PTO/AIA/14 (12-13)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	PAT903988-US-CNT
	Application Number	
Title of Invention	HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
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Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

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City	Fort Worth	State/Province	TX	Country of Residence i	US

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City	Arlington	State/Province	TX	Country of Residence i	US

Mailing Address of Inventor:

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Postal Code	76017	Country i	US

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Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	26356		
Email Address	patent.docketing@alcon.com	Add Email	Remove Email

Application Information:

Title of the Invention	HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION		
Attorney Docket Number	PAT903988-US-CNT	Small Entity Status Claimed	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	5	Suggested Figure for Publication (if any)	1

Filing By Reference :

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country i

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Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	26356		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the application number blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation of	13475607	2012-05-18
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13475607	Claims benefit of provisional	61548957	2011-10-19
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13475607	Claims benefit of provisional	61487789	2011-05-19

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

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This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(d). When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX) [i]the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(h)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country [i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

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Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Authorization to Permit Access:

☒ Authorization to Permit Access to the Instant Application by the Participating Offices

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In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing this Authorization.

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◉ Assignee	○ Legal Representative under 35 U.S.C. 117	○ Joint Inventor
○ Person to whom the inventor is obligated to assign.	○ Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor :

If the Applicant is an Organization check here. ☒

Organization Name	Alcon Research, Ltd.		
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Email Address	patent.docketing@alcon.com

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

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Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication . An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

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Mailing Address Information For Assignee including Non-Applicant Assignee:

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Phone Number		Fax Number	
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Signature	/Scott A. Chapple, 46,287/			Date (YYYY-MM-DD)	2014-06-13
First Name	Scott	Last Name	Chapple	Registration Number	46287

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This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The information provided by you in this form will be subject to the following routine uses:

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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

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HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION

Cross-Reference to Related Application

This application is a continuation application of U.S. Utility Patent Application No. 13/475,607 filed May 18, 2012 (now allowed), which 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 ºC). 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 90-95ºC 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 (122ºC/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 (122ºC/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/

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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

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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.

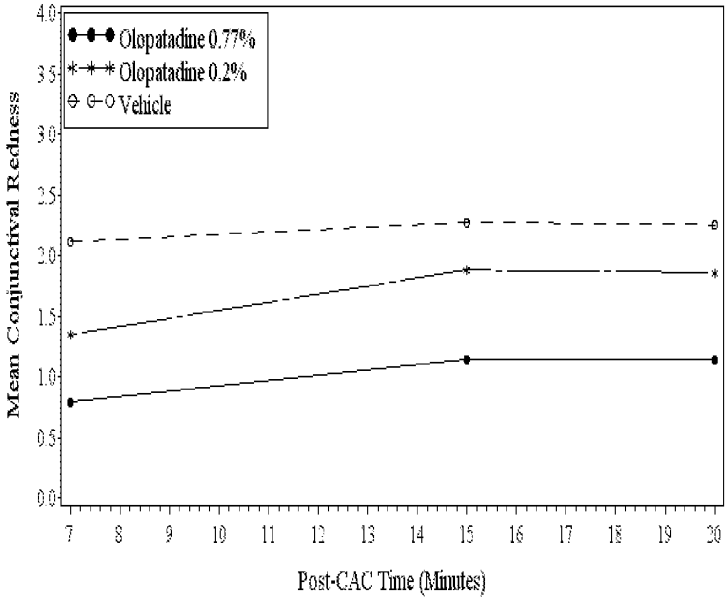

FIG. 1

2 / 5

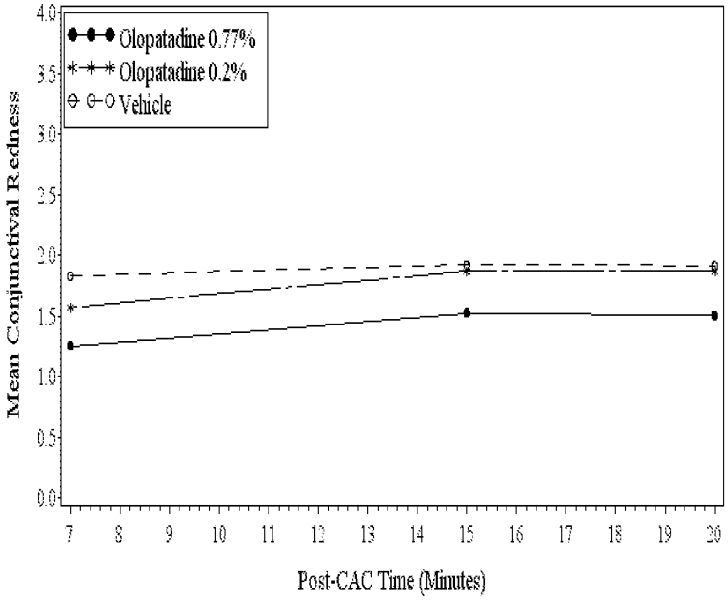

FIG. 2

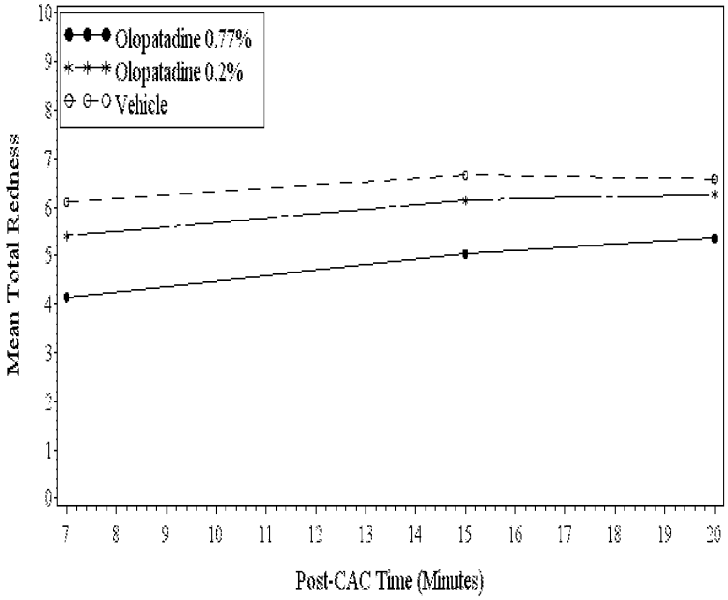
Olopatadine 0.77%
Olopatadine 0.2%
Vehicle
Mean Total Redness
Post-CAC Time (Minutes)
0
1
2
3
4
5
6
7
8
9
10
7
8
9
10
11
12
13
14
15
16
17
18
19
20

FIG. 3

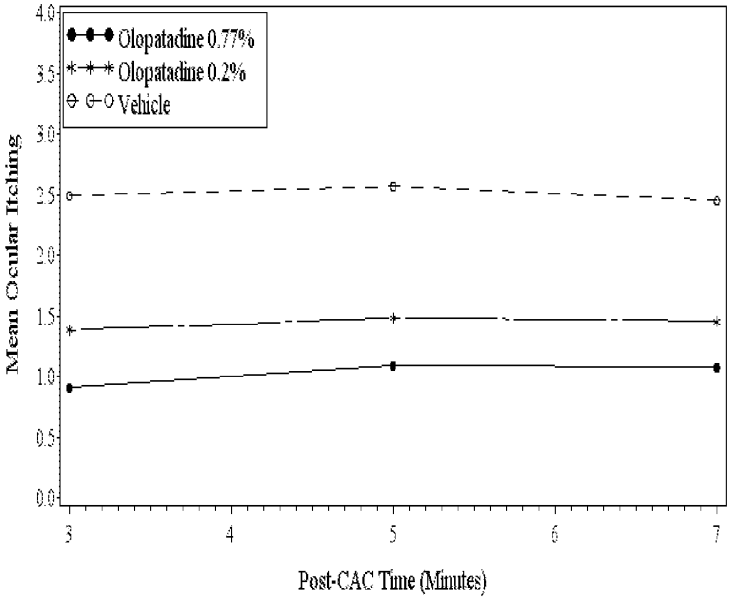
Olopatadine 0.77%
Olopatadine 0.2%
Vehicle
Mean Ocular Itching
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
3
4
5
6
7
Post-CAC Time (Minutes)

FIG. 4

5 / 5

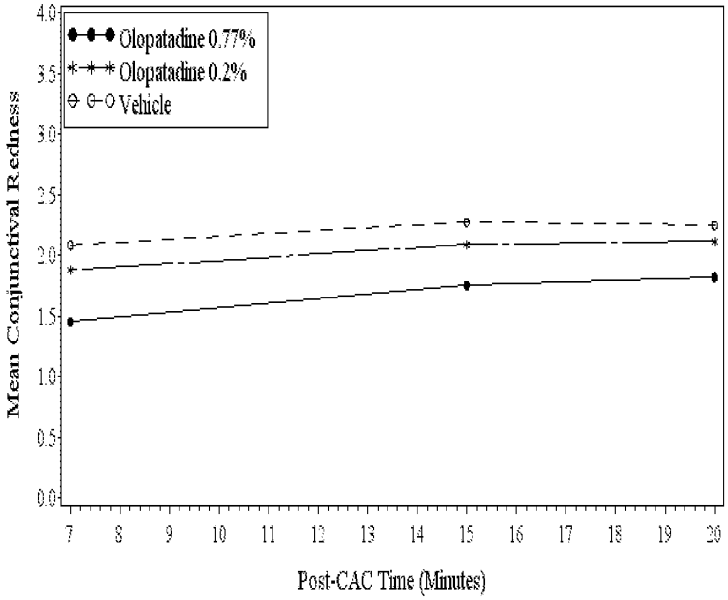

FIG. 5

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/Candy Sanders			
Attorney Docket Number:	PAT903988-US-CNT			
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	280	280
Utility Search Fee	1111	1	600	600
Utility Examination Fee	1311	1	720	720
Pages:				
Claims:				
Claims in Excess of 20	1202	5	80	400
Independent claims in excess of 3	1201	1	420	420
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Late Filing Fee for Oath or Declaration	1051	1	140	140
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**2560**

Electronic Acknowledgement Receipt	
EFS ID:	19300794
Application Number:	14304124
International Application Number:	
Confirmation Number:	1002
Title of Invention:	HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION
First Named Inventor/Applicant Name:	Daniel A. Gamache
Customer Number:	26356
Filer:	Scott Chapple/Candy Sanders
Filer Authorized By:	Scott Chapple
Attorney Docket Number:	PAT903988-US-CNT
Receipt Date:	13-JUN-2014
Filing Date:	
Time Stamp:	14:59:04
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$2560
RAM confirmation Number	1348
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)	

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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	Application Data Sheet	PAT903988-US-CNT_2014-06-13_SUB_ADS_Fillable__.pdf	1562306 300190f620c7cb3d00dc817b74316c227e1d40af	no	9
Warnings:					
Information:					
2		PAT903988-US-CNT_2014-06-13_APP_Final__.pdf	302064 caba8b47147b85c854725bfd21b3a2c937186c32	yes	43
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Specification		1	39	
	Claims		40	42	
	Abstract		43	43	
Warnings:					
Information:					
3	Drawings-only black and white line drawings	PAT903988-US-CNT_2014-06-13_DRW__.pdf	90214 56cff4a70bdc570a4e200ffacf33207ce0c513cb	no	5
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	39609 8bfc876e70e3ed53e808f6b722fff95172f0561a	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1994193		

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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
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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	Tran, My Chau T.
Attorney Docket Number	PAT903988-US-NP

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	1	5874414		1999-02-23	Cydex, Inc.	
	2	6280745	B1	2001-08-28	Alliance Pharmaceutical Corp.	
	3	6407079	B1	2002-06-18	Janssen Pharmaceutica N.V.	

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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	Tran, My Chau T.
	Attorney Docket Number	PAT903988-US-NP

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☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

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A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Scott A. Chapple, 46,287/	Date (YYYY-MM-DD)	2014-02-17
Name/Print	Scott A. Chapple	Registration Number	46,287

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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

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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	My Chau T Tran
	Attorney Docket Number	PAT903988-US-NP

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	1	International Preliminary Report on Patentability for corresponding PCT/US2012/038663 with mailing date November 28, 2013	☐

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Attorney Docket Number	3988 US

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	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.	

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	Art Unit	1629
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	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	

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	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.	

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	31	7429602		2008-09-30	Trach et al.	
	32	7635773		2009-12-22	Antle	

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	1	20020006443		2002-01-17	Curatolo et al.	
	2	20020150616		2002-10-17	Vandecruys	
	3	20030170309		2003-09-11	Babcock et al.	
	4	20050004074		2005-01-06	Lyons et al.	
	5	20050191270		2005-09-01	Gruening et al.	
	6	20050244472		2005-11-03	Hughes et al.	
	7	20060210645		2006-09-21	Du Mee et al.	

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	8	20070020336		2007-01-25	Loftsson et al.	
	9	20080132444		2008-06-05	Li et al.	
	10	20090118262		2009-05-07	Rohrs et al.	
	11	20090232763		2009-09-17	Kabra et al.	
	12	20090239842		2009-09-24	Trach et al.	
	13	20100240625		2010-09-23	Abelson et al.	
	14	20100249062		2010-09-30	Matsumura et al.	
	15	20100324031		2010-12-23	Kabra	

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	1	0862414	EP		2001-12-05	Novartis AG		☐

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	2	0998304	EP		2003-08-20	Janssen Pharmaceutica N.V.		☐
	3	2169508	GB		1986-07-16	Smith and Nephew Associated Companies plc		☐
	4	2001-158750	JP		2001-06-12	Lion Corp.		☒
	5	88/08709	WO		1988-11-17	MDR Group, Inc.		☐
	6	90/04971	WO		1990-05-17	M.D.R. Group, Inc.		☐
	7	91/09523	WO		1991-07-11	Allergan Inc.		☐
	8	96/39147	WO		1996-12-12	Alcon Laboratories, Inc.		☐
	9	01/54687	WO		2001-08-02	Alcon Universal Ltd.		☐
	10	2003/013481	WO		2003-02-20	Khamar et al.		☐
	11	2006/011044	WO		2006-02-02	Pfizer Products Inc.		☐
	12	2008/015695	WO		2008-02-07	Sun Pharmaceutical Ind. Ltd.		☐

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	13	2009/003199	WO		2008-12-31	Cydex Pharmaceuticals, Inc.		☐
	14	2010/107689	WO		2010-09-23	Aciex Therapeutics, Inc.		☐
	15	2 391 076	CA		2001-05-25	Boehringer Ingelheim International GmbH		☐
	16	1 004 309	EP		2000-05-31	Senju Pharmaceutical Co., Ltd.		☐
	17	1 231 920	EP		2007-02-07	Boehringer Ingelheim International GmbH		☐
	18	1 994 931	EP		2008-11-26	Meiji Seika Kaisha Ltd.		☐

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	1	CHIGBU, "The management of allergic eye disease in primary eye care", Contact Lens & Anterior Eye, 32, pgs 260-272, 2009	☐
	2	CHIGBU, "The pathophysiology of ocular allergy: A review", Contact Lens & Anterior Eye, 32, pgs. 3-15, 2009	☐
	3	CIPRANDI et al., "Cetirizine reduces inflammatory cell recruitment and ICAM-1 (or CD54) expression on conjunctival epithelium in both early- and late-phase reactions after allergen-specific challenge", J Allergy Clin Immunol, vol. 95, no. 2, pgs 612-621, Feb. 1995	☐

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	4	DU BUSKE, "Clinical comparison of histamine H1-receptor antagonist drugs", J Allergy Clin Immunol, vol. 98, no. 6, part 3, pgs. S307-S318, Dec. 1996	☐
	5	FUKUDA et al., "Critical role of IgE-dependent mast cell activiation in a murine model of allergic conjunctivitis", J Allergy Clin Immunol, vol. 124, no. 4, 827-833.e2, Oct. 2009	☐
	6	International Search Report for corresponding PCT/US2012/038663 with mailing date July 25, 2012	☐
	7	International Written Opinion for corresponding PCT/US2012/038663 with mailing date July 25, 2012	☐
	8	IZUSHI et al., "The role of histamine H1 receptors in late-phase reaction of allergic conjunctivitis", European Journal of Pharmacology, 440:79-82, 2002	☐
	9	LEONARDI and ABELSON, "Double-Masked, Randomized, Placebo-Controlled Clinical Study of the Mast Cell-Stabilizing Effects of Treatment with Olopatadine in the Conjunctival Allergen Challenge Model in Humans", Clinical Therapeutics, vol. 25, no. 10, pgs. 2539-2552, 2003	☐
	10	OZAKI et al., "Mast-cell activation augments the late phase reaction in experimental immune-mediated blepharoconjunctivitis", Graefe's Arch Clin Exp Ophthalmol, 241:394-402, 2003	☐
	11	UETA et al., letter to editor, "Development of eosinophilic conjunctival inflammation at late-phase reaction in mst cell-deficient mice", J Allergy Clin Immunol, pgs 476-478, Aug. 2007	☐
	12	VOGELSON et al., "Preclinical and Clinical Antiallergic Effect of Olopatadine 0.2% Solution 24 Hours after Topical Ocular Administration", Allergy and Asthma Proc., Vol. 25, No. 1, pgs 69-75, Jan-Feb 2004	☐
	13	YANNI et al., "The In Vitro and In Vivo Ocular Pharmacology of Olopatadine (AL-4943A), an Effective Anti-Allegic/ Antihistaminic Agent", Journal of Ocular Pharmacology and Therapeutics, Vol. 12, No. 4, 1996	☐
If you wish to add additional non-patent literature document citation information please click the Add button Add			

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

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Scott A. Chapple, Reg. #46,287/	Date (YYYY-MM-DD)	2012-08-24
Name/Print	Scott A. Chapple	Registration Number	46,287

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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	14304124
Filing Date	2014-06-13
First Named Inventor	Daniel A. Gamache
Art Unit	1629
Examiner Name	Not Yet Assigned
Attorney Docket Number	PAT903988-US-CNT

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	5641805		1997-06-24	Hayakawa et al.	
	2	6995186	B2	2006-02-07	Castillo et al.	

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	1	20040198828	A1	2004-10-07	Abelson et al.	
	2	20110082145	A1	2011-04-07	Schneider et al.	
	3	20120015953	A1	2012-01-19	Beauregard et al.	

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14304124
	Filing Date	2014-06-13
	First Named Inventor	Daniel A. Gamache
	Art Unit	1629
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	PAT903988-US-CNT

	1							☐

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NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1		☐

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Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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	Application Number	14304124
	Filing Date	2014-06-13
	First Named Inventor	Daniel A. Gamache
	Art Unit	1629
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	PAT903988-US-CNT

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Signature	/Scott A. Chapple, 46,287/	Date (YYYY-MM-DD)	2014-06-18
Name/Print	Scott A. Chapple	Registration Number	46,287

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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	19339610
Application Number:	14304124
International Application Number:	
Confirmation Number:	1002
Title of Invention:	HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION
First Named Inventor/Applicant Name:	Daniel A. Gamache
Customer Number:	26356
Filer:	Scott Chapple/Candy Sanders
Filer Authorized By:	Scott Chapple
Attorney Docket Number:	PAT903988-US-CNT
Receipt Date:	18-JUN-2014
Filing Date:	
Time Stamp:	13:58:43
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	PAT903988-US-CNT_2014-06-18_IDS_Transmittal_Letter__.pdf	100091 76b021cd0330a200aaa509da71455156cd47556e	no	2
Warnings:					
Information:					

2	Information Disclosure Statement (IDS) Form (SB08)	PAT903988-US-CNT_2014-06-18_IDS_Parent_Application_References__.pdf	527228 5c88ec44753a41c517fe1ed7cdf404ece4fe334e	no	19
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Information Disclosure Statement (IDS) Form (SB08)	PAT903988-US-CNT_2014-06-18_IDS_Fillable__.pdf	612287 9cb1a1d2be3254d20706910f6d34c52e7f965014	no	4
Warnings:					
Information:					
		Total Files Size (in bytes):	1239606		

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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Daniel A. Gamache, et al.

Serial No: 14/304124 (confirmation number: 1002)

Filed: June 13, 2014

Examiner: Not Yet Assigned

Group Art Unit: 1629

FOR: HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION

INFORMATION DISCLOSURE STATEMENT PURSUANT TO 37 C.F.R. 1.56, 1.97, AND 1.98

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Pursuant to the duty of disclosure under 37 C.F.R. §1.56, Applicant directs the attention of the Examiner to the references listed on the attached Form PTO/SB/08a. All of the listed references were considered and made of record in the Parent Application No. 13/475607 ("Parent Application"), filed May 18, 2012. The references cited in the Office Action issued in the Parent Application on October 17, 2013 are listed on the attached PTO/SB/08a. In accordance with M.P.E.P. § 609, it is not necessary to provide copies of those documents with this filing. It is assumed that the Examiner can locate copies of the remaining references in the file of the Parent Application. Accordingly, in view of the large number of references, Applicants have not submitted a duplicate set of copies with the present Information Disclosure Statement, but will provide an additional set of copies if requested to do so by the Examiner.

This Information Disclosure Statement is being submitted before expiration of the three-month period following filing of the above-captioned application.

The above information is presented so that the Patent and Trademark Office can, in the first instance, determine any materiality thereof to the claimed invention. *See* 37 CFR 1.104(a) and 1.106(b) concerning the PTO duty to consider and use any such information. It is respectfully requested that the information be expressly considered during the prosecution of this application, and that the documents cited in the attached Form PTO/SB/08a be made of record therein and appear among the References Cited on the first page of any patent to issue therefrom.

This submission does not represent that a search has been made or that no better art exists and does not constitute an admission that each or all of the listed documents are material or constitute "prior art." If the Examiner applies any of the documents as prior art against any claim in this application and Applicant determines that the cited documents do not constitute "prior art" under United States law, Applicant reserves the right to present to the office the relevant facts and law regarding the appropriate status of such documents.

Applicant further reserves the right to take appropriate action to establish the patentability of the disclosed invention over the listed documents, should one or more of the documents be applied against the claims of the present application.

It is believed that no fee is required to make this a complete and timely filing. However, if it is determined that a petition or fee is required, the Commissioner is hereby authorized to charge any fee associated with this statement to Alcon's Deposit Account No. 010682.

Respectfully submitted,

June 18, 2014 /Scott A. Chapple, 46,287/

Date

Scott A. Chapple
Reg. No. 46,287
Attorney for Applicants

ALCON RESEARCH, LTD.
6201 S. Freeway, TB4-8
Fort Worth, TX 76134-2099
(817) 551-8793

Docket #: PAT903988-US-CNT

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
14/304,124	06/13/2014	1629	2560	PAT903988-US-CNT	25	4

CONFIRMATION NO. 1002

FILING RECEIPT

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

OC000000069211681

Date Mailed: 06/26/2014

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**

Inventor(s)

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

Applicant(s)

Alcon Research, Ltd., Fort Worth, TX

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 13/475,607 05/18/2012
which claims benefit of 61/548,957 10/19/2011
and claims benefit of 61/487,789 05/19/2011

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access - A proper **Authorization to Permit Access to Application by Participating Offices** (PTO/SB/39 or its equivalent) has been received by the USPTO.

If Required, Foreign Filing License Granted: 06/24/2014

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/304,124**

Projected Publication Date: 10/02/2014

Non-Publication Request: No

Early Publication Request: No

Title

HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

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 (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

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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
14/304,124	06/13/2014	Daniel A. Gamache	PAT903988-US-CNT

CONFIRMATION NO. 1002

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

NOTICE

OC000000069211683

Date Mailed: 06/26/2014

INFORMATIONAL NOTICE TO APPLICANT

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

The item(s) indicated below are also required and should be submitted with any reply to this notice to avoid further processing delays.

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
  Daniel A. Gamache
  Laman Alani
  Malay Ghosh
  Francisco Javier Galan
  Nuria Carreras Perdiguer
  Onkar N. Singh

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 14/304,124

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	280
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	25 minus 20 =	* 5			OR	x 80 =	400
INDEPENDENT CLAIMS (37 CFR 1.16(h))	4 minus 3 =	* 1				x 420 =	420
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	2420

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	14304124
Filing Date	2014-06-13
First Named Inventor	Daniel A. Gamache
Art Unit	1629
Examiner Name	Not Yet Assigned
Attorney Docket Number	PAT903988-US-CNT

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	5874418		1999-02-23	Stella et al.	

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14304124
	Filing Date	2014-06-13
	First Named Inventor	Daniel A. Gamache
	Art Unit	1629
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	PAT903988-US-CNT

	1		☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14304124
	Filing Date	2014-06-13
	First Named Inventor	Daniel A. Gamache
	Art Unit	1629
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	PAT903988-US-CNT

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Scott A. Chapple, 46,287/	Date (YYYY-MM-DD)	2014-06-26
Name/Print	Scott A. Chapple	Registration Number	46,287

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt	
EFS ID:	19417618
Application Number:	14304124
International Application Number:	
Confirmation Number:	1002
Title of Invention:	HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION
First Named Inventor/Applicant Name:	Daniel A. Gamache
Customer Number:	26356
Filer:	Scott Chapple/Candy Sanders
Filer Authorized By:	Scott Chapple
Attorney Docket Number:	PAT903988-US-CNT
Receipt Date:	26-JUN-2014
Filing Date:	13-JUN-2014
Time Stamp:	11:01:29
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	PAT903988-US-CNT_2014-06-26_IDS_Fillable__.pdf	612092 defb8e2309aaf844ab9f0b213a33c955fcc48e4b	no	4
Warnings:					
Information:					

Total Files Size (in bytes):	612092

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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Daniel A. Gamache, et al.

Serial No: 14/304,124

Group Art Unit: 1629

Confirmation No: 1002

Filed: June 13, 2014

Examiner: Not Yet Assigned

For: HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION

RESPONSE TO NOTICE REGARDING POWER OF ATTORNEY AND INFORMATIONAL NOTICE TO APPLICANT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This is in response to the Notice Regarding Power of Attorney and Informational Notice to Applicant mailed June 26, 2014. Applicant submits herewith:

a) A properly executed inventor's oath or declaration for inventor Daniel A. Gamache;
b) A properly executed inventor's oath or declaration for inventor Laman Alani;
c) A properly executed inventor's oath or declaration for inventor Malay Ghosh;
d) A properly executed inventor's oath or declaration for inventor Francisco Javier Galan;
e) A properly executed inventor's oath or declaration for inventor Nuria Carreras Perdiguer;
f) A properly executed inventor's oath or declaration for inventor Onkar N. Singh; and
g) Form PTO/AIA/82A.

Applicant respectfully submits that no additional parts are required to be filed in the above-referenced application, and, therefore, the application should be processed accordingly.

If any extension of time is required, Applicant hereby requests the appropriate extension of time. If any fees are inadvertently omitted or if any additional fees are required or have been overpaid, please appropriately charge or credit those fees to Deposit Account No. 010682 of Alcon Research, Ltd.

Respectfully submitted,

10 July 2014 /Scott A.Chapple, 46,287/

Date Scott A. Chapple
Reg. No. 46,287

Address for Correspondence:

Scott A. Chapple
IP Legal, Mail Code TB4-8
Alcon Research, Ltd.
6201 South Freeway
Fort Worth, TX 76134-2099
Phone: (817) 551-8793

Attorney Docket: PAT903988-US-CNT

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention:	HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☑ United States application or PCT international application number 14/304,124 filed on June 13, 2014.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I acknowledge the duty to disclose information which is known to me to be material to patentability as defined in 37 C.F.R. § 1.56.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

LEGAL NAME OF INVENTOR

Inventor: Daniel A. Gamache Date: 6-19-2014

Signature:

Note: An application data sheet (PTO/AIA/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional declaration form for each additional inventor.

THIS IS A MODIFIED VERSION OF U.S.P.T.O. FORM PTO/AIA/01.

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention:	HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☑ United States application or PCT international application number 14/304,124 filed on June 13, 2014.

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The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

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I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

LEGAL NAME OF INVENTOR

Inventor: Laman Alani Date: 07/08/2014

Signature: Laman Alani

Note: An application data sheet (PTO/AIA/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional declaration form for each additional inventor.

THIS IS A MODIFIED VERSION OF U.S.P.T.O. FORM PTO/AIA/01.

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention:	HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION

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I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

LEGAL NAME OF INVENTOR

Inventor: Malay Ghosh Date: June 17, 2014

Signature: Malay Ghosh

Note: An application data sheet (PTO/AIA/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional declaration form for each additional inventor.

THIS IS A MODIFIED VERSION OF U.S.P.T.O. FORM PTO/AIA/01.

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention:	HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION

As the below named inventor, I hereby declare that:

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☑ United States application or PCT international application number 14/304,124 filed on June 13, 2014 .

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims.

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I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

LEGAL NAME OF INVENTOR

Inventor: Francisco Javier Galan Date: 01 July, 2014

Signature: _____

Note: An application data sheet (PTO/AIA/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional declaration form for each additional inventor.

THIS IS A MODIFIED VERSION OF U.S.P.T.O. FORM PTO/AIA/01.

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention:	HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☑ United States application or PCT international application number 14/304,124 filed on June 13, 2014

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims.

The above-identified application was made or authorized to be made by me.

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I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

LEGAL NAME OF INVENTOR

Inventor: Nuria Carreras Perdiguer Date: 10 JUL 2014

Signature: Nuria Carreras

Note: An application data sheet (PTO/AIA/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional declaration form for each additional inventor.

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention:	HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☑ United States application or PCT international application number 14/304,124 filed on June 13, 2014

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I acknowledge the duty to disclose information which is known to me to be material to patentability as defined in 37 C.F.R. § 1.56.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

LEGAL NAME OF INVENTOR

Inventor: Onkar N. Singh Date: 06/23/2014

Signature: O. N. Singh

Note: An application data sheet (PTO/AIA/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional declaration form for each additional inventor.

THIS IS A MODIFIED VERSION OF U.S.P.T.O. FORM PTO/AIA/01.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
Approved for use through 11/30/2014. OMB 0651-0051
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	14304124
Filing Date	June 13, 2014
First Named Inventor	Daniel A. Gamache
Title	HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION
Art Unit	1629
Examiner Name	Not Yet Assigned
Attorney Docket Number	PAT903988-US-CNT

SIGNATURE of Applicant or Patent Practitioner

Signature	/Scott A. Chapple, 46,287/	Date (Optional)	July 10, 2014
Name	Scott A. Chapple	Registration Number	46,287
Title (if Applicant is a juristic entity)	Authorized Signatory, Alcon Research, Ltd.		
Applicant Name (if Applicant is a juristic entity)	Alcon Research, Ltd.		

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82B (07-13)
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POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☑ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 26356

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

☑ The address associated with the above-mentioned Customer Number

OR

☐ The address associated with Customer Number:

OR

Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

Alcon Research, Ltd.

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☑ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature	/Scott A. Chapple, 46,287/	Date (Optional)	July 10, 2014
Name	Scott A. Chapple		
Title	Authorized Signatory, Alcon Research, Ltd.		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ Total of forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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POWER OF ATTORNEY BY APPLICANT

No more than ten (10) patent practitioners total may be appointed as set forth below by name and registration number. This page need not be submitted if appointing the Patent Practitioner(s) associated with a Customer Number (see form PTO/AIA/82B):

Name	Registration Number

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt	
EFS ID:	19546153
Application Number:	14304124
International Application Number:	
Confirmation Number:	1002
Title of Invention:	HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION
First Named Inventor/Applicant Name:	Daniel A. Gamache
Customer Number:	26356
Filer:	Scott Chapple/Candy Sanders
Filer Authorized By:	Scott Chapple
Attorney Docket Number:	PAT903988-US-CNT
Receipt Date:	10-JUL-2014
Filing Date:	13-JUN-2014
Time Stamp:	15:57:37
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

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	PAT903988-US-CNT_2014-07-10_RESP_Pre-Exam_Formalities_Notice__.pdf	77741 028d970fc78a3a1c1da3bd75c2ca7484f7fdaa44	no	2
Warnings:					
Information:					

2	Oath or Declaration filed	PAT903988-US-CNT_2014-06-19_DEC_Daniel_A_Gamache_Executed__.pdf	48669 279d93758c3470a24f14cbd1de1398b7d4f232a1	no	1
Warnings:					
Information:					
3	Oath or Declaration filed	PAT903988-US-CNT_2014-07-08_DEC_Laman_Alani_Executed__.pdf	53394 893f9a32610adf6357f9e84e20de3c6150da8c1a	no	1
Warnings:					
Information:					
4	Oath or Declaration filed	PAT903988-US-CNT_2014-06-17_DEC_Malay_Ghosh_Executed__.pdf	48703 65dd2dd922303b3649dd048f1ffac83868f0bc50	no	1
Warnings:					
Information:					
5	Oath or Declaration filed	PAT903988-US-CNT_2014-07-01_DEC_Francisco_Javier_Galan_Executed__.pdf	50221 0320a40cc51c3b88a2a74cd3bcc79696766aecc3	no	1
Warnings:					
Information:					
6	Oath or Declaration filed	PAT903988-US-CNT_2014-07-10_DEC_Nuria_Carreras_Perdiguer_Executed__.pdf	388344 17258a0612dde018917e4e77e3d7dd2133b101a2	no	1
Warnings:					
Information:					
7	Oath or Declaration filed	PAT903988-US-CNT_2014-06-23_DEC_Onkar_N_Singh_Executed__.pdf	55753 51c96da4ae5663c3c160fcb63e2b02a7d3159fb5	no	1
Warnings:					
Information:					
8	Power of Attorney	PAT903988-US-CNT_2014-07-10_POA82A__.pdf	195101 4e240328310e1c0cb06f22e36d953ac3199079ae	no	4
Warnings:					
Information:					
		Total Files Size (in bytes):	917926		

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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.

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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.

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www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/304,124	06/13/2014	Daniel A. Gamache	PAT903988-US-CNT

CONFIRMATION NO. 1002

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

POA ACCEPTANCE LETTER

OC000000069554930

Date Mailed: 07/15/2014

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 07/10/2014.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/byemane/

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

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/304,124	06/13/2014	Daniel A. Gamache	PAT903988-US-CNT

CONFIRMATION NO. 1002

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

PUBLICATION NOTICE

OC000000071120071

Title:HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION

Publication No.US-2014-0296328-A1
Publication Date:10/02/2014

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	Gamache, Daniel A. et al.
Serial No.	:	14/304,124
Filed	:	June 13, 2014
Confirmation No.	:	1002
Examiner	:	Tran, My Chau T
Group Art Unit	:	1629
For	:	High Concentration Olopatadine Ophthalmic Composition

PRELIMINARY AMENDMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Please enter the following amendments prior to formal examination of the above-identified application.

Amendments to the Claims are reflected in the listing of claims that begins on page 2 of this paper.

Remarks begin on page 4 of this paper.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application:

Claims 1-25 (canceled)

Claim 26 (new): An aqueous ophthalmic solution for treatment of ocular allergic conjunctivitis, the solution comprising:

at least 0.67 w/v% olopatadine dissolved in the solution;

PEG having a molecular weight of 200 to 800;

polyvinylpyrrolidone;

a cyclodextrin selected from the group consisting of SAE-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin and hydroxypropyl-γ-cyclodextrin; and

water.

Claim 27 (new): A solution as in claim 26 further comprising benzalkonium chloride.

Claim 28 (new): A solution as in claim 27 further comprising borate.

Claim 29 (new): A solution as in claim 28 further comprising a polyol.

Claim 30 (new): A solution as in claim 26 wherein the concentration of olopatadine is no greater than 1.0 w/v%.

Claim 31 (new): A solution as in claim 26 wherein the concentration of PEG is 2.0 w/v% to 6.0 w/v%, the concentration of polyvinylpyrrolidone is 2.0 w/v% to 6.0 w/v% and the concentration of cyclodextrin is at least 0.5 w/v% but no greater than 2.0 w/v%.

Claim 32 (new): A solution as in claim 26 wherein the solution provides more than a 1.0 unit difference relative to vehicle in relief of redness at onset of action according to FDA accepted CAC model.

Claim 33 (new): An aqueous ophthalmic solution for treatment of ocular allergic conjunctivitis, the solution comprising:

at least 0.67 w/v % olopatadine dissolved in the solution;

PEG having a molecular weight of 200 to 800;

polyvinylpyrrolidone;

a cyclodextrin selected from the group consisting of hydroxypropyl-γ-cyclodextrin and hydroxypropyl-γ-cyclodextrin;

benzalkonium chloride;

hydroxypropylmethyl cellulose; and

water.

Claim 34 (new): A solution as in claim 33 further comprising benzalkonium chloride.

Claim 35 (new): A solution as in claim 34 further comprising borate.

Claim 36 (new): A solution as in claim 35 further comprising a polyol.

Claim 37 (new): A solution as in claim 33 wherein the concentration of olopatadine is no greater than 1.0 w/v%.

Claim 38 (new): A solution as in claim 33 wherein the concentration of PEG is 2.0 w/v% to 6.0 w/v%, the concentration of polyvinylpyrrolidone is 2.0 w/v% to 6.0 w/v% and the concentration of cyclodextrin is at least 0.5 w/v% but no greater than 2.0 w/v%.

Claim 39 (new): A solution as in claim 33 wherein the solution provides more than a 1.0 unit difference relative to vehicle in relief of redness at onset of action according to FDA accepted CAC model.

REMARKS

Claims 1-25 have been canceled and claims 26-39 have been added.

Applicant respectfully requests consideration of the pending claims and believes no fee is due with this response. However, the Commissioner is authorized to charge any fees which may be required or to credit any overpayment to Deposit Account No. 010682 in the name of Alcon Research, Ltd.

Respectfully submitted,

ALCON RESEARCH, LTD.

March 2, 2015
Date

/Scott A. Chapple, 46,287/
Scott A. Chapple, Agent
Reg. No. 46,287

Address for Correspondence:
Scott A. Chapple
Alcon Research, Ltd.
6201 S. Freeway, Mail Code TB4-8
Fort Worth, TX 76134-2099
Phone: 817-551-8793

Attorney Docket: PAT903988-US-CNT

Electronic Acknowledgement Receipt

EFS ID:	21641725
Application Number:	14304124
International Application Number:	
Confirmation Number:	1002
Title of Invention:	HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION
First Named Inventor/Applicant Name:	Daniel A. Gamache
Customer Number:	26356
Filer:	Scott Chapple/Candy Sanders
Filer Authorized By:	Scott Chapple
Attorney Docket Number:	PAT903988-US-CNT
Receipt Date:	02-MAR-2015
Filing Date:	13-JUN-2014
Time Stamp:	16:21:33
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Preliminary Amendment	PAT903988-US-CNT_2015-03-02_SUB_Preliminary_Amendment__.pdf	90709 7f08ce31d979eb047468dbc4d4b2aba8d2975d12	no	4
Warnings:					
Information:					

Total Files Size (in bytes):	90709

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PTO/SB/08a (01-10)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	14304124
Filing Date	2014-06-13
First Named Inventor	Daniel A. Gamache
Art Unit	1629
Examiner Name	TRAN, MY CHAU T
Attorney Docket Number	PAT903988-US-CNT

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	1	2003520813	JP		2003-07-08	Alcon, Inc.		☒

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14304124
	Filing Date	2014-06-13
	First Named Inventor	Daniel A. Gamache
	Art Unit	1629
	Examiner Name	TRAN, MY CHAU T
	Attorney Docket Number	PAT903988-US-CNT

	1		☐

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EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14304124
	Filing Date	2014-06-13
	First Named Inventor	Daniel A. Gamache
	Art Unit	1629
	Examiner Name	TRAN, MY CHAU T
	Attorney Docket Number	PAT903988-US-CNT

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☒ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Scott A. Chapple, 46,287/	Date (YYYY-MM-DD)	2015-22-06
Name/Print	Scott A. Chapple	Registration Number	46,287

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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【公報種別】特許法第１７条の２の規定による補正の掲載
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【誤訳訂正書】
【提出日】平成24年3月19日(2012.3.19)
【誤訳訂正１】
【訂正対象書類名】明細書
【訂正対象項目名】特許請求の範囲
【訂正方法】変更
【訂正の内容】
【特許請求の範囲】
【請求項１】　コンタクトレンズを着用する患者による使用に適する、局所的に投与され得る、抗アレルギー眼用組成物であって、オロパタジンおよびエメダスチンからなる群から選択される薬物の抗アレルギー有効量；および保存剤として、眼に受容可能なポリマー性四級アンモニウム化合物を含むが、但し、該組成物は塩化ベンザルコニウムを含まず、該組成物は、コンタクトレンズを取り外すことなく適用され；そして該組成物は複数回投与として投与されることを特徴とする、眼用組成物。
【請求項２】　前記薬物がオロパタジンであり、かつオロパタジンの抗アレルギー有効量が０．０００１～５％（ｗ／ｖ）である、請求項１に記載の眼用組成物。
【請求項３】　オロパタジンの前記抗アレルギー有効量が０．００１～０．２５％（ｗ／ｖ）である、請求項２に記載の眼用組成物。
【請求項４】　前記オロパタジンが塩酸オロパタジンであり、かつオロパタジンの前記抗アレルギー有効量が０．１～０．２５％（ｗ／ｖ）である、請求項３に記載の眼用組成物。
【請求項５】　前記薬物がエメダスチンであり、かつエメダスチンの前記抗アレルギー有効量が０．０００１～１％（ｗ／ｖ）である、請求項１に記載の眼用組成物。
【請求項６】　エメダスチンの前記抗アレルギー有効量が０．００５～０．１％（ｗ／ｖ）である、請求項５に記載の眼用組成物。
【請求項７】　前記エメダスチンがフマル酸エメダスチンであり、かつエメダスチン

の前記抗アレルギー有効量が０．０８８４％（ｗ／ｖ）である、請求項５に記載の眼用組成物。

【請求項８】　前記ポリマー性四級アンモニウム化合物が、ポリクオタニウム－１である、請求項１に記載の眼用組成物。

【請求項９】　前記ポリマー性四級アンモニウム化合物が、０．０００１～３％（ｗ／ｖ）の量で存在する、請求項８に記載の眼用組成物。

【請求項１０】　前記ポリマー性四級アンモニウム化合物が、０．００１～０．１％（ｗ／ｖ）の量で存在する、請求項９に記載の眼用組成物。

【請求項１１】　請求項１に記載の眼用組成物であって、該組成物がさらに張度調整剤；緩衝剤；キレート剤；ｐＨ調整剤；および粘度改変剤からなる群から選択される１つ以上の成分を含む、眼用組成物。

【請求項１２】　コンタクトレンズを着用する患者における眼のアレルギーを処置または制御するための眼用組成物であって、該組成物は、オロパタジンおよびエメダスチンからなる群から選択される薬物の抗アレルギー有効量；および保存剤としてのポリマー性四級アンモニウム化合物を含み、該組成物は該コンタクトレンズを取り外すことなく適用され、そして該組成物が塩化ベンザルコニウムを含まない、眼用組成物。

【請求項１３】　前記薬物がオロパタジンであり、かつオロパタジンの前記抗アレルギー有効量が０．０００１～５％（ｗ／ｖ）である、請求項１２に記載の眼用組成物。

【請求項１４】　前記オロパタジンが塩酸オロパタジンであり、かつオロパタジンの前記抗アレルギー有効量が０．１～０．２５％（ｗ／ｖ）である、請求項１３に記載の眼用組成物。

【請求項１５】　前記薬物がエメダスチンであり、かつエメダスチンの前記抗アレルギー有効量が０．００５～０．１％（ｗ／ｖ）である、請求項１２に記載の眼用組成物。

【請求項１６】　前記エメダスチンがフマル酸エメダスチンであり、かつエメダスチンの前記抗アレルギー有効量が０．０８８４％（ｗ／ｖ）である、請求項１５に記載の眼用組成物。

【請求項１７】　前記ポリマー性四級アンモニウム化合物が、ポリクオタニウム－１である、請求項１２に記載の眼用組成物。

【請求項１８】　前記ポリマー性四級アンモニウム化合物が、０．０００１～３％（ｗ／ｖ）の量で存在する、請求項１７に記載の眼用組成物。

【請求項１９】　請求項１２に記載の眼用組成物であって、該組成物がさらに、張度調整剤；緩衝剤；キレート剤；ｐＨ調整剤；および粘度改変剤からなる群から選択される１つ以上の成分を含む、眼用組成物。

【誤訳訂正２】
【訂正対象書類名】明細書
【訂正対象項目名】０００２
【訂正方法】変更
【訂正の内容】
【０００２】
眼科用処方物は、一般的に、界面活性剤のような賦形剤、刺激緩和剤（ｃｏｍｆｏｒｔｉｎｇ　ａｇｅｎｔｓ）、錯化剤（ｃｏｍｐｌｅｘｉｎｇ　ａｇｅｎｔｓ）、安定剤、緩衝系、キレート剤、粘度剤（ｖｉｓｃｏｓｉｔｙ　ａｇｅｎｔｓ）、もしくはゲル化ポリマー、および抗酸化剤と共に、１つ以上の活性な化合物を含む。複数回投与での使用が意図される眼科用処方物は保存剤を必要とする。塩化ベンザルコニウム（「ＢＡＣ」）は最も広範囲に使用される眼科用保存剤である。
【誤訳訂正３】
【訂正対象書類名】明細書
【訂正対象項目名】０００３
【訂正方法】変更
【訂正の内容】

【０００３】
局所的に投与され得る複数回投与眼科用製品は、一般的にコンタクトレンズでの使用に適していない。なぜならば、活性物質または保存剤がコンタクトレンズに結合し得るか、またはコンタクトレンズ中に蓄積され得、刺激または毒性作用を生じるからである。
【誤訳訂正４】
【訂正対象書類名】明細書
【訂正対象項目名】０００７
【訂正方法】変更
【訂正の内容】
【０００７】
（発明の要旨）
ここで、保存剤としてポリクオタニウム－１を含むオロパタジンおよびエメダスチンの組成物は、コンタクトレンズでの使用に適していることが見出された。本発明は、保存剤としてポリマー性四級アンモニウム化合物（例えば、ポリクオタニウム－１）を含む、オロパタジンおよびエメダスチンの複数回投与の局所投与可能な組成物に関する。本発明の組成物はＢＡＣを含まない。
【誤訳訂正５】
【訂正対象書類名】明細書
【訂正対象項目名】００１４
【訂正方法】変更
【訂正の内容】
【００１４】
本発明の組成物は、眼科的に受容可能な張度（例えば、２６０～３２０ｍＯｓｍ／ｋｇ）、および眼科的に受容可能なｐＨ（例えば、ｐＨ５～８、そして好ましくはｐＨ６．８～７．６）を有するべきである。本発明の局所投与可能な複数回投与組成物は、必要に応じて、張度調整剤（ｔｏｎｉｃｉｔｙ　ａｄｊｕｓｔｉｎｇ　ａｇｅｎｔｓ）；緩衝剤；キレート剤；およびｐＨ調整剤のような他の賦形剤を含む。例えば、塩化ナトリウム、マンニトールなどは等張化剤として使用され得る；リン酸水素ナトリウム、リン酸二水素ナトリウム、ｐ－ヒドロキシ安息香酸エステル、ホウ酸などは緩衝剤として使用され得る；エデト酸ナトリウムなどはキレート剤または安定剤として使用され得る；そして水酸化ナトリウム、塩酸などはｐＨ調整剤として使用され得る。

Espacenet

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OPHTHALMIC ANTI-ALLERGY COMPOSITIONS SUITABLE FOR USE WITH CONTACT LENSES

Inventor(s):

Applicant(s):

Classification:
- **international:** ***A61K31/335; A61K31/55; A61K31/551; A61K47/34; A61K9/00; A61P27/02; A61P27/14; A61P37/08; C07D313/12; C07D403/04;*** (IPC1-7): A61K31/335; A61K31/551; A61K47/34; A61P27/02; A61P37/08; C07D313/12; C07D403/04
- **cooperative:** **A61K31/335**; **A61K31/55**; **A61K31/551**; **A61K9/0048**; Y10S514/912

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Abstract not available for JP2003520813 (A)
Abstract of corresponding document: WO0154687 (A1)

Topically administrable anti-allergy compositions comprising olopatadine and a polymeric quaternary ammonium preservative are suitable for use by patients wearing contact lenses.

Patent & Utility Model Number Search

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DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
(The background of invention) The
present invention generally relates to the antiallergic composition of an eye. Especially the present invention relates to the local antiallergic composition which may be safely applied by the patient who wears a contact lens.
[0002]
The formula things for ophthalmology are generally an excipient like a surfactant, and stimulus palliative (comforting agents). One or more active compounds are included with a complexing agent (complexing agents), stabilizer, a buffer system, a chelating agent, a viscosity agent (viscosity agents) or gelling polymer, and an anti-oxidant. The formula thing for ophthalmology in which busy quantity type use is meant needs a preservative. The benzalkonium chloride ("BAC") is a preservative for ophthalmology used most broadly.
[0003]
The product for busy quantity type ophthalmology which may be locally prescribed for the patient does not generally fit use with a contact lens. It is because an active substance or a preservative can combine with a contact lens, or it may be accumulated into a contact lens and a stimulus or a toxic effect is produced.
[0004]
An OROPA tajine (olopatadine) is a publicly known antiallergic drug thing. Refer to US,5,641,805,B (Yanni et al.). The solution for olopatadine hydrochloride ophthalmology of a trademark called PATANOL (registered trademark) is marketed as a local antiallergic composition. Emedastine is a publicly known antihistaminic agent. The emedastine difumarate solution of a trademark called EMADINE (registered trademark) is marketed as a local antiallergic composition. These constituents are saved like the antiallergy products which can be prescribed for the patient using BAC locally [others]. Combining BAC with a contact lens or being accumulated into a contact lens is known. Therefore, locally [the others containing BAC] like the ophthalmological drug study products which can be prescribed for the patient, The solution for olopatadine hydrochloride ophthalmology of a trademark called PATANOL (registered trademark), and the solution for emedastine difumarate ophthalmology of a trademark called EMADINE (registered trademark), In label information (labelling information), a contact lens is removed before use, and after prescribing this product for the patient, and before wearing a lens, notes "wait for 10 minutes" are included. The medication regimen of a dosage to antiallergy products requires two to four application per day typically, and makes it inconvenient to deal with the allergies of an eye for the user of a contact lens.
[0005]
The polyquaternium 1 (Polyquatermium-1) (used under the brand name Polyquad (registered trademark)) is one preservative in which it is known that there are a contact lens and conformity. The polyquaternium 1 and other polymeric quaternary ammonium compounds are used as the germicide in a contact lens care, a preservative, and an artificial-tear solution. For example, US,5,037,647,B; refer to 4,525,346; and 4,407,791. The contact lens care product (a

multiple-purpose solution and a washing solution are included) of a trademark called Opti-Free (registered trademark) marketed these days contains the polyquaternium 1 as a germicide and a preservative.
[0006]
In addition to a contact lens care product, in the specific ophthalmological drug thing products which can be locally prescribed for the patient, the polyquaternium 1 may also be used as a preservative. US,5,603,929,B discloses use of the polyquaternium 1 for, saving the constituent for ophthalmology which can be prescribed for the patient locally [an acidic drug (for example, non-steroidal anti-inflammatory drug)] combined with boric acid. Although an ophthalmological drug thing constituent suitable in order to use the 'No. 929 patent with the polyquaternium 1 and a boric acid preservative system is prescribed that the salt, the amide, ester, and the prodrug which can be received are included ophthalmologically [the acidic drug of many molds], This patent in particular has not made [thing / antiallergic drug] reference about an OROPA tajine, either. Refer to three columns of 12-30 lines of the 'No. 929 patent.
[0007]
(Summary of invention)
Here, it was found out that the constituent of the OROPA tajine which contains the polyquaternium 1 as a preservative, and emedastine fits use with a contact lens. The present invention relates to the OROPA tajine which contains a polymeric quaternary ammonium compound (for example, polyquaternium 1) as a preservative, and the constituent in which the busy quantity type local administration of emedastine is possible. The constituent of the present invention does not contain BAC.
[0008]
The present invention relates again the allergy of the eye in the patient who wears a contact lens to the method for taking a measure or controlling, and this method, The process of prescribing locally for the patient the constituent which contains a polymeric quaternary ammonium compound as an OROPA tajine or emedastine, and a preservative is included, and this constituent is applied here, without removing a contact lens.
[0009]
(DETAILED DESCRIPTION) An
OROPA tajine is (Z)-11-(3-dimethylamino propylidene)-6,11-hydrodibenzo [b,e]-oxepin 2-acetic acid. An OROPA tajine may be produced using the method (among those, the whole ** is used as reference by the inside of this Description) disclosed into US,5,116,863,B. the concentration of the OROPA tajine in the constituent of the present invention is based on sterile purified water -- about 0.0001 to 5% (w/v) -- preferable, it is about 0.1 to 0.25% (w/v) of range most preferably about 0.001 to 0.25% (w/v). This OROPA tajine component may exist pharmacologically with the form of the salt which can be received. Unless it is shown by another method, the "OROPA tajine" used in this Description says both an OROPA tajine and its salt which can be received pharmacologically. The most preferable form of an OROPA tajine is olopatadine hydrochloride. The most preferable concentration of olopatadine hydrochloride is about 0.111 to 0.222% (w/v).
This is equivalent to a 0.1 to 0.2% (w/v) OROPA tajine.

[0010]
The chemical name of emedastine is 1-(2-ethoxyethyl)-2-(4-methyl-1-homo piperazinyl)-benzimidazole. The use for ophthalmology of emedastine is disclosed into US,5,441,958,B. Emedastine may be produced using the method disclosed in US,4,430,343,B, and the whole contents are used as reference by the inside of this Description. the concentration of the emedastine in the constituent of the present invention -- about 0.0001 to 1% (w/v) -- preferable, it is about 0.05% (w/v) of range most preferably about 0.005 to 0.1% (w/v). The component of this emedastine may exist pharmacologically with the form of the salt which can be received. Unless it is shown by another method, the "emedastine" used in this Description says both emedastine and its salt which can be received pharmacologically. The most preferable form of emedastine is emedastine difumarate. The most preferable concentration of emedastine difumarate is about 0.0884% (w/v).
This is equivalent to 0.05% (w/v) emedastine.

[0011]
Adding to an OROPA tajine, emedastine, or those salts that can be received pharmacologically, the constituent of the present invention contains a polymeric quaternary ammonium compound as a preservative. In the constituent of the present invention, a useful polymeric quaternary ammonium compound has an antimicrobital action, and can receive it ophthalmologically. This type of preferable compound, US,3,931,319,B; 4,027,020; 4,407,791; 4,525,346; 4,836,986; 5,037,647, 5,300,287, and PCT applicationWO91/09523. It describes in (Dziabo and others). The most preferable polymeric ammonium compound is the polyquaternium 1, and this is known also as Polyquad (registered trademark) or Onamer M (registered trademark), and has a number average molecular weight between 2,000-30,000. Preferably, this number average molecular weight is between 3,000-14,000.
[0012]
A polymeric quaternary ammonium compound is generally used in the constituent of the present invention in about 0.00001 - 3% (w/v) of abbreviation preferably about 0.001 - the quantity of 0.1% (w/v) of abbreviation. Most preferably the constituent of the present invention

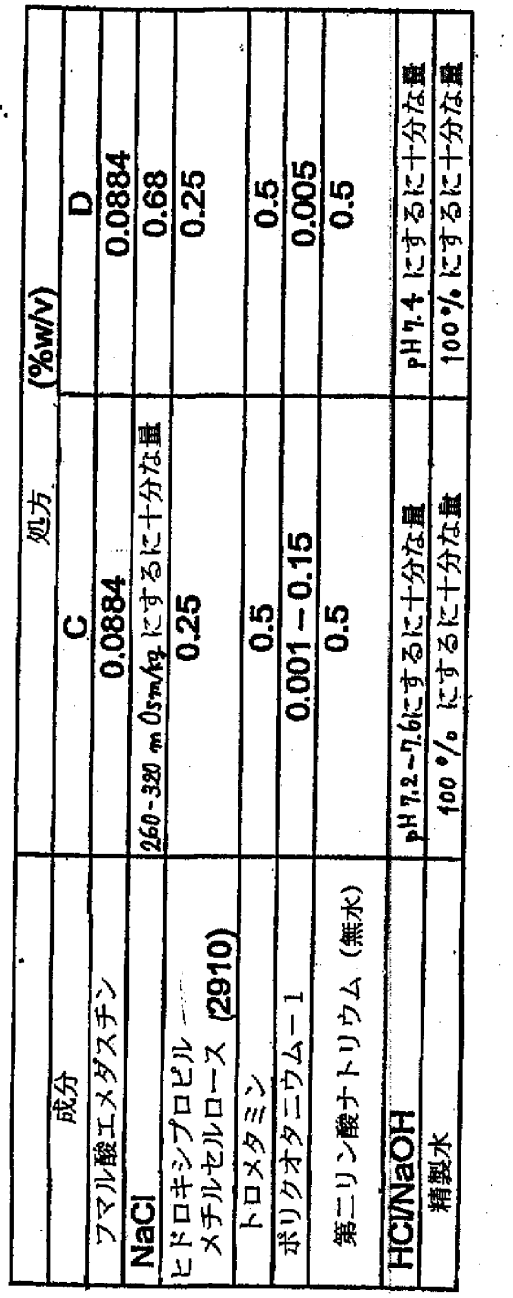
contains about 0.001 - the polymeric quaternary ammonium compound of 0.05% (w/v) of abbreviation.
[0013]
It is required to add boric acid to this constituent in order to attain the preservation effect of the level for which it asks, and it obtains, or may be wanted. Refer to US,5,603,929,B. The whole contents are used as reference by the inside of this Description. As boric acid suitable for the use in the constituent of the present invention, not only boric acid but the type ophthalmologically described in the acid addition salt which can be received, and US,5,342,620,B (Chowhan) of borate polyol composite is mentioned. it exists -- if it becomes -- the quantity of boric acid -- general -- about 0.3- it is about 0.5% (w/v) of range.
[0014]
The constituent of the present invention should have ophthalmologically a tonicity (for example, 260 - 320 mOsm/kg) which can be received, and pH (preferably pH 6.8-7.6 [For example, pH 5-8,]) which can be received ophthalmologically. The busy quantity setup-of-tooling product in which the local administration of the present invention is possible contains other excipients like tonicity regulator (tonicity adjusting agents); buffer; chelating agent; and a pH adjuster if needed. For example, sodium chloride, mannitol, etc. are; dibasic sodium phosphate which may be used as an isotonizing agent. ;, sodium hydroxide, chloride, etc. in which; disodium edetate in which a sodium dihydrogenphosphate, p-hydroxy benzoate ester, boric acid, etc. may be used as a buffer may be used as a chelating agent or stabilizer may be used as a pH adjuster.
[0015]
The constituent of the present invention is; cellulose ether which may contain the following viscosity change agents again. for example, hydroxypropylmethylcellulose (HPMC) and hydroxyethyl cellulose (HEC) -- Ethyl hydroxyethyl cellulose, hydroxypropylcellulose, Methyl cellulose and carboxymethyl cellulose; The carbomer. (For example, Carbopol (registered trademark)) the; polyvinyl alcohol; -- the polyvinyl pyrrolidone; -- the alginate; -- the carrageenin;, guar gum, karaya gum, agarose gum, locust bean (locust bean) gum, and xanthan gum.
[0016]
Although the following working examples are shown and the further various aspects of affairs of the present invention are described, it does not have intention of limiting the range of the present invention at any points.
[0017]
[Table 1]

実施例1

成分	処方 (%w/v) A	B
塩酸オロパタジン	0.111 または 0.222	0.111 または 0.222
NaCl	260 - 320 mOsm/kg にするに十分な量	0.3
ポリエチレングリコール (400)	2.0	2.0
ポリクオタニウム－1	0.001-0.15	0.005
第二リン酸ナトリウム（無水）	0.5	0.5
HCl/NaOH	pH 6.8 - 7.2 にするに十分な量	pH 7 にするに十分な量
精製水	100 % にするに十分な量	100 % にするに十分な量

[0018]
[Table 2]

実施例2



成分	処方 (%w/v) C	D
フマル酸エメダスチン	0.0884	0.0884
NaCl	260-320 mOsm/kg にするに十分な量	0.68
ヒドロキシプロピルメチルセルロース (2910)	0.25	0.25
トロメタミン	0.5	0.5
ポリクオタニウム-1	0.001－0.15	0.005
第二リン酸ナトリウム（無水）	0.5	0.5
HCl/NaOH	pH 7.2-7.6にするに十分な量	pH 7.4 にするに十分な量
精製水	100 % にするに十分な量	100 % にするに十分な量

While the present invention carries out only; currently described with reference to the specific preferable embodiment, it should be understood that shape may be taken in other specific forms or variations of them, without separating the present invention from the meaning or the essential characteristics of the present invention. So, it is considered that the embodiment described above is illustration in all the aspects of affairs, and is not restrictive, and the range of the present invention is shown by the Claims to which the twist was also rather attached by the above-mentioned Description.

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[Translation done.]

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2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

CLAIMS

[Claim(s)]
[Claim 1]A partial target suitable for use by a patient who wears a contact lens may be medicated, A constituent in which the constituent does not contain a benzalkonium chloride although it is a busy quantity type antiallergic composition and a polymeric quaternary ammonium compound which can be received to an eye is included as the antiallergic effective dose; of a drug chosen from an OROPA tajine and a group which consists of emedastine, and a preservative.
[Claim 2]The constituent according to claim 1 whose aforementioned drug is an OROPA tajine and whose antiallergic effective dose of an OROPA tajine is about 0.0001 to 5% (w/v).
[Claim 3]The constituent according to claim 2 whose aforementioned antiallergic effective dose of an OROPA tajine is about 0.001 to 0.25% (w/v). [Claim 4]The constituent according to claim 3 whose aforementioned OROPA tajine is olopatadine hydrochloride and whose aforementioned antiallergic effective dose of an OROPA tajine is about 0.1 to 0.25% (w/v).
[Claim 5]The constituent according to claim 1 whose aforementioned drug is emedastine and whose aforementioned antiallergic effective dose of emedastine is about 0.0001 to 1% (w/v).
[Claim 6]The constituent according to claim 5 whose aforementioned antiallergic effective dose of emedastine is about 0.005 to 0.1% (w/v). [Claim 7]The constituent according to claim 5 whose aforementioned emedastine is emedastine difumarate and whose aforementioned antiallergic effective dose of emedastine is about 0.0884% (w/v). [Claim 8]The constituent according to claim 1 whose aforementioned polymeric quaternary ammonium compound is the polyquaternium 1. [Claim 9]The constituent according to claim 8 in which the aforementioned polymeric quaternary ammonium compound exists in about 0.00001 - quantity of 3% (w/v) of abbreviation. [Claim 10]The constituent according to claim 9 in which the aforementioned polymeric quaternary ammonium compound exists in about 0.001 - quantity of 0.1% (w/v) of abbreviation. [Claim 11]A constituent which is the constituent according to claim 1 and contains one or more components as which the constituent is further chosen from a group which consists of tonicity regulator; buffer; chelating agent; pH adjuster; and a viscosity change agent.
[Claim 12]It is a method to allergy-take a measure or for an eye in a patient who wears a contact lens control, Include a process of prescribing locally for the patient a constituent containing the antiallergic effective dose; of a drug chosen from an OROPA tajine and a group which consists of emedastine, and a polymeric quaternary ammonium compound as a preservative, and here, A way the constituent is applied, without removing the contact lens, and the constituent does not contain a benzalkonium chloride.
[Claim 13]A way according to claim 12 the aforementioned drug is an OROPA tajine and the aforementioned antiallergic effective dose of an OROPA tajine is about 0.0001 to 5% (w/v).
[Claim 14]A way according to claim 13 the aforementioned OROPA tajine is olopatadine hydrochloride, and the aforementioned antiallergic effective dose of an OROPA tajine is about 0.1 to 0.25% (w/v).
[Claim 15]A way according to claim 12 the aforementioned drug is emedastine and the aforementioned antiallergic effective dose of emedastine is about 0.005 to 0.1% (w/v). [Claim

16]A way according to claim 15 the aforementioned emedastine is emedastine difumarate and the aforementioned antiallergic effective dose of emedastine is about 0.0884% (w/v). [Claim 17]A way according to claim 12 the aforementioned polymeric quaternary ammonium compound is the polyquaternium 1. [Claim 18]A way according to claim 17 the aforementioned polymeric quaternary ammonium compound exists in about 0.00001 - quantity of 3% (w/v) of abbreviation. [Claim 19]A way are the method according to claim 12 and the aforementioned constituent contains further one or more components chosen from a group which consists of tonicity regulator; buffer; chelating agent; pH adjuster; and a viscosity change agent.

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[Translation done.]

Patent & Utility Model Number Search

Selected Gazette

JP,2003-520813,A

CORRECTION OR AMENDMENT

*** NOTICES ***

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2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

CORRECTION OR AMENDMENT

[Kind of official gazette]Printing of correction by regulation of Patent Law Article 17bis
[Section Type] The 2nd Type of the part III gate
[Publication date]Heisei 20(2008) February 14 (2008.2.14)

[Official announcement number] ** table 2003-520813 (P2003-520813A)
[Announcement date] Heisei 15(2003) July 8 (2003.7.8)
[Application number]Patent Application No. 2001-554671 (P2001-554671)
[International Patent Classification] ***A61K 31 / 335 (2006.01).A61K 31/551 (2006.01) A61K 47/34 (2006.01) A61P 27/02 (2006.01) A61P 37/08 (2006.01) C07D 313/12*** *(2006.01)*
C07D 403/04 (2006.01)
[FI]

A61K 31/335A61K 31/551A61K 47/34A61P 2 7/02A61P 37/08C07D 13/12C07D403/04

[Written Amendment]
[Filing date]Heisei 19(2007) December 19 (2007.12.19)
[Amendment 1]
[Document to be Amended]Description
[Item(s) to be Amended]Claims
[Method of Amendment]Change
[The contents of correction]
[Claim(s)]
[Claim 1]A partial target suitable for use by a patient who wears a contact lens may be medicated, A constituent in which the constituent does not contain a benzalkonium chloride although it is a busy quantity type antiallergic composition and a polymeric quaternary ammonium compound which can be received to an e is included as the antiallergic effective dose; of a drug chosen from an OROPA tajine and a group which consists of emedastine, and a preservative.
[Claim 2]The constituent according to claim 1 whose aforementioned drug is an OROPA tajine and whose antiallergic effective dose of an OROPA tajine is about 0.0001 to 5% (w/v).
[Claim 3]The constituent according to claim 2 whose aforementioned antiallergic effective dose of an OROPA tajine is about 0.001 to 0.25% (w/v).
[Claim 4]The constituent according to claim 3 whose aforementioned OROPA tajine is olopatadine hydrochloride and whose aforementioned antiallergic effective d of an OROPA tajine is about 0.1 to 0.25% (w/v).

[Claim 5]The constituent according to claim 1 whose aforementioned drug is emedastine and whose aforementioned antiallergic effective dose of emedastine is ab
0.0001 to 1% (w/v).
[Claim 6]The constituent according to claim 5 whose aforementioned antiallergic effective dose of emedastine is about 0.005 to 0.1% (w/v).
[Claim 7]The constituent according to claim 5 whose aforementioned emedastine is emedastine difumarate and whose aforementioned antiallergic effective dose c
emedastine is about 0.0884% (w/v).
[Claim 8]The constituent according to claim 1 whose aforementioned polymeric quaternary ammonium compound is the polyquaternium 1.
[Claim 9]The constituent according to claim 8 in which the aforementioned polymeric quaternary ammonium compound exists in about 0.00001 - quantity of 3%
(w/v) of abbreviation.
[Claim 10]The constituent according to claim 9 in which the aforementioned polymeric quaternary ammonium compound exists in about 0.001 - quantity of 0.1%
(w/v) of abbreviation.
[Claim 11]A constituent which is the constituent according to claim 1 and contains one or more components as which the constituent is further chosen from a grou
which consists of tonicity regulator; buffer; chelating agent; pH adjuster; and a viscosity change agent.
[Claim 12]Are a contact lens a constituent to allergy-take a measure or for an eye in a patient who wears control, and the constituent, The antiallergic effective do
of a drug chosen from an OROPA tajine and a group which consists of emedastine and a polymeric quaternary ammonium compound as a preservative are include
constituent in which the constituent is applied, without removing the contact lens, and the constituent does not contain a benzalkonium chloride.
[Claim 13]The constituent according to claim 12 whose aforementioned drug is an OROPA tajine and whose aforementioned antiallergic effective dose of an OROPA
tajine is about 0.0001 to 5% (w/v).
[Claim 14]The constituent according to claim 13 whose aforementioned OROPA tajine is olopatadine hydrochloride and whose aforementioned antiallergic effective
dose of an OROPA tajine is about 0.1 to 0.25% (w/v).
[Claim 15]The constituent according to claim 12 whose aforementioned drug is emedastine and whose aforementioned antiallergic effective dose of emedastine is
about 0.005 to 0.1% (w/v).
[Claim 16]The constituent according to claim 15 whose aforementioned emedastine is emedastine difumarate and whose aforementioned antiallergic effective dos
emedastine is about 0.0884% (w/v).
[Claim 17]The constituent according to claim 12 whose aforementioned polymeric quaternary ammonium compound is the polyquaternium 1.
[Claim 18]The constituent according to claim 17 in which the aforementioned polymeric quaternary ammonium compound exists in about 0.00001 - quantity of 3%
(w/v) of abbreviation.
[Claim 19]A constituent in which it is the constituent according to claim 12, and the constituent contains further one or more components chosen from a group wh
consists of tonicity regulator; buffer; chelating agent; pH adjuster; and a viscosity change agent.

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Index on Usage Privacy Policy Questionnaire

[Translation done.]

Electronic Acknowledgement Receipt

EFS ID:	22695454
Application Number:	14304124
International Application Number:	
Confirmation Number:	1002
Title of Invention:	HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION
First Named Inventor/Applicant Name:	Daniel A. Gamache
Customer Number:	26356
Filer:	Scott Chapple/Candy Sanders
Filer Authorized By:	Scott Chapple
Attorney Docket Number:	PAT903988-US-CNT
Receipt Date:	22-JUN-2015
Filing Date:	13-JUN-2014
Time Stamp:	12:05:41
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	PAT903988-US-CNT_2015-06-22_IDS_Fillable__.pdf	612181 20fa3e72c4ac72f68d4a91e06bf251850698 0abf	no	4
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2	Foreign Reference	JP2003520813_with_translation__.pdf	664954 0527929fce6a9ac60d7545c2cc1b11576d35dd1e	no	14

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Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	14/304,124	GAMACHE ET AL.	
	Examiner	Art Unit	
	MY-CHAU T. TRAN	1629	

All participants (applicant, applicant's representative, PTO personnel):

(1) Scott Chapple Ph.D. (3) MY-CHAU T. TRAN.

(2) _____. (4) _____.

Date of Interview: 25 June 2015.

Type: ☐ Telephonic ☐ Video Conference
☒ Personal [copy given to: ☐ applicant ☒ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: None.

Identification of prior art discussed: None

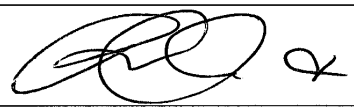
Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Discussed the invention core a potential new application. The examiner states that if there is only ODP rejection(s) in this application the call will be made so that a terminal disclaimer can be filed.

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/304,124	06/13/2014	Daniel A. Gamache	PAT903988-US-CNT	1002

26356 7590 07/06/2015

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IP LEGAL
6201 SOUTH FREEWAY
FORT WORTH, TX 76134

EXAMINER	
TRAN, MY CHAU T	

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
07/06/2015	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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PTOL-90A (Rev. 04/07)

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	14/304,124	GAMACHE ET AL.	
	Examiner	Art Unit	
	MY-CHAU T. TRAN	1629	

All participants (applicant, applicant's representative, PTO personnel):

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(2) _____. (4) _____.

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If Yes, brief description: _____.

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(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: None.

Identification of prior art discussed: None

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

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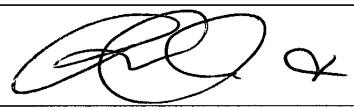
☐ Attachment



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	14304124
Filing Date	2014-06-13
First Named Inventor	Daniel A. Gamache
Art Unit	1629
Examiner Name	TRAN, MY CHAU T
Attorney Docket Number	PAT903988-US-CNT

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	1	20030055102	A1	2003-03-20	Castillo et al.	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14304124
	Filing Date	2014-06-13
	First Named Inventor	Daniel A. Gamache
	Art Unit	1629
	Examiner Name	TRAN, MY CHAU T
	Attorney Docket Number	PAT903988-US-CNT

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Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14304124
	Filing Date	2014-06-13
	First Named Inventor	Daniel A. Gamache
	Art Unit	1629
	Examiner Name	TRAN, MY CHAU T
	Attorney Docket Number	PAT903988-US-CNT

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☒ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☒ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Scott A. Chapple, 46,287/	Date (YYYY-MM-DD)	2015-08-11
Name/Print	Scott A. Chapple	Registration Number	46,287

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal				
Application Number:	14304124			
Filing Date:	13-Jun-2014			
Title of Invention:	HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION			
First Named Inventor/Applicant Name:	Daniel A. Gamache			
Filer:	Scott Chapple/Candy Sanders			
Attorney Docket Number:	PAT903988-US-CNT			
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	**Fee Code**	**Quantity**	**Amount**	**Sub-Total in USD($)**
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt	
EFS ID:	23180093
Application Number:	14304124
International Application Number:	
Confirmation Number:	1002
Title of Invention:	HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION
First Named Inventor/Applicant Name:	Daniel A. Gamache
Customer Number:	26356
Filer:	Scott Chapple/Candy Sanders
Filer Authorized By:	Scott Chapple
Attorney Docket Number:	PAT903988-US-CNT
Receipt Date:	11-AUG-2015
Filing Date:	13-JUN-2014
Time Stamp:	17:01:49
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$180
RAM confirmation Number	3639
Deposit Account	010682
Authorized User	SANDERS, CANDY
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	Transmittal Letter	PAT903988-US-CNT_2015-08-11_IDS_Transmittal_Letter__.pdf	44464 e66a88b54b87e4980cba2abf081fd69c18b30a8d	no	2
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	PAT903988-US-CNT_2015-08-11_IDS_Fillable__.pdf	612184 f221c7c524d29949a4e1b251f3ba37819163b7f4	no	4
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30557 960803dcc923a63dd8c2677c607ae87ccb324a35	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	687205		

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.

Attorney Docket No. PAT903988-US-CNT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF	Art Unit: 1629
Daniel A. Gamache	Examiner: TRAN, MY CHAU T
APPLICATION NO: 14/304124	Confirmation No.: 1002
FILED: June 13, 2014	
FOR: HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION	

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Sir:

This paper is being filed:

☑ supplemental to the Information Disclosure Statement filed June 22, 2015.

☐ within three months of the filing date of the application. Therefore, no fees are required.

☐ before the mailing date of a first Office Action on the merits, and so under 37 C.F.R. §1.97(b)(3) no fees are required.

☐ This Information Disclosure Statement is being filed in accordance with 37 C.F.R. §1.97(c) or 37 C.F.R. §1.97(d).

☑ Payment of the fee set forth in 37 C.F.R. §1.17(p) is enclosed.

In accordance with 37 C.F.R. §1.56, applicants wish to call the Examiner's attention to the references cited on the attached form(s) PTO/SB/08A/B.

☐ The asterisked references were cited in the International Search. Copies of these references are enclosed herewith.

☐ The asterisked references are of record in parent Application No. filed , and copies are available therein.

☐ Copies of the non-asterisked references are enclosed herewith.

☐ Some of the non-asterisked references were cited in a search report in a corresponding application. Copies of these references and the search report are enclosed herewith.

The Examiner is requested to consider the foregoing information in relation to this application and indicate that each reference was considered by returning a copy of the initialed PTO/SB/08A/B form(s).

☑ Certificate under 37 C.F.R. §1.704(d): I, the undersigned Attorney, hereby certify that each item of information contained in the Information Disclosure Statement was first cited in any communication from a foreign patent office in a counterpart application and that this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

☑ Certificate under 37 C.F.R. §1.97(e)(1): I, the undersigned Attorney, hereby certify that each item of information contained in the Information Disclosure Statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the Information Disclosure Statement.

☐ Statement under 37 C.F.R. §1.97(e)(2): I, the undersigned Attorney, hereby certify that no item of information contained in the Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the Information Disclosure Statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the Information Disclosure Statement.

If any fees are inadvertently omitted or if any additional fees are required or have been overpaid, the Commissioner is hereby authorized to appropriately charge or credit those fees to Deposit Account No. 010682 of Alcon Research, Ltd.

Respectfully submitted,

/Scott A. Chapple, 46,287/

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Date: August 11, 2015

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/304,124	06/13/2014	Daniel A. Gamache	PAT903988-US-CNT	1002

26356 7590 02/12/2016

ALCON
IP LEGAL
6201 SOUTH FREEWAY
FORT WORTH, TX 76134

EXAMINER	
TRAN, MY CHAU T	

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
02/12/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patent.docketing@alcon.com

Office Action Summary	Application No. 14/304,124	Applicant(s) GAMACHE ET AL.	
	Examiner MY-CHAU T. TRAN	Art Unit 1629	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08/11/2015*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *26-39* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *26-31 and 33-38* is/are rejected.

8)☒ Claim(s) *32 and 39* is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☒ The drawing(s) filed on *06/13/2014* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *See Continuation Sheet*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

Continuation of Attachment(s) 2). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :6/18/14; 6/26/14; 6/22/15; & 8/11/15.

DETAILED ACTION

Application and Claims Status

1. Applicant's amendment and response filed on 03/02/2015 are acknowledged and entered.

2. Claims 1-25 were pending. Applicants have cancelled claims 1-25; and added claims 26-39. Therefore, claims 26-39 are currently pending and are under consideration in this Office Action.

3. The present application is being examined under the pre-AIA first to invent provisions.

Priority

4. This instant application is a continuation (CON) of 13/475,607 that was filed on 05/18/2012. 13/475,607 claimed priority to two provisional applications, which are 61/487,789 that was filed on 05/19/2011, and 61/548,957 that was filed on 10/19/2011. Thus, the effective filing date of the instant application is 05/19/2011.

Information Disclosure Statement

5. The information disclosure statements (IDSs) that were filed on 06/18/2014; 06/26/2014; 06/22/2015; and 08/11/2015 have been reviewed, and the references that have been considered are initialed as recorded in PTO-1449 forms.

Claim Rejections - 35 USC § 112

6. The following is a quotation of 35 U.S.C. 112(b):

> (b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 26-31 and 33-38 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

A. Claim 26 recite the limitation of "*a cyclodextrin selected from the group consisting of SAE-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin and hydroxypropyl-γ-cyclodextrin*". This limitation is vague and indefinite because it is unclear as to the meets and bounds of the Markush group regarding the instant claimed '*cyclodextrin*'. That is the compound of '*hydroxypropyl-γ-cyclodextrin*' is recited twice. Therefore, claim 26 and its dependent claims are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph.

B. Claim 33 recite the limitation of "*a cyclodextrin selected from the group consisting of hydroxypropyl-γ-cyclodextrin and hydroxypropyl-γ-cyclodextrin*". This limitation is vague and indefinite because it is unclear as to the meets and bounds of the Markush group regarding the instant claimed '*cyclodextrin*'. That is the compound of '*hydroxypropyl-γ-cyclodextrin*' is recited twice. Therefore, claim 33 and its dependent

claims are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph.

8. The following is a quotation of 35 U.S.C. 112(d):

> (d) REFERENCE IN DEPENDENT FORMS.—Subject to subsection (e), a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), fourth paragraph:

> Subject to the [fifth paragraph of 35 U.S.C. 112 (pre-AIA)], a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

9. Claim 34 is rejected under 35 U.S.C. 112(d) or pre-AIA 35 U.S.C. 112, 4th paragraph, as being of improper dependent form for failing to further limit the subject matter of the claim upon which it depends, or for failing to include all the limitations of the claim upon which it depends. Here, claim 33 for which instant claim 34 depends recite the limitation/compound of "*benzalkonium chloride*", and as a result instant claim 34 fails to further limit the subject matter of instant claim 33 upon which it depends. Applicant may cancel the claim(s), amend the claim(s) to place the claim(s) in proper dependent form, rewrite the claim(s) in independent form, or present a sufficient showing that the dependent claim(s) complies with the statutory requirements.

Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/forms/. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens.

An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

11. Claims 26-29 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 8,791,154 B2 (hereinafter refers to as Gamache et al.). Although the claims at issue are not identical, they are not patentably distinct from each other because both the composition of the instant claims 26-29 and the composition of claims 1-3 of Gamache et al. have similar structural features.

14/304,214	US 8,791,154 B2
26. An aqueous ophthalmic solution for treatment of ocular allergic conjunctivitis, the solution comprising: at least 0.67 w/v% olopatadine dissolved in the solution; PEG having a molecular weight of 200 to 800; polyvinylpyrrolidone; a cyclodextrin selected from the group consisting of SAE-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin and hydroxypropyl-γ-cyclodextrin; and water.	**1.** An aqueous ophthalmic solution for treatment of ocular allergic conjunctivitis, the solution comprising: at least 0.67 w/v % olopatadine dissolved in the solution; PEG having a molecular weight of 300 to 500; polyvinylpyrrolidone; hydroxypropyl-γ-cyclodextrin; benzalkonium chloride; and water.
27. A solution as in claim 26 further comprising benzalkonium chloride.	
28. A solution as in claim 27 further comprising borate.	**2.** A solution as in claim 1 further comprising borate.
29. A solution as in claim 28 further comprising a polyol.	**3.** A solution as in claim 2 further comprising a polyol.

That is the composition of the instant application is generic to the composition of Gamache et al. or in other word claims 26-29 are anticipated by claims 1-3 of U.S. Patent No. 8,791,154 B2.

Hence, the examined claims would be obvious over the claims of U.S. Patent No. 8,791,154 B2.

12. Claims 26 and 28-31 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 4-6 of U.S. Patent No. 8,791,154 B2 (hereinafter refers to as Gamache et al.). Although the claims at issue are not identical, they are not patentably distinct from each other because both the composition of the instant claims 26 and 28-31 and the composition of claims 4-6 of Gamache et al. have similar structural features.

14/304,214	US 8,791,154 B2
26. An aqueous ophthalmic solution for treatment of ocular allergic conjunctivitis, the solution comprising: at least 0.67 w/v% olopatadine dissolved in the solution; PEG having a molecular weight of 200 to 800; polyvinylpyrrolidone; a cyclodextrin selected from the group consisting of SAE-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin and hydroxypropyl-γ-cyclodextrin; and water.	**4.** An aqueous ophthalmic solution for treatment of ocular allergic conjunctivitis, the solution comprising: at least 0.67 w/v % but no greater than 1.0 w/v % olopatadine dissolved in the solution; 2.0 w/v % to 6.0 w/v % PEG having a molecular weight of 300 to 500; 2.0 w/v % to 6.0 w/v % polyvinylpyrrolidone; at least 0.5 w/v % but no greater than 2.0
30. A solution as in claim 26 wherein the concentration of olopatadine is no greater than 1.0 w/v%.	

31. A solution as in claim 26 wherein the concentration of PEG is 2.0 w/v% to 6.0 w/v%, the concentration of polyvinylpyrrolidone is 2.0 w/v% to 6.0 w/v% and the concentration of cyclodextrin is at least 0.5 w/v% but no greater than 2.0 w/v%.	w/v % cyclodextrin derivative selected from the group consisting of SAE-β-cyclodextrin, HP-γ-cyclodextrin, HP-β-cyclodextrin and combinations thereof; and water.
28. A solution as in claim 27 further comprising borate.	**5.** A solution as in claim 4 further comprising borate at a concentration of at least 0.18 w/v % but less than 0.5 w/v %.
29. A solution as in claim 28 further comprising a polyol.	**6.** A solution as in claim 5 further comprising a polyol.

That is the composition of the instant application is generic to the composition of Gamache et al. or in other word claims 26 and 28-31 are anticipated by claims 4-6 of U.S. Patent No. 8,791,154 B2.

Hence, the examined claims would be obvious over the claims of U.S. Patent No. 8,791,154 B2.

13. Claims 33-36 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-3 and 15 of U.S. Patent No. 8,791,154 B2 (hereinafter refers to as Gamache et al.). Although the claims at issue are not identical, they are not patentably distinct from each other because both the composition of the instant claims 33-36 and the composition of claims 1-3 and 15 of Gamache et al. have similar structural features.

