US 20080085922A1

(19) United States

(12) Patent Application Publication (10) Pub. No.: US 2008/0085922 A1

Raja et al. (43) Pub. Date: Apr. 10, 2008

(54) METHODS AND OPHTHALMIC DEVICES USED IN THE TREATMENT OF OCULAR ALLERGIES

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(21) Appl. No.: **11/686,979**

(22) Filed: **Mar. 16, 2007**

Related U.S. Application Data

(60) Provisional application No. 60/848,332, filed on Sep. 29, 2006.

Publication Classification

(51) **Int. Cl.**
A61K 31/44 (2006.01)
A61P 27/02 (2006.01)

(52) **U.S. Cl.** **514/324**

(57) **ABSTRACT**

Ophthalmic devices and methods of treating allergic conjunctivitis are disclosed herein.

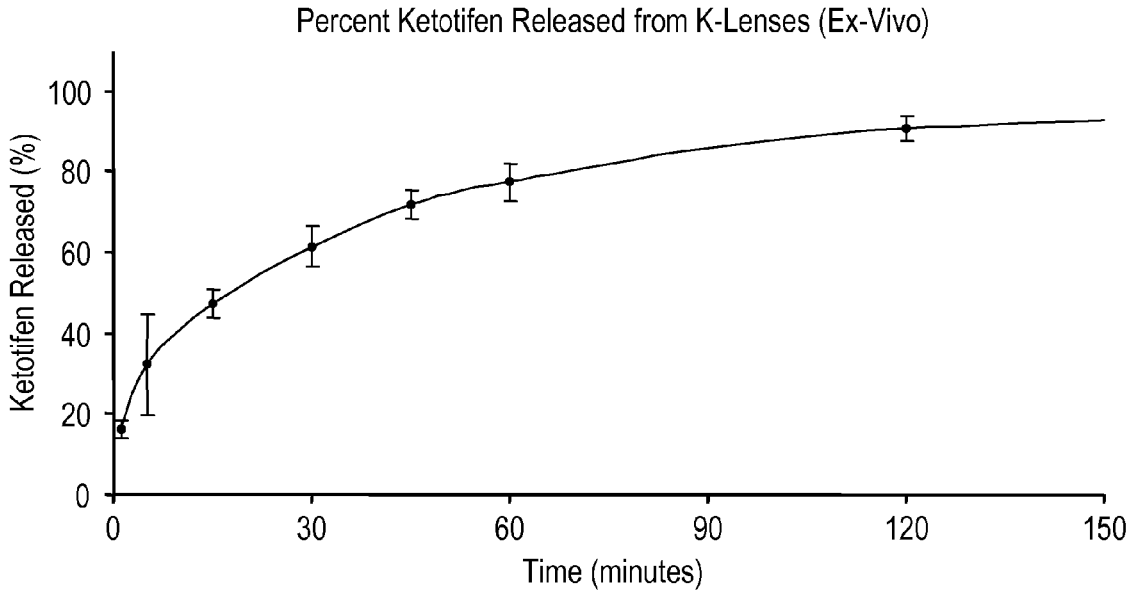
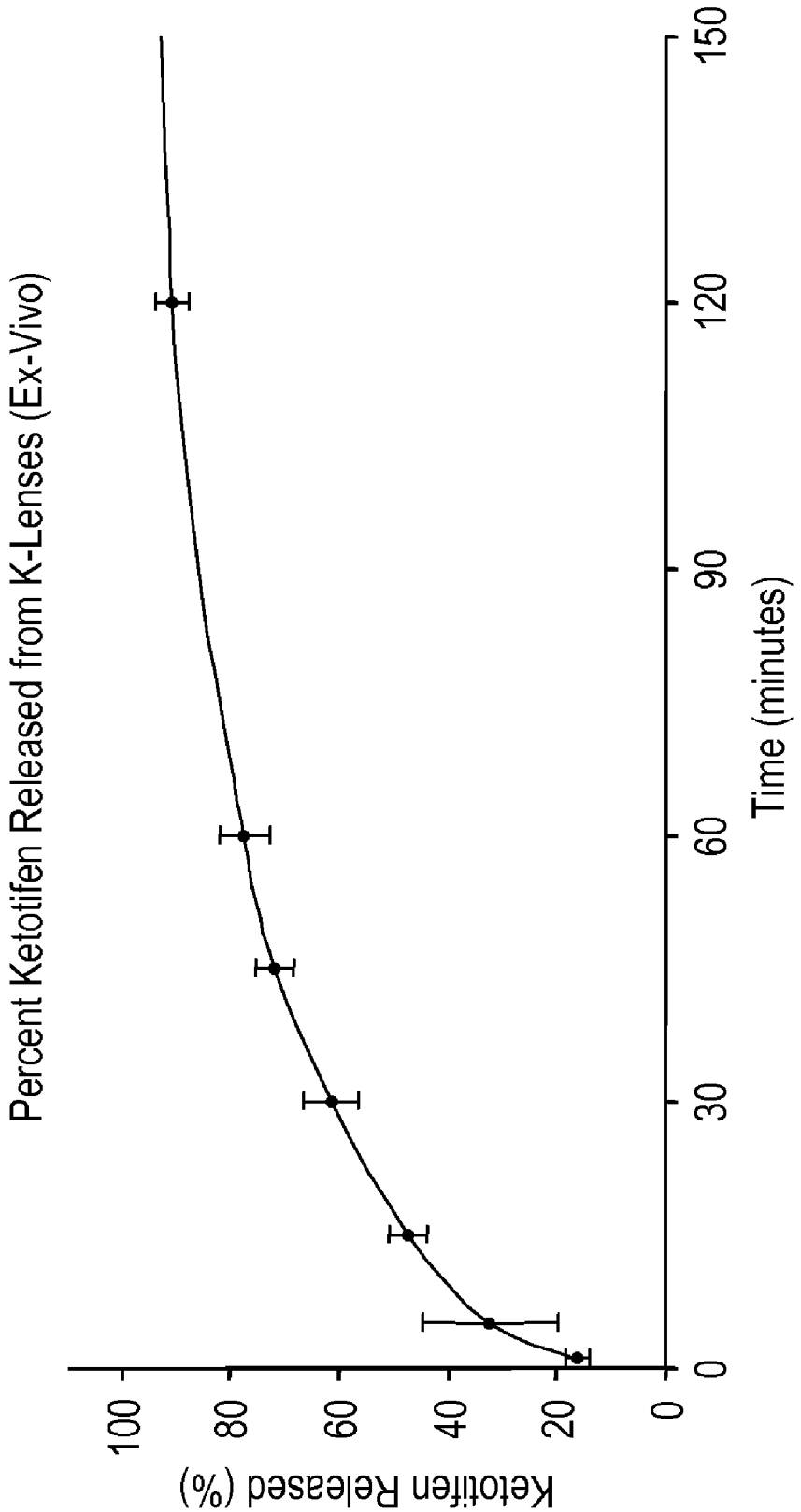


