be combined with particles comprising a cyclodextrin and a water-soluble polymer, a filler such as compressible sugar, microcrystalline cellulose (Avicel PH 101 and Avicel CE), a disintegrant such as Ac-Di-Sol, flavorants, and colorants. These ingredients may be mixed, followed by addition of a lubricant such as magnesium stearate, and then followed by additional mixing. The tablet mixture may be compressed using an F-press and ½" flat-faced beveled edge tooling, resulting in tablets with a hardness of 7 to 9 kP.

Other features and embodiments of the invention will become apparent from the following examples, which are given for illustration of the invention rather than for limiting its intended scope.

EXAMPLES

Example 1

Particles containing β-cyclodextrin and the water-soluble polymer HPMC were prepared using the following procedure. A solution comprising 500 mg β-cyclodextrin and 500 mg hydroxypropyl methyl cellulose (HPMC E3 Prem from Dow) in 15 g deionized water was spray-dried using a "mini spray-drier". The solution was pumped into a "mini" spray-drying apparatus via a Cole Parmer 74900 series rate-controlling syringe pump at a rate of 24 mL/hr. The solution was atomized through a Spraying Systems Co. two-fluid nozzle, Model No. SU1A using a heated stream of nitrogen at a flow rate of 1 SCFM. The spray solution was sprayed into an 11-cm diameter stainless steel chamber. The heated gas entered the chamber at an inlet temperature of 70°C and exited at ambient outlet temperature. The resulting particles were collected on filter paper, dried under vacuum, and stored in a desiccator.

The crystalline β-cyclodextrin used to form the particles and the particles comprising amorphous β-cyclodextrin and HPMC were examined using powder X-ray diffraction with a Bruker AXS D8 Advance diffractometer to determine the amorphous character of the β-cyclodextrin in the particles. Samples (approximately 100 mg) were packed in Lucite sample cups fitted with Si(511) plates as the bottom of the cup to give no background signal. Samples were spun in the j plane at a rate of 30 rpm to minimize crystal orientation effects. The X-ray source (KCua, l = 1.54 A) was operated at a voltage of 45 kV and a current of 40 mA. Data for each sample were collected over a period of 27 minutes in continuous detector scan mode at a scan speed of 1.8 seconds/step and a step size of 0.047step. Diffractograms were collected over the 2Θ range of 4° to 30°. The results for the crystalline β-cyclodextrin are shown in FIG. 1, showing the characteristic sharp peaks associated with crystalline materials. The results for the amorphous β-cyclodextrin-containing particles are shown in FIG. 2. The 50:50 β-cyclodextrin:HPMC particles exhibited a diffraction pattern showing only an amorphous halo, and no sharp peaks characteristic of crystalline material. These data indicate that the β-cyclodextrin in the particles was amorphous and not crystalline.

Example 2

Example 1 is repeated except that the water-soluble polymer is hydroxyethyl cellulose (HEC).

Example 3

Example 1 is repeated except that the water-soluble polymer is hydroxypropyl methyl cellulose acetate succinate (HPMCAS).

Example 4

Example 1 is repeated except that the water-soluble polymer is poloxamer 407.

Example 5

Example 1 is repeated except that the water-soluble polymer is sodium carboxymethyl cellulose.

The terms and expressions which have been employed in the foregoing specification are used therein as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding equivalents of the features shown and described or portions thereof, it being recognized that the scope of the invention is defined and limited only by the claims which follow.

We claim:

1. A composition comprising a plurality of particles, each of said particles comprising a cyclodextrin and a water-soluble polymer, wherein said cyclodextrin is in intimate contact with said water-soluble polymer, and wherein at least a major portion of said cyclodextrin is amorphous.

2. The composition of claim 1 further comprising an active, and wherein said particles are substantially free of an active.

3. The composition of claims 1 or 2 wherein said water-soluble polymer is selected from the group consisting of neutral non-cellulosic polymers, ionizable non-cellulosic polymers, neutral cellulosic polymers, and ionizable cellulosic polymers.

4 The composition of claim 3 wherein said water-soluble polymer is selected from the group consisting of polyvinyl alcohols, polyvinyl pyrrolidone, poloxamers, polymethacrylates and polyacrylates, gelatin, hydroxypropyl methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate, carboxymethyl ethyl cellulose, and sodium carboxymethyl cellulose.

5. The composition of claim 4 wherein said water-soluble polymer is hydroxypropyl methyl cellulose.

6. The composition of claims 1 or 2 wherein said cyclodextrin is selected from the group consisting of *a-,* β- and γ-cyclodextrins.

7. The composition of claim 6 wherein said cyclodextrin is β-cyclodextrin.

8. The composition of claim 2 wherein said active is selected from the group consisting of pharmaceuticals, vitamins, nutriceuticals, agrochemical compounds, nutrients, fertilizers, pesticides, fungicides, botanical extracts, flavoring agents, fruit extracts, spices, cosmetics, coloring agents, and pigments.

9. The composition of claim 8 wherein said active is a pharmaceutical.

10. The composition of claim 9 wherein said pharmaceutical is an unpleasant tasting drug.

11. The composition of claim 9 wherein said pharmaceutical is a low-solubility drug.

12. A process for making a plurality of particles, each of said particles comprising a cyclodextrin and a water-soluble polymer, the process comprising:

(a) forming a solution comprising a cyclodextrin, a water-soluble polymer, and a solvent;

(b) rapidly removing said solvent from said solution to form a solid; and

(c) forming particles from said solid;

wherein at least a major portion of the cyclodextrin in said particles is amorphous.

13. The process of claim 12 wherein step (b) is performed by a process selected from the group consisting of spray-drying, spray-coating, evaporation, lyophilization, and precipitation.

14. The process of claim 13 wherein step (b) is performed by spray drying.

15. The product of the process of any one of claims 12 to 14.

FIG. 1

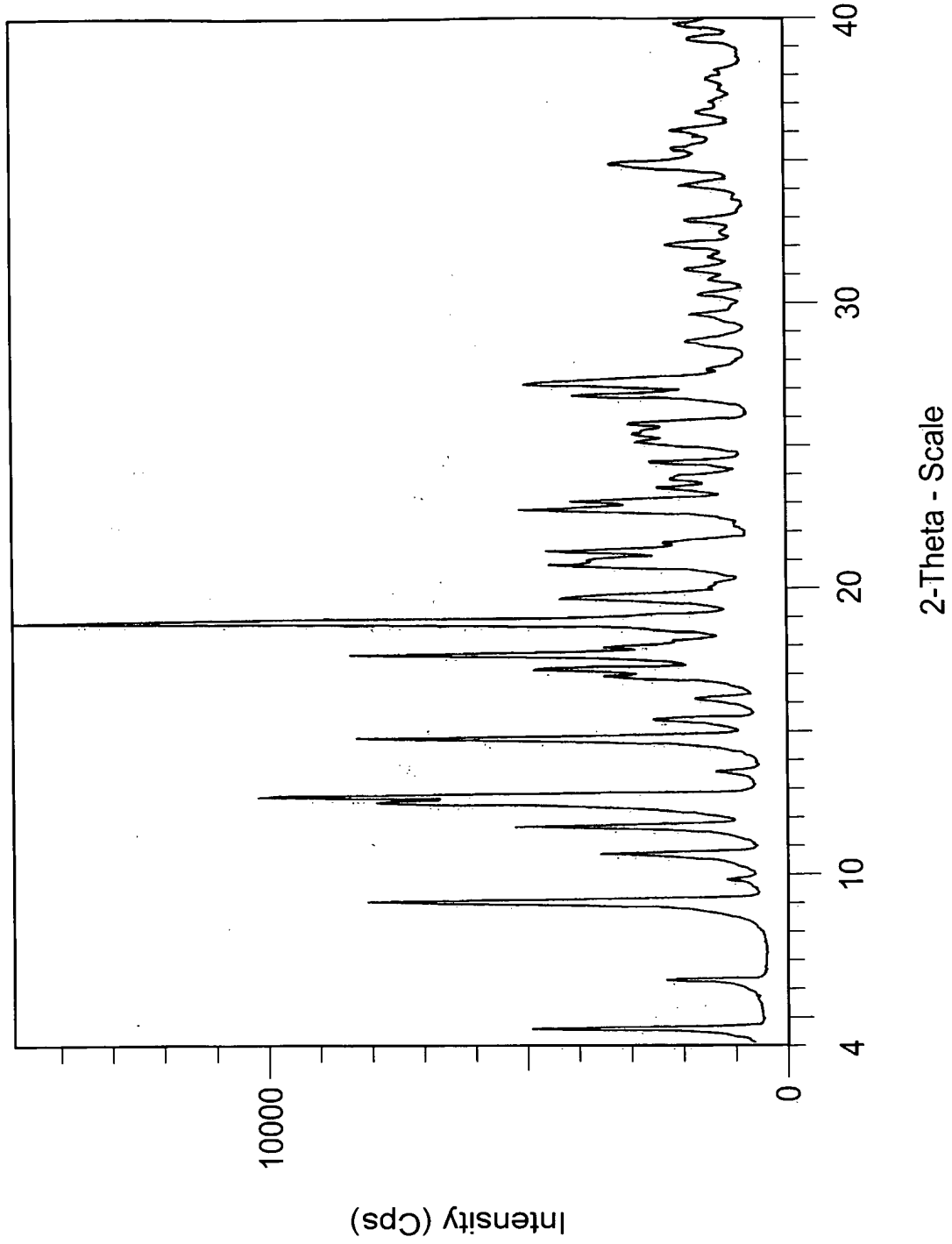
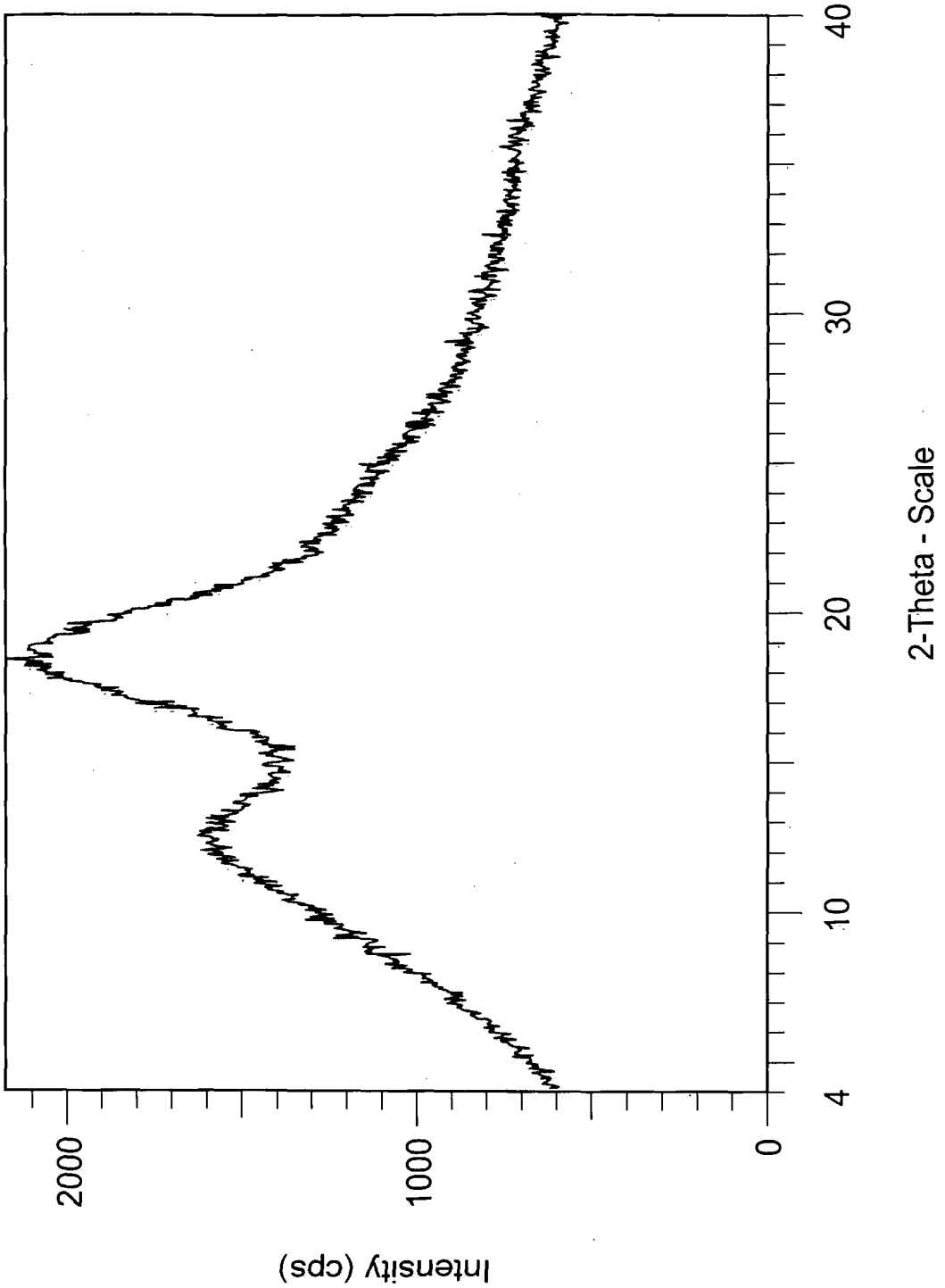


FIG. 2



INTERNATIONAL SEARCH REPORT

PCT/IB2005/002190

A. CLASSIFICATION OF SUBJECT MATTER
A61K47/40 A61K47/38 A61K47/48 C08B37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

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

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

EPO-Internal , BIOSIS, PAJ, **EMBASE, CHEM ABS Data**

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X,Y	WO 03/089008 A (NOVARTIS AG; NOVARTIS PHARMA GMBH; SZENTE, LAJOS; SZEJTLI, JOZSEF; KIS) 30 October 2003 (2003-10-30) the whole document page 1, paragraph 1 page 2, paragraphs 2,3 page 8, paragraph 5 examples 1,4,5,15 page 19 claims 1,21,23	1-15
X,Y	US 5 472 954 A (LOFTSSON ET AL) 5 December 1995 (1995-12-05) the whole document column 1, lines 18-23 example 13 claim 1	1-15

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[X] Further documents are listed in the continuation of box C

[X] Patent family members are listed in annex

° Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 November 2005	05/12/2005

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	WO 02/09782 A (AVERY DENNISON CORPORATION; LIPMAN, ROGER, DAVID, ARNOLD) 7 February 2002 (2002-02-07) the whole document page 1, paragraph 1 examples 1,2 pages 21-23; examples 5,6 claim 1	1-15
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(54) Title: INCLUSION COMPLEX

(57) Abstract: The invention relates to an inclusion complex of olopatadine or its pharmaceutically acceptable salt and hydroxyalkyl-ß-cylcodextrin, preferably hydroxypropyl-ß-cylcodextrin. The present invention also relates to an aqueous topical solution comprising a therapeutically effective amount of olopatadine or its pharmaceutically acceptable salt; hydroxyalkyl-ß-cylcodextrin, preferably hydroxypropyl-ß-cylcodextrin and hydroxypropyl methylcellulose in an amount sufficient to enhance the physical stability of the solution.

WO 2008/015695 A2

INCLUSION COMPLEX

FIELD OF THE INVENTION

The present invention relates to inclusion complex of olopatadine in cyclodextrin and to aqueous solutions of olopatadine or its pharmaceutically acceptable salt for topical administration and process for preparation thereof.

BACKGROUND OF THE INVENTION

Olopatadine hydrochloride is a carboxylic acid derivative of doxepin, chemically described as (Z)-11-[3-(Dimethylamino) propylidene]-6,11-dihydrodibenz [b,e]oxepin-2-acetic acid hydrochloride [$C_{21}H_{23}$ NO_3 .HCl], as disclosed in U.S. Pat Nos.4,871,865 and 4,923,892, both assigned to Burroughs Wellcome. Olopatadine has antihistaminic and antiasthmatic activity.

Olopatadine hydrochloride is commercially available in the U.S as 0.1% and 0.2% sterile ophthalmic solutions under the brand names PATANOL® and PATADAY® respectively, both marketed by Alcon. PATANOL® is indicated for the treatment of signs and symptoms of allergic conjunctivitis and the approved ophthalmic solution contains olopatadine hydrochloride equivalent to 0.1% olopatadine, 0.01% benzalkonium chloride as preservative, dibasic sodium phosphate, sodium chloride, hydrochloric acid and / or sodium hydroxide (to adjust the pH) and purified water. It has a pH of about 7, and osmolality of about 300mOsm/kg. PATADAY® is indicated for the treatment of ocular itching associated with allergic conjunctivitis and the approved ophthalmic solution contains olopatadine hydrochloride equivalent to 0.2% olopatadine, 0.01% benzalkonium chloride as preservative, povidone, dibasic sodium phosphate, sodium chloride, edetate disodium, hydrochloric acid and / or sodium hydroxide (to adjust the pH) and purified water. It has a pH of about 7, and osmolality of about 300mOsm/kg.

One obstacle for preparing olopatadine hydrochloride aqueous solutions for topical delivery is the stability of the aqueous solutions of olopatadine hydrochloride over the storage period. Olopatadine aqueous solutions having a concentrations of 0.17%w/v or higher were found to be

unstable over extended storage periods. The olopatadine hydrochloride precipitates or crystallizes out of the solution when used in concentrations higher than 0.17%w/v. Hence, there is a need for preparing aqueous solutions of olopatadine hydrochloride containing olopatadine in concentrations of about 0.17%w/v or greater, which are stable when stored over the shelf life of the product.

United States Patent No.6,995,186 (Alcon Inc., 2006, the '186 patent) discloses topically administrable solution composition for treating allergic or inflammatory disorders of the eye and nose comprising olopatadine and a polymeric ingredient, where the polymeric ingredient is a polymeric physical stability enhancing ingredient consisting essentially of polyvinylpyrrolidone or polystyrene sulfonic acid in an amount sufficient to enhance the physical stability of the solution, and wherein the composition does not contain polyvinyl alcohol, polyvinyl acrylic acid, hydroxypropyl methyl cellulose, sodium carboxymethyl cellulose, xanthan gum. Polyvinyl alcohol, polyvinyl acrylic acid, hydroxypropyl methylcellulose, sodium carboxy methyl cellulose and xanthan gum have been disclosed in the '186 patent to cause physical instability of olopatadine solutions.

In order to overcome the physical stability problems associated with olopatadine aqueous solutions, we have tried various ingredients selected from hydroxypropyl-β-cyclodextrin (HPβCD), polysorbate 20, polysorbate 80, propylene glycol, hydroxypropyl methylcellulose 2910 (HPMC E4M premium), polyvinylpyrrolidone K-30, xanthan gum, sodium carboxymethylcellulose (Sodium CMC), carbopol 934P, polyvinyl alcohol and mixtures thereof.

We have now surprisingly found that stable aqueous topical solutions of olopatadine hydrochloride can be prepared by forming an inclusion complex with a hydroxyalkyl clodextrin, preferably hydroxypropyl-β-cyclodextrin (HPβCD). Optionally, hydroxypropyl methylcellulose (HPMC) may be used to stabilize the inclusion complex in the pharmaceutical composition.

SUMMARY OF THE INVENTION

In one aspect of the invention, there is provided an inclusion complex of olopatadine or its pharmaceutically acceptable salt and a hydroxyalkyl cyclodextrin, preferably hydroxypropyl-β-cyclodextrin.

In another aspect of the invention, there is provided an aqueous topical solution comprising a therapeutically effective amount of olopatadine or its pharmaceutically acceptable salt; hydroxyalkyl β-cylcodextrin, preferably hydroxypropyl β-cylcodextrin and hydroxypropyl methyl cellulose in amount sufficient to enhance the physical stability of the solution.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides an inclusion complex of olopatadine or its pharmaceutically acceptable salt and hydroxyalkyl-β-cyclodextrin, particularly hydroxypropyl-β-cyclodextrin. The present invention also provides an aqueous topical solution, comprising a therapeutically effective amount of olopatadine or its pharmaceutically acceptable salt; hydroxyalkyl-β-cyclodextrin, particularly hydroxypropyl-β-cyclodextrin and hydroxypropyl methylcellulose in an amount sufficient to enhance the physical stability of the solution.

Unless indicated otherwise, all component concentrations are presented on a %(w/v) basis and all reference to olopatadine are to olopatadine free base.

The term "in an amount sufficient to enhance the physical stability of the solution", as used herein means that the amount of hydroxyalkyl-β-cyclodextrin, particularly hydroxypropyl-β-cyclodextrin is sufficient to form a complex with olopatadine or its pharmaceutically acceptable salt and thus keep it in solution, i.e. Prevent its precipitation or crystallization.

According to one embodiment of the present invention, the aqueous topical solution contains olopatadine or its pharmaceutically acceptable salts. Examples of the pharmaceutically acceptable salts of olopatadine include inorganic acid salts such as hydrochloride, hydrobromide, sulfate and phosphate; organic acid salts such as acetate, maleate, fumarate, tartrate and citrate; alkali metal salts such as sodium salt and potassium salt; alkaline earth metal salts such as magnesium salt and calcium salt; metal salts such as aluminum salt and zinc salt; and organic amine addition salts such as triethylamine addition salt (also known as tromethamine), morpholine addition salt and piperidine addition salt. In a preferred embodiment of the present invention, the olopatadine for use in the aqueous topical solution is a hydrochloride salt. In a most preferred embodiment of the present invention, the olopatadine hydrochloride salt may be used in concentrations such that it is equivalent to the olopatadine free base in amount ranging from about 0.17% to about 0.62%. Preferably, the solution formulations intended for use in the eye contain about 0.17% to about 0.25% olopatadine and the solution formulations intended for use in the nose contain about 0.35% to about 0.62% olopatadine.

According to one embodiment of the present invention, the aqueous topical solution comprises cyclodextrin to enhance the physical stability of the solution. Cyclodextrins are a group of structurally related saccharides which are formed by enzymatic cyclization of starch by a group of amylases termed glycosyltransferases. Cyclodextrins are cyclic oligosaccharides, consisting of (alpha-1,4)-linked alpha-D-glucopyranose units, with a lipophilic central cavity and a hydrophilic outer surface. In aqueous solutions, cyclodextrins form inclusion complexes with many drugs through a process in which the water molecules located in the central cavity are replaced by either the whole drug molecule, or more frequently, by some lipophilic portion of the drug structure. Once included in the cyclodextrin cavity, the drug molecules may be dissociated through complex dilution, by replacement of the included drug by some other suitable molecule or, the drug may be transferred to the matrix for which it has the highest affinity. Importantly, since no covalent bonds are formed or broken during the drug-cyclodextrin complex formation, the complexes are in dynamic equilibrium with free drug and cyclodextrin molecules. In solution, the complexes are usually prepared by addition of an excess amount of the drug to an aqueous cyclodextrin solution. The most common naturally occurring cyclodextrins are alpha-

cyclodextrin, β-cyclodextrin and gamma-cyclodextrin consisting of 6, 7 and 8 glucopyranose units, respectively and their derivatives. β-cyclodextrin appears to be the most useful pharmaceutical complexing agent due to its cavity size, availability and low cost. Examples of cyclodextrin derivatives that may be used in the pharmaceutical compositions of present invention include the hydroxypropyl derivatives of alpha-, beta- and gamma-cyclodextrin, sulfoalkylether cyclodextrins such as sulfobutylether beta-cyclodextrin, alkylated cyclodextrins such as the randomly methylated beta-cyclodextrin, and various branched cyclodextrins such as glucosyl- and maltosyl beta-cyclodextrin, and the like, and mixtures thereof.

The preferred cyclodextrins for use in the present invention include alkyl cyclodextrins, hydroxy alkyl cyclodextrin, such as hydroxy propyl beta-cyclodextrin, carboxy alkyl cyclodextrins and sulfoalkyl ether cyclodextrin, such as sulfo butyl ether beta-cyclodextrin. Examples of suitable cyclodextrins for use in the present invention non-exclusively include alpha-cyclodextrin; beta-cyclodextrin; gamma-cyclodextrin; methyl alpha-cyclodextrin; methyl beta-cyclodextrin; methyl gamma-cyclodextrin; ethyl beta-cyclodextrin; butyl alpha-cyclodextrin; butyl beta-cyclodextrin; butyl gamma-cyclodextrin; pentyl gamma-cyclodextrin; hydroxyethyl beta-cyclodextrin; hydroxyethyl gamma-cyclodextrin; 2-hydroxypropyl alpha-cyclodextrin; 2-hydroxypropyl beta-cyclodextrin; 2-hydroxypropyl gamma-cyclodextrin; 2-hydroxybutyl beta-cyclodextrin; acetyl alpha-cyclodextrin; acetyl beta-cyclodextrin; acetyl gamma-cyclodextrin; propionyl beta-cyclodextrin; butyryl beta-cyclodextrin; succinyl alpha-cyclodextrin; succinyl beta-cyclodextrin; succinyl gamma-cyclodextrin; benzoyl beta-cyclodextrin; palmityl beta-cyclodextrin; toluenesulfonyl beta-cyclodextrin; acetyl methyl beta-cyclodextrin; acetyl butyl beta-cyclodextrin; glucosyl alpha-cyclodextrin; glucosyl beta-cyclodextrin; glucosyl gamma-cyclodextrin; maltosyl alpha-cyclodextrin; maltosyl beta-cyclodextrin; maltosyl gamma-cyclodextrin; alpha-cyclodextrin carboxymethylether; beta-cyclodextrin carboxymethylether; gamma-cyclodextrin carboxymethylether; carboxymethylethyl beta-cyclodextrin; phosphate ester alpha-cyclodextrin; phosphate ester beta-cyclodextrin; phosphate ester gamma-cyclodextrin; 3-trimethylammonium-2-hydroxypropyl beta-cyclodextrin; sulfobutyl ether beta-cyclodextrin; carboxymethyl alpha-cyclodextrin; carboxymethyl beta-cyclodextrin; carboxymethyl gamma-cyclodextrin, and combinations thereof. The most preferred cyclodextrin for use in the

pharmaceutical composition of the present invention is hydroxy propyl beta-cyclodextrin. In a preferred embodiment of the present invention, hydroxypropyl beta-cyclodextrin may be used in concentrations ranging from about 0.1% to about 20%w/v of the composition, and more preferably used in concentrations ranging from about 1.0% to about 10% w/v of the composition. Generally, for solutions meant for ophthalmic administration preferable concentration of hydroxypropyl beta-cyclodextrin is in the range from about 1.0% to about 5%; for solutions meant for nasal administration, the concentration of hydroxypropyl beta-cyclodextrin is in the range from about 1.0% to about 10%.

Olopatadine or its pharmaceutically acceptable salt, according to the present invention, forms an inclusion complex with cyclodextrins, particularly hydroxyalkyl-β-cyclodextrin, more particularly hydroxypropyl-β-cyclodextrin . The term "inclusion complex" as used herein refers to a combination of olopatadine or its pharmaceutically acceptable salt as defined above and a cyclodextrin wherein the olopatadine or its pharmaceutically acceptable salt or a portion thereof is associated with the cyclodextrin. Typically, the olopatadine or its pharmaceutically acceptable salt or guest molecule, is included within the cavity of the cyclodextrin, or the host molecule, wherein the cavity of the cyclodextrin is the space created by the cyclodextrin torous and the cyclodextrin substituents. The ratio of olopatadine or its pharmaceutically acceptable salt to hydroxypropyl β-cylcodextrin in the inclusion complex is from about 1:1.65 to about 1:50 by weight. The amount of hydroxypropyl β-cylcodextrin present in the inclusion complex is sufficient to enhance the physical stability of the olopatadine solution.

According to one embodiment of the present invention, the composition further includes hydroxypropyl methylcellulose (HPMC). The hydroxypropyl methylcellulose (HPMC) used in the composition acts as a stabilizer for the inclusion complex of hydroxypropyl beta-cyclodextrin and olopatadine or its pharmaceutically acceptable salt. Various grades of hydroxypropyl methylcellulose (available from Dow Chemical, U.S.A under the METHOCEL trademark) may be used in the present invention. The grades commercially available are categorized depending upon the chemical substitution and hydration rates, and may be used in the compositions of the present invention. Hydroxypropyl methylcellulose having a methoxy content of 19-24 % and

hydroxypropyl content of 7-12 % with a fastest relative rate of hydration is available commercially under the brand name of Methocel Grade K. Hydroxypropyl methylcellulose with 28-30 % methoxy content and 7-12 % of hydroxypropyl content with a faster relative hydration rate as compared to the above grade is available commercially under the brand name of Methocel Grade E. Hydroxypropyl methylcellulose with 27-30 % methoxy content and 4.0 - 7.5 % of hydroxypropyl content with a slow relative hydration rate is available as Methocel F grade and that with 27.5-31.5 % methoxy content and 0 % hydroxypropyl content and with slowest rate of hydration is available as Methocel Grade A. In a preferred embodiment of the present invention, hydroxypropyl methylcellulose, a 2%w/v aqueous solution of which has a viscosity of 4000 cps at 20°C, and which is commercially available as METHOCEL E4M, is used. In preferred embodiments of the present invention, hydroxypropyl methylcellulose may be used concentrations ranging from about 0.001% to about 5%, and more preferably in concentrations ranging from about 0.01% to about 1 % w/v.