14/304,124	US 8,791,154 B2
33. An aqueous ophthalmic solution for treatment of ocular allergic conjunctivitis, the solution comprising: at least 0.67 w/v % olopatadine dissolved in	**1.** An aqueous ophthalmic solution for treatment of ocular allergic

the solution; PEG having a molecular weight of 200 to 800; polyvinylpyrrolidone; a cyclodextrin selected from the group consisting of hydroxypropyl-γ-cyclodextrin and hydroxypropyl-γ-cyclodextrin; benzalkonium chloride; hydroxypropylmethyl cellulose; and water.	conjunctivitis, the solution comprising: at least 0.67 w/v % olopatadine dissolved in the solution; PEG having a molecular weight of 300 to 500; polyvinylpyrrolidone; hydroxypropyl-γ-cyclodextrin; benzalkonium chloride; and water.
34. A solution as in claim 33 further comprising benzalkonium chloride.	**15.** A solution as in claim **1** farther comprising hydroxypropylmethyl cellulose.
35. A solution as in claim 34 further comprising borate.	**2.** A solution as in claim 1 further comprising borate.
36. A solution as in claim 35 further comprising a polyol.	**3.** A solution as in claim 2 further comprising a polyol.

That is the composition of the instant application is generic to the composition of Gamache et al. or in other word claims 33-36 are anticipated by claims 1-3 and 15 of U.S. Patent No. 8,791,154 B2.

Hence, the examined claims would be obvious over the claims of U.S. Patent No. 8,791,154 B2.

14. Claims 33, 34, 37, and 38 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 21 and 22 of U.S. Patent No. 8,791,154 B2 (hereinafter refers to as Gamache et al.). Although the claims at issue are not identical, they are not patentably distinct from each other because both the composition of the instant claims 33, 34, 37, and 38 and the composition of claims 21 and 22 of Gamache et al. have similar structural features.

14/304,124	US 8,791,154 B2
33. An aqueous ophthalmic solution for treatment of ocular allergic conjunctivitis, the solution comprising: at least 0.67 w/v % olopatadine dissolved in the solution; PEG having a molecular weight of 200 to 800; polyvinylpyrrolidone; a cyclodextrin selected from the group consisting of hydroxypropyl-γ-cyclodextrin and hydroxypropyl-γ-cyclodextrin; benzalkonium chloride; hydroxypropylmethyl cellulose; and water.	**21.** An aqueous ophthalmic solution for treatment of ocular allergic conjunctivitis, the solution comprising: at least 0.67 w/v % but no greater than 1.0 w/v % olopatadine dissolved in the solution; 2.0 w/v % to 6.0 w/v % PEG having a molecular weight of 300 to 500; 2.0 w/v % to 6.0 w/v % polyvinylpyrrolidone; at least 0.5 w/v % but no greater than 2.0 w/v % hydroxypropyl-γ-cyclodextrin; greater than 0.003 w/v % but less than 0.03 w/v % benzalkonium chloride; and water; wherein the pH of the solution is 6.0 to 7.8 and the osmolality of the solution is 200 to 400 mOsm/kg.
34. A solution as in claim 33 further comprising benzalkonium chloride.	
37. A solution as in claim 33 wherein the concentration of olopatadine is no greater than 1.0 w/v%.	
38. A solution as in claim 33 wherein the concentration of PEG is 2.0 w/v% to 6.0 w/v%, the concentration of polyvinylpyrrolidone is 2.0 w/v% to 6.0 w/v% and the concentration of cyclodextrin is at least 0.5 w/v% but no greater than 2.0 w/v%.	**22.** A solution as in claim **21** further comprising at least 0.15 w/v % but no greater than 1.0 w/v % hydroxypropylmethyl cellulose.

That is the composition of the instant application is generic to the composition of Gamache et al. or in other word claims 33, 34, 37, and 38 are anticipated by claims 21 and 22 of U.S. Patent No. 8,791,154 B2.

Hence, the examined claims would be obvious over the claims of U.S. Patent No. 8,791,154 B2.

Allowable Subject Matter

15. Claims 32 and 39 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MY-CHAU T. TRAN whose telephone number is 571-272-0810. The examiner can normally be reached on Monday - Friday: 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey S. Lundgren can be reached on 571-272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/MY-CHAU T. TRAN/
Primary Examiner, Art Unit 1629

February 8, 2016

Notice of References Cited	Application/Control No. 14/304,124	Applicant(s)/Patent Under Reexamination GAMACHE ET AL.	
	Examiner MY-CHAU T. TRAN	Art Unit 1629	Page 1 of 1

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Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14304124	GAMACHE ET AL.
	Examiner	**Art Unit**
	MY-CHAU T TRAN	1629

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
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	36	✓								

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CLAIM		DATE								
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	38	✓								
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First Named Inventor	Daniel A. Gamache
Art Unit	1629
Examiner Name	Tran, My Chau T.
Attorney Docket Number	PAT903988-US-NP

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	Attorney Docket Number	3988 US

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	Attorney Docket Number	3988 US

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Examiner Signature	/My Chau Tran/	Date Considered	02/08/2016

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

WEST Search History for Application 14304124

Creation Date: 2016020811:01

Prior Art Searches

Query	DB	Hits	Op.	Plur.	Thes.	Date
("20020006443" | "20020150616" | "20030170309" | "20050004074" | "20050191270" | "20050244472" | "20060210645" | "20070020336" | "20080132444" | "20090118262" | "20090232763" | "20090239842" | "20100240625" | "20100249062" | "20100324031" | "3767788" | "3843782" | "3856919" | "3931319" | "3947573" | "4027020" | "4120949" | "4283393" | "4407791" | "4470965" | "4525346" | "4836986" | "4923693" | "5037647" | "5068225" | "5116863" | "5134127" | "5141961" | "5300287" | "5376645" | "5472954" | "5591426" | "5597559" | "5624962" | "5888493" | "6153746" | "6511949" | "6828356" | "7074424" | "7147844" | "7429602" | "7635773" | "5874414" | "6280745" | "6407079" | "20040198828" | "5874418" | "20110082145" | "5641805" | "20120015953" | "20030055102" | "6995186").PN.	PGPB, USPT	n/a	ADJ	YES	ASSIGNEE	02-08-2016
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"6828356" | "7074424" | "7147844" | "7429602" | "7635773" | "5874414" | "6280745" | "6407079" | "20040198828" | "5874418" | "20110082145" | "5641805" | "20120015953" | "20030055102" | "6995186").PN.)						
GAMACHE-DANIEL-A$.in.	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	n/a	ADJ	YES	ASSIGNEE	02-08-2016
ALANI-LAMAN$.in.	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	n/a	ADJ	YES	ASSIGNEE	02-08-2016
GHOSH-MALAY$.in.	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	n/a	ADJ	YES	ASSIGNEE	02-08-2016
GALAN-FRANCISCO-JAVIER$.in.	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	n/a	ADJ	YES	ASSIGNEE	02-08-2016
PERDIGUER-NURIA-CARRERAS$.in.	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	n/a	ADJ	YES	ASSIGNEE	02-08-2016

SINGH-ONKAR-N$.in.	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	n/a	ADJ	YES	ASSIGNEE	02-08-2016
(GAMACHE-DANIEL-A$.in.) and (ALANI-LAMAN$.in.) and (GHOSH-MALAY$.in.) and (GALAN-FRANCISCO-JAVIER$.in.) and (PERDIGUER-NURIA-CARRERAS$.in.) and (SINGH-ONKAR-N$.in.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	n/a	ADJ	YES	ASSIGNEE	02-08-2016
(GAMACHE-DANIEL-A$.in.) and (ALANI-LAMAN$.in.) and (GHOSH-MALAY$.in.) and (GALAN-FRANCISCO-JAVIER$.in.) and (PERDIGUER-NURIA-CARRERAS$.in.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	n/a	ADJ	YES	ASSIGNEE	02-08-2016
(GAMACHE-DANIEL-A$.in.) and (ALANI-LAMAN$.in.) and (GHOSH-MALAY$.in.) and (GALAN-FRANCISCO-JAVIER$.in.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	n/a	ADJ	YES	ASSIGNEE	02-08-2016
(GAMACHE-DANIEL-A$.in.) and (ALANI-LAMAN$.in.) and (GHOSH-MALAY$.in.) and (GALAN-FRANCISCO-JAVIER$.in.) and (SINGH-ONKAR-N$.in.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	n/a	ADJ	YES	ASSIGNEE	02-08-2016
olopatadine.clm. and (GAMACHE-DANIEL-A$.in.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD,	n/a	ADJ	YES	ASSIGNEE	02-08-2016

	FPRS					
olopatadine.clm. and (ALANI-LAMAN$.in.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	n/a	ADJ	YES	ASSIGNEE	02-08-2016
olopatadine.clm. and (GHOSH-MALAY$.in.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	n/a	ADJ	YES	ASSIGNEE	02-08-2016
olopatadine.clm. and (GALAN-FRANCISCO-JAVIER$.in.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	n/a	ADJ	YES	ASSIGNEE	02-08-2016
olopatadine.clm. and (PERDIGUER-NURIA-CARRERAS$.in.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	n/a	ADJ	YES	ASSIGNEE	02-08-2016
olopatadine.clm. and (SINGH-ONKAR-N$.in.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	n/a	ADJ	YES	ASSIGNEE	02-08-2016
ALCON RESEARCH$.as.	PGPB, USPT, USOC, EPAB, JPAB,	n/a	ADJ	YES	ASSIGNEE	02-08-2016

	DWPI, TDBD, FPRS					
olopatadine.clm. and (ALCON RESEARCH$.as.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	n/a	ADJ	YES	ASSIGNEE	02-08-2016
(ophthalmic (formulation or composition)).clm. and (olopatadine.clm. and GAMACHE-DANIEL-A$.in.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	n/a	ADJ	YES	ASSIGNEE	02-08-2016
(ophthalmic (formulation or composition)).clm. and (olopatadine.clm. and SINGH-ONKAR-N$.in.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	n/a	ADJ	YES	ASSIGNEE	02-08-2016
(ophthalmic (formulation or composition)).clm. and (olopatadine.clm. and ALCON RESEARCH$.as.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	n/a	ADJ	YES	ASSIGNEE	02-08-2016
(A61K47/40 or B82Y5/00 or A61K47/10 or C08L5/16 or C08B37/0015 or A61K9/08 or A61K47/48969 or A61K47/32 or A61K31/335 or A61K9/0048)![CPC, CPCL]	PGPB, USPT, USOC	n/a	ADJ	YES	ASSIGNEE	02-08-2016
(A61K31/335 | A61K47/40 | A61K9/0048 | A61K9/08)![CPC, CPCL]	PGPB, USPT, USOC	8431	ADJ	YES	ASSIGNEE	02-08-2016
(olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and ((A61K47/40 or B82Y5/00 or A61K47/10 or	PGPB, USPT, USOC	91	ADJ	YES	ASSIGNEE	02-08-2016

C08L5/16 or C08B37/0015 or A61K9/08 or A61K47/48969 or A61K47/32 or A61K31/335 or A61K9/0048)![CPC, CPCL])						
(hydroxypropyl near3 cyclodextrin) and ((olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and (A61K47/40 or B82Y5/00 or A61K47/10 or C08L5/16 or C08B37/0015 or A61K9/08 or A61K47/48969 or A61K47/32 or A61K31/335 or A61K9/0048)![CPC, CPCL])	PGPB, USPT, USOC	22	ADJ	YES	ASSIGNEE	02-08-2016
(polyvinylpyrrolidone same (benzalkonium chloride) same borate) and ((hydroxypropyl near3 cyclodextrin) and (olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and (A61K47/40 or B82Y5/00 or A61K47/10 or C08L5/16 or C08B37/0015 or A61K9/08 or A61K47/48969 or A61K47/32 or A61K31/335 or A61K9/0048)![CPC, CPCL])	PGPB, USPT, USOC	3	ADJ	YES	ASSIGNEE	02-08-2016
(olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and ((A61K31/335 | A61K47/40 | A61K9/0048 | A61K9/08)![CPC, CPCL])	PGPB, USPT, USOC	81	ADJ	YES	ASSIGNEE	02-08-2016
(hydroxypropyl near3 cyclodextrin) and ((olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and (A61K31/335 | A61K47/40 | A61K9/0048 | A61K9/08)![CPC, CPCL])	PGPB, USPT, USOC	22	ADJ	YES	ASSIGNEE	02-08-2016
(polyvinylpyrrolidone same (benzalkonium chloride) same borate) and ((hydroxypropyl near3 cyclodextrin) and (olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and (A61K31/335 | A61K47/40 | A61K9/0048 | A61K9/08)![CPC, CPCL])	PGPB, USPT, USOC	3	ADJ	YES	ASSIGNEE	02-08-2016
(514/449, 450)![CCLS]	PGPB, USPT, USOC	4506	ADJ	YES	ASSIGNEE	02-08-2016

(514/777, 778)![CCLS]	PGPB, USPT, USOC	2259	ADJ	YES	ASSIGNEE	02-08-2016
(olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and ((514/449, 450)![CCLS])	PGPB, USPT, USOC	35	ADJ	YES	ASSIGNEE	02-08-2016
(hydroxypropyl near3 cyclodextrin) and ((olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and (514/449, 450)![CCLS])	PGPB, USPT, USOC	6	ADJ	YES	ASSIGNEE	02-08-2016
(polyvinylpyrrolidone same (benzalkonium chloride) same borate) and ((hydroxypropyl near3 cyclodextrin) and (olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and (514/449, 450)![CCLS])	PGPB, USPT, USOC	3	ADJ	YES	ASSIGNEE	02-08-2016
(olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and ((514/777, 778)![CCLS])	PGPB, USPT, USOC	2	ADJ	YES	ASSIGNEE	02-08-2016
(olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and (hydroxypropyl near3 cyclodextrin)	EPAB, JPAB, DWPI, TDBD, FPRS	3	ADJ	YES	ASSIGNEE	02-08-2016
(olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and (hydroxypropyl near3 cyclodextrin)	PGPB, USPT, USOC	30	ADJ	YES	ASSIGNEE	02-08-2016
(polyvinylpyrrolidone same (benzalkonium chloride) same borate) and ((olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and (hydroxypropyl near3 cyclodextrin))	PGPB, USPT, USOC	3	ADJ	YES	ASSIGNEE	02-08-2016
(CAC model) and ((olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and (hydroxypropyl near3 cyclodextrin))	PGPB, USPT, USOC	3	ADJ	YES	ASSIGNEE	02-08-2016

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	14304124
Filing Date	2014-06-13
First Named Inventor	Daniel A. Gamache
Art Unit	1629
Examiner Name	Not Yet Assigned
Attorney Docket Number	PAT903988-US-CNT

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
/MCT/	1	5641805		1997-06-24	Hayakawa et al.	
/MCT/	2	6995186	B2	2006-02-07	Castillo et al.	

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
/MCT/	1	20040198828	A1	2004-10-07	Abelson et al.	
/MCT/	2	20110082145	A1	2011-04-07	Schneider et al.	
/MCT/	3	20120015953	A1	2012-01-19	Beauregard et al.	

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /MCT/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14304124
	Filing Date	2014-06-13
	First Named Inventor	Daniel A. Gamache
	Art Unit	1629
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	PAT903988-US-CNT

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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
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EXAMINER SIGNATURE

Examiner Signature	/My Chau Tran/	Date Considered	02/08/2016

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

EFS Web 2.1.17

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

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First Named Inventor	Daniel A. Gamache
Art Unit	1629
Examiner Name	TRAN, MY CHAU T
Attorney Docket Number	PAT903988-US-CNT

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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
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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
/MCT/	1	2003520813	JP		2003-07-08	Alcon, Inc.		☒

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /MCT/

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	Application Number	14304124
	Filing Date	2014-06-13
	First Named Inventor	Daniel A. Gamache
	Art Unit	1629
	Examiner Name	TRAN, MY CHAU T
	Attorney Docket Number	PAT903988-US-CNT

	1		☐

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EXAMINER SIGNATURE

Examiner Signature	/My Chau Tran/	Date Considered	02/08/2016

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

Session Began February 08, 2016 at 11:02 AM

Task Began February 08, 2016 11:03 AM

Explore references by patent: (ID 1)

Patent Number: US20140296328
Answer Type: *References*
Result Count: *1*

Detailed display

From ID: 1
Type: High concentration olopatadine ophthalmic composition

Retrieve substance information in 1 reference (ID 2)

From ID: 1
Uses
Answer Type: *Substances*
Result Count: *6*

Retrieve reference information in 6 substances (ID 3)

From ID: 2
Uses
Answer Type: *References*
Result Count: *237044*

Refine by research topic (ID 4)

Research Topic: olopatadine
From ID: 3
Answer Type: *References*
Result Count: *661*

Refine by research topic (ID 5)

Research Topic: hydroxypropyl-beta-cyclodextrin
From ID: 4
Answer Type: *References*
Result Count: *4*

Detailed display

From ID: 5
Type: Drug delivery systems containing inclusion complexes of olopatadine with hydroxyalkyl--cyclodextrin

Detailed display

From ID: 5
Type: Ophthalmic formulation of a selective cyclooxygenase-2 inhibitory drug

Refine by research topic (ID 6)

Research Topic: polyvinylpyrrolidone
From ID: 4
Answer Type: *References*
Result Count: *37*

Refine by research topic (ID 7)

Research Topic: benzalkonium chloride
From ID: 6
Answer Type: *References*
Result Count: *2*

Detailed display

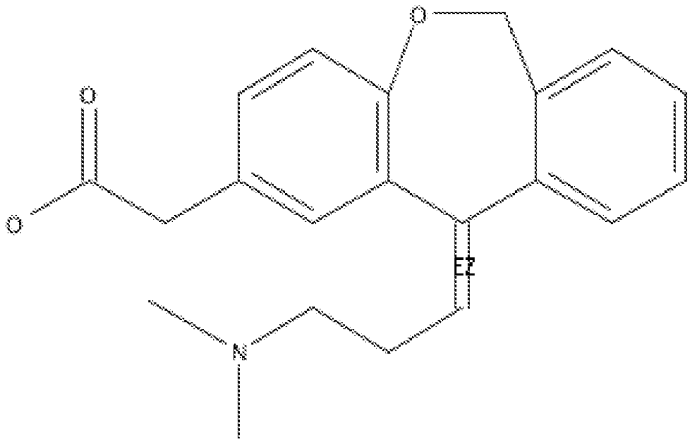
From ID: 7
Type: Compositions comprising azelastine

Refine by research topic (ID 8)

Research Topic: borate
From ID: 6
Answer Type: *References*
Result Count: *4*

Task Began February 08, 2016 11:23 AM

Explore substances by SUBSTRUCTURE



Candidates: *3*

Candidates Selected (ID 10)

Double bond geometry as drawn
Answer Type: *Substances*
Result Count: *155*

Retrieve reference information in 155 substances (ID 11)

From ID: 10
Uses
Answer Type: *References*
Result Count: *811*

Refine by research topic (ID 12)

Research Topic: ophthalmic
From ID: 11
Answer Type: *References*
Result Count: *252*

Refine by research topic (ID 13)

Research Topic: olopatadine
From ID: 12
Answer Type: *References*
Result Count: *249*

Refine by research topic (ID 14)

Research Topic: benzalkonium chloride
From ID: 13

Answer Type: *References*
Result Count: *17*

Refine by research topic (ID 15)
Research Topic: borate
From ID: 14
Answer Type: *References*
Result Count: *1*

Refine by research topic (ID 16)
Research Topic: hydroxypropyl-beta-cyclodextrin
From ID: 13
Answer Type: *References*
Result Count: *1*

Detailed display
From ID: 16
Type: Ophthalmic formulation of a selective cyclooxygenase-2 inhibitory drug

Refine by research topic (ID 17)
Research Topic: hydroxypropyl-beta-cyclodextrin
From ID: 11
Answer Type: *References*
Result Count: *4*

Task Began February 08, 2016 11:26 AM

Explore references by research topic: olopatadine and "hydroxypropyl-beta-cyclodextrin"
Research Topic: olopatadine and "hydroxypropyl-beta-cyclodextrin"
Result Count: 5

Candidates Selected (ID 18)
1 reference was found containing "olopatadine and "hydroxypropyl-beta-cyclodextrin"" as entered.
5 references were found containing both of the concepts "olopatadine" and "hydroxypropyl beta cyclodextrin".
11488 references were found containing either the concept "olopatadine" or the concept "hydroxypropyl beta cyclodextrin".
Answer Type: *References*
Result Count: *11488*

Refine by research topic (ID 19)
Research Topic: olopatadine
From ID: 18
Answer Type: *References*
Result Count: *813*

Refine by research topic (ID 20)
Research Topic: hydroxypropyl-beta-cyclodextrin
From ID: 19
Answer Type: *References*
Result Count: *5*

Detailed display
From ID: 20
Type: Ophthalmic formulation of a selective cyclooxygenase-2 inhibitory drug

Refine by research topic (ID 21)

Research Topic: polyvinylpyrrolidone
From ID: 19
Answer Type: *References*
Result Count: *38*

Refine by research topic (ID 22)

Research Topic: cyclodextrin
From ID: 21
Answer Type: *References*
Result Count: *6*

Detailed display

From ID: 22
Type: High concentration olopatadine ophthalmic composition

Refine by research topic (ID 23)

Research Topic: benzalkonium chloride
From ID: 22

No answers

Refine by research topic (ID 24)

Research Topic: borate
From ID: 22

No answers

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
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Application Number	14304124
Filing Date	2014-06-13
First Named Inventor	Daniel A. Gamache
Art Unit	1629
Examiner Name	TRAN, MY CHAU T
Attorney Docket Number	PAT903988-US-CNT

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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
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/MCT/	1	20030055102	A1	2003-03-20	Castillo et al.	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14304124
	Filing Date	2014-06-13
	First Named Inventor	Daniel A. Gamache
	Art Unit	1629
	Examiner Name	TRAN, MY CHAU T
	Attorney Docket Number	PAT903988-US-CNT

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14304124	GAMACHE ET AL.
	Examiner	Art Unit
	MY-CHAU T TRAN	1629

CPC- SEARCHED		
Symbol	Date	Examiner
A61K47/40; B82Y5/00; A61K47/10; C08L5/16; C08B37/0015; A61K9/08; A61K47/48969; A61K47/32; A61K31/335; A61K9/0048	02/08/2016	MCT

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
514	449, 450, 777, 778	02/08/2016	MCT

SEARCH NOTES		
Search Notes	Date	Examiner
PALM Inventors; WEST - see printout; SciFinder - see printout	02/05/2016	MCT
Reviewed for ODP the following Patent(s) and/or Application(s): US 8,791,154 B2	02/07/2016	MCT

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

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Application Number	14304124
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Art Unit	1629
Examiner Name	Not Yet Assigned
Attorney Docket Number	PAT903988-US-CNT

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/MCT/	1	5874418		1999-02-23	Stella et al.	

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APPLICATION NUMBER	PATENT NUMBER	GROUP ART UNIT	FILE WRAPPER LOCATION
14/304,124		1629	

OC000000082191481

Correspondence Address/Fee Address Change

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PART 1 - ATTORNEY/APPLICANT COPY

CASE PAT903988-US-CNT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF	Art Unit: 1629
Carreras Perdiguer , Nuria et al.	Examiner: Tran, My Chau T
APPLICATION NO: 14/304124	Conf. No.: 1002
FILED: June 13, 2014	
FOR: HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION	

MS: Amendment
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE

Dear Sir or Madam:

This paper is submitted in response to the Office Action dated February 12, 2016 for which the three-month date for response is May 12, 2016.

Applicants believe that no extension of time is required. However, if the U.S. Patent Office deems any fees to be deficient or absent, consider this paragraph such a request and authorization to deduct said fees from Novartis Deposit Account No. **19-0134**.

Allowance of the application is respectfully requested.

Amendments to the Claims are reflected in the listing of the claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claims 1-25 (canceled)

Claim 26 (currently amended): An aqueous ophthalmic solution for treatment of ocular allergic conjunctivitis, the solution comprising:

at least 0.67 w/v% olopatadine dissolved in the solution;

PEG having a molecular weight of 200 to 800;

polyvinylpyrrolidone;

a cyclodextrin selected from the group consisting of SAE-β-cyclodextrin, hydroxypropyl-β-cyclodextrin ~~hydroxypropyl-γ-cyclodextrin~~ and hydroxypropyl-γ-cyclodextrin; and

water.

Claim 27 (original): A solution as in claim 26 further comprising benzalkonium chloride.

Claim 28 (original): A solution as in claim 27 further comprising borate.

Claim 29 (original): A solution as in claim 28 further comprising a polyol.

Claim 30 (original): A solution as in claim 26 wherein the concentration of olopatadine is no greater than 1.0 w/v%.

Claim 31 (original): A solution as in claim 26 wherein the concentration of PEG is 2.0 w/v% to 6.0 w/v%, the concentration of polyvinylpyrrolidone is 2.0 w/v% to 6.0 w/v% and the concentration of cyclodextrin is at least 0.5 w/v% but no greater than 2.0 w/v%.

Claim 32 (original): A solution as in claim 26 wherein the solution provides more than a 1.0 unit difference relative to vehicle in relief of redness at onset of action according to FDA accepted CAC model.

Claim 33 (currently amended): An aqueous ophthalmic solution for treatment of ocular allergic conjunctivitis, the solution comprising:

at least 0.67 w/v % olopatadine dissolved in the solution;

PEG having a molecular weight of 200 to 800;

polyvinylpyrrolidone;

a cyclodextrin selected from the group consisting of hydroxypropyl-β-cyclodextrin ~~hydroxypropyl-γ-cyclodextrin~~ and hydroxypropyl-γ-cyclodextrin;

benzalkonium chloride;

hydroxypropylmethyl cellulose; and

water.

Claim 34 (canceled)

Claim 35 (original): A solution as in claim 34 further comprising borate.

Claim 36 (original): A solution as in claim 35 further comprising a polyol.

Claim 37 (original): A solution as in claim 33 wherein the concentration of olopatadine is no greater than 1.0 w/v%.

Claim 38 (original): A solution as in claim 33 wherein the concentration of PEG is 2.0 w/v% to 6.0 w/v%, the concentration of polyvinylpyrrolidone is 2.0 w/v% to 6.0 w/v% and the concentration of cyclodextrin is at least 0.5 w/v% but no greater than 2.0 w/v%.

Claim 39 (original): A solution as in claim 33 wherein the solution provides more than a 1.0 unit difference relative to vehicle in relief of redness at onset of action according to FDA accepted CAC model.

REMARKS

The Office Action of February 12, 2016 rejected claims 26-31 and 33-38 and objected to claims 32 and 39, but indicated those latter claims as being allowable if rewritten in independent format. Applicants thank Examiner Tran for the indication of allowed and allowable subject matter. The Office Action rejected claims 26-31 and 33-38 under 35 USC 112 and/or for Non-Statutory type Double Patenting. By this Amendment, Applicants have amended the claims to overcome the 112 rejections and have filed a terminal disclaimer to overcome the double patenting rejection. Specifically, Applicants have amended claims 26 and 33 and canceled claim 34. Applicants respectfully request that the claims of the present application be formally allowed.

I. Claim Rejections under 35 USC 112

The Office Action rejected claims 26 and 33 for improperly reciting hydroxypropyl-γ-cyclodextrin twice in a markush group. By this amendment, Applicants have amended claims 26 and 33 such that one occurrence of hydroxypropyl-γ-cyclodextrin now reads hydroxypropyl- β-cyclodextrin in order to overcome the rejection.

The Office Action rejected claim 34 as failing to further limit the claim from which it depends. Applicants have canceled claim 34 making this rejection moot.

II. Double Patenting

The Office Action rejected claims 26-31 and 33-38 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over U.S. Patent No. 8,791,154 B2. Applicants submit herewith a terminal disclaimer making this rejection moot.

In view of the above, Applicants respectfully request formal allowance of the present application.

CONCLUSION:

Applicants respectfully request allowance of the claims of the present application. Should the Examiner have any questions regarding this Amendment, please feel free to contact the undersigned attorney at the phone number listed below.

Respectfully submitted,

/Scott A. Chapple, 46,287/
Scott A. Chapple
Attorney for Applicant
Reg. No. 46,287

Novartis Pharmaceuticals Corporation
One Health Plaza, Bldg. 433
East Hanover, NJ 07936
18175518793

Date: 11 May 2016

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TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket Number (Optional) PAT903988-US-CNT

In re Application of: Gamache, Daniel et al.

Application No.: 14/304124

Filed: June 13, 2014

For: HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION

The applicant, Alcon Research, Ltd., owner of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of **prior patent** No. 8791154 as the term of said **prior patent** is presently shortened by any terminal disclaimer. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the applicant does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the **prior patent**, "as the term of said **prior patent** is presently shortened by any terminal disclaimer," in the event that said **prior patent** later:

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is found invalid by a court of competent jurisdiction;
is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
has all claims canceled by a reexamination certificate;
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is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

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I hereby acknowledge that any willful false statements made are punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

2. ☑ The undersigned is an attorney or agent of record. Reg. No. 46287

/Scott A. Chapple, 46,287/ — Signature
11 May 2016 — Date

Scott A. Chapple — Typed or printed name

Head of Pharma Patents — Title
817 551 8793 — Telephone Number

☑ Terminal disclaimer fee under 37 CFR 1.20(d) included.

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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
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First Named Inventor	Daniel A. Gamache
Art Unit	1629
Examiner Name	TRAN, MY CHAU T
Attorney Docket Number	PAT903988-US-CNT

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	1	4871865		1989-10-03	Lever, Jr. et al.	
	2	5342620		1994-08-30	Chowhan	
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	6	7687646		2010-03-30	Bader et al.	
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	1	20050239745		2005-10-27	Abelson et al.	
	2	20080139531		2008-06-12	Yanni et al.	
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	4	20090156568		2009-06-18	Hughes et al.	
	5	20100010082		2010-01-14	CHONG et al.	

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	1	0214779	EP	B1	1987-03-18	Lever et al.		
	2	0235796	EP	B2	1987-09-09	Oshima et al.		
	3	0799044	EP	B1	1997-10-08	Yanni et al.		

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	4	0078396	WO	A2	2000-12-28	Graff et al.		
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	6	9918963	WO		1999-04-22	Lisi		
	7	2004024126	WO	A1	2004-03-25	Thompson et al.		
	8	2011138801	WO	A1	2011-11-10	Khopade et al.		
	9	2012159064	WO		2012-11-22	Alcon Research, Ltd.		

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	1	ABELSON et al., "Combined Analysis of Two Studies Using the Conjunctival Allergen Challenge Model to Evaluate Olopatadine Hydrochloride, a New Ophthalmic Antiallergic Agent With Dual Activity," American Journal of Ophthalmology, Volume 125, Number 6, pp. 797-804.	
	2	ABELSON and ANDERSON, "Demystifying Dumulcents," Review of Ophthalmology, November 2006, pp. 122-125.	
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	Examiner Name	TRAN, MY CHAU T
	Attorney Docket Number	PAT903988-US-CNT

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	5	CHOI, et al., "Late-phase reaction in ocular allergy," Current Opinion in Allergy and Clinical Immunology, 2008, Volume 8, pp. 438–444.	
	6	GENNARO, Alfonso R., Remington: The Science and Practice of Pharmacy, Philadelphia College of Pharmacy and Science, 1995, Volume 1, pp. 613-627.	
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	8	HARADA, A., "Preparation and structures of supramolecules between cyclodextrins and polymers," Coordination Chemistry Reviews, 148, 1996, pp. 115-133.	
	9	JANSOOK et al., "CDs as solubilizers: Effects of excipients and competing drugs," International Journal of Pharmaceutics, 379, 2009, pp. 32-40.	
	10	LIDE, David R., CRC Handbook of Chemistry and Physics, CRC Press, 2006, pp. 6-4 – 6-5.	
	11	LOFTSSON et al., "Cyclodextrins in eye drop formulations: enhanced topical delivery of corticosteroids to the eye," Acta Ophthamologica Scandinavica, 2002, pp. 144-150.	
	12	LOFTSSON et al., "The effect of water-soluble polymers on the aqueous solubility and complexing abilities of ß-cyclodextrin," International Journal of Pharmaceutics, 1998, Volume 163, pp. 115-121.	
	13	LOFTSSON, et al., "Pharmaceutical Applications of Cyclodextrins. 1. Drug Solubilization and Stabilization," Journal of Pharmaceutical Sciences, October 1996, Volume 85, Number 10, pp. 1017-1025.	
	14	NANDI et al., "Synergistic Effect of PEG-400 and Cyclodextrin to Enhance Solubility of Progesterone," AAPS PharmSciTech 2003; 4 (1), pp 1-5.	

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	15	PATANOL® Label, Revised August 2002.	
	16	PATADAY® Label, Revised August 2010.	
	17	PATANASE® Label, Revised March 2008.	
	18	Polyvinylpyrrolidone K 30, http://www4.mpbio.com/ecom/docs/proddata.nsf/(webtds2)/102787, pp. 1-2.	
	19	PROUD, et al., "Inflammatory mediator release on conjunctival provocation of allergic subjects with allergent provocation of allergic subjects with allergen," Mediator generation in ocular allergy, 1989, Volume 85, Number 5, pp. 896-905.	
	20	SHARIF, et al., "Characterization of the Ocular Antiallergic and Antihistaminic Effects of Olopatadine (AL-4943A), a Novel Drug for Treating Ocular Allergic Diseases," The Journal OF Pharmacology and Experimental Therapeutics, 1996, Volume 278, Number 3, pp. 1252-1261.	
	21	SWEI, et al., "Viscosity Correlation for Aqueous Polyvinylpyrrolidone (PVP) Solutions," Journal of Applied Polymer Science, 2003, Volume 90, pp. 1153-1155.	
	22	United States District Court for the District of Delaware, Complaint, Alcon Research, Ltd. v. Watson Laboratories, Inc. et al., December 16, 2015, pages 1-16.	
	23	United States District Court for the District of Delaware, Defendants' Answer, Separate Defenses, and Counterclaims, Alcon Research, Ltd. v. Watson Laboratories, Inc. et al., February 29, 2016, pages 1-26.	
	24	United States Patent and Trademark Office Before the Patent Trial and Appeal Board, Petition for Inter Partes Review, Argentum Pharmaceuticals LLC v. Alcon Research, Ltd., U.S. Patent No. 8,791,154, February 2, 2016, pages 1-60.	
	25	WADE et al., "Ophthalmic antihistamines and H1–H4 receptors," Current Opinion in Allergy and Clinical Immunology, 2012, Volume 12, Number 5, pp. 510–516.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14304124
	Filing Date	2014-06-13
	First Named Inventor	Daniel A. Gamache
	Art Unit	1629
	Examiner Name	TRAN, MY CHAU T
	Attorney Docket Number	PAT903988-US-CNT

	26	WATSON LABORATORIES, INC., Notification of Certification for U.S. Patent No. 8,791,154 Pursuant to § 505(j)(2)(B)(iv) of the Federal Food, Drug, and Cosmetic Act, November 3, 2015, pages 1-25.	

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CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

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A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Scott A. Chapple, 46,287/	Date (YYYY-MM-DD)	2016-05-10
Name/Print	Scott A. Chapple	Registration Number	46287

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EP-A- 0 037 254
EP-A- 0 130 555
GB-A- 1 018 995
GB-A- 1 412 095
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Burger's Medicinal Chemistry, 4th Edn., Vol. 3, pages 900-905

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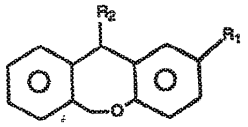
EP 0 214 779 B1

Description

The present invention relates to new chemical compounds which have potent antihistaminic activity, to processes for preparing them and to their use in medicine. Belg. Patent 623 259, Neth. Patent Appl. 6 407 758, Neth. Patent Appl. 6 411 861 and Belg. Patent 641 498 disclose a group of 11-[(dialkylamino)-alkylidene]-6,11-dihydrodibenz[b,e]oxepins as psychotherapeutic agents the most outstanding of which is the compound named, (11-(3-(dimethylamino)propylidene)-6,11-dihydrodibenz[b,e]oxepin), and hereinafter referred to by its generic name, doxepin. Doxepin has been accepted as an antidepressant in human clinical chemotherapy and an antipruritic for veterinary use.

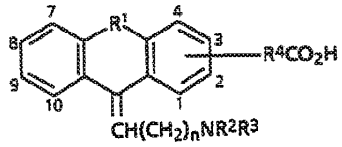
Published European Patent Application No 130 555 discloses compounds of formula:



wherein R_1 represents a cyano group, a 5-tetrazolyl group, a carbamoyl group or $-CO_2R_3$ [wherein R_3 represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms or a 1-(ethoxycarbonyloxy)ethyl group, and R_2 represents a 4-alkylpiperazino group (wherein the alkyl group has 1 to 5 carbon atoms), a 3-quinuclidinylamino group or $-X-(CH_2)_n-NR_4R_5$ (wherein X represents -NH-, -S- or -O-, R_4 and R_5 are same or different and each represents an alkyl group having 1 to 5 carbon atoms and n represents 2 or 3); and the pharmaceutically acceptable acid addition salts or metal salts thereof, which compounds are said to exhibit anti-allergic activity.

We have now discovered that a group of carboxylic acid derivatives of doxepin possess surprisingly potent antihistaminic and antiasthmatic properties. In this invention, compound (Z)-11-(3-(dimethylamino)-propylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid exhibits extremely good antihistaminic activity in vivo.

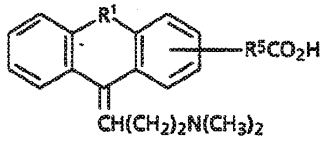
Accordingly this invention provides a compound of the formula (I),



(I)

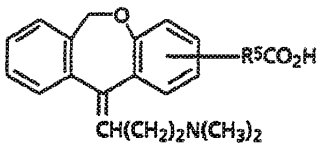
or a salt, ester or amide thereof; wherein R^1 is $-CH_2-O-$ or $-O-CH_2-$;
R^2 and R^3 are the same or different and are each hydrogen, C_{1-4} alkyl or taken together with the nitrogen comprise a nitrogen-containing heterocyclic ring having four to six ring members;
R^4 is a single bond or a C_{1-7} bivalent aliphatic hydrocarbon group and may be joined to the aromatic ring system at the 2, 3, 8 or 9 positions. n is 0 to 3.

Of the compounds of formula (I) those of formula (II), wherein R^1 is as defined herein above, and R^5 is a single bond or -CH=CH-, are preferred.



(II)

The most preferred compounds of formula (II), are those of formula (IIa) wherein R^5 is as defined for formula (II)



(IIA)

Examples of compounds of formula (IIA) include:

(1) (Z)-11-(3-(Dimethylamino)propylidene)-6, 11-dihydrodibenz[b,e]oxepin-2-carboxylic acid
(2) (E)-11-(3-(Dimethylamino)propylidene)-6, 11-dihydrodibenz[b,e]oxepin-2-carboxylic acid
(3) (E)-11-(3-(Dimethylamino)propylidene)-6, 11-dihydrodibenz[b,e]oxepin-3-carboxylic acid
(4) (Z)-11-(3-(Dimethylamino)propylidene)-6, 11-dihydrodibenz[b,e]oxepin-3-carboxylic acid
(5) (E)-11-(3-(Dimethylamino)propylidene)-6, 11-dihydrodibenz[b,e]oxepin-8-carboxylic acid
(6) (Z)-11-(3-(Dimethylamino)propylidene)-6, 11-dihydrodibenz[b,e]oxepin-8-carboxylic acid
(7) (E)-11-(3-(Dimethylamino)propylidene)-6, 11-dihydrodibenz[b,e]oxepin-9-carboxylic acid
(8) (Z)-11-(3-(Dimethylamino)propylidene)-6, 11-dihydrodibenz[b,e]oxepin-9-carboxylic acid
(9) (E)-11-(3-(Dimethylamino)propylidene)-6, 11-dihydrodibenz[b,e]oxepin-2-acrylic acid
(10) (Z)-11-(3-(Dimethylamino)propylidene)-6, 11-dihydrodibenz[b,e]oxepin-2-acrylic acid

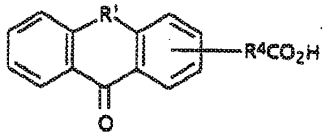
The compounds of the present invention exist in either the cis (Z) or trans (E) isomers (in relation to the bridge oxygen in the case of formula (IIA)). If the compounds of formula (I) or (II) contain a double bond in the acid bearing side chain, i.e. R^4 or R^5, there exists a second possibility of Z and E isomeric forms. All such geometric isomers and the isomeric mixture of these compounds are included within the scope of the present invention. Salts, amides and esters of the compounds of the formula (I) and (II) are included within the scope of the invention. While esters and amides of the compounds of the formulae (I) and (II) have antihistamine activity in their own right, they may also be useful intermediates in the preparation of the carboxy compounds of the formulae (I) and (II). Amides derived from ammonia, primary amines or amino acids, such as glycine, are particularly suitable. Suitable esters include conventional ester groups known to be useful for protecting carboxylic acid groups such as C_{1-6} alkyl esters wherein the alkyl group is straight or branched chain and is optionally substituted by halogen. Alkyl esters (C_{1-4}) are particularly preferred.

Solvates of the compounds of the formulae (I) and (II) are also included within the scope of the present invention. Preferred solvates include hydrates and C_{1-4} alkanolates.

Salts of the compounds of formula (I) may be either acid addition salts or salts formed with the carboxylic acid group. Acid addition salts are preferred but salts formed from the carboxylic acid group may be particularly useful in preparing the corresponding carboxy compound. When used in medicine, the salts of the compounds of formulae (I) and (II) should be both pharmacologically and pharmaceutically acceptable, but non pharmaceutically acceptable salts may conveniently be used to prepare the free active compound or pharmaceutically acceptable salts thereof and are not excluded from the scope of this invention. Such pharmacologically and pharmaceutically acceptable acid addition salts include, but are not limited to, those prepared from the following acids: hydrochloric, sulphuric, nitric, phosphoric, maleic, salicylic, toluene-p-sulphonic, tartaric, citric, methanesulphonic, formic, malonic, isethionic, succinic, naphthalene-2-sulphonic and benzenesulphonic. Also, pharmaceutically acceptable salts can be prepared as ammonium salts, alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts of the carboxylic acid group.

The present invention also provides analogous methods for preparing compounds of formula (I), for example:

a) (i) A compound of formula (I) may be prepared via the well known Wittig method (e.g., U.S. Patents 3,354,155 and 3,509,175) by reaction of a compound of formula (III).



(III)

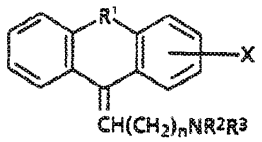
The Wittig reagent, $Ph_3P{=}CH(CH_2)_nNR_2R_3$; i.e., formula (IV), is conveniently

$$(C_6H_5)_3P{=}CH(CH_2)_nNR^2R^3 \qquad (IV)$$

prepared by reacting a compound of the formula $Ph_3PCH_2(CH_2)_nNR_2R_3Br$, with a strong base, such as sodium hydride or C_{1-6} alkyl lithium in a suitable inert solvent, such as tetrahydrofuran or dimethoxyethane at or near room temperature. It will be appreciated by those skilled in the art of organic chemistry that protection of the carboxy group may be desirable or required prior to the Wittig reaction and deprotection after the reaction.

(ii) A compound of formula (I) also may be prepared via the well known Grignard conditions (e.g., Belg. 623 259) in which a Grignard reagent, i.e. $R^2R^3NCH_2CH_2CH_2Mg\ X$ where X is a halogen atom, is reacted with a compound of formula (III), followed by dehydration with a strong acid.

b) A compound of formula (I) wherein R^4 is a single bond can be prepared by carboxylation of a compound of formula (V)



(V)

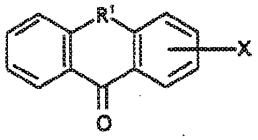
wherein R^1, R^2, R^3 and n are as defined, vide supra and X is a hydrogen or halogen atom (suitably a bromine or chlorine atom attached directly to the ring system in the 2, 3, 8 or 9 positions. For example, a compound of formula (V) can be treated with a metalating agent such as butyl lithium followed by a reaction with carbon dioxide. When X is hydrogen separation of isomers may be required to obtain the desired compound of formula (I). When X is a halogen atom, a compound of formula (V) can be reacted with magnesium in an appropriate solvent followed by reaction with carbon dioxide via the Grignard procedure (The Merck Index, ninth ed., page ONR-38, Merck and Co., Rahway, N.J. (1976).

c) A compound of formula (I) wherein R^4 is other than a single bond can be synthesized by reacting a compound of formula (V) (wherein X is a halogen atom) with a compound of formula (VI),

$$CH_2{=}CH{-}R^6{-}COR^7 \qquad (VI)$$

wherein R^6 is a C_{1-5} bivalent aliphatic hydrocarbon and R^7 is a removable carboxylic acid protecting group such as one derived from a reaction of the carboxylic acid group which has been activated (e.g. converted to an acyl chloride) with an alcohol or amine. In some cases this reaction may need to be facilitated by a palladium catalyst (J. Org. Chem. 42, 3903–3907 (1977)). A variation of this method involves a reaction of a compound of formula (VII) with a compound of formula VI in a similar manner, vide supra, followed by catalytic reduction of the double bond in the carboxylic bearing side chain that followed by the Wittig reaction described in Section a) (i) or (ii), vide supra. The carboxylic acid groups may then be regenerated by deprotection if required.

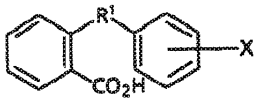
d) When the preparation of a compound of the formula (I) wherein R^4 is CH=CH is required, a compound of the formula (VII)



(VII)

wherein R^1 is as defined, vide supra and X is halogen can be reacted with acrylic acid or an acrylic acid ester, with use of a catalyst if needed, by a method analogous to that described in b), vide supra, followed by a Wittig reaction as described in part a) (i) or (ii), vide supra. The carboxylic acid can be regenerated by deprotection if desired.

A compound of formula (VII) may be prepared by reacting a compound of formula (VIII).



(VIII)

wherein R^1 and X are as defined, vide supra with a dehydrating agent such as $(CF_3CO)_2O/BF_3{\cdot}OEt_2$.

(e) It is possible to convert one compound of the formula (III) to another compound of the formula (III) by methods well known to those skilled in the art, for example the reduction of one or more double bonds or de-esterification of an ester group or hydrolysis of an amide, followed by a Wittig reaction with $Ph_3P{=}CH_2(CH_2)_nNR_2R_3$ as described, vide supra.

(f) A compound of formula (VIII) can be converted to a Grignard reagent or an organolithium reagent by methods well known to those skilled in the art (after protecting the CO_2H group) then reacted with dimethyl formamide to obtain the corresponding aldehyde. Such an aldehyde can be converted to an acid by oxidation or reaction with a trialkyl phosphonium acetate or an equivalent. By methods well known in the art of organic chemistry, after deprotecting such an acid can be dehydrated as described in d), vide supra to give a compound of formula (III).

(g) A compound of the formula (V) where X is halogen can be reacted with a metal (I) cyanide, such as cuprous cyanide to give a corresponding carbonitrile derivative, which can then be converted to compounds of formula (I), eg the carboxylic acid via hydrolysis.

Those intermediates that are novel form an important further aspect of the present invention.

(h) Interconversion of compounds of the formula (I) is possible, e.g., by hydrolysis of esters, amides and by isomerization about the multiple bonds when such bonds are present or by selective reduction of multiple bonds when such bonds are present.

The compounds of this invention having antiallergic activity may be used for the same indications as clinically used antiasthmatic compounds, namely to help to control bronchoconstriction or brochospasm characteristic of allergic asthma and exercise induced asthma and the symptoms of bronchoconstriction and bronchospasm resulting from acute or chronic bronchitis. The compounds are believed to inhibit the release of autacoids (i.e. histamine, serotonin and the like) from mast cells and to inhibit directly the antigen-induced production of histamine. Thus, they may be classified as mast cell stabilizers with antihistaminic action.

The compounds of this invention having antihistamine activity may be used for the same indications as clinically used antihistamines, namely to relieve detrimental symptoms (caused by histamine release) of nasal stuffiness due to colds and vasomotor rhinitis and for the symptomatic control of allergic conditions including nasal allergy, perennial rhinitis, urticaria, angioneurotic oedema, allergic conjunctivitis, food allergy, drug and serum reactions, insect bites and stings and desensitizing reactions. The compound may also be used in conditions responsive to its antipruritic activity including allergic dermatoses, neurodermatitis, anogenital pruritus, and pruritus of non-specific origin such as eczema, and of specific cause such as chickenpox, photosensitivity and sunburn. The present invention therefore provides a method for the symptomatic treatment of allergic conditions by the administration of an effective amount of a compound of formula (I). The present invention also provides a method for the antagonism of endogenously released histamine by the administration of an effective amount of a compound of formula (I). The compounds of formula (I) are substantially free from sedative effects.

The amount of active compound, ie, a compound of formula (I) required for use in the above conditions will vary with the compound chosen, the route of administration and the condition and mammal undergoing treatment, and is ultimately at the discretion of the physician. A suitable oral dose of the active compound for a mammal is in the range of from 0.003 to 1.0 mg per kilogram body weight per day; preferably from 0.04 to 0.24 mg/kg. For example a typical dose for a human recipient of compound (1), (Z)-11-(3-(dimethylamino)propylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid, as the hydrogen chloride salt (see Example 7 and Table 1, vide infra) is between 0.03 and 0.1 mg/kg body weight per day.

The desired daily dose is preferably presented as from one to six sub- doses administered at appropriate intervals throughout the day as needed. Where three subdoses of compounds of formula (I) are employed, each will preferably lie in the range of from 0.014 to 0.08 mg/kg body weight; for example, a typical sub-dose of such a compound for a human recipient is between 1 and 20 mg, for example 4 or 8 mg.

While it is possible for a compound of formula (I) to be administered alone as the raw chemical, it is preferable to present the compound of formula (I) as a pharmaceutical formulation. Thus, the present invention also provides pharmaceutical formulations, both for veterinary and for human medical use, which comprise a compound of formula (I) together with one or more pharmaceutically acceptable carriers therefor and optionally any other therapeutic ingredients. For example, the active compound may be formulated with a sympathomimetic agent such as the decongestant pseudoephedrine, an antitussive such as codeine, an analgesic, an antiinflammatory, an antipyretic, or an expectorant. The carrier(s) must be pharmaceutically acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The formulations include those suitable for oral, rectal, topical, nasal, ophthalmic or parenteral (including subcutaneous, intramuscular and intravenous) administration.

The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active compound into association with a carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active compound into association with a liquid carrier or a finely divided solid carrier or both and then, if necessary, shaping the product into desired formulations.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets or lozenges, each containing a predetermined amount of the active compound (defined herein as a compound of formula (I)); as a powder or granules; or a suspension in an aqueous liquid or nonaqueous liquid such as a syrup, and elixir, an emulsion or a draught. A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, with the active compound being in a free-flowing form such as a powder or granules which is optionally mixed with a binder, disintegrant, lubricant, inert diluent, surface active agent or dispersing agent. Molded tablets comprised of a mixture of the powdered active compound with any suitable carrier may be made by molding in a suitable machine.

A syrup may be made by adding the active compound to a concentrated, aqueous solution of a sugar for example sucrose to which may also be added any accessory ingredient(s). Such accessory ingredient(s) may include flavourings, an agent to retard crystallization of the sugar or an agent to increase the solubility of any other ingredient, such as a polyhydric alcohol, for example glycerol or sorbitol, and suitable preservatives.

Formulations for rectal administration may be presented as a suppository with a usual carrier such as cocoa butter, or hydrogenated fats or hydrogenated fatty carboxylic acids.

Formulations suitable for parenteral administration conveniently comprise a sterile aqueous preparation of the active compound which is preferably isotonic with the blood of the recipient.

Nasal spray formulations comprise purified aqueous solutions of the active compound with preservative agents and isotonic agents. Such formulations are adjusted to a pH and isotonic state compatible with the nasal mucous membranes.

Ophthalmic formulations are prepared by a similar method to the nasal spray except that the pH and isotonic factors are adjusted to match that of the eye.

Topical formulations comprise the active compound dissolved or suspended in one or more media such as mineral oil, petroleum, polyhydroxy alcohols or other bases used for topical pharmaceutical formulations. The addition of other accessory ingredients, vide infra, may be desirable.

In addition to the aforementioned ingredients, the formulations of this invention may further include one or more accessory ingredient(s) selected from diluents, buffers, flavouring agents, binders, disintegrants, surface active agents, thickeners, lubricants, preservatives (including antioxidants) and the like.

The present invention also provides the first use of the compounds of formula (I) in medicine.

The following Examples are provided by the way of illustration of the present invention and should in no way be construed as a limitation thereof. All temperatures indicated are in degrees Celsius

Example 1: (E)/(Z)-11-(3-Dimethylamino)propylidene)-6, 11-dihydro-dibenz[b,e]oxepin-2-carboxylic acid

a) 2-Bromo-6,11-dihydrodibenz[b,e]oxepin-11-one

2-Bromo-6, 11-dihydrodibenz[b,e]oxepin-11-one was prepared as described in US Patent 4,282,365, m.p. 132-134°C (Lit. m.p. 136-139°C). pmr (DMSO/d_6) δ: 8.13 (d, J=2.6 Hz, 1H, H_1), 7.48-7.83 (m, 5H, aromatic), 7.07 (d, J=8.8 Hz, 1H, H_4), 5.31 (s, 2H, CH_2O).

Analysis: Calcd. for $C_{14}H_9BrO_2$: C, 58.16; H, 3.14; Br, 27.64. Found: C, 58.20; H, 3.18; Br, 27.73.

b) (E)/(Z)-3-(2-Bromo-6,11-dihydrodibenz[b,e]oxepin-11-ylidene)-N,N-dimethylpropylamine

Anhydrous 3-(dimethylamino)propyltriphenylphosphonium bromide hydrobromide (39.4 g., 0.08 mole) was suspended in 450 mL of dry tetrahydrofuran and 100 mL of a solution of n-butyl lithium in hexane (1.6 M) was added dropwise at 0°C under a nitrogen atmosphere during a 30 minute period. After an additional 10 minutes, 2-bromo-6, 11-dihydrodibenz[b,e]oxepin-11-one (16.8 g., 0.06 mole) in 150 mL dry tetrahydrofuran was added slowly to the deep red solution and the reaction mixture was then refluxed for 18 hours. The reaction mixture was poured onto ice-water, and the mixture was extracted with diethyl ether. The ether layer was concentrated under reduced pressure and the residue was suspended in water and then acidified with 6N hydrochloric acid. The acidic aqueous layer was washed with hexanes and then was concentrated to give a gummy residue. The residue was crystallized from ethyl acetate/methanol to provide 5.3 g. of pure Z-isomer as its hydrochloride salt, m.p. 201-204°C. The mother liquor was chromatographed on a silica gel column (Waters Associates -Prep. 500) with ethyl acetate/methanol (8:2) to give an additional 2.55 g. of pure Z-isomer as the hydrochloride salt and 2.79 g. of E-isomer as its hydrochlo-

ride salt, m.p. 230-233°C. pmr (Z-isomer) (DMSO/d_6) δ: 7.25-7.44 (m, 6H, aromatic), 6.81 (degenerate d, J=9.1 Hz, 1H, H_4), 5.72 (t, J=7.1 Hz, 1H, CH=), 5.22 (s, 2H, CH_2O), 3.18 (m, 2H, NCH_2), 2.70 (m, 2H, CH_2), 2.66 (s, 6H, NMe_2). pmr (E-isomer) (DMSO/d6) δ: 7.23-7.50 (m, 6H, aromatic), 6.70 (d, J=8.6 Hz, 1H, H4), 6.10 (t, J=7.2 Hz, 1H, CH=) 5.15 (br s, 2H, CH_2O), 3.07 (m, 2H, NCH_2), 2.65 (s, 6H, NMe_2), 2.50 (m overlap with DMSO, 2H, CH_2).

c) (Z)-11-(3-(Dimethylamino)propylidene)-6, 11-dihydrodibenz[b,e]oxepin-2-carboxylic acid (Compound 1)

A solution of n-butyl lithium in hexane (1.6 M, 3.5 mL) was added dropwise to a solution of 1.8 g. pure (Z)-3-(2-bromo-6, 11-dihydrodibenz[b,e]oxepin-11-ylidene)-N,N-dimethylpropylamine in 100 mL of dry tetrahydrofuran at -70°C under a nitrogen atmosphere. After the yellowish-orange solution was stirred at -70°C for 10 minutes, gaseous carbon dioxide was bubbled through the reaction medium to give a pale yellow solution. The solution was allowed to warm gradually to room temperature and was then concentrated under reduced pressure. The foamy residue was dissolved in water, and the mixture was neutralized with 1N hydrochloric acid and then extracted with chloroform. Concentration of the chloroform and recrystallization of the residue from water gave 0.5 g. pure Z-2-carboxylic acid, m.p. 121-123°C. pmr ($CDCl_3$) δ: 7.87 (d, J≤1 Hz, 1H, H_1), 7.81 (dd, J=7.8, 2.2 Hz, 1H, H_3), 7.25-7.28 (m, 4H, aromatic), 6.82 (degenerate d, J=8.8 Hz, 1H, H_4), 6.45 (br s, 1H, CO_2H), 5.50 (m, 1H, CH=), 5.20 (br s, 2H, CH_2O), 2.92 (m, 4H, NCH_2CH_2), 2.66 (s, 6H, NMe_2).

Analysis: Calcd. for $C_{20}H_{21}NO_3 \cdot 0.55\ H_2O$: C, 72.07; H, 6.68; N, 4.20. Found: C, 72.07; H, 6.69; N, 4.18.

d) (E)-11-(3-(Dimethylamino)propylidine)-6, 11-dihydrodibenz[b,e]oxepin-2-carboxylic acid (Compound 2).

Pure (E)-3-(2-bromo-6, 11-dihydrodibenz[b,e]oxepin-11-ylidene)-N,N-dimethylpropylamine (1.55 g., 4.3 mmole), was treated under nitrogen in cold (-70°C) tetrahydrofuran (100 mL) with 4.4 mmole of n-butyl lithium in hexane followed by gaseous carbon dioxide as described for the Z-isomer (Step C).

Isolation of the (E)-2-carboxylic acid was achieved by through chromatography of the crude product on a reverse phase C18 semipreparative column eluted with 20% methanol in water (containing 0.1% triethylamine). Recrystallization of the solid product from water afforded 0.012 g of pure E-2-carboxylic acid, m.p. >200°C (decomp.). pmr ($CDCl_3$) δ: 7.85 (d, J=2.0 Hz, 1H, H_1), 7.06-7.78 (m, 5H, aromatic), 6.47 (d, J=8.5 Hz, 1H, H_4), 6.28 (t, J=4.2 Hz, 1H, CH=), 5.85 (m, 1H, ArCH), 4.70 (m, 1H, ArCH), 2.43 (m, 4H, NCH_2CH_2), 2.28 (s, 6H, NMe_2).

Analysis: Calcd. for $C_{20}H_{21}NO_3 \cdot 0.50\ H_20$: C, 72.27; H, 6.67; N, 4.21. Found: C, 72.15; H, 6.46; N, 4.22.

Example 2: (E)/(Z)-11-(3-(Dimethylamino)propylidene)-6,11-dihydro-dibenz[b,e]oxepin-3-carboxylic acid

a) Methyl 2-(3-bromophenoxymethyl)benzoate

To a mixture of 3-bromophenol (60 g, 0.35 mole) and potassium carbonate (25 g, 0.18 mole) in 250 mL of N,N-dimethylformamide was added methyl α-bromo-2-toluate (65 g, 0.28 mole). The reaction mixture was stirred at room temperature for 18 hours, then heated on a steam bath for 3 hours. The mixture was poured into ice-water, and the solids were collected by filtration and washed with water to give the crude product. Analytical sample was obtained by recrystallization from methylene chloride/hexanes, m.p. 84-85°C. pmr ($CDCl_3$) δ: 8.0 (m, 1H, H_6), 6.93-7.69 (m, 7H, aromatic H), 5.47 (s, 2H, $ArCH_2O$), 3.89 (s, 3H, CO_2CH_3).

Analysis: Calcd. for $C_{15}H_{13}BrO_3$: C, 56.09; H, 4.08; Br, 24.88. Found: C, 56.20; H, 4.12; Br, 24.77.

b) 2-(3-bromophenoxy)methylbenzoic acid

Methyl 2-(3-bromophenoxy)methylbenzoate (34 g) was refluxed in a mixture of 100 mL of 10% sodium hydroxide and 200 mL of methanol for 3 hours. The reaction mixture was concentrated under reduced pressure and water was added to the residue. The mixture was then acidified with concentrated hydrochloric acid. Extracting the acidic solution with ethyl acetate and then concentration of the organic layer gave the 2-(3-bromophenoxy)methyl benzoic acid (35 g) m.p. 158-159°C. pmr ($CDCL_3$) δ: 8.10 (m, 1H, H6), 6.84-7.74 (m, 7H, aromatic H), 6.16 (br s, 1H, CO_2H), 5.49 (s, 2H, $ArCH_2O$).

Analysis: Calcd. for $C_{14}H_{11}BrO_3$: C, 54.74; H, 3.61; Br, 26.02. Found: C, 54.65; H, 3.61; Br, 26.08.

c) 3-Bromo-6, 11-dihydrodibenz[b,e]oxepin-11-one

A suspension of 2-(3-bromophenoxymethyl)benzoate (35 g, 0.11 mole) in 100 mL of trifluoroacetic anhydride containing 20 drops of boron trifluoride-ether complex was refluxed for 4 hours. The mixture was poured into ice-water and then extracted with diethyl ether. Concentration of ether solution under reduced pressure and chromatography of the residue on a silica gel column (Waters Associates, Prep

500) with hexane/methylene chloride (70:30) gave the pure product (14 g). m.p. 110-112°C. pmr ($CDCl_3$) δ: 8.10 (d, J=9.1 Hz, 1H, H_1), 7.90 (dd, J=1.4, 7.6 Hz, 1H, H_{10}) 7.57 (dt, J=1.4, 7.4, 7.4 Hz, 1H H8), 7.48 (dt, J=1.4, 7.6, 7.6 Hz, 1H, H9), 7.36 (dd, J=1.3, 7.3 Hz, 1H, H_7), 7.27 (d,J=1.8 Hz, 1H, H_4), 7.24 (dd, J=1.8, 9.1 Hz, 1H, H_2), 5.18 (s, 2H, $ArCH_2O$).

Analysis: Calcd. for $C_{14}H_9BrO_2$: C, 58.16; H, 3.14; Br, 27.64. Found: C, 58.13; H, 3.19; Br, 27.72.

d) (E)/(Z)-3-(3-Bromo-6,11-dihydrodibenz[b,e]oxepin-11-ylidene)-N,N-dimethylpropylamine

Anhydrous 3-(dimethylamino)propyltriphenylphosphonium bromide hydrobromide (24.5 g, 48.0 mmole), 96 mmole of n-butyl lithium in hexane, and 3-bromo-6, 11-dihydrodibenz[b,e]oxepin-11-one (10 g, 34.6 mmole) were reacted in 580 mL dry tetrahydrofuran by the procedure of Example I, step b. This provided an (E)/(Z)-(1:3) isomeric mixture of bromoamines (6.0 g). Recrystallization of half of the mixtures (3.0 g) from ethyl acetate gave 1.45 g of Z-isomer of ≥93% stereoisomeric purity (assayed by ^{1}H-NMR) as a white solid. pmr ($CDCl_3$) δ: 7.23-7.31 (m, 4H, aromatic H), 6.92-7.05 (m, 3H, aromatic H), 5.91 (t, 1H, CH=, 7% E-isomer), 5.60 (t, 1H, CH=, 93% Z-isomer) 5.15 (very br s, 2H, $ArCH_2O$), 3.12 (m, 2H, CH_2), 2.99 (m, 2H, NCH_2), 2.78 (s, 6H, NMe_2, 93% Z-isomer), 2.71 (s, 6H, NMe_2, 3% E-isomer).

Analysis: Calcd. for $C_{19}H_{20}BrNO \cdot 1.0$ HCl: C, 57.81; H, 5.36; N, 3.55. Found: C, 57.62; H, 5.33; N, 3.54.

e) (E)/(Z)-11-(3-(Dimethylamino)propylidene)-6, 11-dihydrodibenz[b,e]oxepin-3-carboxylic acid (Compounds 3/4)

An isomeric mixture E/Z (1:3) of 3-(3-bromo-6, 11-dihydrodibenz[b,e]-11-ylidene]-N,N-dimethylpropylamine (3.0 g, 8.5 mmole) in 150 mL dry tetrahydrofuran at -70°C was reacted with 9.4 mmole n-butyl lithium in hexane followed by gaseous carbon dioxide by the procedure of Example 1, step c, to provide the corresponding carboxylic acids as an E/Z (1:3) stereoisomeric mixture. The mixture was chromatographed on a reverse phase PRP-1 semi-preparative column with water/acetonitrile (87:13) to provide 0.08 g of E-isomer (lyophilized powder) and 0.50 g of Z-isomer (lyophilized powder). pmr (E-isomer) ($CDCl_3$/TFA) δ: 7.85 (dd, J=8.0, 1.7 Hz, 1H, H_2) 7.50 (d, J=1.7 Hz, 1H, H_4), 7.32-7.43 (m, 4H, aromatic H), 7.16 (m, 1H, H_1), 5.99 (t, 1H, CH=), 5.50 (br s, 1H, ArCHO), 4.85 (br s, 1H, ArCHO), 3.25 (q, 2H, CH_2), 2,86 (s, 3H, NMe), 2.85 (s, 3H, NMe), 2.70 (q, 2H, NCH_2). pmr (Z-isomer) ($CDCl_3$/TFA) δ: 7.26 (m, 2H, H_2 and H_4), 7.24-7.36 (m, 4H, aromatic H), 7.16 (m, 1H, H_1), 5.71 (t, 1H, CH=), 5.20 (very br s, 2H, $ArCH_2O$), 3.32 (q, 2H, CH_2), 2.91 (s, 3H, NMe), 2.90 (s, 3H, NMe), 2.89 (m, 2H, NCH_2).

Analysis: Calcd. for $C_{20}H_{21}NO_3 \cdot 0.5$ HCl$\cdot 0.2$ H_2O: C, 69.58; H, 6.39; N, 4.06. Found (E-isomer): C, 69.64; H, 6.25; N, 4.03. Calcd. for $C_{20}H_{21}NO_3 \cdot 0.25$ H_2O: C, 73.26; H, 6.61; N, 4.27. Found (Z-isomer): C, 73.20; H, 6.60; N, 4.20.

Example 3: (E/(Z)-(11-(3-Dimethylamino)propylidene)-6,11-dihydrodibenz[b,e]oxepin-8-carboxylic acid

a) 8-Bromo-6,11-dihydrodibenz[b,e]oxepin-11-one

Phenol (8 g, 85 mmole) and potassium carbonate (11.7 g, 85 mmole) in 150 mL of N,N-dimethylformamide was reacted with methyl 4-bromo-α-bromo-2-toluate (20 g, 65 mmole) by the procedure of Example 2, step a and followed with alkaline hydrolysis by the procedure of Example 2, step b to give the crude 4-bromo-2-phenoxybenzoic acid (13 g) which was used without further purification.

The crude 4-bromo-(2-phenoxymethyl)benzoic acid (13 g, 42 mmole) was cyclized in 50 mL of trifluroacetic anhydride containing 1 mL of boron trifluorideether complex by the procedure of Example 2, step c. The solid was collected by filtration and washed with water to give 11.9 g of the tricyclic ketone, m.p. 125-126°C. pmr ($CDCL_3$) δ: 8.17-8.30 (m, 1H, H1), 6.99-7.86 (m, 6H, aromatic H), 5.14 (s, 2H, $ArCH_2O$).

Analysis: Calcd. for $C_{14}H_9BrO_2$: C, 58.16; H, 3.14; Br, 27.64. Found: C, 58.15; H, 3.17; Br, 27.73.

b) (E)/(Z)-3-(8-Bromo-6,11-dihydrodibenz[b,e]oxepin-11-ylidene)-N,N-dimethylpropylamine

Anhydrous 3-(dimethylamino)propyltriphenylphosphonium bromide hydrobromide (24.5 g, 48 mmole), 96 mmole of n-butyl lithium in hexane, and 8-bromo-6, 11-dihydrodibenz[b,e]oxepin-11-one (10 g, 34.6 mmole) were reacted in 580 mL dry tetrahydrofuran by the procedure of Example I, step b. This provided an E/Z (1:3.5) isomeric mixture of bromoamines. Recrystallization of the mixture from diethyl ether gave 0.17 g of Z-isomer and 1.8 g of an E/Z (1:4) (assayed by HPLC on C18) isomeric mixture which was used in the next step without further purification. pmr (Z-isomer) ($CDCl_3$) δ: 7.38-7.44 (m, 2H, H_7 and H_9); 7.13-7.18 (m, 3H, aromatic H); 6.84-6.93 (m, 2H, H_2 and H_4); 5.70 (t, 1H, CH=); 5.15 (br s, 2H, $ArCH_2O$); 2.55 (q, 2H, CH_2); 2.43 (t, 2H, NCH_2); 2.22 (s, 6H, NMe_2).

Analysis: Calcd. for $C_{19}H_{20}BrNO$: C, 63.70; H, 5.63; N, 3.91. Found (Z-isomer): C, 63.85; H, 5.65; N, 3.92.

c) (E)/(Z)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b,e]oxepin-8-carboxylic acid (Compounds 5/6).

An isomeric mixture E/Z (1:4) of 3-(8-bromo-6, 11-dihydrodibenz[b,e]-11-ylidene)-N,N-dimethylpropylamine (1.8 g, 5.0 mmole) in 100 mL dry tetrahydrofuran at -70°C was reacted with 5.5 mmole n-butyl lithium in hexane followed by gaseous carbon dioxide by the procedure of Example I, step c, to provide the corresponding carboxylic acid as an E/Z (1:5) stereoisomeric mixture. The mixture was chromatographed on a reverse phase PRP-1 semi-preparative column with water/acetonitrile (85:15) to provide 0.05 of E-isomers (lyophilized powder) and 0.28 g of Z-isomer (lyophilized powder). pmr (E-isomer) ($CDCl_3$) δ: 7.94 (br s, 1H, H_9), 7.70 (br s, 1H, CO_2H), 7.20-7.30 (m, 4H aromatic H), 7.14 (m, 1H, H_3), 6.87 (m, 1H, H_2), 6.76 (m, 1H, H_4), 5.88 (t, 1H, CH=), 5.54 (br s, 1H, ArCHO), 4.85 (br s, 1H, ArCHO), 3.00 (m, 2H, CH_2), 2.78 (m, 2H, NCH_2), 2.60 (s, 6H, NMe_2) pmr (Z-isomer) ($CDCl_3$) δ: 7.55 (d, J=7.0 Hz, 1H, H_9), 7.30 (br s, 1H, CO_2H), 7.00-7.25 (m, 4H, aromatic H), 6.84 (m, 2H, H_2 and H_4), 5.95 (t, 1H, CH=), 5.70 (br s, 1H, ArCHO), 4.80 (br s, H, ArCHO), 3.35 (br s, 1H CHC=), 2.50-3.00 (m, 3H, CHC= and NCH_2), 2.46 (s, 6H, NMe_2)

Analysis: Calcd. for $C_{20}H_{21}NO_3 \cdot HCl \cdot 0.4\ H_2O$: C, 65.44; H, 6.26; N, 3.82. Found (E-isomer): C, 65.55; H, 6.51; N, 3.91. Calcd. for $C_{20}H_{21}NO_3 \cdot 2.2\ H_2O$: C, 66.17; H, 7.05; N, 3.86. Found (Z-isomer): C, 66.25; H, 6.93; N, 3.83.

Example 4: (E)/(Z)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b,e]-oxepin-9-carboxylic acid

a) 9-Bromo-6,11-dihydrodibenz[b,e]oxepin-11-one

9-Bromo-6, 11-dihydrodibenz[b,e]oxepin-11-one was prepared as described in US Patent 4,282,365, m.p. 104-106°C (Lit. m.p. 107.5-108.5°C). pmr ($CDCl_3$) δ: 8.02-8.27 (m, 2H, H_1 and H_{10}), 6.98-7.73 (m, 5H, aromatic), 5.14 (s, 2H, CH_2O).

Analysis: Calcd. for $C_{14}H_9BrO_2$: C, 58.16; H, 3.14; Br, 27.64. Found: C, 58.24; H, 3.18; Br, 27.51.

b) (E)/(Z)-3-(9-Bromo-6, 11-dihydrodibenz[b,e]oxepin-11-ylidene)-N,N-dimethylpropylamine.

Anhydrous 3-(dimethylamino)propyltriphenylphosphonium bromide hydrobromide (31 g., 60.9 mmole), 122 mmole of n-butyl lithium in hexane, and 9-bromo-6, 11-dihydrodibenz[b,e]oxepin-11-one (12.7 g., 43.8 mmole) were reacted in 750 mL dry tetrahydrofuran by the procedure of Example I, Step b. This provided an E/Z (1:6) isomeric mixture of bromoamines. Recrystallization of the mixture from ethyl acetate/methanol gave 1.2 g. of pure Z-isomer as its hydrochloride salt, melting range 91-100°C and 2.16 g. of an E/Z (1:4) isomeric mixture which was used in the next step without further purification. pmr (Z-isomer) ($CDCl_3$) δ: 6.94-7.46 (m, 7H, aromatic), 5.64 (t, J=8.0 Hz, 1H, CH=), 5.15 (br s, 2H, CH_2O), 3.07 (m, 4H, $NCH_2\ CH_2$), 2.75 (s, 6H, NMe_2).

Analysis: Calcd. for $C_{19}H_{20}BrNO \cdot HCl$: C, 57.80; H, 5.36; N, 3.54. Found (Z-isomer): C, 57.56; H, 5.41; N, 3.45.

c) (E)-11-3-(Dimethylamino)propylidene-6, 11-dihydrodibenz[b,e]oxepin-9-carboxylic acid (Compound 7).

An isomeric mixture E/Z (1:4) of 3-(9-bromo-6, 11-dihydrodibenz[b,e]-11-ylidene)-N,N-dimethylpropylamine (2.0 g., 5.6 mmole) in 100 mL dry tetrahydrofuran at -70°C was reacted with 6.2 mmole n-butyl lithium in hexane followed by gaseous carbon dioxide by the procedure of Example I, Step c, to provide the corresponding carboxylic acids as anE/Z (1:4) stereoisomeric mixture. The mixture was chromatographed on a reverse phase PRP-1 semi-preparative column with water/acetonitrile (85:15) to provide 0.06 g of E-isomer of ≥95% stereoisomeric purity (assayed by HPLC on C_{18}) as pale yellow glass. pmr (DMSO-d_6) δ: 7.83 (d, J≤ 1 Hz, 1H, H_{10}), 7.79 (dd, J=7.2, 1.5 Hz, 1H, H_9), 6.69-7.39 (m, 5H, aromatic), 5.85 (t, J=6.4 Hz, 1H, CH=), 5.22 (s, 2H, CH_2O), 2.81 (m, 4H, NCH_2CH_2), 2.61 (s, 6H, NMe_2).

Analysis: Calcd. for $C_{20}H_{21}NO_3 \cdot 2.8\ H_2O$: C, 64.26; H, 7.17; N, 3.75. Found: C, 64.23; H, 6.84; N, 3.76.

d) (Z)-11-3-(Dimethylamino)propylidene-6,11-dihydrodibenz[b,e]oxepin-9-carboxylic acid(Compound 8)

Pure (Z)-3-(9-bromo-6, 11-dihydrodibenz[b,e]oxepin-11-ylidene)-N,N-dimethylpropylamine (0.78 g., 2.2 mmole), in cold (-70°C) dry tetrahydrofuran (50 mL), was treated with 2.4 mmole n-butyl lithium in hexane followed by gaseous carbon dioxide by the procedure of Example I, Step c. This provided the desired carboxylic acid which was recrystallized from water to yield 0.15 g. pure Z-isomer, m.p. >205°C (decomp.) with melting at 210°C. pmr ($CDCl_3/D_2O$) δ: 7.84 (d, J=1.8 Hz, 1H, H_{10}), 7.81 (dd, J=6.4, 1.8 Hz, 1H, H_8), 6.94-7.35 (m, 5H, aromatic), 5.78 (t, J=6.9 Hz, 1H, CH=), 5.25 (s, 2H, CH_2O), 3.20 (m, 2H, NCH_2), 2.80 (s, 6H, NMe_2), 2.50-2.90 (m, 2H, CH_2).

Analysis: Calcd. for $C_{20}H_{21}NO_3 \cdot 0.33\ H_2O$: C, 73.06; H, 6.62; N, 4.26. Found: C, 72.92; H, 6.59; N, 4.13.

Example 5: (E)/(Z)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b,e]oxepin-2-(E)-acrylic acid

a) Ethyl(E)-6,11-dihydro-11-oxodibenz[b,e]oxepin-acrylate

A mixture of palladium acetate (0.4 g, 1.73 mmole), triphenylphosphine (0.9 g, 3.46 mmole), 2-bromo-6, 11-dihydro-11-oxodibenz[b,e]oxepin (10 g, 34.6 mmole), ethyl acrylate (13 g, 130 mmole) and tri-n-butylamine (7.7 g, 57 mmole) was heated at 130-140°C under a nitrogen atmosphere for six hours. The reaction mixture was partitioned between diethyl ether (100 mL) and 0.1N hydrochloric acid (50 mL). Evaporation of the ether under reduced pressure gave a yellow solid residue. The crude material was chromatographed on a silica gel column (Waters Associates - Prep 500) with hexanes/ethyl acetate (8:2) to give 6.12 g of (E)-acrylate product. Recrystallization from ethyl acetate/hexanes gave an analytical sample, m.p. 113-114°C. pmr ($CDCl_3$) δ: 8.39 (d, J=2.4 Hz, 1H, H_1), 7.88 (dd, J=1.5, 7.5 H_z, 1H, H_{10}), 7.70 (d, J=16.4 Hz, 1H, ArCH=), 7.66 (dd, J=2.2, 8.6 H_2, 1H, H_3), 7.46-7.60 (m, 2H, H_8 and H_9), 7.38 (dd, J=1.0, 7.3 Hz, 1H, H_7), 7.07 (d, J=8.6 H_2, 1H, H_4), 6.42 (d, J=16.0 Hz, 1H, =$CHCO_2$), 5.23 (s, 2H, $ArCH_2O$), 4.26 (q, 2H, CH_2), 1.34 (t, 3H, CH_3).
Analysis: Calcd. for $C_{19}H_{16}O_4$: C, 74.01; H, 5.23. Found: C, 73.90; H, 5.28.

b) (E)/(Z)-11-(3-(Dimethylamino)propylidene)-6, 11-dihydrodibenz[b,e]oxepin-2(E)-acrylic acid (Compounds 9/10)

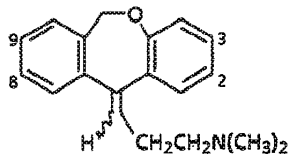
Anhydrous 3-(dimethylamino)propyltriphenylphosphonium bromide hydrobromide (0.8 g, 1.57 mmole) was suspended in 20 mL of dry tetrahydrofuran and 1.8 mL of a solution of n-butyl lithium in hexane (1.6M) was added dropwise at 0°C under a nitrogen atmosphere during a 10 minute period. After an additional 10 minutes, ethyl (E)-6, 11-dihydro-11-oxodibenz[b,e]oxepin-2-acrylate (0.34 g, 1.1 mmole) in 5 mL dry tetrahydrofuran was added slowly to the deep red solution and the reaction mixture was then refluxed for 18 hours. The reaction was worked up as described in Example I, step d. The crude material was dissolved in 1N sodium hydroxide (20 mL) and 20 mL of absolute ethanol, and then stirred at room temperature for 18 hours. After neutralization with 1N hydrochloric acid (20 mL) the solution was evaporated to dryness and the residue was chromatographed on a PRP-1 column with water/acetonitrile (78:22) to give 0.015 g of Z-isomer (lyophilized solid) and 0.009 g of E-isomer (lyophilized powder). pmr (Z-isomer) (CD_3OD) δ: 7.29-7.38 (m, 7H, aromatic H and ArCH=), 6.82 (d, J=8.5 Hz, 1H, H_4) 6.37 (d, J=16.0 H_z, 1H, =$CHCO_2$), 5.70 (t,1H CH=), 5.20 (very br s, 2H, $ArCH_2O$), 2.87 (m, 2H, CH_2), 2.77 (m, 2H, NCH_2), 2.50 (s, 6H, NMe_2). pmr (E-isomer) (CD_3OD) δ: 7.28-7.49 (m, 7H, aromatic H and ArCH=), 6.72 (d, J=8.5 H_z, 1H, H_4), 6.35 (d, J=16.0 H_z, 1H, = $CHCO_2$), 6.10 (t, 1H, CH=), 5.58 (very br s, 2H, $ArCH_2O$), 2.78 (m, 2H, CH_2), 2.50 (m, 2H, NCH_2), 2.40 (s, 6H, NMe_2).

Example 6: Antihistamine Activity

A. In vitro antihistamine activity: The longitudinal muscle was isolated from the intact ileum of guinea-pigs (Hartley, male 250–400 g) and placed in an organ bath under 300 mg tension. After one hour of equilibration, cumulative concentration-response curves (Van Rossum, J.M., Arch. Int. Pharmacodyn. Ther. 143, 299–330, 1963) to histamine were obtained. Following washing, the tissues were incubated for one hour with the test compound and then a second histamine concentration response curve was run. Shifts to the right of the agonist concentration-response curve produced by the antagonists were used to construct Schild plots (Arunlakshana, O. and Schild, H.O., Br. J. Pharmacol. 14, 48–58, 1959). Regression of Log (dr-1) on Log [B], where dr is an equiactive response in the presence and absence of antagonist and [B] is the molar concentration of antagonist, allowed an estimate of pA_2, i.e. the negative log of the concentration of antagonist which shifts the control histamine concentration response curve 2X to the right.

Table I

Antihistaminic Activity in *In Vitro* Assays



Compound No.	Compound	pA 2
-	Doxepin[a]	9.7
1	Z-2-CO_2H	8.3
2	E-2-CO_2H	8.3
6	Z-8-CO_2H	6.7
7	E-9-CO_2H	9.2
8	Z-9-CO_2H	7.8

[a]The Doxepin sample tested here had a Z:E ratio of 4:1

B. In vivo Antihistaminic Activity: Guinea pigs (Hartley, male, 300-350 g) were fasted for 20 hours and then dosed p.o. or i.p. with the test compound. One hour after dosing, on an individual basis, the guinea pigs were placed in a clear plastic chamber which was saturated and continually gassed with 0.25% histamine from an aerosol nebulizer. The guinea pigs were monitored for signs of histamine anaphylaxis (e.g. cough, sneeze, strong abdominal movements, cyanoses or loss of righting). Under the test conditions, control animals collapsed on average within 33 seconds. ED_{50}'s for protection against histamine were calculated by probit analysis. In this test the ED_{50} indicates that at that particular dose 50% of the animals were completely protected against histamine challenge at the time of testing (1 hour post-dosing). Complete protection was defined as no histamine symptoms for six minutes in the aerosol chamber (approximately 10X the collapse time of the control animals).

Table II

Results of *In Vivo* Antihistamine Assays

Compound[a]	ED_{50}[b] (mg/kg, p.o.) 4 hr post dosing
Doxepin (E:Z=4:1)	>>9
Z-2-CO_2H (1)	0.15

[a]The purity of these compounds was in excess of 96%

[b]The number of animals was at least 40

In addition to these results, it was found that Compound 1 could provide very long durations of antihistamic activity.

Example G: Anaphylactoid Activity

Non-fasted, Wister rats (180-300g) were dosed with the test compound (i.p. or p.o.) 2 hours before compound 48/80 challenge. One hour prior to challenge, 5 mg/kg i.p. of propranolol was administered. The anaphylactoid inducing agent, compound 48/80 which is well known in the art of pharmacology, was given intravenously at 2 mg/kg and the animals were monitored for symptoms of respiratory distress.

Data were analyzed by Probit determinations. The response was quantitated by determining the dose of test compound which protected 50% of the animals from death at a given time point.

The above experimental design does not give positive results for selective antihistamines. Also rats do not respond to histamine (i.v.) with symptoms of anaphylaxis. Agents which block the effects of compound 48/80 are commonly classified as inhibitors of anaphylactic mediators or inhibitors of the release of anaphylic mediators.

Table III

Inhibition of Compound 48/80 Induced Anaphylactoid Reaction

Compound	ED_{50}[a,b]
Triprolidine	>30
Doxepin	0.15
Z-2-CO_2H (1)	1.1

[a]Dose of compound (p.o.) providing 50% protection against death induced by compound 48/80.