FIG. 1



METHODS AND OPHTHALMIC DEVICES USED IN THE TREATMENT OF OCULAR ALLERGIES

RELATED APPLICATIONS

[0001] This application claims priority from a non-provisional filing, U.S. application patent Ser. No. 60/848,332 which was filed on Sep. 29, 2006.

FIELD OF THE INVENTION

[0002] This invention related to devices and treatments for allergic conjunctivitis.

BACKGROUND

[0003] Allergic conjunctivitis is a disease of the eye that affects millions of people. The symptoms of this disease include itchiness, tearing, and swelling of the eyes. Sometimes this disease is seasonally associated with the spring and summer hay fever seasons, but many people experience symptoms of this disease throughout the year. The symptoms of allergic conjunctivitis are caused and mediated by the binding of histamine to its receptor. Antihistamines are a class of pharmaceutical agent known to either or both suppress the release of histamine from associated mast cells and prevent the binding of histamine to its associated receptors. These agents have been used to treat the symptoms of allergic conjunctivitis and one such agent is ketotifen fumarate. Topical solutions of ketotifen fumarate are currently sold in the United States. The concentration ketotifen in of the U.S. approved ketotifen fumarate formulation is 0.025% (0.25 mg/mL). At that concentration, the recommended dosing regimen is twice daily. It is known that the recommended dosing can be reduced if the amount of ketotifen fumarate is increased, but it is also known that higher concentrations of ketotifen fumarate sting and burn upon initial administration to the eye.

[0004] Further it is known that they symptoms of allergic conjunctivitis have a greater impact on the wearers of contact lenses. Many contact lens wearers stop using their lenses during the spring and summer hay fever seasons and other peak allergen seasons. Contact lens wearers can administer topical ketotifen solutions to reduce the symptoms of allergic conjunctivitis. However, if the inconvenience of carrying a bottle of solution can be avoided, it would be beneficial. In addition, since it is known that higher concentrations of the ketotifen fumarate can cause stinging and burning, it would be beneficial if the symptoms of allergic conjunctivitis were alleviated by administering an amount of ketotifen fumarate to patients that did not cause stinging in a dose that lasts longer than 6 hours. These benefits are provided by the following invention.