The aqueous topical solution of the present invention may include an effective amount of an antimicrobial preservative. Examples of pharmaceutically acceptable preservatives that may be used in the present invention include, but are not limited to, benzethonium chloride, butylparaben, methyl paraben, ethyl paraben, propyl paraben, benzalkonium chloride, cetyl pyridinium chloride, thimerosal, chlorobutanol, phenylethyl alcohol, benzyl alcohol, potassium sorbate, sodium benzoate, sorbic acid and the like and mixtures thereof. The preferred preservative for the aqueous topical solution of the present invention is benzalkonium chloride. It may be used in an amount ranging from about 0.005% to about 1%w/v.

The aqueous topical solution of the present invention may include an effective amount of a chelating agent. Chelating agents remove trace amounts of metal ions such as iron, copper and lead and act as antioxidants, as otherwise these heavy metals catalyze oxidation reactions. Presently preferred chelating agents include different salts of edetic acid. These non-exclusively include edetate disodium, edetate calcium disodium, edetate tetrasodium, edetate trisodium, and the like and mixtures thereof. The preferred chelating agent for the aqueous topical solution of

the present invention is disodium edetate. It may be present in the concentrations ranging from about 0.005% to about 0.1% w/v.

The aqueous topical solution of the present invention may further include an effective amount of a tonicity agent. Examples of tonicity agents that may be used in the aqueous topical solution of the present invention include all pharmaceutically acceptable and pharmacologically inert water-soluble compounds referred to in the pharmacopoeias such as United States Pharmacopoeia, as well as in Remington: The Science and Practice of Pharmacy; edition 19; Mack Publishing Company, Easton, Pennsylvania (1995). Preferred tonicity agent is sodium chloride, which may be added in an amount which renders the solution isoosmotic. The aqueous topical solution is intended to be administered as nasal solution or eye drops. The osmolality may be adjusted preferably between 150 to 450 mOsm, and more preferably between 250 to 350 mOsm.

The aqueous topical solution of the present invention may include an effective amount of buffering agent. The buffering agents are included to minimize any change in pH during shelf life of the aqueous topical solution. Examples of buffering agents include, but are not limited to, lactic acid, citric acid, tartaric acid, phosphoric acid, acetic acid, hydrochloric acid, nitric acid, tromethamine, sodium or potassium metaphosphate, sodium or potassium phosphate, dibasic sodium phosphate dodecahydrate, sodium or potassium acetate, ammonia, sodium carbonate, sodium or potassium hydroxide, dibasic sodium phosphate, sodium borate, and the like and mixtures thereof. Strong mineral acids like hydrochloric acid or strong bases such as sodium hydroxide may be used for adjusting pH. The aqueous topical solution intended for ophthalmic administration has a pH 4 to 8, preferably pH of 6.5 to 7.5, and most preferably a pH of 6.8 to 7.2. The aqueous topical solution intended for nasal administration has a pH of 3.0 to 6.0, and most preferably a pH of 3.5 to 5.0.

The aqueous topical solution of the present invention may optionally include an effective amount of an antioxidant. The antioxidant may be one or more antioxidants, reducing agents and antioxidant synergist, and may be selected from acetyl cysteine, alpha tocopherol acetate, d-alpha tocopherol, dl-alpha tocopherol, ascorbyl palmitate, butylated hydroxyanisole (BHA),

butylated hydroxytoluene (BHT), cysteine, cysteine hydrochloride, propyl gallate, ascorbic acid, calcium ascorbate, calcium bisulphate, calcium sulphite, ascorbic acid, isoascorbic acid, potassium metabisulfite, sodium ascorbate, sodium bisulphate, sodium metabisulphite, sodium sulphite, sodium thiosulphate, thioglycerol, citric acid , edetic acid(EDTA) and its salts, hydroxyquinoline sulphate, phosphoric acid, sodium citrate and tartaric acid. The antioxidants may be used in amounts conventional to the pharmaceutical art.

The aqueous topical solution of the present invention may optionally include an effective amount of viscosity enhancer. An increase in viscosity of topical solutions will result in a longer residence time in eye or nose, providing a longer time for drug absorption and effect. The list of viscosity enhancers that are conventionally used for topical solutions are given in the pharmacopoeias such as United States Pharmacopoeia, as well as in Remington: The Science and Practice of Pharmacy; edition 19; Mack Publishing Company, Easton, Pennsylvania (1995). The viscosity enhancers may be used in concentrations conventional to the pharmaceutical art.

The aqueous topical solution of the present invention is chemically stable. The term "chemically stable" as used herein means that the aqueous topical solution when stored on the shelf for up to two years has less than 2% total degradation products as determined by the area normalization method. The chemical stability may be assessed by accelerated stability testing. The aqueous topical solution of the present invention may be stored in a closed container at 30°C / 65% relative humidity or 40°C / 75% relative humidity or 2-8°C (refrigeration condition) and analyzed at one month duration for up to three months or six months. It is generally accepted that a product is stable on the shelf over a period of two years, if the product is stable for three months at an accelerated stability test condition of 40°C / 75% relative humidity.

The term "physical stability" as used herein means that when aqueous topical solution of the present invention are stored in a closed container crystals of olopatadine do not appear.

The chemical stability is assessed by evaluating the percent total degradation of olopatadine aqueous topical solutions that are subjected to accelerated stability test conditions and ambient

conditions using high performance liquid chromatography (HPLC). The chromatographic conditions for analyzing the degradation of olopatadine and the procedure for calculating the percent total degradation products in olopatadine aqueous topical solution is given below:

Column	: Hypersil BDS C_8 (250 X 4.6)
Flow rate	: 1.0 ml/min
Temperature	: Ambient
Detection	: 210 nm
Concentration	: 50/65 ppm
Injection volume	: 20µl
Run time	: 40 min
Mobile Phase	: Buffer : Acetonitrile (720 : 280)
	Buffer : 6.8 gm KH_2PO_4 is dissolved in 1000ml of water and the solution is adjusted to a pH of 4.5 with orthophosphoric acid.
Retention time	: 10.5 min
Diluent	: Mobile phase
Standard preparation	: 50/65 mg olopatadine HCl is dissolved in 100 ml with mobile phase. A sample of 5 ml is diluted to 50 ml with mobile phase
Test preparation	: 2 ml of the olopatadine HCl solution is diluted with 200 ml of mobile phase

The percent total degradation products in the olopatadine aqueous topical solution is calculated by area normalization method (excluding peaks from placebo and diluent, if any) from the chromatogram obtained by injecting 20µl of test preparation as described above in chromatographic conditions for analyzing degradation of olopatadine. The formula for calculating the percent total degradation products in olopatadine aqueous topical solution is given below:

$$\% \text{ Individual degradation product} = \frac{\text{Peak area of individual degradation product}}{\text{Total area of all the peaks}} \times 100$$

10

% Total degradation products = Sum of all % individual degradation products

For finished dosage forms (for example - solutions) the value of percent individual degradation product should not be more than 1% and the percent total degradation products should not be more than 2%. A value of percent total degradation products lesser than 2% in the aqueous topical solution of the present invention is considered to be acceptable.

According to one embodiment of the present invention, the aqueous topical solution may be prepared by the following process:

a. Dissolving hydroxypropyl-β-cyclodextrin(HPβCD) in water for injection till clear solution is formed.
b. Dissolving tonicity agent, buffering agent, chelating agent and antimicrobial preservative in the bulk solution of step (a) and stirring to get clear solution.
c. Dissolving olopatadine hydrochloride in water for injection and adding to the solution of step (a).
d. Adjusting pH of the solution between 3.5-5.0 for nasal solution, and between 6.8-7.2 for ophthalmic solution with 0.1N hydrochloric acid and 0.1N sodium hydroxide.
e. Final adjustment of volume with water for injection and measuring pH.
f. Filtering of the solution through 2μm prefilter and then through 0.2μm nylon 66 membrane filter, and transferring the solutions to sterile containers.

The aqueous topical solution of the present invention may be formulated to be dispensed in suitable containers as drops, sprays, metered sprays, aerosols and metered aerosols. The aqueous topical solution to be delivered as nasal spray may be filled in containers fitted with a spray pump with or without a metering valve. The aqueous topical solution to be delivered as aerosol may be filled into canisters suitable for delivering pharmaceutical aerosols. Canisters generally comprise a container capable of withstanding the vapour pressure of the propellant used such as a plastic or plastic-coated glass bottle, or preferably a metal can, for example an aluminium can which may optionally be anodized, lacquer-coated and / or plastic-coated, which container is

closed with a metering valve. The metering valves are designed to deliver a metered amount of the aqueous solution per actuation, and have a gasket to prevent leakage of propellant through the valve. In a preferred embodiment of the present invention, the aqueous topical solution is packed in opaque plastic or glass containers. In a more preferred embodiment of the present invention, the container for an ophthalmic solution is an opaque, white low-density polyethylene container that has been sterilized using ethylene oxide like lupolen bottle. In another preferred embodiment of the present invention, the container for a nasal solution is a U.S.P type I amber color glass container equipped with a suitable nasal spray pump.

It will be understood by those of skill in the art that numerous and various modifications can be made without departing from the spirit of the present invention. Therefore, it should be clearly understood that the following examples are illustrative only and are not intended to limit the scope of the present invention.

COMPARATIVE EXAMPLES A-M

The compositions shown in table 1 and table 2 below were prepared and subjected to stability studies for evaluating the physical stability. The vials were studied for stability at two temperature conditions: one at room temperature ($25^0 \pm 2^0$C) and the other at refrigeration temperature (2-8^0C) condition.

Table 1

Ingredients	Comparative Examples A-H							
	A	B	C	D	E	F	G	H
	Concentration (%w/v)							
Olopatadine hydrochloride	0.527	0.527	0.527	0.527	0.527	0.527	0.527	0.665
Polysorbate 20	0.005	-	-	-	-	-	-	-
Polysorbate 80	-	0.005	0.01	-	-	-	-	-
Propylene glycol	0.05	-	0.05	1.50	0.05	-	-	-
Hydroxypropyl methylcellulose (2910 E4M premium)	-	-	-	-	-	0.10	0.25	0.10
Polyvinyl pyrrolidone K-30	-	-	-	-	-	-	-	2.00
Sodium chloride	-	0.60	-	-	-	0.60	0.80	0.30
Benzalkonium chloride (50%)	0.02	0.02	0.02	-	0.02	0.02	0.02	0.02
Disodium edetate	-	-	-	-	-	-	-	0.01
Dibasic sodium phosphate dodecahydrate	0.20	0.06	0.50	0.50	0.25	0.25	0.15	0.10
NaOH /HCl	pH 4.5 -5.0	pH 4.5 -5.0	pH 4.5 -5.0	pH 4.5 -5.0	pH 4.5 -5.0	pH 4.5 -5.0	pH 3.5 -5.0	pH 3.5 -5.0
Water for Injection	q.s100 ml	q.s100 ml	q.s100 ml	q.s100 ml	q.s100 ml	q.s100 ml	q.s10 0 ml	q.s100 ml

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Table 2

Ingredients	Comparative Examples I-M				
	I	J	K	L	M
	Concentration (%w/v)				
Olopatadine hydrochloride	0.527	0.527	0.527	0.527	0.527
Xantham gum	0.10	-	-	-	-
Sodium CMC	-	0.10		-	-
Carbopol 934P	-	-	0.10		-
Polyvinyl alcohol	-	-	-	2.00	-
Sodium chloride	0.80	0.80	0.80	0.60	0.20
Benzalkonium chloride(50%)	0.02	0.02	0.02	0.02	0.02
Dibasic sodium phosphate anhydrous	0.15	0.15	0.15	0.15	-
NaOH /HCl	pH 3.5 -5.0	pH 3.5 –5.0	pH 3.5 –5.0	pH 3.5 –5.0	pH 4.5 –5.0
Water for Injection	q.s100 ml	q.s100 ml	q.s100 ml	q.s100 ml	q.s100 ml

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The compositions of comparative examples A-M shown in table 1 and table 2 were visually inspected at the end of 14 days for evaluating physical stability. The solutions were found to have crystals, or the solutions were not clear at the end of 14 days. The results obtained are summarized in the table 3 below.

Table 3

Compositions	Observations	
	Room temperature ($25^0 \pm 2^0$C)	Refrigeration temperature (2 - 8^0C)
A	Crystals observed	Crystals observed
B	Crystals observed	Crystals observed
C	Crystals observed	Crystals observed
D	Crystals observed	Crystals observed
E	Crystals observed	Crystals observed
F	Crystals observed	Crystals observed
G	Crystals observed	Crystals observed
H	Crystals observed	Crystals observed
I	Solution not clear	Solution not clear
J	Solution not clear	Solution not clear
K	Crystals observed	Crystals observed
L	Solution not clear	Solution not clear
M	Crystals observed	Crystals observed

EXAMPLE 1

Olopatadine hydrochloride aqueous, nasal solution comprising hydroxypropyl-β-cyclodextrin and hydoxypropyl methylcellulose, was prepared as described in table 4 below.

Table 4

Ingredients	Quantity (%w/v)	
	Composition A	Composition B
Olopatadine hydrochloride	0.527*	0.527*
Hydroxypropyl-β-cyclodextrin (HPβCD)	3.00	5.00
Hydroxypropyl methylcellulose (HPMC 2910)	0.10	0.10
Benzalkonium chloride solution (50%)	0.02	0.10
Sodium chloride	0.80	0.30
Dibasic sodium phosphate dodecahydrate	0.15	0.15
Edetate disodium	0.01	0.02
NaOH / HCl	q.s. pH 3.5-5.0	q.s. pH 3.5-5.0
Water for Injection (WFI)	q.s. to 100	q.s. to 100

*0.527% Olopatadine hydrochloride is equivalent to 0.5% olopatadine free base

Manufacturing procedure:

Stage A

1. Hydroxypropyl methylcellulose was dissolved in water for injection (WFI) till clear solution was formed.

Stage B

1 Hydroxypropyl-β-cyclodextrin (HPβCD) was dissolved in water for injection in a container.

2 Disodium edetate, sodium chloride, benzalkonium chloride solution (50%) and dibasic sodium phosphate dodecahydrate were added to above container and stirred to get a clear solution.

3 Olopatadine hydrochloride was dissolved in water for injection and added to the above solution in the container, under stirring.

Stage C

1. Solution obtained from stage B was added to solution of stage A.

2. The pH of the solution was adjusted such that it is between 3.5-5.0, using 5.0% v/v hydrochloric acid or 2% w/v sodium hydroxide.
3. Final volume was made up with water for injection.
4. The solution was filtered through 2.0μm prefilter and 0.2μm nylon 66 membrane filter and transferred into U.S.P. type I amber glass containers.

EXAMPLE 2

Olopatadine hydrochloride aqueous, solutions of example 1, were packed in vials and stored at 30°C / 65% relative humidity, 40°C / 75% relative humidity and 2-8°C (refrigeration condition) for a period up to 6 months. The samples were analyzed using high performance liquid chromatography (HPLC). The percent total degradation was calculated by area normalization method and the results obtained are summarized in table 5 below.

Table 5

Storage Condition	Time period	Total degradation (%)	
		Composition A of Example 1	Composition B of Example 1
	0 month	0.00	0.02
30°C / 65% Relative humidity	1 month	0.16	0.07
	3 month	0.23	0.01
	6 month	0.15	0.05
40°C / 75% Relative humidity	1 month	0.17	0.19
	3 month	0.22	0.03
	6 month	0.17	0.07
2-8°C Refrigeration condition	3 month	0.16	0.00
	6 month	0.14	0.04

The samples were observed visually for a period of 6 months and the solution was found to be clear without any crystallization or precipitation of olopatadine. The results are summarized in table 6 below.

Table 6

Storage condition	Time period	Observations	
		Composition A of Example 1	Composition B of Example 1
	0 month	Clear solution	Clear solution
30°C / 65% Relative humidity	1 month	Clear solution	Clear solution
	3 month		
	6 month		
40°C / 75% Relative humidity	1 month		
	3 month		
	6 month		
2 - 8°C Refrigeration condition	3 month		
	6 month		

EXAMPLE 3

Olopatadine hydrochloride aqueous solution (Composition B) of example 1 was packed in vials fitted with a conventional pump and actuator. These vials were subjected to freeze-thaw stability studies upto fourteen cycles, where each cycle involved storage for one day at low temperature (i.e. −10°C to −20°C), followed by storage for one day at high temperature (i.e. 40°C and 75%Relative Humidity). The samples were analyzed using high performance liquid chromatography (HPLC). The percent total degradation was calculated by area normalization method and the samples were observed visually for formation of crystals and the results obtained are summarized in table 7 below.

Table 7

Time Period	Total degradation (%)	Observations
At day 0	0.02	Clear solution
At day 28	0.05	

EXAMPLE 4

Olopatadine hydrochloride aqueous solution comprising olopatadine hydrochloride and hydroxypropyl-β-cyclodextrin was prepared as described in table 8 below.

Table 8

Ingredients	Quantity (%w/v)
Olopatadine hydrochloride	0.527*
Hydroxypropyl-β-cyclodextrin (HPβCD)	3.00
Benzalkonium chloride solution (50%)	0.02
Sodium chloride	0.80
Dibasic sodium phosphate dodecahydrate	0.15
Edetate disodium	0.01
NaOH / HCl	q.s. pH 3.5-5.0
Water for Injection (WFI)	q.s. to 100

*0.527% Olopatadine hydrochloride is equivalent to 0.5% olopatadine free base

Manufacturing procedure:

Stage A

1. Hydroxypropyl-β-cyclodextrin (HPβCD) was dissolved in water for injection in a container.
2. Edetate disodium, sodium chloride, benzalkonium chloride solution (50%) and dibasic sodium phosphate dodecahydrate were added to the above container and stirred to get a clear solution.
3. Olopatadine hydrochloride was dissolved in water for injection and added to the above solution in the container, under stirring.

Stage B

1. The pH of the solution was adjusted such that it is between 3.5-5.0, using 5.0% v/v hydrochloric acid or 2% w/v sodium hydroxide.
2. Final volume was made up with water for injection.
3. The solution was filtered through 2.0μm prefilter and 0.2μm nylon 66 membrane filter and transferred into U.S.P. type I amber glass containers.

EXAMPLE 5

Olopatadine hydrochloride aqueous solution of example 4 was packed in vials and stored at 30°C / 65% relative humidity, 40°C / 75% relative humidity and 2-8°C (refrigeration condition) for a period up to 6 months. The samples were analyzed using high performance liquid chromatography (HPLC). The percent total degradation was calculated by area normalization method and the results obtained are summarized in table 9 below.

Table 9

Storage Condition	Time period	Total degradation (%) Composition of Example 4
	0 month	0.00
30°C / 65% Relative humidity	1 month	0.16
	3 month	0.25
	6 month	0.15
40°C / 75% Relative humidity	1 month	0.19
	3 month	0.23
	6 month	0.17
2-8°C Refrigeration condition	3 month	0.33
	6 month	0.14

EXAMPLE 6

Olopatadine hydrochloride aqueous solution of example 4 was packed in vials and stored at 30°C / 65% relative humidity, 40°C / 75% relative humidity and 2-8°C (refrigeration condition) for a period up to 6 months. The samples were observed visually for a period up to 6 months and the solution was found to be clear, without any crystallization or precipitation of olopatadine. The results are summarized in table 10 below.

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Table 10

Storage condition	Time period	Observations
		Composition of Example 4
	0 month	Clear solution
30°C / 65% Relative humidity	1 month	Clear solution
	3 month	
	6 month	
40°C / 75% Relative humidity	1 month	
	3 month	
	6 month	
2 - 8°C Refrigeration condition	3 month	
	6 month	

EXAMPLE 7

Olopatadine hydrochloride aqueous solution was prepared as described in table 11 below.

Table 11

Ingredients	Quantity (%w/v)
Olopatadine hydrochloride	0.22*
Hydroxypropyl-β-cyclodextrin (HPβCD)	1.50
Hydroxypropyl methylcellulose (HPMC 2910)	0.10
Benzalkonium chloride solution (50%)	0.02
Sodium chloride	0.70
Dibasic sodium phosphate anhydrous	0.29
Edetate disodium	0.01
NaOH / HCl	q.s. pH 6.8-7.2
Water for Injection (WFI)	q.s. to 100

*0.22% Olopatadine hydrochloride is equivalent to 0.2% olopatadine free base

Manufacturing procedure:

Stage A

1. Hydroxypropyl methylcellulose was dissolved in water for injection (WFI) till clear solution is formed.

Stage B

1. Hydroxypropyl-β-cyclodextrin (HPβCD) was dissolved in water for injection in a container.
2. Disodium edetate, sodium chloride, benzalkonium chloride solution (50%) and dibasic sodium phosphate anhydrous were added to the above container and stirred to get a clear solution.
3. Olopatadine hydrochloride was dissolved in water for injection and added to the above solution in the container, under stirring.

Stage C

1. Solution obtained from stage B was added to solution of stage A.
2. The pH of the solution was adjusted such that it is between 6.8-7.2, using 5.0% v/v hydrochloric acid or 2% w/v sodium hydroxide.
3. Final volume was made up with water for injection.
4. The solution was filtered through 2.0µm prefilter and 0.2µm nylon 66 membrane filter, and transferred to 5 ml sterile lupolen bottle.

This solution is suitable for administration to the ocular mucosa.

EXAMPLE 8

Olopatadine hydrochloride aqueous solution of example 7 was packed in vials and stored at 25°C / 60% relative humidity, 30°C / 65% relative humidity, 40°C / 75% relative humidity and 2-8°C (refrigeration condition) for a period up to 6 months. The samples were analyzed using high performance liquid chromatography (HPLC). The percent total degradation was calculated by area normalization method and the results obtained are summarized in table 12 below.

Table 12

Storage condition	Time period	Total degradation (%) Composition Of Example 7
	0 month	0.11
40°C / 75% Relative Humidity	1 month	0.25
	2 month	0.38
	3 month	0.40
	6 month	0.86
30°C / 65% Relative Humidity	1 month	0.21
	2 month	0.21
	3 month	0.20
	6 month	0.38
25°C / 60% Relative Humidity	1 month	0.24
	2 month	0.12
	3 month	0.21
	6 month	0.33
2 - 8°C Refrigeration condition	1 month	0.21
	2 month	0.12
	3 month	0.12
	6 month	0.18

Olopatadine hydrochloride aqueous solution of example 7, were packed in vials and stored at 25°C / 60% relative humidity, 30°C / 65% relative humidity, 40°C / 75% relative humidity and 2-8°C (refrigeration condition) for a period up to 6 months. The samples were observed visually for a period up to 6 months and the solution was found to be clear without any crystallization or precipitation of olopatadine. The results are summarized in table 13 below

Table 13

Storage condition	Time period	Observations: Composition of Example 7
	0 month	Clear solution
40°C / 75% Relative humidity	1 month	Clear solution
	2 month	
	3 month	
	6 month	
30°C / 65% Relative humidity	1 month	
	2 month	
	3 month	
	6 month	
25°C / 60% Relative humidity	1 month	
	2 month	
	3 month	
	6 month	
2 - 8°C Refrigeration condition	1 month	
	2 month	
	3 month	
	6 month	

The invention having been described, it will be readily apparent to those skilled in the art that further changes and modifications in actual implementation of the concepts and embodiments described herein can be made or may be learned by practice of the invention, without departing from the spirit and scope of the invention as defined by the following claims.

We claim:

1. An inclusion complex of olopatadine or its pharmaceutically acceptable salt and hydroxyalkyl-β-cylcodextrin.
2. An inclusion complex of claim 1, wherein hydroxyalkyl-β-cylcodextrin is hydroxypropyl-β-cylcodextrin and the ratio of olopatadine or its pharmaceutically acceptable salt to hydroxypropyl β-cylcodextrin is from about 1:1.65 to about 1:50 by weight.
3. A topical solution comprising an inclusion complex of olopatadine or its pharmaceutically acceptable salt and hydroxypropyl β-cylcodextrin.
4. A topical solution as claimed in claim 3, wherein the olopatadine or its pharmaceutically acceptable salt is present in a concentration ranging from about 0.17% to about 0.62%w/v of the solution.
5. A topical solution as claimed in claim 3, wherein the hydroxypropyl β-cylcodextrin is present in a concentration ranging from about 1.0% to about 10% w/v of the solution.
6. A stable aqueous topical solution of olopatadine or its pharmaceutically acceptable salt, comprising:
   (a) therapeutically effective amount of olopatadine or its pharmaceutically acceptable salt;
   (b) hydroxypropyl β-cylcodextrin; and
   (c) hydroxypropyl methylcellulose.
7. A stable aqueous topical solution as claimed in claim 6, wherein the olopatadine or its pharmaceutically acceptable salt is present in a concentration ranging from about 0.17% to about 0.62%w/v of the solution.
8. A stable aqueous topical solution as claimed in claim 7, wherein the olopatadine or its pharmaceutically acceptable salt is present in a concentration ranging from about 0.17% to about 0.25%w/v of the solution and wherein the solution is suitable for administration to the eye of a patient in need thereof.
9. A stable aqueous topical solution as claimed in claim 7, wherein the olopatadine or its pharmaceutically acceptable salt is present in a concentration ranging from about 0.35%

to about 0.62%w/v of the solution and wherein the solution is suitable for administration to the nasal mucosa of a patient in need thereof.

10. A stable aqueous topical solution as claimed in claim 6, wherein hydroxypropyl methylcellulose is present in amount ranging from about 0.01% to about 1%w/v of the solution and hydroxypropyl β-cylcodextrin is present in a concentration ranging from about 1.0% to about 10% w/v of the solution.

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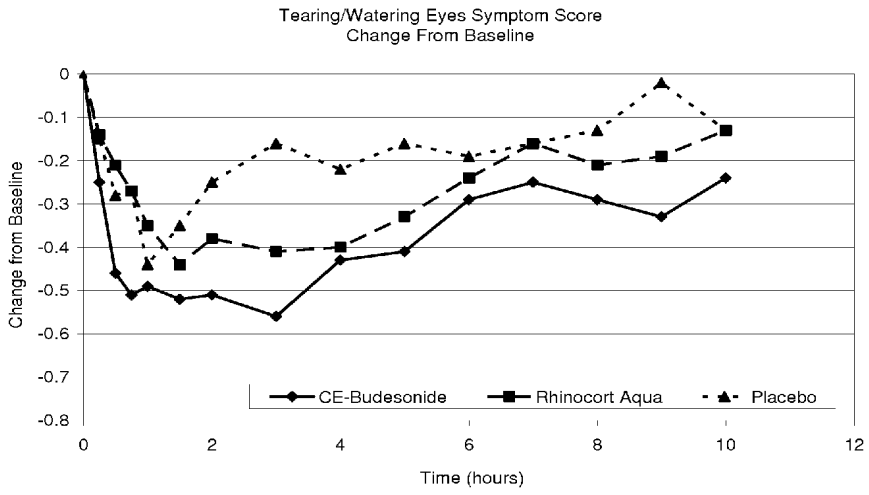
(54) Title: NASAL AND OPHTHALMIC DELIVERY OF AQUEOUS CORTICOSTEROID SOLUTIONS

FIG. 6E



(57) Abstract: The present invention is directed to methods of treating nasal and/or ophthalmic diseases, symptoms, or disorders that are therapeutically responsive to corticosteroid therapy by delivering aqueous solution formulations comprising a corticosteroid to nasal and ophthalmic tissues. The invention is also directed to methods, systems, devices, and compositions for delivering aqueous solution formulations comprising a corticosteroid and an antihistamine to nasal and ophthalmic tissues. watering eyes

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Nasal and Ophthalmic Delivery of Aqueous Corticosteroid Solutions

FIELD OF THE INVENTION

The present invention is directed to methods of treating nasal and/or ophthalmic diseases, symptoms, or disorders that are therapeutically responsive to corticosteroid therapy by delivering aqueous solution formulations comprising a corticosteroid to nasal and ophthalmic tissues. The invention is also directed to methods, systems, devices, and compositions for delivering aqueous solution formulations comprising a corticosteroid and an antihistamine to nasal and ophthalmic tissues.