[b]At least 50 animals were used in each assay.

Compound 1 (example 1) had an approximately LD_{50} in rats of 210 mg/kg (i.p.) and greater than 500 mg/kg (p.o.).

Example 7: Formulations

The active compound is (Z)-11-(3-(dimethylamino)propylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid, i.e., Compound 1.

(A)-Injection

Ingredient	Amount per ampoule
Active Compound	1.0 mg
Water for Injections, q.s.	1.0 mL

The finely ground active compound is dissolved in the water for injections. The solution is filtered and sterilized autoclaving.

(B)-Suppository

Ingredient	Amount per suppository
Active Compound	1.0 mg
Cocoa Butter	2.0 g
or Wecobee™ Base q.s.	

Wecobee is a trademark and is a hydrogenated fatty carboxylic acid.

The finely ground active compound is mixed with the melted suppository base (either Cocoa Butter or Wecobee™ base), poured into moulds and allowed to cool to afford the desired suppositories.

(C)-Syrup

Ingredient	Amount per mL
Active Compound	1.0 mg
Ethanol	0.3 mg
Sucrose	2.0 mg
Methylparaben	0.5 mg
Sodium Benzoate	0.5 mg
Cherry Flavour	q.s.
Colouring	q.s.
Water	Q.S. to 5.0 mL

Ethanol, sucrose, sodium benzoate, methylparaben, and flavouring are combined in 70% of the total batch quantity of water. Colouring and the active compound are dissolved in the remaining water, then the two solutions are mixed and clarified by filtration.

(D)-Tablet

Ingredient	Amount per Tablet
Active Compound	1.0 mg
Lactose	110.0 mg
Corn Starch, Pregelatinized	2.5 mg
Potato Starch	12.0 mg
Magnesium stearate	0.5 mg

The active compound is finely ground and intimately mixed with the powdered excipients lactose, corn starch, potato starch and magnesium stearate. The formulation is then compressed to afford a tablet weighing 126 mg.

(E)-Capsule

Ingredient	Amount per Capsule
Active Compound	1.0 mg
Lactose	440.0 mg
Magnesium Stearate	5.0 mg

The finely ground active compound was mixed with the powdered excipients lactose and magnesium stearate and packed into gelatin capsules.

(F)-Tablet

Ingredient	Amount per Tablet
Active Compound	1.0 mg
Pseudoephedrine HCl	60.0 mg
Lactose	62.5 mg
Potato Starch	14.0 mg
Magnesium Stearate	1.0 mg
Gelatin	2.8 mg

A tablet is prepared from the above formulation by the method previously described in example 7 (D)

(G)-Syrup

Ingredient		Amount per 5 mL
Active Compound		1.0 mg
Pseudoephedrine HCl		30.0 mg
Codeine Phosphate		10.0 mg
Guaifenesin		100 mg
Methylparaben		0.5 mg
Sodium benzoate		0.5 mg
Flavour		q.s.
Glycerol		500 mg
Sucrose		2000 mg
Purified Water	q.s. to	5.0 mL

A syrup containing other active ingredients in addition to a compound of formula (I) is prepared from the above ingredients by an analogous method to that described for Example 7 (C) above.

(H)-Nasal Spray

Ingredient		Amount per 100.0 mL
Active Compound		1 g
Sodium Chloride		0.8 g
Preservative		0.5 g
Purified Water	q.s.	100.0 mL

The preservative is dissolved in warm purified water and after cooling to 25-30°C the sodium chloride and the compound of formula (I) are added. The pH is then adjusted to 5.5-6.5 and purified water is added to bring the final volume to 100.0 mL.

(I)-Ophthalmic Solution

Ingredient		Amount per 100.0 mL
Active Compound		0.1 g
Sodium Chloride		0.8 g
Preservative		0.5 g
Water for Injection	q.s.	100.0 mL

This formulation is prepared in a similar way to the nasal spray.

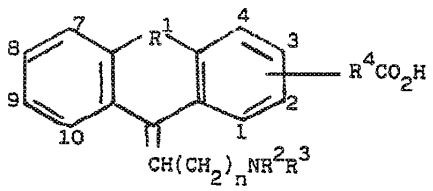
(J)-Topical Cream

Ingredient		Amount per 100.0 g
Active Compound		0.1 g
Emulsifying Wax, N.F.		15.0 g
Mineral Oil		5.0 g
White Petrolatum		5.0 g
Preservative		0.25 g
Purified Water	q.s.	100.0 g

The preservative is dissolved in approximately 50 g of warm purified water and after cooling to about 25°-30°C the compound of formula (I) is added. In a separate container the emulsifying wax, mineral oil and white petrolatum are mixed well and heated to approximately 70°-80°C. The aqueous solution containing the compound of formula (I) is added to the warm mixture of emulsifying wax, mineral oil and petrolatum with vigorous mixing while cooling to 25°C. Additional purified water is added with mixing to bring the total weight of the cream to 100.0 g.

Claims for designated States: BE, CH, DE, FR, GB, IT, LI, NL, SE

1. A compound of formula (I)



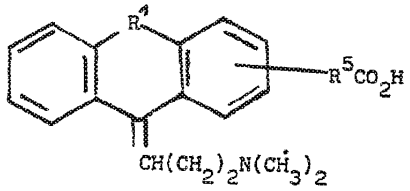
(I)

or a salt, ester or amide thereof; wherein R^1 is CH_2–O– or –OCH_2–; R^2 and R^3 are the same or different and are each hydrogen, C_{1-4} alkyl or taken together with the nitrogen comprise a nitrogen-containing heterocylic ring having four to six ring members; R^4 is a single bond or a C_{1-7} bivalent aliphatic hydrocarbon group and may be joined to the aromatic ring system at the 2, 3, 8 or 9 positions; n is 0 to 3.

2. A compound of formula (I) as defined in claim 1 wherein R^1 represents –CH_2O– or OCH_2–; R^2 and R^3 are the same or different and are each C_{1-4} alkyl, preferably methyl; R^4 is a single bond or a C_{1-7} bivalent aliphatic hydrocarbon group and may be joined to the aromatic ring at the 2, 3, 8 or 9 position, preferably at the 2-position and n is 0 to 3, and salts, amides and esters thereof.

3. A compound of formula (I) as defined in claim 1 wherein R^1 represents –CH_2O–; R^2 and R^3 are the same or different and are each C_{1-4} alkyl, preferably methyl; R^4 is a single bond or a C_{1-7} bivalent aliphatic hydrocarbon group and may be joined to the aromatic ring at the 2, 3, 8 or 9 position, preferably at the 2-position and n is 0 to 3, and salts, esters and amides thereof.

4. A compound of formula (II)



(II)

or a salt, ester or amide thereof; wherein R^1 is $-CH_2-O-$ or $-OCH_2$; and R^5 is a single bond or $-CH=CH$ joined to the aromatic ring system at the 2, 3, 8 or 9 positions.

5. A compound selected from:
(Z)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b.e.]oxepin-2-carboxylic acid
(E)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b.e.]oxepin-2-carboxylic acid
(E)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b.e.]oxepin-3-carboxylic acid
(Z)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b.e.]oxepin-3-carboxylic acid
(E)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b.e.]oxepin-8-carboxylic acid
(Z)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b.e.]oxepin-8-carboxylic acid
(E)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b.e.]oxepin-9-carboxylic acid
(Z)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b.e.]oxepin-9-carboxylic acid
(E)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b.e.]oxepin-2-acrylic acid
(Z)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b.e.]oxepin-2-acrylic acid.

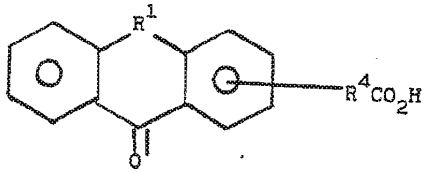
6. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 1 in admixture with a pharmaceutically acceptable carrier.

7. A compound of the formula (I) as defined in claim 1 for use in medicine.

8. A compound of the formula (I) as defined in claim 1 for the manufacture of a medicament for the control of allergy.

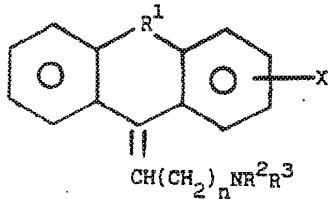
9. A compound of the formula (I) as defined in claim 1 for the manufacture of a medicament for relieving the detrimental effects of histamine, for the control or relief of the effects of an asthmatic condition, or for controlling bronchoconstriction or bronchospasm characteristic of allergic asthma.

10. A process for the preparation of a compound of formula (I) as defined in claim 1 which comprises
a) the reaction of a compound of the formula (III):



(III)

wherein R^1 and R^4 are as hereinbefore defined in Claim 1 with an appropriate Wittig reagent or with an appropriate Grignard reagent followed by dehydration or
b) the hydrolysis of a compound of the formula (V):



(V)

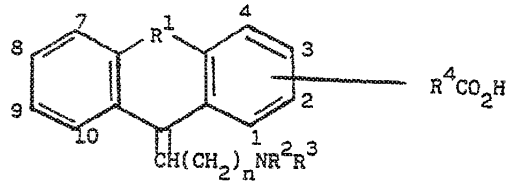
wherein X is R^4CN; and R^1, R^2, R^3, R^4 and n are as defined in Claim 1
c) when it is required to prepare a compound of the formula (I) wherein R^4 is a single bond, a carboxylation reaction on a compound of the formula (V) above wherein R^1 to R^3 and n are as hereinbefore defined in Claim 1 and X is a hydrogen or halogen atom, or
d) when it is required to prepare a compound of the formula (I) wherein R^4 is other than a single bond the reaction of a compound of the formula (V) above wherein X is a halogen atom and R^1 to R^3 and n

are as hereinbefore defined in Claim 1 with a compound: CH_2=CHR^6COR^7 in which R^6 is a C_{1-5} bivalent aliphatic hydrocarbon and R^7 is a protecting group and thereafter removing the protecting group when required, and

e) thereafter converting one compound of the formula (I) to another compound of the formula (I) if desired.

Claims for designated State: AT

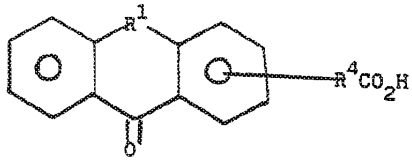
1. A process for the preparation of a compound of formula (I)



(I)

or a salt, ester or amide thereof; wherein R^1 is CH_2–O– or –OCH_2–; R^2 and R^3 are the same or different and are each hydrogen, C_{1-4} alkyl or taken together with the nitrogen comprise a nitrogen-containing heterocyclic ring having four to six ring members; R^4 is a single bond or a C_{1-7} bivalent aliphatic hydrocarbon group and may be joined to the aromatic ring system at the 2, 3, 8 or 9 positions; n is 0 to 3 which process comprises;

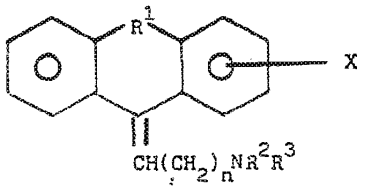
a) the reaction of a compound of the formula (III):



(III)

wherein R^1 and R^4 are as hereinbefore with an appropriate Wittig reagent or with an appropriate Grignard reagent followed by dehydration or

b) the hydrolysis of a compound of the formula (V):



(V)

wherein X is R^4CN; and R^1, R^2, R^3, R^4 and n are as defined in Claim 1,

c) when it is required to prepare a compound of the formula (I) wherein R^4 is a single bond the carboxylation of a compound of the formula (V) above wherein R^1 to R^3 and n are as hereinbefore defined and X is a hydrogen or halogen atom, or

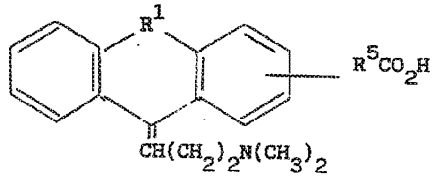
d) when it is required to prepare a compound of the formula (I) wherein R^4 is other than a single bond the reaction of a compound of the formula (V) wherein X is a halogen atom and R^1 to R^3 and n are as hereinbefore defined with a compound: CH_2=CHR^6COR^7 in which R^6 is a C_{1-5} bivalent aliphatic hydrocarbon and R^7 is a protecting group and thereafter removing the protecting group when required, and

e) thereafter converting one compound of the formula (I) to another compound of the formula (I) if desired.

2. A process according to Claim 1 for the preparation of a compound of formula (I) as defined in Claim 1 wherein R^1 represents –CH_2O– or –OCH_2–; R^2 and R^3 are the same or different and are each C_{1-4} alkyl, preferably methyl; R^4 is a single bond or a C_{1-7} bivalent aliphatic hydrocarbon group and may be joined to the aromatic ring at the 2, 3, 8 or 9 position, preferably at the 2-position and n is 0 to 3, and salts, amides and esters thereof.

3. A process according to Claim 1 for the preparation of a compound of formula (I) as defined in Claim 1 wherein R^1 represents $-CH_2O-$; R^2 and R^3 are the same or different and are each C_{1-4} alkyl, preferably methyl; R^4 is a single bond or a C_{1-7} bivalent aliphatic hydrocarbon group and may be joined to the aromatic ring at the 2, 3, 8 or 9 position, preferably at the 2-position and n is 0 to 3, and salts, esters and amides thereof.

4. A process according to claim 1C for the preparation of a compound of formula (II):



wherein R^1 is as defined above and R^5 is a single bond.

5. A process according to claim 1 for the preparation of a compound selected from:
(Z)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b.e.]oxepin-2-carboxylic acid
(E)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b.e.]oxepin-2-carboxylic acid
(E)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b.e.]oxepin-3-carboxylic acid
(Z)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b.e.]oxepin-3-carboxylic acid
(E)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b.e.]oxepin-8-carboxylic acid
(Z)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b.e.]oxepin-8-carboxylic acid
(E)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b.e.]oxepin-9-carboxylic acid
(Z)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b.e.]oxepin-9-carboxylic acid
(E)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b.e.]oxepin-2-acrylic acid
(Z)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b.e.]oxepin-2-acrylic acid.

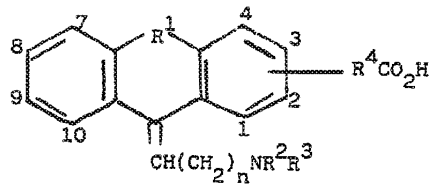
6. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 1 in admixture with a pharmaceutically acceptable carrier.

7. A process for the preparation of a pharmaceutical composition which comprises bringing a compound of the formula (I) as defined in claim 1 into association with a pharmaceutically acceptable carrier.

8. A compound of the formula (I) as defined in claim 1 for use in a method for the control of allergy.

Patentansprüche für die Vertragsstaaten: BE, CH, DE, FR, GB, IT, LI, NL, SE

1. Verbindung der Formel (I)



(I)

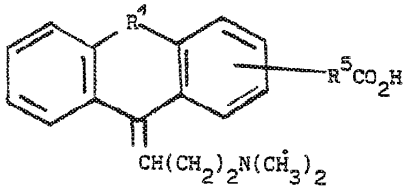
oder Salz, Ester oder Amid dieser Verbindung, worin
R^1 CH_2-O- oder $-O-CH_2-$ bedeutet,
R^2 und R^3 gleich oder verschieden sind und jeweils Wasserstoff oder eine C_{1-4}-Alkylgruppe bedeuten oder zusammengenommen mit dem Stickstoffatom einen Stickstoff enthaltenden heterocyclischen Ring mit 4 bis 6 Ringgliedern umfassen,
R^4 eine Einfachbindung oder eine zweiwertige, aliphatische C_{1-7}-Kohlenwasserstoff-Gruppe ist und mit dem aromatischen Ringsystem an den Positionen 2, 3, 8 oder 9 verbunden sein kann, und
n 0 bis 3 ist.

2. Verbindung der Formel (I) wie in Anspruch 1 definiert, worin
R^1 $-CH_2O-$ oder $-OCH_2-$ bedeutet,
R^2 und R^3 gleich oder verschieden sind und jeweils eine C_{1-4}-Alkylgruppe, vorzugsweise Methyl, bedeuten,
R^4 eine Einfachbindung oder eine zweiwertige, aliphatische C_{1-7}-Kohlenwasserstoff-Gruppe ist und mit dem aromatischen Ring an den Positionen 2, 3, 8 oder 9, vorzugsweise an der Position 2, verbunden sein kann, und

n 0 bis 3 ist,
sowie deren Salze, Amide und Ester.

3. Verbindung der Formel (I) wie in Anspruch 1 definiert, worin
R^1 $-CH_2O-$ bedeutet,
R^2 und R^3 gleich oder verschieden sind und jeweils für einen C_{1-4}-Alkylrest, vorzugsweise Methyl, stehen,
R^4 eine Einfachbindung oder eine zweiwertige, aliphatische C_{1-7}-Kohlenwasserstoff-Gruppe ist und mit dem aromatischen Ring an den Positionen 2, 3, 8 oder 9, vorzugsweise an der Position 2, verbunden sein kann, und
n 0 bis 3 ist,
und deren Salze, Ester und Amide.

4. Verbindung der Formel (II)



(II)

oder Salz, Ester oder Amid, worin
R^1 $-CH_2-O-$ oder $-O-CH_2$ bedeutet, und
R^5 eine Einfachbindung oder die Gruppe $-CH=CH$ bedeutet, die an das aromatische Ringsystem an den Positionen 2, 3, 8 oder 9 gebunden ist.

5. Verbindung, ausgewählt unter folgenden Verbindungen:
(Z)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-2-carbonsäure
(E)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-2-carbonsäure
(E)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-3-carbonsäure
(Z)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-3-carbonsäure
(E)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-8-carbonsäure
(Z)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-8-carbonsäure
(E)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-9-carbonsäure
(Z)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-9-carbonsäure
(E)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-2-acrylsäure
(Z)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-2-acrylsäure.

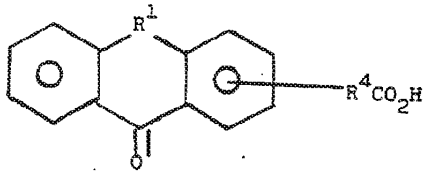
6. Pharmazeutische Zusammensetzung, umfassend eine Verbindung der Formel (I) wie in Anspruch 1 definiert in Abmischung mit einem pharmazeutisch annehmbaren Träger.

7. Verbindung der Formel (I) wie in Anspruch 1 definiert zur Verwendung in der Medizin.

8. Verbindung der Formel (I) wie in Anspruch 1 definiert zur Herstellung eines Arzneimittels für die Kontrolle von Allergie.

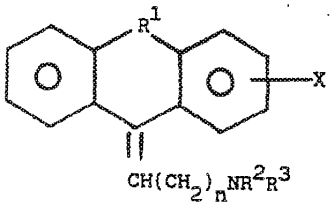
9. Verbindung der Formel (I) wie in Anspruch 1 definiert zur Herstellung eines Arzneimittels zur Verminderung der nachteiligen Wirkungen von Histamin, zur Kontrolle oder Linderung der Wirkungen eines asthmatischen Zustandes oder zur Kontrolle von Bronchokonstriktionen oder Bronchospasmen, wie sie für allergisches Asthma charakteristisch sind.

10. Verfahren zur Herstellung einer Verbindung der Formel (I) wie in Anspruch 1 definiert, wobei das Verfahren umfaßt:
(a) die Reaktion einer Verbindung der Formel (III)



(III)

worin R^1 und R^4 die in Anspruch 1 definierte Bedeutung haben, mit einem geeigneten Wittig-Reagenz oder mit einem geeigneten Grignard-Reagenz und nachfolgende Dehydratation, oder
(b) die Hydrolyse einer Verbindung der Formel (V)

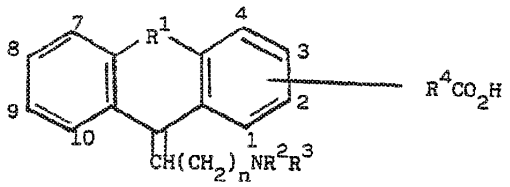


(V)

worin X R^4CN bedeutet und R^1, R^2, R^3, R^4 und n die in Anspruch 1 definierte Bedeutung haben,
(c) wenn es erforderlich ist, eine Verbindung der Formel (I) herzustellen, worin R^4 eine Einfachbindung ist, eine Carboxylierungsreaktion an einer Verbindung der Formel (V) wie oben angegeben, worin R^1 bis R^3 und n die in Patentanspruch 1 definierte Bedeutung haben und X ein Wasserstoff- oder ein Halogenatom ist, oder
(d) wenn es erforderlich ist, eine Verbindung der Formel (I) herzustellen, worin R^4 eine andere Bedeutung als die einer Einfachbindung hat, die Reaktion einer Verbindung der Formel (V) wie oben angegeben, worin X ein Halogenatom ist und R^1 bis R^3 und n die in Anspruch 1 definierte Bedeutung haben, mit einer Verbindung CH_2=CHR^6COR^7, worin R^6 für einen zweiwertigen aliphatischen C_{1-5}-Kohlenwasserstoff-Rest und R^7 für eine Schutzgruppe steht, und danach Entfernung der Schutzgruppe, wenn erforderlich, und
(e) danach Umwandeln einer Verbindung der Formel (I) in eine andere Verbindung der Formel (I), sofern gewünscht.

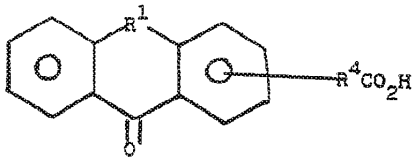
Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung einer Verbindung der Formel (I)



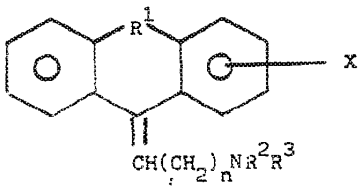
(I)

oder Salz, Ester oder Amid dieser Verbindung, worin
R^1 CH_2–O– oder –O–CH_2– bedeutet,
R^2 und R^3 gleich oder verschieden sind und jeweils Wasserstoff oder eine C_{1-4}-Alkylgruppe bedeuten oder zusammengenommen mit dem Stickstoffatom einen Stickstoff enthaltenden heterocyclischen Ring mit 4 bis 6 Ringgliedern umfassen,
R^4 eine Einfachbindung oder eine zweiwertige, aliphatische C_{1-7}-Kohlenwasserstoff-Gruppe ist und mit dem aromatischen Ringsystem an den Positionen 2, 3, 8 oder 9 verbunden sein kann, und
n 0 bis 3 ist,
wobei das Verfahren umfaßt:
(a) die Reaktion einer Verbindung der Formel (III)



(III)

worin R^1 und R^4 die in Anspruch 1 definierte Bedeutung haben, mit einem geeigneten Wittig-Reagenz oder mit einem geeigneten Grignard-Reagenz und nachfolgende Dehydratation, oder
(b) die Hydrolyse einer Verbindung der Formel (V)



(V)

worin X R^4CN bedeutet und R^1, R^2, R^3, R^4 und n die oben definierte Bedeutung haben,

(c) wenn es erforderlich ist, eine Verbindung der Formel (I) herzustellen, worin R^4 eine Einfachbindung ist, eine Carboxylierungsreaktion an einer Verbindung der Formel (V) wie oben angegeben, worin R^1 bis R^3 und n die oben definierte Bedeutung haben und X ein Wasserstoff- oder ein Halogenatom ist, oder

(d) wenn es erforderlich ist, eine Verbindung der Formel (I) herzustellen, worin R^4 eine andere Bedeutung als die einer Einfachbindung hat, die Reaktion einer Verbindung der Formel (V), worin X ein Halogenatom ist und R^1 bis R^3 und n die oben definierte Bedeutung haben, mit einer Verbindung $CH_2=CR^6COR^7$, worin R^6 für eine zweiwertige aliphatische C_{1-5}-Kohlenwasserstoff-Gruppe und R^7 für eine Schutzgruppe steht, und danach Entfernung der Schutzgruppe, wenn erforderlich, und

(e) danach Umwandeln einer Verbindung der Formel (I) in eine andere Verbindung der Formel (I), sofern gewünscht.

2. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung der Formel (I) wie in Anspruch 1 definiert, worin

R^1 $-CH_2O-$ oder $-OCH_2-$ bedeutet,

R^2 und R^3 gleich oder verschieden sind und jeweils eine C_{1-4}-Alkylgruppe, vorzugsweise Methyl, bedeuten,

R^4 eine Einfachbindung oder eine zweiwertige, aliphatische C_{1-7}-Kohlenwasserstoff-Gruppe ist und mit dem aromatischen Ringsystem an den Positionen 2, 3, 8 oder 9, vorzugsweise an der Position 2, verbunden sein kann, und

n 0 bis 3 ist,

sowie deren Salze, Amide und Ester.

3. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung der Formel (I) wie in Anspruch 1 definiert, worin

R^1 $-CH_2O-$ bedeutet,

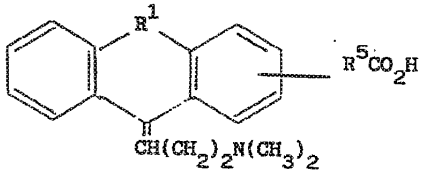
R^2 und R^3 gleich oder verschieden sind und jeweils für einen C_{1-4}-Alkylrest, vorzugsweise einen Methylrest, stehen,

R^4 eine Einfachbindung oder eine zweiwertige, aliphatische C_{1-7}-Kohlenwasserstoff-Gruppe ist und mit dem aromatischen Ring an den Positionen 2, 3, 8 oder 9, vorzugsweise an der Position 2, verbunden sein kann, und

n 0 bis 3 ist,

und deren Salze, Ester und Amide.

4. Verfahren nach Anspruch 1 (c) für die Herstellung einer Verbindung der Formel (II)



(II)

worin R^1 die oben definierte Bedeutung hat und R^5 eine Einfachbindung ist.

5. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung aus der Gruppe

(Z)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-2-carbonsäure
(E)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-2-carbonsäure
(E)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-3-carbonsäure
(Z)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-3-carbonsäure
(E)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-8-carbonsäure
(Z)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-8-carbonsäure
(E)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-9-carbonsäure
(Z)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-9-carbonsäure
(E)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-2-acrylsäure
(Z)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-2-acrylsäure.

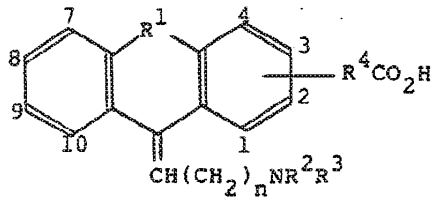
6. Pharmazeutische Zusammensetzung, umfassend eine Verbindung der Formel (I) wie in Anspruch 1 definiert in Abmischung mit einem pharmateutisch annehmbaren Träger.

7. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, wobei das Verfahren den Schritt umfaßt, eine Verbindung der Formel (I) wie in Anspruch 1 definiert, in Verbindung mit einem pharmazeutisch annehmbaren Träger zu bringen.

8. Verbindung der Formel (I) wie in Anspruch 1 definiert zur Verwendung in einem Verfahren zur Kontrolle von Allergie.

Revendications pour les Etats contractants: BE, CH, DE, FR, GB, IT, LI, NL, SE

1. Composé de formule (I)



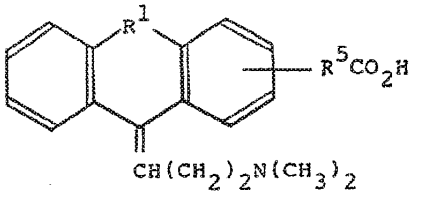
(I)

ou un sel, ester ou amide de celui-ci;
où R^1 est $-CH_2-O-$ ou $-O-CH_2-$;
R^2 et R^3 sont identiques ou différents et sont chacun hydrogène ou C_{1-4}-alcoyle ou bien pris ensemble avec l'atome d'azote forment un hétérocycle azoté comptant quatre à six chaînons de cycle;
R^4 est une liaison simple ou un radical hydrocarboné aliphatique bivalent en C_{1-7} et peut être uni au système cyclique aromatique aux positions 2, 3, 8 ou 9;
n est 0 à 3.

2. Composé de formule (I) tel que défini dans la revendication 1,
où R^1 représente $-CH_2O-$ ou $-OCH_2-$;
R^2 et R^3 sont identiques ou différents et sont chacun C_{1-4}-alcoyle, de préférence méthyle;
R^4 est une liaison simple ou un radical hydrocarboné aliphatique bivalent en C_{1-7} et peut être uni au cycle aromatique à la position 2, 3, 8 ou 9, de préférence à la position 2; et
n est 0 à 3,
et les sels, amides et esters de cellui-ci.

3. Composé de formule (I) tel que défini dans la revendication 1,
où R^1 représente $-CH_2O-$;
R^2 et R^3 sont identiques ou différents et sont chacun C_{1-4}-alcoyle, de préférence méthyle;
R^4 est une liaison simple ou un radical hydrocarboné aliphatique bivalent en C_{1-7} et peut être uni au cycle aromatique à la position 2, 3, 8 ou 9, de préférence à la position 2, et
n est 0 à 3,
et les sels, esters et amides de celui-ci.

4. Composé de formule (II)



(II)

ou un sel, ester ou amide de celui-ci,
où R^1 est $-CH_2-O-$ ou $-O-CH_2-$; et
R^5 est une liaison simple ou $-CH=CH$ uni au cycle aromatique à la position 2, 3, 8 ou 9.

5. Composé choisi parmi:
l'acide (Z)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-2-carboxylique
l'acide (E)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-2-carboxylique
l'acide (E)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-3-carboxylique
l'acide (Z)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-3-carboxylique
l'acide (E)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-8-carboxylique

l'acide (Z)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-8-carboxylique
l'acide (E)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-9-carboxylique
l'acide (Z)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-9-carboxylique
l'acide (E)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-2-acrylique
l'acide (Z)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-2-acrylique.

6. Composition pharmaceutique comprenant un composé de formule (I) tel que défini dans la revendication 1 en mélange avec un excipient pharmaceutiquement acceptable.

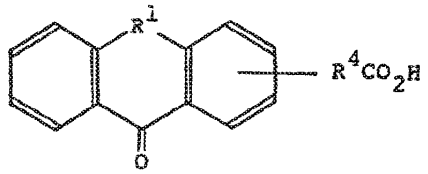
7. Composé de formule (I) tel que défini dans la revendication 1, à utiliser en médecine.

8. Composé de formule (I) tel que défini dans la revendication 1, pour la préparation d'un médicament pour lutter contre l'allergie.

9. Composé de formule (I) tel que défini dans la revendication 1, pour la préparation d'un médicament pour soulager les effets nuisibles de l'histamine, pour maîtriser ou soulager les effets d'un état asthmatique ou pour maîtriser la bronchoconstriction ou le bronchospasme caractéristique de l'asthme allergique.

10. Procédé de préparation d'un composé de formule (I) tel que défini dans la revendication 1, qui comprend

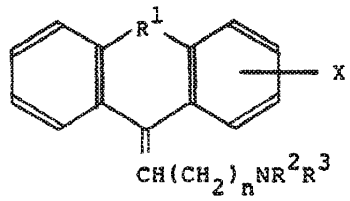
a) la réaction d'un composé de formule (III):



(III)

où R^1 et R^4 sont tels que définis dans la revendication 1, avec un réactif de Wittig approprié ou avec un réactif de Grignard approprié, suivie de la déshydratation, ou

b) l'hydrolyse d'un composé de formule (V):



(V)

où X est R^4CN et R^1, R^2, R^3, R^4 et n sont tels que définis dans la revendication 1,

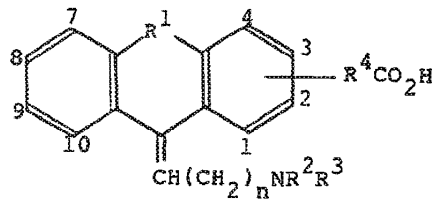
c) lorsqu'il est requis de préparer un composé de formule (I) où R^4 est une liaison simple, une réaction de carboxylation exécutée sur un composé de formule (V) ci-dessus où R^1 à R^3 et n sont tels que définis ci-dessus dans la revendication 1 et X est un atome d'hydrogène ou d'halogène, ou

d) lorsqu'il est requis de préparer un composé de formule (I) où R^4 est autre qu'une liaison simple, la réaction d'un composé de formule (V ci-dessus où X est un atome d'halogène et R^1 à R^3 et n sont tels que définis ci-dessus dans la revendication 1, avec un composé $CH_2=CHR^6COR^7$ où R^6 est un radical hydrocarboné aliphatique bivalent en C_{1-5} et R^7 est un radical protecteur, et ensuite l'élimination du radical protecteur lorsque la chose est nécessaire, et

e) ensuite, la conversion d'un composé de formule (I) en un autre composé de formule (I), si la chose est souhaitée.

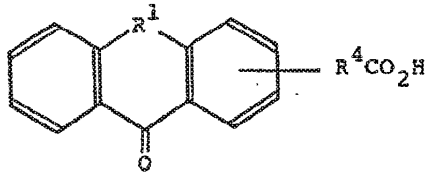
Revendications pour l'Etat contractant: AT

1. Procédé de préparation d'un composé de formule (I)



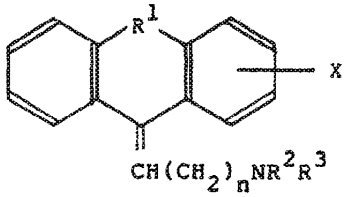
(I)

ou d'un sel, ester ou amide de celui-ci;
où R^1 est $-CH_2-O-$ ou $-O-CH_2-$;
R^2 et R^3 sont identiques ou différents et sont chacun hydrogène ou C_{1-4}-alcoyle ou bien pris ensemble avec l'atome d'azote forment un hétérocycle azoté comptant quatre à six chaînons de cycle;
R^4 est une liaison simple ou un radical hydrocarboné aliphatique bivalent en C_{1-7} et peut être uni au système cyclique aromatique aux positions 2, 3, 8 ou 9;
n est 0 à 3,
lequel procédé comprend:
a) la réaction d'un composé de formule (III):



(III)

où R^1 et R^4 sont tels que définis ci-dessus, avec un réactif de Wittig approprié ou avec un réactif de Grignard approprié, suivie de la déshydratation, ou
b) l'hydrolyse d'un composé de formule (V):



(V)

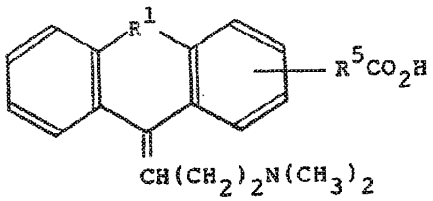
où X est R^4CN, et R^1, R^2, R^3, R^4 et n sont tels que définis dans la revendication 1,
c) lorsqu'il est requis de préparer un composé de formule (I) où R^4 est une liaison simple, la carboxylation d'un composé de formule (V) ci-dessus où R^1 à R^3 et n sont tels que définis ci-dessus et X est un atome d'hydrogène ou d'halogène, ou
d) lorsqu'il est requis de préparer un composé de formule (I) où R^4 est autre qu'une liaison simple, la réaction d'un composé de formule (V) où X est un atome d'halogène et R^1 à R^3 et n sont tels que définis ci-dessus, avec un composé $CH_2=CHR^6COR^7$ où R^6 est un radical hydrocarboné aliphatique bivalent en C_{1-5} et R^7 et un radical protecteur, et ensuite l'élimination du radical protecteur lorsque la chose est requise, et
e) ensuite la conversion d'un composé de formule (I) en un autre composé de formule (I), si la chose est souhaitée.

2. Procédé suivant la revendication 1, de préparation d'un composé de formule (I) tel que défini dans la revendication 1,
où R^1 représente $-CH_2O-$ ou $-OCH_2-$;
R^2 et R^3 sont identiques ou différents et sont chacun C_{1-4}-alcoyle, de préférence méthyle;
R^4 est une liaison simple ou un radical hydrocarboné aliphatique bivalent en C_{1-7} et peut être uni au cycle aromatique à la position 2, 3, 8 ou 9, de préférence à la position 2 et
n est 0 à 3,
et des sels, amides et esters de celui-ci.

3. Procédé suivant la revendication 1, de préparation d'un composé de formule (I) tel que défini dans la revendication 1,

où R^1 représente $-CH_2O$
R^2 et R^3 sont identiques ou différents et sont chacun C_{1-4}-alcoyle, de préférence méthyle;
R^4 est une liaison simple ou un radical hydrocarboné aliphatique bivalent en C_{1-7} et peut être uni au cycle aromatique à la position 2, 3, 8 ou 9, de préférence à la position 2, et
n est 0 à 3,
et des sels, esters et amides de celui-ci.

4. Procédé suivant la revendication 1c) de préparation d'un composé de formule (II):



(II)

où R^1 est tel que défini ci-dessus et R^5 est une liaison simple.

5. Procédé suivant la revendication 1, de préparation d'un composé choisi parmi:
l'acide (Z)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-2-carboxylique
l'acide (E)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-2-carboxylique
l'acide (E)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-3-carboxylique
l'acide (Z)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-3-carboxylique
l'acide (E)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-8-carboxylique
l'acide (Z)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-8-carboxylique
l'acide (E)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-9-carboxylique
l'acide (Z)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-9-carboxylique
l'acide (E)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-2-acrylique
l'acide (Z)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-2-acrylique.

6. Composition pharmaceutique comprenant un composé de formule (I) tel que défini dans la revendication 1 en mélange avec un excipient pharmaceutiquement acceptable.

7. Procédé de préparation d'une composition pharmaceutique, qui comprend la mise en association d'un composé de formule (I) tel que défini dans la revendication 1 avec un excipient pharmaceutiquement acceptable.

8. Composé de formule (I) tel que défini dans la revendication 1, à utiliser dans un procédé pour lutter contre l'allergie.

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(54) **Dibenz [b,e] oxepin derivative and antiallergic and antiinflammatory agent**

Dibenzo[b,e]oxepin-Derivate sowie antiallergische und entzündunghemmende Mittel

Dérivés de dibenzo[b,e]oxépine et agent anti-allergique et anti-inflammatoire

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- **JOURNAL OF MEDICINAL CHEMISTRY, vol. 21, no. 7, July 1978, pages 633-639, American Chemical Society; "Novel arabinofuranosyl derivatives of cytosine resistant to enzymatic deamination and possessing potent antitumor activity"**

Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

EP 0 235 796 B2

ARGENTUM PHARM. 1032

Description

Background of the Invention

Heretofore, it has been known that 11-unsubstituted, 11-hydroxy or 11-oxodibenz[b,e]oxepin derivative is used for antiinflammatory agents [J. Med. Chem., 21, 633 - 639 (1978)].

Further, it is known that dibenz[b,e]oxepin derivative wherein substitutents Ra and Rb at 11-position have the following definitions, is employed in the treatment and control of allergic conditions (USP 4.282.365).

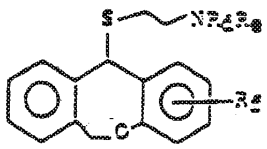
Ra: H, CH, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, arylthio, NH_2, NHCHO or imidazolyl;

Rb: H or lower alkyl;

or Ra and Rb taken together are = O, = CH-Rc wherein Rc is H or aryl.

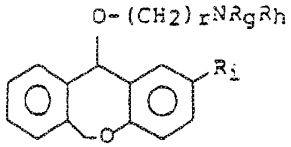
Furthermore, it is known that 11-(4-methylpiperazino) dibenz[b,e]oxepin derivative has an antiasthmatic activity (USP 4.396.550 USP 4.465,835, EP-A-38564).

It is also known that dibenz[b,e]oxepin derivative having the following formula:



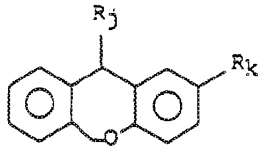
wherein Rd and Re are lower alkyl and Rf is lower alkyl or halogen, has an antiasthmatic activity (EP-A-85870).

Dibenz[b,e]oxepin derivative having an antiallergic activity and having the following structural formula:



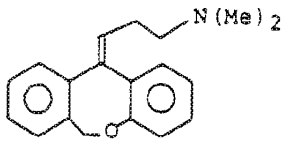
wherein Rg and Rh are alkyl, r is 2 or 3 and Ri is alkyl or halogen is known (JP-A-227879/84).

Dibenz[b,e]oxepin derivative having an antiallergic activity and having the following structural formula:

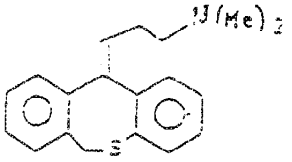


wherein Rj is 4-alkylpiperazino, 3-quinuclidylamino or -Xa-$(CH_2)_s$-$NR_\ell R_m$ wherein Xa is -NH-, -S- or -O-, s is 2 or 3 and R_ℓ and R_m are alkyl, and R_k is CN, 5-tetrazolyl, $CONH_2$ or CO_2R_n wherein R_n is H, alkyl or 1-(ethoxycarbonyloxy) ethyl is known (EP-A-130555).

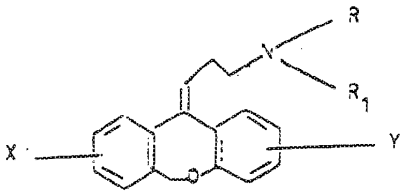
Doxepin having an antidepressant activity and having the following structural formula is known [Drugs, 13. 161 (1977)].



Dothiepin having an antidepressant activity and having the following structural formula is known [Arz.-Forsch., 13 1039 (1963); ibid., 14 100 (1964)].



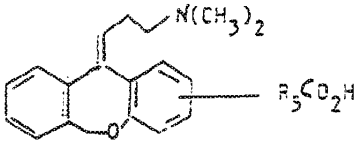
It is also known that dibenz [b,e] oxepin derivatives having the formula :



wherein :

R is hydrogen or methyl ;
R_1 is a lower alkyl, lower alkenyl or lower cycloalkyl ;
X and Y are each hydrogen, lower alkyl, lower alkoxy, lower alkylthio, chloro, fluoro, trifluoromethyl, lower acyl or dialkylsulfonamido, have an antidepressent activity (GB 1,018,955).

It is known that dibenz [b,e] oxepin derivatives of formula :

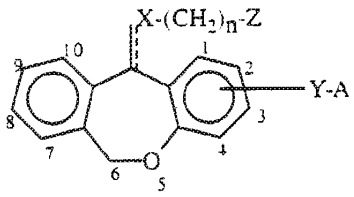


wherein R_5 is a single bond or -CH=CH-, have an anti-asthmatic activity (EP 214779).

As the compound having both an anti-allergic activity and an anti-inflammatory activity, steroids are known.

It is always desired that a novel compound having an antiallergic activity and an antiinflammatory activity be developed.

The present invention relates to a dibenz[b, e]oxepin derivative represented by the formula (I):



(I)

wherein

A represents a carboxyl, a straight or branched (C_1-C_6) alkoxy carbonyl group, -CONHOH or -CONR$_1$R$_2$ wherein R_1 and R_2 are the same or different and represent hydrogen atom or a straight or a branched (C_1-C_6) alkyl

Y represents -(CH_2)-, -CHR$_3$-(CH_2)$_m$- wherein R_3 represents a straight or branched (C_1-C_4) alkyl, and m is 1, 2, 3 or 4, which is the substituent at 2- or 3-position of the mother nucleus and the left side of the group Y is bound to benzene nucleus.

X represents =N-, =CH-;

n is o, 1, 2, 3 or 4;

Z represents 4-methylpiperazino, 4-methylhomopiperazino, piperidino, pyrrolidino, thiomorpholino, morpholino or -NR$_6$R$_7$ wherein R_6 and R_7 are the same or different and represent hydrogen atom or a straight or branched (C_1-C_4) alkyl a ---- means double bond; and the pharmaceutically acceptable salts thereof.

The present invention further pertains to pharmaceutical composition containing an effective amount of Compound (I) or a pharmaceutically acceptable salt thereof as an active ingredient, and a carrier or an excipient.

The present compound (I) is useful for treatment of allergic conditions and inflammation diseases.

DETAILED DESCRIPTION OF THE INVENTION

In the definition of each group of formula (I), the lower alkyl group includes straight or branched chain alkyl groups having 1 to 6 carbon atoms, for example, methyl, ethyl, n-propyl, iso-propyl, n-butyl, etc.

In the definition of the group A, lower alkyl moiety of lower alkoxymethyl group and lower alkoxycarbonyl group has the same meaning as previously defined.

The lower alkoxymethyl group includes methoxymethyl, ethoxymethyl, n-propoxymethyl, isopropoxymethyl, etc. and the lower alkoxycarbonyl group includes methoxycarbonyl, ethoxycarbonyl, etc.

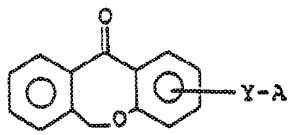
In the definition of the group A, the lower alkyl moiety of lower alkanoyl group and lower alkanyoloxymethyl group has the same meaning as previously defined.

The lower alkanoyl group includes formyl, acetyl, etc. and the lower alkanoyloxymethyl group includes formylocymmethyl, acetyloxymethyl.

The pharmaceutically acceptable salt of compound (I) includes pharmaceutically acceptable acid addition salt, metal salt, ammonium salt, organic amine addition salt, amino acid addition salt, etc..

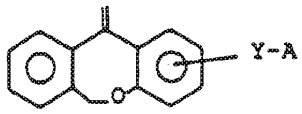
The pharmaceutically acceptable acid addition salt of compound (I) includes inorganic acid salts such as hydrochloride, sulfate, phosphate, etc., and organic acid salts such as acetate, maleate, fumarate, tartrate, citrate, etc.. The pharmaceutically acceptable metal salt includes alkalimetal salts such as sodium salt, potassium salt, etc., alkaline earch metal salts such as magnesium salt, calcium salt, etc., and aluminium salt, zinc salt, etc.. The pharmaceutically acceptable organic amine addition salt includes addition salt of morpholine and piperidine and the pharmaceutically acceptable amino acid addition salt includes addition salt of lysine, glysine, phenylalanine, etc..

Compound (I) is prepared by using a compound represented by the formula (II):



(II)

wherein Y and A have the same meanings as previously defined or a compound represented by the formula (III):



(III)

wherein Y and A have the same meanings as previously defined as the starting compound. Compound (II) is disclosed in J. Med. Chem., 19. 941 (1976), ibid., 20, 1499 (1977) and JP-A-21679/83.

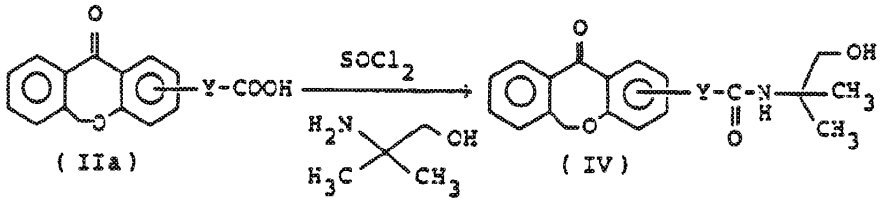
Compound (III) wherein -Y-A is -COOH is disclosed in JP-A-21679/83 and the other Compounds (III) can be prepared according to the method described in the publication though they do not occur in the publication.

The process for preparing Compound (I) is explained, depending on the kind of the group X.

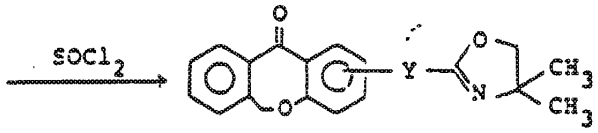
Process A

[Synthesis of Compound (I) wherein X is = CH- (Part 1)]

The carboxy group of Compound (IIa) is protected according to the following reaction scheme.



(IIa) (IV)



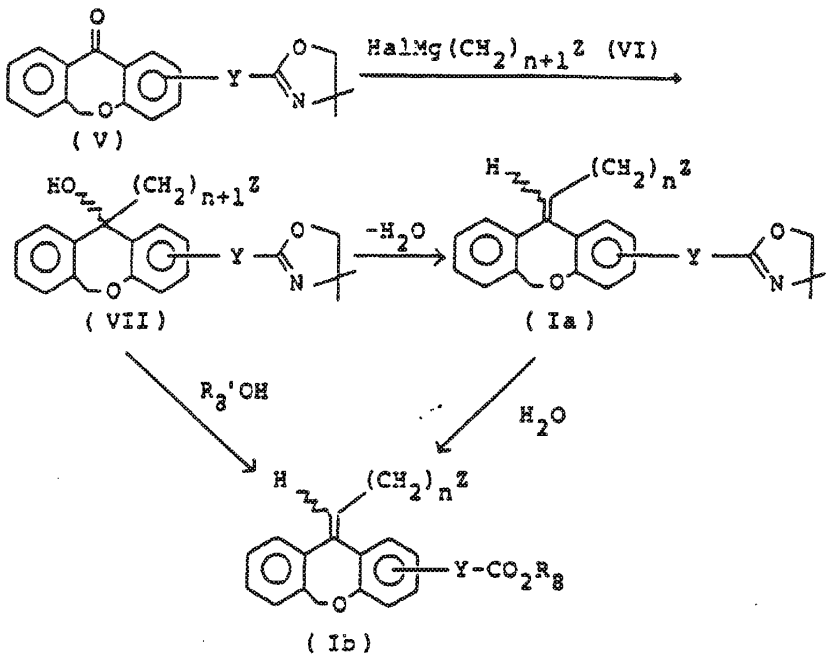
(V)

In the formula, Y has the same meaning as previously defined, and Compound (IIa) is included in Compound (II) (compounds with an alphabet suffix following formula number are likewise included in compounds with common formula no.)

Compound (IIa) is reacted with 1 to 5 equivalents of thionyl chloride and 1 to 5 equivalents of 2-amino-2-methyl-1-propanol on the basis of Compound (IIa) in an inert solvent such as methylene chloride, if necessary in the presence of a base such as triethylamine at a temperature of from 0°C to room temperature for 1-24 hours to form Compound (IV). Compound (IV) can also be obtained by reacting Compound (IIa) with thionyl chloride in advance and then with 2-amino-2-methyl-1-propanol.

Compound (IV) is reacted with 1-5 equivalents of thionyl chloride in an inert solvent such as methylene chloride, toluene and benzene at a temperature of from 0°C to room temperature for l - 24 hours to form Compound (V).

Compounds (Ia) and (Ib) can be prepared from Compound (V) according to the following reaction scheme.



In the formulae, Y, Z, and n have the same meanings as previously defined, R_8 is hydrogen or a lower alkyl group, R'_8 is a lower alkyl group and Hal is halogen.

As used herein, the term lower alkyl has the same meaning as that of lower alkyl in each group of formula (I). Halogen includes chlorine, bromine and iodine.

Compound (V) is reacted with 1 - 5 equivalents of Compound (VI) in an inert solvent such as tetrahydrofuran and diethyl ether under atmosphere of an inert gas such as nitrogen and argon to form Compound (VII). The reaction is carried out at a temperature of from 0°C to room temperature and is usually completed in 1 - 24 hours.

Compound (VII) is reacted with 1 - 5 equivalents of thionyl chloride or phosphoryl chloride in an inert solvent such as methylene chloride in the presence of a base such as pyridine to form Compound (Ia). The reaction is carried out at a temperature of from 0°C to room temperature and is completed in 1 - 24 hours.

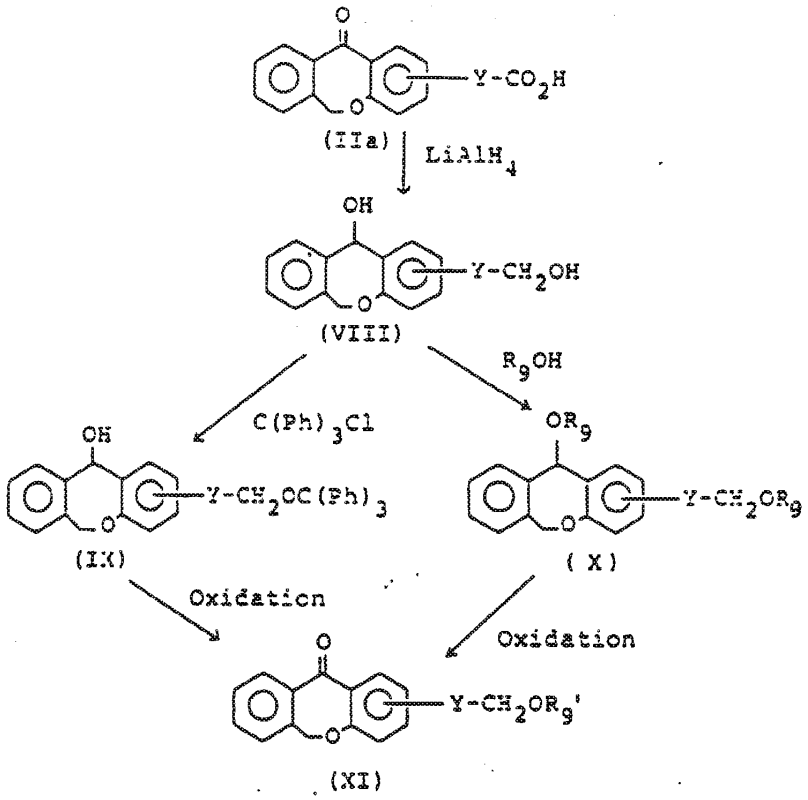
Compound (Ia) is incubated in an alcohol containing water, such as aqueous methanol solution, in the presence of an appropriate acidic catalyst such as p-toluenesulfonic acid at a temperature of from room temperature to the boiling point of the solvent to form Compound (Ib) wherein R_8 is H. The reaction is completed in 1 - 24 hours.

Compound (VII) is incubated in an alcohol $R_8'OH$ in the presence of an appropriate acidic catalyst such as p-toluenesulfonic acid at a temperature of from room temperature to the boiling point of the solvent to form Compound (Ib) wherein R_8 is a lower alkyl. The reaction is completed in 1 - 24 hours.

Process B

[Synthesis of Compound (I) wherein X is =CH- (Part 2)]

The carboxy group of a compound represented by the formula (IIa) can be converted to a lower alkoxymethyl group or a trityloxymethyl group according to the following reaction scheme.



In the formulae, Y has the same meaning as previously defined, R_9 is a lower alkyl group and R_9' is a trityl group or a lower alkyl group. The term lower alkyl has the same meaning as that of lower alkyl in each group in formula (I).

Compound (IIa) is reduced with 1 - 5 equivalents of lithium aluminium hydride in tetrahydrofuran at a temperature of from 0°C to room temperature for 1 - 24 hours to form Compound (VIII).

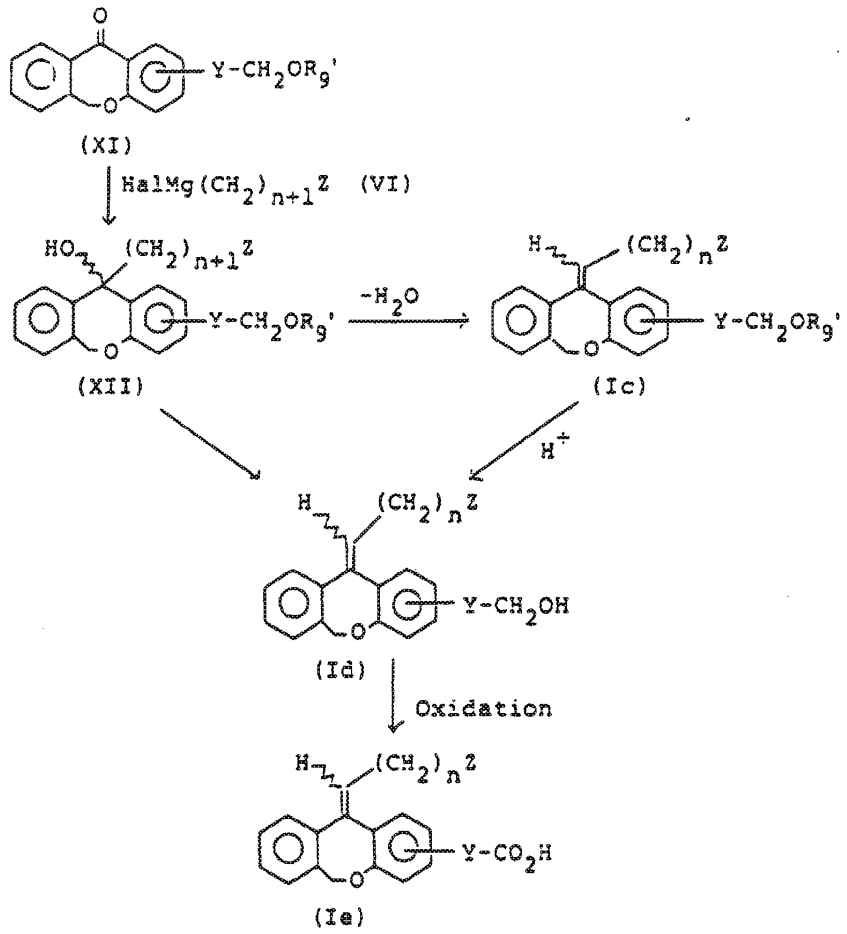
Compound (VIII) is reacted with 1 - 5 equivalents of trityl chloride in pyridine at a temperature of from room temperature to 100°C for 1 - 24 hours to form Compound (IX).

Compound (IX) is oxidized with 1 - 5 equivalents of an appropriate oxidizing agent such as potassium permanganate and pyridinium chlorochromate in an inert solvent such as methylene chloride and acetone to form Compound (XI) wherein R_9 is trityl. The reaction is carried out at a temperature of from 0°C to the boiling point of the solvent and is completed in 1 - 24 hours.

Compound (VIII) is incubated in an alcohol of R_9 OH in the presence of an appropriate acidic catalyst such as sulfuric acid at a temperature of from room temperature to the boiling point of the solvent to form Compound (X). The reaction is usually completed in 1 - 24 hours.

Compound (X) is oxidized with 1 - 5 equivalents of an appropriate oxidizing agent such as Jones reagent in an inert solvent such as acetone to form Compound (XI) wherein R_9' is a lower alkyl. The reaction is carried out at a temperature of from 0°C to the boiling point of the solvent and is usually completed in 1 - 24 hours.

The compounds represented by the formulae (Ic) and (Id) and if desired, the compound represented by the formula (Ie) can be synthesized from Compound (XI) according to the following reaction scheme.



In the formulae. Y, Z, R_9', n and Hal have the same meanings as previously defined.

Compound (XI) is reacted with Compound (VI) which is Grignard reagent according to the same manner as in the reaction step from Compound (V) to Compound (VII) in Process A to form Compound (XII).

Compound (XII) is subjected to reaction according to the same manner as in the reaction step from Compound (VII) to Compound (Ia) in Process A to form Compound (Ic).

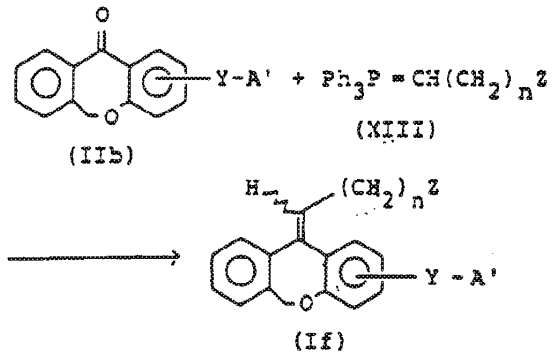
Compound (Ic) is incubated in a solvent containing water such as aqueous dioxane in the presence of an appropriate acidic catalyst such as p-toluenesulfonic acid at a temperature of from room temperature to the boiling point of the solvent to form Compound (Id). The reaction is usually completed in 1 - 24 hours.

Compound (Id) can also be obtained in one step by incubating Compound (XII) in a solvent containing water such as aqueous dioxane in the presence of an appropriate acidic catalyst such as sulfonic acid at a temperature of from room temperature to the boiling point of the solvent. The reaction is usually completed in 1 - 24 hours.

If desired, Compound (Id) is oxidized with 1 - 5 equivalents of an appropriate oxidizing agent such as Jones reagent in an inert solvent such as acetone to form Compound (Ie). The reaction is carried out at a temperature of from 0°C to the boiling point of the solvent and is usually completed in 1 - 24 hours.

Process C

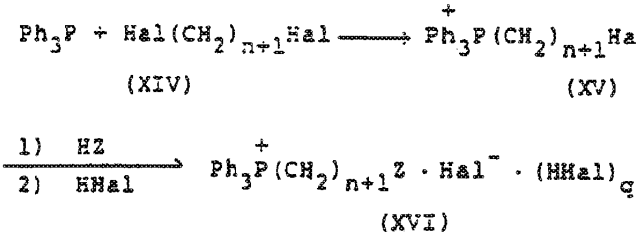
[Synthesis of Compound (I) wherein X is =CH- (Part 3)].



In the formulae, Y, Z, and n have the same meanings as previously defined. A' represents the groups falling within the definition of A but lower alkanoyl group.

Compound (IIb) is reacted with 1 - 5 equivalents of Compound (XIII) in an inert solvent such as tetrahydrofuran under atmosphere of an inert gas such as nitrogen and argon at a temperature of from 0°C to room temperature for 1 - 24 hours to form Compound (I_f).

Compound (XIII) which is ylide, can be prepared according to the method described in C.A. 63 16366a (1965).



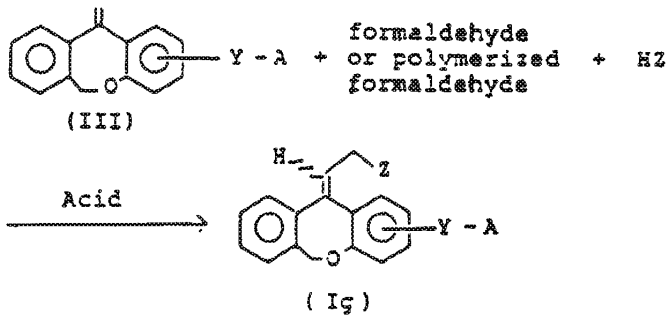
In the formulae, Hal, n and Z have the same meanings as previously defined and q is 1 or 2. Compound (XIV) is reacted with an equivalent of triphenylphosphine in toluene at reflux of the solvent for 1 - 24 hours to form Compound (XV).

Compound (XV) is reacted with 1 - 5 equivalents of HZ in ethanol at reflux of the solvent for 1 - 24 hours and excess HZ is distilled away under reduced pressure. After the addition of 1 - 5 equivalents of HHal on the basis of Compound (XV), the mixture is incubated at a temperature of from 0°C to the boiling point of the solvent for 1 - 24 hours to form Compound (XVI) which is Wittig reagent.

Compound (XVI) is treated with 1 - 2 equivalents of an appropriate base such as n-butyl lithium in an inert solvent such as tetrahydrofuran under atmosphere of an inert gas such as nitrogen and argon to form ylide (XIII). The reaction is carried out at -78°C ~ room temperature and is usually completed in 1 - 24 hours.

Process D

[Synthesis of Compound (I) wherein X is =CH- (Part 4)]



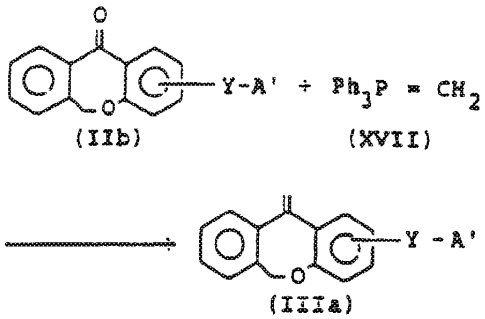
In the formulae, Y, Z and A have the same meanings as previously defined.

The process is known as Prince reaction [New Experimental Chemical Course (Maruzen), Vol. 14, Synthesis and Reaction of Organic Compound III, page 1375 (1977)].

Compound (III), 1 to 5 equivalents of formaldehyde and 1 to 5 equivalents of HZ are subjected to reaction in an inert solvent such as tetrachloroethane in the presence of an acid or reaction in an acid as such serving as a solvent under atmosphere of an inert gas such as nitrogen and argon to yield Compound (Ig).

The formaldehyde or polymerized formaldehyde includes p-formaldehyde, trioxane, etc. The acid includes acetic acid, trichloroacetic acid, trifluoroacetic acid, etc. The reaction is carried out at a temperature of from room temperature to the boiling point of the solvent and is completed in 1 - 24 hours.

Compound (III) which is the starting material can be prepared according to the process described in JP-A-21679/83, as shown below.



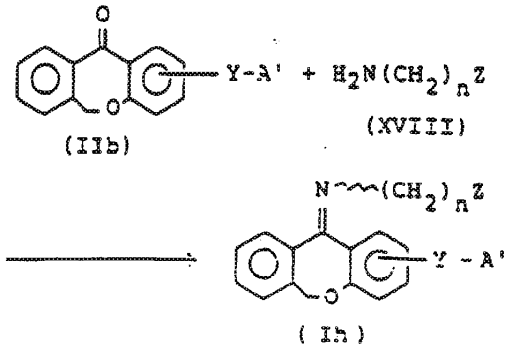
That is, Compound (IIb), 1 to 5 equivalents of methyltriphenylphosphonium bromide and 1 to 5 equivalents of n-butyl lithium on the basis of Compound (IIb) are subjected to reaction in an inert solvent at from -78°C to room temperature for 1 to 5 hours to yield ylide (XVII) which is reacted with an equivalents of Compound (IIb) in an inert solvent at from -78°C to room temperature under atmosphere of an inert gas for 1 to 24 hours to yield Compound (IIIa).

The inert gas includes nitrogen, argon, etc. and the inert solvent includes tetrahydrofuran, etc.

The group A' in Compound (IIIa) can easily be converted to a lower alkanoyl group and therefore, Compound (III) can easily be prepared.

Process E

[Synthesis of Compound (I) wherein X is = N-]



Compound (IIb) and 1 to 10 equivalents of Compound (XVIII) are subjected to reaction in an inert solvent such as benzene in the presence of 1 to 10 equivalents of titanium tetrachloride at from 0°C to the boiling point of the solvent under atmosphere of an inert gas such as nitrogen and argon for 1 to 48 hours to yield Compound (Ih).

Table 1 shows examples of Compound (I) or pharmaceutically acceptable salts thereof and Table 2 shows the structural formula thereof.

Table 3 shows characteristic signals in NMR and Table 4 shows retention time in HPLC.

1	Methyl cis-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate Methyl trans-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate
2	Ethyl cis-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate Ethyl trans-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate
3	Cis-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid Trans-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid
4	Methyl cis-11-(4-dimethylaminobutylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate Methyl trans-11-(4-dimethylaminobutylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate
5	Cis-11-(4-dimethylaminobutylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid Trans-11-(4-dimethylaminobutylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid
6	Methyl cis-11-(3-pyrrolidinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate Methyl trans-11-(3-pyrrolidinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate

7	Cis-11-(3-pyrrolidinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid Trans-11-(3-pyrrolidinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid
8	Methyl cis-11-[2-(4-methylpiperazino)-ethylidene]-6,11-dihydrodibenz[b,e]oxepin-2-acetate Methyl trans-11-[2-(4-methylpiperazino)-ethylidene]-6,11-dihydrodibenz[b,e]oxepin-2-acetate
9	Cis-11-[2-(4-methylpiperazino)-ethylidene]-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid Trans-11-[2-(4-methylpiperazino)-ethylidene]-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid
10	Methyl cis-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-3-acetate Methyl trans-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-3-acetate
11	Cis-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid Trans-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid

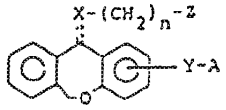
12	Methyl syn-11-(2-dimethylamincethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetate Methyl anti-11-(2-dimethylamincethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetate
13	syn-11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid Anti-11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid
14	Methyl syn-11-(2-diethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetate Methyl anti-11-(2-diethylamincethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetate
15	syn-11-(2-diethylamincethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid Anti-11-(2-diethylamincethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid

16	Methyl anti-11-(3-dimethylaminopropyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetate Methyl anti-11-(3-dimethylaminopropyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetate
17	anti-11-(3-dimethylaminopropyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid Anti-11-(3-dimethylaminopropyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid
18	Methyl cis-2-[11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionate Methyl anti-2-[11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionate
19	anti-2-[11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionic acid Anti-2-[11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionic acid
20	Methyl anti-11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-3-acetate Methyl anti-11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-3-acetate
21	anti-11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid Anti-11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid

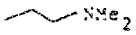
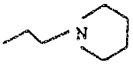
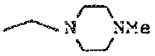
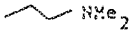
22	Methyl [illegible]-11-(3-dimethylaminopropyl)imino-6,11-dihydrodibenz[b,e]oxepin-3-acetate Methyl anti-11-(3-dimethylaminopropyl)imino-6,11-dihydrodibenz[b,e]oxepin-3-acetate
23	[illegible]-11-(3-dimethylaminopropyl)imino-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid Anti-11-(3-dimethylaminopropyl)imino-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid
24	11-(3-Dimethylaminopropylidene)-2-(4,4-dimethyl-2-oxazoline-2-yl)-6,11-dihydrodibenz-[b,e]oxepin
25	Methyl cis-11-(3-methylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate Methyl trans-11-(3-methylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate
26	Cis-11-(3-methylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acatic acid Trans-11-(3-methylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid
27	Methyl cis-11-(3-aminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate Methyl trans-11-(3-aminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate
28	Cis-11-(3-aminopropylidene)-6,11-dihydrodibenz-[b,e]oxepin-2-acetic acid Trans-11-(3-aminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid

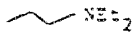
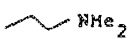
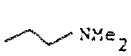
3'	Fumarate · 3/2 hydrate of Compound 3 (trans form 95%)
9'	Fumarate · 2/3 hydrate of Compound 9 (trans form 88%)
19'	Sodium salt 1 hydrate of Compound 19 (anti form 99%)

Table 2



Me : methyl group
Ph : phenyl group
Et : ethyl group

Compound No.	X	-Y-A	-(CH$_2$)$_n$-Z
1	CH	2-CH$_2$COOMe	
2	"	2-CH$_2$COOEt	"
3	"	2-CH$_2$COOH	"
4	"	2-CH$_2$COOMe	
5	"	2-CH$_2$COOH	"
6	"	2-CH$_2$COOMe	
7	"	2-CH$_2$COOH	"
8	"	2-CH$_2$COOMe	
9	"	2-CH$_2$COOH	"
10	"	3-CH$_2$COOMe	"
11	"	3-CH$_2$COOH	"
12		2-CH$_2$COOMe	
13	"	2-CH$_2$COOH	"

Compound No.	X	-Y-A	$-(CH_2)_n-Z$
14	N	2-CH_2COOMe	
15	"	2-CH_2COOH	"
16	"	2-CH_2COOMe	
17	"	2-CH_2COOH	"
18	"	2-$CH(CH_3)COOMe$	
19	"	2-$CH(CH_3)COOH$	"
20	"	3-CH_2COOMe	"
21	"	3-CH_2COOH	"
22	"	3-CH_2COOMe	
23	"	3-CH_2COOH	"
24	CH	2- 	

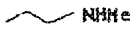
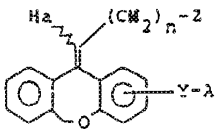
Compound No.	X	-Y-A	$-(CH_2)_n-Z$
25	"	2-CH_2COOMe	
26	"	2-CH_2COOH	"
27	"	2-CH_2COOMe	
28	"	2-CH_2COOH	"

Table 3



Compound	Chemical sift of Ha proton (ppm)		Measure solvent
	Cis	Trans	
1	5.69	6.06	A
2	5.70	6.07	A
3	5.66	6.00	B
4	5.66	6.02	A
5	5.67	6.02	B
6	5.69	5.99	A
7	5.60	5.92	A
8	5.84	6.17	A
9	5.72	6.05	B

Compound	Chemical sift of Ha proton (ppm)		Measure solvent
	Cis	Trans	
25	5.63	-	A
26	5.65	-	B
27	5.68	-	A
28	5.67	-	B

A = $CDCl_3$

B = DMSO-d_6

Table 4

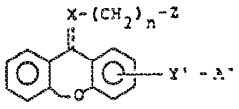
Compound	Retention time in HPLC (Minutes)		Eluent
	Cis	Trans	
3	9.93	7.46	B
5	11.10	8.40	B
7	10.50	8.00	B
9	11.20	8.93	B
26	10.77	-	B
28	10.65	-	B

Instrument: SHIMAZU LC-3A
Column Yamamurakagaku YMC A-312

A 0.01M PIC B-8 in 54.3% MeOH
B 0.01M PIC B-9 in 61,3% MeOH
C 0.01M PIC B-8 in 66.0% MeOH

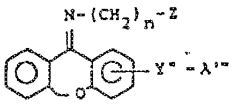
*PIC : PIC reagent (Produced by Water Associates)
Pressure : 85 - 95 kg/cm^2
Temperature : room temperature

Compound (I) has both an antiallergic activity and antiinflammatory activity. Among Compound (I), the compound represented by the formula (I') has strong antiallergic activity and the compound represented by the formula (II') has strong antiinflammatory activity.



(I')

In the formula, X, n and Z are as previously defined. -Y'-A' is -Y-A when X is = CH and is -Y-A which is bound at 2 position of the mother nucleus when X is = N-, and Y and A are as previously defined.



(II")

In the formula, n and Z are as previously defined: Y' is -CH_2- or -CHR_3- substituted at 2 or 3 position of the mother nucleus wherein R_3 is a lower alkyl; A" is, a a carboxyl, a lower alkoxycarbonyl, a -$CONR_1R_2$ wherein R_1 and R_2 are the same or different and are hydrogen atom or -CONHOH.
the preferred compounds according to the invention are the compounds of formula (I) as above defined wherein A is a member selected from the group consisting of lower alkoxycarbonyl, (-$CONR_1R_2$), carboxyl ; Y is bound at 2-position of the mother nucleus ; X is member selected from the group consisting of = N-and =CH- ; n is 1 or 2 ; and Z is a member selected from the group consisting of dimethylamino, diethylamino, methylamino, amino, morpholino and thiomorpholino.
Of those particular compounds, those of formula (I) wherein Y is a member selected from the group

and m is 1 or 2, are preferred and more particulary these of formula (I) wherein X is = CH- and A is a carboxyl. The most preferred compounds are those of formula (I) wherein -Y-A is a member selected from the group consisting of carboxymethyl, X is = CH-, n is 2 and Z is a member selected from the group consisting of dimethylamino, diethylamino methylamino, amino, morpholino and thiomorpholino.

The antiallergic activity and antiinflammatory activity of Compound (I) are described below:

Test for antiallergic activity:

Antiallergic activity was investigated by a homologous PCA (passive cutaneous anaphlaxis) of rats for 48 hours, where Wistar male rats having body weights of 180 to 220 g were used for sampling of antiserum and Wistar male rats having body weights of 120 140 g were used for the PCA test.

A) Preparation of anti EWA rat serum

Anti-egg white albumin (EWA) rat serum was prepared according to Stotland and Share's method [Canad. J. Physiol. Pharmacol. 52, 1114 (1974)]. That is, 1 mg of EWA was mixed with 20 mg of aluminum hydroxide get and 0.5 ml of mixed vaccine of pertussis, diphtheria and tetanus, and the mixture was subcutaneously administered in four portions into rat's footpad. After 14 days, blood was sampled from the carotid artery, and the serum was separated from the sampled blood, and preserved under freezing at -80°C. The potency of the antiserum in the homologous PCA for 48 hours was 1 : 32.

B) Homologous PCA test of rats for 48 hours

Groups each consisting of 3 rats were used, and 0.05 ml of anti-EWA rat serum diluted with a physiological saline solution to 8 times as much was incutaneously injected each at two positions of depilated back to make the animals passively sensitised. After 47 hours, the compound of the present invention, or its solution (physiological saline solution or CMC solution) was orally administered. One hour thereafter, 0.5 ml/100 g of 1% Evan's blue physiological saline solution containing 2 mg of the antigen EWA was administered into the tail vein, and 30 minutes thereafter, the animals were sacrificed by exsanguination. Then, the skins were stripped and the amount of leaked pigment at the blue-dyed parts was measured according to the Katayama et at method [Microbiol. Immunol. 22, 89 (1978)]. That is, the blue-dyed parts were cut out by scissors, and placed in test tubes containing I ml of IN KOH and incubated at 37°C for 24 hours. Then, 9 ml of a mixture of 0.6N phosphoric acid and acetone (5 :13) was added thereto, and the mixture was shaked and centrifuged at 2,500 rpm for 10 minutes. Absorbancy of the supernatant at 620 µm was measured, and the amount of leaked pigment was quantitatively determined by the calibration curve prepared in advance. An average of measurements at the two position was made a value for one zooid, and inhibition rate for the individual zooid was calculated by the following formula

$$\text{Inhibition rate (\%)} = \frac{\text{Average leaked amount of solvent-administered group} - \text{Leaked amount of test compound-administered group}}{\text{Average leaked amount of solvent-administered group}} \times 100$$

Cases where, the inhibition rate is 50% or higher, were regarded as positive PCA inhibition activity, and the minimum administered dosage, where a positive case was observed in at least one of three zooids was regarded as minimum effective dosage (MED). The results are shown in Table 5.

Acute toxicity test:

Groups each consisting of 3 dd, male mice having body weights of 20 ± 1 g were used, and the compound of the present invention was administered orally (po: 300 mg/kg) or intraperitoneally (ip: 100 mg/kg). Mortality 7 days after the administration was observed to obtain MLD (minimum lethal dosage). The results are shown in Table 5.

Antiinflammatory activity test:

Antiinflammatory activity was examined according to Rat carrageenin paw edema [J. Pathol. 104. 15-29 (1971)]. Groups each consisting of three Wistar male rats weighing 150 g were used. The test compound was suspended in 0.3% aqueous CMC solution and the suspension was given orally. Sixty minutes later, 0.1 ml of 0.1% carrageenin solution was subcutaneously injected in a hind paw to form carageenin paw edema.

The volume of paw was measured before the administration and 3 hours after the administration of carageenin with plethysmometer.

The ratio of the volume 3 hours after the administration to that before the administration of carageenin was calculated and each ratio is compared with the ratio of control group (0.3% CMC solution was administered) to give the edema inhibiting percentage. The results are shown in Table 6.

Table 5

Compound	Acute toxicity (MLD) mg/kg		Antiallergic Activity Number of positive zooids in one group of 3 zooids Dosage mg/kg						M E D mg/kg
	po	ip	100	10	1	0.1	0.01	0.001	
3' (trans)	>300	>100	3/3	3/3	3/3	1/3	0/3	-	0.1
3 (trans)	>300	>100	2/3	2/3	3/3	3/3	0/3	0/3	0.1
3 (cis)	>300	>100	3/3	3/3	3/3	3/3	1/3	0/3	0.01
5 (cis:trans = 92 : 8)	>300	>100	3/3	3/3	2/3	1/3	0/3	-	0.1
9' (cis:trans = 12 : 88)	>300	>100	3/3	3/3	2/3	0/3	-	-	1

13 (: anti = 8 : 92)	300>	100>	3/3	3/3	0/3	-	-	-	10
15 (: anti = 2 : 98)	300>	100>	3/3	2/3	3/3	0/3	-	-	1
17 (: anti = 3 : 97)	300>	100>	3/3	2/3	1/3	0/3	-	-	1
19' (anti)	300>	100>	3/3	3/3	2/3	0/3	-	-	1

Compound No.	Carrageenin paw edema inhibiting percentage (%) (Average value in one group of 3 rats. 100 mg kg oral administration)
13	51.6
15	50.2
17	38.7
18	63.1
21	46.0
23	24.1

As is evidenced in Tables 5 and 6. Compound (I) and pharmaceutically acceptable salt thereof have PCA inhibiting activity and or carageenin paw edema inhibiting activity.

PCA inhibiting activity is believed to be on the basis of an activity inhibiting liberation of chemical mediator such as histamine from fat skin cell. Therefore. Compound (I) and pharmaceutically acceptable salts thereof are believed to be useful for treating an allergic disease such as bronchus asthma which is caused by trachea contracting activity of chemical mediator such as histamine.

On the other hand, carageenin paw edema inhibiting activity is believed to be on the basis of prostaglandin biosynthesis inhibiting activity. Thus. Compound (I) and pharmaceutically acceptable salts thereof are believed to be useful for treating an acute inflammation and rheumatism which are ascribed to excessive prostaglandin.

Compound (I) includes a compound having both antiallergic and antiinflammatory activities described above which is useful for the treatment of allergic diseases accompanied by inflammation.

In view of the pharmacological activity of Compound (I). Compound (I) can be used in various medicament forms for the administration purposes.

The present medicament composition can be prepared by uniformly mixing an effective amount of a free Compound (I) or a pharmaceutically acceptable salt thereof as an active component with a pharmaceutically acceptable carrier or excipient. The carrier can take a wide range of forms in accordance with a desirable medicament form for the administration. These medicament compositions are desirably in a unit dosage form suitable for the oral administration or injection administration. In the preparation of a composition in the oral dosage form, any useful, pharmaceutically acceptable carrier can be used. For example, an oral liquid preparation such as a suspended medicament or syrup medicament can be prepared using water; sugars such as sucrose, sorbitol, fructose, etc.; glycols such as polyethylene glycol. propylene glycol, etc.; oils such as sesame oil, olive oil, soybean oil, etc.; antiseptics such as alkyl parahydroxybenzoate, etc.; and flavors such as strawberry flavor, peppermint, etc. Powder, pills, capsules and tablets can be prepared using an excipient such as lactose, glucose, sucrose. mannitol, etc.; a disintegrator such as starch, sodium alginate, etc.; a lubricant such as magnesium stearate, talc, etc.; a binder such as polyvinyl alcohol, hydroxypropylcellulose, galatin, etc.; a surfactant such as fatty acid esters: and a plasticizer such as glycerine, etc. Tablets and capsules are the most useful oral unit dosage forms because of easy administration. To prepare tablets and capsules. solid carriers for medicament are used. Injection solution can be prepared using a carrier consisting of a salt solution, a glucose solution or a mixture of the salt solution and the glucose solution. The effective dosage of Compound (I) is 1 to 20 mg/kg/day for a human being, and number of administration is 3 to 4 per day.

Examples and Reference Examples are given below:

Reference example I

(Raw material I) Methyl 11-oxo-6,11-dihydrodibenz[b,e] oxepin-2-carboxylate

In this example, 348.9 g of sodium salt of methyl p-hydroxybenzoate, 402.4 g of phthalide and 200 g of sodium chloride are mixed with one another and stirred at 150°C for 6 hours. After completion of the reaction, the mixture is cooled until the temperature is brought back to room temperature, 4 t of aqueous 10 % acetic acid solution is added thereto and the mixture is allowed to stand at room temperature overnight. After stirring the mixture at room temperature for 3 hours, deposited crystals are separated by filtration, and 6 t of water is added thereto. After stirring the mixture at room temperature for 30 minutes, the deposited crystals are separated by filtration. After the addition of 31 of toluene to the crystals, the mixture is stirred at room temperature for one hour. The crystals are separated by filtration and dried over heating under reduced pressure to yield 393.9 g of 2-(4-methoxycarbonylphenoxy) methyl benzoic acid.

IR (KBr disk): 3400, 1700, 1610, 1260, 1235 cm^{-1}

The thus obtained 2-(4-methoxycarbonylphenoxy) methyl benzoic acid (392.7 g) is suspended in 5.0 l of methylene chloride and 266.0 g of trifluoroacetic anhydride is added thereto. After stirring the mixture at room temperature for one hour, 19.4 g of boron trifluoride-ethylether complex is added thereto and the mixture is stirred at room temperature for two hours. The reaction solution is poured into ice water. After an organic solvent layer is separated from the mixture, the organic layer is washed with diluted aqueous sodium hydroxide solution and water, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain 335.3 g of methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate as a white crystal

Melting point and elementary analysis are shown in Table 7.

IR (KBr disk): 1710, 1650, 1610, 1250, 1010 cm^{-1}
NMR ($CDCl_3$, δ, ppm): 3.84(s, 3H), 5.14(s, 2H), 6.87-8.93(m, 7H)

Reference examples 2 - 5

(Raw material 2) 11-Oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid
(Raw material 3) 11-Oxo-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid
(Raw material 4) 2-(11-Oxo-6,11-dihydrodibenz[b,e]oxepin-2-yl)-propionic acid
(Raw material 5) 3-(11-Oxo-6,11-dihydrodibenz[b,e]oxepin-2-yl)-propionic acid

Raw materials 2 - 5 are produced by respectively substituting p-hydroxyphenyl acetic acid, m-hydroxyphenyl acetic acid, 2-(p-hydroxyphenyl)-propionic acid and 3-(p-hydroxyphenyl)-propionic acid for methyl p-hydroxybenzoate in Reference example I.

Melting points and elementary analyses thereof are shown in Table 7.