BRIEF DESCRIPTION OF THE DRAWING

[0005] FIG. **1** illustrates the ex-vivo release of ketotifen.

DETAILED DESCRIPTION OF THE INVENTION

[0006] This invention includes an ophthalmic device comprising about a minimum effective amount of an anti-allergic agent. As used herein "anti-allergic agent" refers to chemical substances that alleviate the symptoms of allergic conjunc-

limited to chemical substances that inhibit the release of histamine, that block the binding of histamine to its receptors, inhibit mast cell production. Additional anti-allergic agents include but are not limited to decongestants, non-steroidal anti-inflammatory compound, and steroidal compounds. Particularly, examples of anti-allergic agents include but are not limited to acetmetacin, acrivastine, aldosterone, antazoline, astemizole, azatadine, azelastine, beclometasone, betamethasone, bromfenac, buclizine, carprofen, cetirizine, chloropyriline, chloropheniramine, clemastine, cromolyn, cyclizine, cyproheptadine, dexamethasone, diazoline, diclofenac, diphenhydramine, ebastine, emedastine, epinastine, etodolac, fenbufen, fenoprofen, fexofenadine, fludrocortisone, flurbiprofen, flurometalone, hydroxyzine, ibuprofen, indometacin, ketoprofen, ketorolac tromethamine, ketotifen, levocabastine, levoceterizine, lodoxamide, loratadine, loteprednol, loxoprofen, medrysone, mepivacaine, mequitazine, methdilazine, methapyrilene, nabumetone, naphazoline, naproxen, nedocromil, norastemizole, norebastine, olopatadine, phenidamine, phenylephrine, oxatamide, oxymetazoline, pemirolast, pheniramine, picumast, prednisilone, promethazine, rimexalone, repirinast, sulindac, suprofen, tetrahydozoline, terfenadine, tiaprofenic acid, tometim, tranilast, triamcinolone, trimeprazine, triprolidine, and pharmaceutically acceptable salts and mixtures thereof. Preferred anti-allergic agent include acrivatine, antazoline, astemizole, azatadine, azelastine, clemastine, cyproheptadine, ebastine, emedastine, fexofenadine, hydroxyzine, ketotifen, levocabastine, levoceterizine, mequitazine, methdialazine, methapyrilene, norastemizole, norebastine, picumast, promethazine, terfenadine, trimeprazine, triprolidine, and pharmaceutically acceptable salts and mixtures thereof. The class of substances known as antihistamines are the particularly preferred anti- allergic agents The particularly preferred antihistamines include, azelastine, epinastine, ketotifen, ketotifen fumarate, nor-ketotifen fumarate, olopatadine and mixtures thereof. More particularly preferred antihistamines include ketotifen, its pharmaceutically acceptable salts and mixtures thereof.

[0007] The term "minimum effective amount" refers to the weight of anti-allergic agent contained in an ophthalmic device prior to its use by a patient wherein such minimum effective amount alleviates the symptoms of allergic conjunctivitis. The minimum effective amount may vary depending upon the efficacy of a particular anti-allergic agent. For example, if the anti-allergic agent is ketotifen fumarate, the minimum effective amount is between greater than about 9 μg and about less than 90 μg, more particularly between about 40 μg and greater than about 9 μg, most preferably about for 20 μg. It is preferred that minimum effective amount of anti-allergic agent other than ketotifen fumarate is an amount that exhibits an efficacy equivalent to or more efficacious greater than about 9 μg and about less than 90 μg, more particularly between about 40 μg and about 9 μg of ketotifen fumarate.