BACKGROUND OF THE INVENTION

The nasal administration of drugs allows for their deposition to the nose, sinuses, and other nasal cavities. Intranasal administration of drugs such as corticosteroids and antihistamines may be used to treat nasal symptoms including seasonal allergic rhinitis, perennial allergic rhinitis, perennial non-allergic rhinitis, nasal polyps, as well as prevention of post surgical polyps, chronic sinusitis, recurrent sinusitis, asthma, grass pollen rhinitis, hay fever, snoring, cluster headache, and other diseases and disorders.

The ophthalmic administration of drugs allows for their deposition to the eye, including the ocular mucosa, eye surface, cornea, conjuctiva, sclera, and posterior eye parts such as the retina, choroid, and vitreous and optic nerves, as well as tissues surrounding the eye. Ophthalmic administration of drugs such as corticosteroids and antihistamines may be used to treat ocular symptoms including conjunctivitis, inflammation of tissue(s) in the eye, dry eye, filamentary keratitis, delayed tear clearance, pain, keratoconjunctival dryness, keratoconjunctivitis sicca, lesions/tumors of the eye, infectious processes of the eye, bacterial infections, viral infections, glaucoma, uveitis, diabetic retinopathy, eye trauma, blepharitis, blepharoconjunctivitis, and other diseases or disorders.

Aqueous formulations containing a corticosteroid and a solubilizing agent have been prepared: Saidi et al. (U.S. Patent No. 6,241,969); Keller et al. (Respiratory Drug

Delivery IX (2004) 221-231); Lintz et al. (AAPS Annual Meeting and Exposition, Baltimore, Nov. 8, 2004; Poster M1128); Schueepp et al. (ATS 99th International Conference, Seattle, May 16th-21st, 2003; poster 1607); Russian Patent No. 2180217 to Chuchalin; U.S. Publication No. 2006/0045850; and Waldrep et al. (*J. Aerosol Med.* (1994), 7(2), 135-145); PCT International Publications No. WO 06/108556, No. WO 03/35030, and No. WO 06/37246 and European Publications No. EP1894559 and No. EP1712220 to PARI Pharma GmbH.

Cyclodextrins have been included in nasal or ophthalmic compositions: Kaur et al. (Curr. Drug Deliv. (2004), 1(4), 351-360); Shimpi et al. (Acta Pharm. (2005), 55(2), 139-56); Viegas et al. (U.S. Patents No. 6,136,334, No. 5,587,175, and No. 5,958,443); Pate et al. (U.S. Patent No. 5,977,180); Loftsson et al. (Acta Ophthalmol. Scand. (2002), 80(2), 144-50).

Underivatized and derivatized cyclodextrins can be used to prepare aqueous formulations containing a corticosteroid: U.S. Patents No. 5,376,645 and No. 5,134,127 to Stella et al.; U.S. Patent No. 5,914,122 to Otterbeck et al.; Worth et al. (*24th International Symposium on Controlled Release of Bioactive Materials* (1997)); Kinnarinen et al. (*11th International Cyclodextrin Symposium* CD, (2002)); U.S. Patent No. 5,472,954; U.S. patent No. 5,089,482; Zimmerer et al. in *Respiratory Drug Delivery IX* (2004) 461 – 464); Singh et al. (U.S. Patents No. 7,128,928 and No. 6,696,426); Loftsson (U.S. Patents No. 7,115,586, No. 5,472,954, and No. 5,324,718); Chang et al. (U.S. Patent No. 6,969,706); Beck et al. (U.S. Patents No. 6,723,353 and No. 6,358,935); Buchanan et al. (U.S. Patent No. 6,610,671); Pitha (U.S. Patents No. 6,576,261 and No. 5,935,941); Kis (U.S. Patent No. 6,468,548); Müller et al. (U.S. Patent No. 6,407,079); Wiebe et al. (U.S. Patent No. 5,739,121); Guy (U.S. Patent No. 5,576,311); Babcock et al. (U.S. Patent No. 5,538,721); Folkman et al. (U.S. Patent No. 5,227,372); Lipari (U.S. Patent No. 4,383,992); PCT International Publication No. WO 2004/087043 to Sun Pharmaceutical Industries Ltd.; Saari et al. (Graefes Arch. Clin. Exp. Ophthalmol. (2006), 244(5), 620-6); Kristinsson et al. (Invest. Ophthalmol. Vis. Sci. (1996), 37(6), 1199-203); Usayapant et al. (Pharm. Res. (1991), 8(12), 1495-9); Bary et al. (Eur. J. Pharm. Biopharm. (2000), 50(2), 237-244); U.S. Publication No. 2006/0193783; U.S. Publication No. 2002/0198174; European Publication No. EP 0435682; Lyons et al. (abstract in *AAPS Annual Meeting and Exposition*, Denver, CO USA, October 1-25, 2001); Amselem et al. (U.S. Patent No. 5,747,061).

Sulfoalkyl ether cyclodextrin derivatives can be used to prepare aqueous formulations containing a corticosteroid: U.S. Publication No. 2007/0020336; U.S. Publication No. 2006/0120967; U.S. Publication No. 2002/0150616 to Van de Cruys; U.S. Publications No. 20070249572, No. 20070197487, No. 20070197486, No. 20070191599, No. 20070191327; No. 20070191323, No. 20070185066, No. 20070178050, No. 20070178049, and No. 20070160542 and PCT International Publications No. WO 07/95342, No. WO 07/95341, No. WO 07/95339, No. WO 07/75963, No. WO 07/75859, No. WO 07/75801, No. WO 07/75800, No. WO 07/75799, and No. WO 07/75798 to Hill; U.S. Publications No. 20070202054, No. 20070020299, No. 20070020298, and No. 20070020196, and PCT International Publications No. WO 08/05692, No. WO 08/05691, No. WO 08/05053, No. WO 05/065651, No. WO 05/065649, No. WO 05/065435 to Pipkin et al.; U.S. Publication No. 20060120967 and No. 20060045850 to Namburi et al.; and U.S. Publications No. 2005085446 and No. 20070049552 to Babu.

Corticosteroid-containing formulations for ophthalmic use have been described: Pflugfelder et al. (U.S. Patent No. 6,153,607), Sackeyfio et al. (U.S. Patent No. 6,995,815), Guo et al. (U.S. Patent Nos. 6,548,078 and 6,217,895), Sher (U.S. Patent No. 6,117,907), Clarke et al. (U.S. Patent Nos.5,358,943 and 4,945,089), Schwartz (U.S. Patent Nos. 5,212,168 and 4,904,649), and Saidi et al. (U.S. Patent No. 6,241,969).

The nasal and/or ophthalmic delivery of an aqueous solution formulation comprising a corticosteroid as a therapeutic agent alone or in combination with another therapeutic agent, such as an antihistamine, for the treatment of allergy-related disorders or symptoms would be useful and especially desirable if it could provide an improved clinical benefit over the delivery of other formulations, such as suspension-based formulations.

SUMMARY OF THE INVENTION

The invention provides a method of treating, preventing or ameliorating in a subject a corticosteroid-responsive disease or disorder, meaning a disease or disorder in a subject that can be treated with a therapeutically effective amount of corticosteroid to provide a clinical or therapeutic benefit to the subject. In some embodiments, the corticosteroid-responsive disease or disorder is a disease, disorder, symptom, or condition of the nose or eye.

The invention provides a method for treating an allergic symptom or disorder in a subject in need thereof, comprising:

nasally administering to the subject a corticosteroid solution comprising a therapeutically effective amount of a corticosteroid, SAE-CD, and a pharmaceutically acceptable aqueous liquid carrier,

wherein the corticosteroid solution provides more rapid relief from an allergic symptom or disorder compared to a corticosteroid suspension at the same unit dose.

In some embodiments, the allergic symptom or disorder includes a non-nasal symptom selected from the group consisting of itchy/gritty eyes, tearing/watery eyes, red/burning eyes, itchy eyes and palate, and combinations thereof.

The invention also provides a method for treating an ocular symptom or disorder in a subject in need thereof, comprising:

nasally administering to the subject a corticosteroid solution comprising a therapeutically effective amount of a corticosteroid, SAE-CD, and a pharmaceutically acceptable aqueous liquid carrier,

wherein the ocular symptom or disorder is itchy/gritty eyes, tearing/watery eyes, red/burning eyes, or a combination thereof.

The invention also provides a system for treating an allergic symptom or disorder in a subject in need thereof, comprising:

a corticosteroid solution comprising a therapeutically effective amount of a corticosteroid, a thereapeutically effective amount of an antihistamine, SAE-CD, and a pharmaceutically acceptable aqueous liquid carrier, and

a metered dose device for nasal administration of the corticosteroid solution to the subject, wherein the corticosteroid solution is provided in the device.

In some embodiments, the system is for treating an ocular symptom or disorder in a subject in need thereof.

The invention also provides a metered dose device for nasal administration comprising a corticosteroid solution comprising a therapeutically effective amount of a corticosteroid, a therapeutically effective amount of an antihistamine, SAE-CD, and a pharmaceutically acceptable aqueous liquid carrier.

In some embodiments, the invention provides a method for treating a nasal symptom or disorder in a subject in need thereof, comprising:

nasally administering to the subject a corticosteroid solution comprising a therapeutically effective amount of a corticosteroid, SAE-CD, and a pharmaceutically acceptable aqueous liquid carrier,

wherein the nasal symptom or disorder is selected from the group consisting of: acute or chronic rhinitis, nasal polyps, post surgical nasal polyps, snoring, cluster headache, and combinations thereof.

In some embodiments of the method for treating a nasal symptom or disorder in a subject in need thereof, the symptom or disorder is instead selected from the group consisting of obstructive sleep apnea, eustachian tube dysfunction, serous otitis media, sleep disturbances, daytime somnolesence, nasal furuncles, epistaxis, wounds of the nasal or sinunasal mucosa, dry nose syndrome, nasal bleeding, and combinations thereof.

The invention also provides a method for treating an allergic symptom or disorder in a subject in need thereof, comprising:

ophthalmically administering to the subject a corticosteroid solution comprising a therapeutically effective amount of a corticosteroid, SAE-CD, and a pharmaceutically acceptable aqueous liquid carrier,

wherein the corticosteroid solution provides more rapid relief from an allergic symptom or disorder compared to a corticosteroid suspension at the same unit dose.

The invention also provides a method for treating ocular inflammation in a subject in need thereof, comprising:

ophthalmically administering to the subject a corticosteroid solution comprising a therapeutically effective amount of a corticosteroid, SAE-CD, and a pharmaceutically acceptable aqueous liquid carrier,

wherein the corticosteroid solution provides a more rapid reduction in ocular inflammation compared with a corticosteroid suspension at the same unit dose.

The invention also provides a system for treating an allergic symptom or disorder in a subject in need thereof, comprising:

a corticosteroid solution comprising a therapeutically effective amount of a corticosteroid, a thereapeutically effective amount of an antihistamine, SAE-CD, and a pharmaceutically acceptable aqueous liquid carrier, and

a device for ophthalmic administration of the corticosteroid solution to the subject, wherein the corticosteroid solution is provided in the device.

The invention also provides a device for ophthalmic adminstration comprising a corticosteroid solution comprising a therapeutically effective amount of a corticosteroid, a therapeutically effective amount of an antihistamine, SAE-CD, and a pharmaceutically acceptable aqueous liquid carrier.

The administration device can be: 1) a metered dose device such as a atomizer, sprayer, pump spray, dropper, squeeze tube, squeeze bottle, pipette, ampule, nasal cannula, metered dose device, nasal spray inhaler, nasal continuous positive air pressure device, or breath actuated bi-directional delivery device; or 2) a device for ophthalmic administration such as a dropper, drop dispensing package, tube, eye spray device, or eye wash unit. The device can be adapted to to emit 10 µl to 500 µl of corticosteroid solution per unit dose. The device can also comprise a nozzle, wherein the nozzle comprises a valve, and the valve provides a release of a volume of 25 µl to 260 µl per unit dose through the nozzle upon operation of the device.

In some embodiments, the corticosteroid is beclomethasone dipropionate, beclomethasone monopropionate, betamethasone, budesonide, ciclesonide, desisobutyryl-ciclesonide, dexamethasone, flunisolide, fluticasone propionate, fluticasone furoate, mometasone furoate, triamcinolone acetonide, or a combination thereof.

The invention also includes embodiments wherein the corticosteroid solution further comprises one or more additional therapeutically effective agents, such as an anti-IgE antibody, antibiotic agent, anticholinergic agent, antifungal agent, anti-inflammatory agent, anti-infective agent, antihistamine agent, analgesic agent, decongestant, expectorant, antitussive agent, antimicrobial agent, leukotriene receptor antagonist, or a combination thereof. Specific embodiments of these additional therapeutically effective agents can be selected from those disclosed herein or others suitable for nasal or ophthalmic administration and for treatment of diseases, disorders or symptoms of the nose or eye.

In some embodiments, the method further comprises administering a therapeutically effective amount of an antihistamine. In some embodiments, the antihistamine is diphenhydramine, clemastine, chlorpheniramine, brompheniramine, dexchlorpheniramine, dexbrompheniramine, triprolidine, doxylamine, tripelennamine, heptadine, carbinoaxime, bromdiphenhydramine, hydroxyzine, pyrilamine, acrivastine, AHR-11325, phenindamine, astemizole, azatadine, azelastine, cetirizine, ebastine, fexofenadine, ketotifen, lodoxine, loratadine, descarboethoxyloratadine, levocabastine, mequitazine, oxatomide, setastine, tazifyline, temelastine, terfenadine, tripelennamine, terfenadine carboxylate, phenyltoloxamine, pheniramine, or a combination thereof. In some embodiments, the antihistamine is carebastine, efletirizine, mapinastine, antazoline, bilastine, bepotastine besilate, rupatadine, emedastine, tecastemizole, epinastine, levocetirizine, mizolastine, noberastine, norastemizole, olopatadine, or a combination thereof. In some embodiments the antihistamine is azelastine. In some embodiments, the antihistamine is azelastine, wherein the azelastine is present at an amount of about 30 μg to about 275 μg per unit dose. In some embodiments, the antihistamine is azelastine, wherein the azelastine is present at a concentration of 0.5 to 10 mg/mL. In some embodiments, the antihistamine is olopatadine. In some embodiments, the antihistamine is azelastine, wherein the olopatadine is present at an amount of about 330 μg to about 2660 μg per unit dose. In some embodiments, the antihistamine is azelastine, wherein the olopatadine is present at a concentration of 1 to 15 mg/mL. In some embodiments, the antihistamine is cetirizine. In some embodiments, the antihistamine is cetirizine, wherein the cetirizine is present at an amount of about 0.25 mg to about 4.4 mg per unit dose. In some embodiments, the antihistamine is cetirizine, wherein the cetirizine is present at a concentration of 0.25 to 4.4 mg/mL.

In some embodiments, the administering of the corticosteroid solution is performed once or twice daily.

In some embodiments, the allergic symptom or disorder is or further includes a nasal symptom, non-nasal symptom, allergic rhinitis, seasonal allergic rhinitis, perennial allergic rhinitis, perennial non-allergic rhinitis, grass pollen rhinitis, have fever, nasal polyps, or a combination thereof. In some embodiments, the allergic symptom or disorder is or further includes ocular symptom, bacterial rhinitis, fungal rhinitis, viral rhinitis,

atrophic rhinitis, vasomotor rhinitis, blocked nose, nasal congestion, or a combination thereof.

In some embodiments, the nasal symptom is rhinorrhea, nasal congestion, nasal itchiness, sneezing, nasal obstruction, or a combination thereof.

In some embodiments, the non-nasal symptom is itchy/gritty eyes, tearing/watery eyes, red/burning eyes, itchy ears and palate, or a combination thereof.

In some embodiments, the corticosteroid is budesonide. In some embodiments, the corticosteroid is budesonide, wherein the budesonide is present at an amount of about 5 μg to about 500 μg per unit dose. In some embodiments, the corticosteroid is budesonide, wherein the budesonide is present at a concentration of 40 to 2000 μg/mL.

In some embodiments, the corticosteroid is fluticasone propionate.

In some embodiments, the corticosteroid is fluticasone furoate.

In some embodiments, the corticosteroid is mometasone furoate.

In some embodiments, the molar ratio of the SAE-CD to the corticosteroid is 1:1 or greater. In some embodiments, the molar ratio of the SAE-CD to an additional therapeutic agent is 1:1 or greater. In some embodiments, the molar ratio of the SAE-CD to an antihistamine is greater than 2:1.

Some embodiments of the invention includes those wherein the corticosteroid solution comprises: 1) a corticosteroid, such as budesonide, fluticasone propionate, fluticasone furoate, mometasone furoate, ciclesonide, or a combination thereof; and 2) another therapeutically effective agent, such as azelastine, olopatadine, cetirizine, loratadine, desloratadine, azithromycin, voriconazole, or a combination thereof.

In some embodiments, the aqueous liquid carrier comprises water, buffer, alcohol, organic solvent, glycerin, propylene glycol, poly(ethylene glycol), poloxamer, surfactant or a combination thereof. In some embodiments, the aqueous liquid carrier comprises povidone, polyol or a combination thereof.

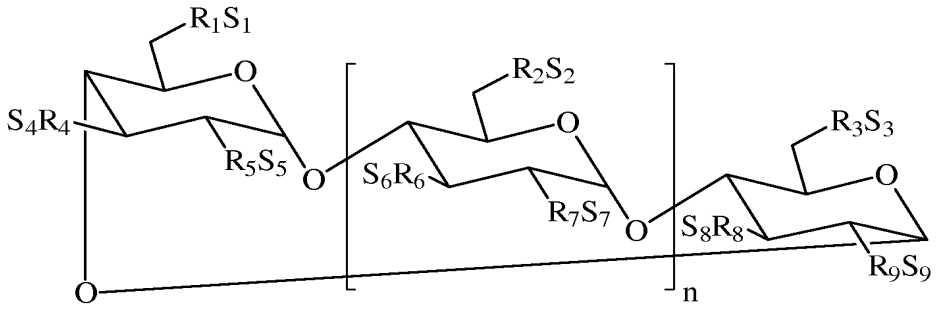
Some embodiments of the invention also provide a unit dose of a therapeutic corticosteroid solution comprising: about 32 μg of budesonide; SAE-CD; pharmaceutically acceptable aqueous liquid carrier; disodium edetate of about 0.005 to about 0.1% by weight of the unit dose; and potassium sorbate of about 0.05 to about 0.2%

by weight of the unit dose, and wherein the corticosteroid solution is suitable for nasal administration to a subject in need thereof.

Some embodiments of the invention also provide a method of treating preventing or ameliorating in a subject a corticosteroid-responsive disease or disorder, the method comprising metering into the nose of the subject a therapeutically effective amount of budesonide that is less than about 320 μg per day, delivered as 8 or more unit doses, wherein each unit dose consists of about 32 μg of budesonide; SAE-CD; disodium edetate of about 0.005 to about 0.1% by weight of the unit dose; potassium sorbate of about 0.05 to about 0.2% by weight of the unit dose; and a pharmaceutically acceptable aqueous liquid carrier.

In some embodiments, the corticosteroid solution has a pH of about 3.5 to about 5 or about about 4.2 to about 4.6.

In some embodiments, the SAE-CD is a compound, or mixture of compounds, of the Formula 1:



Formula 1

wherein:

n is 4, 5 or 6;

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 are each, independently, -O- or a-O-(C_2 - C_6 alkylene)-SO_3^- group, wherein at least one of R_1 – R_9 is independently a -O-(C_2 - C_6 alkylene)-SO_3^- group, a -O-$(CH_2)_mSO_3^-$ group wherein m is 2 to 6, -$OCH_2CH_2CH_2SO_3^-$, or-$OCH_2CH_2CH_2CH_2SO_3^-$); and

S_1, S_2, S_3, S_4, S_5, S_6, S_7, S_8 and S_9 are each, independently, a pharmaceutically acceptable cation.

In some embodiments, the corticosteroid solution further comprises one or more pharmaceutically acceptable excipients, such as a preservative, an antioxidant, a buffering agent, an acidifying agent, an alkalizing agent, a solubility-enhancing agent, a

complexation-enhancing agent, a diluent, an electrolyte, glucose, a stabilizer, a bulking agent, an antifoaming agent, an oil, an emulsifying agent, flavor, sweetener, a taste-masking agent, a tonicity modifier, a surface tension modifier, a viscosity modifier, a density modifier, or a combination thereof.

In some embodiments, the SAE-CD is present at a concentration of about 10 to about 500 mg/mL of corticosteroid solution, and/or the SAE-CD is present in an amount of 100 μg to 1000 mg per unit dose.

The invention includes all combinations of the embodiments and aspects disclosed herein. Accordingly, the invention includes the embodiments and aspects specifically disclosed, broadly disclosed, or narrowly disclosed herein, as well as combinations thereof and subcombinations of the individual elements of said embodiments and aspects.

These and other aspects of this invention will be apparent upon reference to the following detailed description, examples, claims and attached figures.

BRIEF DESCRIPTION OF THE FIGURES

The following drawings are given by way of illustration only, and thus are not intended to limit the scope of the present invention.

FIG. 1A depicts a phase solubility graph of the concentration (molar) of cyclodextrin versus the concentration (molar) of budesonide for γ-CD, HP-β-CD and SBE7-β-CD.

FIG. 1B depicts a phase solubility graph for budesonide concentration (M) versus cyclodextrin concentration (M) for various SBG-γ-CD species and CAPTISOL.

FIG. 2 depicts a phase solubility diagram for fluticasone propionate in the presence of several different cyclodextrins.

FIG. 3 depicts a phase solubility diagram for mometasone furoate in the presence of several different cyclodextrins.

FIG. 4 depicts a phase solubility diagram for esterified and non-esterified fluticasone in the presence of SAE(5-6)-γ-CD.

FIG. 5 depicts a bar chart summarizing the aqueous solubility of beclomethasone dipropionate in the presence of various SAE-CD derivatives.

FIGS. 6A to 6F depict charts detailing the results of a clinical study conducted according to Example 33.

FIG. 7 depicts a graphical summary of the study protocol of Example 33.

FIG. 8A depicts a chart the TNSS change from baseline with onset of action for the first three time points in the study of Example 33.

FIG. 8B depicts a chart the TNNSS change from baseline with onset of action for the first three time points in the study of Example 33.

FIGS. 9A-9C depict the results of the effect that the three solutions of Example 33 have on the EEC-QOLQ as determined using the Quality of Life Questionnaire.

FIGS. 10A-10C depict charts of the pH rate profile for degradation of azelastine in the presence or absence of SAE-CD at varying temperatures and pH's: FIG. 10A- Azelastine pH Rate Profile Area % (25°C), 0.5mg/mL azelastine HCl in 3mM citrate @ pH 4, 5, & 6; with and without 1.75% CAPTISOL, Stored in 25°C Stability Chamber; FIG. 10B- Azelastine pH Rate Profile Area % (40°C), 0.5mg/mL azelastine HCl in 3mM citrate @ pH 4, 5, & 6; with and without 1.75% CAPTISOL, Stored in 40°C Stability Chamber; FIG. 10C- Azelastine pH Rate Profile Area % (60°C), 0.5mg/mL azelastine HCl in 3mM citrate @ pH 4, 5, & 6; with and without 1.75% CAPTISOL, Stored in 60°C Stability Chamber.

FIGS. 11A and 11B depict phase solubility diagrams for budesonide in the presence of varying amounts of azelastine hydrochloride and fixed amounts of SBE-β-CD or SBE-γ-CD.

FIGS. 12A-12C depict charts the TNSS, TOSS, and TSS, respectively, change from baseline with onset of action for the first three time points in the study of Example 34 using budesonide and azelastine.

FIGS. 13A-13B depict charts detailing the changes in ocular pressure of rabbits treated according to Example 41.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to methods of treating nasal and/or ophthalmic diseases, symptoms, or disorders that are therapeutically responsive to corticosteroid therapy by delivering aqueous solution formulations comprising a corticosteroid to nasal and ophthalmic tissues. The invention is also directed to methods, systems, devices, and compositions for delivering aqueous solution formulations comprising a corticosteroid and an antihistamine to nasal and ophthalmic tissues. The systems of the invention comprise an administration device, and a composition of the invention. The composition of the

invention is a corticosteroid solution comprising a corticosteroid and SAE-CD. The composition can be a nasal or non-nasal composition or an ophthalmic composition. In some embodiments, a non-nasal composition excludes an inhalable composition for pulmonary delivery.

By including SAE-CD in a liquid composition containing corticosteroid, the corticosteroid is dissolved. The corticosteroid exhibits greater stability in the presence of SAE-CD than it does in its absence. When a second active agent is present, the second active agent can also exhibit greater stability in the presence of SAE-CD than it does in its absence.

The methods, systems, devices, and compositions of the invention can provide an enhanced pharmacokinetic profile over a suspension formulation comprising approximately the same amount of a therapeutic agent and delivered under substantially the same conditions. The therapeutic agent is a corticosteroid alone or a corticosteroid combined with one or more additional therapeutic agents. As such, one or more therapeutic agents in the methods, systems, devices, and compositions of the invention can demonstrate an enhanced pharmacokinetic profile when compared with the same therapeutic agent or agents in a suspension formulation. The term "enhanced pharmacokinetic profile" is taken to mean a higher AUC (e.g. AUC_{last} or $AUC_{(0\rightarrow\infty)}$) per μg of therapeutic agent delivered or administered, a higher Cmax per μg of therapeutic agent delivered or administered, increased bioavailability, absorption or distribution of the therapeutic agent at the site of delivery, a shorter Tmax, or a longer Tmax. The methods, systems, devices, and compositions of the invention can also provide other enhancements over a suspension-based formulation, such as enhanced drug delivery, increased rate of drug administration, reduced treatment time, reduced toxicity, improved stability, enhanced bioabsorption, increased output rate, increased total output, reduced side effects associated with the therapeutic agent, increased nasal cavity deposition, increased paranasal sinus cavity deposition, increased ocular deposition, improved quality of life, reduced mucociliary clearance, reduced ocular clearance, and/or improved patient compliance.

Alternatively, the methods, systems, devices, and compositions of the invention provide substantially the same pharmacokinetic profile or an enhanced pharmacokinetic profile over a suspension formulation comprising a higher amount of therapeutic agent and delivered under substantially the same conditions. The therapeutic agent in the

formulation can be present at a dose that is less than about 80%, less than about 70%, less than about 60% less than about 50%, less than about 40%, less than about 20%, or less than about 10% of that in the suspension.

The amount and/or concentration of SAE-CD in the composition can be varied as needed or as described herein to provide a composition that possesses a desired physical property, provide therapeutic effectiveness in subjects to which the composition is administered, and/or achieve a desired performance in an administration device. SAE-CD can be present in an amount sufficient to solubilize and/or stabilize the therapeutic agent when the SAE-CD and therapeutic agent are placed in the aqueous carrier. The aqueous carrier can be present in an amount sufficient to aid in dissolution of the therapeutic agent and form a solution of sufficient volume and sufficiently low viscosity to permit administration with an administration device. SAE-CD can be present in solid form or in solution in the aqueous carrier. The therapeutic agent can be present in dry powder/particle form or in suspension in the aqueous carrier. In some embodiments, SAE-CD is present at a concentration of about 10 to about 500 mg/mL of composition, and/or SAE-CD is present in an amount of 100 μg to 1000 mg per unit dose.

In some embodiments, SAE-CD is present in an amount sufficient to decrease the amount of unsolubilized therapeutic agent in the suspension–based composition and to improve the administration of the suspension-based composition. In some embodiments, SAE-CD is present in an amount sufficient to solubilize enough therapeutic agent such that the suspension-based composition to which the SAE-CD was added is converted to a solution, substantially clear solution (containing less than 5% precipitate or solid), or a clear solution. It is possible that other components of the suspension-based composition will not completely dissolve in, or may separate out from, the solution.

In some embodiments, SAE-CD is present in an amount sufficient to solubilize at least 50%, at least 75%, at least 90%, at least 95% or substantially all of the therapeutic agent. Some embodiments of the invention include those wherein at least 50% wt., at least 75% wt., at least 90% wt., at least 95% wt., at least 98% wt., or all of the therapeutic agent is dissolved in the liquid composition.