Reference example 6

(Raw material 6) Methyl 11-methylene-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate

In 100 ml of tetrahydrofuran is suspended 25 g of methyltriphenylphosphonium bromide and 40 ml of 1.6 N-n-butyl lithium hexane solution is dropwise added thereto under a nitrogen atmosphere and ice-cooling. After stirring the mixture under ice-cooling for 30 minutes, a solution obtained by dissolving 15 g of methyl 11-oxo-6,11-dihydrodibenz[b,e] oxepin-2-carboxylate in 250 ml of tetrahydrofuran is dropwise added thereto and the mixture is stirred at room temperature for two hours. The solvent is distilled away under reduced pressure and the residue is purified by column chromatography on silica gel (eluent: hexane : ethyl acetate = 3 :l) to obtain 3.7 g of the desired product as a colorless oily matter.

NMR ($CDCl_3$, δ, ppm): 3.83(s, 3H), 5.15(s, 2H), 5.29 (s, 1H), 5.74(s, 1H), 6.69-8.22(m, 7H)

Melting point and elementary analysis are shown in Table 7.

Reference example 7

(Raw material 7) Methyl 11-methylene-6,11-dihydrodibenz[b,e]oxepin-2-acetate

The desired product is obtained by substituting 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid for methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate in Reference example 6.

Colorless oily matter

NMR ($CDCl_3$, δ, ppm): 3.48(s, 2H), 3.61(s, 3H), 5.05 (s, 2H), 5.20(s, IH), 5.62(s, IH), 6.59-7.43 (m, 7H)
IR (neat, cm^{-1}): 2950, 1740, 1615, 1490, 1010

Melting point and elementary analysis are shown in Table 7.

Reference example 8

(Raw material 8) 11-Methylene-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid

To a mixed solvent of 200 ml of methanol and 50 ml of 2N-aqueous sodium hydroxide solution is added 2.9 g of methyl 11-methylene-6,11-dihydrodibenz[b,e]oxepin-2-acetate (raw material 7, Reference example 7) and the mixture is heated at reflux for two hours. After allowing the mixture to stand for cooling, the mixture is concentrated under reduced pressure, and the pH of the mixture is adjusted to 1.0 with aqueous 4N-hydrochloric acid solution. The mixture is extracted with 500 ml of ethyl acetate, then the organic layer is washed with aqueous 1N-hydrochloric acid solution and saturated aqueous sodium chloride solution in order and dried over anhydrous sodium sulfate The solvent is distilled away under reduced pressure and the resultant crude product is crystallized from hexane to obtain 2.7 g of the desired product as a white solid.

NMR (DMSO-d_6 + D_2O, δ, ppm): 3.45(s, 2H), 5.02(s, 2H), 5.16(s, IH), 5.60(s, IH), 6.45-7.44(m, 7H)

Melting point and elementary analysis are shown in Table 7.

Reference example 9

(Raw material 9) Methyl 11-methylene-6,11-dihydrodibenz[b,e]oxepin-3-acetate

The desired product is obtained by substituting 11-oxo-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid for methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate in Reference example 6.

Reference example 10

(Raw material 10) 11-Methylene-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid

The desired product is obtained by substituting methyl 11-methylene-6,11-dihydrodibenz[b,e]oxepin-3-acetate for methyl 11-methylene-6,11-dihydrodibenz[b,e]oxepin-2-acetate in Reference example 8.

Table 7

Raw material	Melting point (°C)	Elementary analysis (%) or mass spectrum		
1	128 - 129	as $C_{16}H_{12}O_4$		
			C	H
	(Isopropyl ether)	Calculated	71.63	4.51
		Found	71.55	4.48
2	130 - 132	as $C_{16}H_{12}O_4$		
			C	H
	(Ethyl acetate)	Calculated	71.63	4.51
		Found	71.86	4.55

Raw material	Melting point (°C)	Elementary analysis (%) or mass spectrum
3	111 - 114 (Ethyl acetate)	as $C_{16}H_{12}O_4$ C H Calculated 71.63 4.51 Found 71.53 4.66
4	Syrup	as $C_{17}H_{14}O_4$ (M + 282)
5	144 - 145 (Water)	as $C_{17}H_{14}O_4$ C H Calculated 72.33 5.00 Found 72.45 5.20
6	Syrup	as $C_{17}H_{14}O_3$ (M + 266)
7	Syrup	as $C_{18}H_{16}O_3$ (M + 280)
8	162 - 163 (Water)	as $C_{17}H_{14}O_3$ C H Calculated 76.68 5.30 Found 76.29 5.16

Reference example 11

(Reagent I) (3-Dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide

In this example, 350.0 g of triphenylphosphine and 270.0 g of dibromopropane are suspended in 700 ml of toluene and the suspension is heated at reflux for 25 hours. After allowing the suspension to stand for cooling, the formed product is separated by filtration and washed with 2 l of toluene to obtain 550.0 g of (3bromopropyl)-triphenylphosphonium bromide hydrobromide having m.p. 233-234°C.

Then, 100.0 g of (3-bromopropyl)-triphenylphosphonium bromide hydrobromide is suspended in 500 ml of ethanol and 300 ml of 50 % aqueous dimethylamine solution is added thereto. After heating the mixture at reflux for 10 minutes, the mixture is allowed to stand for cooling. The solvent is distilled away under reduced pressure and the resultant crude product is recrystallized from ethanol to obtain 64.0 g of the desired product having the physicochemical properties as identified in Table 8.

Reference examples 12 - 14

(Reagent 2) (3-Diethylaminopropyl)-triphenylphosphonium bromide hydrobromide · 1/3 hydrate

(Reagent 3) (4-Dimethylaminobutyl)-triphenylphosphonium bromide hydrobromide
(Reagent 4) (3-Pyrrolidinopropyl)-triphenylphosphonium bromide hydrobromide · 1/2 hydrate

The above-captioned compounds are prepared according to the same manner as in Reference example II and the physicochemical properties are shown in Table 8.

Table 8

Reagent	Melting point (°C)	Elementary analysis (%)			
1	287 - 289 (Ethanol)	as $C_{23}H_{28}NPBr_2$	C	H	N
		Calculated	54.24	5.54	2.75
		Found	54.12	5.63	2.93
2	228 - 230 (Isopropanol)	as $C_{25}H_{32}NPBr_2 \cdot 1/3H_2O$	C	H	N
		Calculated	55.33	6.05	2.58
		Found	55.31	6.19	2.68
3	255 - 257 (Isopropanol)	as $C_{24}H_{30}NPBr_2$	C	H	N
		Calculated	55.09	5.78	2.68
		Found	55.04	5.91	2.62
4	291 - 293 (Ethanol)	as $C_{25}H_{30}NPBr_2 \cdot 1/2H_2O$	C	H	N
		Calculated	55.17	5.74	2.57
		Found	55.18	5.95	2.66

Example 1

11-(3-Dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid (Compound 3)

In this Example, 2.2 g of 11-(3-dimethylaminopropylidene)-2-(2-hydroxyethyl-6,11-dihydrodibenz[b,e]-oxpein is dissolved in 100 ml of acetone. The Jones reagent is added to the solution until the reaction solution shows an orange color and the mixture is stirred at room temperature for one hour. Sodium bicarbonate is added thereto and an inorganic substance is removed by filtration. The solvent of the filtrate is distilled away under reduced pressure to obtain the desired product. The physicochemical properties of the product coincide with those of the product obtained in Example 17.

Example 2

Methyl 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate (Compound 1)

In this example, 48 g of (3-dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide is suspended in 200 ml of tetrahydrofuran under a nitrogen atmosphere and 80 ml of 1.6N-n-butyl lithium hexane solution is added thereto under ice-cooling. The mixture is stirred under ice-cooling for one hour. A solution obtained by dissolving 5.0 g of 11-oxo-6,11-dihydrodibenz [b,e]oxepin-2-acetic acid in 120 ml of tetrahydrofuran is dropwise added under ice-cooling. After stirring the mixture at room temperature for two hours, the solvent is distilled away under reduced pressure. Then, 200 ml of water is added to the residue and the mixture is washed with 200 ml of diethyl ether. The pH of the mixture is adjusted to 1 with aqueous 4N-hydrochloric acid solution and the mixture is washed with diethyl ether.

Then, aqueous 10N-sodium hydroxide solution is added thereto to adjust the pH of the mixture to 7 and the solvent is distilled away under reduced pressure. The resultant residue is dissolved in 400 ml of methanol and 5 g of p-toluene sulfonic acid is added thereto. After heating the mixture at reflux for two hours, the solvent is distilled away under reduced pressure. The residue is extracted with 300 ml of ethyl acetate, and the organic layer is washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution in order and dried over anhydrous sodium sulfate.

The solvent is distilled away under reduced pressure and the resultant residue is purified by column chromatography on silica gel (eluent: hexane : ethyl acetate : triethylamine = 10 : 10 : 1) to obtain 4.0 g of the desired product as a colorless oily matter.

Cis form

NMR ($CDCl_3$, δ, ppm): 2.06-2.67(m, 4H), 2.16(s, 6H), 3.46(s, 2H), 3.58(s, 3H), 5.08(bs, 2H), 5.69 (t, 1H, J = 7Hz), 6.53-7.30(m, 7H)

Trans form

NMR ($CDCl_3$, δ, ppm): 2.06-2.67(m, 4H), 2.16(s, 6H), 3.46(s, 2H), 3.58(s, 3H), 5.08(bs, 2H), 6.00 (t, 1H, J = 7Hz), 6.53-7.30(m, 7H)

Example 3

Methyl 11-(4-dimethylaminobutylidene)-6,11-dihydrodibenz[b,e]oxepin-2.acetate (Compound 4)

The desired product is obtained by substituting (4-dimethylaminobutyl)-triphenylphosphonium bromide hydrobromide for (3-dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide in Example 2.

Example 4

Methyl 11-(3-pyrrolidinopropylidene)-6-11-dihydrodibenz[b,e]oxepin-2-acetate (Compound 6)

The desired product is obtained by substituting (3-pyrrolidinopropyl)-triphenylphosphonium bromide hydrobromide·1/2 hydrate for (3-dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide in Example 2.

Example 5

Methyl 11-(3-dimethylaminopropylidone)-6,11-dihydrodibenz[b,e]oxepin-3-acetate (Compound 10)

The desired product is obtained by substituting 11-oxo-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid for 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid in Example 6.

Example 6

Methyl 11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetate (Compound 12)

In this example, 22.0 g of methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetate and 68.7 g of N,N-dimethylethylenediamine are dissolved in 700 ml of dried benzene. To the solution is dropwise added a solution of 17.2 ml of titanium

tetrachloride in 40 ml of dried benzene and the mixture is stirred at room temperature overnight. A saturated aqueous sodium bicarbonate solution is added thereto. After removing an insoluble solid by filtration, the filtrate is extracted with 500 ml of ethylacetate, and the organic layer is washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution in order, and dried over anhydrous sodium sulfate. The solvent is distilled away under reduced pressure and the residue is purified by column chromatography on silica gel with ethylacetate triethylamine (10 1) as an eluent to obtain 13.8 g of the desired product as a colorless oily matter.

NMR ($CDCl_3$, δ, ppm): 2.14(s, 6H). 2.63(t, 2H, J=6.9Hz), 3.51(s, 2H). 3.58(s, 3H), 3.38-3.80 (m, 2H). 5.04(bs, 2H). 6.56-7.60 (m, 7H)
IR (neat. cm^{-1}): 2950, 1740, 1630, 1305, 1015
Mass spectrum (m z): 352 (M^+)

Example 7

Methyl 11-(2-diethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetate (Compound 14)

The desired product is obtained by substituting N,N-diethylethylenediamine for N,N-dimethylethylenediamine in Example 6 a colorless oily matter.

Mass spectrum (m z): 380 (M^+) for $C_{23}H_{28}O_3N_2$

Example 8

Methyl 11-(3-dimethylaminopropyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetate (Compound 16)

The desired product is obtained by substituting N,N-dimethylpropylenediamine for N,N-dimethylethylenediamine in Example 6 as a colorless oily matter.

Mass spectrum (m z): 366 (M^+) for $C_{22}H_{26}O_3N_2$

Example 9

Methyl 2-[11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionate (Compound 18)

The desired product is obtained by substituting methyl 2-(11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-yl)-propionate acid for methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetate in Example 6 as a colorless oily matter.

Mass spectrum (m z): 366 (M^+) for $C_{22}H_{26}O_3N_2$

Example 10

Methyl 11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-3-acetate (Compound 20)

The desired product is obtained by substituting methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-3-acetate for methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetate in Example 6 as a colorless oily matter.

Mass spectrum (m/z): 352 (M^+) for $C_{21}H_{24}O_3N_2$

Example 11

Methyl 11-(3-dimethylaminopropyl)imino-6,11-dihydrodibenz[b,e]oxepin-3-acetate (Compound 22)

The desired product is obtained by substituting methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-3-acetate for methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetate in Example 8 as a colorless oily matter.

Mass spectrum (m/z): 366 (M-) for $C_{22}H_{26}O_3N_2$

Reference Exemple 12

Methyl-11-[2-(4-methylpiperazino)ethylidene]-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate (Compound 10)

In this example, 1,5 ml of 4-methylpiperazine and 0.37 g of p-formaldehyde are dissolved in 100 ml of tetrachloroethane. To the solution is dropwise added 5 ml of trifluoroacetic acid. After stirring the mixture at 60°C for 2 hours, a solution obtained by dissolving 1.8 g of methyl 11-methylene-6,11-dihydrodibenz[b,e]-oxepin-2-carboxylate in 30 ml of tetrachloroethane is dropwise added thereto and the mixture is stirred at 90°C for 3 hours.

The mixture is concentrated to dryness under reduced pressure and aqueous 4N-hydrochloric acid solution is added to the residue to adjust the pH to 1. After washing the solution with diethylether, aqueous 10N-sodium hydroxide solution is added thereto to adjust the pH to 13. The mixture is extracted with 200 ml of methylene chloride, washed with saturated aqueous solution chloride solution and dried over anhydrous sodium sulfate. The solvent is distilled away under reduced pressure. The residue is purified by column chromatography on silica gel (eluent: hexane: ethyl acetate : triethylamine = 5 : 5 :1) to obtain 2.2 g of the desired product as a colorless oily matter.

Cis form NMR ($CDCl_3$, δ. ppm):	2.24(s, 3H). 2.45(s, 8H), 2.94-3.32(m, 2H), 3.84(s, 3H) 5.22(bs, 2H), 5.85 (t, IH, J = 6.8Hz), 6.66-8.07(m, 7H)
Mass spectrum (m/z):	378 (M^+)
Trans form NMR ($CDCl_3$, δ, ppm):	2.24(s, 3H). 2.45(s, 8H). 2.94-3.32(m, 2H). 3.84(s, 3H), 5.22(bs, 2H). 6.22 (t, IH, J = 6.8Hz)
Mass spectrum (m/z):	378 (M^+)

Example 12

Methyl 11-[2-(4-methylpiperazino)ethylidene]-6,11-dihydrodibenz[b,e]oxepin-2-acetate (Compound 8)

The desired product is obtained by substituting methyl 11-methylene-6,11-dihydrodibenz[b,e]oxepin-2-acetate for methyl 11-methylene-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate in Reference example 12

Example 13

11-(3-Dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid (Compound 3)

The product is obtained by hydrolysis of methyl 11-(3-dimethylaminopropylidene)-6.11-dihydrodibenz-[b,e]oxepin acetate in presence of sodium hydroxide.

Cis form white crystal

Melting point:	118 - 120°C (Isopropanol)
NMR (DMSO-d_6, δ, ppm):	2.16(s, 6H), 2.30-2.60(m, 4H), 4.04(s, 2H), 5.15(bs, 2H). 5.69(1, IH. J = 7Hz). 6.73-7.40 (m, 7H)
IR (KBr disk, cm^{-1}):	3400. 1580. 1225. 1005
Mass spectrum (m z):	337 (M^+)

Elementary analysis (%): as $C_2{\cdot}H_{23}O_3N$ · monohydrate			
	C	H	N
Found	70.77	7.36	3.74
Calculated	70.96	7.09	3.94

Trans form white crystal

Melting point:	158 - 160°C (Acetonitrile)
NMR (DMS_o-d_6, δ, ppm):	2.05(s, 6H), 2.30-2.60(m, 4H), 4.04(s, 2H), 5.15(bs, 2H), 6.06(t, 1H. J = 7Hz). 6.73-7.40(m, 7H)
IR (neat. cm^{-1}):	3380. 1575. 1220. 1005

Mass spectrum (m/z): 337 (M^+)

Elementary analysis (%): as $C_{21}H_{23}O_3N$ · monohydrate			
	C	H	N
Found	71.06	6.66	3.92
Calculated	70.96	7.09	3.94

Examples 14-16

11-(4-Dimethylaminobutylidene)-6.11-dihydrodibenz[b.e]oxepin 2-acetic acid (Compound 5)

11-(3-Pyrrolidinopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-acetic acid (Compound 7)

11-[2-(4-Methylpiperazino)ethylidene)-6.11-dihydrodibenz[b.e]oxepin-2-acetic acid (Compound 9)

These products are obtained by hydrolysis in the same manner as in Example 13. The physicochemical properties are shown in Table 9.

Table 9

Compound	Melting point (°C)	Elementary analysis (%)
5	White solid 206 - 209 (Isopropanol)	Cis : Trans = 92 : 8 as $C_{22}H_{25}O_3N$ C H N Found 75.20 7.28 4.02 Calculated 75.19 7.17 3.99
9	White solid 206 - 209 (Isopropanol)	Cis : Trans = 1 : 9 as $C_{22}H_{25}O_3N$ C H N Calculated 75.19 7.17 3.99 Found 75.15 7.28 3.96

Example 18

11-(2-Dimethylaminoethyl)imino-6.11-dihydrodibenz [b.e]oxepin-2-acetic acid (Compound 13)

The desired product is obtained as a 8 : 92 mixture of syn-form and anti-form by hydrolysis in the same manner as in Example 12.

White crystal

Melting point 174 - 176°C (as 1 2 hydrate)
NMR (DMSO-d_6. δ, ppm): 2.07(s, 6H). 2.30-2.80(m, 4H). 3.47(s, 2H). 4.90-5.30(broad, 2H). 6.74-7.62 (m, 7H)
IR (K3r disk, cm^{-1}): 3330. 1573. 1370. 1010

Elementary analysis (%): as $C_{20}H_{22}N_2O_3 \cdot 1/2$ hydrate			
	C	H	N
Found	69.47	5.77	8.06
Calculated	69.14	6.67	8.06

Examples 19-23

11-(3-Dimethylaminopropyl)imino-6.11-dihydrodibenz [b.e]oxepin-2-acetic acid (Compound 15)

11-[3-(2-Dimethylaminopropyl)imino-6.11-dihydrodibenz [b.e]oxepin-2-acetic acid (Compound 17)

2-11-(2-Dimethylaminoethyl)imino-6.11-dihydrodibenz [b.e]oxepin-2-yl]-propionic acid (Compound 19)

11-(2-Dimethylaminoethyl)imino-6.11-dihydrodibenz [b.e]oxepin-3-acetic acid (Compound 21)

11-(3-Dimethylaminopropyl)imino-6.11-dihydrodibenz [b.e]oxepin-3-acetic acid (Compound 23)

The desired compounds are obtained by hydrolysis in the same manner as in Example 22. The physicochemical properties are shown in Table 10.

Table 10

Compound	Melting point (°C)	Elementary analysis (%) or Mass spectrum
15	White solid 161 - 162 (Ethyl acetate)	Anti : 98% as $C_{22}H_{26}O_3N_2$ C H N Found 72.25 7.24 7.58 Calculated 72.11 7.15 7.64
17	White solid 171 - 173 (Isopropanol)	Anti : 97% as $C_{21}H_{24}O_3N_2$ C H N Found 71.35 6.92 7.69 Calculated 71.57 6.86 7.95
19	White solid 132 - 135 (Water)	Anti > 95% as $C_{21}H_{24}O_3N_2$ C H N Found 71.39 6.99 7.91 Calculated 71.57 6.86 7.95
21	White solid 194 - 195 (Decomposition) (Methanol)	Anti > 95% as $C_{20}H_{22}O_3N_2$ C H N Found 70.87 6.80 7.93 Calculated 70.98 6.55 8.28

Compound	Melting point (°C)	Elementary analysis (%) or Mass spectrum
23	White solid 174 - 175 (Decomposition) (Isopropanol)	Anti > 95% as $C_{21}H_{24}O_3N_2$ C H N Found 71.42 7.03 8.06 Calculated 71.57 6.86 7.95

reference example 24

1 2 Furamarate · 1 5 hydrate of Compound C (Compound C')

In this example, 3.95 g of 11-(3-dimethylaminopropylidene)-6.11-dihydrobenz[b,e]oxepin-2-carboxylic acid (Compound 3) is dissolved in 100 ml of acetone and 1.42 g of fumaric acid is added thereto. The mixture is stirred at room temperature. The deposited crystals are recovered by filtration and recrystallized from isopropanol to obtain 4.15 g of the 1/2 fumarate 1/5 hydrate of the starting compound as a white solid.

Melting point: 253-254°c
Isomer purity: Trans form 99% (measured by HPLC)

Elementary analysis (%): as $C_{20}H_{21}NO_3 \cdot 1/2C_4H_4O_4 \cdot 1/5H_2O$			
	C	H	N
Found	68.74	6.35	3.61
Calculated	68.63	6.13	3.64

Examples 25-26

The products are identified in Table 11, and then physico-chemical properties are shown in Table 12.

Table 11

Compound No.	
3'	Monofumarate · 3/2 hydrate of Compound 3 (Trans form 95%)
9'	Monofumarate · 2/3 hydrate of Compound 9 (Trans form 88%)

Compound	Melting point (°C)	Elementary analysis (%)			
3'	White solid 135 - 139 (Isopropyl ether)	as $C_{25}H_{27}O_7N \cdot 3/2H_2O$	C	H	N
		Found	62.58	6.12	2.77
		Calculated	62.49	6.29	2.91
9'	White solid 108 - 110 (Isopropanol)	as $C_{27}H_{30}O_7N_2 \cdot 2/3H_2O$	C	H	N
		Found	64.15	6.47	5.24
		Calculated	64.02	6.24	5.53

Reference Example 17

Monosodium salt · monohydrate of Compound 35 (Compound 35')

In this example, 1.00 g of 11-(2-diethylaminoethyl)imino-6.11-dihydrodibenz[b.e]oxepin-2-carboxylic acid (Compound 35) is dissolved in 100 ml of methanol and 5.5 ml of 28% sodium methoxide methanol solution is added thereto. After stirring the mixture for one hour, the solvent is distilled away under reduced pressure. The residue is triturated by adding isopropylether and is recovered by filtration to obtain 0.98 g of the monosodium sal; monohydrate of the starting compound as a white solid.

Melting point: vague owing to absorption of moisture
Ratio to isomer: Syn : Anti = 1 : 1

Elementary analysis: as $C_2 \cdot H_{25}O_4N_2Na \cdot H_2O$			
	C	H	N
Found	64.23	6.62	7.01
Calculated	64.27	6.68	7.14

Example 27

The product is identified in Table 13, and its physicochemical properties are shown in Table 14.

Table 13

Compound No.		
19'	Sodium salt · monohydrate of Compound 19	(Anti form 99%)

Table 14

Compound No.	Melting point (°C)	Elementary analysis (%) as $C_{21}H_{23}O_3N_2Na \cdot H_2O$		
			C	H	N
19'	White solid 140 - 145 (Isopropyl ether)	Found	64.11	6.57	6.99
		Calculated	64.27	6.42	7.14

Example 28 Powder

A powder comprising the following components is prepared in conventional manner.

Trans-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid · monofumarate · 3/2 hydrate (Compound 3'):	30 mg
Lactose:	270 mg

Example 29 Syrup

A syrup comprising the following components is prepared in a conventional manner.

11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid (Compound 13):	300 mg
Purified sucrose:	40 g
Metryl p-oxybenzoate:	40 mg
Propyl p-oxybenzoate	10 mg
Strawberry flavor:	0.1 cc
Water is added to the above components until the total valume becomes 100 cc	

Example 30

Methyl 11-(3-methylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate (Compound 25)

The desired product is obtained by substituting (3-methylaminopropyl)-triphenylphosphonium bromide hydrobromide for (3-dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide in Example 2 as a colorless oily matter.

Mass spectrum (m/z): 337 (M^+) for $C_{21}H_{23}O_3N$

Example 31

Methyl 11-(3-aminopropylidene)-6,11-dihydrodibenz[b.e]oxepin-2-acetate (Compound 27)

The desired product is obtained by substituting (3-aminopropyl)-triphenylphosphonium bromide hydrobromide for (3-dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide in Example 2 as a colorless oily matter.

Mass spectrum (m/z): 323 (M^+) for $C_{20}H_{21}O_3N$

Examples 32-33

11-(3-Methylaminopropylidene)-6,11-dihydrodibenz[b.e]oxepin-2-acetic acid (Compound 26)

11-(3-Aminopropylidene)-6,11-dihydrodibenz[b.e]oxepin-2-acetic acid (Compound 28)

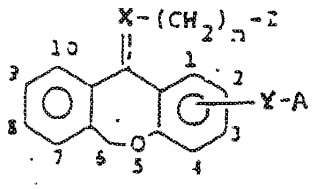
The physicochemical properties of these compounds are shown in Table 15.

Table 15

Compound	Melting point (°C)	Elementary analysis (%) or Mass spectrum			
26	White solid 235 - 238 (Water)	Cis form 100% as $C_{20}H_{21}O_3N$	C	H	N
		Found	74.01	6.60	4.01
		Calculated	74.29	6.55	4.33
28	White solid 250 (Decomposition) (Water)	Cis form 100% as $C_{19}H_{19}O_3N$	C	H	N
		Found	73.57	6.38	4.44
		Calculated	73.77	6.19	4.53

Claims

1. A dibenz[b.e]oxepin compound represented by the formula (I)



(I)

wherein

A represents a carboxyl, a straight or branched (C_1-C_6) alkoxy carbonyl group, -CONHOH or -$CONR_1R_2$ where-

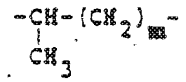
in R_1 and R_2 are the same or different and represent hydrogen atom or straight or branched (C_1-C_6) alkyl:
Y represents -(CH_2)-, -CHR_3-(CH_2)$_m$- wherein R_3 represents a straight or branched (C_1-C_6) alkyl. and m is 1, 2, 3 or 4, which is the substituent at 2- or 3- position of the mother nucleus and the left side of the group Y is bound to benzen nucleus
X represents = N-. =CH- :
n is 0, 1, 2. 3 or 4:
Z represents 4-methylpiperazino, 4-methylhomopiperazino, piperidino, pyrrolidino, thiomorpholino, morpholino or -NR_6R_7 wherein R_6 and R_7 are the same or different and represent hydrogen atom or a straight or branched (C_1-C_6) alkyl and ---- means double bond:

and the pharmaceutically acceptable salts thereof.

2. A Compound according to claim 1, wherein said salt is selected from acid addition salt, metal salt ammonium salt, organic amine addition, salt, and amino acid addition salt.

3. A compound according to claim 1, wherein A is a member selected from the group consisting of a straight or branched (C_1-C_6) alkoxycarbonyl, -$CONR_1R_2$ and carboxyl: Y is bound at 2-position of the mother nucleus; X is a member selected from the group consisting of = N- and = CH-: n is 1 or 2: and Z is a member selected from the group consisting of dimethylamino, diethylamino, methylamino, amino, morpholino and thiomorpholino.

4. A compound according to claim 3, wherein Y is a member selected from the group consisting of -(CH_2).



and m is 1 or 2.

5. A compound according to claim 4, wherein A is a carboxyl, and X is = CH-.

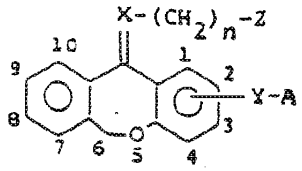
6. A compound according to claim 1, wherein -Y-A is a member selected from the group consisting of carboxymethyl, X is = CH-, n is 2 and Z is a member selected from the group consisting of dimethylamino, diethylamino, methylamino, amino, morpholino and thiomorpholino.

7. A compound according to claim 1, wherein -Y-A is 2-CH_2 COOH. X is =CH-, n is 2 and Z is dimethylamino.

8. Use of a compound as defined in anyone of claims 1 to 7 for the preparation of medicaments for the therapeutic treatment of allergic and inflammatory diseases.

Patentansprüche

1. Dibenz[b,e]oxepin-Verbindung der Formel (I)



(I)

in der

der Rest A eine Carboxylgruppe, einen gerad- oder verzweigtkettigen C_1-C_6-Alkoxycarbonylrest, einen Rest der Formel -CONHOH oder $-CONR_1R_2$ bedeutet, in der R_1 und R_2 gleich oder verschieden sind und ein Wasserstoffatom oder einen gerad- oder verzweigtkettigen C_1-C_6-Alkylrest darstellen;
Y die Bedeutung $-(CH_2)-$ oder $-CHR_3-(CH_2)_m-$ hat wobei R_3 einen gerad- oder verzweigtkettigen C_1-C_6-Alkylrest bedeutet und m den Wert 1, 2, 3 oder 4 hat, der den Substituenten in 2- oder 3-Stellung am Hauptkern darstellt, wobei die linke Seite des Restes Y an den Benzolring gebunden ist,
X die Gruppen =N- oder =CH- bedeutet,
n den Wert 0, 1, 2, 3 oder 4 hat,
Z eine 4-Methylpiperazino-, 4-Methylhomopiperazino-, Piperidino-, Pyrrolidino-, Thiomorpholino-, Morpholinogruppe oder den Rest mit der Formel $-NR_6R_7$ bedeutet, in der R_6 und R_7 gleich oder verschieden sind und ein Wasserstoffatom oder einen gerad- oder verzweigtkettigen C_{1-6}-Alkylrest bedeuten und das Symbol ⎓ eine Doppelbindung bedeutet, und pharmazeutisch verträgliche Salze davon.

2. Verbindung nach Anspruch 1, wobei das Salz ausgewählt ist aus einem Säureadditionssalz, Metallsalz, Ammoniumsalz, organischen Aminadditionssalz und Aminosäureadditionssalz.

3. Verbindung nach Anspruch 1, wobei der Rest A ausgewählt ist aus gerad- oder verzweigtkettigen C_1-C_6-Alkoxycarbonylresten, dem Rest der Formel $-CONR_1R_2$ und der Carboxylgruppe, Y in der 2-Stellung des Hauptkerns gebunden ist, X ausgewählt ist aus den Gruppen =N- und =CH-, n den Wert 1 oder 2 hat und Z ausgewählt ist aus der Dimethylamino-, Diethylamino-, Methylamino-, Amino-, Morpholino- und Thiomorpholinogruppe.

4. Verbindung nach Anspruch 3, wobei der Rest Y ausgewählt ist aus

$$-(CH_2)_m-, \quad -\underset{\displaystyle CH_3}{\underset{|}{CH}}-(CH_2)_m- \text{ und } -CH=CH-(CH_2)_m-$$

und m den Wert 1 oder 2 hat.

5. Verbindung nach Anspruch 4, wobei der Rest A eine Carboxylgruppe bedeutet und X die Gruppe =CH- darstellt.

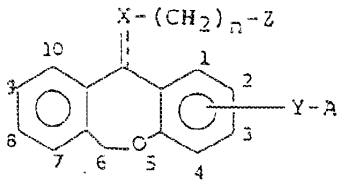
6. Verbindung nach Anspruch 1, wobei der Rest der Formel -Y-A die Carboxymethylgruppe bedeutet, X die Gruppe =CH- bedeutet und n den Wert 2 hat und Z ausgewählt ist aus der Dimethylamino-, Diethylamino-, Methylamino-, Amino-, Morpholino- und Thiomorpholinogruppe.

7. Verbindung nach Anspruch 1, wobei der Rest der Formel -Y-A die Gruppe $2\text{-}CH_2COOH$ bedeutet, X die Gruppe =CH- bedeutet, n den Wert 2 hat und Z eine Dimethylaminogruppe darstellt.

8. Verwendung einer Verbindung gemäß einem der Ansprüche 1 bis 7 zur Herstellung von Arzneimitteln zur therapeutischen Behandlung von allergischen und entzündlichen Erkrankungen.

Revendications

1. Composé de type dibenzo[b,e]oxépine, représenté par la formule (I) :



(I)

dans laquelle :

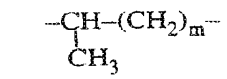
A représente un groupe carboxy, un groupe (alcoxy en C_1-C_6)carbonyle à chaîne droite ou ramifiée, un groupe -CONHOH ou un groupe $-CONR_1R_2$, où R_1 et R_2 sont identiques ou différents et représentent chacun un atome d'hydrogène ou un groupe alkyle en C_1-C_6 à chaîne droite ou ramifiée ;
Y représente un groupe $-(CH_2)-$ ou $-CHR_3-(CH_2)_m-$ où R_3 représente un groupe alkyle en C_1-C_6 à chaîne droite ou ramifiée et m vaut 1, 2, 3 ou 4, ce substituant étant placé en position 2 ou 3 du noyau parent et le côté gauche du groupe Y étant lié au cycle benzénique ;
X représente =N- ou =CH- ;
n vaut 0, 1, 2, 3 ou 4 ;
Z représente un groupe 4-méthyl-pipérazino, 4-méthyl-homopipérazino, pipéridino, pyrrolidino, thiomorpholino ou morpholino, ou un groupe $-NR_6R_7$ où R_6 et R_7 sont identiques ou différents et représentent chacun un atome d'hydrogène ou un groupe alkyle en C_1-C_6 à chaîne droite ou ramifiée ;
et ----- représente une double liaison ;

ainsi que les sels d'un tel composé, acceptables en pharmacie.

2. Composé conforme à la revendication 1, ledit sel étant choisi parmi les sels d'addition d'acide, les sels de métal, les sels d'ammonium, les sels d'addition d'amine organique et les sels d'addition d'acide aminé.

3. Composé conforme à la revendication 1, dans lequel A représente un élément de l'ensemble constitué par les groupes carboxy, (alcoxy en C_1-C_6)carbonyle à chaîne droite ou ramifiée et $-CONR_1R_2$, Y est placé en position 2 du noyau parent, X représente un élément de l'ensemble constitué par =N- et =CH-, n vaut 1 ou 2, et Z représente un élément de l'ensemble constitué par les groupes diméthylamino, diéthylamino, méthylamino, amino, morpholino et thiomorpholino.

4. Composé conforme à la revendication 1, dans lequel Y représente un élément de l'ensemble constitué par les groupes $-(CH_2)-$ et



où m vaut 1 ou 2.

5. Composé conforme à la revendication 4, dans lequel A représente un groupe carboxy et X représente =CH-.

6. Composé conforme à la revendication 1, dans lequel -Y-A représente un groupe carboxyméthyle, X représente =CH-, n vaut 2 et Z représente un élément de l'ensemble constitué par les groupes diméthylamino, diéthylamino, méthylamino, amino, morpholino et thiomorpholino.

7. Composé conforme à la revendication 1, dans lequel -Y-A représente un groupe 2-CH_2-COOH, X représente =CH-, n vaut 2 et Z représente un groupe diméthylamino.

8. Emploi d'un composé défini dans l'une quelconque des revendications 1 à 7, pour la préparation de médicaments destinés au traitement thérapeutique de maladies allergiques et de maladies inflammatoires.

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(54) **TOPICAL OPHTHALMIC FORMULATIONS CONTAINING OLOPATADINE FOR TREATING ALLERGIC EYE DISEASES**

FORMULIERUNG ZUR TOPISCHEN ANWENDUNG AM AUGE, DIE OLOPATADINE ENTHALTEN, ZUR BEHANDLUNG VON ALLERGISCHEN AUGENERKRANKUNGEN

COMPOSITIONS OPHTALMIQUES TOPIQUES CONTENANT OLOPATADINE DESTINEES AU TRAITEMENT D'AFFECTIONS ALLERGIQUES DES YEUX

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- BROCKMAN ET AL: 'A comparison of the effects of olopatadine and ketotifen on model membranes' ACTA OPHTALMOL vol. 78, 2000, pages 10 - 15

Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

Description

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] 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

[0002] 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.

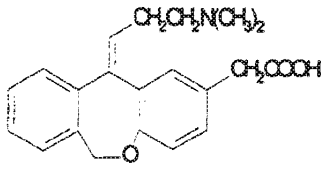
[0003] Although both of the Burroughs Wellcome Patents claim that the variety of pharmaceutical formulations disclosed are effective both for veterinary and for human medical use, neither patent contains an example demonstrating that the carboxylic acid derivatives of doxepin have activity in humans. Example 7 in the Burroughs Wellcome Patents demonstrates antihistamine activity in male guinea pigs and Example G demonstrates anaphylactoid activity in Wistar rats.

[0004] 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).

[0005] 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.

[0006] 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.

[0007] 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.

[0008] 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.

[0009] 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

[0010] The present invention provides the use of a therapeutically effective amount of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid (referred to as "Compound A" hereinafter) or of a pharmaceutically acceptable salt thereof for the preparation of a topical ophthalmic formulation for administering to the eye for treating an allergic eye disease. 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.

[0011] 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

[0012] 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.

[0013] 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 trometharnine), morpholine addition salt and piperidine addition salt.

[0014] 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).

[0015] 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.

[0016] The filtrate obtained from each digestion was centrifuged (825 g, 7 minutes) and pelleted cells were resus-

pended 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).

[0017] 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.

[0018] 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.

[0019] 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.

[0020] 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.

Tablet 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

*p<0.05, Dunnett's t-test

Tablet 1 (continued)

Compound Effect on Histamine Release from Human Conjunctival Tissue Mast Cells upon anti-Human IgE Challenge.			
Compound	**Dose (μM)**	**Treatment (min)**	**Inhibition (%)**
	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

[0021] 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.

[0022] 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

[0023] 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

[0024] 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.

[0025] 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.

[0026] 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.

[0027] If required, other ophthalmologic chemicals such as epinephrine, naphazoline hydrochloride, berberine chloride, sodium azulenesulfonate, lysozyme chloride, glycyrrhizate and the like may be added.

[0028] 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.

[0029] Certain embodiments of the invention are illustrated in the following examples.

Example 1: Preferred Topical Ophthalmic Solution Formulation

[0030]

Ingredient	Concentration (W/V%)
Compound A•HCl	0.111*

* 0.111% Compound A•HCl is equivalent to 0.1% Compound A

(continued)

Ingredient	Concentration (W/V%)
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

Example 2: Topical Ophthalmic Gel Formulation

[0031]

Ingredient	Concentration (WN%)
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

Claims

1. The use of a therapeutically effective amount of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid or a pharmaceutically acceptable salt thereof for the preparation of a topically administrable medicament for treating allergic eye diseases.

2. The use 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 use 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 use 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 use 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 use 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 use 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 use 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 use 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 use 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 use 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 use 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).

Patentansprüche

1. Verwendung einer therapeutisch wirksamen Menge von 11-(3-Dimethylaminopropyliden) -6,11-dihydrodibenz[b,e]oxepin-2-essigsäure oder einem pharmazeutisch annehmbaren Salz davon zur Herstellung eines topisch verabreichbaren Arzneimittels zur Behandlung von allergischen Augenkrankheiten.

2. Verwendung nach Anspruch 1, wobei die Zusammensetzung eine Lösung ist und die Menge an 11-(3-Dimethylaminopropyliden)-6,11-dihydrodibenz[b,e]oxepin-2-essigsäure 0,0001% G/V bis 5% (G/V) ist.

3. Verwendung nach Anspruch 2, wobei die Menge an 11-(3-Dimethylaminopropyliden)-6,11-dihydrodibenz[b,e]oxepin-2-essigsäure 0,001 bis 0,2% (G/V) ist.

4. Verwendung nach Anspruch 3, wobei die Menge an 11-(3-Dimethylaminopropyliden)-6,11-dihydrodibenz[b,e]oxepin-2-essigsäure 0,1% (G/V) ist.

5. Verwendung nach Anspruch 1, wobei die 11-(3-Dimethylaminopropyliden)-6,11-dihydrodibenz[b,e]oxepin-2-essigsäure (Z)-11-(3-Dimethylaminopropyliden)-6,11-dihydrodibenz[b,e]oxepin-2-essigsäure ist, die im Wesentlichen frei von (E)-11-(3-Dimethylaminopropyliden)-6,11-dihydrodibenz[b,e]oxepin-2-essigsäure ist.

6. Verwendung nach Anspruch 5, wobei die Menge an (Z)-11-(3-Dimethylaminopropyliden)-6,11-dihydrodibenz[b,e] oxepin-2-essigsäure 0,0001 bis 5% (G/V) ist.

7. Verwendung nach Anspruch 6, wobei die Menge an (Z)-11-(3-Dimethylaminopropyliden)-6,11-dihydrodibenz [b,e] oxepin-2-essigsäure 0,001 bis 0,2% (G/V) ist.

8. Verwendung nach Anspruch 7, wobei die Menge an (Z)-11-(3-Dimethylaminopropyliden)-6,11-dihydrodibenz[b,e] oxepin-2-essigsäure 0,1% (G/V) ist.

9. Verwendung nach Anspruch 1, wobei die 11-(3-Dimethylaminopropyliden)-6,11-dihydrodibenz[b,e] oxepin-2-essigsäure (E)-11-(3-Dimethylaminopropyliden)-6,11-dihydrodibenz [b,e] oxepin-2-essigsäure ist, die im Wesentlichen frei ist von (Z)-11-(3-Dimethylaminopropyliden)6,11-dihydrodibenz[b,e]oxepin-2-essigsäure.

10. Verwendung nach Anspruch 9, wobei die Menge an (E)-11-(3-Dimethylaminopropyliden)-6,11-dihydrodibenz [b,e] oxepin-2-essigsäure 0,0001 bis 5% (G/V) ist.

11. Verwendung nach Anspruch 10, wobei die Menge an (E)-11-(3-Dimethylaminopropyliden)-6,11-dihydrodibenz[b,e]oxepin-2-essigsäure 0,001 bis 0,2% (G/V) ist.

12. Verwendung nach Anspruch 11, wobei die Menge an (E)-11-(3-Dimethylaminopropyliden)-6,11-dihydrodibenz[b,e] oxepin-2-essigsäure 0,1% (G/V) ist.

Revendications

1. Utilisation d'une quantité thérapeutiquement efficace d'acide 11-(3-diméthylaminopropylidène)-6,11-dihydrodibenz

[b,e]oxépine-2-acétique ou d'un sel pharmaceutiquement acceptable de celui-ci pour la préparation d'un médicament administrable topiquement pour le traitement de maladies oculaires allergiques.

2. Utilisation suivant la revendication 1, dans laquelle la composition est une solution et la quantité d'acide 11-(3-diméthylaminopropylidène)-6,11-dihydrodibenz[b,e]oxépine-2-acétique est de 0,0001 % en poids/volume à 5 % (poids/volume).

3. Utilisation suivant la revendication 2, dans laquelle la quantité d'acide 11-(3-diméthylaminopropylidène)-6,11-dihydrodibenz[b,e]oxépine-2-acétique est de 0,001 à 0,2 % (poids/volume).

4. Utilisation suivant la revendication 3, dans laquelle la quantité d'acide 11-(3-diméthylaminopropylidène)-6,11-dihydrodibenz[b,e]oxépine-2-acétique est de 0,1 % (poids/volume).

5. Utilisation suivant la revendication 1, dans laquelle l'acide 11-(3-diméthylaminopropylidène)-6,11-dihydrodibenz [b,e]oxépine-2-acétique est de l'acide (Z)-11-(3-diméthylaminopropylidène)-6,11-dihydrodibenz[b,e]oxépine-2-acétique, essentiellement exempt d'acide (E)-11-(3-diméthylaminopropylidène)-6,11-dihydrodibenz[b,e]oxépine-2-acétique.

6. Utilisation suivant la revendication 5, dans laquelle la quantité d'acide (Z)-11-(3-diméthylaminopropylidène)-6,11-dihydrodibenz[b,e]oxépine-2-acétique est de 0,0001 à 5 % (poids/volume).

7. Utilisation suivant la revendication 6, dans laquelle la quantité d'acide (Z)-11 -(3-diméthylaminopropylidène)-6,11-dihydrodibenz[b,e]oxépine-2-acétique est de 0,001 à 0,2 % (poids/volume).

8. Utilisation suivant la revendication 7, dans laquelle la quantité d'acide (Z)-11-(3-diméthylaminopropylidène)-6,11-dihydrodibenz[b,e]oxépine-2-acétique est de 0,1 % (poids/volume).

9. Utilisation suivant la revendication 1, dans laquelle l'acide 11-(3-diméthylaminopropylidène)-6,11-dihydrodibenz [b,e]oxépine-2-acétique est de l'acide (E)-11-(3-diméthylaminopropylidène)-6,11-dihydrodibenz[b,e]oxépine-2-acétique, essentiellement exempt d'acide (Z)-11-(3-diméthylaminopropylidène)-6,11 -dihydrodibenz[b,e]oxépine-2-acétique.

10. Utilisation suivant la revendication 9, dans laquelle la quantité d'acide (E)-11-(3-diméthylaminopropylidène)-6,11-dihydrodibenz[b,e]oxépine-2-acétique est de 0,0001 à 5 % (poids/volume).

11. Utilisation suivant la revendication 10, dans laquelle la quantité d'acide (E)-11-(3-diméthylaminopropylidène)-6,11-dihydrodibenz[b,e]oxépine-2-acétique est de 0,001 à 0,2 % (poids/volume).

12. Utilisation suivant la revendication 10, dans laquelle la quantité d'acide (E)-11-(3-diméthylaminopropylidène)-6,11-dihydrodibenz[b,e]oxépine-2-acétique est de 0,1 % (poids/volume).

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(54) Title: TOPICAL OPHTHALMIC MAST CELL STABILIZERS FOR TREATING ALLERGIC EYE DISEASES

(57) Abstract: Topical ophthalmic anti-allergy drugs are identified by the extent of their interaction with a phospholipid model membrane. Disclosed are topically administrable ophthalmic formulations containing amphipathic anti-allergy compounds at concentrations such that the drugs have Surface Activity Ratings from about 2-11.

ARGENTUM PHARM. 1023

TOPICAL OPHTHALMIC MAST CELL STABILIZERS 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 mast cell stabilizers for treating and/or preventing allergic eye diseases.

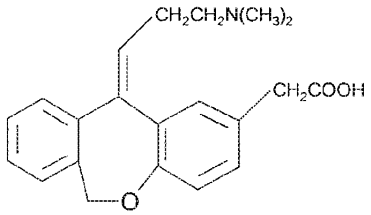
Description of the Related Art

Conventional antihistamine drugs are known to exhibit biphasic effects on mast cells. At lower concentrations, antihistamines promote an inhibition of histamine release from mast cells. As concentrations of antihistamines are increased there is a spontaneous release of histamine from mast cells, which is associated with an apparent loss of mast cell membrane stability. See, for example, Mota et al., *Brit. J. Pharmacol.* 15:396-404. This biphasic behavior has been demonstrated for the anti-allergy drug ketotifen (*4,9-dihydro-4-(1-methyl-4-piperidinyl-idene)-10H-benzo[4,5]cyclohepta-[1,2-b]thiophen-10-one*) in purified preparations of human conjunctival mast cells. Yanni et al., *J. Ocular Pharmacol.*, 12:389-400 (1996).

First generation mast cell stabilizer drugs without antihistaminic activity, such as cromolyn sodium, also exhibit biphasic behavior. Johnson et al., *Monogr. Allergy*, 14:299-306 (1979).

U.S. Patent Nos. 4,871,865 and 4,923,892, both assigned to Burroughs Wellcome Co. ("the Burroughs Wellcome Patents"), describes 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, as mast cell stabilizers with antihistaminic action. These compounds inhibit the release of autacoids (i.e., histamine, serotonin, and the like) from mast cells and 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.

U.S. Patent 5,641,805 discloses topical ophthalmic formulations for treating allergic eye diseases. The topical formulations contain acetic acid derivatives of doxepin and, in particular, *Z-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid* (i.e., olopatadine), which is the *cis* form of the compound having the formula :



Unlike other antihistamine or mast cell stabilizer anti-allergy drugs, olopatadine does not provoke a release of histamine from mast cells at concentrations higher than those for which antihistaminic activity is observed. Other topical ocular anti-allergy drugs that maintain mast cell membrane

stability and prevent histamine release from mast cells over a drug concentration range of 0.01 - 0.5 % (w/v) are desired.

Summary of the Invention

The present invention provides a method for selecting anti-allergy drug concentrations that are suitable for use in the topical treatment of allergic eye diseases. According to the present method, an amphipathic anti-allergy compound's Surface Activity Rating is determined as described below. For topically administrable ophthalmic anti-allergy products, the anti-allergy drug concentration is chosen so that the drug has a Surface Activity Rating (in units of mN/m) from about 2 - 11.

The present invention is also directed toward topically administrable ophthalmic anti-allergy pharmaceutical drug products comprising an amphipathic anti-allergy drug at a concentration such that the drug has a Surface Activity Rating from about 2 – 11.

Among other factors, the present invention is based on the finding that amphipathic anti-allergy compounds formulated at concentrations at which they have a Surface Activity Rating of greater than 11 are likely to cause mast cell membrane instability and leakage of autocoids, including histamine, from human conjunctival mast cells.

Brief Description of the Drawing

Fig. 1 shows the effect of olopatadine and ketotifen drug concentrations on the surface pressure of 1-stearoyl-2-oleoyl-*sn*-glycero-3-phosphocholine (SOPC) monolayers spread at an initial surface pressure of 30 mN/m.

Detailed Description of the Invention

According to the present invention, topically administrable ophthalmic anti-allergy pharmaceutical drug products comprise an amphipathic anti-allergy drug at a concentration such that the drug has a Surface Activity Rating from about 2 – 11, and preferably from about 4 – 11. The drug products of the present invention contain an amphipathic anti-allergy drug at a concentration of about 20 mM or less.

The Surface Activity Rating is obtained by determining the interaction of an amphipathic anti-allergy drug ("test compound") in buffer alone with a phospholipid monolayer. Test compound/mast cell membrane interaction is mimicked in a phospholipid monolayer spread onto an aqueous buffer in a modified Langmuir trough. In this system, test compound-membrane interaction is quantified by determining the change in surface pressure ($\Delta\pi$ in mN/m) of a monomolecular film of 1-stearoyl-2-oleoyl-*sn*-glycero-3-phosphocholine (SOPC) spread at an initial surface pressure of 28 – 32 mN/m on an aqueous buffer sub-phase. The initial surface pressure of 28 – 32 mN/m is chosen because this pressure mimics that of most mammalian cell membranes.

Surface pressure changes are measured at 24°C, while progressively increasing the concentration of test compound in the buffer sub-phase from 0 to at least 5 mM (or to the compound's solubility limit if less than 5 mM), and preferably to at least 20 mM (or the compound's solubility limit if less than 20 mM). Test compound is added to the sub-phase by continuous sub-phase exchange (keeping the total volume of the sub-phase constant) at a rate slow enough to avoid disturbing the SOPC monolayer (0.4 ml/min., for example).

Surface pressure is measured using an automated interfacial monitor-controller built around a Cahn 27 electrobalance equipped with a 24 ga.

nichrome wire Wilhelmy probe. [See Tsujita et al, Regulation of carboxylester lipase adsorption to surfaces. 1. Chemical specificity. *Biochemistry* 26:8423-8429 (1987) and Momsen et al., The suitability of nichrome for measurement of gas-liquid interfacial tension by the Wilhelmy method. *J. Colloid Interface Sci.* 135:547-552 (1990).] The two aqueous compartments (circular and rectangular) of the keyhole-shaped Teflon trough are disconnected; only the circular compartment (area = 25.5 cm^2, volume = 24.4 ml) is used for monolayer formation. Temperature in both compartments is maintained at 24 °C using a thermostated base plate controlled by a precision water bath. Precise positioning of the Wilhelmy probe in the aqueous phase, correction for probe buoyancy due to immersion, sub-phase stirring, and data collection are controlled by microprocessor (Tsujita et al, *id.*).

The effect of test compound on surface pressure is determined by a continuous exchange of the aqueous phase with a concentrated solution of the test compound in buffer. Although the identity of the buffer is not critical as long as the aqueous sub-phase is maintained at a physiological pH, the preferred buffer is 10mM HEPES/100 mM NaCl with the pH adjusted to 7.5. The concentration of test compound in the aqueous phase is determined from the fraction of sub-phase volume exchanged and the concentration of the solute in the concentrated solution. The continuous exchange is necessary to avoid disturbing the SOPC monolayer, and is accomplished by a side or bottom injection/withdrawal ports.

The amphipathic anti-allergy drugs of the present invention preferably possess antihistamine activity, such as tricyclic H_1-receptor antagonists exhibiting an in vitro binding affinity (k_I) in the range of 0.1 – 100 nM for the H_1-receptor. The amphipathic anti-allergy drugs of the present invention exclude olopatadine, ketotifen, emedastine, pheniramine, pyrilamine, cromolyn, nedocromil and levocabastine.

Formulations of the anti-allergy compounds for topical ophthalmic administration can be made using known techniques. Ophthalmically acceptable excipients, such as tonicity-adjusting agents, pH-adjusting agents, buffering agents, preservatives, comfort enhancing agents, viscosity-modifying agents, stabilizing agents, etc. may be included. For example, sodium chloride, glycerin, mannitol 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 desired, formulations containing the anti-allergy agents according to the present invention may also contain other active agents.

Eye drop formulations produced according to the present invention will typically need only be applied to the eyes from once to 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: Topical Ophthalmic Solution Formulation

Ingredient (W/V%)	Concentration
Compound having a Surface Activity Rating ≤ 11.2 at the selected concentration	0.01 – 0.5
Dibasic Sodium Phosphate (Anhydrous), USP	0.5
Sodium Chloride, USP	0.65
Benzalkonium Chloride	0.01
Sodium Hydroxide, NF 7.0	q.s. pH =
Hydrochloric Acid, NF 7.0	q.s. pH =
Purified Water	q.s. 100

Example 2: Topical Ophthalmic Gel Formulation

Ingredient	Concentration (W/V%)
Compound having a Surface Activity Rating ≤ 11.2 at the selected concentration	0.01 – 0.5
Carbopol 974 P	0.8
Edetate Disodium	0.01
Polysorbate 80	0.05
Benzalkonium Chloride, Solution	0.01+5 xs
Sodium Hydroxide 7.2	q.s. pH
Hydrochloric acid 7.2	q.s. pH
Purified Water	q.s. 100

Example 3: Measurement of the Surface Activity Rating of Olopatadine and Ketotifen

Water was purified by reverse osmosis and carbon filtration, passage through an Elix 3 deionization system (Millipore) and passage through a Milli Q UV Plus polishing system (Millipore). Buffer, comprised of 10mM HEPES containing 0.1M NaCl pH 7.5, was used to prepare solutions of olopatadine and ketotifen (and for control experiments). After mixing the drug with the buffer, it was necessary to readjust the pH to a value of 7.5 with 5 M NaOH. All chemicals were reagent grade.

Exchange of aqueous phase contents – The circular compartment of the automated interfacial monitor-controller described above was fitted with an inlet tube (1/32" ID Teflon) and an outlet tube (18 ga. Teflon) which entered through the outer wall of the sample compartment. These were connected to 25-mL, gas-tight syringes (model 1025, Hamilton, Reno, NV) mounted in a microprocessor-controlled push-pull dual syringe pump (model sp260p, World Precision Instruments, Sarasota, FL) through three-way Teflon valves (Hamilton, Reno, NV) which were used for filling and flushing. About 42 cm of the inlet tube was coiled in the water-filled rectangular compartment of the trough in order to equilibrate the incoming solution to the temperature of the circular compartment. A custom Teflon-coated magnetic stirring bar (length = 3.6 cm, diameter 2 mm) was used to mix the aqueous contents. The bar was at approximately 50 rpm by stepper motor-driven magnet mounted beneath the circular compartment and controlled by the microprocessor. The relatively slow stirring speed and small bar diameter were used to minimize disturbance of the lipid monolayer. To exchange the contents of the circular compartment with the solution in the inlet syringe while maintaining constant volume, the syringes were operated in unison, but in opposite directions, by the syringe pump. Control experiments showed that, during exchange of 25 ml of aqueous phase, the volume of liquid removed from a test container remained constant to within an average deviation of 0.023 ml (n = 2), or ~ 0.1%. This insured that the depth of immersion of the Wilhelmy probe was constant to within ~10 μm and, hence, the contact angle of the aqueous phase with the probe, remained essentially constant during exchange experiments.

Measurement of olopatadine's and ketotifen's effect on surface pressure - Saturated solutions of olopatadine and ketotifen, respectively, were prepared for each exchange experiment by gently warming an excess of drug in buffer, adjusting the pH to 7.5 and equilibrating the sample to 24° C. Following filtration to remove undissolved drug, drug concentration in the solution was determined spectrophotometrically. The concentration of drug in diluted

aliquots of the solution was determined by comparing their absorbance to a standard curve obtained with standard solutions of the drug. This solution or buffer (control) was loaded into the injection syringe of the apparatus and a monolayer of SOPC was spread onto the surface of the aqueous phase in the exchange compartment to slightly below the desired surface pressure of 30 mN/m. The lipid film was equilibrated for 90 to 220 min. in order to achieve a surface pressure drift rate of <0.01 %/min, which was considered stable. Once the monolayer was stable, the exchange was carried out at a constant rate of 0.4 ml/min during which surface pressure was recorded as a function of time.

At least duplicate exchange and control (without drug) experiments were conducted. Each set of controls was normalized to the nominal pressure and the traces were averaged. The results are shown in Figure 1, where drug concentration vs. the surface pressure of the SOPC monolayer is plotted for each drug. Olopatadine caused a relatively small increase in surface pressure (7.1 mN/m) as its concentration in the aqueous sub-phase is increased from 0 to 5 mM. In contrast, ketotifen produced a two-fold greater increase in surface pressure (15 mN/m) than olopatadine when tested over a concentration range of 0 – 3.5 mM. Thus, the Surface Activity Rating of olopatadine is 7.1 and of ketotifen is 15.

WHAT IS CLAIMED IS:

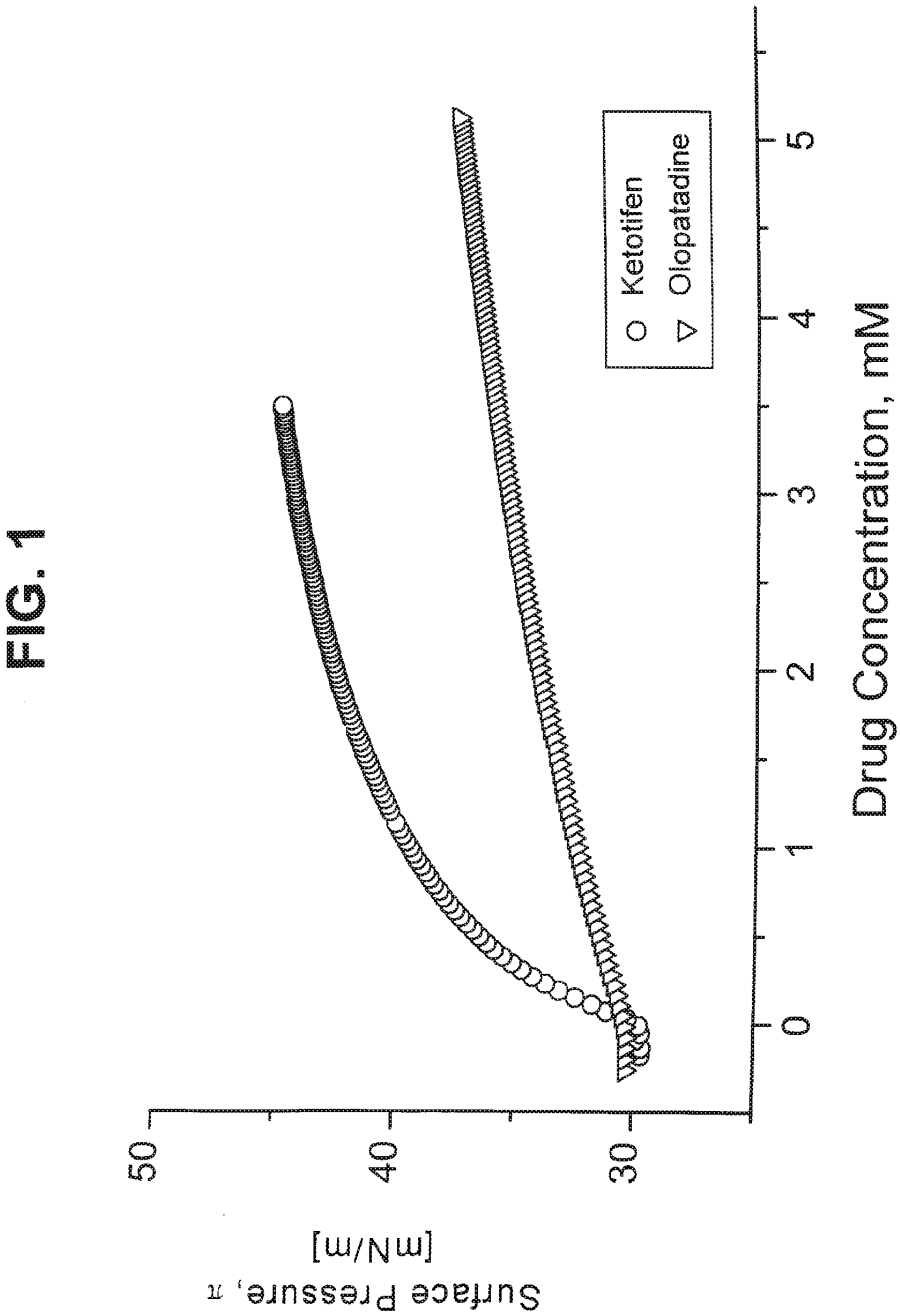
1. A method for selecting an amphipathic drug suitable for topical ophthalmic anti-allergy use comprising the step of determining the drug's Surface Activity Rating.

2. A topically administrable ophthalmic pharmaceutical composition comprising an ophthalmic amphipathic anti-allergy drug at a concentration such that the drug has a Surface Activity Rating from about 2 - 11, provided the drug is not selected from the group consisting of olopatadine; ketotifen; emedastine; pheniramine; pyrilamine; cromolyn; nedocromil; and levocabastine; and further provided that drug is present at a concentration of about 20 mM or less.

3. The composition of Claim 2 wherein the drug has a Surface Activity Rating from 4 – 11.

4. The composition of Claim 2 wherein the anti-allergy drug is an antihistamine drug.

FIG. 1



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(54) Title: SELF-PRESERVED NASAL, INHALABLE, AND TOPICAL OPHTHALMIC PREPARATIONS AND MEDICATIONS

(57) Abstract: Self-preserved nasal, inhalable and topical ophthalmic preparations and medications which destroy, inhibit or therapeutically significantly limit microbial growth within said preparations or medications. The nasal, inhalable, and topical ophthalmic preparations and medications are mildly buffered and maintain a stable pH at pH 3.5 or lower.

ARGENTUM PHARM. 1013

SELF-PRESERVED NASAL, INHALABLE, AND TOPICAL OPHTHALMIC PREPARATIONS AND MEDICATIONS

This application is based on and claims priority of the Provisional application Serial No. 60/234,319, filed on September 20, 2000.

Field of the Invention

The current invention concerns buffered, low pH, self-preserved nasal, inhalable and topical ophthalmic preparations and medications which destroy, inhibit or sufficiently limit microbial growth within said preparations or medications. In particular, the current invention involves nasal, inhalable and topical ophthalmic preparations and medications having low pH of about 3.5 or lower, to inhibit microbial growth, wherein immediately upon application to the eye surface or a mucosal surface, the pH rises to physiologic levels.

BACKGROUND OF THE INVENTION

To prevent infection with use, currently available multidose preparations and medications are sterilized during manufacture and have a variety of preservatives added to destroy or inhibit the growth of microorganisms inadvertently introduced into the product after opening.

It is well recognized that the preservatives used in topical ophthalmic medications and preparations can be toxic to the eye surface and respiratory mucosa. The most widely used ophthalmic preservative, benzalkonium chloride (BAK), can cause damage to the conjunctival and corneal epithelium (Cornea, 1:221-225 (1992); Arch Opthalmol, 110:528-532 (1992) and CLAO J, 18:260-266 (1992)). BAK is now thought to be also a significant cause of rhinitis medicamentosa, as described in Allergy, 52:627-632 (1997), and has been also shown to damage respiratory mucosa (Am Rev Respir Dis, 141:1405-1408 (1990)

and Acta Otolaryngol, 116:868-875 (1996)). Reducing the concentration of BAK reduces its toxic effect, but at too low a concentration, BAK is no longer effective as a preservative. Although alternatives to BAK are available, all preservatives have some potential for toxicity.

Pressurized aerosol containers used for inhalation or as a spray are an exception, needing no preservative since no air or contamination enters the container as doses are extracted. However, such packaging is relatively bulky and expensive, often contains CFC propellants which can harm the atmosphere, and precludes drop administration.

In recent years, preparations and medications have been packaged in unit-dose containers, thus avoiding the need for potentially toxic preservatives. In this arrangement, a single dose of medicine is provided by a given container. With sterile packaging, microbial contamination is theoretically not a concern, since the consumer/patient is instructed to discard the container after each single use. However, there are several problems with unit dose containers. First, the packaging is bulky and inconvenient. Second, cost per dose is significantly higher than with multidose containers. Third, patients often retain the opened container for many hours or even more than one day, contradicting the package instructions. This pattern of use increases the probability of microbial contamination of the medication or preparation.

Thus, it would be desirable to have available preservative-free preparations and medications suitable for topical, mucosal and inhalation use that could be stored in multi-dose containers without risk of microbial contamination.

All patents, patent applications and publications are hereby incorporated by reference.

SUMMARY OF THE INVENTION

One aspect of the current invention is a topical

ophthalmic, nasal, or inhalable preparation or medication which is self-preserved, that is, which destroys, inhibits or sufficiently limits growth and multiplication of various microorganisms without the addition of preservative agents.

Another aspect of the current invention is a mildly buffered, topical ophthalmic, nasal, or inhalable preparation which is self-preserved by having a pH of from about 1.5 to about 3.5 with preferred pH at about 2.5 or lower.

Another aspect of the current invention is a self-preserved topical ophthalmic, nasal, or inhalable preparation or medication comprising a pharmaceutically acceptable excipient or additive selected from the group consisting of dextrose, polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC), sodium chloride, potassium chloride, calcium chloride, magnesium chloride, phosphoric acid, disodium edetate, bicarbonate, phosphate, povidone, carboxymethylcellulose, hydroxyethylcellulose, methylcellulose, microcrystalline cellulose, glycerin, polyvinyl alcohol, dextran 40, dextran 70, mannitol, gelatin, polyol, polysorbate 80, propylene glycol, zinc sulfate, poloxamer 188, 282, 407, ephedrine hydrochloride, naphazoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, lecithin, oleic acid, sorbitan, pheniramine maleate, pyrilamine maleate, antazoline phosphate, glycine, camphor, eucalyptol, menthol, benzyl alcohol, lavender oil, tyloxapol, bornyl acetate, and phenylethyl alcohol, and a buffering agent, said preparation or medication adjusted to a low pH between about 1.5 to about pH 3.5, with most preferred pH at about pH 2.5 or lower, said medication optionally containing analgesics, anti-inflammatories, mast cell stabilizers, diagnostic aids, antibiotics, antiglaucoma drugs, decongestants, bronchodilators, vasoconstricting or

hypertonicity agents, astringents and topical anesthetics.

Still another aspect of the current invention is a physiologically compatible self-preserved lightly buffered topical ophthalmic, nasal, or inhalable preparation or medication containing no preservation agents, formulated and maintained at about pH 2.5 or lower, wherein immediately upon application to the eye or a mucosal surface, such preparation permits the pH to rise to physiologic levels to maintain patient comfort, prevent tissue damage, and enhance drug delivery.

Still yet another aspect of the current invention is a multidose topical ophthalmic, nasal, or inhalable preparation or medication lightly buffered to maintain a stable pH in the multidose container, thereby maintaining its self-preserving characteristic.

Still another aspect of the current invention is a method for preparation of a topical ophthalmic, nasal or inhalable self-preserved solution comprising steps of:

a) preparing a formulation comprising

a pharmaceutically acceptable excipient or additive selected from the group consisting of dextrose, polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC), sodium chloride, potassium chloride, calcium chloride, magnesium chloride, phosphoric acid, disodium edetate, bicarbonate, phosphate, povidone, carboxymethylcellulose, hydroxyethylcellulose, methylcellulose, microcrystalline cellulose, other cellulose derivatives, glycerin, polyvinyl alcohol, dextran 40, dextran 70, mannitol, gelatin, polyols, polysorbate 80, propylene glycol, zinc sulfate, poloxamer 188, 282, 407, ephedrine hydrochloride, naphazoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, lecithin, oleic acid and sorbitan, pheniramine maleate,

pyrilamine maleate, antazoline phosphate, glycine, camphor, eucalyptol, menthol, benzyl alcohol, lavender oil, tyloxapol, bornyl acetate, phenylethyl alcohol, alone or in admixture; and

a buffering agent; and

b) adjusting pH of said formulation to from about pH 1.5 to pH about 3.5.

DEFINITIONS

As used herein:

"Preparation" means a topical ophthalmic, nasal, or inhalable preparations, including topical eye preparations such as artificial tears, contact lens solutions and eye irrigating solutions; nasal preparations such as saline; and inhalable preparations.

"Medication" means topical ophthalmic, nasal, or inhalable preparations comprising a pharmaceutical agent suitable for topical ophthalmic, nasal or inhalable administration wherein the pharmaceutical agent for ophthalmic use is an astringent, analgesic, hypertonicity agent, antihistamine, anti-inflammatory drug, mast cell stabilizer, diagnostic aid, anesthetic, antibiotic, antiglaucoma drug and vasoconstricting agent, the agent for nasal use is a decongestant and the agent for inhalable use is a bronchodilator

"Physiologically compatible" means a preparation or medication which contains pharmaceutically acceptable excipients and additives dissolved or suspended in purified water which is physiologically compatible with the eye surface or the nasal/respiratory mucosa.

"Preservative" means an additive intended to destroy or limit growth and multiplication of microorganisms.

"Self-preserved" means a preservative-free preparation or medication that destroys or inhibits microbial growth without

the addition of preservatives such as benzalkonium chloride (BAK).

"Preservative effectiveness testing" or "PET" means the standardized microbiological testing specified by the USP 24 to determine preservative effectiveness.

DETAILED DESCRIPTION OF THE INVENTION

This invention is based on the finding that certain pharmaceutical preparations and medications, when adjusted and maintained at a low pH of from about pH 1.5 to about pH 3.5, are self-preserved and possess antimicrobial growth properties.

The invention, therefore, concerns buffered, low pH, topical self-preserved ophthalmic, nasal, or inhalable preparations or medications for multidose administration of various drugs and pharmaceuticals topically or by inhalation. These preparations or medications generally comprise one or more pharmaceutically acceptable excipients or additives, such as, for example, dextrose, polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC), sodium chloride, potassium chloride, calcium chloride, magnesium chloride, phosphoric acid, disodium edetate, bicarbonate, phosphate, povidone, carboxymethylcellulose, hydroxyethylcellulose, methylcellulose, microcrystalline cellulose, other cellulose derivatives, glycerin, polyvinyl alcohol, dextran 40, dextran 70, mannitol, gelatin, polyols, polysorbate 80, propylene glycol, zinc sulfate, poloxamer 188, 282, 407, ephedrine hydrochloride, naphazoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, lecithin, oleic acid and sorbitan, pheniramine maleate, pyrilamine maleate, antazoline phosphate, glycine, camphor, eucalyptol, menthol, benzyl alcohol, lavender oil, tyloxapol, bornyl acetate, phenylethyl alcohol, analgesics, anti-inflammatories, mast

cell stabilizers, diagnostic aids, antibiotics, antiglaucoma medications, and topical anesthetics, and a buffering agent, said preparation or medication adjusted to a low pH between about 1.5 to about pH 3.5, with the most preferred pH at about pH 2.5 or lower. These preservations and medications are self-preserved by means of low pH.

The invention is based on observations made during studies performed to determine the stability of amino ester topical anesthetics wherein microbial growth was observed to be moderately inhibited by diluted solutions of these topical anesthetics when the solutions were formulated at pH 3.5 to enhance the anesthetic's stability. A further series of experiments discovered and demonstrated that microbial growth is still somehow inhibited at this pH (3.5) even if the anesthetic is removed. These studies, described in greater detail below, showed that for adequate destruction, inhibition or sufficient limitation of microbial growth to meet preservative effectiveness testing (PET) standards, the pH should be not much higher than approximately 2.5 up to pH 3.5 at most.

Moreover, it was further discovered that with appropriate mild or moderate buffering, these preparations or medications may be advantageously administered to the eye surface or to the nasal or respiratory mucosa without a harmful effect caused by such low pH because the mild buffer, under these conditions, permits instant adjustment of the pH to physiologic levels upon administration to the eye topically or to nasal or respiratory mucosa.

The invention, therefore, in its broadest aspect, concerns the discovery that the self-preserved properties of the topical ophthalmic, nasal or inhalable preparation or medication can be achieved with a mild buffering and with maintenance of low pH under 3.5, preferably pH about 2.5 or

lower and that this preparation or medication can be advantageously administered to the eye surface or to the nasal or respiratory mucosa without causing irritation or injury.

I. Preservative Effectiveness Testing

In order to determine the optimal composition and pH of the self-preserved preparation, various combinations of components and variable pH were tested using preservative effectiveness testing (PET).

PET procedure, description of which can be found in USP 24, §51, pp.1809-1811, Antimicrobial Effectiveness Testing, was first performed on the following solutions formulated at pH values from 2.5 to 6.5.

Solutions Group A

Solution A consisted of the following components:

Dextrose	0-4.0%
Polyethylene Glycol 400	0.001-8.0
Hydroxypropyl methylcellulose	0.30
Edetate Disodium	0-0.02
Sodium Citrate	0.01-0.05
Purified Water	QS
pH adjusted from 2.5 to 6.5	

At pH 5.5 to 6.5, there was inadequate inhibition of microbial growth. At pH 4.5 to 5.5, inhibition of microbial growth did not meet PET standards. At pH 3.5 to 4.5 the inhibition of microbial growth was inconsistent. At pH 2.5 to 3.5, the inhibition of microbial growth met the PET standards. This was still true as the percentages of dextrose, PEG 400, and edetate disodium were varied as shown above. However, inhibition of microbial growth improved as the pH approached 2.5.

Solutions Group B

The above testing clearly indicated that the solutions in Group A having pH above approximately 3.5 did not sufficiently inhibit microbial growth and the best inhibition was seen at pH 2.5. Consequently, two solutions were subjected to further studies performed at pH of about 2.5. However, to reach and

maintain the pH at 2.5 using a sodium citrate buffer was found to be difficult. Citric acid was, therefore, used to replace sodium citrate in the low pH solutions to achieve a stable pH 2.5 for long periods of time.

The following two representative formulations, Solutions 1 and 2, both adjusted to pH 2.5, show excellent inhibition of microbial growth and pH stability.

Group B, Solution 1

Polyethylene glycol 400	8.00%
Hydroxypropyl methylcellulose 2910	0.30
Citric acid	0.01
Purified water	QS
pH 2.5	

Group B, Solution 2

Dextrose	4.00%
Polyethylene glycol 400	1.00
Hydroxypropyl methylcellulose 2910	0.30
Citric acid	0.01
Purified water	QS
pH 2.5	

Both solutions were again tested by the PET procedure.

Results of these testings on five types of microorganisms are described below in Tables 1-4. The results seen in Tables 1-4 clearly show that when the solution comprising a viscosity and/or tonicity agent, here represented by polyethylene glycol, dextrose and hydroxypropyl methylcellulose, and a buffering agent, here represented by citric acid, is adjusted to around pH 2.5, it possesses a definite ability to inhibit microbial growth. Both solutions are also able to maintain this pH (2.5) for at least two months or longer at 40°C, and therefore, they have a good stability and long shelf-life.

II. Low pH, Self-Preserved Preparations and Medications

The preparations and medications of the invention are formulated as a solution or suspension comprising components in percentages shown in the Group A solutions, described above. The pH of the invention is optimally about 2.5 or lower. This is in contrast to the physiologic pH of 7.4, typically used for these types of formulations.

The only disclosed use for low pH is a preservative-free beverage composition with pH 2.2-2.7 described in U.S. Pat. No. 5,417,994.

Self-preserved, pharmaceutically acceptable preparations or medications for topical use utilizing pH 2.5 or below have not been previously described or suggested and such self-preserved low pH preparation or medication for topical ophthalmic, mucosal or inhalable administration are not available.

In practice of the current invention, the pH is adjusted to approximately 2.5 with an acid such as hydrochloric or sulphuric acid or a base such as sodium or ammonium hydroxide. Citric acid, acetic, formic, glutaric, glycolic, lactic, maleic, tartaric acid or other weak acid or a salt thereof, such as sodium citrate, may be used to buffer the preparation or medication. Citric acid is the preferred component for a buffer. It has been discovered as part of the current invention that the desirable concentration of citric acid is approximately 0.01%, to lightly buffer the preparation and allow the pH to rise rapidly when the preparation is applied to the tissue surface.

The function of low pH is very important from the point of view of this invention. It is well known that certain drug solutions are unstable when formulated at or near physiologic pH. For example, pilocarpine is relatively unstable at pH 6.8, but very stable at pH 5.0. The concept of lightly buffering such formulations to make them physiologically compatible despite the low pH used for drug stability has been previously known. However, using very low pH such as pH 2.5 or lower with a preparation or medication for any purpose, and more specifically for the purpose of self-preservation of multidose preparations or medications, has not been previously described.

The preparations described herein contain and may additionally contain and be freely exchangeable with any

example, dextrose, polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC), sodium chloride, potassium chloride, calcium chloride, magnesium chloride, phosphoric acid, disodium edetate, bicarbonate, phosphate, povidone, carboxymethylcellulose, hydroxyethylcellulose, methylcellulose, microcrystalline cellulose, other cellulose derivatives, glycerin, polyvinyl alcohol, dextran 40, dextran 70, mannitol, gelatin, polyols, polysorbate 80, propylene glycol, zinc sulfate, poloxamer 188, 282, 407, ephedrine hydrochloride, naphazoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, lecithin, oleic acid and sorbitan, pheniramine maleate, pyrilamine maleate, antazoline phosphate, glycine, camphor, eucalyptol, menthol, benzyl alcohol, lavender oil, tyloxapol, bornyl acetate, phenylethyl alcohol, and other excipients and additives which are pharmaceutically acceptable.

These excipients and additives are dissolved or suspended in sterile distilled or sterile purified water up to the volumes to provide a solution or suspension containing these components in the desired ratios to each other.

Additionally, the preparations described herein are advantageously formulated into medications by combining said excipient with pharmaceutical agents, such as analgesics, anti-inflammatories, antihistamines, mast cell stabilizers, diagnostic aids, such as fluorescein, anesthetic solutions, miotics, mydriatics, antibiotics, antivirals, antifungals, antiglaucoma drugs, hypertonic agents, astringents, and local anesthetics such as proparacaine, tetracaine, lidocaine, benoxinate, and bupivicaine, etc., and such other therapeutic agents which are typically used for administration to the eye surface and nasal or respiratory mucosa. These pharmaceutical agents are present in from about 0.001% to about 8%.

These solutions are suitable for use as artificial tears and as solution for administration of various drugs and

lenses. The solutions are self-preserved without the addition of any preservative agent. Additionally, when administered to the eye, or other mucosal surface, these solutions permit rapid adjustment of pH to the physiologic levels.

For artificial tears, the formulation comprises from about 0.001 to about 8% of one or two or more viscosity and/or tonicity-providing agents, and from about 0.005 to about 0.02%, preferably above 0.01% of a mild buffering agent. The above components are dissolved in purified water up to 100% and pH is appropriately adjusted with an acid or a base to levels lower than pH 3.5. The percentage of the agents can be increased or decreased to vary the tonicity as desired. For example, the eye can usually tolerate solutions with tonicity equivalent to that provided by 0.5% to 1.8% sodium chloride.

III. Testing of Representative Embodiments

One representative embodiment for an ophthalmic demulcent (artificial tear) is a formulation designated solution 1 which comprises about 8% of polyethylene glycol 400 (PEG 400), about 0.3% of HPMC 2910 and about 0.01% of citric acid dissolved in 100 ml of purified water and adjusted to about pH 2.5.

This formulation has been shown to significantly inhibit the growth of microorganisms, such as *P. aeruginosa*, *E. coli*, *S. aureus*, *C. albicans* and *A. niger* for at least 28 days, as seen in Table 1. In this formulation, PEG 400 provides tonicity and viscosity. The HPMC provides viscosity, and the citric acid lightly buffers the preparation.

TABLE 1

Preservative Effectiveness Testing for Solution 1

Organism	Initial	6 Hours	24 Hours	7 Days	14 Days	21 Days	28 days
P. aeruginosa	$4.8x10^5$	<100	<100	<1	<1	<1	<1
Saline	$1.6x10^6$	$5.6x10^5$	$5.8x10^5$	$7.8x10^5$	$3.4x10^5$	$6.4x10^5$	$6.0x10^5$
E. coli	$2.8x10^5$	$1.6x10^4$	<1000	<1	<1	<1	<1
Saline	$4.1x10^6$	$2.6x10^6$	$3.4x10^6$	$2.7x10^6$	$1.7x10^6$	$2.0x10^6$	$2.6x10^6$
S. aureus	$2.0x10^6$	$1.4x10^5$	<1000	<1	<1	<1	<1

Saline	$3.9x10^5$	$2.2x10^6$	$1.3x10^6$	$1.0x10^5$	$3.0x10^3$	<1000	16
C. albicans	$1.4x10^6$	Not Done	$4.5x10^5$	$6.0x10^2$	$6.6x10^1$	$5.5x10^1$	5
Saline	$1.7x10^6$	Not Done	$8.4x10^5$	$4.8x10^5$	$2.9x10^5$	$2.9x10^5$	$1.4x10^5$
A. niger	$6.1x10^4$	$5.0x10^4$	$1.9x10^4$	$3.1x10^4$	$1.9x10^4$	$2.2x10^4$	$1.1x10^4$
Saline	$2.8x10^5$	$1.7x10^5$	$1.4x10^5$	$5.0x10^4$	$3.3x10^4$	$8.0x10^4$	$1.4x10^4$

Table 1 shows that the concentration in colony forming units (CFU)/ml for the three bacterial organisms inoculated in Solution 1 decreased by greater than 3 logs at 14 days and remained at that level for 28 days, thus meeting the PET requirements.

Both *C. albicans* and *A. niger* met or exceeded the PET requirement for yeasts and molds to remain at or below the initial concentration.

TABLE 2

pH Testing for Solution 1

	Day 1	Day 7	Day 14	Day 21	Day 28
P. aeruginosa	2.43	2.36	2.44	2.41	2.40
E. coli	2.45	2.37	2.45	2.41	2.37
S. aureus	2.41	2.36	2.44	2.41	2.38
C. albicans	2.42	2.41	2.45	2.43	2.42
A. niger	2.42	2.40	2.39	2.35	2.35

As seen in Table 2, Solution 1 maintained its pH close to its original pH value 2.5 for at least 28 days in the presence of all tested organisms.

Solution 1 was also pH stable when incubated at 40°C for greater than two months.

Another representative embodiment for an artificial demulcent is a formulation designated solution 2, which comprises 4% of dextrose, 1% of PEG 400, 0.3% of hydroxypropylmethyl cellulose 2910 and 0.01% of citric acid, dissolved in 100 ml of purified water and pH adjusted to 2.5. In this solution, the dextrose and PEG 400 both serve as tonicity agents. This formulation, designated as Solution 2,

Table 3.