[0008] It is preferred that the minimum effective amount of anti-allergic agent alleviates the symptoms of allergic conjunctivitis for between about 5 minutes, and about 24 hours from insertion of the ophthalmic device into the eye of a user, more preferably between about 5 minutes and about

[0009] As used herein, "ophthalmic device" refers to an object that resides in or on the eye. These devices can provide optical correction or may be cosmetic. Ophthalmic devices include but are not limited to soft contact lenses, intraocular lenses, overlay lenses, ocular inserts, punctual plugs, and optical inserts. The preferred ophthalmic devices of the invention are soft contact lenses made from silicone elastomers or hydrogels, which include but are not limited to silicone hydrogels, and fluorohydrogels and excludes ophthalmic devices that contain phosphate group-containing methacrylates (i.e. CH_2—$C(CH_3)$—$C(O)$—$(CH_2)_n$—O—$P(O)(OH)_2$, where n is 1-4; CH_2C—$C(CH_3)$—$C(O)$—$(CH_2)_2$—O—$P(O)(OH)$—O—$(CH_2)_2$—O—$C(O)$—$C(CH_3)$—CH_2) or pre-polymers as such defined by US Pat. Application Publication No. US 2006/0100408. Soft contact lens formulations are disclosed in U.S. Pat. No. 5,710,302, WO 9421698, EP 406161, JP 2000016905, U.S. Pat. No. 5,998,498, U.S. Pat. No. 6,087,415, U.S. Pat. No. 5,760,100, U.S. Pat. No.5,776, 999, U.S. Pat. No. 5,789,461, U.S. Pat. No. 5,849,811, and U.S. Pat. No. 5,965,631. The foregoing references are hereby incorporated by reference in their entirety. The particularly preferred ophthalmic devices of the inventions are prepared from formulations known by the United States Approved Names of acofilcon A, alofilcon A, alphafilcon A, amifilcon A, astifilcon A, atalafilcon A, balafilcon A, bisfilcon A, bufilcon A, comfilcon, crofilcon A, cyclofilcon A, darfilcon A, deltafilcon A, deltafilcon B, dimefilcon A, drooxifilcon A, epsifilcon A, esterifilcon A, etafilcon A, focofilcon A, galyfilcon A, genfilcon A, govafilcon A, hefilcon A, hefilcon B, hefilcon D, hilafilcon A, hilafilcon B, hioxifilcon B, hioxifilcon C, hixoifilcon A, hydrofilcon A, lenefilcon A, licryfilcon A, licryfilcon B, lidofilcon A, lidofilcon B, lotrafilcon A, lotrafilcon B, mafilcon A, mesifilcon A, methafilcon B, mipafilcon A, nelfilcon A, netrafilcon A, ocufilcon A, ocufilcon B, ocufilcon C, ocufilcon D, ocufilcon E, ofilcon A, omafilcon A, oxyfilcon A, pentafilcon A, perfilcon A, pevafilcon A, phemfilcon A, polymacon, senofilcon A, silafilcon A, siloxyfilcon A, tefilcon A, tetrafilcon A, trifilcon A, vasurfilcon, vifilcon, and xylofilcon A. More particularly preferred ophthalmic devices of the invention are genfilcon A, lenefilcon A, comfilcon, lotrafilcon A, lotraifilcon B, and balafilcon A. More preferred lenses include comfilcon, etafilcon A, galyfilcon A, senofilcon A, nelfilcon A, hilafilcon, tetrafilcon A, vasurfilcon, vifilcon, and polymacon. The most preferred lenses include etafilcon A.

[0010] Further the invention includes a method of alleviating the symptoms of allergic conjunctivitis comprising administering to a patient an ophthalmic device comprising about a minimum effective amount of an anti-allergic agent. The terms ophthalmic device, minimum effective amount and anti-allergic agent all have their aforementioned meanings and preferred ranges. As used herein, the term "administering" means placing the ophthalmic device of the invention onto the surface of the eye, or in the eye, of a patient. If the device is in contact with the anterior surface of the patient's eye, such as a soft contact lens, it is preferred that the ophthalmic device remain in contact with that surface for between about 5 minutes, and about 24 hours from insertion of the ophthalmic device into the eye of a user, more preferably between about 5 minutes and about 16 hours, more preferably between about 5 minutes and about 12 hours, [illegible] within the eye or on the ocular adnexa, such as a punctual plug or an ocular insert, it is preferred that the device remain in contact with the eye for at least 24 hours.

[0011] Still further the invention includes a method of making an ophthalmic device comprising about a minimum effective amount of an anti-allergic agent comprising the step of treating an ophthalmic device with a solution comprising said anti-allergic agent, wherein the amount of said anti-allergic agent in said solution exceeds the minimum effective amount. It is preferred that the minimum effective amount is exceeded by between about 1.0% and about 1000%, in a volume of solution that is between about 500 μL and about 5000 μL preferably between about 50% and about 500%, in a volume of solution that is between about 500 μL and about 3000 μL most preferably about 50% in a volume of solution that is about 1000 μL.