The compositions of the inventions are suitable for nasal and/or ophthalmic administration. The compositions can be administered via an administration device suitable for nasal administration or ophthalmic administration of pharmaceutical compositions. As used herein, an administration device is any pharmaceutically

acceptable device adapted to deliver a composition of the invention to a subject's nose or eye(s). A nasal administration device can be a metered administration device (metered volume, metered dose, or metered-weight) or a continuous (or substantially continuous) aerosol-producing device. Suitable nasal administration devices also include devices that can be adapted or modified for nasal administration. An ophthalmic administration device can be a dropper, drop dispensing package, tube, eye spray device, eye wash unit, and other devices known to those of ordinary skill in the art. In some embodiments, the nasally or ophthalmically administered dose can be absorbed into the bloodstream of a subject.

A metered nasal administration device delivers a fixed (metered) volume or amount (dose) of a nasal composition upon each actuation. Exemplary metered dose devices for nasal administration include, by way of example and without limitation, an atomizer, sprayer, dropper, squeeze tube, squeeze-type spray bottle, pipette, ampule, nasal cannula, metered dose device, nasal spray inhaler, breath actuated bi-directional delivery device, pump spray, pre-compression metered dose spray pump, monospray pump, bispray pump, and pressurized metered dose device. The administration device can be a single-dose disposable device, single-dose reusable device, multi-dose disposable device or multi-dose reusable device.

The compositions of the invention can be used with any known metered administration device. In some embodiments, the device is a pump nasal spray or a squeeze bottle. The performance of a composition of the invention in a metered administration device is detailed in Example 35.

A continuous aerosol-producing device delivers a mist or aerosol comprising droplet of a nasal composition dispersed in a continuous gas phase (such as air). A nebulizer, pulsating aerosol nebulizer, and a nasal continuous positive air pressure device are exemplary of such a device. Suitable nebulizers include, by way of example and without limitation, an air driven jet nebulizer, ultrasonic nebulizer, capillary nebulizer, electromagnetic nebulizer, pulsating membrane nebulizer, pulsating plate (disc) nebulizer, pulsating/vibrating mesh nebulizer, vibrating plate nebulizer, a nebulizer comprising a vibration generator and an aqueous chamber, a nebulizer comprising a nozzle array, and nebulizers that extrude a liquid formulation through a self-contained nozzle array.

Commercially available administration devices that are used or can be adapted for nasal administration of a composition of the invention include the AERONEB™

(Aerogen, San Francisco, CA), AERONEB GO (Aerogen); PARI LC PLUS™, PARI BOY™ N, PARI eflow (a nebulizer disclosed in U.S. Patent No. 6,962,151), PARI LC SINUS, PARI SINUSTAR™, PARI SINUNEB, VibrENT™ and PARI DURANEB™ (PARI Respiratory Equipment, Inc., Monterey, CA or Munich, Germany); MICROAIR™ (Omron Healthcare, Inc, Vernon Hills, Illinois), HALOLITE™ (Profile Therapeutics Inc, Boston, MA), RESPIMAT™ (Boehringer Ingelheim Ingelheim, Germany) AERODOSE™ (Aerogen, Inc, Mountain View, CA), OMRON ELITE™ (Omron Healthcare, Inc, Vernon Hills, Illinois), OMRON MICROAIR™ (Omron Healthcare, Inc, Vernon Hills, Illinois), MABISMIST ™ II (Mabis Healthcare, Inc, Lake Forest, Illinois), LUMISCOPE ™ 6610, (The Lumiscope Company, Inc, East Brunswick, New Jersey), AIRSEP MYSTIQUE™, (AirSep Corporation, Buffalo, NY), ACORN-1 and ACORN-II (Vital Signs, Inc, Totowa, New Jersey), AQUATOWER™ (Medical Industries America, Adel, Iowa), AVA-NEB (Hudson Respiratory Care Incorporated, Temecula, California), AEROCURRENT™ utilizing the AEROCELL™ disposable cartridge (AerovectRx Corporation, Atlanta, Georgia), CIRRUS (Intersurgical Incorporated, Liverpool, New York), DART (Professional Medical Products, Greenwood, South Carolina), DEVILBISS™ PULMO AIDE (DeVilbiss Corp; Somerset, Pennsylvania), DOWNDRAFT™ (Marquest, Englewood, Colorado), FAN JET (Marquest, Englewood, Colorado), MB-5 (Mefar, Bovezzo, Italy), MISTY NEB ™ (Baxter, Valencia, California), SALTER 8900 (Salter Labs, Arvin, California), SIDESTREAM™ (Medic-Aid, Sussex, UK), UPDRAFT-II™ (Hudson Respiratory Care; Temecula, California), WHISPER JET ™ (Marquest Medical Products, Englewood, Colorado), AIOLOS™ (Aiolos Medicnnsk Teknik, Karlstad, Sweden), INSPIRON™ (Intertech Resources, Inc., Bannockburn, Illinois), OPTIMIST™ (Unomedical Inc., McAllen, Texas), PRODOMO™, SPIRA™ (Respiratory Care Center, Hameenlinna, Finland), AERx™ Essence™ and Ultra™, (Aradigm Corporation, Hayward, California), SONIK™ LDI Nebulizer (Evit Labs, Sacramento, California), ACCUSPRAY™ (BD Medical, Franklin Lake, NJ), ViaNase ID ™ (electronic atomizer; Kurve, Bothell, WA), OptiMist device or OPTINOSE (Oslo, Norway), MAD Nasal (Wolfe Tory Medical, Inc., Salt Lake City, UT), Freepod™ (Valois, Marly le Roi, France), Dolphin™ (Valois), Monopowder™ (Valois), Equadel™ (Valois), VP3™ and VP7™ (Valois), VP6 Pump™ (Valois), Standard Systems Pumps (Ing. Erich Pfeiffer, Radolfzell, Germany), AmPump (Ing. Erich Pfeiffer), Counting Pump (Ing. Erich Pfeiffer), Advanced Preservative Free System (Ing. Erich Pfeiffer), Unit Dose System

(Ing. Erich Pfeiffer), Bidose System (Ing. Erich Pfeiffer), Bidose Powder System (Ing. Erich Pfeiffer), Sinus Science™ (Aerosol Science Laboratories, Inc., Camarillo, CA), ChiSys® (Archimedes, Reading, UK), Fit-Lizer® (Bioactis, Ltd, an SNBL subsidiary (Tokyo, JP), Swordfish V™ (Mystic Pharmaceuticals, Austin, TX), DirectHaler™ Nasal (DirectHaler, Copenhagen, Denmark) and SWIRLER® Radioaerosol System (AMICI, Inc., Spring City, PA).

Particularly suitable administration devices include single dose and multi-dose embodiments of: a pump spray bottle; the PARI eFlow (a nebulizer equipped with a vibrating mesh nebulizer comprising a vibration generator, an aerosol chamber, an inhalation valve, and an exhalation valve; U.S. Patents No. 5,954,047, No. 6,026,808, No. 6,095,141, and No. 6,527,151, the entire disclosures of which are hereby incorporated by reference); AERx Essence and AERx Ultra (from ARADIGM; an aerosol generator comprising a nozzle array, whereby a liquid formulation is extruded through a self-contained nozzle array); Aeroneb Go (a nebulizer equipped with a vibrating mesh nebulizer comprising a vibration generator, an aerosol chamber, an inlet and an outlet); VibrENT™ (a nebulizer that delivers a pressure-pulsed aerosol; the delivery rate of liquid composition is about 0.160 mL/min; in PCT International Publications No. WP 2004/20029 and No. WO 2001/34232; Schuschnig et al. in European Patent Publication No. EP 1820493, and *Respiratory Drug Delivery* (2008), the entire disclosures of which are hereby incorporated by reference); PARI SINUSTAR (a nebulizer adapted for nasal administration that delivers an aqueous liquid composition at a rate of about 0.18 mL/min); and the PARI SINUS (including PARI LC Star, PARI LL and PARI Sprint).

The Aradigm AERx delivery system, the AERx Essence and AERx Ultra, is particularly suitable for use according to the invention, as it is recognized in the art as providing controlled dose expression, control of generated aerosol particle size, control of aerosol particle size, and management of the inspiration and delivery process (Farr et al., Drug Delivery Technology May 2002 Vol. 2, No. 3, 42-44). For example, the PARI eFlow vibrating plate nebulizer is particularly suitable for use according to the invention, as it is recognized in the art as providing the above-mentioned desired performance parameters (Keller et al. (ATS 99th International Conference, Seattle, May 16th-21st, 2003; poster 2727).

The parameters used to effect nebulization via an electronic nebulizer, such as flow rate, mesh membrane size, aerosol inhalation chamber size, mask size and materials, inlet

and outlet valves, outflow tube, internal channel plurality of air outputs communicating with the internal chamber, vibration generator and power source may be varied in accordance with the principles of the present invention to maximize their use with different types of aqueous corticosteroid compositions. In some embodiments, substantially all of a dose (weight or volume) is delivered in less than 1.5 minutes or continuously delivered over 1.5 to 60 minutes.

Valves and actuators can be obtained from Bespak (Milton Keynes, UK). Actuators used in the administration device can be horizontal or vertical. The administration device can incorporate the VelocityJet™ micropump. The administration devices can be equipped with different types of baffles, valves, tubes, channels, reservoirs, mixing chambers, vortex chamber, particle dispersion chamber, nasal adapter, vibrating pulse and/or sound wave generator.

Nebulizers that nebulize liquid formulations containing no propellant are suitable for use with the compositions provided herein. Any of these and other known nebulizers can be used to deliver the formulation of the invention including but not limited to the following: nebulizers available from Pari GmbH (Starnberg, Germany), DeVilbiss Healthcare (Heston, Middlesex, UK), Healthdyne, Vital Signs, Baxter, Allied Health Care, Invacare, Hudson, Omron, Bremed, AirSep, Luminscope, Medisana, Siemens, Aerogen, Mountain Medical, Aerosol Medical Ltd. (Colchester, Essex, UK), AFP Medical (Rugby, Warwickshire, UK), Bard Ltd. (Sunderland, UK), Carri-Med Ltd. (Dorking, UK), Plaem Nuiva (Brescia, Italy), Henleys Medical Supplies (London, UK), Intersurgical (Berkshire, UK), Lifecare Hospital Supplies (Leies, UK), Medic-Aid Ltd. (West Sussex, UK), Medix Ltd. (Essex, UK), Sinclair Medical Ltd. (Surrey, UK), and many other companies. The AERx and RESPIMAT nebulizers are described by D. E. Geller (*Respir. Care* (2002), 47 (12), 1392-1404), the entire disclosure of which is incorporated by reference.

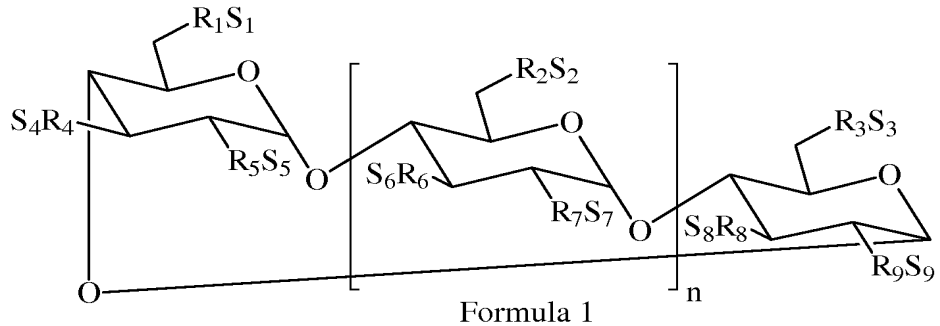
Nebulizers for use herein include, but are not limited to, jet nebulizers (optionally sold with compressors), ultrasonic nebulizers, vibrating membrane, vibrating mesh nebulizers, vibrating plate nebulizers, vibrating cone nebulizer, and others. Exemplary jet nebulizers for use herein include Pari LC plus/ProNeb, Pari LC plus/ProNeb Turbo, Pari LC Plus/Dura Neb 1000 & 2000 Pari LC plus/Walkhaler, Pari LC plus/Pari Master, Pari LC star, Omron CompAir XL Portable Nebulizer System (NE-C18 and JetAir Disposable nebulizer), Omron compare Elite Compressor Nebulizer System (NE-C21 and Elite Air Reusable Nebulizer, Pari LC Plus or Pari LC Star nebulizer with Proneb Ultra compressor,

Pulomo-aide, Pulmo-aide LT, Pulmo-aide traveler, Invacare Passport, Inspiration Healthdyne 626, Pulmo-Neb Traverler, DeVilbiss 646, Whisper Jet, Acorn II, Misty-Neb, Allied aerosol, Schuco Home Care, Lexan Plasic Pocet Neb, SideStream Hand Held Neb, Mobil Mist, Up-Draft, Up-Draft II, T Up-Draft, ISO-NEB, Ava-Neb, Micro Mist, and PulmoMate. Exemplary ultrasonic nebulizers for use herein include MicroAir, UltraAir, Siemens Ultra Nebulizer 145, CompAir, Pulmosonic, Scout, 5003 Ultrasonic Neb, 5110 Ultrasonic Neb, 5004 Desk Ultrasonic Nebulizer, Mystique Ultrasonic, Lumiscope's Ultrasonic Nebulizer, Medisana Ultrasonic Nebulizer, Microstat Ultrasonic Nebulizer, and Mabismist Hand Held Ultrasonic Nebulizer. Other nebulizers for use herein include 5000 Electromagnetic Neb, 5001 Electromagnetic Neb 5002 Rotary Piston Neb, Lumineb I Piston Nebulizer 5500, Aeroneb Portable Nebulizer System, Aerodose™ Inhaler, and AeroEclipse Breath Actuated Nebulizer. Exemplary vibrating membrane, mesh or plate nebulizers are described by R. Dhand (*Respiratory Care*, (Dec. 2002), 47(12), p. 1406-1418), the entire disclosure of which is hereby incorporated by reference.

The volume or amount of composition administered can vary according to the intended delivery target and administration device used. The amount of active agent in a dose or unit dose can vary according to the intended delivery target and administration device used.

During operation of a nebulizer based system, the corticosteroid can be delivered at a rate of at least about 20-50 μg/min, or 10-200 μg/min, wherein this range may increase or decrease according to the concentration of corticosteroid in the composition in the administration device.

The present invention provides SAE-CD based formulations, wherein the SAE-CD is a compound of the Formula 1:



Formula 1

wherein:

n is 4, 5 or 6;

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 are each, independently, -O- or a -O-(C_2 - C_6 alkylene)-SO_3^- group, wherein at least one of R_1 to R_9 is independently a -O-(C_2 - C_6 alkylene)-SO_3^- group, preferably a -O-$(CH_2)_mSO_3^-$ group, wherein m is 2 to 6, preferably 2 to 4, (e.g.-$OCH_2CH_2CH_2SO_3^-$ or-$OCH_2CH_2CH_2CH_2SO_3^-$); and

S_1, S_2, S_3, S_4, S_5, S_6, S_7, S_8 and S_9 are each, independently, a pharmaceutically acceptable cation which includes, for example, H^+, alkali metals (e.g. Li^+, Na^+, K^+), alkaline earth metals (e.g., Ca^{+2}, Mg^{+2}), ammonium ions and amine cations such as the cations of (C_1 - C_6)- alkylamines, piperidine, pyrazine, (C_1 - C_6)-alkanolamine and (C_4 - C_8)-cycloalkanolamine.

Exemplary embodiments of the SAE-CD derivative of the invention include derivatives of the Formula II (SAEx-α-CD), wherein "x" ranges from 1 to 18; of the Formula III (SAEy-β-CD), wherein"y" ranges from 1 to 21; and of the Formula IV (SAEz-γ-CD), wherein"z" ranges from 1 to 24 such as:

SAEx-α-CD	**SAEy-β-CD**	**SAEz-γ-CD**	**Name**
SEEx-α-CD	SEEy-β-CD	SEEz-γ-CD	Sulfoethyl ether CD
SPEx-α-CD	SPEy-β-CD	SPEz-γ-CD	Sulfopropyl ether CD
SBEx-α-CD	SBEy-β-CD	SBEz-γ-CD	Sulfobutyl ether CD
SptEx-α-CD	SPtEy-β-CD	SPtEz-γ-CD	Sulfopentyl ether CD
SHEx-α-CD	SHEy-β-CD	SHEz-γ-CD	Sulfohexyl ether CD

"SAE" represents a sulfoalkyl ether substituent bound to a cyclodextrin. The values "x", "y" and "z" represent the average degree of substitution as defined herein in terms of the number of sulfoalkyl ether groups per CD molecule. Some suitable SAE-CD's include, for example, sulfobutyl ether 4-β-CD or sulfobutyl ether 7-β-CD, sulfobutyl ether 6-γ-CD, sulfobutyl ether 4-γ-CD, sulfobutyl ether 3 to 8-γ-CD, or a sulfobutyl ether 5-γ-CD, or a compound of the formula 1 or a mixture thereof.

The SAE-CD used is described in U.S. Patents No. 5,376,645 and No. 5,134,127 to Stella et al, the entire disclosures of which are hereby incorporated by reference. U.S. Patent No. 3,426,011 to Parmerter et al. discloses anionic cyclodextrin derivatives having sulfoalkyl ether substituents. Lammers et al. (*Recl. Trav. Chim. Pays-Bas* (1972), 91(6),

733-742); *Staerke* (1971), 23(5), 167-171) and Qu et al. (*J. Inclusion Phenom. Macro. Chem.*, (2002), 43, 213-221) disclose sulfoalkyl ether derivatized cyclodextrins. U.S. Patent No. 6,153,746 to Shah et al. discloses a process for the preparation of sulfoalkyl ether cyclodextrin derivatives. An SAE-CD can be made according to the disclosures of Stella et al., Parmerter et al., Lammers et al. or Qu et al., and if processed to remove the major portion (>50%) of the underivatized parent cyclodextrin, used according to the present invention. The SAE-CD can contain from 0% to less than 50% wt. of underivatized parent cyclodextrin.

The terms "alkylene" and "alkyl," as used herein (e.g., in the -0-(C_2 - C_6-alkylene)SO_3^- group or in the alkylamines), include linear, cyclic, and branched, saturated and unsaturated (i.e., containing one double bond) divalent alkylene groups and monovalent alkyl groups, respectively. The term "alkanol" in this text likewise includes both linear, cyclic and branched, saturated and unsaturated alkyl components of the alkanol groups, in which the hydroxyl groups can be situated at any position on the alkyl moiety. The term "cycloalkanol" includes unsubstituted or substituted (e.g., by methyl or ethyl) cyclic alcohols.

In some embodiments of the present invention, compositions contain a mixture of cyclodextrin derivatives, having the structure set out in formula (I), where the composition overall contains on the average at least 1 and up to 3n + 6 alkylsulfonic acid moieties per cyclodextrin molecule. The present invention also provides compositions containing a single type of cyclodextrin derivative, or at least 50% of a single type of cyclodextrin derivative. The invention also includes formulations containing cyclodextrin derivatives having a narrow or wide and high or low degree of substitution. These combinations can be optimized as needed to provide cyclodextrins having particular properties.

The present invention also provides compositions containing a mixture of cyclodextrin derivatives wherein two or more different types of cyclodextrin derivatives are included in the composition. By different types, is meant cyclodextrins derivatized with different types of functional groups e.g., hydroxyalkyl and sulfoalkyl. Each independent different type can contain one or more functional groups, e.g. SBE-CD where the cyclodextrin ring has only sulfobutyl functional groups, and hydroxypropyl-ethyl-β-CD where the cyclodextrin ring has both hydroxypropyl functional groups and ethyl functional groups. The amount of each type of cyclodextrin derivative present can be varied as desired to provide a mixture having the desired properties.

Exemplary SAE-CD derivatives include SBE4-β-CD, SBE7-β-CD, SBE11-β-CD, SBE3.4-γ-CD, SBE4.2-γ-CD, SBE4.9-γ-CD, SBE5.2-γ-CD, SBE6.1-γ-CD, SBE7.5-γ-CD, SBE7.8-γ-CD and SBE5-γ-CD which correspond to SAE-CD derivatives of the formula I wherein n = 5, 5, 5 and 6; m is 4; and there are on average 4, 7, 11 and 5 sulfoalkyl ether substituents present, respectively. These SAE-CD derivatives increase the solubility of poorly water soluble active agents to varying degrees.

Since SAE-CD is a poly-anionic cyclodextrin, it can be provided in different salt forms. Suitable counterions include cationic organic atoms or molecules and cationic inorganic atoms or molecules. The SAE-CD can include a single type of counterion or a mixture of different counterions. The properties of the SAE-CD can be modified by changing the identity of the counterion present. For example, a first salt form of SAE-CD can have a greater corticosteroid stabilizing and/or solubilizing power than a different second salt form of SAE-CD. Likewise, an SAE-CD having a first degree of substitution can have a greater corticosteroid stabilizing and/or solubilizing power than a second SAE-CD having a different degree of substitution.

The liquid compositions and systems of the invention provide an improved clinical benefit or therapeutic benefit over an otherwise similar suspension-based formulations excluding SAE-CD but comprising substantially the same dose of active agent, such as corticosteroid. Exemplary advantages may include enhanced drug delivery, increased rate of drug administration, reduced treatment time, reduced toxicity, ease of manufacture, assurance of sterility, improved stability, enhanced bioabsorption, no concern for solid particle growth, enhanced pharmacokinetic profile, reduced corticosteroid-related side effects, improved patient quality of life, and/or improved clinical or pharmaceutic performance over the suspension formulation.

The enhanced solubilization of a corticosteroid by one SAE-CD versus another is demonstrated by the data in the following tables which depict the molar solubility for fluticasone propionate with different SAE-CDs at about 0.03 to 0.12M concentrations such that the solubilizing power followed about this rank order over this concentration range of SAE-CD: SBE5.2-γ-CD > SPE5.4-γ-CD > SBE6.1-γ-CD > SBE9.7-γ-CD >> SBE7-α-CD > SBE6.7-β-CD > SPE7-β-CD. For mometasone furoate, the solubilizing power followed about this rank order over this concentration range of SAE-CD: SBE9.7-γ-CD > SBE6.1-γ-CD > SBE5.2-γ-CD >> SPE5.4-γ-CD > SBE7-α-CD > SBE6.7-β-CD > SPE7-β-CD.

Differences were also observed for the binding of budesonide (and triamcinolone with specific embodiments of SAE-CD. According to the invention, a SAE-γ-CD binds a corticosteroid better than a SAE-β-CD does. Also, a SAE-β-CD binds budesonide better than a SAE-α-CD does. The phase solubility data is summarized in Example 23 and FIGS. 2-3.

The inventors have also discovered that SAE-γ-CD is particularly suitable for use in complexing esterified and non-esterified corticosteroids as compared to complexation of the same corticosteroids with SAE-β-CD or SAE-α-CD. The table in Example 23 summarizes the phase solubility data depicted in FIG. 4 for fluticasone and fluticasone propionate with various different SAE-γ-CD species having a degree of substitution in the range of 5-10.

SAE-γ-CD is more effective at binding with a particular regioisomer of esterified corticosteroids than is SAE-β-CD or SAE-α-CD. The procedure set forth in Example 18 details the comparative evaluation of the binding of SAE-γ-CD and SAE-β-CD with a series of structurally related corticosteroid derivatives.

By "complexed" is meant "being part of a clathrate or inclusion complex with", i.e., a complexed therapeutic agent is part of a clathrate or inclusion complex with a cyclodextrin derivative. By "major portion" is meant at least about 50% by weight. Thus, a formulation according to the present invention can contain an active agent of which more than about 50% by weight is complexed with a cyclodextrin. The actual percent of active agent that is complexed will vary according to the complexation equilibrium binding constant characterizing the complexation of a specific cyclodextrin to a specific active agent. The invention also includes embodiments wherein the active agent is not complexed with the cyclodextrin or wherein a minor portion of the active agent is complexed with the derivatized cyclodextrin. It should be noted that an SAE-CD, or any other anionic derivatized cyclodextrin, can form one or more ionic bonds with a positively charged compound. This ionic association can occur regardless of whether the positively charged compound is complexed with the cyclodextrin either by inclusion in the cavity or formation of a salt bridge.

The binding of a drug to the derivatized cyclodextrin can be improved by including an acid or base along with the drug and cyclodextrin. For example, the binding of a basic drug with the cyclodextrin might be improved by including an acid along with the basic

drug and cyclodextrin. Likewise, the binding of an acidic drug with the cyclodextrin might be improved by including a base (alkaline material) along with the acidic drug and cyclodextrin. The binding of a neutral drug might be improved by including a basic, acidic or other neutral compound along with the neutral drug and cyclodextrin. Suitable acidic compounds include inorganic and organic acids. Examples of inorganic acids are mineral acids, such as hydrochloric and hydrobromic acid. Other suitable acids include sulfuric acid, sulfonic acid, sulfenic acid, and phosphoric acid. Examples of organic acids are aliphatic carboxylic acids, such as acetic acid, ascorbic acid, carbonic acid, citric acid, butyric acid, fumaric acid, glutaric acid, glycolic acid, α-ketoglutaric acid, lactic acid, malic acid, mevalonic acid, maleic acid, malonic acid, oxalic acid, pimelic acid, propionic acid, succinic acid, tartaric acid, or tartronic acid. Aliphatic carboxylic acids bearing one or more oxygenated substituents in the aliphatic chain are also useful. A combination of acids can be used.

Suitable basic compounds include but are not limited to inorganic and organic bases. Suitable inorganic bases include ammonia, metal oxide and metal hydroxide. Suitable organic bases include primary amine, secondary amine, tertiary amine, imidazole, triazole, tetrazole, pyrazole, indole, diethanolamine, triethanolamine, diethylamine, methylamine, tromethamine (TRIS), aromatic amine, unsaturated amine, primary thiol, and secondary thiol. A combination of bases can be used.

An anionic derivatized cyclodextrin can complex or otherwise bind with an acid-ionizable agent. As used herein, the term acid-ionizable agent is taken to mean any compound that becomes or is ionized in the presence of an acid. An acid-ionizable agent comprises at least one acid-ionizable functional group that becomes ionized when exposed to acid or when placed in an acidic medium. Exemplary acid-ionizable functional groups include a primary amine, secondary amine, tertiary amine, quaternary amine, aromatic amine, unsaturated amine, primary thiol, secondary thiol, sulfonium, hydroxyl, enol and others known to those of ordinary skill in the chemical arts.

The degree to which an acid-ionizable agent is bound by non-covalent ionic binding versus inclusion complexation formation can be determined spectrophotometrically using methods such as ^{1}HNMR, ^{13}CNMR, or circular dichroism, for example, and by analysis of the phase solubility data for the acid-ionizable agent and anionic derivatized cyclodextrin. The artisan of ordinary skill in the art will be able to use these conventional methods to approximate the amount of each type of binding that is

occurring in solution to determine whether or not binding between the species is occurring predominantly by non-covalent ionic binding or inclusion complex formation. An acid-ionizable agent that binds to derivatized cyclodextrin by both means will generally exhibit a bi-phasic phase solubility curve. Under conditions where non-covalent ionic bonding predominates over inclusion complex formation, the amount of inclusion complex formation, measured by NMR or circular dichroism, will be reduced even though the phase solubility data indicates significant binding between the species under those conditions; moreover, the intrinsic solubility of the acid-ionizable agent, as determined from the phase solubility data, will generally be higher than expected under those conditions.

As used herein, the term non-covalent ionic bond refers to a bond formed between an anionic species and a cationic species. The bond is non-covalent such that the two species together form a salt or ion pair. An anionic derivatized cyclodextrin provides the anionic species of the ion pair and the acid-ionizable agent provides the cationic species of the ion pair. Since an anionic derivatized cyclodextrin is multi-valent, an SAE-CD can form an ion pair with one or more acid-ionizable agents.

The parent cyclodextrins have limited water solubility as compared to SAE-CD and HPCD. Underivatized α-CD has a water solubility of about 14.5% w/v at saturation. Underivatized β-CD has a water solubility of about 1.85% w/v at saturation. Underivatized γ-CD has a water solubility of about 23.2% w/v at saturation. Dimethyl-beta-cyclodextrin (DMCD) forms a 43% w/w aqueous solution at saturation. The SAE-CD can be combined with one or more other cyclodextrins or cyclodextrin derivatives in the composition to solubilize the corticosteroid.