TABLE 3

Preservative Effectiveness Testing for Solution 2

Organism	Initial	6 Hours	24 Hours	7 Days	14 Days	21 Days	28 Days
P aeruginosa	$1.3x10^6$	$1.8x10^4$	<100	<1	<1	<1	<1
Saline	$1.6x10^6$	$5.6x10^5$	$5.8x10^5$	$7.8x10^5$	$3.4x10^5$	$6.4x10^5$	$6.0x10^5$
E. coli	$4.0x10^6$	$1.6x10^4$	<1,000	<1	<1	<1	<1
Saline	$4.1x10^6$	$2.6x10^6$	$3.4x10^6$	$2.7x10^6$	$1.7x10^6$	$2.0x10^6$	$2.6x10^5$
S. aureus	$1.5x10^6$	$2.0x10^5$	<1,000	<1	<1	<1	<1
Saline	$3.9x10^6$	$2.2x10^6$	$1.3x10^6$	$1.0x10^5$	$3.0x10^3$	<1,000	16
C. albicans	$1.9x10^6$	N/A	$8.6x10^5$	$1.7x10^5$	$2.0x10^4$	$5.8x10^2$	17
Saline	$1.7x10^6$	N/A	$8.4x10^5$	$4.8x10^5$	$2.6x10^5$	$2.9x10^5$	$1.4x10^5$
A. niger	$7.8x10^4$	$1.9x10^4$	$1.4x10^3$	$2.7x10^4$	$2.4x10^4$	$1.5x10^4$	$1.0x10^4$
Saline	$2.8x10^5$	$1.7x10^5$	$1.4x10^5$	$5.0x10^4$	$3.3x10^4$	$8.0x10^4$	$1.4x10^4$

Table 3 shows that Solution 2 was also able to meet or exceed the PET standards for inhibition of the growth of all tested microorganisms over the 28 day test.

TABLE 4

pH Testing for Solution 2

	Day 1	Day 7	Day 14	Day 21	Day 28
P. aeruginosa	2.42	2.32	2.41	2.41	2.40
E. coli	2.41	2.30	2.41	2.40	2.37
S. aureus	2.43	2.32	2.41	2.39	2.38
C. albicans	2.40	2.41	2.41	2.40	2.36
A. niger	2.40	2.40	2.33	2.25	2.08

Solution 2 was also able to maintain a stable pH of around 2.0 to 2.5 for at least 28 days in the presence of all tested organisms, as seen in Table 4, and for up to three months when incubated at 40°C.

These findings clearly show that the solutions of the invention are able to destroy, inhibit and therapeutically significantly limit the microbial growth when the pH is maintained at pH about pH 2.5 or lower.

All excipients and additives, alone or in varieties of combinations, in percentages as disclosed, with or without the presence of a pharmaceutical agent, are intended to be within the scope of this invention as long as they are formulated and maintained at pH lower than 3.5.

EXAMPLE 1

Artificial Tears Formulation

This example describes preparation and testing of Solutions 1 and 2.

One formulation of the invention was prepared for artificial tears. The formulation consists of polyethylene glycol 400 (PEG 400) 8%, HPMC 0.3%, citric acid 0.01%, and purified water QS, with pH adjusted to 2.5 with hydrochloric acid.

This formulation was instilled in one eye of ten subjects. The other eye was treated with Genteal, a commercially available artificial tear. The formulation drops were consistently at least as comfortable as Genteal, administered in the fellow eye. There was variable slight to moderate stinging in most subjects if the citric acid concentration was increased to 0.02 or 0.03%. Therefore, approximately 0.01 % is the maximum desired citric acid concentration for comfort.

The same formulation was used in a further pilot clinical experiment to test safety. Following baseline slit lamp examination, one drop of the formulation was placed in the right eye of the subject every 15 minutes for eight hours. The left eye was similarly treated with Genteal artificial tears as a control. Drop instillation was completely comfortable in both eyes. Follow-up slit lamp examination revealed no corneal fluorescein staining in either eye. The same formulation and control solution were used in a similar manner in one subject wearing soft contact lenses. Again, drop instillation was comfortable in both eyes, and no corneal fluorescein staining was seen on follow-up examination.

was filled with the preparation of Solution 1. It was repeatedly sprayed into the right and left nostril of the subject. No irritation or unpleasant sensation was noted on either side.

Another formulation of the invention for artificial tears consists of dextrose 4.0%, PEG 400 1.0%, HPMC 0.3%, citric acid 0.01 %, and purified water OS, with the pH adjusted to 2.5 with hydrochloric acid. In this formulation, dextrose is the main tonicity agent. Similar molecules such as mannitol, or electrolytes such as sodium chloride, can also be used to adjust the tonicity. This formulation, described above as Solution 2, was tested in the same manner as Solution 1.

EXAMPLE 2

Preparation of Solutions 1 and 2

This example describes a procedure used for preparation of Solutions 1 and 2 and with moderate modifications is suitable for preparation of all combinations of various excipients and/or additives and pharmaceutical agents and salts thereof.

Solutions were prepared as follows:

All of the solutions were prepared using Class A volumetric flasks and pipettes. Test solutions were prepared on weight basis, except for the pH adjustments which were made volumetrically. One (1) liter of each test solution was made.

The hydroxypropyl methylcellulose was weighed out and mixed into 500 mL of cold de-ionized water (4°C). The solution was mixed using a stir bar and stir plated until the cellulose dissolved completely. The rest of the ingredients were then added in the following order: polyethylene glycol, citric acid, glucose (if used), another 400 mL of de-ionized water was added, stirred and adjusted to the correct pH with hydrochloric acid (0.1 N). The solutions were then made up to volume with de-ionized water and allowed to sit overnight. The pH was rechecked and adjusted, if needed, and then filtered through a one (1) liter 0.22 μm polyethersulfone

EXAMPLE 3

Stability and Storage

This example describes conditions suitable for stability and storage.

The formulations disclosed in Example 1 was stored at 40°C for more than 2 months for accelerated pH stability testing. The solution was sterilized before storage. The pH was tested weekly for 11 weeks. All samples tested were found to be stable with pH around 2.5 for the 11 weeks.

WHAT IS CLAIMED

1. A self-preserved preservative-free topical ophthalmic, inhalable or nasal formulation comprising:

a pharmaceutically acceptable excipient or additive selected from the group consisting of a pharmaceutically acceptable excipient or additive selected from the group consisting of dextrose, polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC), sodium chloride, potassium chloride, calcium chloride, magnesium chloride, phosphoric acid, disodium edetate, bicarbonate, phosphate, povidone, carboxymethylcellulose, hydroxyethylcellulose, methylcellulose, microcrystalline cellulose, other cellulose derivatives, glycerin, polyvinyl alcohol, dextran 40, dextran 70, mannitol, gelatin, polyols, polysorbate 80, propylene glycol, zinc sulfate, poloxamer 188, 282, 407, ephedrine hydrochloride, naphazoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, lecithin, oleic acid and sorbitan, pheniramine maleate, pyrilamine maleate, antazoline phosphate, glycine, camphor, eucalyptol, menthol, benzyl alcohol, lavender oil, tyloxapol, bornyl acetate, and phenylethyl alcohol, alone or in admixture; and

a buffering agent;

said formulation adjusted to pH from about pH 1.5 to pH about 3.5.

2. The formulation of claim 1 wherein pH is adjusted to pH from about pH 2.0 to about 2.5.

3. The formulation of claim 2 wherein the pH is about 2.5.

4. The formulation of claim 3 wherein the buffering agent is acetic, citric, formic, glutaric, glycolic, lactic,

5. The formulation of claim 4 wherein the buffering agent is citric acid.

6. The formulation of claim 5 wherein the excipient, additive or a pharmaceutical agent is present in amount from 0.001 to about 8% and wherein the buffering agent is present in amount from about 0.001 to about 0.02%.

7. The formulation of claim 6 comprising about 1-8% of polyethylene glycol, about 0.1% to about 0.3% of hydroxypropyl methylcellulose, about 0.01% to about 0.02% citric acid and purified water, wherein the pH is adjusted to about pH 2.5.

8. The formulation of claim 7 comprising about 8% of polyethylene glycol, about 0.3% of hydroxypropyl methylcellulose, about 0.01% citric acid and purified water, wherein the pH is adjusted to about pH 2.5.

9. The formulation of claim 8 wherein the pH is adjusted with an acid or a base.

10. The formulation of claim 9 wherein the acid is hydrochloric acid or sulphuric acid and wherein the base is sodium hydroxide or ammonium hydroxide.

11. The formulation of claim 7 additionally comprising about 2 to 6% of dextrose.

12. The formulation of claim 11 comprising about 4% of dextrose, about 1% of polyethylene glycol, about 0.3% of hydroxypropyl methylcellulose and about 0.01% of citric acid.

13. The formulation of claim 12 wherein the pH is adjusted with an acid or a base.

14. The formulation of claim 9 wherein the acid is hydrochloric acid, phosphoric acid or sulphuric acid and wherein the base is sodium hydroxide or ammonium hydroxide.

15. A method for preparation of a topical ophthalmic, nasal or inhalable self-preserved solution comprising steps of:

a) preparing a formulation comprising

a pharmaceutically acceptable excipient or additive selected from the group consisting of dextrose, polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC), sodium chloride, potassium chloride, calcium chloride, magnesium chloride, phosphoric acid, disodium edetate, bicarbonate, phosphate, povidone, carboxymethylcellulose, hydroxyethylcellulose, methylcellulose, microcrystalline cellulose, other cellulose derivatives, glycerin, polyvinyl alcohol, dextran 40, dextran 70, mannitol, gelatin, polyols, polysorbate 80, propylene glycol, zinc sulfate, poloxamer 188, 282, 407, ephedrine hydrochloride, naphazoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, lecithin, oleic acid and sorbitan, pheniramine maleate, pyrilamine maleate, antazoline phosphate, glycine, camphor, eucalyptol, menthol, benzyl alcohol, lavender oil, tyloxapol, bornyl acetate, and phenylethyl alcohol, alone or in admixture; and

a buffering agent; and

b) adjusting pH of said formulation to from about pH 1.5 to pH about 3.5.

16. The method of claim 15, wherein the buffering agent is citric acid or sodium citrate and wherein the pH is adjusted to pH about 2.0 to about 2.5.

17. The method of claim 16, wherein the pH is adjusted

18. The method of claim 17, wherein the solution is used as a topical eye preparation for administration of a pharmaceutical agent, artificial tear, contact lens solution or eye irrigating solution.

19. The method of claim 18 wherein the pharmaceutical agent is selected from the group consisting of an analgesic, anti-inflammatory, astringent, antihistamine, mast cell stabilizer, diagnostic aid, fluorescein, miotic, mydriatic, antibiotic, antiviral, antifungal, vasoconstricting agent, antiglaucoma medication, hypertonicity agent, decongestant, bronchodilator and topical anesthetic, said pharmaceutical agent present in from about 0.001 to about 8%.

20. The method of claim 19 wherein the anesthetic is proparacaine, tetracaine, lidocaine, benoxinate, and bupivicaine.

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A. CLASSIFICATION OF SUBJECT MATTER

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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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,E	US 6,309,633 B1 (EKWURIBE et al) 30 October 2001, see Abstract; column 21, lines 25-47; column 22, line 67; column 24, lines 7-10; Table 1.	1-20

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

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(54) Title: USE OF FLUNARIZINE FOR THE TOPICAL TREATMENT OF GLAUCOMA

(57) Abstract

Use of flunarizine, a calcium channel blocking agent known for use as cerebral and peripheral vasodilator, in the treatment of glaucoma by topical administration. Differently from other calcium channel blockers already tested for use as antiglaucoma agents, flunarizine is highly active in lowering the intraocular pressure when administered by the topical ophthalmic route. The invention also comprises anti–glaucoma preparations containing flunarizine, or combinations of flunarizine with beta–blockers such as timolol.

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USE OF FLUNARIZINE FOR THE TOPICAL TREATMENT OF GLAUCOMA

SPECIFICATION

The present invention concerns the use of flunarizine for the topical treatment of glaucoma. More specifically, this invention relates to the use of flunarizine, a calcium channel blocking agent known and employed as cerebral and peripheral vasodilator, in a new indication as an antiglaucoma agent for topical ophthalmic treatment.

As it is known, glaucoma is a pathological ophthalmic condition the underlying causes of which are not well understood at present. This condition is usually shown by a progressive increase of the intraocular pressure, leading to severe impairment of the eye structures, in particular to damage to the optic nerve disc and to decrease in the visual field, finally resulting in optic atrophy. The disease is generally connected to an insufficient outflow of aqueous humour from the eye, although other causes, such as, e.g., the production of aqueous humour and the episcleral veins pressure, take part in the regulation of the intraocular pressure.

The rationale of the pharmacological therapy presently in use is to lower the intraocular pressure. The drugs currently used to that aim, divided into classes according to their mechanism of action, are beta-blockers (such as timolol, betaxolol, levobunolol), sympathomimetics (such as epinephrine and dipivephrine), parasympathomimetics or miotics (such as pilocarpine and acetylcholine) and carbonic anhydrase inhibitors (such as acetazolamide and dichlorphenamide). Besides the foregoing drugs well established in use, the search for agents having less side effects and longer lasting activity has lead to evaluate, more recently, the possibility of using for the treatment of glaucoma another class of drugs, i.e. the calcium blocking agents. The latter, also known as "calcium entry blockers" or "calcium antagonists", are currently used as vasodilators and in the treatment of cardiac affections. For such indications, the most widespread calcium antagonists are, e.g., nifedipine,

diltiazem and verapamil.

The role of calcium in the dynamics of aqueous humour and in the control of intraocular pressure has not yet been entirely clarified, although it is known that the production and the outflow of aqueous are modulated also by calcium. As concerns the formation of aqueous, it is to be noted, firstly, that the hydrostatic component due to the arterial pressure and to the pressure of the vessels feeding the ciliary body is calcium-dependent, as it is confirmed by the known systemic vascular action of calcium antagonists. Further, the osmotic pressure due to ionic secretion at the level of the non-pigmented ciliary epithelium is likely to be modulated by calcium, as hypothesised by Abelson et al. (Abelson M.B., Gilbert C.M., Smith L.M., Sustained reduction of intraocular pressure in humans with the calcium channel blocker verapamil, Am. J. Ophthamol. 105; 155 (1988)).

As far as the outflow of the aqueous humour is concerned, calcium ions play a direct role in modulating the pressure of episcleral veins, and some studies suggest that calcium influences the outflow capacity, by maintaining the structural integrity of the trabecuale and of the exterior wall of the Schlemm's canal.

In spite of the foregoing suggestions several experimental works, both on animal models and clinical, and involving both systemic and topical administration, reported contradictory results about the activity of calcium channel blockers in the therapy of glaucoma. For instance, Monica et al. (Monica M.L., Hesse R.J., Messerli F.H., The effect of a calcium-channel blocking agent on intraocular pressure, Am. J. Ophthalmol. 96, 814 (1983)) reports that the oral administration of nitrendipine to patients with moderate hypertension but with normal intraocular pressure slightly lowered the latter, while Beatty and co-workers (Beatty J.F., Krupin T., Nichols P.F., Elevation of intraocular pressure by calcium-channel blockers, Arch. Ophthalmol. 102; 1072, (1984)) did not evidence any effect upon oral administration of verapamil to rabbits, and did even report an increase in the intraocular pressure upon topical administration. More recently, for instance, Payene and co-workers (Payene, L.J., Slagle T.M., Cheeks L.T., Effect of calcium-channel

blockers on intraocular pressure, Ophthalmic Res. 22; 337, (1990)) obtained a reduction in the intraocular pressure upon systemic administration of verapamil or nifedipine to rabbits, but did not detect any significant effect upon topical administration of the same agents or of diltiazem by the topical route.

In general, however, at least as far as verapamil is concerned, it may be said that the administration of this drug to man normally results in a reduction of the intraocular pressure. A more consistent reduction upon topical administration has been explained, in particular, by a work of Ettl et al. (Ettl A., Daxer A., Hoffmann U., Calcium channel blockers in the management of low-tension and open-angle glaucoma, Am. J. Ophthalmol. 116; 778, (1993)). These authors have detected, in the rabbit eye, verapamil levels 200 times higher than the levels obtainable by systemic administration.

Accordingly, the use of verapamil in the treatment of ocular hypertension is the object of the international PCT application No. WO 92/07563, filed by Abelson (i.e., the first author cited above) et al.. A later publication in the name of the same author is the international application No. WO 96/03986, concerning the treatment of a particular form of glaucoma, referred to as low-tension glaucoma. This pathology is characterised by an intraocular pressure which is almost normal, in spite of the fact that all of the other symptoms of glaucoma are present. In the latter document the therapeutic proposal is generically extended to all calcium-antagonists, many representatives of which are mentioned in a preliminary list. However, the only example of active agent disclosed in the document and supported by experimental data is verapamil.

Another calcium blocking agent that was specifically proposed for use, in a patent document, in the treatment of intraocular hypertension is diltiazem (French patent No. 2593395, published in 1987), while a list of more than one hundred calcium antagonists is presented in the international PCT application No. WO 93/23082. The latter concerns, for use in the treatment of glaucoma, a combination of a compound which lowers the intraocular pressure (i.e., a conventional antiglaucoma agent) and a calcium channel blocking agent. The disclosure does not contain any specific example of preferred

combination, nor any experimental detail regarding the activity of any combination.

Some experimental trials on verapamil also allowed to ascertain that the ophthalmic use of the said agent causes an undesirable swelling of the cornea. (Green K., Cheeks L., Hull D.S., Effects of calcium channel blockers on rabbit corneal endothelial function, Curr. Eye Res. 13; 401-408, (1994)). This is particularly critical if one considers the use for the treatment of a chronic condition as is, actually, glaucoma.

Although the entire class of calcium antagonists has already been considered for its potential use in the treatment of glaucoma, there does not seem to have been evidenced the particular activity, against this type of pathologies, of a specific agent belonging to the said class, i.e. flunarizine. It has now been found, and it is the subject-matter of this invention, that the specific calcium antagonist flunarizine, when administered through the topical ocular route, is able to lower the intraocular pressure in a surprisingly more marked way than the other calcium antagonists so far proposed and tested for the therapy of glaucoma.

Within the frame of the studies connected with this invention, it has also been found that some known receptors, referred to as σ receptors, are localised in the ocular region, in particular in the ciliary body and in the iris, and that some specific "ligands", having a σ-agonist activity, significantly lower the ocular pressure. Since it has been experimentally found that flunarizine shows a σ-agonist activity which is far higher than the activity of other calcium antagonists, this property may explain the unexpectedly greater activity of flunarizine in lowering the intraocular pressure, if it is hypothesised that such activity is exerted according to mechanisms of action that are at least partially different from the other calcium blocking agents.

In order to identify the presence of σ receptor sites in the eye the technique of "receptor binding" has been exploited. The latter has been carried out on cell membranes obtained from the irido-ciliary body complex. The irido-ciliary body complex had been explanted, after sacrifice, from male al-

bino rabbits of the New Zealand strain. The tissue was homogenised in buffer and a fraction rich in cell membrane proteins was isolated, obtained by centrifugation. The concentration of total proteins has been evaluated by the method of Lowry (Lowry, J. Biol. Chem. 193; 265 (1951)). Aliquots of the said fraction of the homogenate containing 300 μg of total proteins were incubated with scalar amounts of [^{3}H](+)-pentazocine (which is used, for experimental purposes only, as a σ ligand). The reaction was carried out at 37°C for 150 minutes and then, after filtering, the radioactivity left on the filters was measured by liquid scintillation. The apparent dissociation constant (Kd) and the total number of receptors were determined, and it was thus ascertained that [^{3}H](+)-pentazocine selectively binds to receptor sites present in the iridociliary body region of the rabbit. On the basis of the present scientific knowledge, the said receptors appear to be of the type σ-1.

Further, "competitive binding" assays carried out with a constant amount of [^{3}H](+)-pentazocine and scalar amounts of (+)-N-allil-nor-methazocine (NANM) (which is used, for experimental purposes only, as a σ ligand), showed that the latter shift the radioactive ligands from the receptor sites. It has also been observed, by analysing the Hill coefficient, that NANM interacts with one only class of σ receptor sites.

In the frame of the same research it has been found that σ-agonist agents show an ocular anti-hypertensive activity. A 1% preparation of NANM was administered (50 μl) in the conjunctival fornix of the right eye of male albino rabbits of the New Zealand strain, after measuring the (baseline) intraocular pressure. Upon measuring again the intraocular pressure 60, 120, 180 e 240 minutes after the instillation, it has been ascertained that the intraocular pressure was significantly reduced ($p<0.01$) 60 minutes after the instillation, in comparison with the formulation containing the vehicle only.

Lastly, as it was pointed out before, studies of receptor binding carried out with flunarizine (some of which are presented in the following) have shown that flunarizine has an affinity for σ-1 receptors which is not even comparable to the affinity shown by the other calcium channel blocking agents

tested.

Another advantageous aspect distinguishing flunarizine from the other calcium channel blocking agents proposed so far for the topical treatment of glaucoma is, as it has now been found, that flunarizine does not show any side effect of corneal swelling.

Therefore, the present invention specifically provides the use of flunarizine, optionally in the form of a pharmaceutically acceptable salt, for the topical treatment of glaucoma, i.e. the use of flunarizine, or of a pharmaceutically acceptable salt thereof, in the manufacture of a topical ophthalmic medicament for the treatment and/or the prophylaxis of glaucoma. In general, the topical administration of flunarizine may take place by using a preparation in the form of an aqueous solution or suspension, or in the form a gel, an ointment or a cream in a pharmaceutically acceptable ophthalmic vehicle, or in the form of an erodible ocular insert or of a "reservoir" system with a polymer membrane, to be placed in the conjunctival sac.

The concentration of flunarizine in an ophthalmic vehicle may range from 10 µg/ml to 5 mg/ml, i.e. from 0.001 to 0.500% by weight. The optimal concentration is chosen firstly on the basis of the dosage to be administered: in the case of use in eye-drop form, for instance, one drop should contain a sufficient amount of flunarizine for the drop to be effective as such or when instilled twice (i.e., two drops). Other criteria for the choice of the concentration are the ocular tolerability (it should be considered that the conjunctival sac, into which the ophthalmic preparation is to be instilled, has a limited capacity) and the stability of the active ingredient. The preferred concentration for an aqueous solution formulation (eye-drops) is 0.050% by weight, and preferably the product is present in the form of the corresponding hydrochloride salt (optimal concentration of flunarizine hydrochloride: 0.052%).

According to a particularly preferred embodiment of this invention, the anti-glaucoma activity of the proposed ophthalmic preparation is further enhanced by the presence, in combination with flunarizine, of an effective amount of a beta-blocking agent. The class of beta-blockers (or β-adrenergic

blockers), referred to in the foregoing, represents to date the most widespread class of anti-glaucoma agents. These agents are used in the topical treatment of chronic open angle glaucoma and, more generally, in the treatment of intraocular hypertension. Their mechanism of action mainly consists in reducing the production of the aqueous humour, and therefore the unexpected enhanced activity of the proposed combination of flunarizine (which has been found to be active in increasing the outflow of aqueous) with a beta-blocker may reasonably be explained in terms of a complementarity of the two actions.

Preferably, the concentration of beta-blocking agent in the combination according to the invention is from 0.1 to 2.5% by weight, and most preferably said beta-blocking agent is timolol or a pharmaceutically acceptable salt thereof.

A vehicle that may be employed in an eye-drop preparation according to the invention is the simple physiological saline solution containing 0.9% by weight of sodium chloride. Such solution is isotonic with respect to the tear fluid, and therefore it is well tolerated by the eye. However, also hypotonic solutions or suspensions may be employed, as it is known that these preparations are well tolerated by the ocular tissues.

Other excipients may be added to the composition of the invention in order to adjust the tonicity of the solutions or suspensions, so as to stabilise the active ingredient(s) and to increase the tolerability of the preparation. Specifically, any buffers should maintain the pH into the range 4-8. For instance, the above saline solution may be buffered with any one of the buffers well known in the pharmaceutical art for ophthalmic use, such as, e.g., phosphate buffer, or trizma buffer (i.e., tri-hydroxymethyl amino methane), so as to obtain a physiological pH, in the range of 7.0-7.4. Further, the solution may also have an osmolarity in the physiological range (295-305 mOsm/l). This allows to obtain a better ocular tolerability. In addition, the formulation may advantageously contain an antioxidant, such as, e.g., gallates, ascorbic acid, superoxide dismutase (SOD), BHT, sodium metabisulphite, tocopherols, BHA, nordihydroguaiaretic acid, ascorbic acid esters, dimethylthiourea and the like.

The tolerability may be further enhanced by means of other excipients such as cyclodextrins, polysorbate 80 (or Tween 80), dextrane (e.g., dextrane 70), polyethylene glycol (e.g. PEG 400), poloxamers and other similar agents. The formulation may include viscosifying/thickening agents such as methylcellulose, polyvinyl alcohol, glucosamine glucans, polyvinyl pyrrolidone and the like, in order to increase the ocular bioavailability, the stability and the tolerability of the active ingredient(s).

The ocular bioavailability of flunarizine may be further enhanced by the addition of substances which increase the corneal permeation of the drug, such as, e.g., dimethyl sulphoxide, taurocholates, membrane phospholipides, benzalkonium chloride and other surface active agents for ophthalmic use (such as disodium lauryl sulphosuccinate).

Lastly, in the preparations to be packaged in multidose bottles compositions a preservative with antimicrobial activity will have to be added, in order to prevent contamination of the product. Such agent may be chosen among the preservative agents well known for this use in the pharmaceutical art.

Products to be administered in the form of suspensions should contain suitable agents such as carboxymethyl cellulose and the like. In the event that the preparation is to be employed in the form of an ointment, a gel or a cream for ophthalmic use, flunarizine will be admixed with carriers such as polyethylene glycols, polyacrylates, polyethylene oxides, fatty acids and alcohols or lanolin, paraffin and other similar products. Suitable ingredients for the production of emulsions or microemulsions may be chosen among the following: diethylene glycol-monobutyl ether, di(ethylene glycol) buthyl ether, caprylic acid ethyl ester, oleic acid ethyl ester, soybean oil, hexadecane, tributyrin, ethylene glycol-monobutyl ether, 1-hexadecene, n-heptane, 1-heptene, Tween 80, PEG, poloxamers, polyoxyethylene ethers.

The dosage of the main active ingredient of the invention, to be administered by the topical route, may vary from about 20 µg to about 200 µg per day for each eye. The prescription dosage of the ophthalmic preparations based on flunarizine will depend on the daily dose that will be necessary to

achieve the therapeutic effect and, obviously, on the specific formulation employed. Ophthalmic solutions or suspensions will require from 1 to 4 instillations per day; ointments, gels and creams will require 1 or 2 applications; solid inserts with polymeric matrix, either biodegradable or not, will require one only administration per day.

The present invention further concerns compositions which allow the administration of flunarizine through the topical ophthalmic route, and specific ophthalmic compositions for use in the treatment and/or in the prophylaxis of glaucoma comprising, as an active ingredient, a therapeutically effective amount of flunarizine. A group of preferred compositions have the following formulation (wherein all percentages are by weight):

flunarizine hydrochloride	0.059	%
(corresponding to 0.05% flunarizine)		
sodium chloride	0.10-0.80	%
trizma buffer	0.02-0.20	%
PEG 400	1.00-6.00	%
Tween 80	2.00-12.00	%
sodium metabisulphite	0.01-0.20	%
propyl gallate	0.01-0.50	%
EDTA	0.005-0.20	%
purified water	q.s. to 100	%

optionally comprising further pharmaceutically acceptable ingredients.

In a particularly preferred embodiment of this invention, the compositions for use in the treatment and/or in the prophylaxis of glaucoma further contain from 0.1 to 2.5% by weight of a beta-blocking agent, the latter being by preference timolol or a pharmaceutically acceptable salt thereof, such as timolol maleate.

Some specific embodiments of the invention are described below for merely illustrative purposes, together with the results of the experimental studies carried out on the proposed anti-glaucoma agent, including comparative tests with other calcium-blocking agents.

EXAMPLE 1

Ophthalmic solution based on flunarizine

A composition according to the invention that turned out to be particularly effective (the performance of which was experimentally evaluated as it is partly reported further on) has the following composition (the percentages being given by weight):

flunarizine hydrochloride	0.059 %
(corresponding to 0.050% flunarizine)	
sodium chloride	0.485 %
trizma buffer	0.100 %
PEG 400	2.500 %
Tween 80	5.000 %
sodium metabisulphite	0.050 %
propyl gallate	0.050 %
EDTA	0.010 %
purified water	q.s. to 100 %

The above composition is suitable for being packaged in single dose containers; in the event that a multidose packaging is desired, a preservative (such as, e.g., benzalkonium chloride) will have to be added in order to maintain the sterility of the product for the whole period of use.

EXAMPLE 2

Ophthalmic microemulsion based on flunarizine

A composition suitable for use as an ophthalmic ointment was prepared according to the formulation given below (weight percentages) :

flunarizine hydrochloride	0.059 %
(corresponding to 0.050% flunarizine)	
trizma buffer (to pH 7.20)	0.100 %
PEG 400	10.000 %
soybean oil	2.00 %
Tween 80	20.000 %
sodium metabisulphite	0.050 %
sorbitol	2.057 %

propyl gallate	0.050 %
purified water	q.s. to 100 %

As a tonicity adjusting agent, 455 mg of sodium chloride per 100 ml (i.e. 0.455 wt. %) may be used in place of the above amount of sorbitol.

EXAMPLE 3

Ophthalmic emulsion based on flunarizine

An ophthalmic product similar to that shown in the previous example, but having a coarser size of the drops of the dispersed phase, was obtained excluding the soybean oil from the composition, according to the following formulation (weight percentages) :

flunarizine hydrochloride	0.059 %
(corresponding to 0.050% flunarizine)	
trizma buffer (to pH 7.20)	0.100 %
PEG 400	2.000 %
Tween 80	7.000 %
sodium metabisulphite	0.050 %
sorbitol	2.014 %
propyl gallate	0.050 %
purified water	q.s. to 100 %

As an alternative to sorbitol as a tonicity adjusting agent, the composition may include 433 mg of sodium chloride per 100 ml (i.e. 0.433 wt. %).

EXAMPLE 4

Ophthalmic solution based on a combination of flunarizine and timolol

A particularly preferred composition according to the invention was obtained by adding to the formulation of Example 1 a sufficient amount of timolol maleate to achieve a concentration of 0.5% by weight of timolol in the overall composition (corresponding to about 0.68% by weight of timolol maleate). The concentrations of the other ingredients were the same as specified above for Example 1.

Similarly, also the formulations given in Examples 2 and 3 can be modified with the addition of a proper amount of timolol maleate. Also in this case, it is preferred to obtain a concentration of 0.5% by weight of timolol in

the overall composition.

Experimental results

An isotonic solution, buffered and viscosified according to the formulation of Example 1, but having variable concentrations of flunarizine (ranging from 0.01% to 0.1% by weight), was generally referred to as MEG 01 in the experimental work the results of which are set forth below. The experimentation also considered combinations of flunarizine and beta-blocking agents formulated as shown for timolol in Example 4. The combination of flunarizine and timolol was referred to as MEG 02. Some of the said experimental results are also shown in the graphs of the accompanying drawings, wherein:

Figure 1 shows the percent reduction in the intraocular pressure obtained upon instillation of flunarizine in the eyes of rabbits with hypertension, in comparison with the corresponding reduction obtained with the instillation of placebo and with the instillation of other calcium antagonists;

Figure 2 shows the percent reduction in the intraocular pressure obtained upon instillation, in the eyes of rabbits with ocular hypertension, of flunarizine at various concentrations; and

Figure 3 shows the percent reduction in the intraocular pressure obtained upon instillation, in the eyes of rabbits with ocular hypertension, of flunarizine in combination with various beta-blocking agents.

Pharmacodynamic studies

a. Study on rabbits with normal intraocular pressure

The effects of the agent of the invention on the intraocular pressure of rabbits showing normal baseline intraocular pressure were evaluated in comparison with the action of a placebo, and with that of various other calcium channel blocking agents. Female pigmented rabbits of the Vienna Blue strain were used (supplied by Charles River Italiana, of Calco (CO)). The age of the animals at the time of starting the experimentation was 9 weeks, and their weight was 2.0-2.5 kg.

The choice of a species with pigmented iris is due to the fact that the latter represents a reliable model for the evaluation of possible modifications of the intraocular pressure caused by the products under test. The strain

chosen is genetically defined, so as to limit to a minimum the variability of the biological characteristics between one animal and the other.

The animals were kept in rooms maintained under constant and controlled conditions of temperature and humidity, illuminated for 12 hours a day with artificial light and with continuous renovation of the air. The feed consisted of a standard diet having a constant and known composition, and both feed and water were available *ad libitum* during the whole period of the test. The rabbits were stabled for 21 days before starting the test, so as to allow a sufficient acclimatation and to suitably evaluate the health conditions of the rabbits. Each experimental group consisted of 4 animals, which were allotted to the treatment groups in a randomised way.

Each different group of animals received, by instillation in the right conjunctival fornix, 50 µl of the following products:

a) eye-drops of MEG 01, containing 0.050 wt. % flunarizine (0.052 wt. % flunarizine hydrochloride);

b) placebo solution (i.e., the vehicle of MEG 01);

c) eye-drops containing 0.056 wt. % verapamil in the vehicle of MEG 01;

d) eye-drops containing 0.051 wt. % diltiazem in the vehicle of MEG 01;

e) eye-drops containing 0.043 wt. % nifedipine in the vehicle of MEG 01.

The weight concentrations of the various agents under test are chosen so as to correspond to the same molar concentration.

The pressure in the treated eye was measured by flattening tonometer (TonopenXL®, Mentor), 15 minutes before the instillation of the eye-drops (time 0) and then 30, 60, 90, 120, 180 and 240 minutes after. As a local anaesthetic, 5 minutes before carrying out each measurement 25 µl of a commercial ophthalmic solution containing 0.4% oxybuprocaine hydrochloride (Novesine®, Sandoz) was instilled. To carry out the measurement the rabbits were placed in a suitably designed cage, that prevents any sudden movement of the animal under test.

For each animal and at each of the times listed above the average of three subsequent measurements was calculated and recorded, each one said

measurements being made after 1 minute from the previous one. The intraocular pressure values at the various times were compared with the values obtained before the treatment, by means of the Student's "t" test. The comparisons between different groups were made by processing the data by the variance analysis (ANOVA) and, where possible, by the Student's "t" test for the comparison of two different experimental groups. Values of $p < 0.05$ were considered to be statistically significant.

The following table shows the values of intraocular pressure determined on each one of the animals treated, as well as the average values for each test group (± standard deviation).

TABLE 1

Intraocular pressure in rabbits with normal pressure treated with the tested agents

		Intraocular pressure (mmHg) at the time (min)						
Rabbit No.	Eye	0	30	60	90	120	180	240
Eye-drops with 0.050% flunarizine (MEG 01)								
01	RE	17	15	14	15	15	15	17
02	RE	16	14	13	14	14	15	16
03	RE	14	13	12	12	14	14	16
04	RE	16	12	12	14	14	14	16
average±S.D.		15.7±1.2	13.5±1.3	12.7±0.95	13.7±1.2	14.2±0.5	14.5±0.5	16,2±0,5
Placebo								
05	RE	15	16	16	15	15	16	16
06	RE	16	15	14	16	16	17	17
07	RE	17	15	16	16	16	17	17
08	RE	15	15	16	16	16	15	17
average±S.D.		15.7±0.9	15.2±0.5	15.5±1.0	15.7±0.5	15.7±0.5	16.2±0.9	16.7±0.5
Eye-drops with 0.056% verapamil								
09	RE	17	16	15	15	16	16	17
10	RE	15	14	14	13	13	16	15
11	RE	16	17	15	15	16	17	17
12	RE	16	15	15	15	16	16	17
average±S.D.		16±0.8	15±1.3	14.7±0.5	14±1.0	15.7±0.5	16.2±0.5	16.5±1.0
Eye-drops with 0.051% diltiazem								
13	RE	15	14	14	14	15	15	16
14	RE	16	15	14	14	15	16	16
15	RE	18	17	17	16	16	17	17
16	RE	18	15	13	15	16	17	17
average±S.D.		16.7±1.5	15.2±1.2	14.7±0.9	14.7±0.9	15±0.5	16.2±0.95	16±0.6
Eye-drops with 0.043% nifedipine								
17	RE	16	15	14	16	16	17	17
18	RE	15	15	13	15	16	15	17
19	RE	14	13	13	15	16	15	14
20	RE	18	16	15	16	16	17	18
average±S.D.		15.7±1.7	14.7±1.2	13.7±0.9	15.5±0.6	16.0±1.5	16.5±1.7	16±0

As it is shown by the previous table, the MEG 01 eye-drops (containing 0.050% flunarizine) produced a significant reduction in the intraocular pressure after one hour from the administration, while a product consisting in the corresponding vehicle without flunarizine did not cause any significant modification in the intraocular pressure. In the latter case, the pressure values measured upon administration of the eye-drops are not statistically different from the values recorded before the instillation (time 0: 15 minutes before the administration).

Furthermore, neither the verapamil formulation nor the diltiazem formulation, both using the same vehicle as MEG 01, did produce any intraocular pressure decrease with respect to the placebo. Some minor reduction could be detected with the administration of nifedipine, but this effect appears to be negligible in comparison with the response obtained with MEG 01 containing 0.050 wt. % flunarizine.

Another series of tests was carried out on rabbits with normal baseline intraocular pressure in order to compare the activity of flunarizine with that of the proposed combination of flunarizine with a beta-blocking agent, and with the activity of a beta-blocking agent alone.

The following well-known beta-blockers were tested: timolol (which is a non-selective beta-blocker, being active both on β_1 and on β_2 adrenergic receptors), betaxolol (a cardioselective beta-blocker, active on the β_1 adrenergic receptors only) and carteolol (which is not selective, but is endowed with an intrinsic sympathomimetic activity). The tests were carried out according to the same experimental protocol described above, treating each different group of animals with the following compositions:

f) eye-drops of MEG 02, containing 0.050 wt. % flunarizine (0.052 wt. % flunarizine hydrochloride) in combination with 0.5 wt. % timolol (0.68 wt. % timolol maleate);

g) eye-drops containing 0.050 wt. % flunarizine and 0.5 wt. % betaxolol in the vehicle of MEG 02;

h) eye-drops containing 0.050 wt. % flunarizine and 2.0 wt. % carteolol in the

vehicle of MEG 02.

The results of this series of tests, obtained and processed in the same way as those shown in Table 1, are presented in the following table. In order to make any comparison easier, the data obtained with flunarizine alone and with the placebo, i.e. with the groups of animals a) and b) of the previous experiment, are shown again in the following table.

TABLE 2

Intraocular pressure in rabbits with normal pressure treated with the tested agents

		Intraocular pressure (mmHg) at the time (min)						
Rabbit No.	Eye	0	30	60	90	120	180	240
Eye-drops with 0.050% flunarizine (MEG 01)								
01	RE	17	15	14	15	15	15	17
02	RE	16	14	13	14	14	15	16
03	RE	14	13	12	12	14	14	16
04	RE	16	12	12	14	14	14	16
average±S.D.		15.7±1.2	13.5±1.3	12.7±0.95	13.7±1.2	14.2±0.5	14.5±0.5	16,2±0,5
Placebo								
05	RE	15	16	16	15	15	16	16
06	RE	16	15	14	16	16	17	17
07	RE	17	15	16	16	16	17	17
08	RE	15	15	16	16	16	15	17
average±S.D.		15.7±0.9	15.2±0.5	15.5±1.0	15.7±0.5	15.7±0.5	16.2±0.9	16.7±0.5
Eye-drops with 0.5% timolol								
101	RE	16	15	14	14	15	16	16
102	RE	16	14	13	14	15	16	17
103	RE	16	15	13	15	16	17	16
104	RE	15	15	14	15	16	15	15
average±S.D.		15.7±0.5	14.7±0.5	13.5±0.6	14.5±0.6	15.5±0.6	16.0±0.8	16.0±0.8
Eye-drops with 0.050% flunarizine and 0.5% timolol (MEG 02)								
105	RE	16	14	13	14	15	16	16
106	RE	17	13	14	14	14	15	17
107	RE	16	14	12	14	15	16	16
108	RE	16	14	12	13	14	15	15
average±S.D.		16.2±0.5	13.7±0.5	12.7±1.0	13.7±0.5	14.5±0.6	15.5±0.6	16.2±0.5
Eye-drops with 0.050% flunarizine and 0.5% betaxolol								
109	RE	15	14	14	14	15	16	15
110	RE	16	14	14	14	16	16	17
111	RE	17	15	15	16	16	16	17
112	RE	17	16	15	15	16	16	16
average±S.D.		16.2±1.0	14.7±1.0	14.5±0.6	14.7±1.0	15.7±0.5	16.0±0	16.2±1.0
Eye-drops with 0.050% flunarizine and 2.0% carteolol								
113	RE	17	16	14	15	16	17	16
114	RE	16	15	15	15	16	16	16
115	RE	16	13	14	15	16	16	17
116	RE	15	12	14	15	15	16	16
average±S.D.		16.0±0.8	14.0±1.8	14.2±0.5	15.0±0.0	15.7±0.5	16.2±0.5	16.2±0.5

From the experimental results of the previous table it appears on one hand that, in the conditions of the test, flunarizine alone had a better performance in lowering the intraocular pressure than timolol alone. On the other hand, the data show that that the activity of flunarizine was further enhanced by the addition of timolol in the formulation, as the performance of the combination was better than that of flunarizine alone.

b. Study on rabbits with ocular hypertension

Rabbits of the same type as those described in the previous section were used for the following tests. The rabbits had been preliminarily treated in the same way, and the stabling conditions were the same.

The experimental increase in the intraocular pressure was induced by administration of α- chymotrypsin. In the rabbit, the injection of this enzyme in the posterior chamber causes, after one month from the administration, an effect of ocular hypertension. This experimental model is widely used, and has often been employed in order to evaluate the activity of various anti-glaucoma agents.

At the end of the quarantine period the rabbits were anaesthetised by intramuscular administration of ketamine hydrochloride and xylazine hydrochloride (RBI). The right eye was gently pushed outwardly after instilling 25 µl of Novesine® eye-drops, containing oxybuprocaine as an anaesthetic; then, a sterile solution of α-chymotrypsin (SIGMA, Milan; 150 units in 100 µl of physiologic sterile solution) was injected in the posterior chamber of the right eye by means of a 30G sterile needle. After the administration of the enzyme, the eye was thoroughly washed with physiologic sterile solution in order to remove any traces of α-chymotrypsin which could damage the ocular tissues. Then, 2 drops of a commercial ophthalmic antibiotic solution (Colbiocin®, SIFI S.p.A., containing chloramphenicol, rolitetracycline, colistin methanesulphonate) were instilled. The treatment was carried out 3 times a day (at 8.00 a.m., 12.00 a.m. and 6.00 p.m.) for one week after the administration of α-chymotrypsin. The rabbits were employed in the tests after one month from the induction of ocular hypertension by means of the enzyme.

The rabbits, divided also in this case in groups of 4 animals, were treated by instillation of 50 µl of the product under test in the right conjunctival fornix. In a first experiment the agents employed were the same as in the first test reported in the foregoing (MEG 01 eye-drops with 0,050% flunarizine, placebo, and eye-drops with 0,056% verapamil, 0,051% diltiazem and 0,043% nifedipine respectively).

The intraocular pressure in the treated eye was measured, according to the same procedure as in the previous tests, 15 minutes before the instillation of the eye-drops and 30, 60, 90, 120, 180 and 240 minutes after. The values obtained were statistically analysed according to the criteria mentioned in the foregoing.

The following table shows, for each test group, both the individual intraocular pressure responses and their average values (± standard deviation). The average values of the intraocular pressure reduction, expressed in terms of percentage, are also diagrammatically translated into the graph of Figure 1.

TABLE 3

Intraocular pressure in rabbits with ocular hypertension treated with the tested agents

		Intraocular pressure (mmHg) at the time (min)						
Rabbit No.	Eye	0	30	60	90	120	180	240
Eye-drops with 0.050% flunarizine (MEG 01)								
21	RE	57	47	45	50	51	56	56
22	RE	46	38	37	38	39	44	45
23	RE	36	30	28	32	34	37	37
24	RE	52	43	41	43	45	51	51
average±S.D.		47.7±9.03	39.5±7.32	37.75±7.25	40.7±7.63	42.2±7.36	47.0±8.28	47.25±8.18
Placebo								
25	RE	57	56	57	58	56	57	57
26	RE	47	48	46	47	48	48	47
27	RE	41	42	43	42	41	42	43
28	RE	52	50	51	51	50	53	52
average±S.D.		49.25±6.84	49.0±5.77	49.25±6.13	49.5±6.75	48.75±6.18	50.0±6.48	49.75±6.07
Eye-drops with 0.056% verapamil								
29	RE	56	55	56	55	55	57	56
30	RE	47	48	49	46	47	46	48
31	RE	42	40	43	41	41	42	43
32	RE	51	52	52	50	51	50	51
average±S.D.		49.0±5.94	48.7±6.5	50.0±5.47	48.0±5.94	48.5±5.97	48.75±6.39	49.5±5.44
Eye-drops with 0.051% diltiazem								
33	RE	55	55	53	54	56	56	55
34	RE	52	53	51	52	52	51	52
35	RE	47	48	46	46	47	46	47
36	RE	42	42	40	41	43	43	41
average±S.D.		49.0±5.71	49.5±5.80	47.5±5.80	48.2±5.90	49.5±5.68	49.0±5.71	48.7±6.13
Eye-drops with 0.043% nifedipine								
37	RE	54	55	53	52	53	54	54
38	RE	50	52	50	50	49	48	49
39	RE	47	45	45	46	46	45	47
40	RE	41	39	39	38	40	41	42
average±S.D.		48.0±5.47	47.75±7.18	46.75±6.13	46.5±6.19	47.0±5.47	48.00±4.96	48.00±4.96

Table 3 shows that the administration of the vehicle alone does not result in any significant variation in the intraocular pressure, while MEG 01 (with 0.050% flunarizine) caused a reduction in the intraocular pressure remarkably higher than that obtainable with the administration of the other calcium antagonists tested. As it may be observed, the values of intraocular pressure in rabbits with ocular hypertension after treatment with ophthalmic solutions containing equivalent amounts of verapamil, diltiazem or nifedipine, in the same vehicle as MEG 01, do not show any significant reduction.

In a second series of trials, employing identical procedure steps, the ophthalmic solution according to the invention was tested at different concentrations of flunarizine, i.e. 0.1% and 0.01% by weight of active ingredient. The aim was to compare the response so obtained with the response observed with the MEG 01 eye-drops containing 0.05 wt. % flunarizine. The results are presented in the following table, and are also illustrated (as average percent amounts of the intraocular pressure reduction detected) in the graph of Figure 2.

TABLE 4

Intraocular pressure in rabbits with ocular hypertension treated with flunarizine

		Intraocular pressure (mmHg) at the time (min)						
Rabbit No.	Eye	0	30	60	90	120	180	240
Eye-drops with 0.010% flunarizine								
41	RE	60	58	55	53	58	60	61
42	RE	65	61	59	60	62	64	65
43	RE	53	51	49	48	52	52	52
44	RE	52	50	48	49	51	50	52
average±S.D.		57.5±6.13	55.0±5.35	52.7±5.18	52.5±5.44	55.7±5.18	56.5±6.60	57.5±6.55
Eye-drops with 0.050% flunarizine								
21	RE	57	47	45	50	51	56	56
22	RE	46	38	37	38	39	44	45
23	RE	36	30	28	32	34	37	37
24	RE	52	43	41	43	45	51	51
average±S.D.		47.7±9.03	39.5±7.32	37.7±7.27	40.7±7.63	42.2±7.36	47.0±8.28	47.2±8.18
Eye-drops with 0.100% flunarizine								
45	RE	58	48	45	49	51	56	57
46	RE	48	40	38	41	43	47	49
47	RE	42	36	34	36	38	41	43
48	RE	51	45	40	46	48	50	50
average±S.D.		49.7±6.6	42.2±5.31	39.2±4.57	43.0±5.71	45.0±5.71	48.5±6.24	49.7±5.73

From the foregoing table it may be observed that the highest percent reduction in the intraocular pressure was shown by the MEG 01 preparation with 0.05% flunarizine, while the preparation with the highest concentration (0.1%) showed an activity comparable with that of the 0.05% preparation. This is shown more clearly in the graph of Figure 2.

In a further series of tests the activity of combinations of flunarizine with a beta-blocking agent was tested on rabbits with hypertension. The experimental conditions were exactly the same as before. Three groups of animals were treated with the compositions defined under f), g) and h) in the previous section, and the results obtained are summarised in the following table. Also in this case, the data already obtained in the same experimental conditions for flunarizine alone and for the placebo are repeated for ease of comparison.

TABLE 5

Intraocular pressure in rabbits with ocular hypertension treated with the tested agents

		Intraocular pressure (mmHg) at the time (min)						
Rabbit No.	Eye	0	30	60	90	120	180	240
Eye-drops with 0.050% flunarizine (MEG 01)								
21	RE	57	47	45	50	51	56	56
22	RE	46	38	37	38	39	44	45
23	RE	36	30	28	32	34	37	37
24	RE	52	43	41	43	45	51	51
average±S.D.		47.7±9.0	39.5±7.3	37.7±7.2	40.7±7.6	42.2±7.4	47.0±8.3	47.2±8.2
Placebo								
25	RE	57	56	57	58	56	57	57
26	RE	47	48	46	47	48	48	47
27	RE	41	42	43	42	41	42	43
28	RE	52	50	51	51	50	53	52
average±S.D.		49.2±6.8	49.0±5.8	49.2±6.1	49.5±6.7	48.7±6.2	50.0±6.5	49.7±6.1
Eye-drops with 0.5% timolol								
117	RE	53	43	42	42	46	52	53
118	RE	54	45	42	42	45	48	51
119	RE	46	39	39	38	39	42	45
120	RE	43	40	36	37	40	42	44
average±S.D.		49.0±5.3	41.7±2.7	39.7±2.9	39.7±2.6	42.5±3.5	46.0±4.9	48.2±4.4
Eye-drops with 0.050% flunarizine and 0.5% timolol (MEG 02)								
121	RE	52	35	33	33	36	38	41
122	RE	58	39	36	37	41	46	48
123	RE	47	31	29	32	35	37	38
124	RE	45	32	26	30	36	36	35
average±S.D.		50.5±5.8	34.2±3.6	31.0±4.4	33.0±2.9	37.0±2.7	39.2±4.6	40.5±5.6
Eye-drops with 0.050% flunarizine and 0.5% betaxolol								
125	RE	49	39	36	38	42	42	43
126	RE	45	35	37	37	39	40	41
127	RE	56	44	42	46	47	49	49
128	RE	55	45	41	43	47	46	51
average±S.D.		51.2±5.2	40.7±4.6	39.0±2.9	41.0±4.2	43.7±3.9	44.2±4.0	46.0±4.8
Eye-drops with 0.050% flunarizine and 2.0% carteolol								
129	RE	57	53	40	42	50	54	56
130	RE	52	46	44	45	48	49	49
131	RE	47	37	39	40	44	43	43
132	RE	46	36	37	39	40	41	43
average±S.D.		50.5±5.1	43.0±8.0	40.0±2.9	41.5±2.6	45.5±4.4	46.7±5.9	47.7±6.2

The data reported in Table 5, and even more clearly the diagram of Figure 3, evidence the remarkable activity of the combination of flunarizine with timolol and, in general, the good performance of the combinations of flunarizine with beta-blocking agents. Also in this case, flunarizine alone showed an effectiveness comparable to or better than that of timolol alone.

Toxicity studies

a. Evaluation of the corneal swelling

The evaluation of the thickness of the cornea was carried out ecographically by means of a UBM System 840 (Humphrey Instruments, San Leandro, CA, USA). The apparatus includes a 50 MHz probe and allows to visualise images on a display with a resolution of about 504 and a visualisation field of 5x5mm. The software incorporated allows to modify the focalisation depth of the ultrasound beam, and to capture the image while varying its amplification.

The animals employed in this test were of the same type as those described in the foregoing, and were treated in the same way. The test was carried out, after having anaesthetised the animal (with ketamine hydrochloride and xylazine hydrochloride), by placing into contact with the eyeball tiny cups filled in with a coupling means (ultrasound gel). The rabbits received in the right eye a single instillation (50 µl) of each of the same agents employed in the pharmacodinamic studies: a) MEG 01 eye-drops with 0.050% flunarizine, c) eye-drops containing 0.056 wt. % verapamil; d) eye-drops containing 0.051 wt. % diltiazem; d) eye-drops containing 0.043 wt. % nifedipine. In the left eye the rabbits received an instillation of an equal amount of placebo (vehicle of MEG 01 without any active ingredient).

The following table shows the corneal thickness as detected on various groups of 4 rabbits each, before the instillation and at fixed time intervals after the instillation.

TABLE 6

Corneal thickness in rabbits topically treated with calcium antagonists

		Corneal thickness (mm) at the time (min)			
Rabbit No.	Eye	Baseline	1 hour	2 hours	3 hours
RE: MEG 01 with 0.050% flunarizine - LE: Placebo					
49	RE	0.394	0.394	0.394	0.394
49	LE	0.394	0.394	0.394	0.394
50	RE	0.347	0.347	0.347	0.347
50	LE	0.347	0.347	0.347	0.347
51	RE	0.386	0.386	0.386	0.386
51	LE	0.386	0.386	0.386	0.386
52	RE	0.363	0.363	0.363	0.363
52	LE	0.363	0.363	0.363	0.363
RE: eye-drops with 0.056% verapamil - LE: Placebo					
53	RE	0.356	0.376	0.385	0.383
53	LE	0.356	0.358	0.360	0.367
54	RE	0.384	0.398	0.406	0.402
54	LE	0.384	0.382	0.388	0.380
55	RE	0.372	0.387	0.400	0.402
55	LE	0.372	0.374	0.368	0.372
56	RE	0.392	0.401	0.494	0.410
56	LE	0.392	0.390	0.396	0.388
RE: eye-drops with 0.051% diltiazem - LE: Placebo					
57	RE	0.377	0.380	0.382	0.384
57	LE	0.377	0.380	0.380	0.377
58	RE	0.389	0.392	0.394	0.396
58	LE	0.389	0.389	0.325	0.387
59	RE	0.396	0.400	0.400	0.400
59	LE	0.396	0.396	0.394	0.398
60	RE	0.358	0.362	0.364	0.364
60	LE	0.358	0.358	0.360	0.360
RE: eye-drops with 0.043% nifedipine - LE: Placebo					
61	RE	0.375	0.380	0.380	0.380
61	LE	0.375	0.375	0.376	0.375
62	RE	0.372	0.380	0.378	0.378
62	LE	0.372	0.374	0.372	0.372
63	RE	0.396	0.398	0.400	0.400
63	LE	0.396	0.396	0.396	0.396
64	RE	0.384	0.388	0.389	0.390
64	LE	0.384	0.382	0.984	0.382

As it may be observed from the foregoing data, with the use of the product according to the invention no alteration has been detected in the corneal thickness for the whole period of the test. On the contrary, the ophthalmic solution containing 0.056% verapamil caused corneal swelling, with increases in thickness of about 15-20 µm/hour. No significant effect has been noted for the eye-drops containing diltiazem (only slight swelling) or nifedipine.

b. Acute tolerability

In order to evaluate the tolerability of the calcium channel blocking agent according to the invention when topically applied to the eye, rabbits (of the same kind as those employed in the previous experimentation) were treated as follows, after an initial acclimatation period. On the first day, 12 instillations of MEG 01 (0.05%) in the right conjunctival fornix, of 0.05 ml each, were made at intervals of 30 minutes. The contralateral eye was treated with placebo and served as a control.

The condition of the ocular tissues was observed according to the Draize modified test (Spampinato S., Marino A., Bucolo C., Canossa M., Bachetti T., Mangiafico S., Effect of sodium naproxen eye drops on rabbit ocular inflammation induced by sodium arachidonate, J. Ocular Pharm., 7 (2); 125-133, (1991)). The examination was carried out every hour starting from the first administration for 7 hours, and then 24, 48 and 72 hours after the last treatment, giving arbitrary scores to the various aspects of the palpebral and bulbar conjunctiva, of the iris and of the cornea.

No significant reddening of the conjunctiva was observed for the whole period of the test, both in the eyes treated with MEG 01 eye-drops (0.05% wt. % flunarizine) and in the eyes treated with placebo. No oedema was detected in any of the eyes tested. In addition, no alteration involving the iris was noted in any of the eyes treated, and the presence of drain material was maintained at a normal level. Neither any damage has been detected in the corneal tissues; two eyes only showed a slight desepithelisation.

The results obtained show that the MEG 01 ophthalmic solution based on 0.05% flunarizine is well tolerated in the rabbit eye after repeated

instillation in the conjunctival fornix.

Binding studies

The receptor binding technique was carried out on cell membranes obtained from the irido-ciliary body complex explanted, after sacrifice, from male albino rabbits of the New Zealand strain (Charles River Italiana, of Calco (CO)). The tissue was homogenised in buffer and the P_2, fraction, rich in cell membrane proteins, was isolated. The said fraction was obtained by centrifugation according to what described in the literature (Mach R.H., Smith C.R., Childers S.R. Ibogaine possesses a selective affinity for sigma 2 receptors, Life Sci. 57(4); 57-62). The La total protein concentration was determined with the Lowry method.

Aliquots of the P_2 fraction of the homogenate respectively containing 300 µg of total proteins were incubated in polypropylene test tubes containing scalar amounts of the calcium antagonists under test (i.e. flunarizine, verapamil, nifedipine and nimodipine), and a known amount of ^{3}H(+)-N-allyl-normethazocine (SKF) (experimentally used as a σ ligand). The non specific binding was evaluated in presence of haloperidol.

All tests were carried out in duplicate. The reaction was maintained at 37°C for 150 minutes, followed by filtration on WhatmannGF/B filters. The radioactivity left on the filters was measured by liquid scintillation spectrometry. The IC_{50} was determined, and the results obtained are shown in the following table.

TABLE 7

Effects of various calcium antagonists on the inhibition of ^{3}H(+)-N-allyl-nor-methazocine binding

Substance	IC_{50} (nM)
flunarizine	23.9
verapamil	> 10,000
nifedipine	> 10,000
nimodipine	> 10,000
diltiazem	> 10,000

The preceding data confirm the findings of the research that lead to the present invention, which have been discussed in the introduction. Namely, the data show that flunarizine has an affinity on σ-1 receptors, as opposed to the other more known and studied calcium channel blocking agents, such as verapamil, nifedipine and diltiazem. This finding suggests that the σ-1 receptors are involved in the mechanism responsible of the intraocular pressure decrease caused by flunarizine, and that this particular feature is responsible of the surprisingly higher activity of flunarizine as an anti-glaucoma agent for topical use.

The present invention has been disclosed with particular reference to some specific embodiments thereof, but it should be understood that modifications and changes may be made by the persons skilled in the art without departing from the scope of the invention as defined in the appended claims.

CLAIMS

1. Use of flunarizine, or of a pharmaceutically acceptable salt thereof, in the manufacture of a topical ophthalmic medicament for the treatment and/or the prophylaxis of glaucoma.

2. Use according to claim 1, wherein said topical ophthalmic medicament is in the form of an aqueous solution or suspension, or in the form a gel, an ointment or a cream in a pharmaceutically acceptable ophthalmic vehicle, or in the form of an erodible ocular insert or of a "reservoir" system with a polymer membrane, to be placed in the conjunctival sac.

3. Use according to claims 1 or 2, wherein the flunarizine concentration in said ophthalmic medicament is from 0.001 to 0.500% by weight.

4. Use according to claim 3, wherein the flunarizine concentration is 0.050% by weight.

5. Use according to any one of the preceding claims, wherein flunarizine is present in the said ophthalmic medicament in the form of its hydrochloride salt.

6. Use according to any one of claims 1-5, wherein said topical ophthalmic medicament further contains a beta-blocking agent.

7. Use according to claim 6 wherein the concentration of beta-blocking agent in said ophthalmic medicament is from 0.1 to 2.5% by weight.

8. Use according to claims 6 or 7, wherein said beta-blocking agent is timolol or a pharmaceutically acceptable salt thereof.

9. Use according to any one of claims 1-8, wherein said topical ophthalmic medicament is in the form of an aqueous solution and further contains one or more tonicity adjusting agents, one or more buffers and one or more antioxidants.

10. Use according to claim 9, wherein said topical ophthalmic medicament further contains one or more agents improving the ocular tolerability chosen from cyclodextrins, polysorbate 80 (or Tween 80), dextrane, polyethylene glycol and poloxamers.

11. Use according to claims 10 or 11, wherein said topical ophthalmic

medicament further contains one or more preservatives or antimicrobial agents.

12. A topical ophthalmic composition for the treatment and/or the prophylaxis of glaucoma comprising, as an active ingredient, a therapeutically effective amount of flunarizine.

13. The composition according to claim 12, containing an amount of flunarizine comprised between 0.001 and 0.500% by weight.

14. The composition according to claim 13, having the following formulation (wherein all percentages are by weight):

flunarizine hydrochloride (corresponding to 0.05% flunarizine)	0.059	%
sodium chloride	0.10-0.80	%
trizma buffer	0.02-0.20	%
PEG 400	1.00-6.00	%
Tween 80	2.00-12.00	%
sodium metabisulphite	0.01-0.20	%
propyl gallate	0.01-0.50	%
EDTA	0.005-0.20	%
purified water	q.s. to 100	%

optionally comprising further pharmaceutically acceptable ingredients.

15. The composition according to any one of claims 12-14, further containing from 0.1 to 2.5% by weight of a beta-blocking agent.

16. The composition according to claim 15, wherein said beta-blocking agent is timolol or a pharmaceutically acceptable salt thereof.

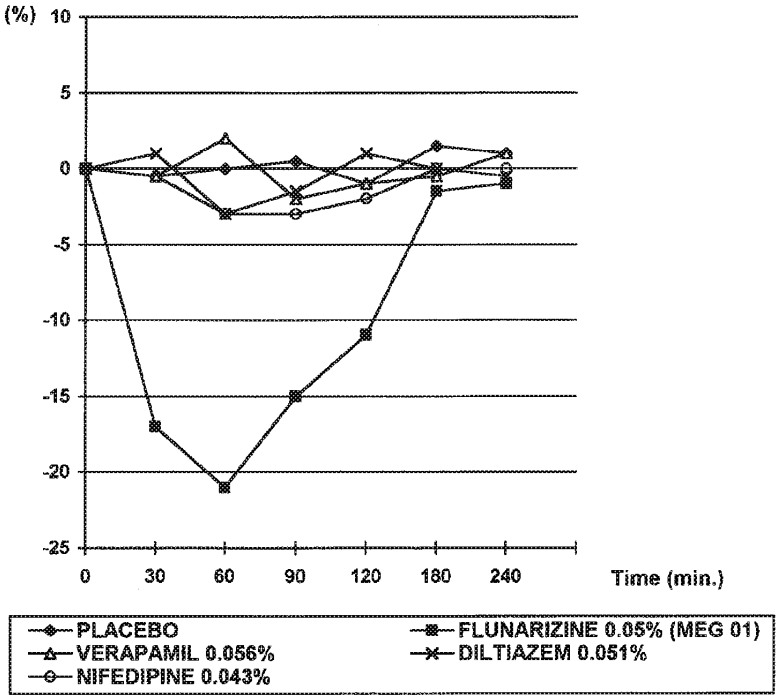

Fig. 1

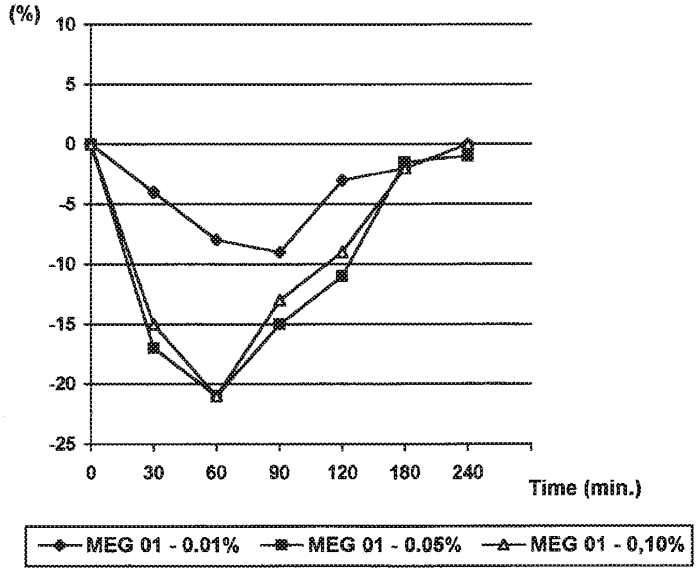

Fig. 2

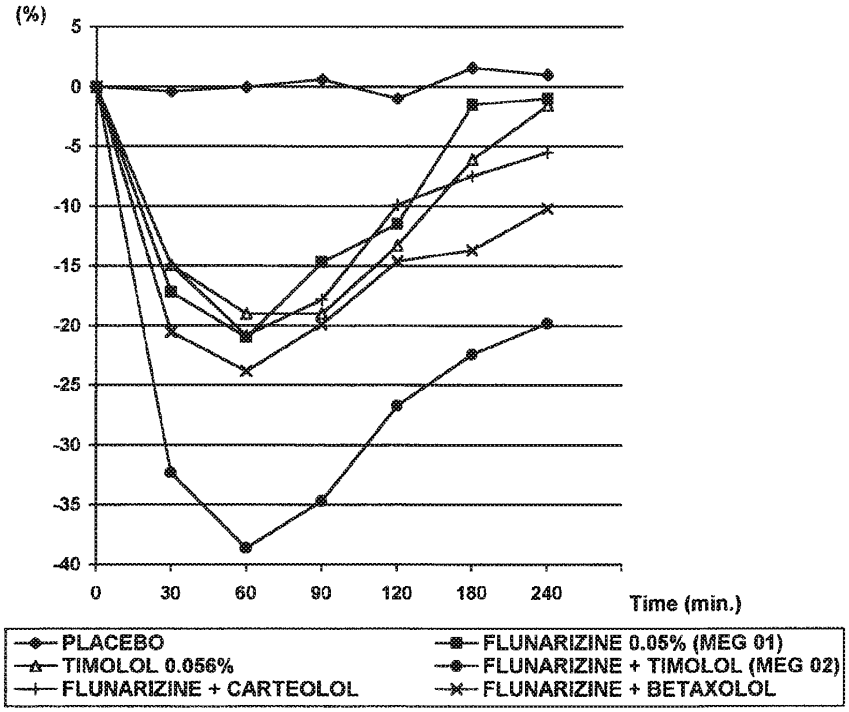

Fig. 3

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/IT 98/00266

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/495

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 6 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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 23082 A (ALCON LABORATORIES, INC.) 25 November 1993 cited in the application see page 6, line 3 see page 7, line 5 see page 7, line 8 - line 15 see page 9, line 3 - line 19 see page 10, line 16 - line 19 see claims 1,2,5-15,18 --- -/---	1-16

[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

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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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European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Alvarez Alvarez, C

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IT 98/00266

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE BIOSIS BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US Acc. Nr. 1989:364537, 1989 K.FUJITA ET AL.: "Effects of flunarizine on primary open angle and low tension glaucomas" XP002091122 see abstract & JPN. J. CLIN. OPHTALMOL., vol. 43, no. 5, 1989, pages 865-868,	1
X	CELLINI ET AL.: "The use of flunarizine in the management of low-tension glaucoma: A Color Doppler study" ACTA OPHTHALMOLOGICA SCANDINAVICA, vol. 224, no. Supp., March 1997, pages 57-58, XP002091121 Copenhagen see the whole document	1

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int tional Application No
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9323082 A	25-11-1993	AU 4246793 A	13-12-1993
		CA 2131101 A	25-11-1993
		EP 0639986 A	01-03-1995
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(54) Title: CAPSULES CONTAINING AQUEOUS FILL COMPOSITIONS STABILIZED WITH DERIVATIZED CYCLODEXTRIN

(57) Abstract: A capsule containing an aqueous fill composition that comprises water, a derivatized cyclodextrin, such as sulfoalkyl ether cyclodextrin (SAE-CD) or hydroxypropyl cyclodextrin (HPCD), optionally one or more active agents and optionally one or more excipients is stabilized from degradation, erosion, swelling or dissolution of its shell during storage. The derivatized cyclodextrin is present in an amount sufficient to reduce, eliminate or inhibit degradation, erosion, swelling and/or dissolution of the shell by water present in the fill composition. Alternatively, the derivatized cyclodextrin and another shell-stabilizing material together stabilize the shell from degradation, erosion, swelling and/or dissolution by water present in the fill composition. The derivatized cyclodextrin can reduce the water activity of the fill composition.

ARGENTUM PHARM. 1034

Capsules Containing Aqueous Fill Compositions Stabilized with Derivatized Cyclodextrin

By:

Diane O. Thompson, James D. Pipkin, Rupert O. Zimmerer

FIELD OF THE INVENTION

The present invention relates to a capsule containing a derivatized cyclodextrin in an aqueous fill, wherein the cyclodextrin is present in an amount sufficient to stabilize the shell of the capsule from erosion, dissolution, swelling or degradation by water in the fill.

BACKGROUND OF THE INVENTION

Liquid, or semi-solid filled capsules are widely known. These fill compositions are generally preferred over solid filled capsules, since it is easier to obtain a higher content uniformity for liquid or semi-solid filled capsules than it is for solid filled capsules.

Capsule fill compositions can be aqueous or non-aqueous. Materials generally used for capsule fill compositions include: 1) water-immiscible, volatile and nonvolatile liquids, 2) water miscible, volatile and nonvolatile liquids, and 3) miscellaneous carriers such as glycerin, propylene glycol, water, and low-molecular weight alcohols, ketones, acids, amines, and esters. Suspensions of the active are often included in vegetable or mineral oils, triglycerides, glycols such as polyethylene glycols and propylene glycol, surfactants such as polysorbates, or combinations of these.

The shell-forming material of the capsule is chosen so as to maximize the stability of the shell toward the fill composition, while at the same time maintaining the desired release profile for the active agent. Non-aqueous fill compositions are used widely because the shell of a capsule must be water soluble, erodible or degradable in order to be useful for use in an aqueous environment, e.g., for oral administration to a subject. Quite often, however, it is desirable to include water in the fill composition in order to obtain the desired active agent release profile, increase dissolution of active agent in the fill composition and/or maximize stability of the ingredients in the fill composition. When an aqueous fill composition is used, the shell of the capsule is generally made of material that is more resistant to water dissolution, erosion or degradation.

A number of different relatively water stable shell compositions are known. Those shell compositions generally include materials or are made by processes that reduce the instability of the shell toward water in the fill composition. For example, Banner Pharmacaps and Cardinal Health provide capsules that are somewhat stabilized for a lipophilic fill and other for a hydrophilic fill. However, using such a shell results in altered performance of the capsule formulation. Accordingly, the pharmaceutical scientist must carefully balance the amount of water included in the fill composition against the aqueous stability properties of the shell. Moreover, the known aqueous fill compositions are limited in the amounts of water and the combination of active agents and excipients that can be included therein. In other words, known shells containing fill compositions with high amounts of water still degrade, dissolve, swell or erode during storage.

A number of references disclose capsule dosage forms filled with an aqueous liquid or semi-solid vehicle, an active agent, and another component added to reduce or stop dissolution, erosion or degradation of the shell by the fill composition.

Kuentz et al. (*International Journal of Pharmaceutics* (2002), 236(1-2), 145-152) disclose capsules filled with a liquid composition comprising water, PEG and poly(vinylpyrrolidone) or comprising water, glycerides (LABRASOL®) and colloidal silicon dioxide (AEROSIL®). The components were added to determine which combination thereof would be able to reduce or stop dissolution, erosion or degradation of the shell by the fill composition. Kuentz et al. do not disclose the use of cyclodextrins.

Bowtle (Presentation entitled "Liquid-encapsulation technology for oral delivery") discloses the use of hydrogenated glucose syrup as a material suitable for use in liquid-filled capsules. Bowtle does not disclose the use of cyclodextrins to reduce or stop dissolution, erosion or degradation of the shell by the fill composition.

Japanese Patent No. JP 61207329 to Mochizuki et al. discloses a soft gelatin capsule filled with an aqueous liquid vehicle, a sugar and an active agent. The sugar is present in amounts of ≥ 55% wt. with respect to the fill composition. Sugars such as sucrose, glucose, fructose, and maltose are disclosed. The sugar is present in an amount sufficient to reduce or stop dissolution, erosion or degradation of the shell by the fill

composition. Mochizuki et al. do not disclose the use of cyclodextrins to reduce or stop dissolution, erosion or degradation of the shell by the fill composition.

German Patent No. DE 19545043 to Lucks et al. discloses a liquid-filled soft gelatin capsule. The liquid is present in a single phase. The fill composition comprises 1-20% wt. polyol (such as glycerol, propanediol or PEG) or benzyl alcohol, 1-20% wt. surfactant, 79-98% wt. co-surfactant (such as glycerides), <5% wt. ethanol and <10% wt. water. Lucks et al. do not disclose cyclodextrins. Water is present in an amount low enough to minimize dissolution, erosion or degradation of the shell by the fill composition. Lucks et al. do not disclose the use of cyclodextrins to reduce or stop dissolution, erosion or degradation of the shell by the fill composition.

U.S. Patent No. 5,037,698 to Brunel discloses a solid or semi-solid filled capsule wherein the fill composition comprises water (0.1-10% wt.), a thickening agent (≥35% wt.), a hygroscopic or deliquescent agent (0.1-50% wt.) and optionally an equilibrium protecting agent (0.1-15% wt.). The water is present at or near stoichiometric amounts with respect to the hygroscopic or deliquescent agent so that a hydrate can form but degradation of the shell by water is minimized. The thickening agent is a thermosoftening solid or semi-solid excipient. The equilibrium protecting agent includes compounds such as aliphatic or aromatic hydroxy compounds including for example demulcents (glycerin) and oils. Brunel does not disclose the use of cyclodextrins.

U.S. Patent No. 5,707,648 to Yiv discloses a biphasic liquid-filled capsule containing an oil phase and an aqueous phase. The aqueous phase includes water (2-30% wt.) and PEG (60-95% wt.), wherein the ratio of PEG to water is ≥2:1 or 2:1-99:1. The formulation also requires a surfactant and an active agent. The PEG is present in an amount sufficient to reduce or stop dissolution, erosion or degradation of the shell by the fill composition. Yiv does not disclose the use of cyclodextrins.

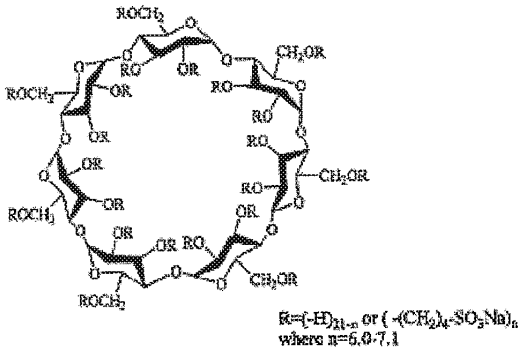
U.S. Patent Pregrant Publication No. 2003/0133974 to Curatolo et al. discloses an encapsulated dosage form containing sertraline; however, that dosage form comprises a water immiscible carrier medium.

Cyclodextrins and their derivatives are widely used in liquid formulations to enhance the aqueous solubility of hydrophobic compounds. Cyclodextrins are cyclic

carbohydrates derived from starch. The unmodified cyclodextrins differ by the number of glucopyranose units joined together in the cylindrical structure. The parent cyclodextrins contain 6, 7, or 8 glucopyranose units and are referred to as α-, β-, and γ-cyclodextrin respectively. Each cyclodextrin subunit has secondary hydroxyl groups at the 2 and 3-positions and a primary hydroxyl group at the 6-position. The cyclodextrins may be pictured as hollow truncated cones with hydrophilic exterior surfaces and hydrophobic interior cavities. In aqueous solutions, these hydrophobic cavities provide a haven for hydrophobic organic compounds, which can fit all, or part of their structure into these cavities. This process, known as inclusion complexation, may result in increased apparent aqueous solubility and stability for the complexed drug. The complex is stabilized by hydrophobic interactions and does not involve the formation of any covalent bonds.

Chemical modification of the parent cyclodextrins (usually at the hydroxyl moieties) has resulted in derivatives with sometimes improved safety while retaining or improving the complexation ability of the cyclodextrin. A number of different cyclodextrin derivatives are currently available including sulfobutyl ether derivatives such as SBE1-β-CD and SBE4-β-CD (degree of substitution~4), SBE7-β-CD (degree of substitution~7; CAPTISOL® cyclodextrin); hydroxypropyl derivatives such as ENCAPSIN™ (degree of substitution~4; HP4-β-CD) and MOLECUSOL™ (degree of substitution~8; HP8-β-CD); carboxylated derivatives; sulfated derivatives; alkylated derivatives; hydroxyalkylated derivatives; methylated derivatives; and carboxy-β-cyclodextrins, e.g. succinyl-β-cyclodextrin, 6^A-amino-6^A-deoxy-N-(3-carboxypropyl)-β-cyclodextrin.

The SAE-CDs are a class of negatively charged cyclodextrins, which vary in the nature of the alkyl spacer, the salt form, the degree of substitution and the starting parent cyclodextrin. The sodium salt of the sulfobutyl ether derivative of beta-cyclodextrin, with an average of about 7 substituents per cyclodextrin molecule (SBE7-β-CD), is being commercialized by CyDex, Inc. (Kansas) as CAPTISOL® cyclodextrin.



Sulfobutyl Ether-β-Cyclodextrin (Captisol®)

The anionic sulfobutyl ether substituent dramatically improves the aqueous solubility of the parent cyclodextrin. Reversible, non-covalent, complexation of drugs with the CAPTISOL® cyclodextrin generally allows for increased solubility and stability of drugs in aqueous solutions.

A number of references disclose capsule dosage forms comprising a fill composition comprising a cyclodextrin, aqueous or non-aqueous vehicle, active agent and other pharmaceutical excipients.

U.S. Patents No. 6,287,594 to Wilson et al. and No. 6,365,180 to Meyer et al. disclose oral liquid compositions that can be included in capsule dosage forms. The liquid compositions comprise an acidic active agent, a dispersing agent, a solubilizing agent (0-90% or 60-90% wt.), an optional surfactant (0-10% wt.) and an optional plasticizing agent (0-25% wt.). The dispersing agent can be a carbohydrate-based agent, for example a "derivatized cyclodextrin". The solubilizing agent is water or poly(ethylene glycol). The ratio of active agent to dispersing agent is about 3:1 to about 1:30. The patents do not disclose that the cyclodextrin can reduce or stop dissolution, erosion or degradation of the shell by the aqueous fill composition. Moreover, no examples including a cyclodextrin are disclosed.

U.S. Patent No. 6,383,471 to Chen et al. discloses a liquid composition comprising an ionizable hydrophobic active agent, ionizing agent, surfactant and

optionally solubilizers, triglycerides and neutralizing agents. The liquid composition can be used in capsules. Chen et al. disclose that solubilizers can include cyclodextrins, among many other compounds. A sulfobutyl ether cyclodextrin is listed as an exemplary cyclodextrin. Chen et al. do not disclose or suggest that the cyclodextrin is present in an amount sufficient to reduce or stop dissolution, erosion or degradation of the shell by the aqueous fill composition.

U.S. Patents No. 6,046,177 and No. 5,874,418 to Stella et al. disclose capsule dosage forms containing a non-aqueous solid physical mixture of an SAE-CD and an active agent. The physical mixture is not a liquid or semi-solid composition and water is not included in the physical mixture in order to reduce the formation of an inclusion complex between the cyclodextrin and the active agent. Stella et al. do not disclose that the cyclodextrin can be present in an amount sufficient to reduce or stop dissolution, erosion or degradation of the shell by water in the fill composition.

U.S. Patents No. 5,376,645 and No. 5,134,127 to Stella et al. disclose pharmaceutical compositions comprising an active agent, an SAE-CD and a liquid or solid carrier. The SAE-CD and active agent are present as an inclusion complex. Stella et al. generally disclose "soft gelatin capsules wherein the active ingredient (the mixture containing the inclusion complex of SAE-CD and active agent) is mixed with water or oil". They also disclose that, "Pharmaceutical formulations suitable for oral administration wherein the carrier is liquid may conveniently be presented as a solution in an aqueous liquid or a non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion." Stella et al. do not disclose or suggest that an SAE-CD can be present in an aqueous fill composition (for capsules) in an amount sufficient to reduce or stop dissolution, erosion or degradation of the shell by water in the fill composition. Moreover, Stella et al. disclose combinations wherein the SAE-CD must form an inclusion complex with the active agent.

U.S. Patent No. 3,426,011 to Parmerter et al. discloses anionic cyclodextrin derivatives having sulfoalkyl ether substituents. Parmerter et al. do not disclose the use of sulfoalkyl ether cyclodextrins in an aqueous composition contained within a capsule. Lammers et al. (*Recl. Trav. Chim. Pays-Bas* (1972), 91(6), 733-742); *Staerke* (1971),

23(5), 167-71) disclose sulfoalkyl ether derivatized cyclodextrins; however, they do not disclose the use of cyclodextrins to reduce or stop dissolution, erosion or degradation of a shell by an aqueous fill composition.

A need remains for improved capsule fill compositions that stabilize a shell from dissolution, erosion, swelling or degradation by water in the fill composition. None of the art discloses or suggests the invention as claimed herein. The prior art does not disclose an aqueous fill composition for a capsule, wherein the fill composition comprises a derivatized cyclodextrin, such as an SAE-CD, an active agent, and an aqueous carrier, and the derivatized cyclodextrin is present in an amount sufficient to reduce or stop dissolution, erosion, swelling or degradation of the capsule shell by water in the fill composition. Moreover, the prior art does not disclose or suggest a method of stabilizing a water soluble, erodible, swellable or degradable capsule shell surrounding an aqueous fill composition by including a derivatized cyclodextrin in the fill composition.

SUMMARY OF THE INVENTION

The present invention seeks to overcome some or all of the disadvantages inherent in other known formulations. The invention provides a commercially viable composition for use in hard or soft capsules, such that capsules filled with the aqueous fill composition can be prepared and stored without significant degradation, erosion, swelling or dissolution of the capsule shell during the acceptable shelf-life of the filled capsule. The invention provides a capsule dosage form and an aqueous fill composition therefor. The capsule comprises a soft or hard shell. In one aspect, the invention provides a sulfoalkyl ether cyclodextrin (SAE-CD)-based (derivatized cyclodextrin-based) aqueous fill composition. The fill composition comprises an aqueous vehicle, a sulfoalkyl ether cyclodextrin (SAE-CD), an active agent, and optionally other ingredients. The shell is generally made from water soluble, erodible, swellable or degradable material(s); however, a shell material that is not water soluble, erodible, swellable or degradable can also be used. The SAE-CD, or other derivatized cyclodextrin, is present in an amount sufficient to reduce or stop dissolution, erosion, swelling or degradation of the shell by water in the fill composition. In other words, the derivatized cyclodextrin reduces dissolution, erosion, swelling or degradation of the shell by the fill composition as compared to a similar fill composition excluding the derivatized cyclodextrin, i.e.,

wherein the derivatized cyclodextrin is replaced by water or another non-shell-stabilizing material. In the absence of other shell-stabilizing material(s), the SAE-CD stabilizes the capsule shell against dissolution, erosion, swelling or degradation caused by water in the fill composition.

The capsule dosage form comprises a shell and an aqueous fill composition comprising an SAE-CD, or water soluble derivatized cyclodextrin. In the absence of other shell-stabilizing materials and depending upon the materials that comprise the shell, the fill composition can include at least about 30% by weight of SAE-CD, or derivatized cyclodextrin, based upon the total weight of water and SAE-CD, or derivatized cyclodextrin, present. The amount of derivatized cyclodextrin required to provide the desired level of shell stabilization will vary according to the composition of the shell and the materials comprising the fill composition. The more stable a shell is toward water, the lower the amount of derivatized cyclodextrin that may be required. The less stable the shell is toward water, the greater the amount of derivatized cyclodextrin that may be required. In the absence of other shell-stabilizing materials, the fill composition comprises less than about 70% by weight of water based upon the total weight of water and SAE-CD present. The minimum shelf life of the filled capsule is at least about 1 week, 2 weeks, 3 weeks, 1 month, 3 months, 6 months, or 1 year, or more than about 1 year.

The invention also provides a method of stabilizing a water soluble, erodible or degradable capsule shell surrounding an aqueous fill composition. The method comprises the step of including an SAE-CD, or derivatized cyclodextrin, in the fill composition such that the SAE-CD, or derivatized cyclodextrin, is present in an amount sufficient to reduce or stop the dissolution, erosion, swelling or degradation of the capsule shell caused by the water in the fill composition.

The fill composition can include other shell-stabilizing materials and/or other water activity-reducing materials if desired. The fill composition can also include other ingredients suitable for use in capsule fill compositions.

It is not necessary for the active agent to complex with the derivatized cyclodextrin in order for the derivatized cyclodextrin to exert its stabilizing effect upon

the capsule shell. The fill composition can include one or more active agents, and each active agent independently may or may not complex with the derivatized cyclodextrin.