[0012] As used herein treating means physical methods of contacting the solution containing an anti-allergic agent and the ophthalmic device. Preferably treating refers to physical methods of contacting the anti-allergic agent with the ophthalmic devices prior to selling or otherwise delivering the ophthalmic devices to a patient. The ophthalmic devices may be treated with the anti-allergic agent anytime after they are polymerized. Polymerization refers to the process in which components of an ophthalmic device including but not limited to monomers, pre-polymers, diluents, catalysts, initiators, tints, UV blockers, antibacterial agents, polymerization inhibitors, and the like are reacted by thermal, chemical, and light initiated curing techniques to produce a formed polymer. The preferred methods of polymerization are the light initiated techniques disclosed in U.S. Pat. No. 6,822,016 which is hereby incorporated by reference in its entirety. It is preferred that the polymerized ophthalmic devices be treated with anti-allergic agent at temperature of greater than about 50° C. For example in some processes to manufacture contact lenses, an un-polymerized, or partially polymerized formulation is placed between two mold halves, spincasted, or static casted and polymerized. See, U.S. Pat. Nos. 4,495,313; 4,680,336; 4,889,664, 3,408.429; 3,660,545; 4,113,224; and 4,197,266, all of which are incorporated by reference in their entirety. In the case of hydrogels, the ophthalmic device formulation is a hardened disc that is subjected to a number of different processing steps including treating the polymerized ophthalmic device with liquids (such as water, inorganic salts, or organic solutions) to swell, or otherwise equilibrate this polymerized ophthalmic device prior to enclosing the polymerized ophthalmic device in its final packaging. Polymerized ophthalmic devices that have not been swelled or otherwise equilibrated are known as un-hydrated polymerized ophthalmic devices. The addition of the anti-allergic agent to any of the liquids of this "swelling" or "equilibrating" step at room temperature or below is considered "treating" the lenses with anti-allergic agent as contemplated by this invention. In addition, the polymerized un-hydrated ophthalmic devices may be heated above room temperature with the anti-allergic agent during swelling or equilibrating steps. The preferred temperature range is from about 50° C. for about 15 minutes to about sterilization conditions as described below, more preferably from about 50° C. to about 85° C. for about 5 minutes.

[0013] [illegible]

hereby incorporated by reference in their entirety, U.S. Pat. Nos. D435,966; 4,691,820; 5,467,868; 5,704,468; 5,823,327; 6,050,398, 5,696,686; 6,018,931; 5,577,367; and 5,488,815. This portion of the manufacturing process presents another method of treating the ophthalmic devices with anti-allergic agent, namely adding anti-allergic agents to a solution prior to sealing the package, and subsequently sterilizing the package. This is the preferred method of treating ophthalmic devices with anti-allergic agents.

[0014] Sterilization can take place at different temperatures and periods of time. The preferred sterilization conditions range from about 100° C. for about 8 hours to about 150° C. for about 0.5 minute. More preferred sterilization conditions range from about 115° C. for about 2.5 hours to about 130° C. for about 5.0 minutes. The most preferred sterilization conditions are about 124° C. for about 18 minutes.

[0015] The "solutions" that are used in methods of this invention may be water-based solutions. Typical solutions include, without limitation, saline solutions, other buffered solutions, and deionized water. The preferred aqueous solution is deionized water or saline solution containing salts including, without limitation, sodium chloride, sodium borate, sodium phosphate, sodium hydrogenphosphate, sodium dihydrogenphosphate, or the corresponding potassium salts of the same. These ingredients are generally combined to form buffered solutions that include an acid and its conjugate base, so that addition of acids and bases cause only a relatively small change in pH. The buffered solutions may additionally include 2-(N-morpholino)ethanesulfonic acid (MES), sodium hydroxide, 2,2-bis(hydroxymethyl)-2,2',2"-nitrilotriethanol, n-tris(hydroxymethyl)methyl-2-aminoethanesulfonic acid, citric acid, sodium citrate, sodium carbonate, sodium bicarbonate, acetic acid, sodium acetate, ethylenediamine tetraacetic acid and the like and combinations thereof. Preferably, the solution is a borate buffered or phosphate buffered saline solution or deionized water. The particularly preferred solution contains about 500 ppm to about 18,500 ppm sodium borate, most particularly preferred about 1000 ppm of sodium borate.