Other water soluble cyclodextrin derivatives that can be used according to the invention include the hydroxyethyl, hydroxypropyl (including 2- and 3-hydroxypropyl) and dihydroxypropyl ethers, their corresponding mixed ethers and further mixed ethers with methyl or ethyl groups, such as methylhydroxyethyl, ethyl-hydroxyethyl and ethyl-hydroxypropyl ethers of alpha-, beta- and gamma-cyclodextrin; and the maltosyl, glucosyl and maltotriosyl derivatives of alpha, beta- and gamma-cyclodextrin, which can contain one or more sugar residues, e.g. glucosyl or diglucosyl, maltosyl or dimaltosyl, as well as various mixtures thereof, e.g. a mixture of maltosyl and dimaltosyl derivatives. Specific cyclodextrin derivatives for use herein include hydroxypropyl-beta-cyclodextrin, hydroxyethyl-beta-cyclodextrin, hydroxypropyl-gamma-cyclodextrin, hydroxyethyl-

gamma-cyclodextrin, dihydroxypropyl-beta-cyclodextrin, glucosyl-alpha-cyclodextrin, glucosyl-beta-cyclodextrin, diglucosyl-beta-cyclodextrin, maltosyl-alpha-cyclodextrin, maltosyl-beta-cyclodextrin, maltosyl-gamma-cyclodextrin, maltotriosyl-beta-cyclodextrin, maltotriosyl-gamma-cyclodextrin and dimaltosyl-beta-cyclodextrin, and mixtures thereof such as maltosyl-beta-cyclodextrin/dimaltosyl-beta-cyclodextrin, as well as methyl-beta-cyclodextrin. Procedures for preparing such cyclodextrin derivatives are well-known, for example, from Bodor United States Patent No. 5,024,998 dated June 18, 1991, and references cited therein. Other cyclodextrins suitable for use in the present invention include the carboxyalkyl thioether derivatives such as ORG 26054 and ORG 25969 made by ORGANON (AKZO-NOBEL), hydroxybutenyl ether derivatives made by EASTMAN, sulfoalkyl-hydroxyalkyl ether derivatives, sulfoalkyl-alkyl ether derivatives, and other derivatives as described in US Pregrant Patent Application Publications No. 2002/0128468, No. 2004/0106575, No. 2004/0109888, and No. 2004/0063663, or U.S. Patents No. 6,610,671, No. 6,479,467, No. 6,660,804, or No. 6,509,323.

The HP-β-CD can be obtained from Research Diagnostics Inc. (Flanders, NJ). HP-β-CD is available with different degrees of substitution. Exemplary products include ENCAPSIN™ (degree of substitution~4; HP4-β-CD) and MOLECUSOL™ (degree of substitution~8; HP8-β-CD); however, embodiments including other degrees of substitution are also available. Since HPCD is non-ionic, it is not available in salt form.

Dimethyl cyclodextrin is available from FLUKA Chemie (Buchs, CH) or Wacker (Iowa). Other derivatized cyclodextrins suitable in the invention include water soluble derivatized cyclodextrins. Exemplary water-soluble derivatized cyclodextrins include carboxylated derivatives; sulfated derivatives; alkylated derivatives; hydroxyalkylated derivatives; methylated derivatives; and carboxy-β-cyclodextrins, e.g. succinyl-β-cyclodextrin (SCD), and 6^A-amino-6^A-deoxy-N-(3-carboxypropyl)-β-cyclodextrin. All of these materials can be made according to methods known in the prior art. Suitable derivatized cyclodextrins are disclosed in, e.g., Modified Cyclodextrins: Scaffolds and Templates for Supramolecular Chemistry (Eds. Christopher J. Easton, Stephen F. Lincoln, Imperial College Press, London, UK, 1999) and New Trends in Cyclodextrins and Derivatives (Ed. Dominique Duchene, Editions de Santé, Paris, France, 1991).

Sulfobutyl ether β-cyclodextrin (CAPTISOL, CyDex Inc., degree of substitution = 6.6), 2-hydroxypropyl β-cyclodextrin (HP-β-CD, CERESTAR, degree of substitution =

5.5), succinylated-β-cyclodextrin (S-CD, Cyclolab), and 2,6,di-o-methyl-β-cyclodextrin (DM-CD, Fluka) %w/w solutions were prepared at their native pH or buffered as needed. Sulfoalkyl ether γ-CD and sulfoalkyl ether α-CD derivatives were obtained from CyDex, Inc. (Lenexa, KS) and The University of Kansas (Lawrence, KS).

The amount of derivatized cyclodextrin required to provide the desired effect will vary according to the materials comprising the formulation.

Different cyclodextrins are able to solubilize a corticosteroid to different extents. FIG. 1A depicts a molar phase solubility curve for budesonide with HP-β-CD, SBE7-β-CD, and γ-CD as compared to water. The inventors have found that SAE-CD is superior to other cyclodextrins and cyclodextrin derivatives at solubilizing budesonide. On a molar basis, SBE-β-CD is a better solubilizer of budesonide than HP-β-CD. In addition, the solubilizing power among the SAE-CD derivatives followed about this rank order for budesonide over a SAE-CD concentration range of 0.04 to 0.1 M: SBE5.2-γ-CD ~ SPE5.4-γ-CD > SBE6.1-γ-CD > SBE7-α-CD > SBE9.7-γ-CD ~ SBE6.7-β-CD > SPE7-β-CD. For example, a 0.1 M concentration of SBE7-β-CD was able to solubilize a greater amount of budesonide than either γ-CD or HP-β-CD. Moreover, SAE-CD-containing nebulizable formulations provide a greater output rate for corticosteroid by nebulization as compared to γ-CD or HP-β-CD administered under otherwise similar conditions. Additional phase solubility data is depicted in FIG. 1B for various SBE-γ-CD derivatives (SBE4.9-γ-CD, SBE5.23-γ-CD, SBE6-γ-CD, SBE9.67-γ-CD, and SBE4.9-γ-CD) and CAPTISOL. The data indicate that the SBE-γ-CD derivatives generally outperform CAPTISOL in dissolution of budesonide.

The output rate (the rate at which the dose of the therapeutically effective agent(s) in the corticosteroid solution is administered or delivered) will vary according to the performance parameters of the device used to administer the dose. The higher the output rate of a given device, the lower the amount of time required to deliver or administer the corticosteroid solution, as defined herein, or the dose of the therapeutically effective agent(s) in the corticosteroid solution.

Nebulization of CAPTISOL solutions provides several advantages with respect to other cyclodextrins. The droplets leaving the nebulizer are of a more advantageous size and the CAPTISOL solutions are nebulized faster than similar solutions of other Cyclodextrins. The smaller droplet size of aerosolized composition is favored for delivery

of active agents such as a corticosteroid to the paranasal sinus cavities and/or deep nasal cavity.

CAPTISOL is emitted from a nebulizer faster and also to a greater extent than the other cyclodextrins, thus the output rate of the nebulizer is greater when CAPTISOL is nebulized. The output rate is highest for the CAPTISOL solution as compared to other cyclodextrin solutions indicating that an equivalent amount of drug can be delivered in a shorter period of time. Under the conditions used, β-CD is unable to solubilize an equivalent amount of corticosteroid due to the limited solubility of β-CD in water.

The compositions of the invention can be made from other suspension-based aqueous formulations, which formulations can be adapted for nasal delivery, by addition of SAE-CD thereto. Exemplary suspension-based aqueous formulations include the UDB formulation (Sheffield Pharmaceuticals, Inc.), VANCENASE™ AQ (beclomethasone dipropionate aqueous suspension; Schering Corporation, Kenilworth, NJ), ATOMASE™ (beclomethasone dipropionate aqueous suspension; Douglas Pharmaceuticals Ltd., Aukland, Australia), BECONASE™ (beclomethasone dipropionate aqueous suspension; Glaxo Wellcome), NASACORT AQ™ (triamcinolone acetonide nasal spray, Aventis Pharmaceuticals), TRI-NASAL™ (triamcinolone acetonide aqueous suspension; Muro Pharmacaceuticals Inc.) and AEROBID-M™ (flunisolide inhalation aerosol, Forest Pharmaceuticals), NASALIDE™ and NASAREL™ (flunisolide nasal spray, Ivax Corporation), FLONASE™ (fluticasone propionate, GlaxoSmithKline), and NASONEX™ (mometasone furoate, Schering-Plough Corporation).

The suspension formulation can comprise corticosteroid present in particulate, microparticulate, nanoparticulate or nanocrystalline form. Accordingly, an SAE-CD can be used to improve the administration of a corticosteroid suspension-based formulation. Moreover, the SAE-CD outperforms other cyclodextrin derivatives.

In some embodiments, SAE-CD (in solid or liquid form) and a suspension-based formulation comprising corticosteroid are mixed. The SAE-CD is present in an amount sufficient to increase the amount of solubilized corticosteroid, i.e. decrease the amount of unsolubilized corticosteroid, therein. Prior to administration, the liquid can be optionally aseptically filtered or terminally sterilized. The liquid is then nasally administered to a subject. As a result, the amount of drug that the subject receives is higher than the subject would have received had the unaltered suspension formulation been administered.

In some embodiments, SAE-CD (in liquid form, as ready-to-use liquid or as a concentrate) and a solid formulation comprising corticosteroid are mixed to form a liquid composition. The SAE-CD is present in an amount sufficient to solubilize a substantial portion of the corticosteroid. The liquid is then administered nasally or ophthalmically using a suitable administration device.

In other embodiments, SAE-CD (in solid form) and a solid formulation comprising corticosteroid are mixed to form a solid mixture to which is added an aqueous liquid carrier in an amount sufficient to form a nebulizable formulation. Mixing and/or heating are optionally employed upon addition of the liquid carrier to form the formulation. The SAE-CD is present in an amount sufficient to solubilize a substantial portion of the corticosteroid. The formulation is then administered nasally using an administration device as defined herein.

In some embodiments, the nasal device is a nebulizer for nasal administration. The size of the reservoir varies from one type of nebulizer to another. The volume of the liquid formulation can be adjusted as needed to provide the required volume for loading into the reservoir of a particular type or brand of nebulizer. The volume can be adjusted by adding additional liquid carrier or additional solution containing SAE-CD. In general, the reservoir volume of a nebulizer is about 10 µl to 100 mL. Low volume nebulizers, such as ultrasonic and vibrating mesh/vibrating plate/vibrating cone/vibrating membrane nebulizers, pre-filled reservoir strips inclusive of delivery nozzle typically have a reservoir volume of 10 µl to 6 mL or 10 µl to 5 mL. The low volume nebulizers provide the advantage of shorter administration times as compared to large volume nebulizers.

Example 28 details a procedure for preparation of a solution of the invention to be used with a low volume (low reservoir volume and/or low reservoir residual volume) nebulizer, such as an AERx nebulizer. The solutions of the invention can be nebulized with any nebulizer; however, with an AERx delivery system that coordinates both the nasal inspiration and delivery processes to optimize deep paranasal sinus cavity penetration, an initial sample volume of about 10 µl to 100 µl, or 50 µl can be used to load AERx Strip multiple unit dose container. Administration of this solution with the system makes it feasible for a therapeutic dose to be administered to a subject in a single puff (a single full nasal inspiration by a subject, i.e. 3 – 5 seconds) via nebulization. Based on general performance expectations of such devices the corticosteroid can be expected to be

delivered to the nose in a single dosing event using corticosteroid solutions prepared with SAECD.

Example 32 details a procedure for the comparison of nebulization parameters in four different nebulizers using a formulation of the invention and PULMICORT RESPULES (suspension-based formulation). In each case, the formulation of the invention out performs the suspension-based formulation. The solution of the invention provide a 1.25, 1.4, 2.1, 3.3, 3.67, 1.25 to 3.7, or 1.25 to 4 fold increase in the amount of budesonide delivered. Under the conditions tested, the AIRSEP MYSTIQUE was most efficient at emitting/nebulizing the SAE-CD / budesonide formulation.

In some embodiments, a suspension-based formulation is converted to a liquid formulation prior to administration (as a mist or aerosol) to a subject. The conversion can take place in the same container in which the suspension is provided, in a different container, or in the reservoir of an administration device. In order to form a liquid composition, a substantial portion of the corticosteroid must be dissolved. As used in reference to the amount of dissolved corticosteroid, a "substantial portion" is at least 20% wt., at least 30% wt., at least 40% wt., or at least 20% wt and less than 50% wt. of the corticosteroid. As used in reference to the amount of dissolved corticosteroid, a "major portion" is at least 50% wt. of the corticosteroid.

Pharmacists working in compounding pharmacies can and do prepare suspension-based formulations comprising corticosteroid. Such pharmacists will now be able to prepare a single use or multi-use liquid compositions by employing a method described herein. Alternatively, a subject (patient) undergoing corticosteroid treatment can convert the suspension-based formulation to a liquid formulation of the invention by employing a method described herein. Instead of preparing the liquid formulation from the suspension at the pharmacy, a kit containing the suspension formulation and SAE-CD can be prepared.

The concentration of SAE-CD in solution can be expressed on a weight to weight or weight to volume basis; however, these two units are interconvertible. When a known weight of cyclodextrin is dissolved in a known weight of water, the %w/w cyclodextrin concentration is determined by dividing the cyclodextrin weight in grams by the total weight (cyclodextrin + water weight) in like units and multiplying by 100. When a known weight of cyclodextrin is dissolved to a known total volume, the %w/v cyclodextrin concentration is determined by dividing the cyclodextrin weight in grams by the total

volume in milliliters and multiplying by 100. The correlation between the two cyclodextrin concentration percentages was experimentally determined by preparing various %w/w cyclodextrin solutions and measuring the density of each with a pycnometer at 25°C. The density (g/mL) of each %w/w CAPTISOL solution is presented in the table below.

CAPTISOL % w/w	Density (g/mL)	Viscosity (Cp, 25C)
59.4	1.320	527.0
49.4	1.259	51.9
39.7	1.202	17.0
29.8	1.149	5.91
19.7	1.095	2.78
8.5	1.041	1.75
0.0	1.002	1
slope =	0.0053	
y-intercept =	0.995	
correlation =	0.9989	

The resulting linear relationship readily enables the conversion of CAPTISOL concentrations expressed in %w/w to that of %w/v by the following equation:

$$\%w/v = ((\%w/w * slope) + y\text{-intercept}) * \%w/w$$

where the slope and intercept values are determined from a linear regression of the density data in the table. For example, by using the above equation, a 40%w/w CAPTISOL solution would be equivalent to a ~48.3% w/v CAPTISOL solution.

In some embodiments, the composition comprises less than or about 25% wt./wt. of SAE-CD for administration by nebulizer, or less than or about 50% wt./wt. of SAE-CD for administration with metered administration devices.

The nose comprises the nostrils, or nares, which admit and expel air for respiration, nose hairs (vibrissae), which catch airborne particulate contaminants and prevent them from reaching the lungs, olfactory mucosa, and the nasal cavity. Within the nasal cavity, target sites for delivery or active agent include the middle meatus, superior turbinate and posterior regions. The paranasal sinuses (paranasal sinus cavities) are connected to the nasal cavity by small orifices call ostia. The paranasal sinuses include the: (1) the maxillary sinuses, also called the antra, which are located under the eyes, in the upper jawbone; (2) the frontal sinuses, which lie above the eyes, in the bone of the forehead; (3)

the ethmoid sinuses, positioned between the nose and the eyes, backwards into the skull; and (4) the sphenoid sinuses, which are more or less in the centre of the skull base.

The nasal cavity and the paranasal sinuses are lined with mucosa. These mucosae can be often affected by conditions such as allergies and infections. Nasal administration of the solutions of the methods, systems, devices, and compositions of the invention provide improved means to deliver therapeutically useful active agents to these mucosae and to treat diseases, disorders and/or symptoms thereof.

Anatomically, the eyes and nose are connected via the nasolacrimal duct and indirectly through local neurosensory (e.g. the trigeminal nerve) mechanisms. Allergens and allergic treatments from the ocular surface drain through the nasolcarimal duct into the inferior turbinate of the nose. Through the nasolacrimal duct, ocular treatments can affect nasal symptoms in patients suffering from allergic rhinitis. Fluids can travel from the eyes to the nose within five minutes, and topical treatments can positively affect nasal symptoms induced by a conjunctival allergen challenge (Spangler *et al.*, *Clin Ther 25*(8): 2245-2267 (2003)). Thus, topical ocular treatments can be beneficial in treating both ocular and nasal symptoms of allergic rhinitis.

The paranasal sinuses are, under normal circumstances, poorly ventilated during breathing. Most of the air exchange of the sinuses occurs through the diffusion of air through the ostia, whereas little or no convective flow is observed. If an aerosol, such as a therapeutic aerosol generated by a conventional nebuliser, is inspired through the nose, the aerosol will flow through the nasal cavity. Since there is virtually no active flow into the paranasal sinuses, very little or almost none of the aerosol is deposited therein. However, the droplet size of the aerosol or mist administered nasally to a subject can be varied to provide preferential deposition in the nasal cavity versus paranasal sinus cavities or vice versa. The relative percentage of paranasal sinus cavity deposition can be increased by employing a nasal administration device capable of generating appropriately sized droplets and/or capable of generating a variable pressure aerosolized plume.

The mass median diameter (MMD) which will lead to the relatively largest aerosol deposition can depend on individual factors, in particular on the geometry of the paranasal sinuses including the ostia through which the aerosol reaches the sinuses. For example, the volume of the sinuses and the diameter of the ostia differ substantially between individuals. A larger diameter of the ostia is believed to favor the entrance of larger aerosol droplets into the sinuses, even though the diameters of the ostia and of the droplets

are of completely different magnitudes. If the individual sinunasal anatomy, or a parameter derived therefrom, of a person to be treated with an aerosol is at least partially known, it is possible to select a particular MMD for optimised sinunasal or sinus delivery.

The target site for delivery of the formulation will depend upon the MMD of droplets (aerosol, mist, vapor, plume, or spray) administered to a subject. Generally, the smaller the droplet size the greater the percentage of paranasal sinus cavity, turbinate, and/or posterior nasal cavity deposition, and vice versa. In order to maximize nasal delivery (nose, sinus cavity, nasopharyngeal cavity, nasal vestibule, anterior region, superior turbinate, middle turbinate, inferior turbinate, and/or olfactory region), the formulation can be administered nasally and the MMAD can be at least about 3.5 microns, at least about 5 microns, at least about 10 microns, at least about 20 microns, at least about 35 microns, at least about 50 microns, at least about 100 microns, or at least about 150 microns.

In some embodiments, the MMD of the droplets in the aerosol (liquid phase dispersed within a continuous gas phase) can range from about 2 μm to about 6 μm, as measured by laser diffraction. In some embodiments, the most useful MMD for depositing the aerosol in the nasal cavity and in the paranasal sinuses can range from 3 μm to 3.5 μm. In some embodiments, the aerosol of the invention can have a MMD of about 2.5 μm to about 4.5 μm, about 3 μm to about 4 μm, or about 2.8 μm to about 3.5 μm. In further embodiments, the MMD is approximately 2.8 μm ± 0.2 μm, 3.0 μm ± 0.2 μm, 3.2 μm ± 0.2 μm, 3.4 μm ± 0.2 μm, 3.6 μm ± 0.2 μm, 3.8 μm ± 0.2 μm, or 4.0 μm ± 0.2 μm. Various appropriate analytical apparatuses to determine the mass median diameter are known and commercially available, such as the Malvern MasterSizer X or Malvern SprayTec. The geometric distribution of the aerosolised liquid particles or droplets can be determined simultaneously with the mass median diameter.

Delivery of active agent to the deep nasal cavity or paranasal sinus cavities can also be promoted by an aerosol generating administration device comprising a droplet dispersion chamber suitable to provide for vortical particle flow of the aerosol prior to administration to a subject, wherein the administration device is capable of producing droplets substantially having a uniform mean diameter from about 5 μm to about 30 μm, about 8 μm to about 25 μm, about 10 μm to about 20 μm, about 10 μm to about 17 μm, about 10 μm to about 15 μm, and about 12 μm to about 17 μm. In some embodiments, the

aerosol comprises droplets substantially having a uniform mean diameter of about 2 μm to about 50 μm, about 5 μm to about 50 μm, about 5 μm to about 40 μm, about 5 μm to about 35 μm, about 5 μm to about 30 μm, about 5 μm to about 20 μm, about 5 μm to about 17 μm, about 5 μm to about 15 μm, about 8 μm to about 30 μm, about 8 μm to about 25 μm, about 8 μm to about 20 μm, about 10 μm to about 30 μm, about 10 μm to about 25 μm, about 11 μm to about 40 μm, about 11 μm to about 30 μm, about 11 μm to about 20 μm, about 11 μm to about 15 μm, about 15 μm to about 25 μm, about 15 μm to about 20 μm, or about 17 μm to about 23 μm. The phrase "substantially having a uniform mean diameter," as used herein with respect to the particle diameter ranges, refers to the use of particle collections, wherein at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or at least 98% have the preferred diameter range. In some embodiments, at least 60%, at least 70%, at least 80%, at least 90% or at least 95% of the nebulized particles are of the particle diameter range. In some embodiments, at least 70%, at least 80%, at least 90% or at least 95% of the nebulized particles are of the particle diameter range. The ViaNase ID™ (Kurve, Bothell, WA) electronic atomizer is particularly suitable for this mode of administration, and it delivers an aqueous liquid composition at a rate of about 0.1 mL/min.

Another method of promoting paranasal sinus cavity delivery of the composition is by: providing the liquid composition; and aerosolizing the liquid composition with an aerosol generator capable of emitting an aerosol whose pressure pulsates with a frequency in the range from about 10 Hz to about 90 Hz, wherein the aerosol generator is adapted to maintain an amplitude of pressure pulsation of the emitted aerosol of at least about 5 mbar. In some embodiments, the liquid composition has a volume of less than or about 5 mL. An aerosol flow which is superimposed with pressure fluctuations, or pressure pulses, creates periodic transient pressure gradients extending from the actively ventilated nasal cavity through the ostia to the paranasal sinuses, which gradients cause a short period of convective flow of air and aerosol into the sinuses until the pressure therein has become equal to the air pressure in the nasal cavity. A portion of the aerosol droplets which thus enter the paranasal sinuses are deposited therein onto the mucosa. The extent to which the aerosol is deposited depends on the droplet size. Droplets that are smaller than the preferred particle size are relatively likely to be expelled from the sinuses during the subsequent pulsation phase in which the aerosol pressure, and thus the pressure in the

nasal cavity, is lower than the pressure within the sinuses, and during which a convective flow of air from the paranasal sinuses to the nasal cavity occurs. In order that an effective flow of air and aerosol into the paranasal sinuses is induced, it is important to generate the pulsating aerosol with an appropriate device which is capable of emitting such aerosol, such as the PARI SINUS (including PARI LC Star, PARI LL and PARI Sprint) or VibrENT™ (PARI) nebulizer families whose compressors are adapted to generate a pulsating aerosol by employing pressure pulses of appropriate frequency and altitude.

Following administration of a dose of active agent to a subject, the relative percentage of the dose delivered to the nasal cavity versus the paranasal sinus cavities can vary such that: 1) a major portion (greater than 50% wt.) of the dose is delivered to the nasal cavity and a minor portion (less than 50% wt.) of the dose is delivered to the paranasal sinus cavities; 2) a major portion (greater than 50% wt.) of the dose is delivered to the paranasal sinus cavities and a minor portion (less than 50% wt.) of the dose is delivered to the nasal cavity; or 3) approximately 50% wt. of the dose is delivered to each the nasal cavity and the paranasal sinus cavities.

The invention can provide at least about 30% wt., at least about 40% wt., at least about 50% wt., at least about 60% wt., at least about 70% wt., at least about 80% wt., at least about 90% wt. or at least about 95% wt. for delivery of active agent into the nasal cavity and/or paranasal sinus cavities based upon the emitted dose.

As drug in solution will be distributed equally in the large and small droplets leaving the nebulizer, the fine particle fraction will contain more corticosteroid resulting in a greater inspirable dose that can reach the paranasal sinus cavities.

The in-vitro spray characteristics of the budesonide containing aqueous preparations of Example 33 were determined. The spray pattern at 3 and 6 cm, droplet size using a Malvern SprayTec, and respirable fraction using a cascade impactor were determined for Solution A and Suspension B. There were no apparent differences between Solution A and Suspension B in terms of axis lengths and ovality ratios at each spray distance. The average droplet size (D50) was 35 μm and 38 μm, respectively. The small droplets (D10) were 17 μm and 17 μm, respectively. The respirable fraction (% <9 μm) averaged less than 1% for both Solution A and Suspension B.

The performance of a solution of the invention in a nebulizer can depend upon the viscosity of the solution in its reservoir, the nebulization solution. The viscosity of an aqueous solution of SBE7-β-CD changes with respect to concentration approximately as

indicated in the table above. Viscosity of the composition can have an impact on percentage of nebulization composition emitted from a nebulizer, output rate of nebulized corticosteroid and droplet size distribution.

The amount of residual composition left in the reservoir of the nebulizer may be greater for solutions containing SAE-CD than for a budesonide-containing suspension. Under similar nebulization conditions, some nebulizers more efficiently reduce the volume of nebulization suspension than of nebulization solution in the reservoir of the nebulizer; however, this does not necessarily correspond with the total amount of drug emitted by the nebulizer.

In other words, the output rate of an SAE-CD nebulization solution versus that of a suspension can differ such that the solution has a higher output rate (in terms of drug output) than does the suspension.

An SAE-CD (SBE7-β-CD) concentration of less than or about 25% wt./wt. was identified as the approximate upper acceptable level for a composition adapted for use in a nebulizer, "acceptable" being defined as the upper concentration of SAE-CD that can be used without building up excessive viscosity, which can adversely affect the nebulization time and output rate. An SAE-CD concentration of less than or about 50% wt./wt. was identified as the approximate upper acceptable level for a composition adapted for use in a metered administration device. The practical upper limit for concentration of SAE-CD will vary among the particular type of administration device used. The upper acceptable concentration of SAE-CD in a liquid composition can vary according to the DS of the derivative, the alkyl chain length of the sulfoalkyl functional group, and/or the CD ring size of the SAE-CD.

Viscosity of the liquid composition can impact droplet size and droplet size distribution of the aerosolized composition. For example, the present compositions tend to form larger droplets, in terms of Dv50, at the lower concentrations, and thereby lower viscosity, of SAE-CD in the absence of corticosteroid, e.g. budesonide. A significant portion of the aerosolized mass is of a respirable size range. Moreover, the solutions containing SAE-CD apparently form droplets that are comparable in size to those of the nebulized suspension.

A solution (aqueous liquid composition) made by mixing a suspension of corticosteroid with SAE-CD is suitable for use in a variety of different air driven jet nebulizers.

The SAE-CD containing solutions are suitable for administration with an administration device, e.g. by nebulization, across a range of concentrations. Moreover, the droplet size distribution can be partially controlled by adjusting the concentration of SAE-CD.

Depending upon the nebulizer used, the conditions under which the nebulizer is operated and the concentration of SAE-CD in solution, different maximum output rates can be achieved. Use of SAE-CD in a composition, however, can result in an increased output rate of corticosteroid, e.g. budesonide, regardless of the format of the administration device.

Accordingly, the total nebulization time of the AERONEB GO is one fourth the time to sputter for the Pari LC+ air jet nebulizer. As a result, treatment time would be reduced with the pulsating membrane nebulizer as compared to the air jet nebulizer, and the amount of budesonide emitted from the pulsating membrane nebulizer is 2 to 3 times more than from the air jet nebulizer. It was also determined that the percent of drug exiting the nebulizer (the emitted dose) was 81% of the amount initially loaded into the reservoir (the nominal dose). Hence, less drug would need to be loaded into the pulsating membrane nebulizer to treat the patient in need thereof to provide the same "dose to subject" as provided by an air jet nebulizer.

A comparison of the AUC data can be made by consideration of the dose delivered to each subject ("dose to subject") or dose delivered to the nasal or paranasal cavities of each subject ("dose to nose") or dose delivered to the ocular surface of each subject ("dose to eye") or dose emitted by the administration device ("emitted dose") or dose available for administration or delivery ("nominal dose" or "nominal available dose" or "loaded dose").

Practice of the method or system of the invention with the composition of the invention can result in differences in the amount of corticosteroid absorbed systemically when compared to administration of a suspension-based corticosteroid composition, e.g. RHINOCORT AQUA. In some embodiments, the composition, method and system of the invention provide a higher AUC ((pg*h/mL)/μg of corticosteroid administered), lower AUC, or approximately the same AUC as does a suspension-based corticosteroid composition administered under substantially the same conditions. Similarly, in some embodiments, the composition, method and system of the invention provide a higher Cmax (pg of corticosteroid/mL of plasma), lower Cmax, or approximately the same Cmax

as does a suspension-based corticosteroid composition administered under substantially the same conditions.