Any shell forming material suitable for use in hard or soft shell capsules or the encapsulation of fill composition can be used in the present invention.

The SAE-CD formulation has a sufficiently high stability for use as a commercial product. The formulation can be prepared as a clear aqueous composition that is sterilizable by sterile filtration (for example, filter pore size of less than or equal to 0.22 μm) and other conventional methods. The aqueous composition is stable under a variety of storage conditions. The SAE-CD can be used to enhance the solubility of active agents by non-covalent ionic binding and/or by complexation via the formation of inclusion complexes.

The fill composition may or may not be clear depending upon the identity and amounts of ingredients included therein. During storage the clarity of the fill composition may or may not change. In other words, one or more components of the fill composition may further dissolve or precipitate during storage. The fill composition, which is a water-containing composition, can be a gel, syrup, fluid, semi-solid, solid, suspension, emulsion, paste, or glassy material.

Accordingly, one aspect of the invention provides an aqueous fill composition in a water erodible, degradable, swellable or soluble shell (or encapsulating material), the fill composition comprising water, one or more derivatized cyclodextrins, optionally one or more active agents and optionally one or more excipients, wherein the derivatized cyclodextrin is present in an amount sufficient to reduce or stop the erosion, degradation, swelling or dissolution of the shell by the fill composition.

Specific embodiments of the invention include those wherein: 1) the derivatized cyclodextrin is SAE-CD and is present in an amount of at least about 30% by wt. based upon the total weight of water and SAE-CD; 2) the fill composition further comprises a shell-stabilizing material; 3) the fill composition has a pH in the range of about 1-11; 4) the fill composition comprises one or more excipients; 5) the shell is a soft shell; 6) the shell is a hard shell; 7) the water activity of the fill composition is less than about 0.95 as measured according to the procedures detailed herein; 8) the fill composition further

comprises a solubility-enhancing agent; 9) the SAE-CD complexes with one or more of the active agents; 10) the SAE-CD does not complex with the one or more active agents; 11) the fill composition further comprises a liquid carrier other than water; 12) the fill composition is a liquid; 13) the fill composition is a semi-solid; 14) the fill composition is a solid; 15) the fill composition has been prepared at a temperature at or above 5°C, at or above 25°C, at or above 35°C, at or above 45°C or at or above 50°C; 16) the formulation has been prepared at a temperature approximating ambient temperature; 17) the SAE-CD, or derivatized cyclodextrin, reduces the water activity of the aqueous fill composition; 18) the shell is a hard gelatin shell and the fill composition comprises at least 60% wt. of derivatized cyclodextrin; 19) the shell is a soft gelatin shell and the fill composition comprises at least 50% wt. of derivatized cyclodextrin; 20) the shell is a hard shell comprising cellulose, cellulose derivative, starch, starch derivative, or a combination thereof and optionally other excipients, and the fill composition comprises at least 30% wt. of derivatized cyclodextrin; and/or 21) the fill composition further comprises a water activity-reducing material.

The invention also provides a first capsule within a second capsule. In this case the first and/or second capsule can contain the aqueous fill composition.

Another aspect of the invention provides a method of stabilizing an aqueous composition-filled capsule from erosion, dissolution, swelling or degradation of its shell by water present in the fill, the method comprising the step of including in the aqueous fill a derivatized cyclodextrin present in an amount sufficient to reduce or stop the rate of erosion, dissolution, swelling or degradation of the shell by water in the fill composition as compared to the rate of erosion, dissolution, swelling or degradation of the shell by a similar fill composition excluding the derivatized cyclodextrin, i.e., a fill composition wherein the derivatized cyclodextrin is replaced by water or another material that does not stabilize the shell (a non-shell-stabilizing material). The derivatized cyclodextrin is capable of stabilizing the shell against erosion, dissolution, swelling or degradation of the shell by water in the fill composition either in the absence, and optionally presence, of another shell-stabilizing material.

Yet another aspect of the invention provides an aqueous fill composition enclosed within an encapsulating material, the fill composition comprising a derivatized cyclodextrin and an aqueous carrier, wherein the derivatized cyclodextrin is present in an amount sufficient to reduce the water activity of the fill composition thereby reducing the rate of erosion, dissolution, swelling or degradation of the encapsulating material by water in the aqueous fill. The water activity of the fill composition is generally reduced to less than about 0.95±0.025, less than 0.95±0.01, less than 0.925, or less than 0.90. The preferred water activity value may vary according to the components present in the fill and according to the composition of the capsule shell itself. The observed water activity value can also vary according to the instrument used to measure it as well as the calibration of the instrument and reproducibility of measurements (as expressed by standard deviation) taken by the instrument. The preferred water activity value will also vary according to the composition of the shell. Generally, the more water stable the shell, the higher the water activity of the fill composition can be, and the less water stable the shell, the lower the water activity of the fill composition should be, if the fill composition does not contain any other shell-stabilizing material(s).

Specific embodiments of the invention include those wherein: 1) the derivatized cyclodextrin is SAE-CD, HPCD, a water soluble derivatized cyclodextrin capable of reducing the water activity of the fill composition or a mixture thereof; 2) the fill composition further comprises a shell-stabilizing material; 3) the fill composition further comprises a water activity-reducing agent; 4) the fill composition further comprises an active agent; and/or 5) the fill composition further comprises one or more pharmaceutical excipients.

The invention also provides a method of reducing the water activity of an aqueous composition, the method comprising the step of including a water soluble derivatized cyclodextrin in the aqueous composition at a concentration sufficient to reduce the water activity.

The invention also provides capsule formulations that provide active agent release according to a controlled, sustained, extended, slow, rapid, pulsed, timed, targeted, colonic, zero order, pseudo-zero order, first order, pseudo-first order, and/or enteric

release profile, wherein release of the active agent begins immediately (less than 30 minutes) or after passage of a delay period (≥ 30 min) after exposure to an environment of use. In other words, initial release of drug can be immediate or delayed as well as being released according to the modified release profiles mentioned herein. The capsule formulation can be a coated capsule, uncoated capsule, osmotic capsule, capsule within a capsule, or multi-layered capsule.

The invention also provides a capsule comprising:

a water soluble, erodible, degradable and/or swellable shell; and

an aqueous fill composition comprising water present in an amount sufficient to solubilize, erode, degrade and/or swell the shell, one or more active agents, and a water soluble cyclodextrin derivative present in an amount sufficient to suppress dissolution, erosion, degradation or swelling of the shell by water in the fill composition, wherein the capsule has a shelf-life of at least one week.

Another embodiment of the invention provides a stabilized capsule formulation having a shelf-life of at least one week, the formulation comprising:

a water soluble, erodible, swellable and/or degradable shell, and

an aqueous fill composition comprising a water soluble cyclodextrin derivative, an aqueous carrier and optionally one or more active agents; wherein, the capsule formulation has an increased shelf life as compared to a similar capsule formulation excluding the cyclodextrin derivative and any other shell-stabilizing material; water in the aqueous carrier is present in an amount sufficient to at least partially dissolve, erode, swell and/or degrade the shell; and the cyclodextrin derivative is present in an amount sufficient to reduce the rate of or eliminate dissolution, erosion, swelling or degradation of the shell by water in aqueous carrier.

Still another embodiment of the invention provides

An aqueous fill composition enclosed within a water soluble, erodible, swellable and/or degradable encapsulating material, the fill composition comprising:

an aqueous carrier present in an amount sufficient to at least partially dissolve, erode, swell and/or degrade the encapsulating material;

a water soluble cyclodextrin derivative present in an amount insufficient to on its own stop dissolution, erosion, swelling and/or degradation of the encapsulating material by the aqueous carrier;

a shell-stabilizing material present in an amount insufficient to on its own stop dissolution, erosion, swelling and/or degradation of the encapsulating material by the aqueous carrier;

optionally, one or more active agents; and

optionally, one or more excipients; wherein,

the cyclodextrin derivative and the shell-stabilizing material synergistically at least reduce the rate of or stop dissolution, erosion, swelling and/or degradation of the encapsulating material by the aqueous carrier.

In specific embodiments: 1) the aqueous fill composition is water miscible; 2) the active agent is present in a therapeutically effective amount; 2) the active agent is present in a sub-therapeutically effective amount; 3) the active agent is sparingly soluble, slightly soluble, very slightly soluble, practically insoluble or insoluble in water; 4) the active agent is more soluble in the aqueous fill composition than it is in water; 5) the active agent is soluble, freely soluble or very soluble in water; 6) the active agent complexes with the derivatized cyclodextrin to form an inclusion complex and/or a non-covalent ionic complex; 7) the active agent is selected from the active agents or therapeutic categories disclosed herein; 8) the fill composition further comprises alcohol; 9) the fill composition further comprises a water miscible hydroxy moiety-containing material, e.g., poly-ol, glycol, polymeric glycol, alcohol, or saturated glycolized glycerides, PEG 660 12-hydroxystearate (SOLUTOL™-15); 10) the water soluble cyclodextrin derivative is present in an amount sufficient to solubilize the active agent when it is released into an environment of use, such as the gastrointestinal tract or an aqueous fluid.

Other features, advantages and embodiments of the invention will become apparent to those skilled in the art by the following description, accompanying examples.

BRIEF DESCRIPTION OF THE FIGURES

The following drawings are part of the present specification and are included to further demonstrate certain aspects of the invention. The invention may be better

understood by reference to one or more of these drawings in combination with the detailed description of the specific embodiments presented herein.

FIG. 1 depicts a graph of concentration of derivatized cyclodextrin (SBE-CD or HPCD) present in a fill composition versus H.S.I.T. rating for soft gelatin capsules LFB (lipophilic fill shells from Banner) and LFC (lipophilic fill shells from Cardinal) containing the fill composition versus water activity of the fill composition.

FIG. 2 depicts a graph of concentration of cyclodextrin present in a fill composition versus H.S.I.T. rating for soft gelatin capsules HFB (hydrophilic fill shells from Banner) and HFC (hydrophilic fill shells from Cardinal) containing the fill composition versus water activity of the fill composition.

FIG. 3 depicts a graph of concentration of cyclodextrin present in a fill composition versus H.S.I.T. rating for various different capsule shells HGC (hard gelatin capsule from Capsugel), HGS (hard gelatin capsule from Shionogi), HPC (hard hydroxypropyl methylcellulose capsule from Capsugel), HPS (hard hydroxypropyl methylcellulose capsule from Shionogi), SSS (soft starch capsule from Swisscaps).

FIG. 4 depicts a graph of H.S.I.T. rating of various different aqueous fill compositions comprising different cyclodextrins and cyclodextrin derivatives when placed in contact with a hydrophilic fill soft gelatin capsule.

FIG. 5 depicts a graph of concentration of PEG (poly (ethylene glycol)) in a fill composition versus the H.S.I.T. rating of the fill composition for a soft gelatin capsule containing the fill composition and versus the water activity of the fill composition.

FIGS. 6a-6b depict ternary graphs of cyclodextrin concentration, PEG concentration and water concentration versus H.S.I.T. rating for soft gelatin capsules recognized by their manufacturers as being suitable for use with a hydrophilic fill composition.

FIGS. 7a-7b depict ternary graphs of cyclodextrin concentration, PEG concentration and water concentration versus H.S.I.T. rating for soft gelatin capsules recognized by their manufacturers as being suitable for use with a lipophilic fill composition.

FIG. 8 depicts a graph of concentration of water in a fill composition comprising SBE versus the H.S.I.T. rating of the fill composition for a soft gelatin capsule containing the fill composition and versus the water activity of the fill composition. The different lines represent different concentrations of PEG.

FIG. 9 depicts a graph of concentration of poly (vinyl pyrrolidone) (PVP) in a fill composition versus the H.S.I.T. rating of the fill composition for a soft gelatin capsule containing the fill composition and versus the water activity of the fill composition.

FIGS. 10a-10i depict ternary graphs of cyclodextrin concentration, PVP concentration and water concentration versus H.S.I.T. rating for various different capsules.

FIG. 11 depicts dissolution profiles for a commercial tablet containing fexofenadine hydrochloride (FEX) and a capsule according to the invention containing SAE-CD, FEX and water.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "aqueous fill composition" according to the invention means a composition that is used as a fill for a capsule or other encapsulated dosage form, e.g., a coated dosage form, and that contains water and SAE-CD, wherein the water is present in an amount of at least about 10%, 15%, 17%, or 20% wt. of the fill composition. In the absence of a water soluble cyclodextrin derivative, such as SAE-CD, the water is present in an amount sufficient to at least partially erode, dissolve, degrade and/or swell the shell of the capsule to the point that the capsule will not be stable for at least a predetermined shelf-life. The fill composition can be a liquid, solution, suspension, dispersion, microemulsion, particulate mass, emulsion, gel, glass, semi-solid, syrup, cream, meltable solid or solid. In the absence of other shell-stabilizing materials and depending upon the materials comprising the shell, the fill composition can contain up to about 70% by weight of water with respect to the total weight of the fill composition, and the balance of the fill composition comprises a water soluble cyclodextrin derivative, optionally one or more active agents, optionally a water-activity-reducing agent, optionally a shell-stabilizing material, and optionally one or more excipients. In some specific embodiments, the aqueous fill composition is water

miscible. Accordingly, the water soluble cyclodextrin derivative suppresses the ability of water in the aqueous fill composition to degrade, erode, dissolve or swell the shell.

The table below depicts the results of preliminary stability studies performed on soft gelatin shells by exposure to aqueous fill compositions. The samples were prepared according to Example 1 and contained varying amounts of water and SAE-CD.

[SAE-CD] (% wt.)	Capsule Type (Banner)	Time for failure	Observations	Increase in shell size
40%	LFB	3 days	shape intact	2.5x
	HFB	3 days	shape intact	2x
50%	LFB	7 days	Deformed	2.5x original
	HFB	16 days	Slightly deformed	2.5x original
55%	LFB	10 days	Deformed	2x original
	HFB	10 days	Deformed	2x original
60%	LFB	≥ 21 days	Slight widening	no change in length
	HFB	≥ 21 days	No change	no change

LFB denotes a shell made for a lipophilic fill. HFB denotes a shell made for hydrophilic fill.

According to the above data, soft gelatin shells obtained from BANNER PHARMACAPS containing less than 40% by wt. SAE-CD were unstable under the conditions tested. As the concentration of SAE-CD was increased, the stability of the shell toward the fill composition increased. Soft gelatin capsules containing ≥50% wt. SAE-CD were stable for at least one week. Those containing ≥55% wt. SAE-CD were stable for at least ten days, and those containing ≥60% wt. were stable for at least three weeks. Applicants note that capsules having an approximately one-week shelf-life are suitable for use in pharmacies that compound active prior to use.

The same tests were performed on gelatin capsules obtained from CARDINAL HEALTH. The results are detailed in the table below.

[SAE-CD] (% wt.)	Capsule Type (Cardinal)	Time for failure	Observations	Increase in shell size
40%	LFC	4 days	shape intact	>3x original
	HFC	4 days	deformed	3x original
50%	LFC	7 days	deformed	2x original
	HFC	7 days	shape intact	2x original
55%	LFC	≥14 days	No deformities	Slightly enlarged
	HFC	≥14 days	No deformities	No change
60%	LFC	> 21 days	no change	no change
	HFC	> 21 days	no change	no change

LFC denotes a shell made for a lipophilic fill. HFC denotes a shell made for hydrophilic fill.

According to the above data, soft gelatin shells obtained from CARDINAL HEALTH containing less than 40% by wt. SAE-CD were unstable under the conditions tested. As the concentration of SAE-CD was increased, the stability of the shell toward the fill composition increased. Soft gelatin capsules containing ≥50% wt. SAE-CD were stable for at least one week. Those containing ≥55% wt. SAE-CD were stable for at least two weeks, and those containing ≥60% wt. were stable for at least 21 days.

Soft gelatin capsules are stabilized from dissolution, erosion, swelling or degradation by water in the fill composition by including in the composition SAE-CD present in an amount of 50% wt. or more based upon the total weight of water and SAE-CD or upon the total weight of the fill composition, so that the capsules have a shelf-life of at least one week. Higher concentrations of SAE-CD result in longer shelf-life.

HPCD, hydroxypropyl derivatized cyclodextrin, was evaluated under the same conditions described above using the same HFB, LFB, HFC, and LFC soft gelatin capsules. The results are detailed in the table below.

[HP-CD] (% wt.)	Capsule Type	Time for failure	Observations	Increase in shell size
40%	LFC	2 days	Deformed	>3x original
	HFC	2 days	Deformed	>3x original
	LFB	2 days	Deformed	>3x original
	HFB	2 days	Deformed	>3x original
50%	LFC	4 days	Shape intact	2x original
	HFC	4 days	shape intact	2x original
	LFB	4 days	shape intact	2x original
	HFB	4 days	shape intact	2x original
60%	LFC	7 days	Slight deformity	2x original
	HFC	7 days	Slight deformity	2x original
	LFB	7 days	Shape intact	2x original
	HFB	7 days	Shape intact	2x original
70%	LFC	14 days	Shape intact	1.5 x original
	HFC	14 days	Shape intact	1.5 x original
	LFB	14 days	Shape intact	1.5 x original
	HFB	14 days	Shape intact	1.5 x original

Soft gelatin capsules are stabilized from dissolution, erosion, swelling or degradation by water in the fill composition by including in the composition HPCD present in an amount of 60% wt. or more based upon the total weight of water and HP-CD, so that the capsules have a shelf-life of at least one week. Higher concentrations of HPCD result in longer shelf-life.

FIG. 1 depicts a chart of the relationship between concentration of derivatized cyclodextrin, H.S.I.T. (half-shell integrity test) rating and water activity. SBE (sulfobutyl ether cyclodextrin having a degrees of substitution (DS) of about 6.5-7.5), when present at an amount of about ≥50% wt., provided at least a one week stability for LFB and LFC soft gelatin capsules. Likewise HPCD (hydroxypropyl cyclodextrin having a degrees of substitution (DS) of about 5.5), when present at an amount of about ≥60% wt., provided at least a one-week stability for LFB and LFC soft gelatin capsules.

FIG. 2 depicts a chart of the relationship between concentration of derivatized cyclodextrin and H.S.I.T. (half-shell integrity test) rating. SBE (sulfobutyl ether cyclodextrin having a degrees of substitution (DS) of about 6.5-7.5), when present at an amount of about ≥50% wt., provided at least a one week stability for LFB and LFC soft gelatin capsules. Likewise HPCD (hydroxypropyl cyclodextrin having a degrees of substitution (DS) of about 5.5), when present at an amount of about ≥60% wt., provided at least one week stability for LFB and LFC soft gelatin capsules. The maximum achievable concentration of DMCD was about 42% wt., and at that concentration, it only slightly increased the stability of the shell.

FIG. 3 depicts a chart of the relationship between concentration of SBE cyclodextrin and H.S.I.T. (half-shell integrity test) rating for HGC (hard gelatin capsule from CAPSUGEL), HGS (hard gelatin capsule from SHIONOGI), HPC (hard hydroxypropyl methylcellulose shell from CAPSUGEL), and HPS (hard hydroxypropyl methylcellulose shell from SHIONOGI), and SSS (soft starch shell SWISSCAPS). The stability obtained was dependent upon the composition of the capsule gel. For hard gelatin capsules, SBE concentration of about ≥60% wt. provided at least a one-week stability. For hard hydroxypropyl methylcellulose capsules, SBE concentration of about ≥40% wt. provided at least a two-week stability. For soft starch capsules, SBE concentration of about ≥30% wt. provided at least a one-week stability.

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/w at saturation. Underivatized β-CD has a water solubility of about 1.85% w/w at saturation. Underivatized γ-CD has a water solubility of about 23.2% w/w at saturation. At these concentrations, these parent cyclodextrins are unable to stabilize the soft gelatin capsules from dissolution, erosion, swelling or degradation by water in the fill composition. Dimethylcyclodextrin (DMCD) forms a 43% w/w aqueous solution at saturation. At this concentration, DMCD is unable to stabilize the soft gelatin capsules from dissolution, erosion, swelling or degradation by water in the fill composition. FIG. 4 depicts a chart of the relationship between H.S.I.T. rating and concentration of these cyclodextrins as present in a fill composition exposed to a soft gelatin capsule.

Hard shell capsules and soft shell capsules differ in their thickness, amount of cross-linking, rigidity, composition, shape and other ways. Accordingly, an aqueous fill composition suitable for filling a soft shell capsule might not be suitable for filling a hard shell capsule and vice versa. That said, an artisan will be able to select the appropriate and approximate initial conditions for concentration of derivatized cyclodextrin in the fill composition by following the selection/evaluation procedures described herein, especially in Example 2.

Two types of hard shell capsules obtained from CAPSUGEL® were evaluated. A conventional hard gelatin capsule (HCAP) and a hard HPMC (hydroxypropyl methylcellulose) capsule (VCAP) were evaluated under identical conditions using aqueous solutions differing in the concentration of SBE-CD (sulfobutyl ether cyclodextrin). Results from the evaluation are included in the table below.

Soln	capsule	failure time	observations	size
30% SBE	hardcap	24hrs	deformed/bends	2x length
	vcap	>14 days		
40% SBE	hardcap	48hrs	deformed/closed	>2x width
	vcap	>14days		
50% SBE	hardcap	48hrs	deformed/closed	2x width
	vcap	>14days		
60% SBE	hardcap	4 days	closed/stuck	2x width
	vcap	>14days		

In the absence of SBE or another shell-stabilizing material, these shell materials were unstable to erosion, dissolution, swelling and degradation by water. Under the conditions of the assay, SBE cyclodextrin was able to stabilize the VCAP shells for ≥14 days even at concentrations of ≥30% wt. of the fill composition. In this assay, monitoring was discontinued after fourteen days.

Without being held bound to a particular mechanism, it is believed that the increasing the concentration of derivatized cyclodextrin present in the aqueous fill composition results in reduced water activity for the fill composition. The table below provides a summary of water activity versus concentration of cyclodextrin derivatives or some shell-stabilizing materials in water at about 20-25° C, or ambient temperature.

Concentration (% w/w)	Water Activity (approximate values)			
	SBE7-β-CD	HP-β-CD DS=5.5	PEG 400	PVP K17
0	1.00	1.00	1.00	1.00
10	~0.98	~0.99	-	~0.99
20	~0.98	~0.99	~0.99	~0.99
30	~0.97	~0.98	~0.97	~0.99
40	~0.95	~0.98	~0.95	~0.97
50	~0.91	~0.97	~0.90	~0.95
55	~0.88			
60	~0.86	~0.94	~0.84	~0.87
70	~0.76	~0.93		

PEG-400 denotes poly(ethylene glycol) having an approximate molecular weight of 400.

The values detailed above are approximate and can vary from instrument to instrument. These values were determined according to the procedure described herein on a water activity meter described herein. The numbers can also vary within the standard deviation of a particular instrument. It is also possible for the numbers to vary according to the accuracy and reproducibility of the instrument used as well as the method for calibrating the instrument with solution standards of known water activity.

Under the test conditions, the water activity of a solution containing dimethyl cyclodextrin (DMCD; 43% wt.; the approximate saturation concentration of DMCD) and water was approximately 0.996. All SAE-CD or HPCD containing fill compositions evaluated were clear.

As depicted in FIG. 1, as the concentration of water soluble derivatized cyclodextrin is increased, the water activity of the fill composition decreases while the H.S.I.T. rating of the fill composition increases. This means that a water soluble derivatized cyclodextrin such as SAE-CD is capable of decreasing the water activity of an aqueous fill composition and consequently increasing the stability (shelf-life) of a shell in contact with the fill composition. For SAE-CD in a soft-gelatin capsule, a fill

composition having a water activity of less than about 0.95 or less than about 0.94 provides an increase in the stability of the shell toward the fill composition.

Accordingly, the invention also provides a method of reducing the water activity of an aqueous fill composition in a capsule, the method comprising the step of including a derivatized cyclodextrin in the fill composition in an amount sufficient to reduce the water activity to less than about 0.95 ±0.015 as determined according to the method and instrument described herein. The standard deviation of reproducibility and accuracy can vary more widely or narrowly depending upon the experimental conditions used to measure the water activity or operator skill. Typically a standard deviation of ±0.02 is permissible. The activity of the water in the fill composition can be reduced by a water soluble derivatized cyclodextrin or a combination of a water soluble derivatized cyclodextrin and one or more other components, such as a shell-stabilizing material or water activity-reducing material.

PEG is used as a fill material in aqueous fill compositions for capsules and is recognized as a shell stabilizing material. The present inventors believe that, among its other properties, the ability of PEG to reduce water activity is responsible for its usefulness in this fill composition. FIG. 5 depicts a chart of the relationship between concentration of PEG in a fill composition versus the H.S.I.T. rating of the fill composition for a soft gelatin capsule and versus the water activity of the fill composition. As the concentration of PEG is increased, the water activity of the fill composition decreases while the H.S.I.T. rating of the fill composition increases. For PEG in a soft-gelatin capsule, a fill composition having a water activity of less than about 0.95 or less than about 0.9±0.02 provides an increase in the stability of the shell toward the fill composition.

According to the data above, water soluble poly(vinyl pyrrolidone) is an effective water-activity reducing agent.

The maximum amount of water permissible in the fill composition will depend upon the amount of SAE-CD present, the presence or absence of other shell-stabilizing materials and/or water activity-reducing materials, the composition of the shell, the pH of

the fill composition, the storage conditions for the capsules, the formulation of the fill composition and other variables.

An aqueous fill composition can comprise a derivatized cyclodextrin, a water activity-reducing agent and an aqueous carrier, wherein the derivatized cyclodextrin and water activity-reducing agent are together present in an amount sufficient to reduce the water activity to less than about 0.95 or less than about 0.90±0.02. In one embodiment, neither the derivatized cyclodextrin nor the water activity-reducing agent is present in an amount sufficient to individually reduce the water activity to the desired value. In other words, the water activity-reducing material and derivatized cyclodextrin together can provide an improved, additive or synergistic enhancement over the shell-stabilizing effect of either material alone.

A water activity-reducing agent is a compound or mixture of compounds capable of reducing the water activity of the fill composition. Increasing the concentration of a water activity-reducing agent in the fill composition causes a decrease in the water activity of the fill composition. A shell-stabilizing material can also serve as a water activity reducing agent. As used herein, a shell-stabilizing material is one or more materials (other than cyclodextrin derivative) included in the fill composition to minimize dissolution, erosion, swelling or degradation of the shell by the aqueous fill composition. Suitable materials include PEG (poly(ethylene glycol); in particular water soluble or water swellable PEG), glycol, polyol, glycerin, propanediol, surfactant, detergent, soap, benzyl alcohol, sugar, salt, thickening agent, hygroscopic agent, equilibrium protecting agent, deliquescent agent, hydrogenated glucose syrup (lycasin), mannitol, triacetin, tetraglycol, PVP (in particular water soluble or water swellable PVP) and combinations thereof. One or more shell-stabilizing materials can be used in combination with one or more derivatized cyclodextrins in the fill composition. Likewise, one or more water activity-reducing materials can be used in combination with one or more derivatized cyclodextrins in the fill composition.

When a shell-stabilizing material is present, it can be present in an amount insufficient to, on its own, stabilize the shell from degradation, erosion, dissolution or swelling by water in the fill composition. In other words, when another shell-stabilizing

material is present, the derivatized cyclodextrin may need to be present in order to stabilize the shell from dissolution, erosion, swelling or degradation by water from the fill composition.

Likewise, when a shell-stabilizing material and derivatized cyclodextrin are present, the derivatized cyclodextrin can be present in an amount insufficient to, on its own, stabilize the shell. In other words, the derivatized cyclodextrin would also need the shell-stabilizing material in order to stabilize the shell. In the absence of a shell-stabilizing material, the derivatized cyclodextrin will be able to stabilize the shell on its own provided the derivatized cyclodextrin is present in an amount sufficient to do so. The invention also includes embodiments wherein each is present in an amount sufficient to, on its own, stabilize the shell as described herein.

It has been discovered that PEG has a beneficial effect upon the shell-stabilizing property of an aqueous fill composition comprising SAE-CD. FIG. 6a depicts a ternary graph correlating the concentration of SAE-CD, water and PEG in a fill composition to the H.S.I.T. rating of a soft shell capsule exposed to the fill composition. Aqueous fill solutions comprising differing amounts of PEG, SAE-CD and water were prepared. The stability tests were conducted as described below. The HFC soft gelatin capsules described herein were used. For a composition comprising 40% wt. SBE-CD, 40% wt. water and 20% wt. PEG, the shell was stable for greater than 5 days. For a composition comprising 35% wt. SBE-CD, 35% wt. water and 30% wt. PEG, the shell was stable for greater than 5 days. For a composition comprising 18% wt. SBE-CD, 42% wt. water and 40% wt. PEG, the shell was stable for greater than 5 days. Under each of the conditions tested, the control sample excluded SAE-CD, i.e., containing only water and PEG at the indicated concentration, and failed within 24 hours. About the same results were obtained for the HFB (FIG. 6b), LFB (FIG. 7a) and LFC (FIG. 7b) soft gelatin capsules. Increasing the SAE-CD concentration to values higher than those indicated further increases the shelf-life of the shell or provides an HSIT rating of at least 4. Stabilized aqueous fill composition-containing capsule formulations can be achieved with each capsule if the following fill compositions are used.

CAPSULE	SAE-CD (%)	PEG + SAE-CD (%)	Water (%)
HFC	≥18	≥50	≤50
HFB	≥12	≥52	≤48
LFB	≥18	≥50	≤50
LFC	≥18	≥52	≤48

FIG. 8 depicts a graph of correlating the concentration of water of a fill composition versus the H.S.I.T. rating of a soft gelatin capsule exposed to the fill composition versus water activity of the fill composition. The data of FIG. 8 is a different expression of the same data of FIG. 6b. The fill composition comprises water, SBE-CD and PEG, and the fill composition was made by mixing PEG with an aqueous SBE-CD-containing solution. The concentration of water is expressed as the concentration of water in the entire fill composition. Based upon the results detailed in FIG. 8, a fill composition comprising SBE-CD, PEG and water will form a stable soft gelatin capsule formulation as long as the water activity of the fill composition is about ≤0.90±0.02.

Specific embodiments of a capsule containing an aqueous fill composition comprising water, SAE-CD and PEG can be prepared according to invention by employing the following criteria:

1. Water comprises ≤ 50% of the fill composition, and the combination of SAE-CD, PEG, one or more optional excipients and one or more optional active agents comprises ≥ 50% of the fill composition; wherein SAE-CD can comprise up to 90% (85%, 83%, or 80%) of the weight of the fill composition, and PEG can comprise less than 90%, respectively, of the weight of the fill composition, provided that PEG ≥ 45% when SAE-CD comprises ≤ 5 % of the weight of the fill composition, and when PEG < 45% then SAE-CD ≥ 18%, wherein both PEG (preferably water soluble or water swellable) and SAE-CD are present.
2. Water comprises ≤ 45% of the fill composition, and the combination of SAE-CD, PEG, one or more optional excipients and one or more optional active agents

comprises ≥ 50% of the fill composition; wherein SAE-CD can comprise up to 90% (85%, 83%, or 80%) of the weight of the fill composition, and PEG can comprise less than 90%, respectively, of the weight of the fill composition, provided that PEG ≥ 45% when SAE-CD comprises ≤ 5 % of the weight of the fill composition, and when PEG < 45% then SAE-CD ≥ 10%, wherein both PEG (preferably water soluble or water swellable) and SAE-CD are present.

Accordingly, the invention provides a method of increasing the shelf-life of a capsule formulation containing an aqueous fill composition comprising an aqueous carrier and first shell-stabilizing material present in an amount insufficient to, on its own, stabilize the shell from erosion, dissolution, degradation or swelling, the method comprising the step of including a derivatized cyclodextrin in the fill composition. By so doing, the first shell-stabilizing material and derivatized cyclodextrin cooperate to improve the shelf-life of the capsule formulation. This can be done even when the derivatized cyclodextrin is present in an amount insufficient to, on its own, stabilize the shell from erosion, dissolution, degradation or swelling by the aqueous fill composition.

When either one or both of the derivatized cyclodextrin and the other shell-stabilizing material (or water activity-reducing agent) is present in an amount that, on its own, is insufficient to stabilize the shell, then the cyclodextrin and the other shell-stabilizing material (or water activity-reducing agent) cooperate to synergistically stabilize the shell.

The invention also provides a water-stabilized capsule formulation comprising a water soluble, erodible, swellable and/or degradable shell, and an aqueous fill composition comprising a derivatized cyclodextrin and an aqueous carrier, wherein the capsule formulation has an increased shelf life as compared to a similar capsule formulation excluding the derivatized cyclodextrin.

Surprisingly, PVP can on its own (in the absence of a derivatized cyclodextrin) also stabilize a shell exposed to an aqueous fill composition. FIG. 9 depicts a graph correlating the concentration of water soluble PVP in a fill composition versus the H.S.I.T. rating of a soft gelatin capsule exposed to the fill composition and the water activity of the fill composition. The data indicate that an aqueous fill composition

comprising at least about 25-30% wt. of PVP can stabilize a shell from water in the fill composition. A solution containing 25-30% wt of PVP has a water activity of approximately ≤0.996± the standard deviation. Accordingly, the invention also provides a method of stabilizing a shell material from erosion, dissolution, swelling or degradation by water in an aqueous fill composition, the method comprising the step of including water soluble PVP in the fill composition in an amount sufficient to stabilize the shell.

FIGS. 10a-10i depict ternary graphs correlating the concentration of SAE-CD, water and PVP in a fill composition to the H.S.I.T. rating of a soft shell capsule exposed to the fill composition. Aqueous fill solutions comprising differing amounts of PVP, SAE-CD and water were prepared. The stability tests were conducted as described below. The capsules described herein were used: SHIONOGI HGC (hard gelatin capsule) (FIG. 10a), CAPSUGEL HPMC hard shell capsule (FIG. 10b), SHIONOGI HPMC hard shell capsule (FIG. 10c), CAPSUGEL HGC (FIG. 10d), VEGAGEL hard shell capsule (FIG. 10e), hydrophilic fill-grade CARDINAL SGC (soft gelatin capsule) (FIG. 10f), lipophilic fill-grade CARDINAL SGC (FIG. 10g), hydrophilic fill-grade BANNER SGC (FIG. 10h), and lipophilic fill-grade BANNER SGC (FIG. 10i). No other shell-stabilizing material(s) was(were) included in the fill compositions evaluated. The results varied according to the capsule used. Stabilized aqueous fill composition-containing capsule formulations can be achieved with each capsule if one or more of the following fill compositions detailed below are used.

1- Water comprises ≤ 55% of the fill composition, and the combination of SAE-CD, PVP, one or more optional excipients and one or more optional active agents comprises ≥ 45% of the fill composition; wherein SAE-CD can comprise up to 90% (85%, 83%, or 80%) of the weight of the fill composition, and PVP can comprise less than 90%, respectively, of the weight of the fill composition, provided that the fill composition comprises ≥ 35% PVP when SAE-CD comprises ≤ 15 % of the weight of the fill composition, and wherein both PVP (preferably water soluble or water swellable) and SAE-CD are present.

2- Water comprises ≤ 45% of the fill composition, and the combination of SAE-CD, PVP, one or more optional excipients and one or more optional active agents

comprises ≥ 55% of the fill composition; wherein SAE-CD can comprise up to 90% (85%, 83%, or 80%) of the weight of the fill composition, and PVP can comprise less than 90%, respectively, of the weight of the fill composition, provided that the fill composition comprises ≥ 35% PVP when SAE-CD comprises ≤ 20 % of the weight of the fill composition, and wherein both PVP (preferably water soluble or water swellable) and SAE-CD are present.

3- Water comprises ≤ 70% of the fill composition, and the combination of SAE-CD, PVP, one or more optional excipients and one or more optional active agents comprises ≥ 30% of the fill composition; wherein SAE-CD can comprise up to 90% (85%, 83%, or 80%) of the weight of the fill composition, and PVP can comprise less than 90%, respectively, of the weight of the fill composition, provided that PVP ≥ 35% when SAE-CD comprises ≤ 15 % of the weight of the fill composition, and when PVP ≤ 35% then SAE-CD > 15% when water ≥ 50%, and wherein both PVP (preferably water soluble or water swellable) and SAE-CD are present.

4- Water comprises ≤ 65% of the fill composition, and the combination of SAE-CD, PVP, one or more optional excipients and one or more optional active agents comprises ≥ 35% of the fill composition; wherein SAE-CD can comprise up to 90% (85%, 83%, or 80%) of the weight of the fill composition, and PVP can comprise less than 90%, respectively, of the weight of the fill composition, provided that both PVP (preferably water soluble or water swellable) and SAE-CD are present.

5- Water comprises ≤ 45% of the fill composition, and the combination of SAE-CD, PVP, one or more optional excipients and one or more optional active agents comprises ≥ 55% of the fill composition; wherein SAE-CD can comprise up to 90% (85%, 83%, or 80%) of the weight of the fill composition, and PVP can comprise less than 90%, respectively, of the weight of the fill composition, wherein both PVP (preferably water soluble or water swellable) and SAE-CD are present.

6- Water comprises ≤ 50% of the fill composition, and the combination of SAE-CD, PVP, one or more optional excipients and one or more optional active agents comprises ≥ 50% of the fill composition; wherein SAE-CD can comprise up to 90% (85%, 83%, or 80%) of the weight of the fill composition, and PVP can comprise less than 90%, respectively, of the weight of the fill composition, provided that the fill composition comprises ≥ 35% PVP when SAE-CD comprises ≤ 15 % of the weight of the fill composition, and wherein both PVP (preferably water soluble or water swellable) and SAE-CD are present.

The above values for water, SAE-CD, PVP, optional drug(s) and optional excipient(s) add up to 100% wt. of the fill composition. Depending upon the shell being used, fill compositions made according to the above-noted ranges provide an HSIT rating of at least "3" for a capsule containing the aqueous fill composition.

The table below summarizes some of the data observed in FIGS. 10a-10i for obtaining capsules according to the invention, wherein the capsule has an HSIT rating of at least "3".

CAPSULE	SAE-CD (%)	PVP + SAE-CD + OTHER (%)	Water (%)
SHIONOGI HGC	≥6	≥46	≤54
CAPSUGEL HPMC hard shell capsule	≥6	≥30	≤70
SHIONOGI HPMC hard shell capsule	≥6	≥40	≤60
CAPSUGEL HGC	≥24	≥64	≤36
VEGAGEL hard shell capsule	≥6	≥36	≤64
hydrophilic fill-grade CARDINAL SGC	≥6	≥46	≤54

CAPSULE	SAE-CD (%)	PVP + SAE-CD + OTHER (%)	Water (%)
lipophilic fill-grade CARDINAL SGC	≥6	≥61	≤49
hydrophilic fill-grade BANNER SGC	≥6	≥46	≤54
lipophilic fill-grade BANNER SGC	≥6	≥46	≤54

Under each of the conditions tested, the control sample excluded SAE-CD, i.e., containing only water and PVP at the indicated concentration, and failed within 24 hours (See FIG. 9). Increasing the SAE-CD and/or the PVP concentration to values higher than those indicated above or in the ternary graphs further increases the shelf-life of the shell or provides an HSIT rating of at least 4.

As used herein, the term "water-stabilized capsule shell" refers to a shell that has been rendered stable for at least a predetermined period of time to an aqueous fill composition therein, wherein the stability is expressed in terms of the erosion, degradation, dissolution or swelling of the shell by water in the aqueous fill composition. A water-stabilized capsule shell has an increased shelf life due to the presence of a derivatized cyclodextrin, and optionally a shell-stabilizing material and/or water activity reducing material, in an aqueous fill composition contained within the shell.

A capsule according to the invention will have a storage shelf life of no less than one week, three weeks, one month, three months, six months, or one year. In this case, shelf life is determined only as regards the stability of the shell toward erosion, dissolution, swelling or degradation of the shell by water in the fill composition. For example, for a capsule having a shelf life of at least six months, the shell of the capsule will not fail storage stability tests due to erosion, dissolution, swelling or degradation of the shell by water from the fill composition for a storage period of at least six months. The criteria for acceptable shelf-life are set as needed according to a given capsule product and its storage stability requirements. It should be noted that a shelf-life of as

little as one week is suitable for products that are compounded by a pharmacist and sold to customers of a pharmacy.

As used herein, a pharmaceutically acceptable liquid carrier is any aqueous or nonaqueous medium used in the pharmaceutical sciences such as water, organic solvent, organic compound, or a combination thereof.

The shell can be hard or soft and any materials suitable for preparing such shells can be used in the capsule of the invention. Materials suitable for the preparation of the capsule shell include soft gelatin, hard gelatin, hydroxypropyl methylcellulose, starch, animal gelatin, agar, fish (piscine) gelatin or a combination thereof. Other suitable materials include: polvinyl alcohol/polyvinyl acetate copolymer (U.S. Pat. No. 3,300,546); a blend of hydroxybutyl methylcellulose and hydroxypropyl methylcellulose (U.S. Pat. No. 4,765,916); polyvinyl acetate (U.S. Pats. No. 2,560,649, No.3,346,502); water-soluble gelatin (U.S. Pat. No. 3,525,426); polyvinyl alcohol (U.S. Patents No. 3,528,921, No. 3,534,851, No. 3,556,765, No. 3,634,260, No. 3,671,439, No. 3,706,670, No. 3,857,195, No. 3,877,928, No. 4,367,156, No. 4,747,976, No. 5,270,054); polymers derived from such monomers as vinyl chloride, vinyl alcohol, vinyl pyrrolidone, furan, acrylonitrile, vinyl acetate, methyl acrylate, methyl methacrylate, styrene, vinyl ethyl ether, vinyl propyl ether, acrylamide, ethylene, propylene, acrylic acid, methacrylic acid, maleic anhydride, salts of any of the aforementioned acids and mixtures thereof; polyvinyl chloride; polypropylene; acrylic/maleic copolymers; sodium polyacrylate; polyvinyl pyrrolidone; glucomannan and optionally another natural polysaccharide with a polyhydric alcohol such as glycerin (U.S. Pat. No. 4,851,394); plastic and polylactide/polyglycolide (Elanco Animal Health Co.); HPMC (Shionogi Qualicaps Co. Ltd (Nara Japan); SUHEUNG CAPSULES CO.LTD. (KYUNGGI-DO, KOREA) and Capsugel); or a combination thereof. Essentially any material known to those of ordinary skill in the art as being for the preparation of capsule shell can be used in a capsule according to the invention. Suitable starch capsules can be made and used according to Vilivalam et al. (*Pharmaceutical Science & Technology Today* (2000), 3(2), 64-69). A chitosan capsule for colonic delivery can be made and used according to Yamamoto

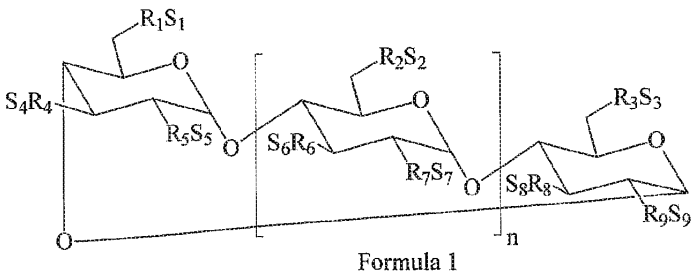
(*Kobunshi* (1999), 48(8), 595) or Tozaki et al. (*Drug Delivery System* (1997), 12(5), 311-320).

Capsules from the following suppliers were evaluated herein:

- Banner Pharmacaps hydrophilic and lipophilic fill, soft gelatin capsules (SGC).
- Cardinal Health hydrophilic and lipophilic fill SGC.
- Swiss Caps VegaGel flaxseed oil filled, potato starch soft capsules
- Shionogi Qualicaps Posilok hard gelatin capsules (HGC) and QualiV (HPMC) capsules. Capsugel HGC and Vcap (HPMC) capsules. The term "shell" as used herein is taken to mean the shell of a capsule dosage form or the encasement or encapsulation material used to encapsulate fill compositions. Any material suitable for use in forming a capsule shell or in encapsulating another composition can be used according to the invention. An aqueous composition according to the invention is surrounded by a water erodible, soluble, swellable and/or degradable shell or encapsulating material.

Other suitable shell materials are disclosed in U.S. Patent Application Publication No. 2002/0081331 to R.P. Scherer Technologies Inc. (Cardinal Health, Inc.), which discloses film-forming compositions comprising modified starches and iota-carrageenan.

The formulation of the invention can comprise a sulfoalkyl ether cyclodextrin 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_2, R_3, R_4, R_5, R_6, R_7, R_8 and 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 cation which includes, for example, H^+, alkali metal (e.g. Li^+, Na^+, K^+), alkaline earth metal (e.g., Ca^{+2}, Mg^{+2}), ammonium cation and organic amine cation such as the cation of (C_1 - C_6)- alkylamines, piperidine, pyrazine, (C_1 - C_6)-alkanolamine and (C_4 - C_8)-cycloalkanolamine.

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 water activity reducing power than a different second salt form of SAE-CD. Likewise, an SAE-CD having a first degree of substitution can have a greater water activity reducing power than a second SAE-CD having a different degree of substitution.

The SAE-CD used in the formulation 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. The preparation process may comprise dissolving the cyclodextrin in aqueous base at an appropriate temperature, e.g., 70° to 80° C., at the highest concentration possible. For example, to prepare the cyclodextrin derivatives herein, an amount of an appropriate alkyl sultone, corresponding to the number of moles of primary CD hydroxyl group present, is added with vigorous stirring to ensure maximal contact of the heterogeneous phase. According to one embodiment, the SAE-CD is SBE-7-β-CD (CAPTISOL® cyclodextrin), or SBE-4-β-CD (ADAVASEP®). An SAE-CD made according to other known procedures should also be suitable for use in the invention as long as the SAE-CD has the ability to reduce water activity.

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 may be situated at any position on the alkyl moiety. The term "cycloalkanol" includes unsubstituted or substituted (e.g., by methyl or ethyl) cyclic alcohols.

The present invention provides compositions containing a mixture of cyclodextrin derivatives wherein two or more different types of cyclodextrin derivatives are included in the fill composition. By different types, is meant cyclodextrins derivatized with different types of functional groups e.g., hydroxyalkyl and sulfoalkyl, and not to the heterogeneous nature of derivatized cyclodextrins due to their varying degrees of substitution. The amount of each type of cyclodextrin derivative present can be varied as desired to provide a mixture having the desired properties.

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 compositions 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 cyclodextrin derivatives of the present invention are obtained as purified compositions, i.e., compositions containing at least 50% wt. of cyclodextrin derivative(s). In other words, a derivatized cyclodextrin can include a minor (less than 50% wt.) amount of underivatized cyclodextrin. In a preferred embodiment, purified compositions containing at least 90 wt. % cyclodextrin derivative(s) are obtained.

In some of the compositions of the invention unreacted/underivatized cyclodextrin has been substantially removed, with the remaining impurities being inconsequential to the performance of the cyclodextrin derivative-containing composition.

Exemplary SAE-CD derivatives include SBE4-β-CD, SBE7-β-CD, SBE11-β-CD, and SBE4-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 4, 7, 11 and 4 sulfoalkyl ether substituents present, respectively. It has been found that these SAE-CD derivatives increase the solubility of poorly water soluble active agents to varying degrees.

By "complexed" is meant "being part of a clathrate or inclusion complex with", i.e., a complexed active agent is part of a clathrate or inclusion complex with a cyclodextrin derivative.

By active agent/ CD complex is generally meant a clathrate or inclusion complex of a cyclodextrin derivative and an active agent. The ratio of active agent: CD present in the molecular complex can vary and can be in the range of about 10 to about 0.1, on a molar basis. Thus, the CD will generally be, but need not be, present in excess of the active agent. The amount of excess will be determined by the intrinsic solubility of the agent, the expected dose of the agent, and the binding constant for inclusion complexation between the specific drug (agent) and the specific CD derivative used. It should be noted that the cyclodextrin derivative can be present in uncomplexed form and therefore in amounts substantially in excess of the amount of active agent present. The weight ratio or molar ratio of derivatized cyclodextrin to active agent can exceed 100, 1000 or even more.

Under conditions wherein an ionized cyclodextrin derivative can form one or more ionic bonds with a positively charged acid-ionizable compound, the derivatized cyclodextrin can be present in low concentrations and the ratio of compound to derivatized cyclodextrin can be greater than one. Therefore, it is possible for the compound to be complexed by way of an inclusion complex with the derivatized cyclodextrin and to be non-covalently ionically bound to the derivatized cyclodextrin.

These derivatized cyclodextrins differ in their degree of substitution by functional groups, the number of carbons in the functional groups, their molecular weight, the number of glucopyranose units contained in the base cyclodextrin used to form the derivatized cyclodextrin and or their substitution patterns. In addition, the derivatization of β-cyclodextrin with functional groups occurs in a controlled, although not exact

manner. For this reason, the degree of substitution is actually a number representing the average number of functional groups per cyclodextrin (for example, SBE7-β-CD, has an average of 7 substitutions per cyclodextrin). In addition, the regiochemistry of substitution of the hydroxyl groups of the cyclodextrin is variable with regard to the substitution of specific hydroxyl groups of the hexose ring. For this reason, substitution of the different hydroxyl groups is likely to occur during manufacture of the derivatized cyclodextrin, and a particular derivatized cyclodextrin will possess a preferential, although not exclusive or specific, substitution pattern. Given the above, the molecular weight of a particular derivatized cyclodextrin may vary from batch to batch and will vary from derivatized cyclodextrin. All of these variations can lead to changes in the complexation equilibrium constant $K_{1:1}$ which in turn will affect the required molar ratios of the derivatized cyclodextrin to active agent. The equilibrium constant is also somewhat variable with temperature and allowances in the ratio are required such that the agent remains solubilized during the temperature fluctuations that can occur during manufacture, storage, transport, and use. The equilibrium constant is also variable with pH and allowances in the ratio are required such that the agent remains solubilized during pH fluctuations that can occur during manufacture, storage, transport, and use. The equilibrium constant is also variable by the presence of other excipients (e.g., buffers, preservatives, antioxidants) Accordingly, the ratio of derivatized cyclodextrin to active agent may need to be varied from the ratios set forth herein in order to compensate for the above-mentioned variables.

The HPCD can be obtained from Research Diagnostics Inc. (Flanders, NJ). HPCD 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. As with other derivatized cyclodextrins of the invention, changes in the degree of substitution can result in changes in the ability of the HPCD to stabilize the shell. One grade of HPCD used was C☆Cavitron 82005 (Cerestar USA, Inc. Hammond, IN). It has an average degree of substitution of 5.5.

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, 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 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).

Although not necessary, the formulation of the present invention may include a preservative, antioxidant, buffering agent, acidifying agent, alkalizing agent, antibacterial agent, antifungal agent, colorant, solubility-enhancing agent, complexation enhancing agent, solvent, electrolyte, salt, water, glucose, stabilizer, tonicity modifier, antifoaming agent, oil, plasticizer, flavors, sweeteners, other excipients known by those of ordinary skill in the art for use in aqueous fill capsules, or a combination thereof.

A complexation-enhancing agent can be added to the aqueous liquid formulation of the invention. A complexation-enhancing agent is a compound, or compounds, that enhance(s) the complexation of an active agent with the derivatized cyclodextrin. When the complexation-enhancing agent is present, the required ratio of derivatized cyclodextrin to active agent may need to be changed such that less derivatized cyclodextrin is required. Suitable complexation enhancing agents include one or more pharmacologically inert water soluble polymers, hydroxy acids, and other organic compounds typically used in liquid formulations to enhance the complexation of a particular agent with cyclodextrins. Suitable water soluble polymers include water soluble natural polymers, water soluble semisynthetic polymers (such as the water soluble derivatives of cellulose) and water soluble synthetic polymers. The natural polymers include polysaccharides such as inulin, pectins, algin derivatives and agar, and polypeptides such as casein and gelatin. The semi-synthetic polymers include cellulose

derivatives such as methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, their mixed ethers such as hydroxypropyl methylcellulose and other mixed ethers such as hydroxyethyl ethylcellulose, hydroxypropyl ethylcellulose, hydroxypropyl methylcellulose phthalate and carboxymethylcellulose and its salts, especially sodium carboxymethylcellulose. The synthetic polymers include polyoxyethylene derivatives (polyethylene glycols) and polyvinyl derivatives (polyvinyl alcohol, polyvinylpyrrolidone and polystyrene sulfonate) and various copolymers of acrylic acid (e.g. carbomer). Suitable hydroxy acids include by way of example, and without limitation, citric acid, malic acid, lactic acid, and tartaric acid and others known to those of ordinary skill in the art.

A solubility-enhancing agent can be added to the aqueous liquid formulation of the invention. A solubility-enhancing agent is a compound, or compounds, that enhance(s) the solubility of active agent in the liquid composition. When a solubility-enhancing agent is present, the ratio of derivatized cyclodextrin to active agent may need to be changed such that less derivatized cyclodextrin is required. Suitable solubility enhancing agents include one or more organic solvents, detergents, soaps, surfactants and other organic compounds typically used in parenteral formulations to enhance the solubility of a particular agent. Suitable organic solvents include, for example, ethanol, glycerin, poly(ethylene glycols), propylene glycol, poly(propylene glycols), poloxomers, and others known to those of ordinary skill in the art.

As used herein, the term "alkalizing agent" is intended to mean a compound used to provide alkaline medium for product stability. Such compounds include, by way of example and without limitation, ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium carbonate, sodium bicarbonate, sodium hydroxide, triethanolamine, diethanolamine, organic amine base, alkaline amino acids and trolamine and others known to those of ordinary skill in the art.

As used herein, the term "acidifying agent" is intended to mean a compound used to provide an acidic medium for product stability. Such compounds include, by way of example and without limitation, acetic acid, acidic amino acids, citric acid, fumaric acid

and other alpha hydroxy acids, hydrochloric acid, ascorbic acid, phosphoric acid, sulfuric acid, tartaric acid and nitric acid and others known to those of ordinary skill in the art.

As used herein, the term "preservative" is intended to mean a compound used to prevent the growth of microorganisms. Such compounds include, by way of example and without limitation, benzalkonium chloride, benzethonium chloride, benzoic acid, benzyl alcohol, cetylpyridinium chloride, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate, phenylmercuric acetate, thimerosal, metacresol, myristylgamma picolinium chloride, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, sorbic acid, thymol, and methyl, ethyl, propyl, or butyl parabens and others known to those of ordinary skill in the art.

As used herein, the term "antioxidant" is intended to mean an agent that inhibits oxidation and thus is used to prevent the deterioration of preparations by the oxidative process. Such compounds include by way of example and without limitation, acetone, sodium bisulfate, ascorbic acid, ascorbyl palmitate, citric acid, butylated hydroxyanisole, butylated hydroxytoluene, hydrophosphorous acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium citrate, sodium sulfide, sodium sulfite, sodium bisulfite, sodium formaldehyde sulfoxylate, thioglycolic acid, sodium metabisulfite, EDTA (edetate), pentetate and others known to those of ordinary skill in the art.

As used herein, the term "buffering agent" is intended to mean a compound used to resist change in pH upon dilution or addition of acid or alkali. Such compounds include, by way of example and without limitation, acetic acid, sodium acetate, adipic acid, benzoic acid, sodium benzoate, citric acid, maleic acid, monobasic sodium phosphate, dibasic sodium phosphate, lactic acid, tartaric acid, glycine, potassium metaphosphate, potassium phosphate, monobasic sodium acetate, sodium bicarbonate, sodium tartrate and sodium citrate anhydrous and dihydrate and others known to those of ordinary skill in the art.

As used herein, the term "stabilizer" is intended to mean a compound used to stabilize a active agent against physical, chemical, or biochemical process that would otherwise reduce the therapeutic activity of the agent. Suitable stabilizers include, by way of example and without limitation, albumin, sialic acid, creatinine, glycine and other

amino acids, niacinamide, sodium acetyltryptophonate, zinc oxide, sucrose, glucose, lactose, sorbitol, mannitol, glycerol, polyethylene glycols, sodium caprylate and sodium saccharin and others known to those of ordinary skill in the art.

As used herein, the term "colorant" is intended to mean a compound used to impart color to pharmaceutical preparations. Such compounds include, by way of example and without limitation, FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel, and iron oxide (black, red, yellow), other F.D. & C. dyes and natural coloring agents such as grape skin extract, beet red powder, beta-carotene, annato, carmine, turmeric, paprika, combinations thereof and other such materials known to those of ordinary skill in the art.

The capsule of the invention can also include oils such as fixed oils, fish oil, peanut oil, sesame oil, cottonseed oil, corn oil and olive oil; fatty acids such as oleic acid, stearic acid and isostearic acid; and fatty acid esters such as ethyl oleate, isopropyl myristate, fatty acid glycerides and acetylated fatty acid glycerides. The capsule can also include alcohol such as ethanol, isopropanol, hexadecyl alcohol, glycerol and propylene glycol; glycerol ketals such as 2,2-dimethyl-1, 3-dioxolane-4-methanol; ethers such as poly (ethyleneglycol) 450; petroleum hydrocarbons such as mineral oil and petrolatum; water; mixtures thereof; or a pharmaceutically suitable surfactant, suspending agent or emulsifying agent.

Soaps and synthetic detergents may be employed as surfactants and as vehicles for detergent compositions. Suitable soaps include fatty acid alkali metal, ammonium, and triethanolamine salts. Suitable detergents include cationic detergents such as dimethyl dialkyl ammonium halides, alkyl pyridinium halides, and alkylamine acetates; anionic detergents such as alkyl, aryl and olefin sulfonates, alkyl, olefin, ether and monoglyceride sulfates, and sulfosuccinates; non-ionic detergents such as fatty amine oxides, fatty acid alkanolamides, and poly(oxyethylene)-*block*-poly(oxypropylene) copolymers; amphoteric detergents such as alkyl β-aminopropionates and 2-alkylimidazoline quaternary ammonium salts; and mixtures thereof.

As used herein, the term "tonicity modifier" is intended to mean a compound or compounds that can be used to adjust the tonicity of the liquid formulation. Suitable tonicity modifiers include glycerin, lactose, mannitol, dextrose, sodium chloride, sodium sulfate, sorbitol, trehalose and others known to those or ordinary skill in the art.

As used herein, the term "antifoaming agent" is intended to mean a compound or compounds that prevents or reduces the amount of foaming that forms on the surface of the fill composition. Suitable antifoaming agents include by way of example and without limitation, dimethicone, simethicone, octoxynol and others known to those of ordinary skill in the art.

It should be understood, that compounds used in the pharmaceutical arts generally serve a variety of functions or purposes. Thus, if a compound named herein is mentioned only once or is used to define more than one term herein, its purpose or function should not be construed as being limited solely to that named purpose(s) or function(s).

The chemical stability of the fill composition of the invention, in terms of forming a precipitate or gel, may be enhanced by adjusting the pH of the liquid carrier.

The pH of the fill composition will generally range from about pH 1 to about pH 11; however, fill compositions having pH values that are neutral, basic or acidic can also be prepared. An acidic fill composition would be suitable for a capsule which shell is stable to acid in the fill composition. Likewise, a basic fill composition would be suitable for a capsule which shell is stable to alkaline materials in the fill composition.

The release profile of active agent from the capsule can be any release profile known for capsule/encapsulated formulations. For example after oral administration, the release of active agent can be gastric (release in the stomach), delayed (release in the gastrointestinal tract downstream of the stomach), enteric (release in the small intestine) or colonic (release in the colon). Release of active agent from the capsule can be rapid or sustained (extended or controlled) release. A sustained release capsule can be made according to Miyao (*Pharm. Tech. Jpn.* (1988), 4(2), 141-3) and modified according to the invention to include an aqueous fill composition. A controlled release capsule can be made according to Okahata (*Sen'I Gakkaishi* (1987), 43(12), 482-488) and modified according to the invention to include an aqueous fill composition. Hard gelatin capsules

can be made according to Berezovskaya et al. (*Khim.-Farm. Zh.* (1978), 12(10), 87-97) and modified according to the invention to include an aqueous fill composition. Microencapsulated dosage forms can be made according to Luzzi (*Drugs Pharm. Sci.* (1976), 3(microencapsulation), 193-206) and modified according to the invention to include an aqueous fill composition.

The TARGIT™ colonic delivery (West Pharmaceutical Services (Nottingham, UK; U.S. Patent No. 6,228,396) capsule technology can be used to make capsules according to the invention by injection molding of starch capsules and then coating of the capsules with a mixture of plasticized enteric polymers such as EUDRAGIT™ L and EUDRAGIT™ S. By changing the thickness of the coating, drug delivery to the terminal ileum, ascending colon, transverse colon or descending colon can be achieved.

BANNER PHARMACAPS (Highpoint, North Carolina) manufactures a line of soft gelatin capsules under the trademark GELATIN BINARY SYSTEM®, which capsules are adapted for enteric delivery of drugs. Those uncoated capsules achieve enteric delivery of drug due to the enteric release properties incorporated within the gelatin material itself. Such capsules can be used to deliver a fill composition according to the invention.

Enteric and colonic release capsules according to the invention provide a substantial advantage over solid non-aqueous enteric and colonic release dosage forms. In particular for colonic delivery, the water included within the present capsules serves to aid in distribution of the fill composition in the colon and avoids the step of dissolving the fill composition in the intestine prior to delivery as must be done with non-aqueous colonic delivery dosage forms. The capsules also have increased osmotic pressure in the colon and small intestines, as compared to those other dosage forms. As a result, the present capsules can employ the increased osmotic pressure to enhance drug release.

The invention also includes an embodiment comprising a capsule within a capsule. The inner and/or outer capsule can contain an aqueous fill composition according to the invention or another composition. Such a system can be made according to Bakhshaee et al. (PCT International Publication No. WO 02/07710 A2 (01/31/2002)

and modified according to the present invention by including the present aqueous fill composition.

The loading or filling of a liquid composition into a capsule can be achieved by any known method for preparing liquid, gel, semi-solid or solid melt filled capsules. In particular, the methods described by R.P. Scherer company, Alza or MW Encap Ltd. can be used. One exemplary method is described by Bowtle (*Pharmaceutical Technology Europe* (1998), 10(10), 84, 86, 88-90.

A liquid filled capsule having a biphasic release profile can be made according to Bowtle (*International Journal of Pharmaceutics* (1996) 141(1-2), 9-16) and modified as described herein to include an aqueous fill composition as described herein.

A multi-layered capsule can be made according to Ishibashi et al. (*Int. J. Pharm.* (1998), 168, 31-40) and modified as described herein to include an aqueous fill composition as described herein. The multi-layered capsule would have an inner capsule coated with a layer of cationic polymer, then a layer of water soluble or erodible material and finally an outer layer containing a material that dissolves at a pH of about 5 or higher. This capsule would provide delayed release (release after the stomach) for a predetermined lag time such that the content of the fill composition would be release abruptly upon rupture, erosion or dissolution of the innermost shell.

Polyvinyl acetate phthalate (PVAP) can be used as a coating material for capsules. This material is suitable for enteric release of an active agent included in the capsule. When a capsule coated with PVAP is administered orally to a subject, the active agent is released in the GI tract downstream from the stomach.

Since the fill composition does not require PEG or other similar materials known to affect crosslinking of a soft gelatin shell, a capsule dosage form is generally free of the crosslinking the occurs during storage.

The fill composition of the invention can be prepared by numerous different methods. According to one method, a first aqueous solution comprising derivatized cyclodextrin and optionally one or more excipients is prepared. Then, a second solution comprising an active agent and optionally one or more excipients is prepared. Finally, the first and second solutions are mixed to form the fill composition. The first and

second solutions can independently comprise other excipients and agents described herein. Additionally, the second solution can be water and/or an organic solvent-based solution.

Another method of preparation is similar to the above-described method except that the active agent is added directly to the first solution without the formation of a second solution.

A third method of preparing the fill composition is similar to the above-described first method except that the derivatized cyclodextrin is added directly to an aqueous second solution containing the active agent without formation of the first solution.

A fourth method of preparing the fill composition comprises the steps of adding an aqueous solution comprising an active agent to a powdered or particulate derivatized cyclodextrin and mixing the solution until the derivatized cyclodextrin has dissolved.

A fifth method of preparing the fill composition comprises the steps of adding the active agent directly to the powdered or particulate derivatized cyclodextrin and then adding an aqueous solution and mixing until the derivatized cyclodextrin and active agent have dissolved.

A sixth method for preparing the fill composition comprises the steps of heating either the first solution or heating the second solution, or heating a combination thereof of any solutions described in the above methods followed by the step of cooling the respectively heated solution.

Another method for preparing the fill composition comprises the step concentrating a solution of derivatized cyclodextrin. The step of concentrating can be by accomplished by evaporation, drum drying, tray drying or other conventional methods of reducing the amount of water in a composition.

Any of the above solutions can contain other pharmaceutical excipients or ingredients as described herein.

Specific embodiments of the method of preparing the fill composition include those wherein the method further comprises the step of: 1) sterile filtering the fill composition through a filtration medium wherein the pore size is about 0.22 μm or smaller; 2) sterilizing the fill composition by irradiation; 3) sterilizing the fill composition

by treatment with ethylene oxide; 4) purging the fill composition with an inert gas to reduce the amount of dissolved oxygen therein; and/or 5) heating one or more of the solutions used to prepare the fill composition.

A unit dosage form is a single or multiple dose form containing a quantity of the active ingredient and the diluent or carrier, said quantity being such that one or more predetermined units are normally required for a single therapeutic administration. In the case of multiple dose forms, such as capsules, said predetermined unit will be one fraction such as a half or quarter of the multiple dose form. It will be understood that the specific dose level for any patient will depend upon a variety of factors including the indication being treated, active agent employed, the activity of active agent, severity of the indication, patient health, age, sex, weight, diet, and pharmacological response, the specific dosage form employed and other such factors.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, the term "patient" or "subject" is taken to mean warm blooded animals such as mammals, for example, cats, dogs, mice, guinea pigs, horses, bovine cows, sheep, and humans.

The fill composition can include one or more of any known active agents. The active agent included in the present invention can possess a wide range of values for water solubility, bioavailability and hydrophilicity. Active agents to which the present invention is particularly suitable include water insoluble, poorly water soluble, slightly water soluble, moderately water soluble, water soluble, very water soluble, hydrophobic, or hydrophilic therapeutic agents. It will be understood by the artisan of ordinary skill that an active agent used in the fill composition of the present invention is independently selected at each occurrence from any known active agent and from those disclosed herein. It is not necessary that the active agent complex with the derivatized cyclodextrin.

Active agents generally include physiologically or pharmacologically active substances that produce a systemic or localized effect or effects on animals and human beings. Active agents also include pesticides, herbicides, insecticides, antioxidants, plant growth instigators, sterilization agents, catalysts, chemical reagents, food products, nutrients, cosmetics, vitamins, sterility inhibitors, fertility instigators, microorganisms, flavoring agents, sweeteners, cleansing agents and other such compounds for pharmaceutical, veterinary, horticultural, household, food, culinary, agricultural, cosmetic, industrial, cleaning, confectionery and flavoring applications. The active agent can be present in its neutral, ionic, salt, basic, acidic, natural, synthetic, diastereomeric, isomeric, enantiomerically pure, racemic, hydrate, chelate, derivative, analog, or other common form.

The capsule of the invention can be used to deliver two or more different active agents. Particular combinations of active agents can be provided by the present capsule. 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.

Figure 11 shows the dissolution profiles obtained according to Example 6. The percent fexofenadine hydrochloride dissolved as a function of time in USP Simulated Gastric Fluid TS as dissolution media is depicted for a commercial immediate release tablet (Allegra® 60 mg. From Aventis Pharmaceuticals, Inc., Kansas City, MO 64137 USA) and a capsule according to the invention. Because the capsules used were made from gelatin, the enzymes in the USP test solutions were not excluded from the dissolution medium. Initially, the tablet provides a more immediate release of drug; however, the capsule quickly surpasses the tablet in terms of the rate of drug release and the total amount of drug released within a one-hour period. After a short initial lag time, the aqueous filled capsule dissolved much more rapidly in the dissolution apparatus. The

results indicate that a capsule of the invention may improve the rate and extent of absorption of the drug and be especially useful for drugs where a rapid on set of activity is desired.

The effect of dissolution medium upon the release of drug from the capsule versus the commercial tablet was evaluated. The table below shows the results.

Sample	Media	Time for 80% to dissolve
Capsule	USP Simulated Gastric Fluid, TS (Test Solution)	19 minutes
Tablet	USP Simulated Gastric Fluid, TS (without enzymes)	41 minutes
Capsule	USP Simulated Intestinal Fluid, TS	27 minutes
Tablet	USP Simulated Intestinal Fluid, TS (without enzymes)	9 minutes
Capsule	Water	26 minutes
Tablet	Water	8 minutes

The aqueous filled capsules dissolved rapidly, (less than 30 minutes for 80% of the drug to dissolve), regardless of the media used. It was fastest in simulated gastric fluid. Dissolution of the commercial tablet was slowest in simulated gastric fluid. As this media is most like the environment first encountered by an oral dosage form, aqueous filled compositions stabilized with derivatized cyclodextrins could be expected to be especially useful for active ingredients that dissolve slowly in simulated gastric fluid. The invention provides an improved method of orally delivering a drug to the gastric region of a subject, the improvement comprising administering the drug in a gastric fluid soluble, erodible and/or degradable capsule comprising an aqueous fill composition comprising SAE-CD, the drug, water, and one or more optional excipients, wherein the SAE-CD is present in amount sufficient to stabilize the capsule against dissolution, erosion, swelling or degradation caused by water in the fill composition but not against dissolution, erosion, swelling or degradation caused by gastric fluid.

Whenever mentioned and unless otherwise specified, the term "active agent" includes all forms of the active agent including optically pure, racemic, free base, free acid, salt, diastereomeric, regioisomeric, amorphous, hydrate, anhydrous and/or crystalline forms.

The active agent can be independently selected at each occurrence from active agents such as an antibiotic agent, antihistamine agent, decongestant, anti-inflammatory agent, antiparasitic agent, antiviral agent, local anesthetic, antifungal agent, amoebicidal agent, trichomonocidal agent, analgesic agent, anti-arthritic agent, anti-asthmatic agent, anticoagulant agent, anticonvulsant agent, antidepressant agent, antidiabetic agent, antineoplastic agent, anti-psychotic agent, neuroleptic agent, antihypertensive agent, hypnotic agent, sedative agent, anxiolytic energizer agent, antiparkinson agent, muscle relaxant agent, antimalarial agent, hormonal agent, contraceptive agent, sympathomimetic agent, hypoglycemic agent, antilipemic agent, ophthalmic agent, electrolytic agent, diagnostic agent, prokinetic agent, gastric acid secretion inhibitor agent, anti-ulcerant agent, anti-flatulent agent, anti-incontinence agent, cardiovascular agent or a combination thereof.

Protease inhibitors which can be included in the present formulations include, by way of example and without limitation, antipain, leupeptin, chymostatin, amistatin, puromycin and others known to those of ordinary skill in the art.

Penetration enhancers which can be included in the present formulations include, by way of example and without limitation, calcium chelators such as EDTA, methylated β-cyclodextrin, and polycarboxylic acids; surfactants such as sodium lauryl sulfate, sodium dodecyl sulfate, carnitine, carnitine esters, and tween; bile salts such as sodium taurocholate; fatty acids such as oleic and linoleic acid; and non-surfactants such as AZONE™ and dialkyl sulfoxides; E-flux inhibitors such as AV171 (AyMax, Inc., South San Francisco, CA), D-α- tocopheryl polyethylene glycol 1000 succinate (TPGS), and peppermint oil; chitosan and chitosan derivatives such as N-methyl chitosan, N-trimethyl chitosan, mono-N-carboxymethyl chitosan, quaternized chitosan derivatives; SNAC (*N*-(8-[2-hydroxybenzoyl]amino)caprylate) and SNAD (N-[10-(2-hydroxybenzoyl)amino]-decanoate) (Emisphere Technologies, Inc., Tarrytown, NY); N-acylated non-alpha amino acids; EMISPHERE® brand delivery agents; Gélucire 44/14 or Vitamin E TPGS; Carbopol® 934P; others known to those of ordinary skill in the art; and combinations thereof.

Drugs suitable for use in the compositions described herein include the following categories and examples of drugs and alternative forms of these drugs such as alternative salt forms, free acid forms, free base forms, and hydrates:

- analgesics/antipyretics (e.g., aspirin, acetaminophen, ibuprofen, naproxen sodium, buprenorphine, propoxyphene hydrochloride, propoxyphene napsylate, meperidine hydrochloride, hydromorphone hydrochloride, morphine, oxycodone, codeine, dihydrocodeine bitartrate, pentazocine, hydrocodone bitartrate, levorphanol, diflunisal, trolamine salicylate, nalbuphine hydrochloride, mefenamic acid, butorphanol, choline salicylate, butalbital, phenyltoloxamine citrate, diphenhydramine citrate, methotrimeprazine, cinnamedrine hydrochloride, and meprobamate);
- antiasthamatics (e.g., ketotifen and traxanox);
- antibiotics (e.g., neomycin, streptomycin, chloramphenicol, cephalosporin, ampicillin, penicillin, tetracycline, and ciprofloxacin);
- antidepressants (e.g., nefopam, oxypertine, doxepin, amoxapine, trazodone, amitriptyline, maprotiline, phenelzine, desipramine, nortriptyline, tranylcypromine, fluoxetine, doxepin, imipramine, imipramine pamoate, isocarboxazid, trimipramine, and protriptyline);
- antidiabetics (e.g., biguanides and sulfonylurea derivatives);
- antifungal agents (e.g., griseofulvin, ketoconazole, itraconizole, amphotericin B, nystatin, and candicidin);
- antihypertensive agents (e.g., propanolol, propafenone, oxyprenolol, nifedipine, reserpine, trimethaphan, phenoxybenzamine, pargyline hydrochloride, deserpidine, diazoxide, guanethidine monosulfate, minoxidil, rescinnamine, sodium nitroprusside, rauwolfia serpentina, alseroxylon, and phentolamine);
- anti-inflammatory agents (e.g., (non-steroidal) indomethacin, ketoprofen, flurbiprofen, naproxen, ibuprofen, ramifenazone, piroxicam, (steroidal) cortisone, dexamethasone, fluazacort, celecoxib, rofecoxib, hydrocortisone, prednisolone, and prednisone);

- antineoplastics (e.g., cyclophosphamide, actinomycin, bleomycin, daunorubicin, doxorubicin, epirubicin, mitomycin, methotrexate, fluorouracil, carboplatin, carmustine (BCNU), methyl-CCNU, cisplatin, etoposide, camptothecin and derivatives thereof, phenesterine, paclitaxel and derivatives thereof, docetaxel and derivatives thereof, vinblastine, vincristine, tamoxifen, and piposulfan);
- antianxiety agents (e.g., lorazepam, buspirone, prazepam, chlordiazepoxide, oxazepam, clorazepate dipotassium, diazepam, hydroxyzine pamoate, hydroxyzine hydrochloride, alprazolam, droperidol, halazepam, chlormezanone, and dantrolene);
- immunosuppressive agents (e.g., cyclosporine, azathioprine, mizoribine, and FK506 (tacrolimus));
- antimigraine agents (e.g., ergotamine, propanolol, isometheptene mucate, and dichloralphenazone);
- sedatives/hypnotics (e.g., barbiturates such as pentobarbital, pentobarbital, and secobarbital; and benzodiazapines such as flurazepam hydrochloride, triazolam, and midazolam);
- antianginal agents (e.g., beta-adrenergic blockers; calcium channel blockers such as nifedipine, and diltiazem; and nitrates such as nitroglycerin, isosorbide dinitrate, pentaerythritol tetranitrate, and erythrityl tetranitrate);
- antipsychotic agents (e.g., haloperidol, loxapine succinate, loxapine hydrochloride, thioridazine, thioridazine hydrochloride, thiothixene, fluphenazine, fluphenazine decanoate, fluphenazine enanthate, trifluoperazine, chlorpromazine, perphenazine, lithium citrate, and prochlorperazine);
- antimanic agents (e.g., lithium carbonate);
- antiarrhythmics (e.g., bretylium tosylate, esmolol, verapamil, amiodarone, encainide, digoxin, digitoxin, mexiletine, disopyramide phosphate, procainamide, quinidine sulfate, quinidine gluconate, quinidine polygalacturonate, flecainide acetate, tocainide, and lidocaine);

- antiarthritic agents (e.g., phenylbutazone, sulindac, penicillanine, salsalate, piroxicam, azathioprine, indomethacin, meclofenamate, gold sodium thiomalate, ketoprofen, auranofin, aurothioglucose, and tolmetin sodium);
- antigout agents (e.g., colchicine, and allopurinol);
- anticoagulants (e.g., heparin, heparin sodium, and warfarin sodium);
- thrombolytic agents (e.g., urokinase, streptokinase, and alteplase);
- antifibrinolytic agents (e.g., aminocaproic acid);
- hemorheologic agents (e.g., pentoxifylline);
- antiplatelet agents (e.g., aspirin);
- anticonvulsants (e.g., valproic acid, divalproex sodium, phenytoin, phenytoin sodium, clonazepam, primidone, phenobarbitol, carbamazepine, amobarbital sodium, methsuximide, metharbital, mephobarbital, mephenytoin, phensuximide, paramethadione, ethotoin, phenacemide, secobarbitol sodium, clorazepate dipotassium, and trimethadione);
- antiparkinson agents (e.g., ethosuximide);
- antihistamines/antipruritics (e.g., hydroxyzine, diphenhydramine, chlorpheniramine, brompheniramine maleate, cyproheptadine hydrochloride, terfenadine, clemastine fumarate, triprolidine, carbinoxamine, diphenylpyraline, phenindamine, azatadine, tripelennamine, dexchlorpheniramine maleate, methdilazine, and);
- agents useful for calcium regulation (e.g., calcitonin, and parathyroid hormone);
- antibacterial agents (e.g., amikacin sulfate, aztreonam, chloramphenicol, chloramphenicol palirtate, ciprofloxacin, clindamycin, clindamycin palmitate, clindamycin phosphate, metronidazole, metronidazole hydrochloride, gentamicin sulfate, lincomycin hydrochloride, tobramycin sulfate, vancomycin hydrochloride, polymyxin B sulfate, colistimethate sodium, and colistin sulfate);
- antiviral agents (e.g., interferon alpha, beta or gamma, zidovudine, amantadine hydrochloride, ribavirin, and acyclovir);
- antimicrobials (e.g., cephalosporins such as cefazolin sodium, cephradine, cefaclor, cephapirin sodium, ceftizoxime sodium, cefoperazone sodium, cefotetan

disodium, cefuroxime e azotil, cefotaxime sodium, cefadroxil monohydrate, cephalexin, cephalothin sodium, cephalexin hydrochloride monohydrate, cefamandole nafate, cefoxitin sodium, cefonicid sodium, ceforanide, ceftriaxone sodium, ceftazidime, cefadroxil, cephradine, and cefuroxime sodium; penicillins such as ampicillin, amoxicillin, penicillin G benzathine, cyclacillin, ampicillin sodium, penicillin G potassium, penicillin V potassium, piperacillin sodium, oxacillin sodium, bacampicillin hydrochloride, cloxacillin sodium, ticarcillin disodium, azlocillin sodium, carbenicillin indanyl sodium, penicillin G procaine, methicillin sodium, and nafcillin sodium; erythromycins such as erythromycin ethylsuccinate, erythromycin, erythromycin estolate, erythromycin lactobionate, erythromycin stearate, and erythromycin ethylsuccinate; and tetracyclines such as tetracycline hydrochloride, doxycycline hyclate, and minocycline hydrochloride, azithromycin, clarithromycin);

- anti-infectives (e.g., GM-CSF);
- bronchodilators (e.g., sympathomimetics such as epinephrine hydrochloride, metaproterenol sulfate, terbutaline sulfate, isoetharine, isoetharine mesylate, isoetharine hydrochloride, albuterol sulfate, albuterol, bitolterolmesylate, isoproterenol hydrochloride, terbutaline sulfate, epinephrine bitartrate, metaproterenol sulfate, epinephrine, and epinephrine bitartrate; anticholinergic agents such as ipratropium bromide; xanthines such as aminophylline, dyphylline, metaproterenol sulfate, and aminophylline; mast cell stabilizers such as cromolyn sodium; inhalant corticosteroids such as beclomethasone dipropionate (BDP), and beclomethasone dipropionate monohydrate; salbutamol; ipratropium bromide; budesonide; ketotifen; salmeterol; xinafoate; terbutaline sulfate; triamcinolone; theophylline; nedocromil sodium; metaproterenol sulfate; albuterol; flunisolide; fluticasone proprionate;
- steroidal compounds and hormones (e.g., androgens such as danazol, testosterone cypionate, fluoxymesterone, ethyltestosterone, testosterone enathate, methyltestosterone, fluoxymesterone, and testosterone cypionate; estrogens such as estradiol, estropipate, and conjugated estrogens; progestins such as

methoxyprogesterone acetate, and norethindrone acetate; corticosteroids such as triamcinolone, betamethasone, betamethasone sodium phosphate, dexamethasone, dexamethasone sodium phosphate, dexamethasone acetate, prednisone, methylprednisolone acetate suspension, triamcinolone acetonide, methylprednisolone, prednisolone sodium phosphate, methylprednisolone sodium succinate, hydrocortisone sodium succinate, triamcinolone hexacetonide, hydrocortisone, hydrocortisone cypionate, prednisolone, fludrocortisone acetate, paramethasone acetate, prednisolone tebutate, prednisolone acetate, prednisolone sodium phosphate, and hydrocortisone sodium succinate; and thyroid hormones such as levothyroxine sodium);

- hypoglycemic agents (e.g., human insulin, purified beef insulin, purified pork insulin, glyburide, chlorpropamide, glipizide, tolbutamide, and tolazamide);
- hypolipidemic agents (e.g., clofibrate, dextrothyroxine sodium, probucol, pravastitin, atorvastatin, lovastatin, and niacin);
- proteins (e.g., DNase, alginase, superoxide dismutase, and lipase);
- nucleic acids (e.g., sense or anti-sense nucleic acids encoding any therapeutically useful protein, including any of the proteins described herein);
- agents useful for erythropoiesis stimulation (e.g., erythropoietin);
- antiulcer/antireflux agents (e.g., famotidine, cimetidine, and ranitidine hydrochloride);
- antinauseants/antiemetics (e.g., meclizine hydrochloride, nabilone, prochlorperazine, dimenhydrinate, promethazine hydrochloride, thiethylperazine, and scopolamine);
- oil-soluble vitamins (e.g., vitamins A, D, E, K, and the like);
- as well as other drugs such as mitotane, halonitrosoureas, anthrocyclines, and ellipticine.

Other useful agents include decongestant, antiparasitic agent, local anesthetic, amoebicidal agent, trichomonocidal agent, neuroleptic agent, anxiolytic energizer, muscle relaxant agent, antimalarial agent, hormonal agent, contraceptive agent, sympathomimetic agent, antilipemic agent, ophthalmic agent, electrolytic agent,

diagnostic agent, prokinetic agent, gastric acid secretion inhibitor agent, anti-flatulent agent, anti-incontinence agent, cardiovascular agent, nootropic, and vasodilators. A description of these and other classes of useful drugs and a listing of species within each class can be found in Martindale, The Extra Pharmacopoeia, 31st Ed. (The Pharmaceutical Press, London 1996), the disclosure of which is incorporated herein by reference in its entirety.

Examples of still other drugs suitable for use in the compositions and methods described herein include ceftriaxone, ketoconazole, ceftazidime, oxaprozin, albuterol, valacyclovir, urofollitropin, famciclovir, flutamide, enalapril, mefformin, itraconazole, buspirone, gabapentin, fosinopril, tramadol, acarbose, lorazepan, follitropin, glipizide, omeprazole, fluoxetine, lisinopril, tramsdol, levofloxacin, zafirlukast, interferon, growth hormone, interleukin, erythropoietin, granulocyte stimulating factor, nizatidine, bupropion, perindopril, erbumine, adenosine, alendronate, alprostadil, benazepril, betaxolol, bleomycin sulfate, dexfenfluramine, diltiazem, fentanyl, flecainid, gemcitabine, glatiramer acetate, granisetron, lamivudine, mangafodipir trisodium, mesalamine, metoprolol fumarate, metronidazole, miglitol, moexipril, monteleukast, octreotide acetate, olopatadine, paricalcitol, somatropin, sumatriptan succinate, tacrine, verapamil, nabumetone, trovafloxacin, dolasetron, zidovudine, finasteride, tobramycin, isradipine, tolcapone, enoxaparin, fluconazole, lansoprazole, terbinafine, pamidronate, didanosine, diclofenac, cisapride, venlafaxine, troglitazone, fluvastatin, losartan, imiglucerase, donepezil, olanzapine, valsartan, fexofenadine, calcitonin, and ipratropium bromide. These drugs are generally considered to be water soluble.