[0016] If the anti-allergic agents are subject to oxidative degradation, agents that stabilize solutions containing such anti-allergic agents may be added. Such "oxidative stabilization agents" include but are not limited to chelants such as EDTA, Dequest, Desferal, silica, chitin derivatives such as chitosan, cellulose and its derivatives, and N,N,N',N',N",N"-hexa(2-pyridyl)-1,3,5-tris(aminomethyl)benzene, and certain macrocyclic ligands such as crown ethers, ligand containing knots and catenands. See, David A. Leigh et al *Angew. Chem Int. Ed.,* 2001, 40, No. 8, pgs. 1538-1542 and Jean-Claude Chambron et al. *Pure & Appl. Chem.,* 1990, Vol. 62, No. 6, pgs. 1027-1034. Oxidative stabilization agents may include other compounds that inhibit oxidations such as those selected from the group consisting of 2,2',2",6,6',6"-Hexa-(1,1-dimethylethyl)4,4',4"-[(2,4,6-trimethyl-1,3,5-benzenetriyl)-trismethylene]-triphenol (Irganox 1330), 1,3,5tris[3,5-di(1,1-dimethylethyl)4-hydroxybenzyl]-1H,3H,5H-1,3,5-triazine-2,4,6-trione, pentaerythrityl tetrakis[3-[3,5-di(1,1-dimethylethyl)-4-hydroxyphenyl]-propionate], octadecyl-3-[3,5-di(1,1-dimethylethyl)-4-hydroxyphenyl]-propionate, tris[2,4-di(1,1-dimethylethyl)-phenyl]-phos- [illegible] thiodipropionate, dioctadecyl-3,3'-thiodipropionate, butylhydroxytoluene, ethylene bis[3,3-di[3-(1,1-dimethylethyl)-4-hydroxyphenyl]butyrate] and mixtures thereof. The preferred oxidative stabilization agents are diethylenetriaminepentaacetic acid ("DTPA"), or salts of DTPA such as $CaNa_3DTPA$, $ZnNa_3DTPA$, and Ca_2DTPA. See, U.S. application patent No. 60/783,557 filed on, Mar. 17, 2006, entitled "Methods for Stabilizing Oxidatively Unstable Pharmaceutical Compositions" and its corresponding non-provisional filing which are hereby incorporated by reference in their entirety. Therefore, the invention includes a method of preventing oxidation of an ophthalmic device comprising an anti-allergic agent, wherein the method includes treating said ophthalmic device with a solution comprising an oxidative stabilization agent. It is preferred that at the concentration of oxidative stabilization agents in the solution be from about 2.5 μmoles/liter to about, 5000 μmoles/liter more preferably from about 20 μmoles/liter to about 1000 μmoles/liter, more preferably from about 100 μmoles/liter to about 1000 μmoles/liter, most preferably from about 100 μmoles/liter to about 500 μmoles/liter.

[0017] Yet still further the invention includes an ophthalmic device comprising about a localized amount of an anti-allergic agent. As used herein the terms anti-allergic agent and ophthalmic device have their afore mentioned preferred identities and preferred ranges.

[0018] As used herein, the term "localized amount" refers to an amount of anti-allergic agent that located in discrete portions of the ophthalmic device. For example, the localized amount may be on the front or back surface (using those terms as applied to contact lenses) of the device, or in any other area or surface. It is preferred that the localized amount remain in contact with the conjunctiva of the eye when placed in the eye of a user. It is preferred that the localized amount of anti-allergic agent is between about 1 μg and about 200 μg, preferably between about 1 μg and about 90 μg, more preferably between about 1 μg and about 50 μg, most preferably between about 2 μg and about 20 μg. The anti-effective agent may be adding to a discrete area of the device by including the anti-allergic agent in coatings or pigments that may be added to the devices. See, U.S. Pat. Nos. 7,172,286; and 6,767,097, WO 02/057837, WO 03/057837 U.S. Pat. App. Nos. US 2002/0133889, and US 2003/0000028 coatings and pigments that may be applied to ophthalmic devices as well methods of applying the same to such devices

[0019] Yet further still the invention includes a method of alleviating the symptoms of allergic conjunctivitis comprising administering to a patient an ophthalmic device comprising about a localized amount of an anti-allergic agent. As used herein the terms anti-allergic agent, localized amount, and ophthalmic device have their afore mentioned preferred identities and preferred ranges.

[0020] Still further, the invention includes a method alleviating the symptoms of allergic conjunctivitis in a patient for an extended period of time, wherein said method comprises administering to the eye of said patient an administration system comprising said anti-allergic agent, wherein said administration system releases to said patient a dosing effective amount of an anti-allergic agent. The term anti- [illegible]

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