The solutions of the invention can provide an enhanced pharmacokinetic profile over suspension-based formulations following their nasal or ophthalmic administration.

The corticosteroids that are useful in the present invention generally include any steroid produced by the adrenocortex, including glucocorticoids and mineralocorticoids, and synthetic analogs and derivatives of naturally occurring corticosteroids having anti-inflammatory activity. Suitable synthetic analogs include prodrugs and ester derivatives. Examples of corticosteroids that can be used in the compositions of the invention include aldosterone, beclomethasone, betamethasone, budesonide, ciclesonide (Altana Pharma AG), cloprednol, cortisone, cortivazol, deoxycortone, desonide, desoximetasone, dexamethasone, difluorocortolone, fluclorolone, flumethasone, flunisolide, fluocinolone, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluorocortisone, fluorocortolone, fluorometholone, flurandrenolone, fluticasone, fluticasone valerate, halcinonide, hydrocortisone, icomethasone, loteprednol etabonate, meprednisone, methylprednisolone, mometasone, paramethasone, prednisolone, prednisone, rofleponide, RPR 106541, tixocortol, triamcinolone, and their respective pharmaceutically acceptable derivatives, such as beclomethasone dipropionate (anhydrous or monohydrate), beclomethasone monopropionate, dexamethasone 21-isonicotinate, fluticasone propionate, icomethasone enbutate, tixocortol 21-pivalate, and triamcinolone acetonide. In some embodiments, the corticosteroid is beclomethasone dipropionate, budesonide, flunisolide, fluticasone propionate, mometasone furoate, triamcinolone acetonide, or a combination thereof. Other corticosteroids not yet commercialized, but that are commercialized subsequent to the filing of this application, are considered useful in the present invention unless it is otherwise established experimentally that they are not suitable.

Corticosteroids can be provided as the UDB (unit dose budesonide) formulation (Sheffield Pharmaceuticals, Inc.), VANCENASE AQ (beclomethasone dipropionate aqueous suspension; Schering Corporation, Kenilworth, NJ), ATOMASE (beclomethasone dipropionate aqueous suspension; Douglas Pharmaceuticals Ltd., Aukland, Australia), BECONASE (beclomethasone dipropionate aqueous suspension; Glaxo Wellcome, NASACORT AQ (triamcinolone acetonide nasal spray, Aventis Pharmaceuticals), TRI-NASAL (triamcinolone acetonide aqueous suspension; Muro Pharmacaceuticals Inc.) and AEROBID-M, (flunisolide inhalation aerosol, Forest

Pharmaceuticals), NASALIDE and NASAREL (flunisolide nasal spray, Ivax Corporation), FLONASE (fluticasone propionate, GlaxoSmithKline), VERAMYST (fluticasone furoate,GSK) and NASONEX (mometasone furoate, Schering-Plough Corporation). Corticosteroid commercially available for ophthalmic administration include perdnisolone sodium phosphate opthalmic solution (INFLAMASE) and prednisolone acetate opthalmic solution (PRED FORTE). SAE-CD can be added to all such commercial formulations to provide a composition of the invention.

Corticosteroids can be grouped according to their relative lipophilicity as described by Barnes et al. (*Am. J. Respir. Care Med.* (1998), 157, p. S1-S53), Miller-Larsson et al. (*Am J. Respir. Crit. Care Med.* (2003), 167, A773), D.E. Mager et al. (*J. Pharm. Sci.* (Nov. 2002), 91(11), 2441-2451) or S. Edsbäcker (Uptake, retention, and biotransformation of corticosteroids in the lung and airways. In: Schleimer RP, O'Byrne PMO, Szefler SJ, Brattsand R, editor(s). Inhaled steroids in asthma: optimizing effects in the airways. New York: Marcel Dekker, 2002: 213–246). Generally, the less lipophilic a corticosteroid is, the lower the amount of SAE-CD required to dissolve it in an aqueous medium and vice versa.

Some embodiments of the invention comprise a corticosteroid having a lipophilicity approximating or exceeding that of flunisolide. Some embodiments of the invention comprise a corticosteroid having a lipophilicity less than than that of flunisolide. Some embodiments of the invention exclude a corticosteroid having a lipophilicity less than flunisolide, i.e, embodiments excluding hydrocortisone, prednisolone, prednisone, dexamethasone, betamethasone, methylprednisolone, triamcinolone, and fluocortolone.

Corticosteroids that are less lipophilic than flunisolide generally require a SAE-CD to corticosteroid molar ratio of less than 10:1 to dissolve the corticosteroid in an aqueous medium. Exemplary corticosteroids of this group include hydrocortisone, prednisolone, prednisone, dexamethasone, betamethasone, methylprednisolone, triamcinolone, and fluocortolone. Some embodiments of the invention exclude corticosteroids that are less lipophilic than flunisolide. Other embodiments of the invention include corticosteroids that are more lipophilic than flunisolide.

Corticosteroids that are at least as lipophilic as or more lipophilic than flunisolide generally require a SAE-CD to corticosteroid molar ratio of more than 10:1 to dissolve the corticosteroid in an aqueous medium. In some embodiments, the corticosteroid used in the invention is at least as lipophilic as or more lipophilic than flunisolide. Exemplary

corticosteroids of this group include beclomethasone, beclomethasone dipropionate, beclomethasone monopropionate, budesonide, ciclesonide, desisobutyryl-ciclesonide, flunisolide, fluticasone, fluticasone propionate, mometasone, mometasone furoate, and triamcinolone acetonide.

Budesonide ((R,S)-11β, 16α, 17, 21-tetrahydroxypregna-1, 4-diene-3, 20-dione cyclic 16, 17-acetal with butyraldehyde; $C_{25}H_{34}O_6$; Mw: 430.5) is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity.

Commercial formulations of budesonide are sold by AstraZeneca LP (Wilmington, DE) under the trademarks ENTOCORT EC, PULMICORT RESPULES, RHINOCORT AQUA, RHINOCORT NASAL INHALER and PULMICORT TURBOHALER, and under its generic name. PULMICORT RESPULES suspension, which is a sterile aqueous suspension of micronized budesonide, is administered by inhalation using a nebulizer. The general formulation for a unit dose of the PULMICORT RESPULES is set forth in U.S. Patent No. 6,598,603, and it is an aqueous suspension in which budesonide is suspended in an aqueous medium comprising about 0.05 to 1.0 mg of budesonide, 0.05 to 0.15 mg of NaEDTA, 8.0 to 9.0 mg of NaCl, 0.15 to 0.25 mg of polysorbate, 0.25 to 0.30 mg of anhydrous citric acid, and 0.45 to 0.55 mg of sodium citrate per one mL of water. RHINOCORT NASAL INHALER is a metered-dose pressurized aerosol unit containing a suspension of micronized budesonide in a mixture of propellants. RHINOCORT® AQUA™ (U.S. Patents No. 6,986,904, No. 6,565,832, and No. 5,976,573; the entire disclosures of which are hereby incorporated by reference) is an unscented metered-dose manual-pump spray formulation (for nasal administration) containing a suspension of micronized budesonide in an aqueous medium. A unit dose of the formulation consists of: (a) about 32 μg budesonide; and (b) a mixture consisting of (1) microcrystalline cellulose and sodium carboxymethyl cellulose, the mixture present at about 0.5 to 2.5% by weight of the therapeutic composition, (2) dextrose, (3) Polysorbate 80 present at about 0.005 to 0.5% by weight of the therapeutic composition, (4) disodium edetate present at about 0.005 to 0.1% by weight of the therapeutic composition, (5) and potassium sorbate present at about 0.05 to 0.2% by weight of the therapeutic composition, wherein the budesonide is in the form of finely divided particles, at least 90% of which have a mass equivalent sphere diameter of less than 20 μm, suspended in an aqueous medium. Budesonide is commercially available as a mixture of two isomers (22R and 22S) and can also be prepared as a single isomer 22R-Budesonide.

The invention also provides compositions comprising a water soluble γ-CD derivative, a corticosteroid (either esterified or unesterified) and an aqueous liquid medium. In certain embodiments, the invention also provides compositions comprising a water soluble β-CD derivative, and an aqueous liquid carrier

The suitability of a corticosteroid for use in the liquid composition/formulaion can be determined by performing a phase solubility binding study as detailed in Example 23. Phase solubility binding data is used to determine the saturated solubility of a corticosteroid in the presence of varying amounts of SAE-CD in an aqueous liquid carrier. The phase solubility binding curve depicted in FIG. 3 demonstrates the saturated solubility of budesonide in an aqueous liquid carrier comprising γ-CD, HP-β-CD or SBE7-β-CD. A phase solubility curve in the graph defines the boundary for the saturated solubility the corticosteroid in solutions containing various different concentrations of cyclodextrin. A molar phase solubility curve can be used to determine the molar ratio of SAE-CD to corticosteroid or of corticosteroid to SAE-CD at various concentrations of corticosteroid. The area below the phase solubility curve, e.g. of FIG. 3, denotes the region where the corticosteroid is solubilized in an aqueous liquid medium to provide a substantially clear aqueous solution. In this region, the SAE-CD is present in molar excess of the corticosteroid and in an amount sufficient to solubilize the corticosteroid present in the liquid carrier. The boundary defined by the phase solubility curve will vary according to the corticosteroid and SAE-CD within a composition or formulation of the invention. The data detailed in Example 23 provides a summary of the minimum molar ratio of SAE-CD to corticosteroid required to achieve the saturated solubility of the corticosteroid in the composition or formulation of the invention under the conditions studied.

Depending upon the corticosteroid used in the formulation, the molar ratio of corticosteroid to SAE-CD (or of SAE-CD to corticosteroid) can vary in order to obtain a solution suitable for administration. Some embodiments of the invention include those wherein the corticosteroid to SAE-CD molar ratio is 0.5 to 0.0001 (1:2 to 1:10,000), 1:1 to 1:100, 1:1 to 1:10,000, 0.1 (1:10) to 0.03 (1:33.33), about 0.072 (1:13.89 or about 1:14) to 0.0001 (1:10,000), or 0.063 (1:15.873 or about 1:16) to 0.003 (1:333.33 or about 1:333). In some embodiments, the corticosteroid is budesonide and the molar ratio of SAE-CD to budesonide is greater than 10:1, or at least 14:1.

In some embodiments, the minimum molar ratio of SAE-CD to corticosteroid is about 1:1 or greater, about 1.5:1 or greater, about 1.6:1 or greater, about 1.8:1 or greater,

about 2:1 or greater, about 2.2:1 or greater, about 3:1 or greater, about 3.4:1 or greater, about 3.8:1 or greater, about 4:1 or greater, about 5:1 or greater, about 5.7:1 or greater, about 6:1 or greater, about 7:1 or greater, about 8:1 or greater, about 8.8:1 or greater, about 9:1 or greater, greater than about 10:1, about 12:1 or greater, greater than about 11:1, greater than about 13:1, greater than about 14:1, about 16:1 or greater, about 20:1 or greater, about 25:1 or greater, about 30:1 or greater, about 40:1 or greater. In some embodiments, the molar ratio of SAE-CD to corticosteroid ranges about from > 10:1 to about 1000:1, about from > 10:1 to about 100:1, about from > 10:1 to about 50:1, about from > 10:1 to about 30:1, about from > 10:1 to about 500:1. In some embodiments, the maximum molar ratio of SAE-CD to corticosteroid can be about 4,000:1 or less, about 3,000:1 or less, about 2,000:1 or less, about 1,500:1 or less, about 1,400:1 or less, about 1,200:1 or less, about 1,000:1 or less, about 900:1 or less, about 800:1 or less, about 600:1 or less, about 500:1 or less, about 400:1 or less, about 360:1 or less, about 300:1 or less, about 275:1 or less, about 250:1 or less, about 200:1 or less, about 150:1 or less, about 100:1 or less, about 80:1 or less, or about 60:1 or less. Combinations of the upper and lower molar ratios are useful.

The solubility of a corticosteroid in a composition is affected by its intrinsic solubility in the aqueous medium and its binding constant with SAE-CD. The higher the intrinsic solubility of the corticosteroid, the lesser the amount of SAE-CD required to solubilize a dose of it in the composition. The maximum concentration of corticosteroid in an aqueous solution containing SAE-CD is known as its concentration at saturated solubility. The saturated solubility of a corticosteroid in the presence of a fixed amount of SAE-CD will vary according to the identity of the corticosteroid and the SAE-CD. The higher the concentration at saturated solubility, the more soluble the corticosteroid is in the presence of SAE-CD. Example 45 summarizes saturated solubility data for some corticosteroids in the absence (intrinsic solubility of corticosteroid in the aqueous test medium) and in the presence of two different SAE-CD's as determined herein.

The binding of a corticosteroid to the SAE-CD can be characterized by its equilibrium binding constant. The higher the binding constant, the more tightly the corticosteroid is bound to the SAE-CD. Example 46 summarizes the equilibrium binding constants (K) for some corticosteroids in the presence of Captisol® or SBE6.1-γ-CD (0.04 M).

The equilibrium binding constant data can be used in combination with the phase solubility data (saturated solubility data) to prepare compositions according to the invention having a target concentration of corticosteroid and SAE-CD. Accordingly, some embodiments of the invention comprise a corticosteroid having an intrinsic solubility in water that approximates or is less than the intrinsic solubility of flunisolide (less than about $11x10^{-5}$ M or less than about 11.3 $x10^{-5}$ M) in water as determined herein. In some embodiments, the invention comprises a corticosteroid having an intrinsic solubility in water that is greater than that of flunisolide.

Even though a composition or formulation of the invention can comprise the corticosteroid present in an aqueous medium at a concentration up to its saturated solubility in the presence of a particular concentration of SAE-CD, some embodiments of the invention include those wherein the corticosteroid is present at a concentration that is less than its saturated solubility in the presence of that concentration of SAE-CD. The corticosteroid can be present at a concentration that is 95% or less, 90% or less, 85% or less, 80% or less, or 50% or less of its saturated solubility as determined in the presence of SAE-CD. It is generally easier to prepare solutions that comprise the corticosteroid at a concentration that is less than its saturated solubility in the presence of SAE-CD.

Therefore, the molar ratio of SAE-CD to corticosteroid in a formulation or composition of the invention can exceed the molar ratio obtained at the saturated solubility of the corticosteroid in the presence of SAE-CD, such as defined by the phase solubility binding curve for the corticosteroid. In such a case, the molar ratio of SAE-CD to corticosteroid in the composition or formulation can be at least about 1%, at least about 2%, at least about 5%, at least about 7.5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 50%, at least about 75%, at least about 100%, or at least about 200% greater than the molar ratio at the saturated solubility of the corticosteroid in the presence of SAE-CD. For example, if the molar ratio at the saturated solubility is about 14:1, then the molar ratio in the composition or formulation can be at least about 14.1:1 (for at least 1% higher), at least about 14.3:1 (for at least 2% higher), at least about 14.7:1 (for at least 5% higher), at least about 15.4:1 (for at least 10% higher), at least about 16.1:1 (for at least 15% higher), at least about 16.8:1 (for at least 20% higher), at least about 17.5:1 (for at least 25% higher), at least about 21:1 (for at least 50% higher), at least about 24.5:1 (for at least 75% higher), at least about 28:1 (for at least 100% higher), or at least about 42:1 (for at least 100% higher).

Changes in the molar ratio of SAE-CD to corticosteroid can also have an impact upon the dissolution rate of corticosteroid in an aqueous medium. Generally, increasing the molar ratio results in an increase in the rate of dissolution of the corticosteroid.

The corticosteroid compound can be present in the final, diluted corticosteroid nebulizable composition in an amount from about 1 μg/mL to about 10 mg/mL, about 10 μg/mL to about 1 mg/mL, or about 20 μg/mL to about 500 μg/mL. For example, the drug concentration can be between about 30 and 1000 μg/mL for triamcinolone acetonide, and between about 50 and 2000 μg/mL for budesonide, depending on the volume to be administered. By following the preferred methods of the present invention, relatively high concentrations of the corticosteroid can be achieved in an aqueous-based composition.

Similarly, the corticosteroid compound is present in the final, diluted corticosteroid composition designed for nasal administration in an amount from about 10 μg/mL to 6 mg/mL, 50 μg/mL to about 10 mg/mL, about 100 μg/mL to about 2 mg/mL, or about 300 μg/mL to about 1 mg/mL. For example, the drug concentration can range from about 250 μg/mL and about 1 mg/mL or about 250 μg/mL and about 6 mg/mL for triamcinolone acetonide, and range from about 400 μg/mL to about 1.6 mg/mL, 40 μg/mL to about 6 mg/mL, 40 μg/mL to about 3 mg/Ml, 250 μg/mL to about 6 mg/mL, or about 250 μg/mL to about 3 mg/mL for budesonide, depending on the volume to be administered.

For the treatment of nasal cavity, paranasal sinus cavity, and/or ophthalmic disease, symptoms or disorders, the corticosteroid composition is prepared as described herein. The corticosteroid for such treatment can be, beclomethasone dipropionate, beclomethasone monopropionate, betamethasone, budesonide, ciclesonide, desisobutyryl-ciclesonide, flunisolide, fluticasone, fluticasone propionate, fluticasone furoate, mometasone, mometasone furoate, or triamcinolone acetonide, and can be formulated in the concentrations set forth herein.

The corticosteroid or any other therapeutic (active) agent herein can be present in its neutral, ionic, salt, basic, acidic, natural, synthetic, diastereomeric, isomeric, enantiomerically pure, enantiomerically enriched, racemic, solvate, anhydrous, hydrate, hemi-hydrate, sesqui-hydrate, chelate, derivative, analog, esterified, non-esterfied, polymorph, co-crystal, other common form, or a combination thereof. When used in reference to a therapeutic agent, "combination thereof" is taken to mean a combination of any two or more of the forms of the therapeutic agent defined herein. Accordingly,

whenever a therapeutic agent is named herein, all such forms available are included. For example, all known forms of budesonide are considered within the scope of the invention.

As used herein, a dose includes a unit dose, a nominal dose, emitted dose, nominal available dose, dose to subject, dose to nose, dose to eye, or other such term of art. Unless otherwise specified, the term a "unit dose" is a single dose, such as a single spray from a metered spray device. An administration of an effective amount, effective dose, or therapeutically effective amount to a subject can comprise one or more unit doses. In certain embodiments, the effective dose can be a single unit dose administered to one nostril or one eye. In certain embodiments, the therapeutically effective amount can be two unit doses administered to one nostril or one eye. In certain embodiments, the effective dose can be two unit doses, with one unit dose administered to each eye or each nostril. In some embodiments, the therapeutically effective amount can be more than two unit doses, with more than one dose administered to a nostril(s) or eye(s). The term "effective amount" or "effective dose" or "therapeutically effective amount" is the amount or quantity of active agent that is sufficient to elicit the required or desired therapeutic effect, or the amount that is sufficient to elicit an appreciable biological response when administered to a subject when given at one event or period of administration. A single period of administration can comprise administration of 1, 2, 3, 4, 5, 6, 7, 8, or more unit doses. For administration with a nebulizer, or any other device that continuously generates an aerosol over a period of time, the "period of administration" is that period of time required to deliver a therapeutically effective amount of an active agent to one or both nostrils of a subject. For administration with a nebulizer, or any other device that continuously generates an aerosol over a period of time, the unit dose is an amount contained in the reservoir of the device that is delivered in one period of administration, i.e., for a nebulizer, the unit dose is the therapeutically effective dose delivered in one period of administration. A nebulizer can contain a single unit dose that is administered over a single period of administration. Alternatively, a nebulizer can contain multiple unit doses that are administered in multiple periods of administration, for example, 1 to 8 unit doses administered in 1 to 8 periods of administration. A nebulizer can also contain multiple reservoirs containing single or multiple unit doses. For administration with a metered administration device, i.e., a device that provides a fixed volume or amount of composition upon actuation, e.g., pump nasal spray, squeeze bottle, atomizer, dropper, and other similar devices, the event of administration, for delivery of an effective dose, is a

predetermined number of actuations of the device which releases a corresponding predetermined number of unit doses, e.g., 1 to 8 actuations of the administration device releases 1 to 8 unit doses in one or both nostrils of a subject. The unit dose of active agent delivered is assumed to be the amount of active agent emitted from the administration device, i.e., the emitted dose.

The term "nominal dose" refers to an amount of active agent placed in the reservoir of a nebulizer, wherein the volume of liquid in the reservoir is determined according the size of the reservoir. The term "nominal available dose" refers to the amount of active agent that is determined could be or should have been available to a subject when administered a formulation of the invention by nebulization but formulation is/was not administered in its entirety. The term "emitted dose" refers to the amount of active agent emitted from a nebulizer. The term "dose to subject" refers to the amount of active agent delivered to and retained by a subject following administration of a formulation of the invention by nebulization. The term "dose to nose" refers to the amount of active agent delivered to and retained by the nose (nasal cavity and/or paranasal sinus cavities) of a subject following administration of a formulation of the invention by nebulization.

The daily dose of the corticosteroid is generally about 0.05 mg to 10 mg, depending on the drug and the disease, in accordance with the 2006 Physician's Desk Reference (PDR). However, in view of the improved bioavailability of a corticosteroid when administered as a solution of the invention, the dose required to achieve a desired clinical endpoint, clinical benefit or therapeutic benefit can be lower than the corresponding dose indicated in the PDR.

The following table provides exemplary dosing regimens for various corticosteroids as included in the commercially available branded nasal administration products in particular dosage strengths. The composition of the invention can be dosed according to these same dosing regimens or other dosing regimens herein.

Generic Name /Brand Name	**Dosing Regimen**	**Drug Amount per unit dose (Total Dose Range per day)**	**Total Weight/ Volume administered**
Beclomethasone Dipropionate Beconase® AQ (GSK)	1-2 sprays in each nostril twice daily	42 mcg (168-336 mcg/day)	100 mg

Generic Name /Brand Name	Dosing Regimen	Drug Amount per unit dose (Total Dose Range per day)	Total Weight/ Volume administered
Ciclesonide Omnaris® (Sepracor)	2 sprays in each nostril once daily	50 mcg (200 mcg/day)	70 µL
Fluticasone Propionate Flonase® (GSK)	Starting: 2 sprays in each nostril once daily or 1 spray twice daily Maintenance: 1 spray in each nostril once daily	50 mcg Starting: (200 mcg/day) Maintenance: (100 mcg/day)	100 mg
Fluticasone Furoate Veramyst® (GSK)	Starting: 2 sprays in each nostril once daily Maintenance: 1 spray in each nostril once daily	27.5 mcg Starting: (110 mcg/day) Maintenance: (55 mcg/day)	50 µL
Budesonide Rhinocort® Aqua (AZ)	1-2 sprays in each nostril once or twice daily	32 mcg (64 mcg in Canada) (64 – 320 mcg/day)	51 mg
Triamcinolone Acetonide Nasacort® AQ (Sanofi-Aventis)	2 sprays in each nostril once daily	55 mcg (220 mcg/day)	100 mg
Mometasone Furoate Nasonex® (Schering-Plough)	2 sprays in each nostril once daily	50 mcg (200 mcg/day)	100 mg
Flunisolide Nasarel® (Ivax)	2 sprays in each nostril twice daily Titrate: 2 sprays per nostril three times daily	29 mcg- Nasarel (232-464 mcg/day)	100 mg
Dexamethasone Dexacort®Turbinaire (USB)		84mcg (inhalation vapor)	
Betamethasone + Neomycin sulphate Betnesol-N® Nasal Drops (GSK)	2-3 drops instilled in each nostril 2-3 times daily	Strength: 1 mg/mL (1.04 mg – 3.6 mg/day)	0.13 – 0.20 mL

Generic Name /Brand Name	Dosing Regimen	Drug Amount per unit dose (Total Dose Range per day)	Total Weight/ Volume administered
Fluticasone Propionate Flixonase® Nasule Drops (Allen & Hanbury/GSK)	1 nasule contents instilled in each nostril 1-2 times daily	400 mcg/ Nasule (400-800 mcg/day)	400 µL
Dexamethasone + tramazoline HCl (Dexa-Rhinapray® Duo	1 spray per nostril up to 6 times daily; not for use for more than 14 consecutive days	Dexamethasone: 20 mcg; (40-240 mcg/day)_ Tramazoline: 120 mcg (240-1440 mcg/day)	

The following table provides exemplary dosing regimens for various corticosteroids as included in the commercially available branded ocular administration products in particular dosage strengths. The composition of the invention can be dosed according to these same dosing regimens or other dosing regimens herein.

Generic Name	Brand Name	Drug Strength	Dosing Regimen per Affected Eye	Total Drug Delivered Per Day*
Dexamethasone (susp)	Maxidex® (Alcon)	0.1% w/v	1-2 drops every 4-6 hours	0.16 – 0.48 mg*
Dexamethasone Sodium phosphate (soln)	Decadron® (Merck)	0.1% w/v	1-2 drops every hour while awake & every 12 hours at night	0.8 – 1.6 mg* Also assumes 20 drops/day
Fluorometholone	Fluor-Op® (Novartis)	0.1%, 0.25% w/v	1 drop 2 -4 times a day	0.06 – 0.24 mg
Loteprednol etabonate	Alrex® (Bausch & Lomb)	0.2% w/v	1 drop 4 times a day	0.32 mg*
Prednisolone Acetate (susp)	Pred-Forte® (Allergan)	0.12%, 0.125, 1% w/v	1-2 drops 2 to 4 times a day	1.2 – 9.4 mg (for the 1% susp)
Prednisolone Sodium Phosphate (soln)	Inflamase Forte® (Novartis)	0.125%, 0.1% w/v	1-2 drops every hour while awake & every 12 hours at night	0.8 – 2 mg* Also assumes 20 drops/day

*A typical volume of an eye drop has been found to range from 25 to 50 mcL. So if the volume is not specified in the product label, it was assumed for the purposes of this chart that the volume is 40 mcL as indicated by a asterisk.

A dose of corticosteroid, such as budesonide, can also be administered once daily, once every two days, seven days per week, once every week, once every month, for an extended period of time, such as several days, weeks, or even longer, or even less frequently. A dose of budesonide, or corticosteroid, can be administered twice, thrice or more times per day or on an as-needed basis. Administration can be during the daytime and/or nighttime. In some embodiments, such as set forth in U.S. Patents No. 6,598,603 and No. 6,899,099, a dose comprises 0.05 to 2.0 mg or 0.25 to 1.0 mg of budesonide.

In some embodiments, a dose comprises about 1 μg to about 20 mg, about 1 μg to about 10 mg, about 0.01 mg to about 10 mg, about 0.025 mg to about 10 mg, about 0.05 mg to about 5 mg, about 0.1 mg to about 5 mg, about 0.125 mg to about 5 mg, about 0.25 mg to about 5 mg, about 0.5 mg to about 5 mg, about 0.05 mg to about 2 mg, about 0.1 mg to about 2 mg, about 0.125 mg to about 2 mg, about 0.25 mg to about 2 mg, about 0.5 mg to about 2 mg, about 10 μg to about 2.5 mg, about 5 μg to about 500 μg, about 5 μg to about 250 μg, about 5 μg to about 130 μg, about 45 μg to about 1000 μg, about 1 μg, about 10 μg, about 16 μg, about 25 μg, about 27.5 μg, about 29 μg, about 32 μg, at least about 25 μg, about 40 μg, about 42 μg, about 45 μg, about 48 μg, about 50 μg, about 55 μg, about 64 μg, about 84 μg, about 96 μg, about 100 μg, about 125 μg, about 128 μg, about 200 μg, about 250 μg, about 400 μg, about 800 μg, about 25 μg to about 66 μg, about 48 μg to about 81 μg, about 73 μg to about 125 μg, about 95 μg, about 35 μg to about 95 μg, about 25 μg to about 125 μg, about 60 μg to about 170 μg, about 110 μg, about 170 μg, about 45 μg to about 220 μg, about 45 μg to about 85 μg, about 48 μg to about 82 μg, about 85 μg to about 160 μg, about 140 μg to about 220 μg, about 120 μg to about 325 μg, about 205 μg, about 320 μg, about 325 μg, about 90 μg to about 400 μg, about 95 μg to about 170 μg, about 165 μg to about 275 μg, or about 275 μg to about 400 μg of corticosteroid, such as budesonide, said dose being a unit dose, nominal dose, nominal available dose, emitted dose, delivered dose, dose to subject, dose to eye, or dose to nose.