Preferred drugs include albuterol, adapalene, doxazosin mesylate, mometasone furoate, ursodiol, amphotericin, enalapril maleate, felodipine, nefazodone hydrochloride, valrubicin, albendazole, conjugated estrogens, medroxyprogesterone acetate, nicardipine hydrochloride, zolpidem tartrate, amlodipine besylate, ethinyl estradiol, omeprazole, rubitecan, amlodipine besylate/ benazepril hydrochloride, etodolac, paroxetine hydrochloride, paclitaxel, atovaquone, felodipine, podofilox, paricalcitol, betamethasone dipropionate, fentanyl, pramipexole dihydrochloride, Vitamin D_3 and related analogues, finasteride, quetiapine fumarate, alprostadil, candesartan, cilexetil, fluconazole, ritonavir,

busulfan, carbamazepine, flumazenil, risperidone, carbemazepine, carbidopa, levodopa, ganciclovir, saquinavir, amprenavir, carboplatin, glyburide, sertraline hydrochloride, rofecoxib carvedilol, halobetasolproprionate, sildenafil citrate, celecoxib, chlorthalidone, imiquimod, simvastatin, citalopram, ciprofloxacin, irinotecan hydrochloride, sparfloxacin, efavirenz, cisapride monohydrate, lansoprazole, tamsulosin hydrochloride, mofafinil, clarithromycin, letrozole, terbinafine hydrochloride, rosiglitazone maleate, diclofenac sodium, lomefloxacin hydrochloride, tirofiban hydrochloride, telmisartan, diazapam, loratadine, toremifene citrate, thalidomide, dinoprostone, mefloquine hydrochloride, trandolapril, docetaxel, mitoxantrone hydrochloride, tretinoin, etodolac, triamcinolone acetate, estradiol, ursodiol, nelfinavir mesylate, indinavir, beclomethasone dipropionate, oxaprozin, flutamide, famotidine, nifedipine, prednisone, cefuroxime, lorazepam, digoxin, lovastatin, griseofulvin, naproxen, ibuprofen, isotretinoin, tamoxifen citrate, nimodipine, amiodarone, and alprazolam.

Other drugs that can be included in the capsule include progesterone, acetohexamide, dapsone, ivermectin, pilocarpine, spironolactone, tegaserod maleate, tolbutamide, 1,2-dithiole-3-thiones, 5-niro-2-(3-phenylpropylamino)benzoic acid, 5-phenyl-1,2-dithiole-3-thione, 9-aminocamptothecin, alosetrom, ampotericin B, aripiprazole, artemisinin, ascomycin, bafilomycin A, benzylguanine, BMS 214662, BMS -247550, bumetanide, bupivacaine, calcipotriol, ceterizine, chloropropamide, chlorotoxin, ciclesonide, cimetideine, cinnarizine, concanamycin A, darifenacin, des-loratadine, dexmedetomidine, dextromethorphan+ pseudoephedrine, dihydroergotamine, dipyridamole, ditiazem, DY-9760e, elitriptan, eplerenone, epothilone B, erlotinib, fenofibrate, flurbiprofen, fluticasone diproprionate, fluticasone propionate salmeterol xinafoate, furosemide, gentamycin, glibenclamide, hexylresorcinol, idarubicin, irenotecan, ketanserin, ketodolac, ketorolac, kynostatin, leuprolide, linezolid, loratidine, mechlorethamine, melphalan, metfomin, methoxy-morpholinodoxorubicin, methylphenidate, metoclopramide, miconazole, mirtazapine, o6-benzylguanine, ondansetron, pantoprazole, pen G, pentamidine, pioglitazone hydrochloride, prilocaine hydrochloride, propofol, r-(+)-dioa, r(+)-iaa-94, rabeprazole, rapamycin, rifampicin, sanguinarine chloride, saquinavir mesylate, silatecan, tarceva (OSI-774), teniposide, teva

TV-4701, tirilazid mesylate, topotecan, triclosan, triptans, vindesine, vinpocetine, voriconazole, clotrimazole, zaleplon, ziprasidone, zopiclone, zyvox, escitalopram, ropinirole, and vinorelbine.

The above-mentioned lists should not be considered exhaustive and is merely exemplary of the many embodiments considered within the scope of the invention. Many other active agents can be administered with the capsule of the present invention.

The active agent(s) contained within the present capsule can be formulated as its pharmaceutically acceptable salts. As used herein, "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the active agent is modified by reacting it with an acid or base as needed to form an ionically bound pair. Examples of pharmaceutically acceptable salts include conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. Suitable non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfonic, sulfamic, phosphoric, nitric and others known to those of ordinary skill in the art. The salts prepared from organic acids such as amino acids, acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and others known to those of ordinary skill in the art. The pharmaceutically acceptable salts of the present invention can be synthesized from the parent active agent which contains a basic or acidic moiety by conventional chemical methods. Lists of other suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th. ed., Mack Publishing Company, Easton, PA, 1985, the relevant disclosure of which is hereby incorporated by reference.

As used in this disclosure, the term vitamin refers to trace organic substances that are required in the diet. For the purposes of the present invention, the term vitamin(s) include, without limitation, thiamin, riboflavin, nicotinic acid, pantothenic acid, pyridoxine, biotin, folic acid, vitamin B12, lipoic acid, ascorbic acid, vitamin A, vitamin D, vitamin E and vitamin K. Also included within the term vitamin are the coenzymes thereof. Coenzymes are specific chemical forms of vitamins and can include thiamin

pyrophosphates (TPP), flavin mononucleotide (FMN), and flavin adenine dinucleotive (FAD). Nicotinamide adenine dinucleotide (NAD), Nicotinamide adenine dinucleotide phosphate (NADP), Coenzyme A (CoA), pyridoxal phosphate, biocytin, tetrahydrofolic acid, coenzyme B12, lipolysine, 11-cis-retinal, and 1,25-dihydroxycholecalciferol. The term vitamin(s) also includes choline, carnitine, and alpha, beta, and gamma carotene.

As used in this disclosure, the term "mineral" refers to inorganic substances, metals, and the like required in the human diet. Thus, the term "mineral" as used herein includes, without limitation, calcium, iron, zinc, selenium, copper, iodine, magnesium, phosphorus, chromium, mixtures thereof and others known to those of ordinary skill in the art.

The term "dietary supplement" as used herein means a substance, which has an appreciable nutritional effect when, administered in small amounts. Dietary supplements include, without limitation, such ingredients as bee pollen, bran, wheat germ, kelp, cod liver oil, ginseng, and fish oils, amino-acids, proteins, plant extracts, plant powder, herbs, herbal extracts and powders, vitamins, minerals, combinations thereof and others known to those of ordinary skill in the art. As will be appreciated, essentially any dietary supplement may be incorporated into the present capsule.

The amount of active agent incorporated in a capsule of the invention will be at least one or more dosage form and can be selected according to known principles of pharmacy. An effective amount of active agent is specifically contemplated. By the term "effective amount", it is understood that, with respect to, for example, pharmaceuticals, a pharmaceutically effective amount is contemplated. A pharmaceutically effective amount is the amount or quantity of a drug or pharmaceutically active substance which is enough for the required or desired therapeutic response, or in other words, the amount, which is sufficient to elicit an appreciable biological response when, administered to a patient. The appreciable biological response may occur as a result of administration of single or multiple unit doses of an active substance. Depending upon the active agents used and upon the amount of active substance present in a particular capsule according to the invention, a unit dose may comprise one or more such capsules. As used with reference to a vitamin or mineral, the term "effective amount" means an amount at least about 10%

of the United States Recommended Daily Allowance ("RDA") of that particular ingredient for a patient. For example, if an intended ingredient were vitamin C, then an effective amount of vitamin C would include an amount of vitamin C sufficient to provide 10% or more of the RDA. Typically, where the tablet includes a mineral or vitamin, it will incorporate higher amounts, preferably about 100% or more of the applicable RDA.

When combinations of active agents are used, one or both of the active agents can be present in a sub-therapeutic amount. As used herein, a sub-therapeutic amount is that amount of first drug which provides less than a normal therapeutic response in patient to which the first drug is administered in the absence of the second drug of the combination. In other words, the first and second drugs may together provide an enhanced, improved, additive or synergistic therapeutic benefit as compared to the administration of each drug alone, i.e., in the absence of the other drug.

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 (CD), for example, and by analysis of the phase solubility data for the acid-ionizable agent and SAE-CD. 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 SAE-CD 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 CD, 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. The SAE-CD provides the anionic species of the ion pair and the acid-ionizable agent provides the cationic species of the ion pair. Since the SAE-CD is multi-valent, an SAE-CD can form an ion pair with one or more acid-ionizable agents.

As used herein in reference to the active agent, the terms "very soluble", "freely soluble", "soluble", "sparingly soluble", "slightly soluble", "very slightly soluble", and "practically insoluble" or "insoluble" are defined as they are defined in the U.S.P. 23rd Ed. as follows:

Term	Solubility of component in water (parts of solvent per part of component)
Very soluble	<1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1,000
Very slightly soluble	1,000-10,000
Practically insoluble or insoluble	Over 10,000

When an active agent is included in a capsule of the invention, it need not necessarily complex with the SAE-CD. A study was conducted to determine whether or not complexation of a drug to the SAE-CD alters the ability of the SAE-CD to stabilize the capsule shell against dissolution, erosion, swelling or degradation caused by water in the fill composition enclosed within the capsule shell. Banner's hydrophilic, HFB, and

lipophilic, LFB, air fill size 35 oval gelatin capsules were used in this study, which was performed as described below. The aqueous fill compositions tested in this experiment comprise 60% w/w and 70% w/w SAE-CD in combination with various marketed drugs. The 60% w/w SAE-CD was prepared by weighing a known amount of water and SAE-CD in two separate containers. The SAE-CD was slowly added to the water while it was stirring and on a hot plate. Agitation continued until all the SAE-CD dissolved. The SAE-CD was divided by weighing in equal amounts into nine vials (one for each drug). The solid active drug was then added to the SAE-CD solution. The amount of drug added produced a composition that contained a normal dose of drug in 1 gram. The vials were agitated and heated until a solution was obtained or the active was uniformly suspended. Four grams (3mL) of the 60% w/w SAE-CD/ drug solution or suspension was added to the various capsule halves and the vials were shaken for the duration of the study. The results for the HSIT in 60% w/w SAE-CD with drug are found in the table below. The active ingredients in the table form an inclusion complex with SAE-CD to varying degrees depending on their binding constants.

Active ingredient	Amount of drug in 1 gram (mg)	Fill composition appearance	HSIT	
			HFB	LFB
Cinnarizine	25	suspension	5	5
Indomethacin	25	solution	5	5
Hydrocortisone	5	clear solution	5	4
Fexofenadine HCl	60	solution	5	5
Testosterone	10	clear solution	5	5
Methyltestosterone	10	clear solution	5	5
Budesonide	3	suspension	5	5
Carvedilol	25	solution	5	5
Sertraline HCl	50	solution	5	4

An HSIT study was also conducted with the same amounts of drug as above but with 70% w/w SAE-CD. The results of that evaluation are found in table below.

Active ingredient	Amount of drug in 1 gram (mg)	Fill composition appearance	HSIT	
			HFB	LFB

Cinnarizine	25	suspension	5	5
Indomethacin	25	clear solution	5	5
Hydrocortisone	5	clear solution	5	5
Fexofenadine HCl	60	clear solution	5	5
Testosterone	10	clear solution	5	5
Methyltestosterone	10	clear solution	5	5
Budesonide	3	suspension	5	5
Carvedilol	25	clear solution	5	5
Sertraline HCl	50	clear solution	5	5

The results indicate complexation of the drug with SAE-CD does not significantly reduce the ability of SAE-CD to extend the shelf-life of a capsule containing an aqueous fill composition according to the invention.

Capsules containing sertraline in an aqueous fill composition of the invention were prepared according to Example 9. The table below includes a summary the drug release profiles of two 50mg capsules of the invention in SGF.

Sertraline HCL Release from Soft Gelatin Capsules

	Time in Minutes		
Time $_{\text{fraction released}}$	$t_{10\%}$	$t_{50\%}$	$t_{90\%}$
Capsule 1	7.5	11.5	16
Capsule 2	10	12	15
Average	8.8	11.8	15.5

It is thought that the initial drug release may be due to some fill composition on the outside of the gelatin capsule and that the slow release at the end of the profile may be due to some drug trapped in the gelatin that had been heat-sealed.

In view of the above description and the examples below, one of ordinary skill in the art will be able to practice the invention as claimed without undue experimentation. The foregoing will be better understood with reference to the following examples that detail certain procedures for the preparation of formulations according to the present invention. All references made to these examples are for the purposes of illustration. The following examples should not be considered exhaustive, but merely illustrative of only a few of the many embodiments contemplated by the present invention.

EXAMPLE 1

The following general method is used for the preparation of aqueous fill compositions comprising water, a derivatized cyclodextrin and optionally an active agent.

A known amount of derivatized cyclodextrin is placed in a known amount of water while mixing. The water is optionally heated prior to mixing or the mixture is heated during and/or after mixing. The active agent, if present, is added to the water before, along with or after addition of the derivatized cyclodextrin. Alternatively, the active agent is mixed or complexed with the derivatized cyclodextrin prior to addition to water.

Alternatively, a concentrated stock composition comprising the derivatized cyclodextrin and water is added to an aqueous solution optionally comprising an active agent to form a diluted aqueous fill composition.

Alternatively, a diluted stock composition comprising the derivatized cyclodextrin and water, and optionally active agent and optionally excipient(s), is concentrated by removal of water there from. Removal of water can be done by desiccation, evaporation, vacuum drying, oven drying, tray drying or other conventional procedures for removal of water.

Other excipients useful in the fill composition can be added as needed at any point along the above-described process.

EXAMPLE 2

The following general method is used to evaluate the aqueous fill compositions to determine whether or not they are suitable for use according to the invention.

Method A: Half-shell integrity test (H.S.I.T.)

In a closed container, a portion of a capsule shell is exposed to an aqueous fill composition comprising a known amount of derivatized cyclodextrin, water and optionally one or more other excipients. Observation of changes, or lack thereof, on the exposed portion's size, appearance, shape, dissolution, erosion, degradation, hardness, and/or translucence are recorded periodically over time. A rating scale is used to quantify the overall performance of the capsule portion during the test. Although many different rating scales can be used, an exemplary rating scale includes the following: 0 rating: capsule portion dissolved within <24hrs; 1 rating: shape and/or size of capsule changed such that the portion is extremely deformed or enlarged within ≥24 hours and

<48 hrs; 2 rating: shape and/or size of capsule changed such that the portion is extremely deformed or enlarged within ≥2 days and <5 days; 3 rating: shape and/or size of capsule changed such that the portion is partially changed, e.g., the capsule is enlarged and may have slight deformities, within ≥5days and <10 days; 4 rating: shape and/or size of capsule changed slightly such that the portion may be enlarged but not deformed within ≥10 days and <14 days; 5 rating: shape and/or size of capsule changed such that the portion is unchanged or not visibly changed after ≥14 days.

Method B: Filled capsule shell integrity test

A capsule shell is filled with an aqueous fill composition comprising a known amount of derivatized cyclodextrin, water and optionally one or more other excipients. The filled capsule is placed in a closed container. Observations of changes, or lack thereof, on the exposed portion's size, appearance, shape, dissolution, erosion, degradation, hardness, leaking and/or translucence are recorded periodically over time. A rating scale such as the one described in Method A of this example is used to quantify the overall performance of the filled capsule during the test.

EXAMPLE 3

Water activity was measured by placing a sample solution in a small, sealed container and determining the equilibrium humidity and temperature in the container. Instruments such as the HygroLab 3 from Rotronic Instrument Corp., Huntington, NY were used to measure the water activity. The humidity is determined using a thin film capacitive sensor in the headspace of the container. The temperature is determined using a Pt RTD 100 sensor. From these measurements the activity of water (Aw) is calculated by the instrument. The instrument has an accuracy of about ±0.015 Aw and a repeatability of about ±0.005 Aw. Carefully prepared salt-containing stock solutions of known concentration and water activity were used to calibrate the instrument prior to use.

EXAMPLE 4

The following general method is used to evaluate aqueous fill compositions comprising water, a derivatized cyclodextrin and a shell-stabilizing material.

Water activity approximation

A fill composition is prepared by mixing known amounts of water, derivatized cyclodextrin and shell-stabilizing material optionally in the presence of heat. The water activity of the aqueous fill composition is measured according to Example 3. Depending upon the value of water activity, the fill composition is then evaluated according to Example 2 to determine a performance rating. If the water activity approximates or is less than 0.95 ± 0.025, then the fill composition is optionally evaluated according to Example 2 to determine its suitability for use according to the invention. Depending upon the composition of the shell being used, a different water activity value may be used as the initial screening value. For example, a water activity value of less than about 0.9±0.025 may be used to screen formulations containing water, a derivatized cyclodextrin and a shell-stabilizing material for use in a gelatin capsule shell. Also, a water activity value of less than about 0.95±0.025 may be used to screen formulations containing water and a derivatized cyclodextrin for use in a gelatin capsule shell. In addition, the target water activity value may vary according to the derivatized cyclodextrin being used in the test.

EXAMPLE 5

Clarity of the fill compositions herein can be determined by visual inspection; however, other known methods for determining the clarity of a fill composition can be performed. Exemplary other methods include transmittance spectrophotometry at a wavelength of 800 nm.

EXAMPLE 6

The following example was followed to obtain the dissolution profiles of FIG. 11. Dissolution studies were performed according to United States Pharmacopeia 26 <711> DISSOLUTION. Apparatus 2, paddles, at 50 rpm, was utilized with 900 mL of various dissolution media. A 60% w/w SAE-CD (Captisol) was prepared by adding a known weight of SAE-CD to a known weight of water and stirring until a clear solution was obtained. A weighed amount of fexofenadine HCl was added to a known volume of this solution. The mixture was stirred to prepare a 60 mg/mL solution of fexofenadine HCl. One gram of this solution was then filled into HFB soft gelatin capsules and the capsules

sealed prior to testing. For comparison, commercial 60 mg fexofenadine HCl tablets were tested using the same apparatus. Samples of the dissolution media were withdrawn periodically, filtered, and assayed using high performance chromatography (Radhakrishna, T and Reddy, G. Om; "Simultaneous determination of fexofenadine and its related compounds by HPLC" Journal of Pharmaceutical and Biomedical Analysis 29(2002) 681-690).

EXAMPLE 7

This procedure was used to prepare soft gelatin capsules containing 25mg of carvedilol per capsule. The capsules, which are enteric coated, provide a delayed release of the carvedilol. After oral administration to a subject, release of the drug does not begin until after the capsule has passed the acidic environment of the stomach. This capsule is a post-gastric release (or enteric release) capsule.

a. Preparation of 25mg Carvedilol Soft Gelatin Capsules

To a ten-gram sample of a 60% (w/w) Captisol solution was added 250mg of Carvedilol (received from Ultra-tech, India) and 200mg of sodium bitartrate. The sample in a 25 cc bottle was rotated overnight to allow dissolution of the drug. From observation under the microscope most if not all of the carvedilol had dissolved; however, not all of the sodium bitartrate was in solution based on the appearance of its characteristic crystal shape. The bottle was centrifuged at low speed to remove the undissolved sodium bitartrate from solution. Nine soft air filled capsules (HFC shells) were filled with 1g (± 5%) of the solution from above using a syringe and needle. The hole in the capsule was then heat-sealed.

b. Enteric Coating of Soft Gelatin Capsules

The capsule was then coated with ACRYL-**EZE**™, an aqueous acrylic enteric coating system formulated and available from Colorcon (West Point, PA) based on the enteric polymer EUDRAGIT®L100-55 (otherwise known as methacrylic acid copolymer type C). The ACRYL-**EZE**™coating formulation contained:

ACRYL-**EZE**™	200g
Antifoam A Solution	6 drops
Water	800g

A Uni-Glatt fluidized bed coater with Wuster column was used for coating the filled capsules according to the following parameters:

Inlet air temperature	40°C
Outlet air temperature	36°C
Coating rate	5 g per minute

The fluidized bed was loaded with 400g of high-density polyethylene drops previously coated with ACRYL-EZE™ and the nine filled soft gelatin capsules. An estimate was made of the amount of coating applied by weighing some of the coated capsules and subtracting the approximate weight of the filled capsules. The percent coat weight was estimated to be about 12%.

These capsules provide a delayed release of carvedilol. After oral administration to a subject, release of the drug does not begin until after the capsule has passed the acidic environment of the stomach. Therefore, release of drug does not generally occur in an acidic environment. This capsule is a post-gastric release (or enteric release) capsule.

EXAMPLE 8

This procedure was used to evaluate the dissolution and drug release properties of enteric soft gelatin capsules, for example, those of Example 7 containing 25mg of carvedilol per capsule.

Three capsules were placed into an acid phase consisting of simulated gastric fluid (SGF) without enzyme (USP pH 1.2) in a USP Apparatus 2 dissolution system with 50-rpm paddle rotation, 37°C, and using flow through spectrophotometer set to monitor the appearance of carvedilol at 332nm. No release of carvedilol was observed over the 2 hours in SGF. The capsules were transferred to a phosphate buffer (pH 6.8), otherwise known as simulated intestinal fluid (SIF). The enteric coating was observed to dissolve by way of the appearance of talc and titanium dioxide released into the dissolution media. The appearance of carvedilol was observed to increase in the dissolution media as indicated by the increase in UV absorption at 332nm. Visual observation showed that the capsules were completely dissolved at 1 hour after the transfer to the SIF. Filtered

samples of the dissolution media gave absorption readings of 0.30 to 032 at 332nm indicating that the drug was all in solution.

EXAMPLE 9

This procedure was used to evaluate the performance of the soft gelatin capsules of Example 7 when exposed to disintegrating conditions.

A USP disintegration test was set up to observe the dissolution of the capsules in just the pH 6.8 SIF. The following observations were made by changing the media every 10 minutes to facilitate viewing by reducing the interference from the coating particulate matter:

TIME (min)	RESULT
0 to 10	coating intact
10 to 20	first observation of soft gelatin capsule surface
20 to 30	some evidence of drug being released into media
30 to 40	most capsule contents gone, some coating and capsule pieces visible
40 to 50	most gelatin dissolved but some coating still visible

EXAMPLE 10

This procedure was used to prepare a soft gelatin capsule that provides a rapid release of sertraline, wherein the capsule comprises a water-miscible aqueous fill composition. Soft gelatin capsules containing 50 and 100 mg per capsule of sertraline as the HCL salt in 70% CAPTISOL/Water (w/w) are prepared as follows. Then, the drug release profile in simulated gastric fluid (SGF) is determined.

a. Preparation

A stock solution containing 88mg of sertraline per gram and 70% wt. of SBE-CD was prepared. Two air-filled soft gelatin capsules (HFB shells) were filled with 0.57g and one air-filled SGC was filled with 1.14 g of a solution of 88 mg of setraline per gram using a pipette and then the holes in the capsules were heat-sealed.

b. Drug Release in Simulated Gastric Fluid (SGF)

Release of sertraline was followed using a spectrophotometer equipped with flow-through cells at a wavelength of 272.2 nm. A USP Apparatus No. 2 with a paddle rpm of 50, temperature 37°C and 900mL of simulated gastric fluid (SGF, pH 1.2 HCl with 2g

per liter sodium chloride) was used. The capsules were place in the SGF and release of drug over time measured.

The disclosures of the references cited herein are hereby incorporated in their entirety.

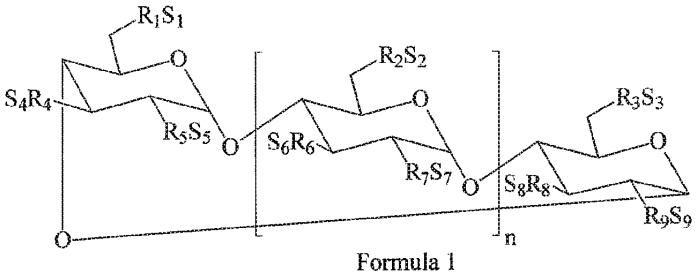
The above is a detailed description of particular embodiments of the invention. It will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without departing from the spirit and scope of the invention. Accordingly, the invention is not limited except by the appended claims. All of the embodiments disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure.

CLAIMS

We claim:

1. A capsule comprising:
    a. a water soluble, erodible, degradable and/or swellable shell; and
    b. an aqueous fill composition comprising one or more active agents, water present in an amount sufficient to at least partially solubilize, erode, degrade and/or swell the shell, and a water soluble cyclodextrin derivative present in an amount sufficient to suppress dissolution, erosion, degradation and/or swelling of the shell caused by water in the fill composition, wherein the capsule has a shelf-life of at least one week.
2. The capsule of claim 1, further comprising a shell-stabilizing material and/or a water activity-reducing agent.
3. The capsule of claim 1, wherein an active agent is released according to a controlled, sustained, extended, slow, rapid, pulsed, timed, targeted, colonic, zero order, pseudo-zero order, first order, pseudo-first order, and/or enteric release profile.
4. The capsule of claim 3, wherein release of the active agent begins within less than 30 minutes after exposure of the capsule to an environment.
5. The capsule of claim 3, wherein release of the active agent begins after passage of a delay period of ≥ 30 min after exposure of the capsule to an environment
6. The capsule of claim 1, wherein the aqueous fill composition is water miscible.
7. The capsule of claim 1, wherein the active agent is present in a therapeutically effective amount.
8. The capsule of claim 1, wherein the active agent is present in a sub-therapeutically effective amount.
9. The capsule of claim 1, wherein the active agent is sparingly soluble, slightly soluble, very slightly soluble, practically insoluble or insoluble in water.
10. The capsule of claim 1, wherein the active agent is more soluble in the aqueous fill composition than it is in water.

11. The capsule of claim 1, wherein the water soluble cyclodextrin derivative is present in an amount sufficient to solubilize the active agent when it is released into an environment of use.
12. The capsule of claim 1, wherein the active agent complexes with the derivatized cyclodextrin to form an inclusion complex and/or a non-covalent ionic complex.
13. The capsule of claim 1, wherein the active agent is soluble, freely soluble or very soluble in water.
14. The capsule of claim 1, wherein the fill composition further comprises alcohol or other water miscible hydroxy moiety-containing material.
15. The capsule of claim 1, wherein the water soluble cyclodextrin derivative is a sulfoalkyl ether cyclodextrin.
16. The capsule of claim 15, wherein the sulfoalkyl ether cyclodextrin is of the formula 1:



Formula 1

wherein:

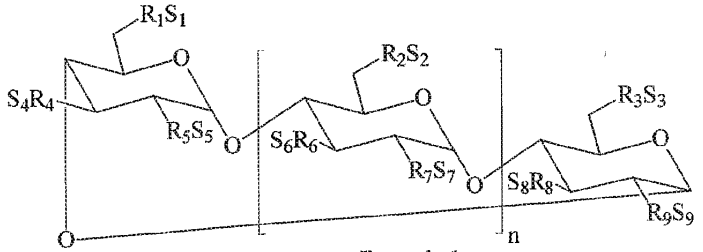
n is 4, 5 or 6;

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_2, R_3, R_4, R_5, R_6, R_7, R_8 and 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, $-OCH_2CH_2CH_2SO_3^-$, $-OCH_2CH_2CH_2CH_2SO_3^-$; and

S_1, S_2, S_3, S_4, S_5, S_6, S_7, S_8 and S_9 are each, independently, a cation.

17. The capsule of claim 16, wherein the cation is independently selected at each occurrence from the group consisting of H^+, alkali metal cation, alkaline earth metals, ammonium cation, and organic amine cation.

18. A stabilized capsule formulation having a shelf-life of at least one week, the formulation comprising:
    a. a water soluble, erodible, swellable and/or degradable shell, and
    b. an aqueous fill composition comprising a water soluble cyclodextrin derivative, an aqueous carrier and optionally one or more active agents; wherein, the capsule formulation has an increased shelf life as compared to a similar capsule formulation excluding the cyclodextrin derivative and any other shell-stabilizing material; water in the aqueous carrier is present in an amount sufficient to at least partially dissolve, erode, swell and/or degrade the shell; and the cyclodextrin derivative is present in an amount sufficient to reduce the rate or eliminate dissolution, erosion, swelling or degradation of the shell by water in aqueous carrier.
19. The capsule formulation of claim 18, wherein the aqueous fill composition further comprises a water activity-reducing agent and/or a shell-stabilizing material.
20. The capsule formulation of claim 19, wherein the shell-stabilizing material is PVP or PEG, and the cyclodextrin derivative is a sulfoalkyl ether cyclodextrin derivative.
21. The capsule formulation of claim 20, wherein the sulfoalkyl ether cyclodextrin is 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_2, R_3, R_4, R_5, R_6, R_7, R_8 and 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, -$OCH_2CH_2CH_2SO_3^-$, -$OCH_2CH_2CH_2CH_2SO_3^-$; and

S_1, S_2, S_3, S_4, S_5, S_6, S_7, S_8 and S_9 are each, independently, a cation.

22. The capsule formulation of claim 21, wherein the cation is independently selected at each occurrence from the group consisting of H^+, alkali metal cation, alkaline earth metals, ammonium cation, and organic amine cation.

23. The capsule formulation of claim 18, wherein one or more active agents are present.

24. The capsule formulation of claim 23, wherein the active agent is sparingly soluble, slightly soluble, very slightly soluble, practically insoluble or insoluble in water; and the cyclodextrin derivative is present in an amount sufficient to solubilize the active agent when it is released into an environment of use.

25. The capsule formulation of claim 23, wherein the active agent is released according to a controlled, sustained, extended, slow, rapid, pulsed, timed, targeted, colonic, zero order, pseudo-zero order, first order, pseudo-first order, and/or enteric release profile.

26. The capsule formulation of claim 25, wherein release of the active agent begins within less than 30 minutes after exposure of the capsule to an environment.

27. The capsule formulation of claim 25, wherein release of the active agent begins after passage of a delay period of ≥ 30 min after exposure of the capsule to an environment.

28. An aqueous fill composition enclosed within a water soluble, erodible, swellable and/or degradable encapsulating material, the fill composition comprising:

a. an aqueous carrier present in an amount sufficient to at least partially dissolve, erode, swell and/or degrade the encapsulating material;

b. a water soluble cyclodextrin derivative present in an amount insufficient to on its own stop dissolution, erosion, swelling and/or degradation of the encapsulating material by the aqueous carrier;

c. a shell-stabilizing material present in an amount insufficient to on its own stop dissolution, erosion, swelling and/or degradation of the encapsulating material by the aqueous carrier;

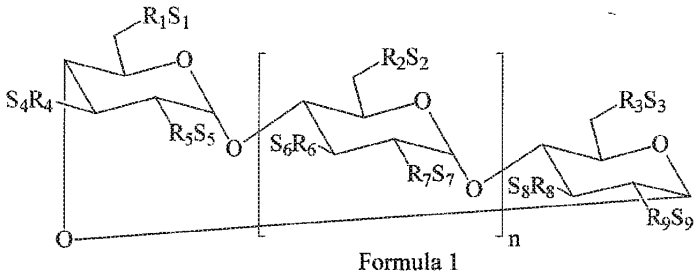
d. optionally, one or more active agents; and

e. optionally, one or more excipients; wherein,

f. the cyclodextrin derivative and the shell-stabilizing material together at least reduce the rate of or stop dissolution, erosion, swelling and/or degradation of the encapsulating material by the aqueous carrier.

29. The fill composition of claim 28, wherein the shell-stabilizing material is PVP or PEG, and the cyclodextrin derivative is a sulfoalkyl ether cyclodextrin derivative.

30. The fill composition of claim 29, wherein the sulfoalkyl ether cyclodextrin is 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_2, R_3, R_4, R_5, R_6, R_7, R_8 and 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, $-OCH_2CH_2CH_2SO_3^-$, $-OCH_2CH_2CH_2CH_2SO_3^-$; and

S_1, S_2, S_3, S_4, S_5, S_6, S_7, S_8 and S_9 are each, independently, a cation.

31. The fill composition of claim 30, wherein the cation is independently selected at each occurrence from the group consisting of H^+, alkali metal cation, alkaline earth metals, ammonium cation, and organic amine cation.

32. The fill composition of claim 28, wherein the active agent is sparingly soluble, slightly soluble, very slightly soluble, practically insoluble or insoluble in water;

and the cyclodextrin derivative is present in an amount sufficient to solubilize the active agent when it is released into an environment of use.

33. The fill composition of claim 28, wherein the active agent is released according to a controlled, sustained, extended, slow, rapid, pulsed, timed, targeted, colonic, zero order, pseudo-zero order, first order, pseudo-first order, and/or enteric release profile.

34. The fill composition of claim 33, wherein release of the active agent begins within less than 30 minutes after exposure of the capsule to an environment.

35. The fill composition of claim 33, wherein release of the active agent begins after passage of a delay period of ≥ 30 min after exposure of the capsule to an environment.

36. The fill composition of claim 29, wherein the shell-stabilizing material is PEG; both PEG and sulfoalkyl ether cyclodextrin are present; water comprises ≤ 50% wt. of the fill composition; the combination of sulfoalkyl ether cyclodextrin, PEG, one or more optional excipients and one or more optional active agents comprises ≥ 50% wt. of the fill composition; the sulfoalkyl ether cyclodextrin comprises up to 90% wt. of the weight of the fill composition; and PEG comprises less than 90% wt., respectively, of the fill composition; provided that PEG ≥ 45% when the sulfoalkyl ether cyclodextrin comprises ≤ 5 % wt. of the fill composition, and when PEG < 45% wt. then the sulfoalkyl ether cyclodextrin ≥ 18% wt. of the fill composition.

37. The fill composition of claim 29, wherein the shell-stabilizing material is PEG; both PEG and sulfoalkyl ether cyclodextrin are present; water comprises ≤ 45% of the fill composition; the combination of sulfoalkyl ether cyclodextrin, PEG, one or more optional excipients and one or more optional active agents comprises ≥ 55% of the fill composition; the sulfoalkyl ether cyclodextrin comprises up to 90% wt. of the weight of the fill composition; and PEG comprises less than 90% wt., respectively, of the weight of the fill composition; provided that PEG ≥ 45% when the sulfoalkyl ether cyclodextrin comprises ≤ 5 % of the weight of the fill composition, and when PEG < 45% then the sulfoalkyl ether cyclodextrin ≥ 10%.

38. The fill composition of claim 29, wherein the shell-stabilizing material is PVP; both PVP and sulfoalkyl ether cyclodextrin are present; water comprises ≤ 55% wt. of the fill composition; the combination of sulfoalkyl ether cyclodextrin, PVP, one or more optional excipients, and one or more optional active agents comprises ≥ 45% wt. of the fill composition; the sulfoalkyl ether cyclodextrin comprises up to 90% wt. of the fill composition; PVP comprises less than 90% wt., respectively, of the fill composition; provided that PVP comprises ≥ 35% wt. of the fill composition when sulfoalkyl ether cyclodextrin comprises ≤ 15 % wt. of the fill composition.
39. The fill composition of claim 29, wherein the shell-stabilizing material is PVP; both PVP and sulfoalkyl ether cyclodextrin are present; water comprises ≤ 45% wt. of the fill composition; the combination of sulfoalkyl ether cyclodextrin, PVP, one or more optional excipients, and one or more optional active agents comprises ≥ 55% wt. of the fill composition; the sulfoalkyl ether cyclodextrin comprises up to 90% wt. of the fill composition; PVP comprises less than 90% wt., respectively, of the fill composition; provided that PVP comprises ≥ 35% wt. of the fill composition when sulfoalkyl ether cyclodextrin comprises ≤ 20 % wt. of the fill composition.
40. The fill composition of claim 29, wherein the shell-stabilizing material is PVP; both PVP and sulfoalkyl ether cyclodextrin are present; water comprises ≤ 70% wt. of the fill composition; the combination of sulfoalkyl ether cyclodextrin, PVP, one or more optional excipients, and one or more optional active agents comprises ≥ 30% wt. of the fill composition; the sulfoalkyl ether cyclodextrin comprises up to 90% wt. of the fill composition; PVP comprises less than 90% wt., respectively, of the fill composition; provided that PVP comprises ≥ 35% wt. of the fill composition when sulfoalkyl ether cyclodextrin comprises ≤ 15 % wt. of the fill composition; when PVP < 35% wt. of the fill composition, then sulfoalkyl ether cyclodextrin > 15% wt. of the fill composition when water ≥ 50% wt. of the fill composition.

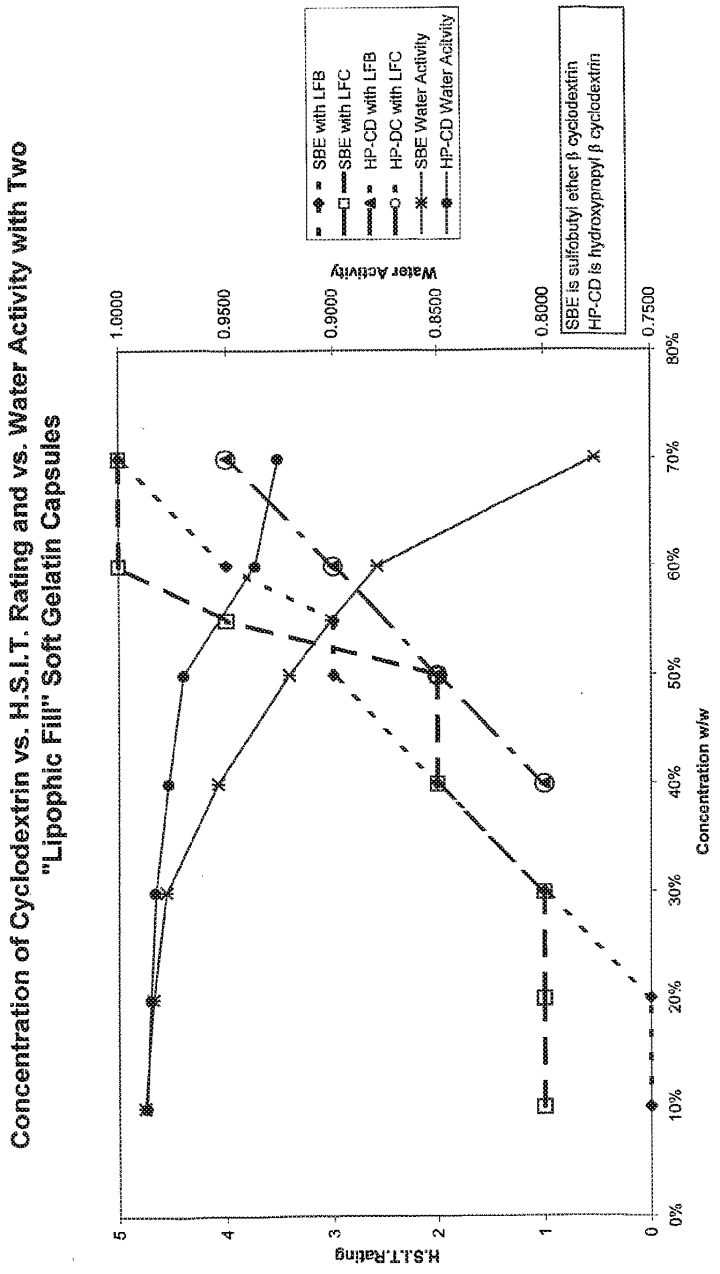
41. The fill composition of claim 29, wherein the shell-stabilizing material is PVP; both PVP and sulfoalkyl ether cyclodextrin are present; water comprises ≤ 65% wt. of the fill composition; the combination of sulfoalkyl ether cyclodextrin, PVP, one or more optional excipients, and one or more optional active agents comprises ≥ 35% wt. of the fill composition; the sulfoalkyl ether cyclodextrin comprises up to 90% wt. of the fill composition; PVP comprises less than 90% wt., respectively, of the fill composition.
42. The fill composition of claim 29, wherein the shell-stabilizing material is PVP; both PVP and sulfoalkyl ether cyclodextrin are present; water comprises ≤ 45% wt. of the fill composition; the combination of sulfoalkyl ether cyclodextrin, PVP, one or more optional excipients, and one or more optional active agents comprises ≥ 55% wt. of the fill composition; the sulfoalkyl ether cyclodextrin comprises up to 90% wt. of the fill composition; PVP comprises less than 90% wt., respectively, of the fill composition.
43. The fill composition of claim 29, wherein the shell-stabilizing material is PVP; both PVP and sulfoalkyl ether cyclodextrin are present; water comprises ≤ 50% wt. of the fill composition; the combination of sulfoalkyl ether cyclodextrin, PVP, one or more optional excipients, and one or more optional active agents comprises ≥ 50% wt. of the fill composition; the sulfoalkyl ether cyclodextrin comprises up to 90% wt. of the fill composition; PVP comprises less than 90% wt., respectively, of the fill composition; provided that PVP comprises ≥ 35% wt. of the fill composition when sulfoalkyl ether cyclodextrin comprises ≤ 15 % wt. of the fill composition.
44. An aqueous fill composition in a water erodible, degradable, swellable and/or soluble shell, the fill composition comprising water, a water soluble derivatized cyclodextrin, one or more active agents and optionally one or more excipients, wherein the derivatized cyclodextrin is present in an amount sufficient to reduce or stop the erosion, degradation, swelling or dissolution of the shell caused by water in the fill composition for a period of at least one week even in the absence of another shell-stabilizing material.

45. An aqueous fill composition comprising a derivatized cyclodextrin, a water activity-reducing agent and an aqueous carrier, wherein the derivatized cyclodextrin and water activity-reducing agent are together present in an amount sufficient to reduce the water activity to less than about 0.95.
46. An aqueous fill composition comprising a derivatized cyclodextrin, a water activity-reducing agent and an aqueous carrier, wherein the derivatized cyclodextrin and water activity-reducing agent are together present in an amount sufficient to reduce the water activity to less than about 0.996.
47. A method of stabilizing an aqueous composition-filled capsule from erosion, dissolution, swelling or degradation of its shell by water present in the aqueous composition, the method comprising the step of including in the composition a derivatized cyclodextrin present in an amount sufficient to reduce or stop the erosion, dissolution, swelling or degradation of the shell by water in the composition for a period of at least one week even in the absence of another shell-stabilizing material.
48. A method of stabilizing an aqueous composition-filled capsule from erosion, dissolution, swelling or degradation of its shell by water present in the fill, the method comprising the step of including in the aqueous fill a derivatized cyclodextrin present in an amount sufficient to reduce or stop the rate of erosion, dissolution, swelling or degradation of the shell by water in the fill composition as compared to the rate of erosion, dissolution, swelling or degradation of the shell by a similar fill composition excluding the derivatized cyclodextrin, wherein the derivatized cyclodextrin is replaced by water or another material that does not stabilize the shell.
49. A method of reducing the water activity of an aqueous fill composition, the method comprising the step of including a derivatized cyclodextrin in the aqueous fill composition at a concentration sufficient to reduce the water activity of the fill composition.
50. A method of increasing the shelf-life of a capsule formulation containing an aqueous fill composition comprising an aqueous carrier and first shell-stabilizing

material present in an amount insufficient to, on its own, stabilize the shell from erosion, dissolution, degradation or swelling, the method comprising the step of including a derivatized cyclodextrin in the fill composition.

51. An aqueous fill composition comprising a derivatized cyclodextrin and an aqueous carrier, wherein the derivatized cyclodextrin is present in an amount sufficient to reduce the water activity to less than about 0.95.

FIG. 1


Concentration of Cyclodextrin vs. H.S.I.T. Rating and vs. Water Activity with Two "Lipophic Fill" Soft Gelatin Capsules
H.S.I.T.Rating
Water Activity
Concentration w/w
SBE with LFB
SBE with LFC
HP-CD with LFB
HP-DC with LFC
SBE Water Activity
HP-CD Water Activity
SBE is sulfobutyl ether β cyclodextrin
HP-CD is hydroxypropyl β cyclodextrin
0
1
2
3
4
5
1.0000
0.9500
0.9000
0.8500
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20%
30%
40%
50%
60%
70%
80%

000080

FIG. 2

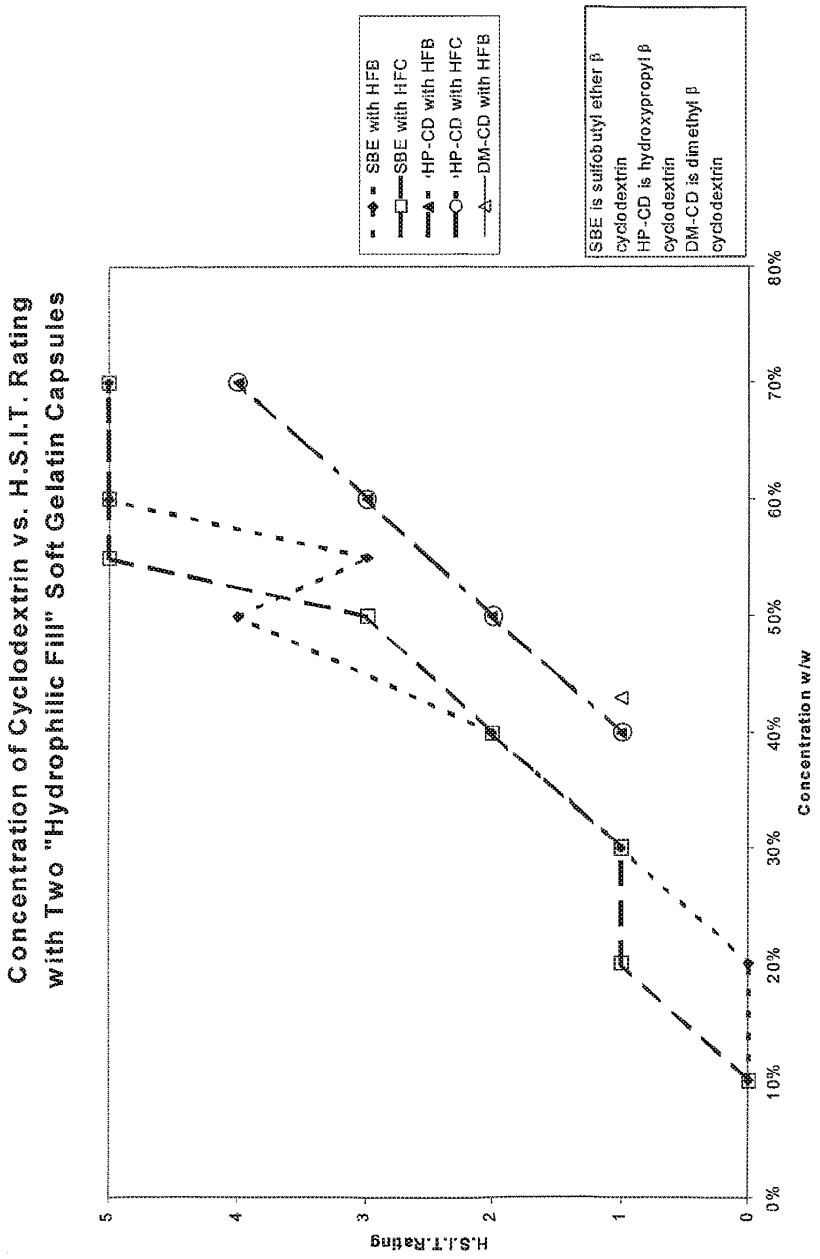


FIG. 3

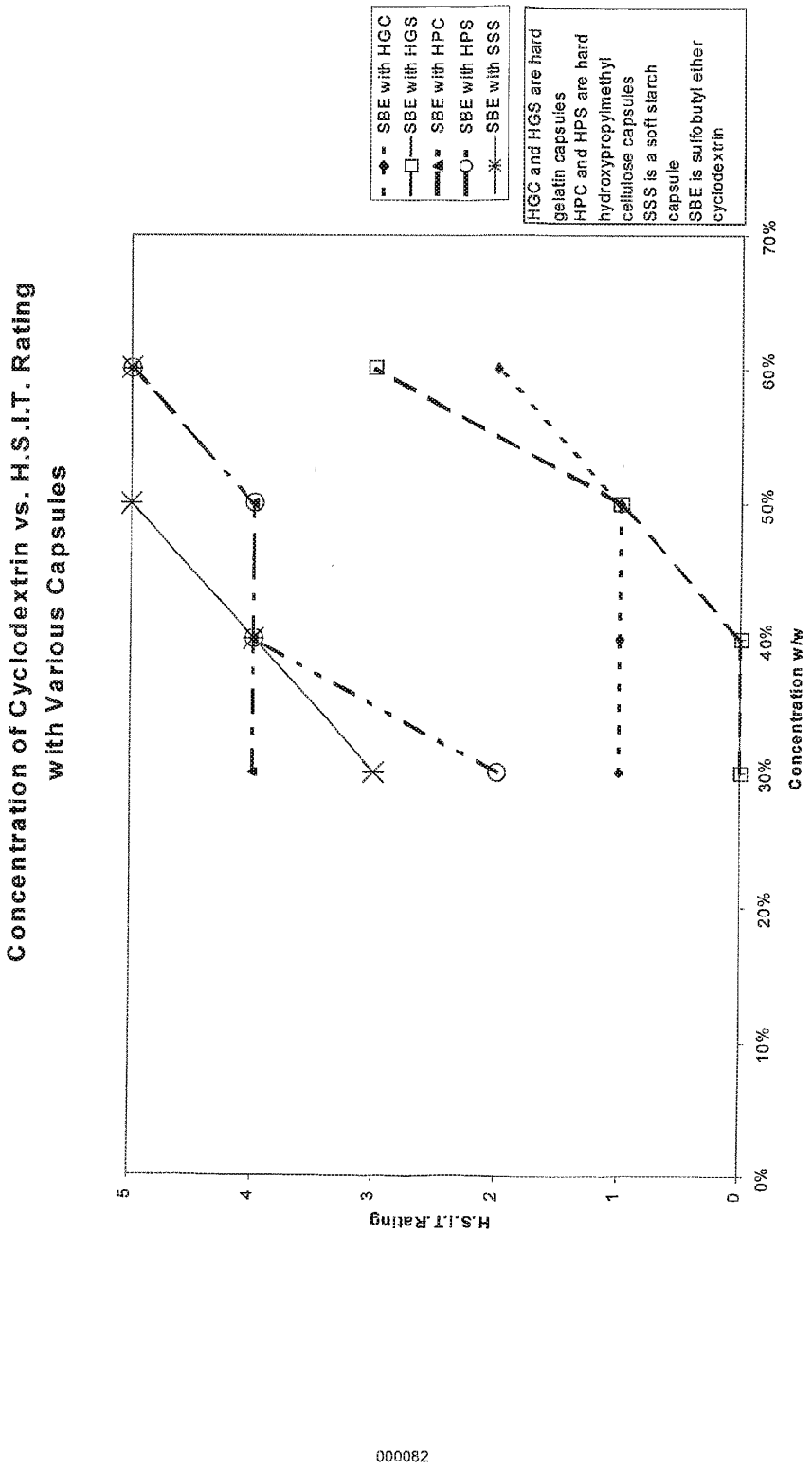


FIG. 4

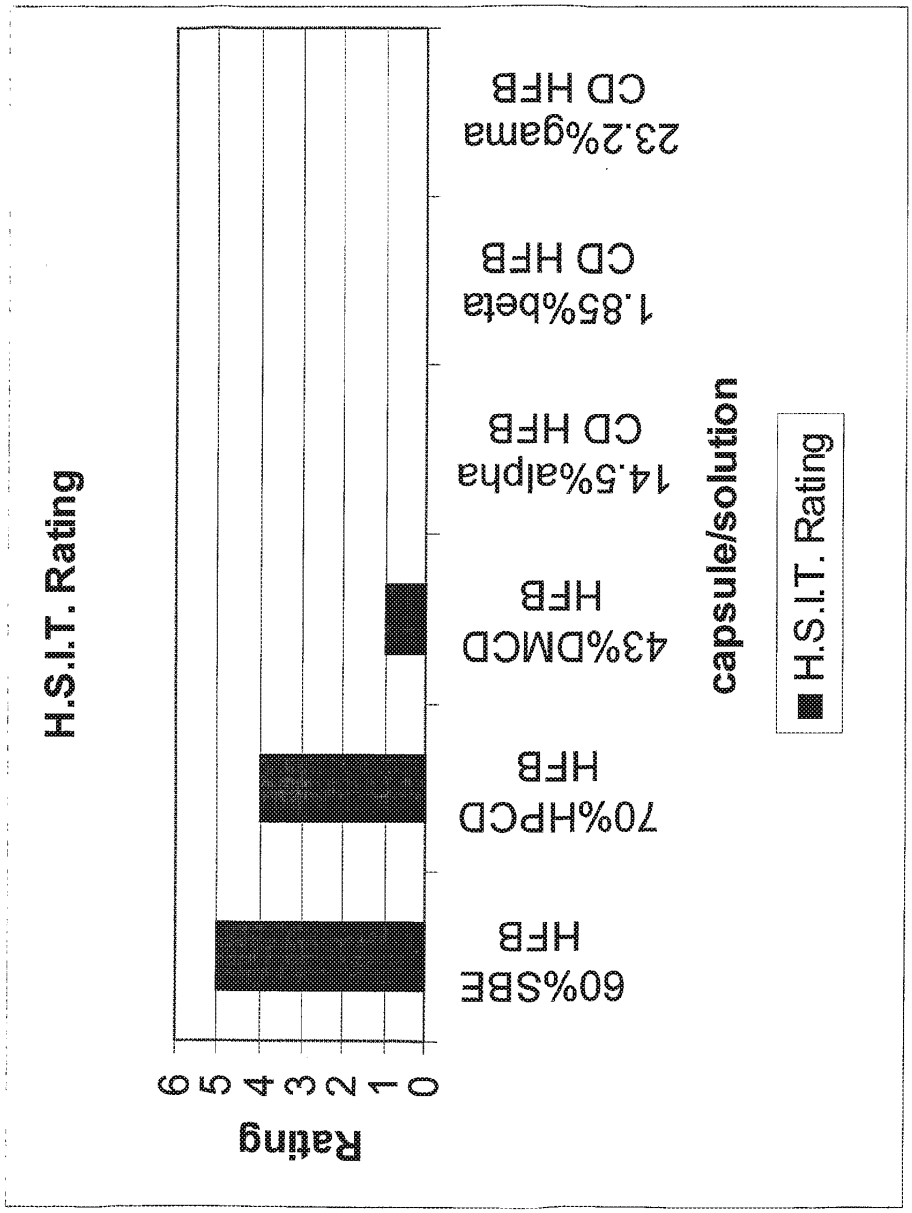


FIG. 5

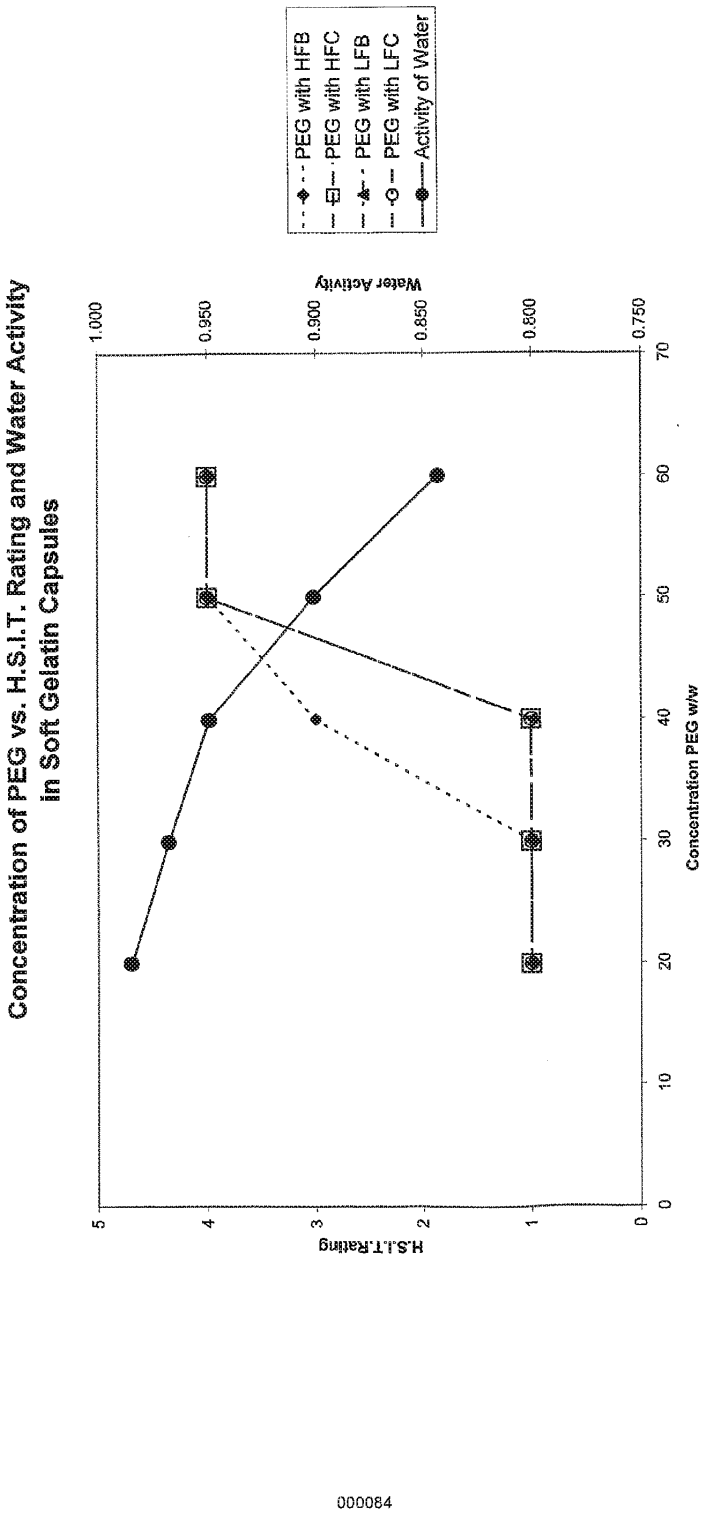


FIG. 6a

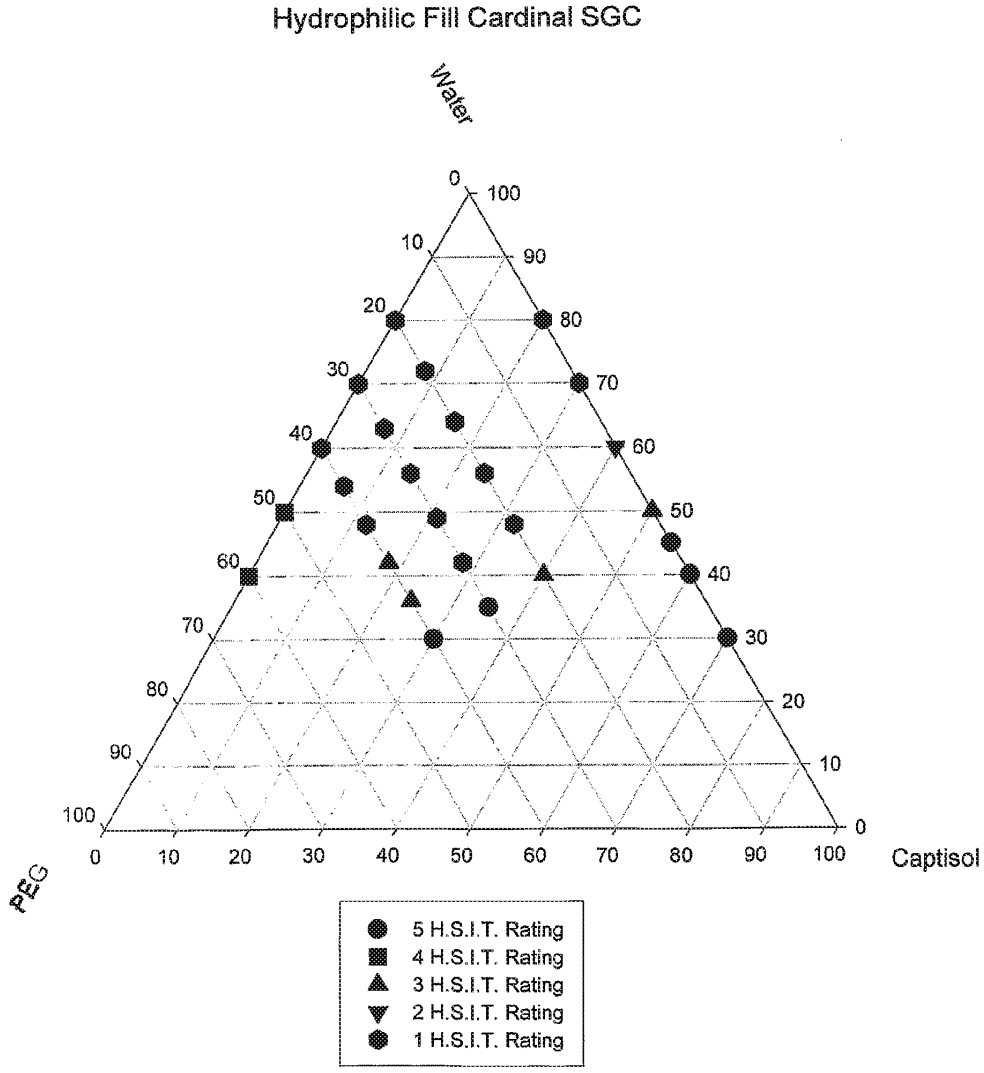


FIG. 6b

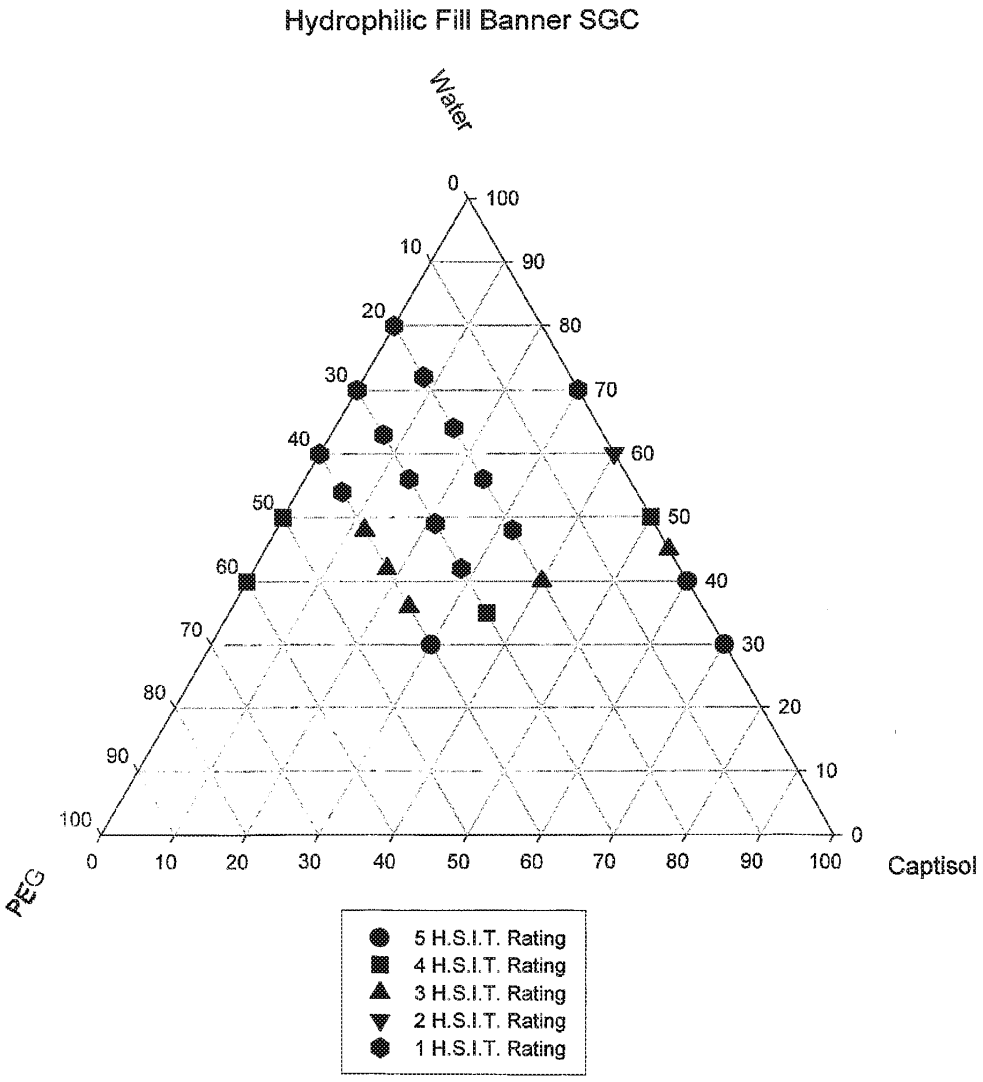


FIG. 7a

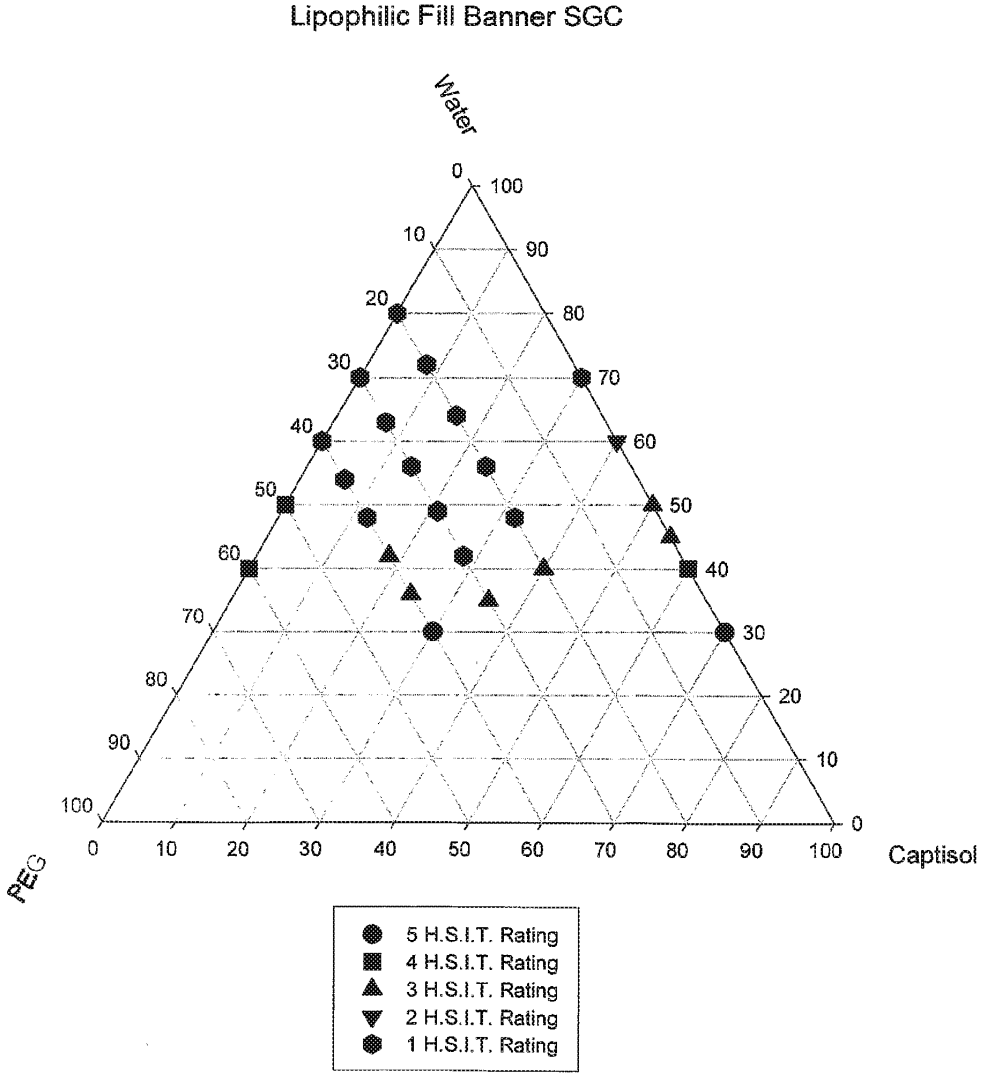
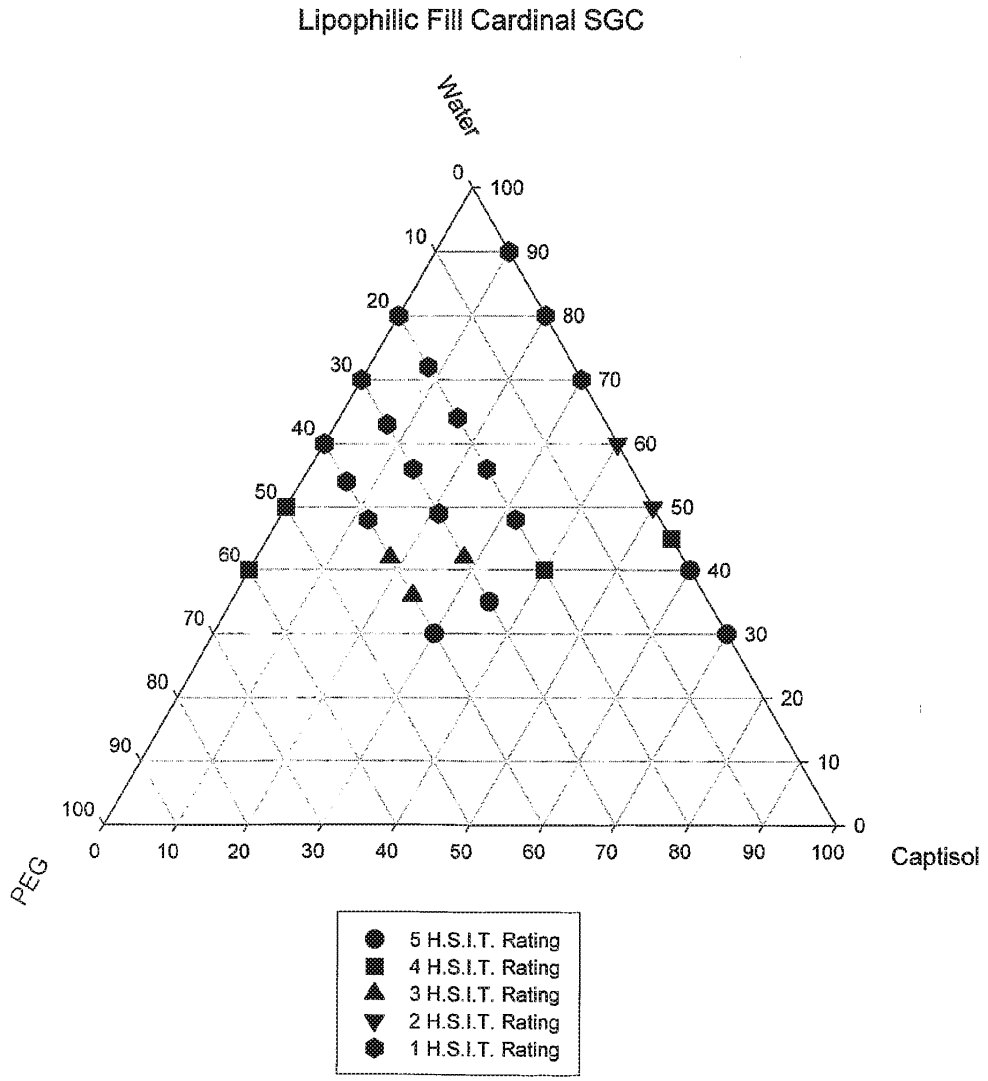


FIG. 7b



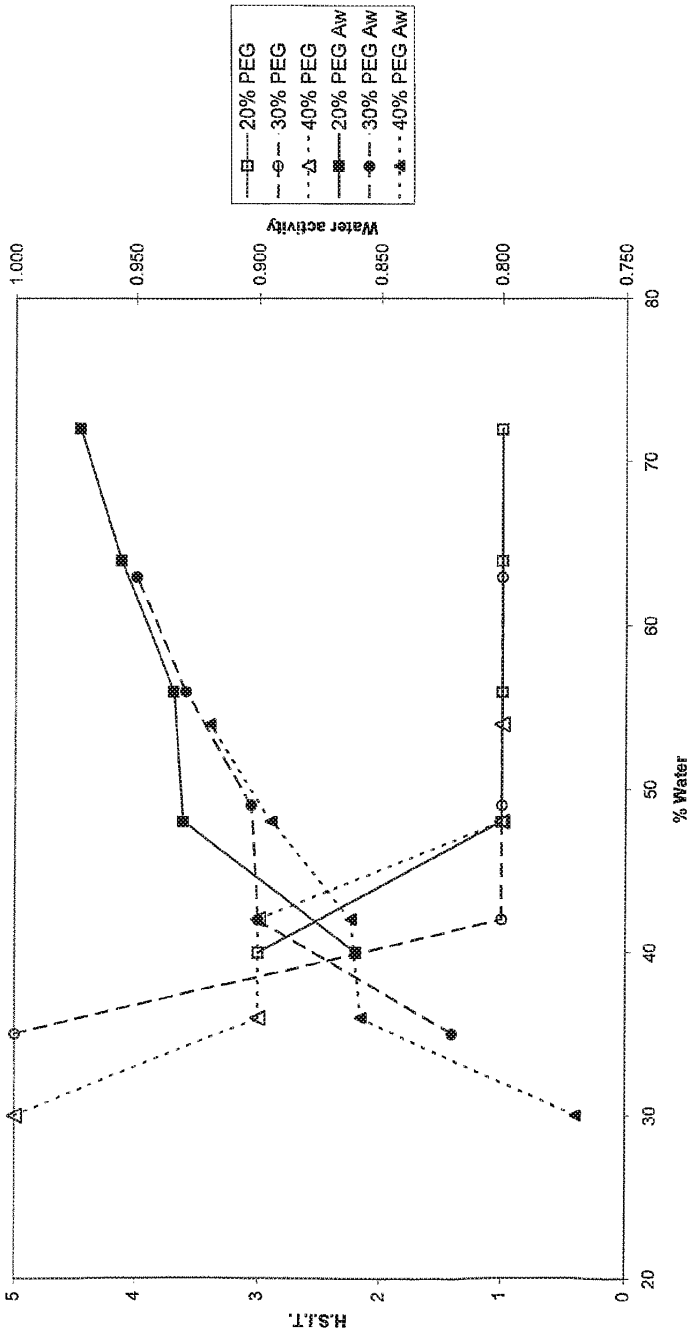


FIG. 8

HFC

FIG. 9

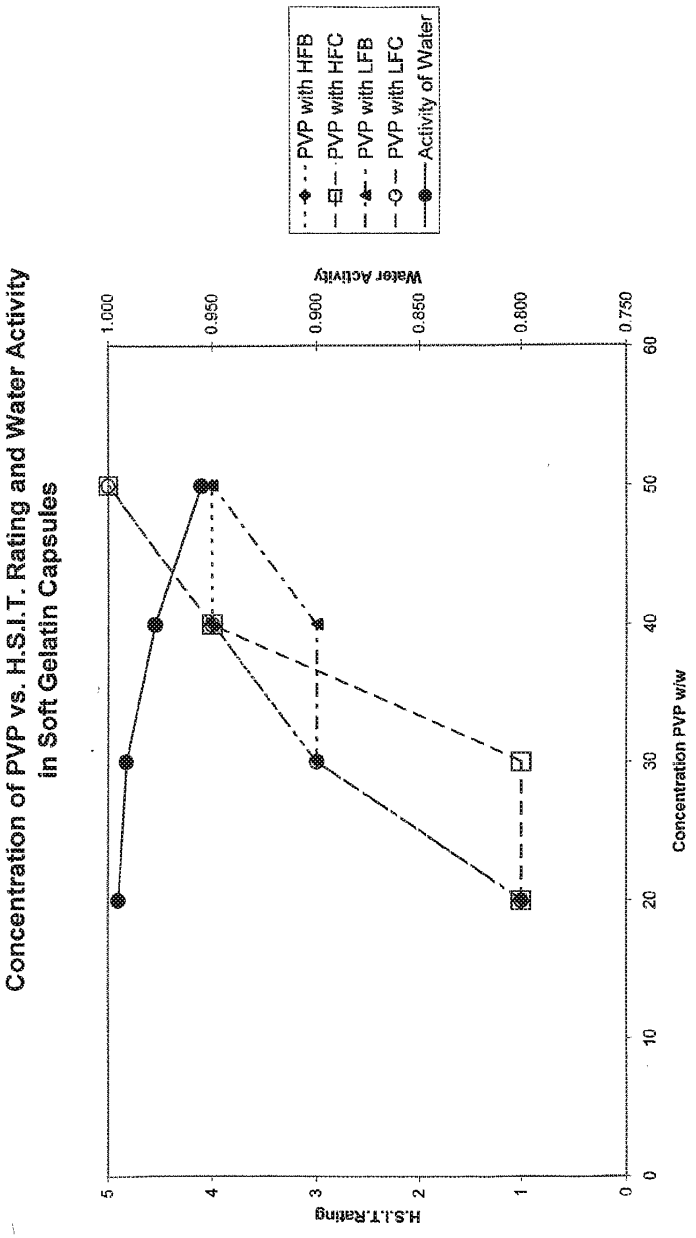


FIG. 10a

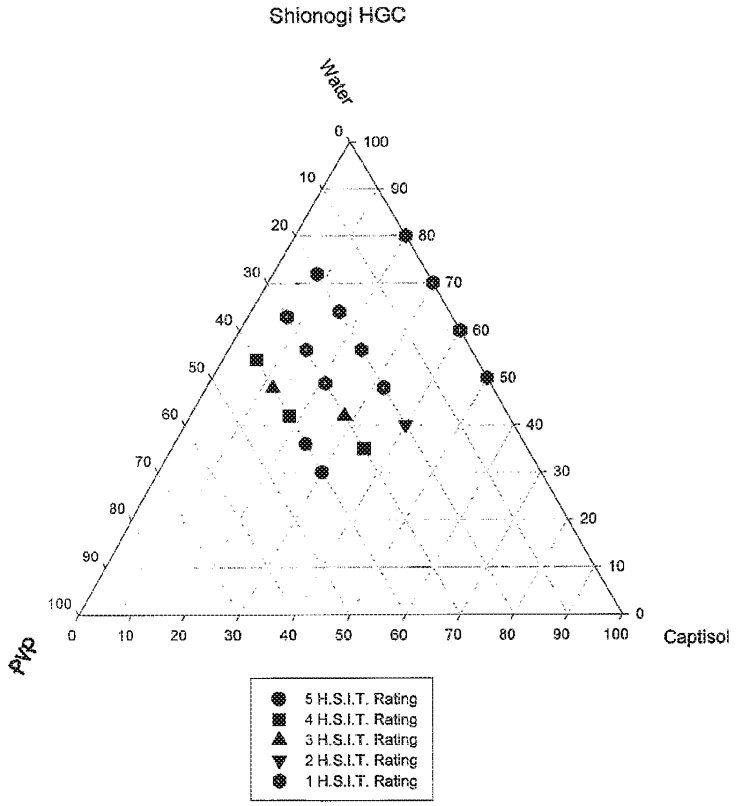


FIG. 10b

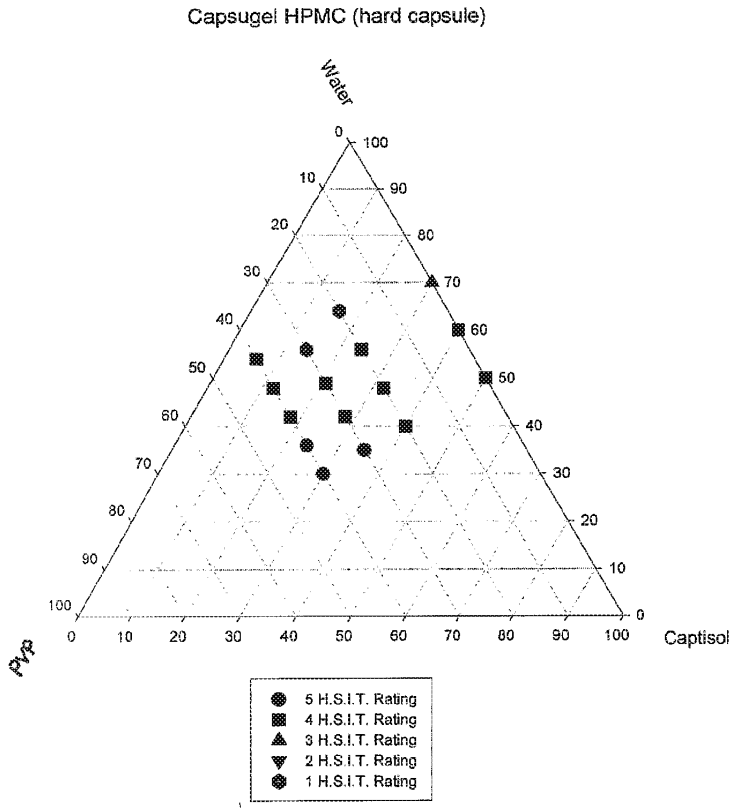


FIG. 10c

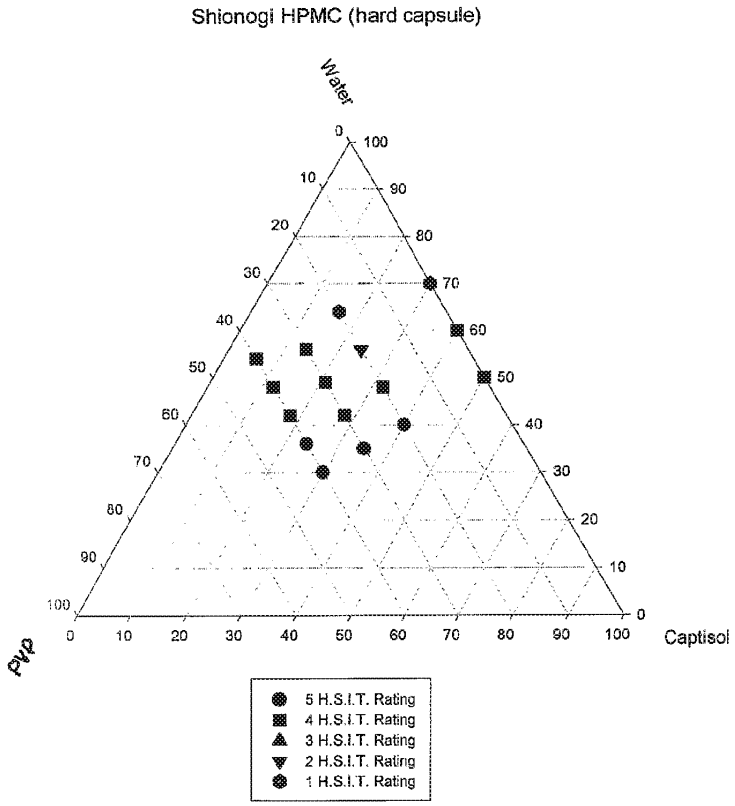


FIG. 10d

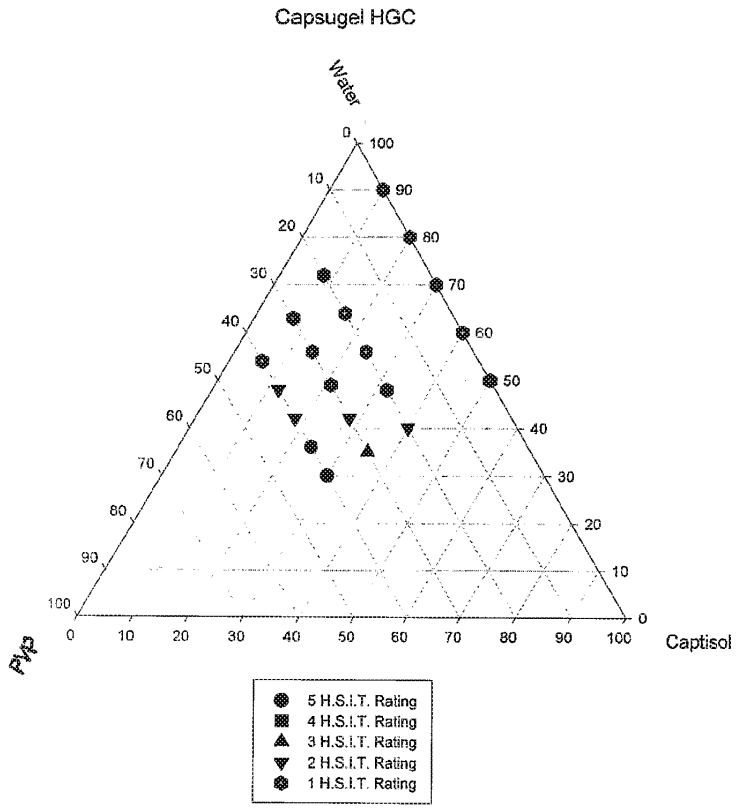


FIG. 10e

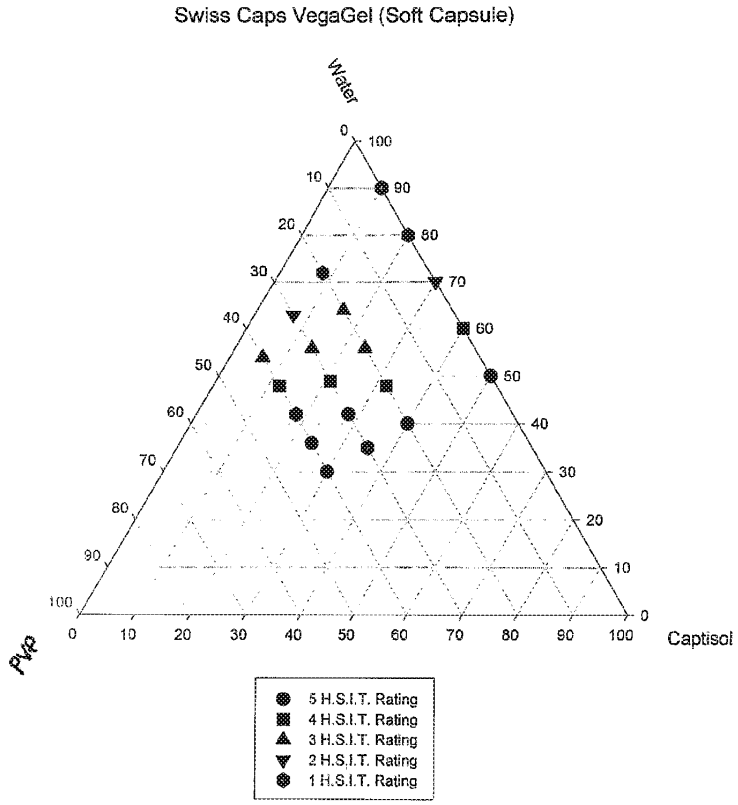


FIG. 10f

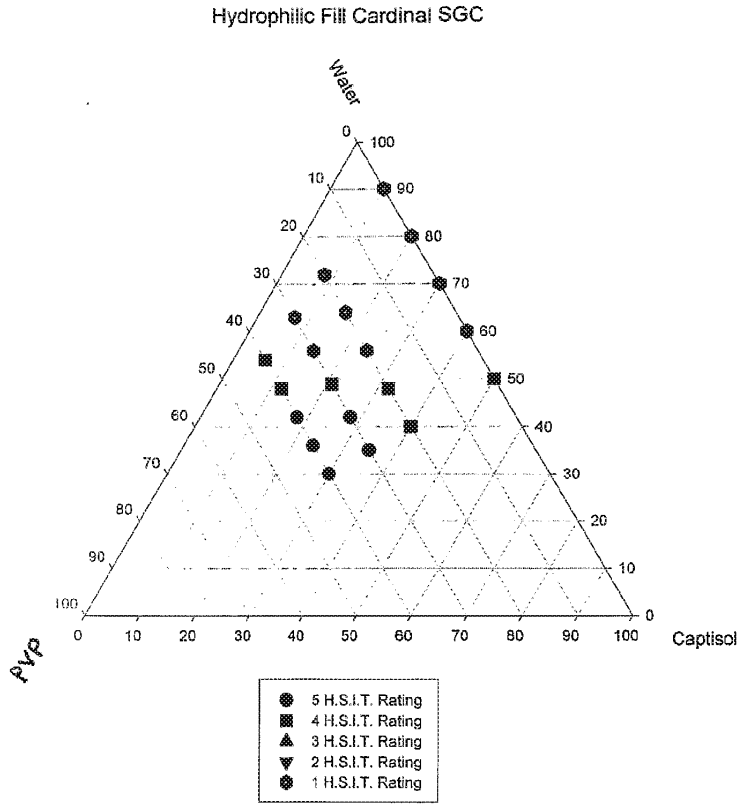


FIG. 10g

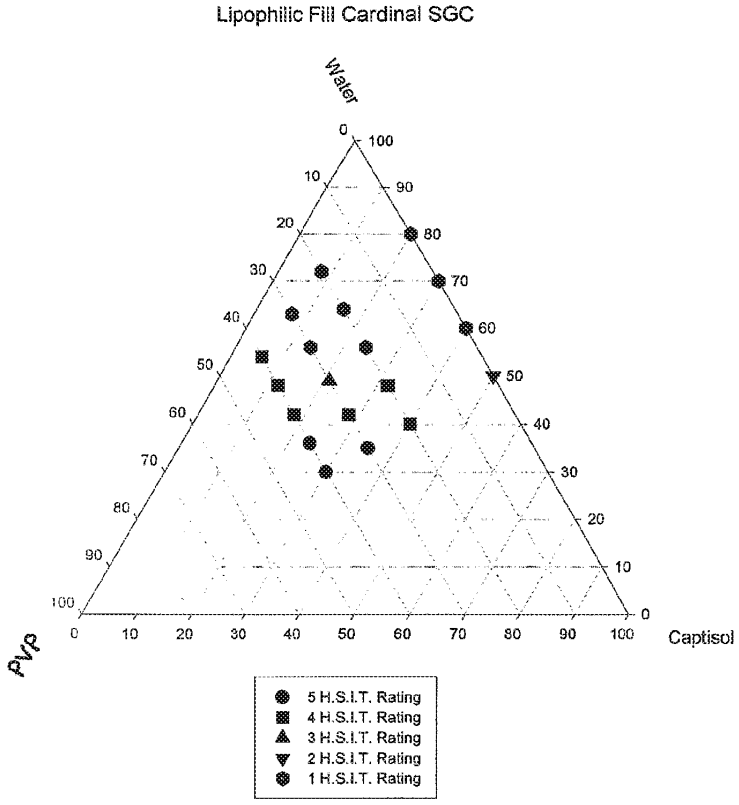


FIG. 10h

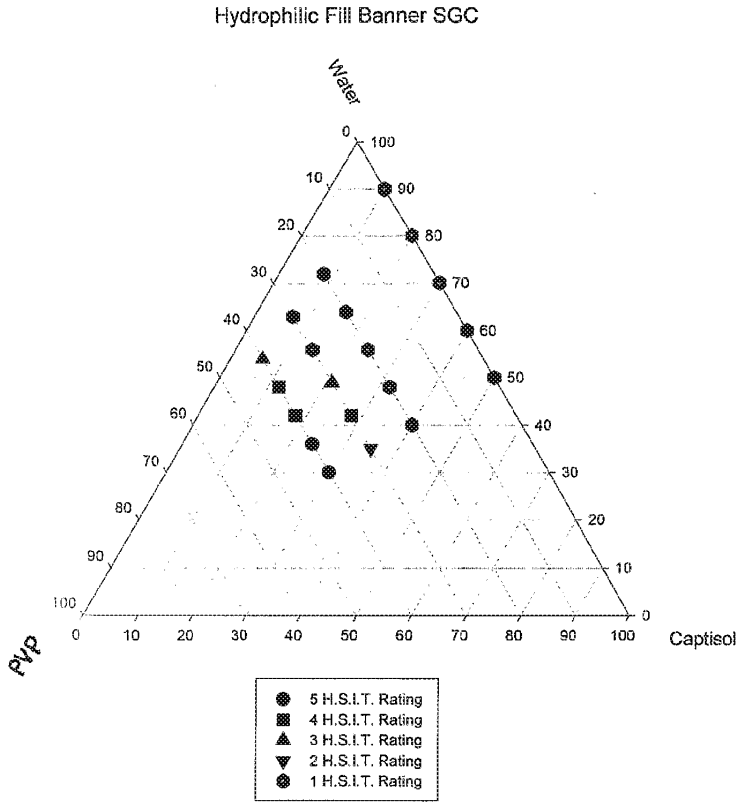


FIG. 10i

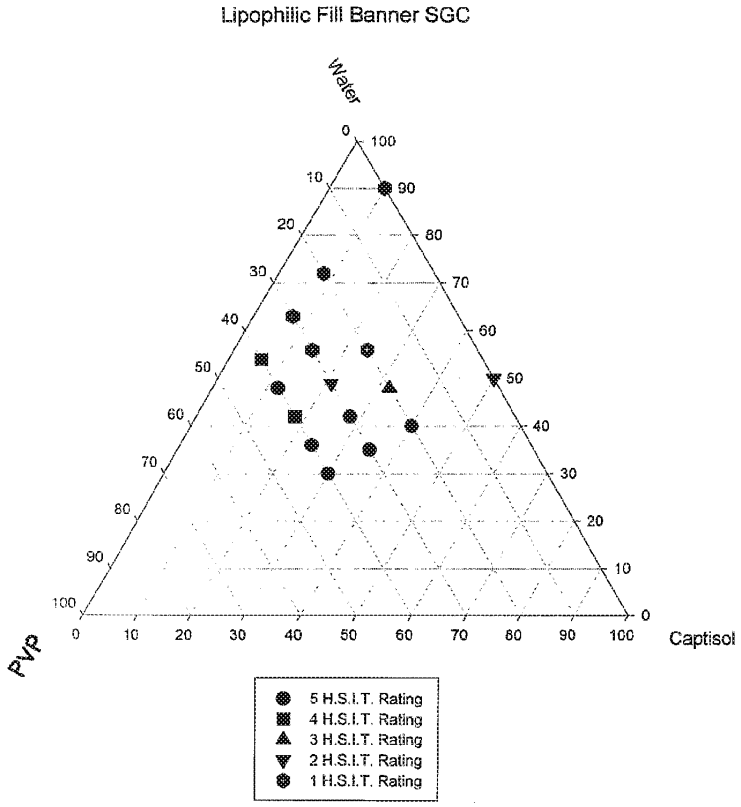
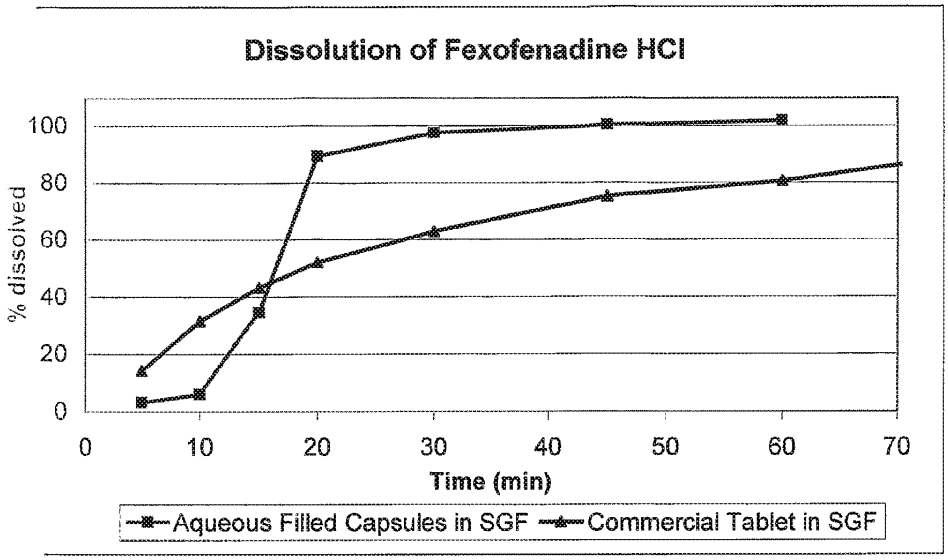