Some embodiments of the invention also provide a unit dose of a therapeutic corticosteroid solution comprising: about 32 μg to 64 μg of budesonide; SAE-CD; pharmaceutically acceptable aqueous liquid carrier; disodium edetate present at of about 0.005 to about 0.1% by weight of the therapeutic compositionunit dose; and potassium sorbate present at of about 0.05 to about 0.2% by weight of the therapeutic

compositionunit dose, and wherein the corticosteroid solution is suitable for nasal administration to a mammal as a unit dose. subject in need thereof.

Some embodiments of the invention also provide a method of treating of treating, preventing or ameliorating in a subject a corticosteroid-responsive disease or disorder, the method comprising:

metering into the nose of a mammal a the subject a therapeutically effective amount of budesonide that is less than about 320 μg per day, delivered as 8 or more unit doses, wherein each unit dose consists of: about 32 μg of budesonide; SAE-CD; disodium edetate present at of about 0.005 to about 0.1% by weight of the therapeutic compositionunit dose; potassium sorbate present atof about 0.05 to about 0.2% by weight of the therapeutic compositionunit dose; and a pharmaceutically acceptable aqueous liquid carrier. In some embodiments, the therapeutically effective amount of budesonide is delivered as 7 unit doses, 6 unit doses, 5 unit doses, 4 unit doses, 3 unit doses, 2 unit doses or as one unit dose. In some embodiments, the unit dose comprises 64 μg, 96 μg, 128 μg, 160 μg, 192 μg, 224 μg, 256 μg, 288 μg, or 320 μg of budesonide.

In some embodiments, the corticosteroid solution has a pH of about 3.5 to about 5 or about about 4.2 to about 4.6.

The corticosteroid can be present at a concentration of about 20 μg to about 30 mg of corticosteroid per mL of solution. As a result, about 10 mg to 500 mg of SAE-CD, or 10 mg to 250 mg of SAE-CD, or 10 mg to 300 mg of SAE-CD per mL or per g of solution in order to dissolve a substantial portion of the corticosteroid.

Due to the wide range of reservoir volumes available for administration devices and of varying dose requirements among the corticosteroids, a formulation of the invention can comprise 1 μg to 20 mg of corticosteroid in 0.01 mL to 100 mL of solution volume. The compositions of the invention can comprises a dose or unit dose of corticosteroid in an approximate solution volume of 10 μl to 100 mL, 10 μl to 5000 μl, 10 μl to 2.5 mL, 20 μl to 5 mL, 10 μl to 500 μl, 10 μl to 200 μl, 10 μl to 400 μl, 50 μl to 50 mL, 50 μl to 10 mL, 50 μl to 5 mL, 0.1 to 10 mL, 0.1 mL to less than 10 mL, 0.1 mL to 7.5 mL, 0.1 mL to 5 mL, 0.1 mL to 3 mL, 0.1 mL to 2 mL, 0.1 mL to 1 mL, 0.05 mL to 7.5 mL, 0.05 mL to 5 mL, 0.05 mL to 3 mL, 0.05 mL to 2 mL, 0.05 mL to 1 mL, 50 μl to 137 μl, 50 μl to 70 μl, 137 μl to 400 μl, 50 μl to 200 μl, 25 μl, 50 μl, 75 μl, 100 μl, 150 μl, 200 μl, 250 μl, 500 μl, 750 μl, 1 mL, 2 mL, 5 mL, or 10 mL.

An administration device can be adapted to emit about 10 to about 500 µl, about 0.2 to about 5 mL, or about 0.5 to about 100 mL of a liquid composition per actuation or per dose. In some embodiments, the administration device comprises a nozzle which comprises a valve. Together, the nozzle and valve can be adapted to release 25 µl to 260 µl, 50 µl to 137 µl, 50 µl to 70 µl, 137 µl to 400 µl, or 51 to 100 mg of a liquid composition of the invention.

The composition of the invention can be packaged for single-use or multi-use. A single use package comprises a single dose of corticosteroid and a multi-use package comprises two or more doses of corticosteroid. The packaging can comprise one or more containers. A container can comprise one or more doses. A single use container comprises a single dose, and a multi-use container comprises two or more doses. Suitable packaging and containers include, by way of example and without limitation, a bottle, vial, ampoule, syringe, blister, capsule, or blow/fill/seal container, or other devices such as those detailed in the examples. The packaging can in a preservative free system such as the Advanced Preservative Free system from Pfeiffer, or the Freepod from Valois, or in a single use spray device such as the Pfeiffer Bidose System or Unitdose System.

The composition can exit the device as a liquid, gel, vapor, fine aerosol, mist, cloud or plume. Depending upon the mode of administration, the composition can be delivered to the nasal cavity, paranasal sinus cavities, or delivered topically to the eye(s) of a subject.

The administration device can employ single use (single dose) or multi-use (multi-dose) packaging. An administration device can be used repeatedly with single use or multi-use packages and/or containers.

The fill volume for the reservoir of a multi-dose, metered dose nasal spray must be sufficient to provide for the number of actuations required to initially prime the spray pump, periodically reprime the pump, and to provide the desired number of doses in a consistent manor. Since the tail-off characteristics (performance when container is nearly empty) can vary as a function of pump design, container geometry and formulation, the fill volume should be sufficient to compensate for all these variables. As such, the reservoir in an administration device can comprise an overfill. As used herein, "overfill" is the amount or percentage of extra composition (either in terms of the volume or weight of the composition or the amount of drug in the composition) added to the composition in the reservoir to compensate for the tail-off characteristics of the device. In some

embodiments, the overfill is at least about 1%, at least about 2.5%, at least about 5%, at least about 7.5%, at least about 10%, at least about 15%, at least about 25%, at least about 35%, at least about 45%, at least about 50% of the target volume or weight of composition in a unit dose or dose of the composition.

The time required to administer or deliver a dose of the invention will depend upon its mode of administration, i.e., the administration device used. For administration with an administration device that substantially continuously emits an aerosol over a period of time, e.g. nebulizer, the time required to administer or deliver a dose of corticosteroid is less than 30 min, less than 20 min, less than 10 min, less than 7 min, less than 5 min, less than 3 min, or less than 2 min, or the time is about 0.05 min to 10 min, about 0.1 min to 5 min, about 0.1 min to 3 min, about 0.1 min to 2 min, about 0.1 min to 1.5 min, about 0.5 min to about 1.5 min, or about 1 min. The time will vary according to the dose of active agent in, the concentration of active agent in, and the volume of the composition in the reservoir of an administration device, and it will also depend upon the format of the administration device, aerosolization efficiency, and reservoir volume. In a given administration device, the lower the volume of the liquid composition, the more quickly a corresponding dose of active agent is administered or delivered. The higher the concentration of active agent in the composition, the faster a dose of the active agent can be administered or delivered.

For metered volume (or metered weight) administration devices that generate a plume or aerosol by actuation, e.g., squeeze bottle pump spray, pump spray, atomizer, the time for administration of a dose is merely the time it takes to affect one, two or more actuations of the device in one or both nostrils of a subject or about the time it takes for a subject to take a single breath (about 1 sec to 3 sec, or 1 sec to 5 sec).

The formulation of the invention can be used to deliver two or more different active agents (active ingredients, therapeutic agents, etc.). Particular combinations of active agents can be provided by the present formulation. Some combinations of active agents include: 1) a first drug from a first therapeutic class and a different second drug from the same therapeutic class; 2) a first drug from a first therapeutic class and a different second drug from a different therapeutic class; 3) a first drug having a first type of biological activity and a different second drug having about the same biological activity; 4) a first drug having a first type of biological activity and a different second drug having a

different second type of biological activity. Exemplary combinations of active agents are described herein.

A corticosteroid, such as budesonide, can be administered as its isomeric pair or single isomer and in combination with one or more other drugs (active ingredients, therapeutic agents, active agents, etc., the terms being used interchangeably herein unless otherwise specified). Such other drugs include: B_2 adrenoreceptor agonist, topical anesthetic, D_2 receptor agonist, anticholinergic agent, antiinfective agent, antibiotic, antifungal agent; hormones such as insulin, growth hormone, growth hormone releasing factor, glucagon, somatostatin, chorionic gonadotropin, adrenocorticotropic hormone (ACTH), and interferon; antiinflammatory agents such as aspirin, aminopyrine, acetaminophen, ibufenac, ibuprofen, indomethacin, colchicine, sulpyrine, mefenamic acid, phenacetin, phenylbutazone, flufenamic acid and probenecid; antibiotics such as penicillin or its derivatives, cephalosporin or its derivatives; erythromycin, tetracycline, furadiomycin, leucomycin; chemotherapeutic agents such as sulfathiazole and nitrofurazone; cardiac agents such as digitalis and digoxin; blood vein dilating agents such as nitroglycerin and papaverine hydrochloride; cough curing agents such as codeine; azulen; phenovalin; pepsin; enzymes such as lysozyme hydrochloride; other systemic agents such as antihypertensives and diuretic; tranquilizers; sex hormone; vitamin; ulcer medication; analgesic; decongestant; expectorant; antitussive; antihistamine agent; bronchodilator; topical anesthetic; sensory agents; oral care agents; miscellaneous respiratory agent; gastrointestinal agent; and combinations thereof.

B_2-Adrenoreceptor agonists for use in combination with the compositions provided herein include, but are not limited to, Albuterol (alpha^1-(((1,1 -dimethylethyl)amino)methyl)-4-hydroxy-1,3-benzenedimethanol); Bambuterol (dimethylcarbamic acid 5-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,3-phenylene ester); Bitolterol (4-methylbenzoic acid 4-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,2-phenyleneester); Broxaterol (3-bromo-alpha-(((1,1-dimethylethyl)amino)methyl)-5-isoxazolemethanol); Isoproterenol (4-(1-hydroxy-2-((1-methylethyl-)amino)ethyl)-1,2-benzene-diol); Trimetoquinol (1,2,3,4-tetrahydro-1-((3,4- , 5-trimethoxyphenyl)-methyl)-6,7-isoquinolinediol); Clenbuterol (4-amino-3,5-dichloro-alpha-(((1,1-diemthylethyl)amino)methyl)benzenemethanol); Fenoterol (5-(1-hydroxy-2-((2-(4-hydroxyphenyl)-1-methylethyl)amino)ethyl)-1,3-benzenediol); Formoterol (2-hydroxy-5-((1RS)-1-hydroxy-2-(((1RS)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)

formanilide); (R,R)-Formoterol; Desformoterol ((R,R) or (S,S)-3-amino-4-hydroxy-alpha-(((2-(4-methoxyphenyl)-1-methyl-ethyl)amino)methyl)benzenemethanol); Hexoprenaline (4,4'-(1,6-hexane-diyl)-bis(imino(1-hydroxy-2,1-ethanediyl)))bis-1,2-benzenediol); Isoetharine (4-(1-hydroxy-2-((1-methylethyl)amino)butyl)-1,2-benzenediol); Isoprenaline (4-(1-hydroxy-2-((1-methylethyl)amino)ethyl)-1,2-benzenediol); Meta-proterenol (5-(1-hydroxy-2-((1-methylethyl)amino)ethyl)-1,3-benzened- iol); Picumeterol (4-amino-3,5-dichloro-alpha-(((6-(2-(2-pyridinyl)ethoxy)hexyl)-amino)methyl) benzenemethanol); Pirbuterol (.alpha.^{6}-(((1,1-dimethylethyl)-amino)methyl)-3-hydroxy-2,6-pyridinemethanol); Procaterol (((R*,S*)-(.+-.)-8-hydroxy-5-(1-hydroxy-2-((1-methylethyl)amino)butyl)-2(1H)-quinolin-one); Reproterol ((7-(3-((2-(3,5-dihydroxyphenyl)-2-hydroxyethyl)amino)-propyl)-3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione); Rimiterol (4-(hydroxy-2-piperidinylmethyl)-1,2-benzenediol); Salbutamol ((.+-.)-alpha^{1}-(((1,1-dimethylethyl)amino)methyl)-4-hydroxy-1,3-b- enzenedimethanol); (R)-Salbutamol; Salmeterol ((.+-.)-4-hydroxy-.alpha^{1}-(((6-(4-phenylbutoxy)hexyl)-amino)methyl)-1,3-benzenedimethanol); (R)-Salmeterol; Terbutaline (5-(2-((1,1-dimethylethyl)amino)-1-hydroxyethyl)-1,3-benzenediol); Tulobuterol (2-chloro-.alpha.-(((1,1 -dimethylethyl)amino)methyl)benzenemethanol); and TA-2005 (8-hydroxy-5-((1R)-1-hydroxy-2-(N-((1R)-2-(4-methoxyphenyl)-1-methylethyl)amino)ethyl)carbostyril hydrochloride).

Dopamine (D_2) receptor agonists include, but are not limited to, Apomorphine ((r)-5,6,6a,7-tetrahydro-6-methyl-4H-dibenzo[de,glquinoline-10,11-diol); Bromocriptine ((5'.alpha.)-2-bromo-12'-hydroxy-2'-(1-methylethyl)-5'-(2-methylpropyl)ergotaman-3',6',18-trione); Cabergoline ((8.beta.)-N-(3-(dimethylamino)propyl)-N-((ethylamino)carbonyl)-6-(2-propenyl)ergoline-8-carboxamide); Lisuride (N'-((8-alpha-)-9,10-didehydro-6-methylergolin-8-yl)-N,N-diethylurea); Pergolide ((8-beta-)-8-((methylthio)methyl)-6-propylergoline); Levodopa (3-hydroxy-L-tryrosine); Pramipexole ((s)-4,5,6,7-tetrahydro-N^{6}-prop- yl-2,6-benzothiazolediamine); Quinpirole hydrochloride (trans-(-)-4aR-4,4a,5,6,7,8,8a,9-octahydro-5-propyl-1H-pyrazolo[3,4-g]quinoline hydrochloride); Ropinirole (4-(2-(dipropylamino)ethyl)-1,3-dihydro-2H-indol-2-one); and Talipexole (5,6,7,8-tetrahydro-6-(2-propenyl)-4H-thia-zolo[4,5-d]azepin-2-amine). Other dopamine D_2 receptor agonists for use herein are disclosed in International Patent Application Publication No. WO 99/36095, the relevant disclosure of which is hereby incorporated by reference.

Anticholinergic agents for use herein include, but are not limited to, ipratropium bromide, oxitropium bromide, atropine methyl nitrate, atropine sulfate, ipratropium, belladonna extract, scopolamine, scopolamine methobromide, homatropine methobromide, hyoscyamine, isopriopramide, orphenadrine, benzalkonium chloride, tiotropium bromide and glycopyrronium bromide. In certain embodiments, the compositions contain an anticholinergic agent, such as ipratropium bromide or tiotropium bromide, at a concentration of about 5 μg/mL to about 5 mg/mL, or about 50 μg/mL to about 200 μg/mL. In other embodiments, the compositions for use in the methods herein contain an anticholinergic agent, including ipratropium bromide and tiotropium bromide, at a concentration of about 83 μg/mL or about 167 μg/mL.

Other active ingredients for use herein in combination therapy, include, but are not limited to, IL-5 inhibitors such as those disclosed in U.S. Patents No. 5,668,110, No. 5,683,983, No. 5,677,280, No. 6,071,910 and No. 5,654,276, the relevant disclosures of which are hereby incorporated by reference; antisense modulators of IL-5 such as those disclosed in U.S. Pat. No. 6,136,603, the relevant disclosure of which is hereby incorporated by reference; milrinone (1,6-dihydro-2-methyl-6-oxo-[3,4'-bipyridine]-5-carbonitrile); milrinone lactate; tryptase inhibitors such as those disclosed in U.S. Pat. No. 5,525,623, the relevant disclosure of which is hereby incorporated by reference; tachykinin receptor antagonists such as those disclosed in U.S. Patents No. 5,691,336, No. 5,877,191, No. 5,929,094, No. 5,750,549 and No. 5,780,467, the relevant disclosures of which are hereby incorporated by reference; leukotriene receptor antagonists such as montelukast sodium (Singular™, R-(E)]-1-[[[1-[3-[2-(7-chloro-2-quinolinyl)ethenyl-]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]-propyl]thio]methyl] cyclopro- paneacetic acid, monosodium salt), 5-lypoxygenase inhibitors such as zileuton (Zyflo™, Abbott Laboratories, Abbott Park, Ill.), and anti-IgE antibodies such as Xolair™ (recombinant humanized anti-IgE monoclonal antibody (CGP 51901; IGE 025A; rhuMAb-E25), Genentech, Inc., South San Francisco, Calif.), and topical anesthetics such as lidocaine, N-arylamide, aminoalkylbenzoate, prilocaine, etidocaine (U.S. Patents No. 5,510,339, No. 5,631,267, and No. 5,837,713, the relevant disclosures of which are hereby incorporated by reference).

Analgesics useful for this invention include any narcotic and non-narcotic analgesics, such as menthol, acetaminophen, NSAIDs, salicylates including aspirin (acetylsalicylic acid), salsalate, sodium salicylate, diflunisal, etc. and mixtures thereof,

indomethacin and optically active isomers or racemates or active metabolites of NSAIDs (NSAIDs include propionic acid derivatives, acetic acid derivatives, fenamic acid derivatives, biphenylcarboxylic acid derivatives and oxicams) including fenoprofen, flurbiprofen, ibuprofen, ketoprofen, naproxen, oxaprozin, etodolac, indomethacin, ketorolac, nabumetone, sulindac, tolmetin, meclofenamate, mefenamic acid, piroxicam, bromfenac, carprofen, tiaprofenic acid, cicloprofen, diclofenac, benzydomine, their pharmaceutically acceptable salts and mixtures thereof. All of these, as well as acceptable dosage ranges, are described in the following: U.S. Pat. No. 4,749,720 to Sunshine et al. issued Jun. 7, 1988; U.S. Pat. No. 4,749,721 to Sunshine et al. issued Jun. 7, 1988; U.S. Pat. No. 4,749,722 to Sunshine et al. issued Jun. 7, 1988; U.S. Pat. No. 4,749,723 to Sunshine et al. issued Jun. 7, 1988; U.S. Pat. No. 4,749,711 to Sunshine et al. issued Jun. 7, 1988, U.S. Pat. No. 4,749,697 to Sunshine et al. issued Jun. 7, 1988, U.S. Pat. No. 4,783,465 to Sunshine et al., issued Nov. 8, 1988, U.S. Pat. No. 4,619,934 to Sunshine et al., issued Oct. 28, 1986, U.S. Pat. No. 4,840,962 to Sunshine et al. issued Jun. 20, 1989; U.S. Pat. No. 4,906,625 to Sunshine et al. issued Mar. 6, 1990; U.S. Pat. No. 5,025,019 to Sunshine et al. issued Jun. 18, 1991; U.S. Pat. No. 4,552,899 to Sunshine et al. issued Nov. 12, 1985, Facts and Comparisons, 1998, p. 242-260, all of which are incorporated by reference herein, in their entirety.

The decongestants used in the compositions of the present invention include, for example, pseudoephedrine, phenylpropanolamine, phenylephrine, epinephrine, ephedrine, naphazoline, xylometazoline, oxymetazoline, propylhexedrine, tetrahydrozoline, their pharmaceutically acceptable salts, and mixtures thereof.

The expectorants (also known as mucolytic agents) used in the present invention include, for example, guaifenesin, iodinated glycerol, glyceryl guaiacolate, terpin hydrate, ammonium chloride, N-acetylcysteine and bromhexine, ambroxol, iodide, their pharmaceutically acceptable salts, and mixtures thereof.

The antitussives used in the present invention include, for example, menthol (can also be used as an analgesic), dextromethorphan, chlophedianol, car-betapentane, caramiphen, noscapine, diphenhydramine, codeine, hydrocodone, hydromorphone, fominoben, benzonatate, their pharmaceutically-acceptable salts, and mixtures thereof.

Examples of antihistamine agent used in the present invention include both sedating and non-sedating antihistamines, such as diphenhydramine, clemastine, chlorpheniramine, brompheniramine, dexchlorpheniramine, dexbrompheniramine,

triprolidine, doxylamine, tripelennamine, heptadine, carbinoaxime, bromdiphenhydramine, hydroxyzine, pyrilamine, acrivastine, AHR-11325, phenindamine, astemizole, azatadine, azelastine, cetirizine, carebastine, efletirizine, mapinastine, ebastine, fexofenadine, ketotifen, lodoxine, loratadine, descarboethoxyloratadine, levocabastine, mequitazine, oxatomide, setastine, tazifyline, temelastine, terfenadine, tripelennamine, terfenadine carboxylate, phenyltoloxamine, pheniramine, antazoline, bilastine, bepotastine besilate, rupatadine, emedastine, tecastemizole, epinastine, levocetirizine, mizolastine, noberastine, norastemizole, olopatadine, pharmaceutically acceptable salts thereof, pharmaceutically active metabolites thereof, optically active isomers or racemates, and mixtures thereof. All of these antihistamines, as well as their acceptable dosage ranges, are described in: U.S. Patents to Sunshine et al. listed above under analgesics; Facts and Comparisons, 1998, p. 188-195, which is incorporated by reference herein in its entirety.

Antihistamines are commercially widely available. The invention includes embodiments wherein the antihistamine is azelastine, olopatadine, cetirizine, or loratadine. Azelastine (4-[(4-chlorophenyl)methyl]-2- (1-methylazepan-4-yl)-phthalazin-1-one) is an antihistamine and mast cell stabilizer commercially available as ASTELIN® (MedPointe Inc., Cranbury, NJ; MEDA Pharmaceuticals, Solna, Sweden) and indicated for the treatment of hay fever, seasonal allergies, and allergic conjunctivitis. Olopatadine is also an antihistamine and is commercially available as PATANASE® (Alcon. Ft. Worth, TX). These drugs are administered as follows. The compositions of the invention comprising these drugs can be administered according to the dosing regimens below or other dosing regimens disclosed herein.

Generic Name	Brand Name	Drug Strength	Dosing Regimen per Affected Eye	Total Drug Delivered per Day*
Ketotifen Fumerate	Zaditor® (Novartis)	0.025% w/v	1 drop every 12 hours	0.02 - 0.04 mg
Olopatadine HCl	Patanol®; Pataday™ (Alcon)	0.1%; 0.2% w/v	1-2 drops twice daily; 1 drop once daily	0.08 – 0.16 mg
Azelastine HCl	Optivar® (Meda)	0.05% w/v	1 drop twice daily	0.03 – 0.06 mg

Epinastine HCl	Elestat® (Allergan)	0.05% w/v	1 drop twice daily	0.04 mg*
Emadastine Difumerate	Emadine® (Alcon)	0.05% w/v	1 drop four times daily	0.08 mg*
Levocabastine HCl	Livostin® (Novartis)	0.05% w/v	1 drop four times daily	0.06 – 0.12 mg

*A typical volume of an eye drop has been found to range from 25 to 50 mcL. So if the volume is not specified in the product label, it was assumed for the purposes of this chart that the volume is 40 mcL as indicated by a asterisk.

In some embodiments, the composition of the invention comprises a dose or unit dose of azelastine present at an amount of about 30 µg to about 275 µg , about 65 mcg to about 1100 mcg, about 130 mcg to about 650 mcg, about 30 µg, about 65 µg, about 137 mcg, about 274 mcg, about 548 mcg, or about 1096 mcg.

In some embodiments, the composition of the invention comprises a dose or unit dose of olopatadine present at an amount of about 330 mcg to about 5500 mcg, about 330 mcg to about 2660 mcg, about 660 mcg to about 5320 mcg, about 660 mcg to about 2660 mcg, about 550 mcg to about 1330 mcg, about 665 mcg, about 1330 mcg, about 1995 mcg, about 2660 mcg, about 3325 mcg, about 3990 mcg, about 4655 mcg, or about 5320 mcg.

In some embodiments, the composition of the invention comprises a dose or unit dose of cetirizine present at an amount of about 0.25 mg to 5.55 mg, 0.25 mg to about 4.4 mg, 0.55 mg to 4.4 mg, 0.55 mg to 3.3 mg, 0.55 mg to 2.2 mg, about 0.55 mg, about 1.1 mg, about 2.2 mg, about 3.3 mg, about 4.4 mg, or about 5.5 mg per unit dose.

Bronchodilators used in the invention include, for example, terbutaline sulfate, isoetharine, aminophylline, oxtriphylline, dyphylline, ethylnorepinephrine, isoproterenol, epinephrine, isoprenaline, metaproterenol, bitoterol, theophylline, albuterol, isoproterenol and phenylephrine bitartrate, bitolterol, ephedrine sulfate, pirbuterol acetate, pharmaceutically acceptable salts thereof, and mixtures thereof. All of these bronchodilators, as well as their acceptable dosage ranges, are described in Facts and Comparisons, 1998, p. 173b-179e, which is incorporated by reference herein in its entirety.

Topical anesthetics include, for example, lidocaine, dibucaine, dyclonine, benzocaine, butamben, tetracaine, pramoxine, their pharmaceutically-acceptable salts, and mixtures thereof. All of these agents, as well as their acceptable dosage ranges, are

described in Facts and Comparisons, 1998, p. 601-607, which is incorporated by reference herein in its entirety.

Sensory agents include, for example, coolants, salivating agents, and warming agents. These agents are present in the compositions at a level of from about 0.001% to about 10%, preferably from about 0.1% to about 1%, by weight of the composition. Suitable cooling agents include carboxamides, menthols, thymol, camphor, capsicum, phenol, eucalyptus oil, benzyl alcohol, salicyl alcohol, ethanol, clove bud oil, and hexylresorcinol, ketals, diols, and mixtures thereof. Coolants can be paramenthan carboxyamide agents such as N-ethyl-p-menthan-3-carboxamide (WS-3 supplied by Sterling Organics), taught by U.S. Pat. No. 4,136,163, issued Jan. 23, 1979, to Watson et al., which is incorporated herein by reference in its entirety. Another paramenthan carboxyamide agent is N,2,3-trimethyl-2-isopropylbutanamide, known as "WS-23", and mixtures of WS-3 and WS-23. Additional coolants are selected from menthol, 3-1-menthoxypropane-1,2-diol, known as TK-10 supplied by Takasago Perfumery Co., Ltd., Tokyo, Japan, menthone glycerol acetal known as MGA, manufactured by Haarmann and Reimer, menthyl lactate known as Frescolat™ manufactured by Haarmann and Reimer, and mixtures thereof. Additional cooling agents include cyclic sulphones and sulphoxides and others, all of which are described in U.S. Pat. No. 4,032,661, to Rowsell et al., which is herein incorporated by reference. The terms "menthol" and "menthyl" as used herein include dextro- and levoratotory isomers of these compounds and racemic mixtures thereof. TK-10 is described in detail in U.S. Pat. No. 4,459,425, to Amano et al. and incorporated herein by reference.

Salivating agents include Jambu™ manufactured by Takasago Perfumery Co., Ltd., Tokyo, Japan. Warming agents include capsicum and nicotinate esters, such as benzyl nicotinate.

Miscellaneous respiratory agents include, for example, leukotriene receptor antagonists such as zafirlukast, zileuton; nasal inhalant products such as corticosteroids, other steroids, beclomethasone, flunisolide, triamcinolone; mucolytics such as acetylcysteine; anticholinergics such as ipratropium bromide; cromolyn sodium, nedocromil sodium; surfactants; and mixtures thereof. These agents can be present in the compositions at a level of from about 0.001% to about 10%, or from about 0.1% to about 5% by weight of the composition.

Antimicrobial agents can also be present. Such agents can include, but are not limited to, triclosan, 5-chloro-2-(2,4-dichlorophenoxy)-phenol, as described in The Merck Index, 11th ed. (1989), pp. 1529 (entry no. 9573) in U.S. Pat. No. 3,506,720, and in European Patent Application No. 0,251,591 of Beecham Group, PLC, published Jan. 7, 1988; chlorhexidine (Merck Index, no. 2090), alexidine (Merck Index, no. 222; hexetidine (Merck Index, no. 4624); sanguinarine (Merck Index, no. 8320); benzalkonium chloride (Merck Index, no. 1066); salicylanilide (Merck Index, no. 8299); domiphen bromide (Merck Index, no. 3411); cetylpyridinium chloride (CPC) (Merck Index, no. 2024; tetradecylpyridinium chloride (TPC); N-tetradecyl-4-ethylpyridinium chloride (TDEPC); octenidine; delmopinol, octapinol, and other piperidino derivatives; nicin preparations; zinc/stannous ion agents; antibiotics such as augmentin, amoxicillin, tetracycline, doxycycline, minocycline, and metronidazole; nystatin, tannic acid (forms protective film over cold sores, fever blisters, and canker sores), clotrimazole, carbamide peroxide, amlexanox (indicated for treatment of aphthous ulcers); and analogs and salts of the above antimicrobial antiplaque agents. The antimicrobial agents generally comprise from about 0.1% to about 5% by weight of the compositions of the present invention.

Exemplary suitable antiinfective, antibiotic and antifungal compounds for use in combination in a formulation of the invention are listed in the table below. A combination composition of the invention can comprise one or more corticosteroids and one or more other therapeutic agents and can be administered according to the dosing regimens below or other dosing regimens herein.

Generic Name	**Brand Name**	**Class**	**Dosing Range**
Amikacin	Amikin	Aminoglycoside	50-500 mg
Amphotericin B	Fungizone	Antifungal	2.5-45 mg
Azithromycin	Zithromax	Macrolide	50-400 mg
Aztreonam	Azactam	Monobactam	250-1000 mg
Cefazolin	Ancef, Kefzol	Cephlasporin (Gen I)	250-1000 mg
Cefepime	Maxipime	Cephlasporin (Gen IV)	125-1000 mg

Generic Name	Brand Name	Class	Dosing Range
Cefonicid	Moniacid	Cephlasporin (Gen II)	250-1000 mg
Cefoperazone	Cefobid	Cephlasporin (Gen III)	250-1000 mg
Cefotaxime	Claforan	Cephlasporin (Gen III)	250-1000 mg
Cefotetan	Cefotan	Cephlasporin (Cephamycin)	250-1000 mg
Cefoxitin	Mefoxin	Cephlasporin (Cephamycin)	250-1000 mg
Ceftazidime	Fortaz, Ceptaz	Cephlasporin (Gen III)	250-1000 mg
Ceftizoxime	Cefizox	Cephlasporin (Gen III)	250-1000 mg
Ceftriaxone	Rocephin	Cephlasporin (Gen III)	250-1000 mg
Cefuroxime	Ceftin	Cephlasporin (Gen II)	100-600 mg
Cephapirin	Cefadyl	Cephlasporin (Gen I)	250-1000 mg
Ciprofloxacin	Cipro	Quinolone	25-200 mg
Clindamycin	Cleocin	Lincosamide	50-600 mg
Doxycycline	Vibramycin	Tetracycline	10-100 mg
Fluconazole	Diflucan	Antifungal	12.5-150 mg
Gentamycin	Garamycin	Aminoglycoside	10-200 mg
Itraconazole	Sporanox	Antifungal	12.5-150 mg
Levofloxacin	Levaquin	Quinolone	40-200 mg
Meropenem	Merrin	Carbapenem	200-750 mg
Mezlocillin	Mezlin	Penicillin	300-1500 mg
Miconazole	Monistat	Antifungal	12.5-300 mg
Nafcilin	Nafcil	Penicillin	100-1000 mg

Generic Name	Brand Name	Class	Dosing Range
Ofloxacin	Floxin	Quinolone	25-200 mg
Piperacillin	Pipracil	Penicillin	100-1000 mg
Rifampin	Rifadin	Miscellaneous	500-5000 mg
Ticarcillin + Clavulanate	Timentin	Penicillin	500-5000 mg
Tobramycin	Nebcin	Aminoglycoside	10-200 mg
Vancomycin	Vancocin	Antifungal	50-400 mg

Other suitable antifungal agents include butoconazole, econazole, oxiconazole, sulconazole, tioconazole, posaconazole, terconazole, tiniconazole, voriconazole, anidulafungin (LY303366, VER-002), micafungin (FK463), Echinocandins, Cyclic Peptide Antifungals, Triazoles, genaconazole, ravuconazole, TAK-456 and TAK-457, ZD0870, UR-9625, UR-9746, UR-975 1 and UR-9825, T-8581, CS-758, SS-750, Echinocandin B (A30912A), Cilofungin (LY 121 01 9), FR901379 (echinocandin-type peptide, WF11899A), FR901469 (lipopeptidolactone), FR131535, FR203903, Aculeacin A-G, Mulundocandin, Sporiofungin, Pneumocandin A, S3 1794lF1, Corynecandin, Mer-WF3010, Fusacandin, Arthrichitin, Furanocandin, Azalomycins, LY 329960, DB 289, aminocandin, naftifine, terbinafine, caspofungin, nystatin, flucytosine, griseofulvin, and mixtures thereof.

The amount and/or concentration of corticosteroid and/or other therapeutically effective agent in a unit dose or dose of the composition can be as specified herein or as customarily present in known dosage forms comprising the same drugs.

The corticosteroid and/or other therapeutically effective agent, if present, can be administered to a subject in need thereof according to a dosing regimen as described herein or as recognized in the art as being suitable for the treatment of a disease, disorder or symptom therapeutically responsive to the corticosteroid and/or other therapeutically effective agent.

Methods of the invention can further comprise administering an additional therapeutically effective agent. In some embodiments, the corticosteroid and additional therapeutically effective agent are administered simultaneously, sequentially, or separately.

Dosing, use and administration of the therapeutic agents disclosed herein is generally intended to follow the guidelines set forth in the Physician's Desk Reference, 55th Edition (Thompson Healthcare, Montvale, NJ, 2005) the relevant disclosure of which is hereby incorporated by reference. The amount of drug included in the compositions of the present invention will be whatever amount is therapeutically effective and will depend upon a number of factors, including the identity and potency of the chosen drug, the disorder being treated, the health of the subject being treated and other such factors common to the pharmaceutical industry for prescription of drugs to a subject. The drugs will generally be administered according to their known dosing regimens such as those disclosed in the Pharmaceutical Desk Reference or those recognized as suitable by the Food and Drug Administration (USA), European Medicines Agency (Europe), National Institute of Health Sciences (Japan), and National Administration of Drugs, Food, and Medical Technology (Administración Nacional de Medicamentos, Alimentos y Tecnología Médica, Argentina).

Non-limiting exemplary compositions of the invention comprising a corticosteroid and another active agent can comprise the following components.

FORM.	Corticosteroid (A)	Other Active Ingredient (B)
I	Budesonide	Olopatadine*
II	Budesonide	Azelastine*
III	Budesonide	Azithromycin
IV	Budesonide	Voriconazole
V	Budesonide	Azithromycin and voriconazole
VI	Mometasone furoate	Azelastine*
VII	Mometasone furoate	Olopatadine*
VIII	Mometasone furoate	Azithromycin
IX	Fluticasone proprionate	Loratadine
X	Fluticasone proprionate	Desloratadine
XI	Fluticasone propionate	Cetirizine*
XII	Fluticasone propionate	Azelastine*
XIII	Fluticasone propionate	Olopatadine*
XIV	Fluticasone furoate	Azelastine*
XV	Fluticasone furoate	Olopatadine*
XVI	Ciclesonide	Azelastine*
XVII	Ciclesonide	Olopatadine*

* denotes use as its salt, e.g. hydrochloride salt, or free base

A combination formulation of the invention can comprise one or more corticosteroids and one or more second therapeutic (active) agents selected from azithromycin, clinafloxacin, gemifloxacin (Factive®), moxifloxacin (Avelox®), gatifloxacin (Tequin®, Zymar®), sitafloxacin, roxithromycin, norfloxacin, cetirizine hydrochloride, desloratadine, fexofenadine hydrochloride, natamycin, fluconazole itraconazole ketoconazole, capsaicin, benzocaine, tetrahydrozoline hydrochloride, oxymetazoline HCl, epinephrine, zileuton, cromolyn sodium, triazolam, a pharmaceutically acceptable salt thereof, and an isomer thereof.

A composition comprising a corticosteroid and another active agent can be prepared according to the examples below. In some embodiments, the SAE-CD is present in an amount sufficient to solubilize the corticosteroid and the other active agent. In other embodiments, the SAE-CD is present in an amount sufficient to solubilize the corticosteroid or the other active agent.

Depending upon the other active agent used, it may or may not bind competitively against the corticosteroid with the SAE-CD. In some embodiments, the SAE-CD has a higher equilibrium binding constant for the other active agent than it has for the corticosteroid. In some embodiments, the SAE-CD has a higher equilibrium binding constant for the corticosteroid than it has for the other active agent. In some embodiments, the SAE-CD has approximately the same equilibrium binding constant for the other active agent as it has for the corticosteroid. Alternatively, the other active agent does not bind with the SAE-CD even though the corticosteroid does. Accordingly, the invention provides embodiments wherein, the SAE-CD solubilizes the corticosteroid, the other active agent, or a combination thereof. The invention also provides embodiments wherein, the SAE-CD solubilizes at least a major portion of the corticosteroid, the other active agent, or of each. The invention also provides embodiments wherein, the SAE-CD does not solubilize the other active agent.

The molar ratio of SAE-CD to corticosteroid and SAE-CD to other active agent can vary as needed to provide a combination formulation as described herein. The SAE-CD is generally present in molar excess over the corticosteroid, the other active agent, or both.

A composition of the invention can comprise SAE-CD, corticosteroid, aqueous liquid carrier, and an antihistamine. In some embodiments, the composition contains SAE-

CD, budesonide, water (or aqueous buffer) and azelastine. Example 14 details the preparation of such a composition. Other solutions of azelastine in buffer with varying amounts of SAE-CD, in the absence of budesonide, were prepared and scanned by UV Spectrometer. The change in absorption as a function of SAE-CD concentration was plotted and used to determine the equilibrium binding constant of azelastine with SAE-CD, according to the Benesi-Hildebrand equation. The equilibrium binding constant of azelastine with Captisol was found to be approximately 10,000 at pH 4.5. The binding constant for budesonide under similar conditions was determined to be about 1000; therefore, azelastine will compete with budesonide, or another corticosteroid, for binding to SAE-CD. Accordingly, the amount of SAE-CD present can be increased to permit complete dissolution of both drugs.

The equilibrium binding constant of the corticosteroid can change when a second active agent is present in a composition of the invention. Since azelastine hydrochloride (AZ-HCl) has an approximately 10-fold higher binding constant for SBE-β-CD than does budesonide (BUD), the amount of SBE-β-CD present in an aqueous composition of the three needs to be sufficient to solubilize both drugs. Example 19 details a procedure for determination of the phase solubility of budesonide in the presence of varying amounts of azelastine. The results are depicted in FIGS. 11A (for SBE-β-CD) and 11B (for SBE-β-CD and SBE-γ-CD). FIG. 11A is a chart of the phase solubility of BUD as a function of AZ-HCl concentration in solution in the presence of 20-40 mM CAPTISOL. The data indicate that the concentration of BUD at saturated solubility decreases as the concentration of AZ-HCl increases. FIG. 11B is a chart of the phase solubility of BUD as a function of SBE-β-CD or SBE-γ-CD concentration in solution using various different concentrations of AZ-HCl (1.00 – 2.75 mg.mL). The data indicate that the concentration of BUD at saturated solubility decreases as the concentration of AZ-HCl increases and that higher concentrations of SBE-CD are required in order to dissolve the BUD as the concentration of AZ-HCl increases. Thus, increasing the amount of AZ-HCl in the solution decreases the overall solubility of BUD. The equilibrium complex stability constant between Azelastine and SBE-β-CD is surprisingly about 5-times greater than that between Azelastine and SBE-γ-CD (~ 10000 M-1 versus 2200 M^{-1}) while the equilibrium complex stability constant for budesonide with SBE-β-CD is half that of the equilibrium complex stability constant for budesonide with SBE-γ-CD (i.e.1000 M^{-1} versus 2000 M^{-1}).

Surprisingly, the nominal amount of SBE-β-CD required to solubilize a similar dose of budesonide in the presence of azelastine is greater than in the absence of azelastine as well as greater than the increase required if the cyclodextrin was SBE-γ-CD. Therefore, it is advantageous to prepare solution compositions of these combinations using SBE-γ-CD due to the efficiency of interaction so as to require less of one SAExCD versus another different SAEyCD to solubilize similar amounts of actives in the presence of each other.

In some embodiments of the invention, the concentrations of budesonide, azelastine (free base or HCl salt), and SAE-CD (e.g. SBE-CD) in the composition are as follows:

a) budesonide is present at a concentration of about 0.627 mg/g (32 mcg/51 mg), about 0.457 mg/mL (32 mcg/70 mcL), 0.320 mg/mL (32 mcg/100mcL), about 0.320 mg/g (32 mcg/100mg), from 0.04 mg/mL to 2 mg/mL,or from 0.04 mg/mL to 1 mg/mL;

b) azelastine is present at a concentration of about 0.5 to about 10 mg/mL, about 0.5 to about 6 mg/mL, about 1 to about 5 mg/mL, about 1 to about 3 mg/mL, about 2 to about 3 mg/mL, about 2.5 to about 3 mg/mL, about 2.75 mg/mL about 0.137 mg/ 51 mg, about 0.137 mg/0.137 mL, about 0.137 mg/0.050 mL, about 0.137 mg/0.070 mL, about 0.137 mg/0.1 mL, or about 1 mg/mL to 10 mg/mL (0.137 mg/0.020 mL); and/or

c) SAE-CD is present at a concentration of about 100 mg/mL, about 10 to about 500 mg/mL, or about 10 to about 500 mg/g.

In some embodiments, the concentrations of budesonide, azelasatine and SAE-CD in the composition are as set forth in the table below.

[budesonide]	[azelastine]	[SBE-CD]
32 mcg/ 51 mg of composition	137 mcg/51 mg of composition	7 mg/51 mg
32 mcg/ 70 mcL of composition	137 mcg/70 mcL of composition	7 mg/70 mcL
32 mcg/ 100 mg of composition	137 mcg/100 mg of compostition	7mg/100 mg
0.04 to 2 mg/mL of composition	1 to 10 mg/mL of composition	10 to 500 mg/mL of composition (or per g of composition)

In some embodiments of the invention, the concentrations of budesonide, olopatadine (free base or HCl salt), and SAE-CD (e.g. SBE-CD) in the composition are as follows:

a) budesonide is present at a concentration of about 0.627 mg/g (32 mcg/51 mg), about 0.457 mg/mL (32 mcg/70 mcL), 0.320 mg/mL (32 mcg/100mcL), about 0.320 mg/g (32 mcg/100mg), from 0.04 mg/mL to 2 mg/mL, or from 0.04 mg/mL to 1 mg/mL;

b) olopatadine is present at a concentration of about 0.5 to about 15 mg/mL, about 1 to about 10 mg/mL, about 1 to about 15 mg/mL, about 5 to about 10 mg/mL, about 6 to about 7 mg/mL, about 0.665 mg/0.10 mL, about 0.665 mg/0.70 mL, about 0.665 mg/0.50 mL, 5.32 mg/ 0.2mL, or about 6.5 mg/ 5mL; and/or

c) SAE-CD is present at a concentration of about 100 mg/mL, about 10 to about 500 mg/mL, or about 10 to about 500 mg/g.

In some embodiments of the invention, the concentrations of budesonide, cetirizine (free base or HCl salt), and SAE-CD (e.g. SBE-CD) in the composition are as follows:

a) budesonide is present at a concentration of about 0.627 mg/g (32 mcg/51 mg), about 0.457 mg/mL (32 mcg/70 mcL), 0.320 mg/mL (32 mcg/100mcL), about 0.320 mg/g (32 mcg/100mg), from 0.04 mg/mL to 2 mg/mL, or from 0.04 mg/mL to 1 mg/mL;

b) cetirizine is present at a concentration of about 0.25 to about 4.4 mg/mL, about 0.55 to about 4.4 mg/ mL, about 1.1 to about 4.4 mg/ mL, about 1.1 to about 2.2 mg/ mL, about 1 to about 25 mg/mL, about 2 to about 24 mg/mL, about 5 to about 20 mg/mL, about 7 to about 15 mg/mL, about 10 to about 12 mg/mL, about 1.1 mg/0.1mL, about 1.1 mg/0.05 mL, about 1.1 mg/0.70 mL, about 1.1 mg/0.2 mL, or about 2.2 mg/ 5 mL; and/or

c) SAE-CD is present at a concentration of about 100 mg/mL, about 10 to about 500 mg/mL, or about 10 to about 500 mg/g.

In some embodiments of the invention, the concentrations of mometasone furoate, olopatadine (free base or HCl salt), and SAE-CD (e.g. SBE-CD) in the composition are as follows:

a) mometasone furoate is present at a concentration of about 0.5 mg/mL (50 mcg/100 mcL), about 0.71 mg/mL (50 mcg/70 mcL), about 1.0 mg/mL (50 mcg/100 mcL), about 1.0 mg/mL (200 mcg/200 mcL), or about 0.1 mg/mL (500mcg/5000 mcL);

b) olopatadine is present at a concentration of about 0.5 to about 15 mg/mL, about 1 to about 10 mg/mL, about 1 to about 15 mg/mL, about 5 to about 10 mg/mL, about 6 to about 7 mg/mL, about 0.665 mg/0.10 mL, about 0.665 mg/0.70 mL, about 0.665 mg/0.50 mL, 5.32 mg/ 0.2mL, or about 6.5 mg/ 5mL; and/or

c) SAE-CD is present at a concentration of about 300 mg/mL, about 10 to about 500 mg/mL, or about 10 to about 500 mg/g.

In some embodiments of the invention, the concentrations of fluticasone propionate, cetirizine (free base or HCl salt), and SAE-CD (e.g. SBE-CD) in the composition are as follows:

a) fluticasone propionate is present at a concentration of about 0.5 mg/mL (50 mcg/100 mcL), about 0.71 mg/mL (50 mcg/70 mcL), about 1.0 mg/mL (50 mcg/100 mcL), about 1.0 mg/mL (200 mcg/200 mcL), or about 0.1 mg/mL (500mcg/5000 mcL);

b) cetirizine is present at a concentration of about 0.55 to about 4.4 mg/ mL, about 1.1 to about 4.4 mg/ mL, about 1.1 to about 2.2 mg/ mL, about 1 to about 25 mg/mL, about 2 to about 24 mg/mL, about 5 to about 20 mg/mL, about 7 to about 15 mg/mL, about 10 to about 12 mg/mL, about 1.1 mg/0.1mL, about 1.1 mg/0.05 mL, about 1.1 mg/0.70 mL, about 1.1 mg/0.2 mL, orabout 2.2 mg/ 5 mL; and/or

c) SAE-CD is present at a concentration of about 300 mg/mL, about 10 to about 500 mg/mL, or about 10 to about 500 mg/g.

Embodiments of the present invention allow for combination compositions (those containing two or more active agents (therapeutic agents)) to be prepared in a variety of ways:

1) Mixing ready to use solutions of a second therapeutic agent with a ready to use solution of a corticosteroid in SAE-CD;

2) Mixing ready to use solutions of a second therapeutic agent with a concentrated solution of a corticosteroid dissolved using SAE-CD;

3) Mixing a ready to use solution of a second therapeutic agent with substantially dry SAE-CD and a substantially dry corticosteroid;

4) Mixing a ready to use solution of a second therapeutic agent with a substantially dry mixture of SAE-CD and a corticosteroid or more conveniently a pre-measured amount of the mixture in a unit container such as a capsule (empty a capsule into ready to use solution);

5) Mixing a ready to use solution of a corticosteroid such as budesonide with a substantially dry second therapeutic agent; or

6) Dissolving a substantially dry second therapeutic agent and a substantially dry SAE-CD plus a substantially dry corticosteroid.

The materials used herein can be used in micronized or non-micronized form and crystalline, polymorphic or amorphous form. This is particularly true of the corticosteroids and other active ingredients.

It is well understood by those of ordinary skill in the art that the above solutions or powders can optionally contain other ingredients such as buffers and/or tonicity adjusters and/or antimicrobials and/or additives or other such excipients as set forth herein or as presently used in nasally administered liquid formulations.

A corticosteroid-responsive disease, symptom or disorder is one wherein a subject suffering from such will receive a clinical benefit after administration of a corticosteroid according to the invention. A type of corticosteroid-responsive disease, symptom or disorder is any allergic and/or inflammatory disease, symptom or disorder. Exemplary ones include nasal symptom, non-nasal symptom, ocular symptom, acute or chronic rhinitis, nasal polyps, post surgical polyps, obstructive sleep apnea, eustachian tube dysfunction, serous otitis media, sleep disturbances, daytime somnolesence, snoring, cluster headache, nasal furuncles, epistaxis, wounds of the nasal or sinunasal mucosa, dry nose syndrome, nasal bleeding, herpes, sarcoidosis, fibrosis, cancer, autoimmune reaction, or a combination thereof.

In some embodiments, acute or chronic rhinitis is selected from the group consisting of allergic rhinitis, seasonal allergic rhinitis, perennial allergic rhinitis, perennial non-allergic rhinitis, bacterial rhinitis, fungal rhinitis, viral rhinitis, atrophic rhinitis, grass pollen rhinitis, have fever, blocked nose, nasal congestion, vasomotor rhinitis, or a combination thereof.

In some embodiments, the nasal symptom is rhinorrhea, nasal congestion, nasal itchiness, sneezing, nasal obstruction or a combination thereof. In some embodiments, the non-nasal symptom is itchy/gritty eyes, tearing/watery eyes, red/burning eyes, itchy ears and palate, or a combination thereof.

In some embodiments, the invention excludes a method of or system for treating asthma, allergic asthma, rhinosinusitis, and/or sinusitis.

Conjunctivitis is an inflammation of the conjuncitva, the membrane lining the external surface of the eye, and is most often caused by an allergic reaction. Allergic conjuctivitis is one of the most common eye conditions in children and adults with symptoms including itching, stinging, burning, redness, tearing and swelling of the eyelids and the whites of the eye. Allergic conjunctivitis is most often associated with allergic rhinitis (Hay Fever) and can be associated with asthma.

Allergic rhinitis is one of the most chronic atopic diseases that is associated with considerable cost and co-morbidity. Allergic rhinitis is initiated by an IgE-mediated

response to allergens and results in a consequent relase of preformed mediators and sytokines, which induce inflammatory cell recruitment and their activation at the target organ. Seasonal allergic rhinitis (SAR), triggered by pollen from trees, grasses and weeds, is characterized by sneezing, nasal congestion, nasal itching, rhinorrhea, and pruritic, watery red eyes.

Animal dander, mold, dust, and dust mites can also trigger symptoms of rhinitis. Non-allergic rhinitis can also be induced by viruses, and environmental factors such as toxins and tobacco smoke.

Corticosteroids can also be used to treat ocular conditions such as: (1) inflammatory conditions including conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjuncitivitis; (2) corneal injuries including injury from chemical, radiation, or thermal burns or pentration by foreign bodies; and (3) ocular pain and burning/stinging following ocular surgery such as corneal refractive surgery.

The compositions of the invention can generally have a storage shelf life of 6 months. In this case, shelf life is determined only as regards the increase in the amount of corticosteroid degradation by-products or a reduction in the amount of corticosteroid remaining in the composition. For example, for a composition having a shelf life of at least six months, the composition will not demonstrate an unacceptable and substantial increase in the amount of degradants during the storage period of at least six months. The criteria for acceptable shelf-life are set as needed according to a given product and its storage stability requirements. In other words, the amount of degradants in a composition having an acceptable shelf-life will not increase beyond a predetermined value during the intended period of storage. On the other hand, the amount of degradants of a composition having an unacceptable shelf-life will increase beyond the predetermined value during the intended period of storage.

The method of Example 3 can be followed to determine the stability of the active agent in solution. The shelf-life can be defined as the time to loss of less than about 10%, less than about 5%, less than about 3%, less than about 2% or less than about 1% potency. Under the conditions tested, the loss of potency was first order. The shelf life of a CAPTISOL-ENABLED Budesonide Nasal Solution (a solution comprising budesonide and SBE7-β-CD) is greater than about 3 years at a pH between 4 and 5, i.e. about 90

months at pH 4.0 and about 108 months at pH 5.0 without the need to add any other stabilizers, such as EDTA, in water in the presence of about 5% wt./vol. SAE-CD.

SAE-CD is also capable of stabilizing the isomers of budesonide to different extents. SBE7-β-CD stabilized both R- and S-isomers of budesonide in solutions at both pH 4 and 6. The with/without CAPTISOL ratio of rate constants was much less than 1 at all temperatures. SBE7-β-CD had a greater effect on the stability of both the R and S-isomer at pH 6 than at pH 4. At a given temperature the ratio of rate constants with/without SBE7-β-CD was less at pH 6 than at pH 4. Although SBE7-β-CD stabilized both isomers, the S-isomer appears to be stabilized to an even greater extent than the R. At all temperatures and pHs tested, the ratio of rate constants with/without SBE7-β-CD was lower for the S isomer. The degree of stabilization affected by SBE7-β-CD at 60°C is greater than at 80°C. An even greater degree of stabilization would be expected at 40°C and/or room temperature (20-30°C). Accordingly a solution comprising SAE-CD and budesonide is stable at a pH from 4 to 6, from 4 to 5, or about 4.5.

SBE7-β-CD also significantly reduced the photodecomposition of budesonide. The loss of budesonide was first order and independent of pH.

SAE-CD is also capable of stabilizing a second active agent included in the composition. Example 16 details a procedure for evaluating the stability of azelastine in the presence of SAE-CD at varying temperatures and in solutions of different pH's. The results are depicted in FIGS. 10A to 10C. The SAE-CD stabilized the azelastine for the period of sixteen weeks regardless of the temperature or pH of the solution. The lower the temperature, the greater the stabilization. Of the three pH values evaluated, the greatest stabilization was observed at pH 5. Accordingly, a solution comprising SAE-CD and azelastine is most stable at a pH from 4 to 6 or from 4.5 to 5.5.

The composition of the invention can be provided as a powder adapted to form an aqueous solution for nasal, non-nasal and/or ophthalmic administration. The powder can also be adapted for administration with a powder-administering device. The power can instead comprise an admixture of a solid derivatized cyclodextrin and solid corticosteroid and, optionally, at least one solid pharmaceutical excipient, such that a major portion of the active agent is not complexed with the derivatized cyclodextrin prior to reconstitution of the admixture with an aqueous carrier. Alternatively, the composition can comprise a solid mixture comprising the inclusion complex of a derivatized cyclodextrin and an active

agent, wherein a major portion of the active agent is complexed with the derivatized cyclodextrin prior to reconstitution of the solid mixture with an aqueous carrier.

A powder composition of the invention can be prepared according to any of the following processes. A liquid composition of the invention is first prepared, then a solid is formed by lyophilization (freeze-drying), spray-drying, spray freeze-drying, antisolvent precipitation, various processes utilizing supercritical or near supercritical fluids, or other methods known to those of ordinary skill in the art to make a solid for reconstitution. Examples 25, 26, 27, 29 details a method for the preparation of a lyophilized solid composition comprising corticosteroid and SAE-CD by lyophilization of a liquid composition or formulation of the invention.

A liquid vehicle (carrier) included in a formulation of the invention comprises a pharmaceutically acceptable aqueous liquid carrier, such as water or buffer, aqueous alcohol, propylene glycol, glycerin, poly(ethylene glycol), poloxamer, povidone, polyol (such as sorbitol), aqueous organic solvent or a combination thereof. Example 30 details the preparation of a liquid formulation comprising 20% w/v SAE-CD, corticosteroid, water and ethanol (0-5%). Increasing the concentration of the ethanol in the liquid resulted in a decrease in the maximum saturated solubility of the corticosteroid. For nasal administration, an aqueous liquid carrier can be aqueous saline (which generally contains sodium chloride as the salt, and is fully described in Remington's Pharmaceutical Sciences, 19.sup.th edition (1995) p. 1502, which is herein incorporated by reference). The salt can be present in the solution at a level of about 0.01% to about 2%, preferably from about 0.5% to about 1.0% by weight of solution. Suitable nontoxic pharmaceutically acceptable nasal carriers are known to those skilled in the art. The choice of a suitable carrier will depend on the exact nature of the particular nasal dosage form required, e.g., whether the active agent is to be formulated into a nasal solution (for use as drops or as a spray), a nasal ointment, a nasal gel or another nasal form.

The compositions of the invention can include a preservative, antioxidant, buffering agent, acidifying agent, alkalizing agent, colorant, solubilizing agent, solubility-enhancing agent, complexation-enhancing agent, diliuent, electrolyte, glucose, stabilizer, bulking agent, antifoaming agent, oil, emulsifying agent, cryoprotectant, plasticizer, flavors, sweeteners, taste-masking agent, tonicity modifier, surface tension modifier, surfactant, viscosity modifier, density modifier, volatility modifier, saline, other excipients