FIG. 11



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/30960

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 9/48, 9/52
US CL : 424/451, 452, 457,
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)
U.S. : 424/451, 452, 457,

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)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6,287,594 A (WILSON et al) 11 September 2001 (11.09.2001), see entire document.	1-51
Y	US 6,383,471 A (CHEN et al) 07 May 2002 (07.05.2002), see entire document.	1-51
Y	US 5,134,127 A (STELLA et al) 28 July 1992 (28.07.1992), see entire document.	1-51
Y	US 3,426,011 A (PARMERTER et al) 04 February 1969 (04.02.1969), see entire document.	1-51

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

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Date of the actual completion of the international search	Date of mailing of the international search report
09 January 2004 (09.01.2004)	06 FEB 2004
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230	Authorized officer Humera N. Sheikh Telephone No. (703) 308-4429

Form PCT/ISA/210 (second sheet) (July 1998)

Continuation of B. FIELDS SEARCHED Item 3:
WEST
cyclodextrin, capsule, aqueous

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A61K 9/00 (2006.01) *A61K 31/5377* (2006.01)
A61K 31/557 (2006.01) *A61K 47/32* (2006.01)

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(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KHOPADE, Ajay Jaysingh** [IN/IN]; Sun Pharma Advanced Research Centre, Nima Compound, Near Pratham Enclave, Tandalja Road, Baroda 390 020 (IN). **HALDER, Arindam** [IN/IN]; Sun Pharma Advanced Research Centre, Nima Compound, Near Pratham Enclave, Tandalja Road, Baroda 390 020 (IN). **BHOWMICK, Subhas Balaram** [IN/IN]; Sun Pharma Advanced Research Centre, Nima Compound, Near Pratham Enclave, Tandalja Road, Baroda 390 020 (IN).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to the identity of the inventor (Rule 4.17(i))*

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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(54) Title: NOVEL OPHTHALMIC COMPOSITIONS

(57) Abstract: An ophthalmic solution comprising therapeutically effective amount of a prostaglandin or its analog and water soluble excipient(s) dissolved in a pharmaceutically acceptable vehicle, wherein the solution is free of a surfactant.

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ARGENTUM PHARM. 1016

NOVEL OPHTHALMIC COMPOSITIONS

The present invention relates to a novel ophthalmic solution prostaglandin or its analogs alone or in combination with other antiglaucoma agents.

BACKGROUND OF THE INVENTION

Prostaglandins are well known active substances administered to humans or animals via the topical route in the form of ophthalmic solutions for the treatment of glaucoma. The prostaglandins may also be used in combination with a second anti-glaucoma agent such as a beta-blocker, a carbonic anhydrase inhibitor or an alpha-adrenergic agonist.

Prostaglandin or its analogs, particularly the ester derivatives such as latanoprost, travoprost or the amide derivatives such as bimatoprost have notoriously low water solubility. The use of compounds which exert a surfactant like activity in to solubilize them is therefore, very common. Currently available prostaglandin ophthalmic solution, are found to contain a typical surfactant or a quaternary ammonium salt which is known to have a surfactant like activity apart from preservative property. Representative examples of typical surfactants incorporated in the ophthalmic solutions of prostaglandin analogs alone or in combination with other antiglaucoma agent, like for example, beta adrenergic blocking agent or alpha adrenergic blocking agent or any other active agent, are tabulated here:

Product	Active Ingredient	Surfactant
Xalatan®	Latanoprost	Benzalkonium chloride
Travatan Z®	Travoprost	polyoxyl 40 hydrogenated castor oil (Cremphore)
Xalacom®	Latanoprost and timolol	Benzalkonium chloride
Lumigan®	Bimatoprost	Benzalkonium chloride
Ganfort®	Bimatoprost and timolol	Benzalkonium chloride
Duotrav®	Travoprost and timolol	Benzalkonium chloride
Rescula®	Unoprostone isopropyl	Polyoxyethylene-20-sorbitan-monooleate

Apart from the approved products, the patent literature also represents numerous efforts of solubilizing prostaglandins with the help of solubilizers such as polyoxyethylene-20-sorbitan-monooleate, polyoxy stearates like Solutol® with or without other antiglaucoma agent like beta adrenergic blocking agent. Below is a list of patent documents that

disclose the use of surfactant in a prostaglandin ophthalmic solution alone or in combination with other antiglaucoma agent.

Product disclosed in Literature	Prostaglandin	Surfactant
US7074827	Latanoprost	Polyoxyethylene-20-sorbitan-monooleate
US20100201720	Prostaglandin	Solutol
WO/2009/145356	Tafluprost	Polyoxyethylene-20-sorbitan-monooleate
US20030018079	Latanoprost and Timolol	Polyoxyethylene-20-sorbitan-monooleate and Benzalkonium chloride

Generally, the formulation development of ophthalmic solution of prostaglandin or their combination with other active ingredient, over the years, is directed towards achieving a stable composition particularly in view of the fact that prostaglandins are also known to chemically unstable. Further, the literature provides evidences that the prostaglandins were associated with an adsorption problem to the poly-ethylene multidose containers. Some solutions to solve these problems are described in patent documents such as, for example, United States patent number US 6,235,781 which discloses that use of a surfactant to prevent the adsorption of prostaglandin analogues on to the plastic containers. The inventor of the present invention also faced and tackled this problem of adsorption of prostaglandin as described in WO 2009/084021. It was found out by inventors that a micro-emulsion formulation of prostaglandin containing polyoxy hydroxystearate (commonly known as Solutol HS) provides the solution to stability problem associated with adsorption. Another patent application, namely, United States Patent number US 20090234013A1, discloses a solution which include a therapeutic agent and a relatively low amount of surfactant for providing higher bioavailability of prostaglandin such as travoprost. Thus, this prior art as well teaches to include some amount of a surfactant such as ethoxylated and/or hydrogenated vegetable oil. This implies that the surfactant is always desirable to make the solution however it is preferable to keep it as low as possible.

Now, the inventors surprisingly and unexpectedly found that the prostaglandin analogs can be effectively formulated into an ophthalmic solution vehicle having a water soluble excipient(s) dissolved in the vehicle, wherein the ophthalmic solution is free of a surfactant. When the efficacy of the ophthalmic solution was compared with an ophthalmic solution comprising a surfactant, it was found that the ophthalmic solution provided equivalent or improved efficacy in reducing the intraocular pressure. Particularly, the ophthalmic solution of present invention was found to provide equivalent efficacy at half the dose compared to the marketed product available under the tradename of Xalatan® when tested in animals. This achievement of equivalent efficacy at half the dose of latanoprost was indeed unexpected and surprising. It was further found that the % intraocular pressure reduction at 12 hour time point, which apparently provides a peak IOP reduction was higher compared to the % intraocular pressure reduction at 12 hours, for Xalatan® which is a latanoprost ophthalmic solution having benzalkonium chloride as a surfactant. This effect of improved efficacy inspite of the absence of a surfactant, was also observed when the ophthalmic solution of the present invention was made of a prostaglandin or its analog and another antiglaucoma agent like a beta adrenergic blocking agent. The ophthalmic composition comprising prostaglandin or its nalog and a beta-adrenergic blocking agent that is free of surfactant, the composition remained stable and did not show any hazyness. The composition was clear on storage and was chemically stable.. Thus, the invention not only provided a physically stable composition comprising the two active ingredients, but also provided an ophthalmic composition that was more efficacious. Since the compositions are intended for ophthalmic purposes, it is always desirable that the compositions are devoid of excessive additives. Therefore, the present invention can be said to achieve not only the patient compliance but also achieved an improved efficacious composition.

Thus, the ophthalmic composition of the present invention comprises a combination of a prostaglandin and a beta-adrenergic blocking agent, characterized in that it does not use any surfactant or a surfactant preservative in a concentration that acts as a solubilizer such as those from alkyl quaternary ammonium surfactant like benzalkonium chloride,

benzdodecinium chloride and like and mixtures thereof. In one preferred embodiment, the ophthalmic composition includes a vehicle that is free of surfactants and added preservatives and is able to provide a beta-adrenergic blocking agent when administered topically such that effect is sustained for 24 hours, that is the ophthalmic composition is said to be suitable for once-a-day administration. Therefore, one of the embodiment of the present invention can be said to provide an ophthalmic composition comprising latanoprost and once-a-day composition of a beta-adrenergic blocking agent, wherein the composition is free of surfactant and optionally, free of added preservative and is found to be suitable for treating the affected eye of a glaucoma patient.

The ophthalmic solution of the present invention is free of a surfactant as well as free of anti-microbial preservatives defined by the class of quaternary ammonium compounds, organo-mercurials and substituted alcohol and phenols. It is known that these antimicrobials are often toxic to the sensitive tissues of the eye. The present invention thereofore fulfils the need of an ophthalmic solution which is stable as well having improved efficacy while not compromising on the antimicrobial activity. The present invention provides an ophthalmic solution comprising prostaglandins which obtains dual benefits of improved efficacy and avoidance of undesirable effects of the preservatives.

OBJECTS OF THE INVENTION

The object of the invention is to provide an ophthalmic solution that allows dose reduction of the prostaglandin while achieving equivalent efficacy.

The present invention relates to an ophthalmic solution comprising therapeutically effective amount of a prostaglandin analogue and another active ingredient, wherein the solution provides therapeutic effect sustaining for 24 hours i.e. to provide a once -a-day therapy.

The object of the present invention to provide a stable ophthalmic solution of prostaglandin analogs.

The object of the present invention to provide a stable ophthalmic solution of prostaglandin analogs and beta adrenergic active agents.

SUMMARY OF THE INVENTION

Thus, the present invention provides an ophthalmic solution comprising prostaglandins which obtains dual benefit of improved efficacy and avoidance of undesirable effects of the preservatives. The ophthalmic solution of the present invention is free of a surfactant as well as free of anti-microbial preservatives defined by the class of quaternary ammonium compounds, organo-mercurials, and substituted alcohol and phenols, It is known that these antimicrobials are often toxic to the sensitive tissues of the eye. A need therefore exists for ophthalmic solutions which have a stability, efficacy, but whose antimicrobial efficacy is not compromised.

The present invention provides an ophthalmic solution comprising therapeutically effective amount of a prostaglandin or its analog and optionally, one or more other therapeutic agents and water soluble excipient(s) dissolved in a pharmaceutically acceptable vehicle, wherein the solution is free of a surfactant.

The present invention also provides a method of treating glaucoma or ocular hypertension which comprises topically administering to an affected eye an ophthalmic solution comprising therapeutically effective amount of a prostaglandin or its analog and optionally, one or more other therapeutic agents and water soluble excipient(s) dissolved in a pharmaceutically acceptable vehicle, wherein the solution is free of a surfactant.

BRIEF DESCRIPTION OF FIGURE

Figure I: A comparative % reduction in the intraocular pressure of the dogs within 24 hours when the ophthalmic solution of the present invention was administered and % reduction in the intraocular pressure after the administration of already available marketed products like Xalatan®, Xalacom®, Timoptic®. It was found that the ophthalmic solution of example 3 provided a 29.43 % IOP reduction at 2 hr compared to 18.19 % IOP reduction when Xalatan® was administered or 12.02% IOP reduction when Xalacom® was administered or 19.82 %IOP reduction when Timoptic® was administered.

Similarly, example 3 provided a 29.67 % IOP reduction at 12 hr compared to 25.31 % IOP reduction when Xalatan® was administered or 21.28 %IOP reduction when Xalacom® was administered or 7.16 %IOP reduction when Timoptic® was administered. Similarly, example 3 provided a 24.87 % IOP reduction at 24 hr compared to 12.77 % IOP reduction when Xalatan® was administered or 9.84 %IOP reduction when Xalacom® was administered or 9.72 %IOP reduction when Timoptic® was administered.

Figure II: A comparative % mean reduction in the intraocular pressure of the affected eye of dogs when the solution of the present invention was administered Vs % mean reduction in the intraocular pressure after the administration of marketed reference products such as like Xalatan®, Xalacom®, Timoptic®. The % mean reduction of the intraocular pressure was found to be higher compared to the marketed product which either contains a beta-adrenergic blocking agent such as Timoptic® or a Xalatan® which alone or their combination (Xalacom®). It was found that the mean intraocular pressure reduction achieved by administration of the ophthalmic solution of Example 3, was 34.377 % compared to 26.765 % achieved by Xalatan® or 28.258 % achieved by Xalacom® or 21.088 % achieved by Timoptic® alone.

Figure III: It is a graph of comparison % IOP reduction when the ophthalmic solution of the present invention was administered, with % IOP reduction after the concomitant administration of marketed latanoprost and timolol products like Xalatan® and Timoptic® to the dogs. It was found that the overall, mean intraocular pressure reduction achieved by the ophthalmic solution of the present invention administered once a day was 28.63 % compared to 26.49 % which was achieved by the concomitant administration of the marketed product of latanoprost (once a day) and timolol (twice a day) present alone in the products.

Figure IV: A comparative % mean reduction in the intraocular pressure of the affected eye of dogs when the solution of the present invention Example.3 was administered Vs % mean reduction in the intraocular pressure after the administration of marketed reference products Xalacom® over 2 h and 12 h which represent the peak effect of Timolol and

latanoprost, respectively. It is noted that the solution of example 3 has a significantly higher IOP reductions at both time points. At 2 h $p = 0.0054$, $p < 0.01$, at 12 h $p = 0.0019$, $p < 0.01$.

DETAILED DESCRIPTION OF THE INVENTION

The term 'surfactant' as used herein means an amphiphilic compound that has the following properties

- It has hydrophobic groups and hydrophilic groups
- Can form micelles
- Capable of migrating to the water surface, where the insoluble hydrophobic alkyl chains may extend out of the bulk water phase, either into the air or, if water is mixed with oil, into the oil phase, while the water soluble head group remains in the aqueous phase.
- Can solubilize water insoluble substances through micellar solubilization.

The ophthalmic solutions of the present invention are characterized as being clear aqueous solution. These *"solution"* as stated herein, are defined as those solutions which do not cause any visual disturbance and/or do not affect vision, upon topical instillation to the eye and when examined under suitable conditions of visibility, are practically clear and practically free from particles. Ophthalmic solutions containing polymers which show percent transmission greater than 90% are referred to as 'solution'. When light is allowed to pass through the ophthalmic solution of the present invention, the percentage of incident light which is transmitted through the solution is referred to as "Percent Transmission". The clarity of the solution is poor if percent transmission is less than 85%. Preferably the percent transmission is greater than 90%. Generally, the percent transmission is determined at a wavelength of about 650 nm, but any other suitable wavelength may be selected for determining the clarity of the solution.

The prostaglandin or its analog used in the ophthalmic solution of the present invention includes, but are not limited to, all pharmaceutically acceptable prostaglandins, their derivatives and analogs, and their pharmaceutically acceptable esters and salts

(hereinafter collectively referred to as "prostaglandins" or "PG's"), which are useful for reducing intraocular pressure when applied topically to the eye. Such prostaglandins include the natural compounds, such as for example PGE_1, PGE_2, PGE_3, PGD_2, $PGF_{1\alpha}$, $PGF_{2\alpha}$, $PGF_{3\alpha}$, PGI_2 (prostacyclin), as well as analogs and derivatives of these compounds which are known to have similar biological activities of either greater or lesser potencies. Analogs of the natural prostaglandins include but are not limited to: alkyl substitutions (e.g., 15-methyl or 16,16-dimethyl), which confer enhanced or sustained potency by reducing biological metabolism or alter selectivity of action; saturation (e.g. 13,14-dihydro) or unsaturation (e.g., 2,3-didehydro, 13,14-didehydro), which confer sustained potency by reducing biological metabolism or alter selectivity of action; deletions or replacements (e.g. 11-deoxy, 9-deoxo-9-methylene), which enhance chemical stability and/or selectivity of action; and omega chain modifications (e.g., 18,19,20-trinor-17-phenyl, or 17,18,19,20-tetranor-16-phenoxy), which enhance selectivity of action and reduced biological metabolism.

Derivatives of these prostaglandins that may be formulated in the solution of the present invention include all pharmaceutically acceptable esters or amides, which may be attached to the 1-carboxyl group or any of the hydroxyl groups of the prostaglandin by use of the corresponding alcohol or organic acid reagent, as appropriate. The terms "analogs" and "derivatives" include compounds which exhibit functional and physical responses similar to those of prostaglandins per se. Prostaglandins are well known in the art. Particular prostaglandins that may be formulated in the solutions of the present invention include for example trimoprostil, rioprostil, cloprostenol, fluprostenol, luprostiol, etiproston, tiaprost, latanoprost, travoprost, bimatoprost, tafluprost, unoprostone and its derivatives like unoprostone isopropyl, misoprostol, sulfoprostone, gemeprost, alfaprostol, delprostenate, and the like. Pharmaceutical solutions of the present invention include one or more prostaglandins as described above in an amount between about 0.0001% w/v and about 0.2% w/v. The presently preferred amount of prostaglandin or its derivative is from about 0.001% to 0.05%, preferably about 0.0015% to about 0.03%.

In one embodiment, the ophthalmic solution of the present invention is free of surfactant and preservative as well as free of any cyclodextrin which solubilizes the prostaglandins by inclusion complexes. The ophthalmic solutions disclosed in patent application EP0435682 A2 uses cyclodextrin to solubilize the TRIS derivatives of the prostaglandins. This patent also teaches to include one or more preservatives.

In one embodiment of the present invention, latanoprost which is a prostaglandin F2α analogue, namely isopropyl-(Z)-7[(1R,2R,3R,5S)3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5- heptenoate is used. It may be present in an amount ranging from about 0.0001% w/v to about 0.2% w/v. Preferably, latanoprost is used in amounts of about 0.005% w/v. In another embodiment, travoprost is used as the prostaglandin derivative in amounts ranging from about 0.0001% w/v to about 0.2% w/v preferably in an amount 0.004% w/v. In yet another embodiment, bimatoprost is used as the prostaglandin derivative in amounts ranging from about 0.0001% w/v to about 0.2%w/v, preferably in an amount 0.03% w/v. In yet another embodiment tafluprost is used in amounts ranging from about 0.0001% w/v to about 0.2%w/v, preferably in an amount 0.0015% w/v.

In one preferred embodiment of the present invention, the ophthalmic solution is free of surfactant as well as free of a preservative or antimicrobial preservatives defined by the class of quaternary ammonium compounds, organic mercurial compounds, and substituted alcohol and phenol. Particularly, the ophthalmic solution is free of surfactant as well as free of a antimicrobial preservatives defined by the class of quaternary ammonium compounds such as for example, benzalkonium chloride. These classes of compounds are known to have a surfactant effect as well.

In one embodiment, the ophthalmic solution of the present invention consisting essentially of therapeutically effective amount of a prostaglandin esters or amides, cosolvent(s) and self preserving systems and optionally, pharmaceutically acceptable excipients selected from the group consisting of viscosity enhancing agents and buffers. Examples of the self preserving systems are used in the ophthalmic solution of the

present invention are Polyquad®, disappearing preservatives include stabilized hydrogen peroxide, stabilized oxy-chlorocomplex, sodium perborate, borate-polyol complex and like.

Therefore, the present invention may be further described as an ophthalmic solution consisting essentially of therapeutically effective amount of a prostaglandin or its analog and, cosolvent(s) and self preserving systems and optionally, pharmaceutically acceptable excipients selected from the group consisting of viscosity enhancing agents and buffers. Since the quaternary ammonium compounds are known to exhibit surfactant activity, the term 'consisting essentially of' means that the ophthalmic solution is free of preservatives, particularly, quaternary ammonium preservatives such as Benzalkonium Chloride (BAK), Benzethonium Chloride, Benzyl Alcohol, Busan, Cetrimide, Chlorhexidine, Chlorobutanol, Mercurial Preservatives, or phenylmercuric Nitrate, Phenylmercuric Acetate, Thimerosal, phenylethyl Alcohol and like. However, the safer preservative systems and preservative efficacy enhancers such as edetate disodium, borates, pyruvates, parabens, stabilized oxychloro compounds, Sorbic Acid/Potassium Sorbate Polyaminopropyl Biguanide, Polyquaternium-1, Polyhexamethylene biguanide (PHMB), PVP-Iodine complex, metal ions, peroxides, aminoacids, arginine, tromethamine and mixtures thereof may be included within the scope of the present invention. These compounds are generally regarded as safe and are recommended for long term use.

In certain embodiments of the present invention, another active ingredient may be included in the ophthalmic solution. The another active ingredient that may be included in the ophthalmic solution of the present invention, may be a beta-adrenergic blocking agent which is selected from the group consisting of timolol maleate, betaxalol, levobunolol hydrochloride and their therapeutically active salts or esters. The most commonly used and first line drug for the treatment of glaucoma is timolol maleate. Timolol, a non-selective beta-adrenergic blocking agent, when applied topically as an ophthalmic solution, reduces the intraocular pressure in the eye. It is thus indicated in patients with ocular hypertension or open angle glaucoma. It also shows certain systemic

effects which includes (1) beta-adrenergic blockade in the heart causing reduction in cardiac output in both healthy subjects and patients with heart disease and (2) beta-adrenergic receptor blockade in the bronchi and bronchioles resulting in increased airway resistance from unopposed parasympathetic activity. Therefore, the drug must be used with caution in patients in whom beta-adrenergic blockade may be undesirable. Timolol for glaucoma therapy is thus contraindicated in patients with compromised pulmonary functions and in patients who cannot tolerate its systemic cardiovascular action. Hence it is also desirable to reduce the frequency of the use of Timolol maleate wherever possible, preferably as a solution that provides once-a-day administration. Timolol maleate is used in the solutions of the present invention in therapeutically effective amounts. Timolol maleate may be used in an amount ranging from about 0.01% w/v to about 2.0 % w/v by weight of the solution, preferably from about 0.05 % w/v to about 1.0 % w/v by weight of the solution and most preferably from about 0.1 % w/v to about 0.5 % w/v by weight of the solution. Other beta-adrenergic blocking agent, that is suitable for the present invention is levobunalol or its pharmaceutically acceptable salt. It is used in therapeutically effective amounts 0.5 %. In another embodiment, betaxolol or its pharmaceutically acceptable salt is used in amounts ranging from 0.1 % w/v to 0.8 % w/v, preferably, 0.5 % w/v of the ophthalmic solution of the present invention. The preferred amount of beta-adrenergic blocking agent may be included in the concentration of 0.1% w/v to 0.7% w/v, preferably from 0.25% w/v to 0.5% w/v.

The ophthalmic solution of the present invention comprises one or more water soluble excipients selected from a group consisting of a water soluble polymer and a penetration enhancer and mixtures thereof. Examples of the water soluble polymers that may be used in the ophthalmic solution of the present invention, include, but are not limited to, polymers- natural and synthetic, polysaccharides, polyaminoglycosides, cellulose derivatives, guar gum, xanthan gum, geltrite, dextran, hyaluroante, chondroitin sulfate, locust bean gum, polyvinyl alcohol, polyvinyl pyrrolidone, hydroxypropyl methyl cellulose, hydroxyethyl cellulose, carbopol, polystyrene sulfonate and like and mixtures thereof.

The ophthalmic solution of the present invention may further comprise pharmaceutically acceptable excipients conventional to the pharmaceutical art. Typical of such pharmaceutically acceptable excipients include osmotic/tonicity-adjusting agents, one or more pharmaceutically acceptable buffering agents and pH-adjusting agents, viscosity enhancing agents, penetration enhancing vehicles and other agents conventional in art that may be used in formulating an ophthalmic solution or imparting a functional property such as gel-forming, bioadhesion, penetration enhancement and like. In certain embodiments, a combination of two water soluble such as hydroxypropyl methylcellulose and guar gum; hydroxypropyl methylcellulose and a carboxyvinyl polymer; hydroxypropyl methylcellulose and hydroxyethylcellulose; hydroxypropyl methylcellulose and hyaluronic acid; hyaluronic acid and a carboxyvinyl polymer; hyaluronic acid and guar gum; or a carboxyvinyl polymer and guar gum may be incorporated.

The ophthalmic solution of the present invention may be required to be isotonic with respect to the ophthalmic fluids present in the human eye. These solutions are characterized by osmolalities of 250-375 mOsm/kg. Osmolality of the solutions is adjusted by addition of an osmotic/tonicity adjusting agent. Osmotic agents that may be used in the solutions of the present invention to make it isotonic with respect to the ophthalmic fluids present in the human eye, are selected from the group comprising sodium chloride, potassium chloride, calcium chloride, sodium bromide, sodium phosphate sodium sulfate, mannitol, glycerol, sorbitol, propylene glycol, dextrose, sucrose, polyethylene glycols (PEG), PEG-400, PEG-200, PEG300 and the like, and mixtures thereof. In preferred embodiments of the present invention, PEG-400 is used as the osmotic agent. PEG-400 may be present in the solutions of the present invention in an amount ranging from about 1.0 % to about 5.0 % by weight of the solution, preferably from about 2.5 % to about 4.0 % by weight of the solution and most preferably in an amount of about 3.0 % by weight of the solution.

According to one embodiment, the preservative systems that are considered safer than quaternary ammonium preservatives are preferred such as polyquad®, stabilized oxy-

chlorocomplex, stabilized peroxides and perborates, EDTA, tromethamine, borates, sorbates (such as potassium sorbate and sodium sorbate), parabens (such as methyl-propyl, isopropyl and butyl- paraben) may be used. According to another embodiment of the present invention, the ophthalmic solution may be self preserving. The ingredients that make the solution self preserving includes, but are not limited to, inorganic metal salts such as zinc salts, boric acid, pyruvic acid presence of tromethamine, arginine, histidine, guanidine, disodium edetate or like and mixtures thereof.

In order to achieve, and subsequently maintain, an optimum pH, the ophthalmic solution may contain a pH adjusting agent and/or a buffering agent. The preferred range of pH for an ophthalmic formulation is about 4.0 to about 8.0, and the most preferred pH is about 5.5-7.5. The ophthalmic solution of the present invention comprises a pharmaceutically acceptable pH adjusting agents that may be selected from the group comprising acetic acid or salts thereof, boric acid or salts thereof, phosphoric acid or salts thereof, citric acid or salts thereof, tartaric acid or salts thereof, sodium hydroxide, potassium hydroxide, sodium carbonate, sodium hydrogen carbonate, trometamol, arginine, lysine, histidine, guanine and the like and mixtures thereof. Particularly, preferred pH adjusting agents that may be used in the ophthalmic solution of the present invention include acetic acid, hydrochloric acid, tromethamine, arginine and sodium hydroxide. These agents are used in amounts necessary to produce a pH ranging from about 4.5 to about 8.0.

According to one embodiment the solution of the present invention comprises of one or more solvents or co-solvents. The pharmaceutically acceptable solvents may be selected from a group of alcohols, such as ethanol, glycols such as ethylene glycol, propylene glycol, polyethylene glycol, glycofurol and like.

Besides above mentioned ingredients, one embodiment of the present invention may comprise a number of additional components to provide various functional effects, as is well known in this field. For example, small organic acids may be included as buffers

The present invention also provides a method of treating glaucoma or ocular hypertension which comprises topically administering to an affected eye an ophthalmic solution comprising therapeutically effective amount of a prostaglandin or its analog and a beta-adrenergic blocking agent and water soluble excipient(s) dissolved in a pharmaceutically acceptable vehicle, wherein the solution is free of a surfactant.

In one embodiment, the efficacy of the ophthalmic solution of the present invention was determined by administered the solution to the eyes of the normotensive beagle dogs. The reduction in the intraocular pressure was recorded at time points specifically, 2 hours- which is a time indicator for peak efficacy of a beta-adrenergic blocking agent, 12 hour time point which is a time indicator for peak of therapeutic action for a prostaglandin, and 24 hour time point, being an indicator of the trough level for prostaglandin. Surprisingly, it was found that the method of treating glaucoma or ocular hypertension of the present invention provided improved efficacy in reducing the intraocular pressure when compared to a solution containing a surfactant as such or a preservative that acts like a surfactant within the solution, such as in case of Xalacom® which contains benzalkonium chloride which exerts a surfactant effect apart from acting like a preservative. It is believed by the inventors, without wishing to be bound by any theory, that the surfactant free solution provided improved efficacy because the active agent is directly available on the ocular surface for absorption/ partition. It may be postulated that the prostaglandins like latanoprost bind to the micellar core hence less free latanoprost would not be available for absorption/partitioning on the ocular surface. The solution of the present invention is further advantageous in that the ophthalmic solutions having surfactant like BKC or other additives like preservatives cause tearing and eye irritation. Because of which a person skill in the art can expect a significant portion of dose of the active ingredient to be lost. It is also possible that the positively charged benzalkonium chloride resorbs negatively charged latanoprost acid active formed from the pro-drug latanoprost from the ocular surface. This improved effect is evidenced by the data represented in the Figure I at time points 2 hours or 12 hours. The improved effect is also evidenced at 24 h time point (Figure I) which is considered trough when the minimum effect is expected.

When the % mean reduction in the intraocular pressure of the affected eye of dogs when the solution of the present invention was administered vs % mean reduction in the intraocular pressure after the administration of marketed reference products such as like Xalatan®, Xalacom®, Timoptic® was studied, it was surprising found that the % mean reduction of the intraocular pressure was higher compared to the marketed product which either contains a beta-adrenergic blocking agent such as Timoptic® or a Xalatan® which is alone or their combination (Xalacom®). It was found that the mean intraocular pressure reduction achieved by administration of the ophthalmic solution of Example 3, was about 34.377 % compared to about 26.765% achieved by Xalatan® -latanoprost alone solution or about 28.258 % achieved by Xalacom® a combination product of latanoprost and timolol or about 21.088 % achieved by Timoptic® which is a timolol alone solution. Please refer to Figure II.

Surprisingly, it was further found that % reduction in the intraocular pressure when the ophthalmic solution of the present invention was administered when compared with the % reduction in the intraocular pressure after the concomitant administration of marketed latanoprost and Timolol products like Xalatan® and Timoptic® to the dogs, overall, mean intraocular pressure reduction achieved by the ophthalmic solution of the present invention was about 28.63 % compared to about 26.49 % which was achieved by the concomitant administration of the marketed product of latanoprost (once a day) and Timolol (twice a day) present alone in the products. Concomitant administration may not be desirable due to patient compliance problems and the possible side effects due to higher number of timolol doses.

In another embodiment of the present invention, the IOP reduction from the solution of present invention is more or non-inferior than the reference solutions of latanoprost and Timolol alone or as a fixed dose combination containing a surfactant such as BKC. The IOP reduction was said to be more or non-inferior when at least 50% of the time point at which the IOP readings are taken through out the treatment period show higher or equivalent mean IOP reduction.

Since the solution of the present invention, relates to combination of two active ingredient which vary in their solubility, dose etc. it is important to derive a pharmaceutical vehicle that can incorporate both the actives, particularly without the use of any surfactant, without facing any processing issues, such as drug loss due to incomplete solubilization, precipitation. Thus, in one preferred embodiment, the ophthalmic solution comprises non aqueous solvents such as ethanol, sorbitol, propylene glycol, polyethylene glycol and the like and mixtures thereof. In one embodiment, when the solution is prepared without the application of heat to dissolve the prostaglandin or its derivatives in absence of surfactant, the use of the non aqueous solvents was found to be particularly beneficial, in that the prostaglandin or its derivatives.

One embodiment of the present invention further provides a process of preparation of an ophthalmic solution wherein the solution comprises a polymeric vehicle. In one embodiment, the solution is prepared on a large scale batch such as more beta-adrenergic blocking agent is dissolved in a pharmaceutical vehicle, and preparing the polymeric vehicle separately. The polymeric material in the powder form should be slowly added into the vortex of vigorously agitated water for injection. This process of preparation of polymeric vehicle may be carried out at elevated temperature depending upon the type and nature of the polymer. The solution may be slowly stirred to dissolve the swollen or gelatinized particles completely. Once the water soluble excipient such as the polymeric vehicle is prepared, the active ingredient phase is prepared that is, timolol maleate is separately dissolved in water for injection. Separately, one or more buffering agents such as boric acid may be added and dissolved in the above solution under stirring. Similarly, self preservative agents such as zinc chloride and pH adjusting agents tromethamine are added and dissolved to above solution under stirring. Separately, the prostaglandin derivative such as for example, Latanoprost is taken in a non aqueous solvent such as polyethylene glycol 400 and stirred. This non aqueous solution is added to the timolol maleate aqueous solution under stirring. Since the latanoprost dose is very low, any solution which contains such a low dose drug needs to be done very carefully and with lot of precision. The solution is then filtered. The volume is made up to 20L with aseptically filtered water for injection and stirred for 30 minutes. The pH is monitored and adjusted

to 5.7-6.3, if required. Preferable the pH adjustment step is not carried out. Again the solution is filtered aseptically through 2-20μm glass fiber disc filter. This step is termed as polishing to make a homogenous polymer solution without the presence of fish-eye type gel particles of polymer. The solution is then filled into containers and the containers are subsequently sealed. The container may be purged with nitrogen.

In one embodiment, the process for the preparation of the ophthalmic solution of the present invention comprises:

a. Preparation of the sterile polymer phase by autoclaving
b. Preparation of the sterile drug phase by aseptic filtration
c. Combining the two phases under aseptic conditions.
d. Optionally, polishing by filtration though 2 micron to 75 micron filter
e. Filling and packaging in eye drop dispensing containers.

In one embodiment, the process for the preparation of the ophthalmic solution of the present invention comprises:

a. Making a prostaglandin phase in a non-aqueous solvent.
b. Adding non-aqueous prostaglandin phase into an aqueous beta-adrenergic blocking agent solution slowly and gradually with stirring
c. Preparation of the sterile polymer phase by autoclaving
d. Combining the two phases under aseptic conditions.
e. Optionally, polishing by filtration though 2 micron to 75 micron filter to remove foreign particulates
f. Filling and packaging in eye drop dispensing containers.

While the present invention is disclosed generally above, additional aspects are further discussed and illustrated with reference to the examples below. However, the examples are presented merely to illustrate the invention and should not be considered as limitations thereto.

EXAMPLE 1-2

Table 1: Composition of the ophthalmic solution

S. No	Ingredients	Example 1	Example 2
		Qty (%w/v)	
1.	Latanoprost	0.0025	0.005
2.	Polyethylene glycol 400	3.0	3.0
3.	Hydroxypropyl methylcellulose	-	0.5
4.	polyvinyl pyrrolidone	-	2.0
5.	Boric acid	1.0	1.0
6.	Zinc Chloride	0.0025	0.0025
7.	Tromethamine	0.375	0.375
8.	Water for injection	qs	qs

The ophthalmic solution according to example 1 and 2 are prepared by the procedure.

The ophthalmic solutions of Example 1, was stored in parylene coated containers as well as uncoated LDPE containers. Surprisingly, it was found that the solution remained stable in terms of chemical assay when stored in parylene coated bottles.

Table 2: Stability results of the ophthalmic solution of Example 1

Stability data					
Assay of Latanoprost in Parylene coated bottles			Assay of Latanoprost in Uncoated LDPE containers		
Initial	1D/85°C	3D/60°C	Initial	1D/85°C	3D/60°C
106.15	97.02	98.01	103.21	58.76	71.38

Further, the chemically stable ophthalmic solution of Example 1 was tested for efficacy in six beagle dogs for its antihypertensive action. The duration of the study was 10 days. 30 microlitres of the solution of Example 1 which contains 25 ng/µl of latanoprost was instilled into the eye of the beagle dogs. The measurement of reduction in intraocular

pressure was recorded at initial 12 hour and 24 hour time points. The results of the efficacy study are tabulated in Table 3 as follows:

Table 3: Results of the efficacy of the ophthalmic solution of latanoprost as per Example 1 that is free of surfactant in comparison to marketed product, Xalatan® which contains benzalkonium chloride, a surfactant

Test	Concentration of latanoprost (ng/microlitre)	Dose instilled (micrograms)	Average % IOP reduction at 12 hour time point	Ratio of % IOP reduction per microgram
Example 1	25 ng/µl	0.75	27.43±6.23	36.57
Xalatan®	50 ng/µl	1.5	29.86± 5.33	19.90

It may be concluded from the Table 3, that the ophthalmic solution of present invention which is free of surfactant, when administered at half the dose compared to the Xalatan®, the solution achieved almost equivalent efficacy in terms of intraocular pressure reduction. Thus, there is a surprising effect of achievement of equivalent efficacy at half the dose of latanoprost. This effect is indeed surprising and unexpected. Further, only half of the latanoprost dose present in the ophthalmic solution of the present invention compared to Xalatan®, was found to provide reduction in the intraocular pressure at time points of 6 hours, 12 hours and 24 hours. Unexpectedly, it was further found that the % intraocular pressure reduction at 12 hour time point is higher compared to the % intraocular pressure reduction at 12 hours, for Xalatan®.

EXAMPLE 3

Table 4: Ophthalmic solution of the present invention

S. No	ingredients	Qty (%w/v)
1.	Timolol Maleate eq to Timolol	0.50
2.	Latanoprost	0.005
3.	Polyethyleneglycol 400	3.0
4.	Hypromellose 2910	0.5
5.	PVP K 90	2.0
6.	Boric acid	1.0
7.	Zinc Chloride	0.0025
8.	Tromethamine	0.375
9.	Water for injection	qs

The solution was prepared as described in the description text without the use of any surfactant. The transmittance of the final solution was found to be 98.45%. The % transmission when stored at varying conditions for one month showed the following values. Also, the solution was found to be stable when stored in parylene coated containers as compared to the uncoated LDPE containers as shown in table 4.

Table 5: Stability data

Storage container	Assay of Latanoprost (% of label Claim) at different storage conditions				
	Initial and 1 month at varying storage conditions				
	Initial	2-8°C	25°C/ 40%RH	30°C/ 35%RH	40°C/ 25%RH
Uncoated LDPE container	99.32	94.89	87.45	82.12	77.60
Parylene Coated container	98.89	100.93	101.20	101.69	101.08
Clarity on storage	% Transmission				
Solution of example 3	98.5	99.3	99.2	98.6	99.7

Although there was no potency loss of active ingredient when the solution was kept in coated bottles for one month in stability, however significant potency loss of drug substance was observed in uncoated LDPE plastic bottles. This indicates that Parylene coating can prevent the absorption/adsorption of drug substance on to the LDPE plastic containers.

EXAMPLE 4

The ophthalmic solution of the present invention which is surfactant free, and preferably, substantially free of preservative, was subjected to antimicrobial Effectiveness Test as per USP/JP. The results are documented in Table 6 below.

Table 6: Results of antimicrobial test as per USP/JP monograph

Acceptance Criteria as per USP monograph	Organism	Observation
NLT 1.0 log reduction from initial count at 7 days; NLT 3.0 log reduction from initial count at 14 days and no increase from the 14 days count at 28 days.	*Escherichia coli.*	Complies
	Pseudomonas aeruginosa	
	Staphylococcus aureus	
No increase** from the initial calculated count at 7, 14, and 28 days	Candida albicans	Complies
	Aspergillus Niger	

It may be concluded that the ophthalmic solution of the present invention, passes the compendial antimicrobial effectiveness testing criteria.

EXAMPLE 5

Table 7: Composition of the ophthalmic solution

S. No	ingredients	Qty (%w/v)
1.	Timolol Maleate eq to Timolol	0.50
2.	Travoprost	0.004
3.	Polyethyleneglycol 400	3.0
4.	Hypromellose 2910	0.5
5.	PVP K 90	2.0
6.	Boric acid	1.0
7.	Zinc Chloride	0.0025
8.	Tromethamine	q.s.
9.	WFI	q.s.

The ophthalmic solution according to the constituents Example 5 was prepared by a process similar to Example 3, except, latanoprost was substituted by travoprost. The pH was adjusted to 6.0. The % Transmittance was found to be 98.913.

EXAMPLE 6

Table 8: Composition of the ophthalmic solution

Sl. No	Ingredients	Qty (%w/v)
1.	Betaxolol Hydrochloride eq to Betaxolol	0.50
2.	Latanoprost	0.005
3.	Polyethyleneglycol 400	3.0
4.	Hypromellose 2910	0.5
5.	PVP K 90	2.0
6.	Boric acid	1.0
7.	Zinc Chloride	0.0025
8.	Tromethamine	qs
9.	Water for injection	qs

The ophthalmic solution according to the constituents Example 6 was prepared by a process similar to Example 3, except, timolol maleate was substituted by Betaxolol another beta-adrenergic blocking agent. The pH was adjusted to 6.0. The % Transmittance was found to be 96.473.

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EXAMPLE 7

Table 9: Composition of the ophthalmic solution

Sl. No	ingredients	Qty (%w/v)
1.	Betaxolol Hydrochloride eq to Betaxolol	0.50
2.	Travoprost	0.004
3.	Polyethyleneglycol 400	3.0
4.	Hypromellose 2910	0.5
5.	PVP K 90	2.0
6.	Boric acid	1.0
7.	Zinc Chloride	0.0025
8.	Tromethamine	q.s.
9.	WFI	q.s.

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The ophthalmic solution according to the constituents Example 7 was prepared by a process similar to Example 3, except, timolol maleate was substituted by Betaxolol another beta-adrenergic blocking agent and latanoprost was substituted by travoprost. The pH was adjusted to 6.0. The % Transmittance was found to be 98.266.

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EXAMPLE 8

The solution prepared according to example 3 was subjected to a comparative efficacy study in normotensive beagle dogs. The efficacy was compared with three marketed reference formulations namely, (Xalacom®, Xalatan® and Timoptic®) which contains 20 latanoprost and timolol Maleate in combination; latanoprost alone and timolol Maleate alone, respectively.

Three healthy beagle dogs were taken for each group. Pretreatment measurement of intraocular pressure were obtained for both eyes at 8.00 AM and 8.00 PM for 2 days preceding treatment with the help of 30 Classic Pneumatonometer Model 30 (Reichert, USA) and considered as initial intraocular pressure reading. 30 µl of solution of example 3, Xalacom and Xalatan were instilled in the treated eyes once a day at 8 am whereas 30 µl of Timoptic was instilled in the treated eyes two times a day at 8 am and 8 pm on day 3 to day 12. On day 3 IOP was measured at 2, 6, 12 and 24 h after medicament instillation and from day 4 to day 12 the IOP was measured at 2, 12 and 24 h after dosing. After the treatment period, on day 13 to day 17 IOP measurements were obtained once each day at 9.00 am.

A comparative % reduction in the intraocular pressure of the dogs within 24 hours when the solution of the present invention was administered and % reduction in the intraocular pressure after the administration of already available marketed products like Xalatan®, Xalacom®, Timoptic® was calculated.

For representation purposes, the reduction in the intraocular pressure was plotted at 2 hours, 12 hours and 24 hours time points and is plotted as provided in Figure I. During the first 24 h when the treated eyes were first exposed to the medicaments, the IOP reduction of solution of present invention was more than other marketed formulations such as Xalatan®, Xalacom® and Timoptic®. Further it was observed that throughout the treatment period, the intraocular pressure reduction by administration of the solution of the present invention was higher in comparison to the marketed formulations.

EXAMPLE 9

The solution prepared according to example 3 was subjected to a comparative efficacy study in normotensive beagle dogs. The efficacy was compared with marketed reference formulations namely, Xalatan® and Timoptic® which contain latanoprost and timolol Maleate, respectively, was co-administered. Pretreatment measurement of IOP was obtained for both the eyes of each beagle dogs at 8 am and 8 pm for two days preceding treatment (day1 to day 2). On day 3 animals were divided into 2 groups consisting of 6

animals. One group of animals received 30-µL instillation of Test (example 3 of the present invention) to one eye once daily and another group received 30-µL Xalatan® once daily and 30-µL Timoptic® instilled twice daily in same eye received for 10 days and IOP readings were measured, as described above. Almost equivalent or slightly improved efficacy was found when ophthalmic solution of the present invention was compared to concomitant administration of Xalatan® and Timoptic® (Figure III).

COMPARATIVE EXAMPLE 1

Table 10

Sr. No	ingredients	Qty (%w/v)
1.	Timolol Maleate eq to Timolol	0.50
2.	Latanoprost	0.005
3.	Castor oil	0.15
4.	Solutol HS 15	0.25
5.	HPMC	0.5
6.	PVP K 90	2.0
7.	Boric acid	1.0
8.	Polyethylene glycol	3.0
9.	Zinc Chloride	0.0025
10.	Tromethamine	0.375
11.	Water for Injection	q.s.
pH		6.5-7.5

Procedure:

1. Collect Water for Injection (WFI) of temperature between 20 to 25°C in a vessel. Add and dissolve Boric acid, sodium borate/Borax,Edetate disodium, potassium sorbate and timolol maleate with continuous stirring. Ensure complete solubilisation of all the ingredients added above and clarity of solution visually.

2. Take Latanoprost and castor oil in a glass beaker. Stir it with glass rod. Take Macrogol 15 Hydroxystearate in a separate beaker and heat it at 65 – 70°C. After melting, transfer it to the above oil phase. Stir using dry glass rod at 65-70°C. Maintain the temperature at 65-70°C with heating.

3. Take WFI and heat it at 70-75°C in a vessel fitted with silverson homogenizer. Take additional small quantity of WFI and heat it at 70-75°C in another 316 vessel and maintain the temperature between 70-75°C until use.

4. Add the Oil phase drop wise to WFI at 70-75°C under high speed stirring.

5. Rinse the containers used for oil phase and Macrogol-15-Hydroxystearate with additional pre-heated WFI and add to the above solution at 70-75°C under high speed stirring. Continued the high speed stirring for 10 min. Reduce the speed. Bring down the temperature. Add propylene glycol under mild stirring.

6. Add the Timolol solution prepared at step 1 to the solution under stirring.

7. Check pH.

8. Make up the volume with WFI.

The % transmittance was recorded as per the description. It was found to be only 2.19%.

COMPARATIVE EXAMPLE 2

Table 11

Sr. No	ingredients	Qty (%w/v)
1.	Timolol Maleate eq to Timolol	0.50
2.	Latanoprost	0.005
3.	Castor oil	0.10
4.	Solutol HS 15	0.25
5.	HPMC	0.5
6.	PVP K 90	2.0
7.	Boric acid	1.0
8.	Sodium chloride	0.65
9.	Zinc Chloride	0.0025
10.	Tromethamine	q.s.
11.	Water for Injection	q.s.
pH		6.5-7.5

The comparative example 2 was prepared as per the procedure followed for preparing comparative example 1. The comparative example 2 is different than the comparative

example 1 in that it contains reduced amount of the castor oil compared to the comparative example 1. The solution so prepared was checked for the % transmittance. The % transmittance was found to be 79.1 at initial point and when stored for 6 months at 2-8°C it was found to be to 65.7.

Thus, it could be concluded that the incorporation of an oil along with surfactant into the solution of combination of a prostaglandin and a beta-adrenergic blocking agent, do not provide a clear solution.

Claims:

1. An ophthalmic solution comprising therapeutically effective amount of a prostaglandin or its analog and water soluble excipient(s) dissolved in a pharmaceutically acceptable vehicle, wherein the solution is free of a surfactant.

2. An ophthalmic solution as claimed in claim 1 further comprises a beta adrenergic blocking agent.

3. An ophthalmic solution as claimed in claim 1 wherein water soluble excipient(s) are water soluble polymer or one or more penetration enhancing agents.

4. An ophthalmic solution as claimed in claim 1 wherein the solution is free of preservatives which are organic mercurial compounds, quaternary ammonium compound or substituted alcohol or phenol.

5. An ophthalmic solution as claimed in claim 3 wherein the solution is stored in a parylene coated plastic bottle.

6. An ophthalmic solution consisting essentially of therapeutically effective amount of a prostaglandin or its analog, co-solvent(s) and self preserving system and optionally, pharmaceutically acceptable excipients selected from the group consisting of viscosity enhancing agents and buffers.

7. An ophthalmic solution as claimed in claim 6 wherein viscosity enhancing agents is a water soluble polymer.

8. A method of treating glaucoma or ocular hypertension which comprises topically administering to an affected eye an ophthalmic solution defined by any of the claims 1 to 7.

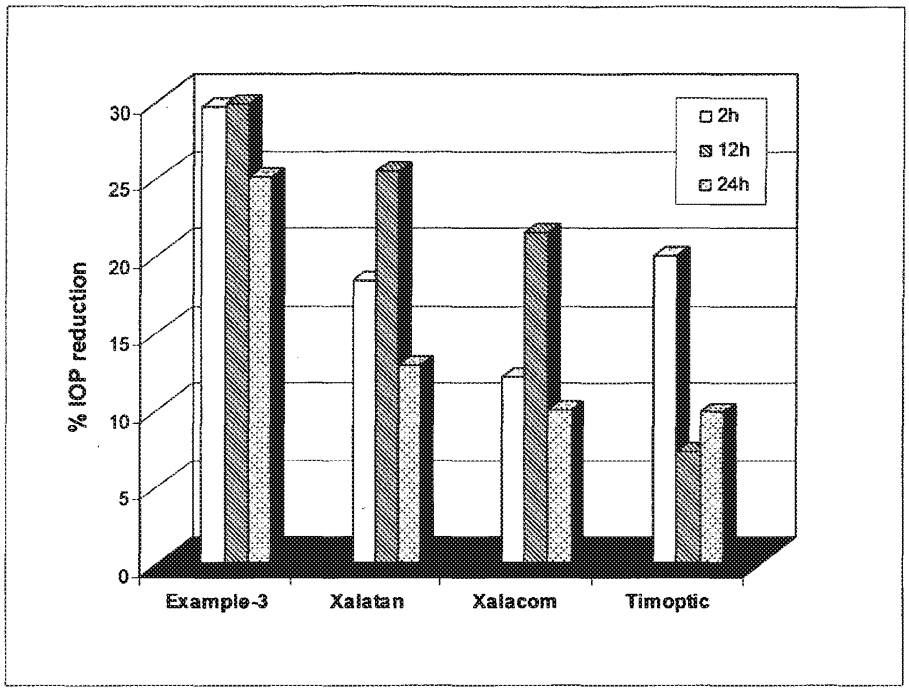

Figure I

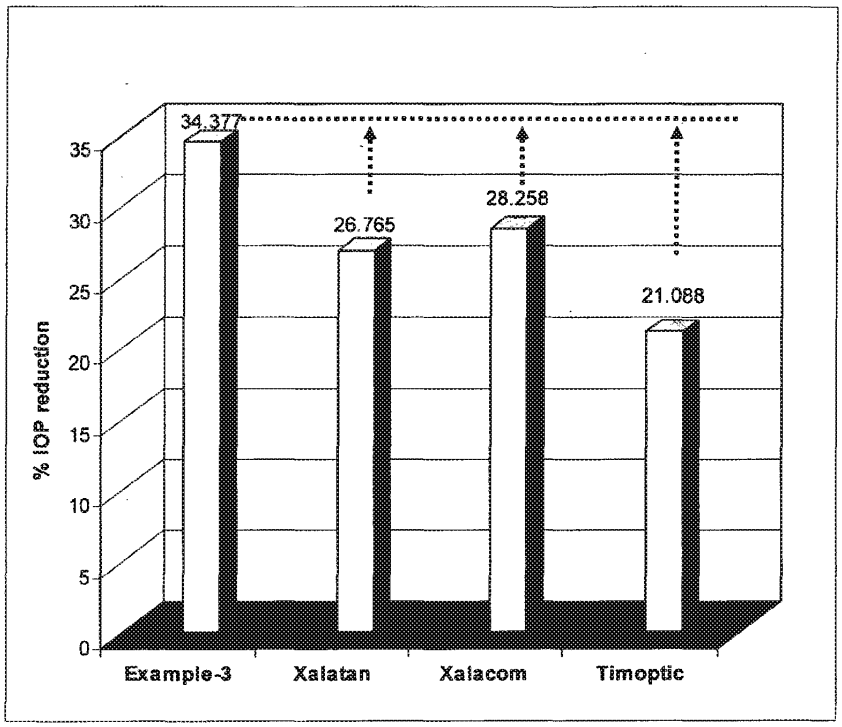

Figure II

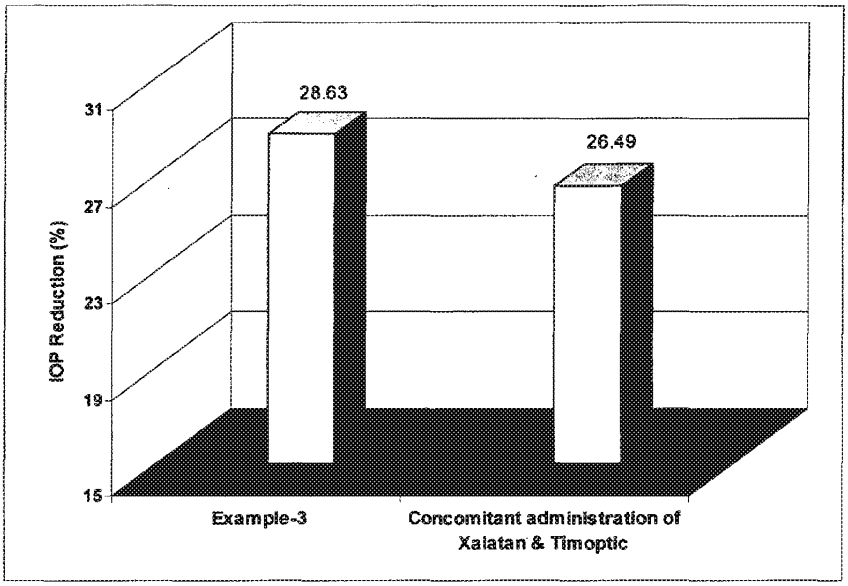

Figure III

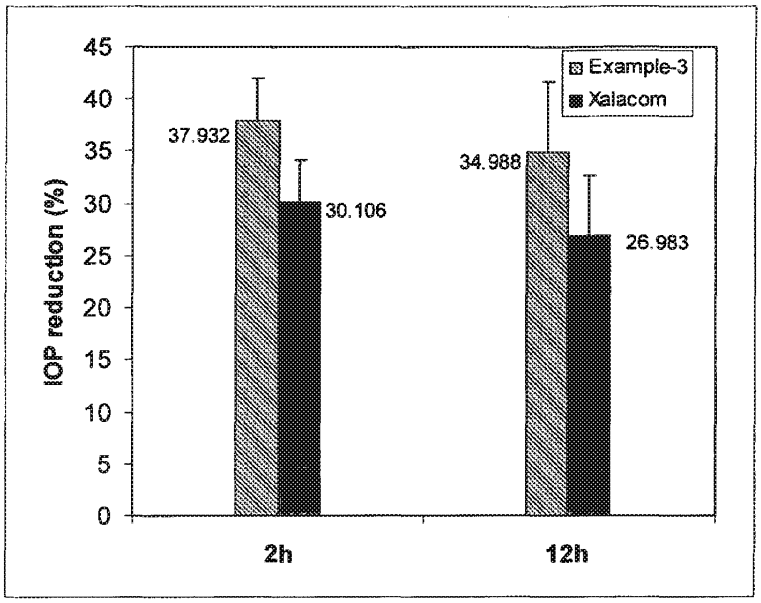

Figure IV

INTERNATIONAL SEARCH REPORT

International application No.
PCT / IN 2011/000320

A. CLASSIFICATION OF SUBJECT MATTER
IPC: ***A61K 9/00*** (2006.01); ***A61K 31/557*** (2006.01); ***A61K 31/5377*** (2006.01); ***A61K 47/32*** (2006.01)
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 practicable, search terms used)
EPODOC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1661573 A1 (SUCAMPO AG) 31 May 2006 (31.05.2006) Claims 1, 9; Description Paragraphs [0069], [0072] - [0074]	1-4, 6-8
X	JP 2001081048 A (WAKAMOTO PHARMACEUT CO LTD) 27 March 2001 (27.03.2001) WPI-Abstract [online] [retrieved on 25.08.201] Retrieved from: EPOQUE EPODOC Database	1-4, 6-8
X	EP 1234582 A1 (SANKYO COMPANY, LIMITED) 28 August 2002 (28.08.2002) Claims 1, 5, 7; Description Paragraphs [0029], [0030], [0037], [0038]	1-4, 6-8
E	WO 2011061298 A1 (NOVAGALI PHARMA SA) 26 May 2011 (26.05.2011) Claims 1, 2, 3, 10-12; Description Page 16 Line 10ff	1-4, 6-8

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

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 August 2011 (25.08.2011)	01 September 2011 (01.09.2011)
Name and mailing address of the ISA/AT Austrian Patent Office Dresdner Straße 87, A-1200 Vienna Facsimile No. +43 / 1 / 534 24-535	Authorized officer HUNGER U. Telephone No. +43 / 1 / 534 24-363

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT / IN 2011/000320

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

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

1. ☒ Claims Nos.: 8
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 8 refers to a method of treatment of the human or animal body by therapy, a search was based on the alleged effect of the composition.

2. ☒ Claims Nos.: 5
because they relate to parts of the national application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claim 5 characterizes an ophthalmic composition by the container in which it is stored. This is not allowed. A kit of part can be claimed if a certain interaction of composition and container is given.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

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

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

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is only those claims for which fees were paid, specifically claims Nos.:

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT / IN 2011/000320

Patent document cited in search report			Patent family member(s)			Publication date
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			US	B2	7307096	2007-12-11
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			WO	A1	2011061298	2011-05-26

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WIPO | PCT

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61/548,957 19 October 2011 (19.10.2011) US

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(54) Title: HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION

(57) 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.

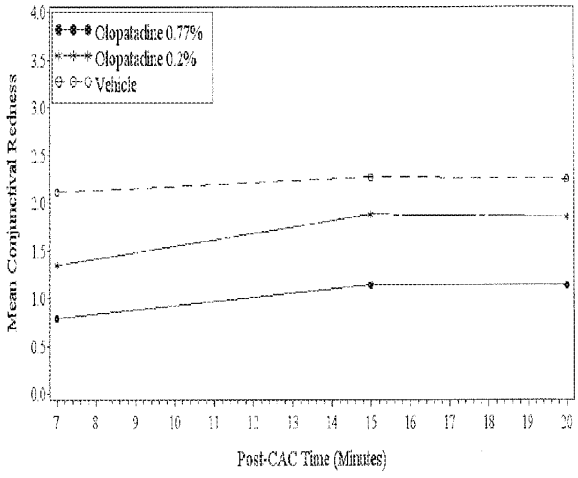

FIG. 1

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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 varicty 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/

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**

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.

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 or 2 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, 2 or 3 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 any of claims 1-5 further comprising a polyether.

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

8. A composition as in any of claims 1-7 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 any of claims 9-13 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%.

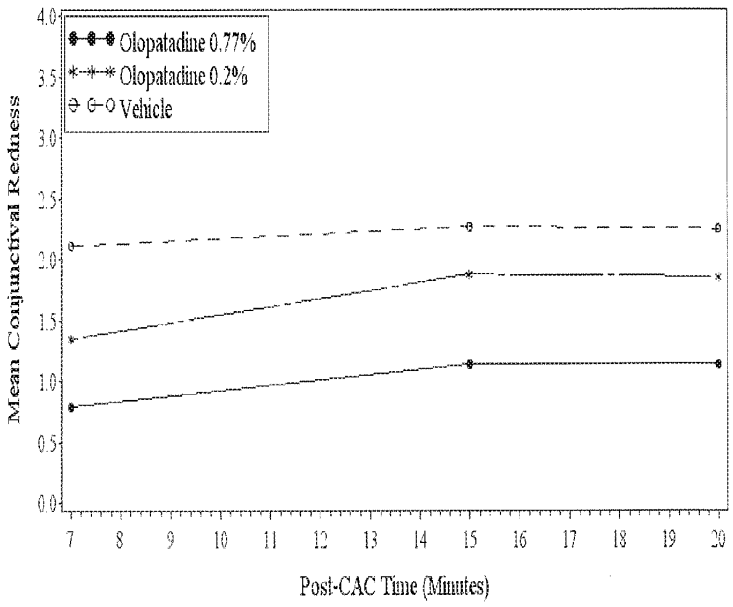
22. A composition as in claim 21 further comprising polyol.

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 any of the preceding claims 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.


Olopatadine 0.77%
Olopatadine 0.2%
Vehicle
Mean Conjunctival Redness
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3.5
3.0
2.5
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1.0
0.5
0.0
7
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11
12
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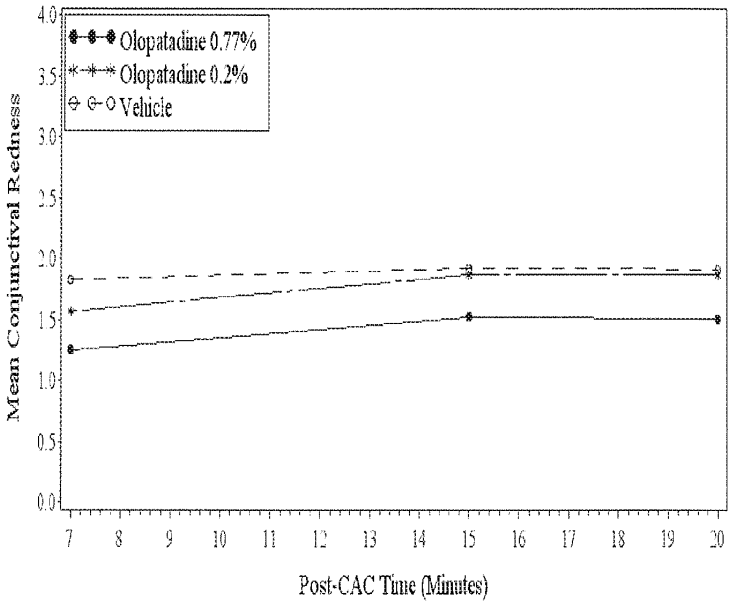
15
16
17
18
19
20
Post-CAC Time (Minutes)

FIG. 1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Vehicle
Mean Conjunctival Redness
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3.5
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2.5
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1.5
1.0
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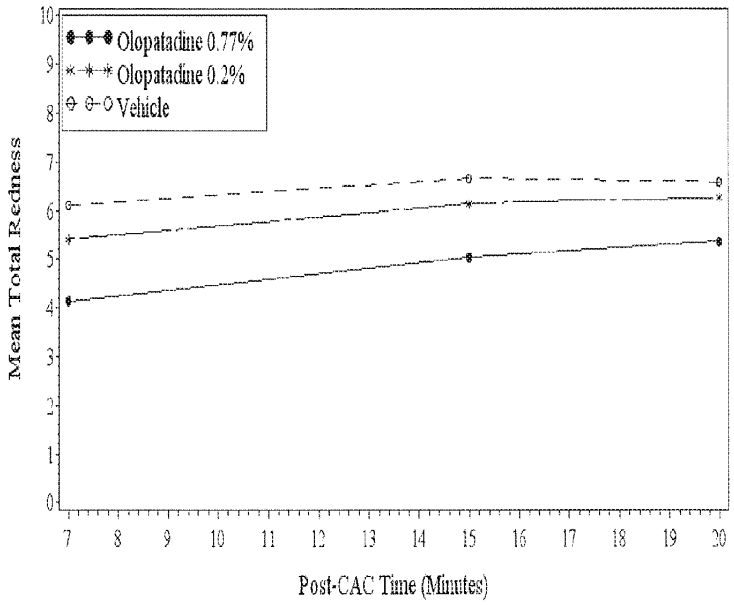
Post-CAC Time (Minutes)

FIG. 2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Olopatadine 0.2%
Vehicle
Mean Total Redness
Post-CAC Time (Minutes)
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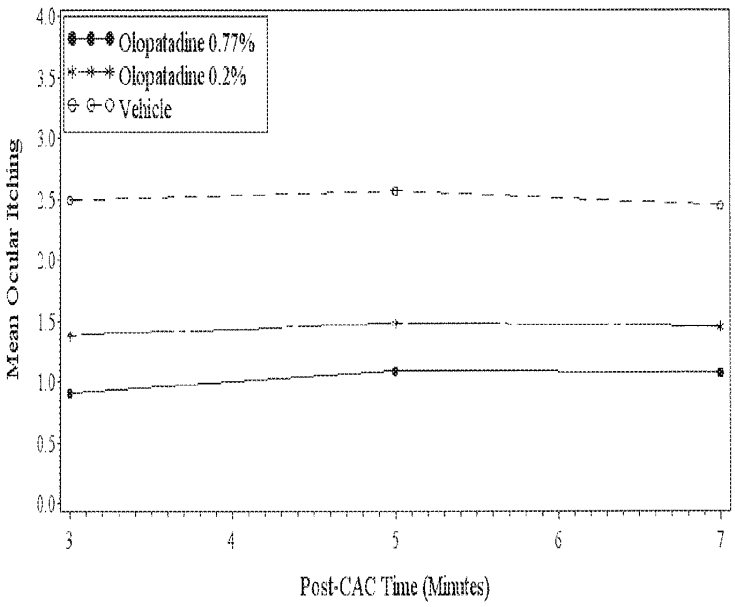
19
20

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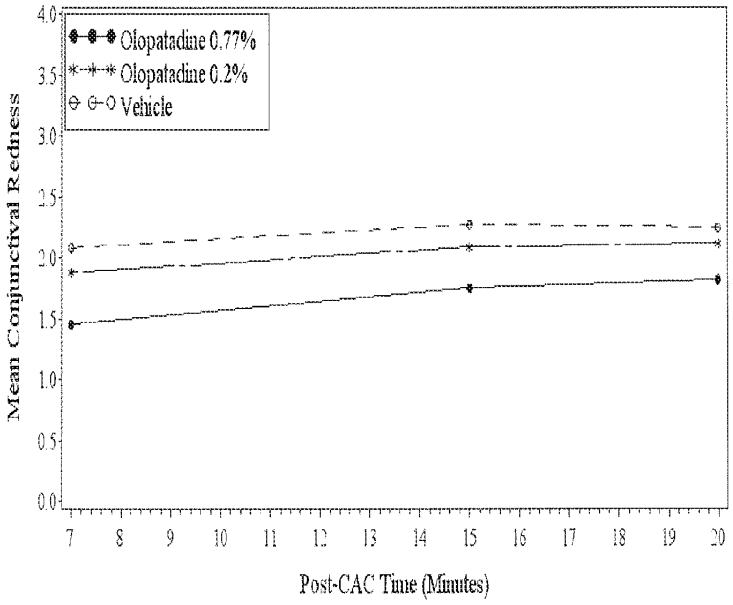
3.0
2.5
2.0
1.5
1.0
0.5
0.0
3
4
5
6
7
Post-CAC Time (Minutes)

FIG. 4


Olopatadine 0.77%
Olopatadine 0.2%
Vehicle
Mean Conjunctival Redness
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0.0
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8
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14
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16
17
18
19
20
Post-CAC Time (Minutes)

FIG. 5

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/038663

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/335 A61K9/00 A61P27/14
ADD.

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 A61P

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)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/003199 A1 (CYDEX PHARMACEUTICALS INC [US]; PIPKIN JAMES D [US]; ZIMMERER RUPERT O) 31 December 2008 (2008-12-31) the whole document page 1, line 2 - line 7 page 4, line 11 - line 26 page 5, line 14 - line 27 page 8, line 18 - line 26 page 57, line 10 - line 15 page 66, line 22 - line 33 page 71, line 27 - page 73, line 10 page 78, line 31 - page 80, line 32 example 20 -----	1-25
X	WO 96/39147 A2 (ALCON LAB INC [US]) 12 December 1996 (1996-12-12) the whole document claims 1-2 -----	1,2,24, 25
	-/--	

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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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

Date of the actual completion of the international search	Date of mailing of the international search report
18 July 2012	25/07/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Economou, Dimitrios

1

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/038663

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/54687 A1 (ALCON UNIVERSAL LTD [CH]; YANNI JOHN M [US]) 2 August 2001 (2001-08-02) the whole document claims 1-2	1,2,9, 24,25
X	WO 2008/015695 A2 (SUN PHARMACEUTICAL IND LTD [IN]; BHOWMICK SUBHAS BALARAM [IN]; LADDHA) 7 February 2008 (2008-02-07) the whole document examples A-M examples 1-7	1-25

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2012/038663

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009003199 A1	31-12-2008	CN 101795565 A	04-08-2010
		EP 2173169 A1	14-04-2010
		JP 2010531898 A	30-09-2010
		WO 2009003199 A1	31-12-2008
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		DE 69622527 T2	05-12-2002
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		EP 0799044 A2	08-10-1997
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		JP 2003520813 A	08-07-2003
		JP 2011132259 A	07-07-2011
		PT 1250133 E	31-05-2005
		US 2001056093 A1	27-12-2001
		WO 0154687 A1	02-08-2001
WO 2008015695 A2	07-02-2008	NONE	

Electronic Patent Application Fee Transmittal

Application Number:	14304124
Filing Date:	13-Jun-2014
Title of Invention:	HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION
First Named Inventor/Applicant Name:	Daniel A. Gamache
Filer:	Scott Chapple/Cindy Klepacky
Attorney Docket Number:	PAT903988-US-CNT

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

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

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
Statutory or Terminal Disclaimer	1814	1	160	160
		Total in USD ($)		**340**

Electronic Acknowledgement Receipt	
EFS ID:	25742953
Application Number:	14304124
International Application Number:	
Confirmation Number:	1002
Title of Invention:	HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION
First Named Inventor/Applicant Name:	Daniel A. Gamache
Customer Number:	1095
Filer:	Scott Chapple/Cindy Klepacky
Filer Authorized By:	Scott Chapple
Attorney Docket Number:	PAT903988-US-CNT
Receipt Date:	11-MAY-2016
Filing Date:	13-JUN-2014
Time Stamp:	10:50:50
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$340
RAM confirmation Number	9126
Deposit Account	190134
Authorized User	Chapple, Scott
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 CFR 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		PAT903988_US_CNT_2016_MAY12_AMENDMENT.pdf	126206 81588502e9449091e74075cec4be1afba3426be2	yes	5
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Amendment/Req. Reconsideration-After Non-Final Reject		1	1	
	Claims		2	3	
	Applicant Arguments/Remarks Made in an Amendment		4	5	
Warnings:					
Information:					
2	Terminal Disclaimer Filed	PAT903988_US_CNT_2016_MAY12_TERMINAL_DISCL.pdf	160951 2f40092f1b2a039c390a38b3dadc6901230bc9b9	no	2
Warnings:					
Information:					
3	Information Disclosure Statement (IDS) Form (SB08)	PAT903988_US_CNT_2016_MAY12_IDS.pdf	1184123 af7cdfb6314455b489ff3a89b23f7422d063c9a3	no	8
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4	Foreign Reference	EP0214779.pdf	3524593 ffa53103f0cc9a5b2f63d5747c040d7621b3ec5d	no	26
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5	Foreign Reference	EP0235796.pdf	3171804 316a0d55946c68f2915e35883e190071e76bb606	no	39
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6	Foreign Reference	EP0799044.pdf	107274 bbee70c3aefa3d85af21b9379bdab7f8f7ef101d	no	10

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7	Foreign Reference	WO0078396.pdf	1103299 2eb31187e7f2e1dfe37e409927881d4c4ab61ceb	no	13
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Information:					
8	Foreign Reference	WO0224116.pdf	2476060 c6b64cda2f3f2d586f04aaa8468c6fc8cf6a8560	no	23
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9	Foreign Reference	WO9918963.pdf	3907251 dc066bccaa7267066f6a2910a094101cb416f427	no	38
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10	Foreign Reference	WO2004024126.pdf	10879351 3e1d41b56ecaa2c0f90685cdbcf621e17ed097a0	no	102
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11	Foreign Reference	WO2011138801.pdf	3774657 0b2ad42959c7522e1cbfaef397e9cad9c65aed6e	no	38
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Information:					
12	Foreign Reference	WO2012159064.pdf	5535413 9e44e2eaa216ba188fee9e367b3ad1c535ab730f	no	52
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Information:					
13	Non Patent Literature	Abelson_797.pdf	126634 2e04a4892620874bde4b24b34b7bc922abb4f505	no	8
Warnings:					
Information:					
14	Non Patent Literature	Abelson_and_Anderson122_125.pdf	366566 e3f0aca613d7a56f624ab4f8b914c1c62b22d4f9	no	4
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15	Non Patent Literature	Ansel_2010_82.pdf	103089 6600633940376d03284ab1fee06d8fdd6ad7b455	no	4

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16	Non Patent Literature	Chaudhari_2007_1586.pdf	612897 35bf4e5ceb61f0120b6e00074b7d1c342440e6e4	no	6
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17	Non Patent Literature	Choi_2008_438.pdf	132256 84a8c909c418dc2025eeb35d0d926fca11192ac1	no	7
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18	Non Patent Literature	Gennaro_1995_613.pdf	1951660 307fdb7308ef2d08afdbd106874dec6a0fc35c1b	no	21
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19	Non Patent Literature	Gennaro_1995_1563.pdf	2104611 5fd2db719776c946bd69824538ee4d556f31eb52	no	18
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22	Non Patent Literature	Lide_2006_6_4.pdf	812079 8a14c3a0a18512f33d79fdfd0d50cc70fae0cebd	no	4
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23	Non Patent Literature	Loftsson_2002_144.pdf	292055 07111f5976a90efeb316231fc8dc77f39de36962	no	7
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24	Non Patent Literature	Loftsson_1998_115.pdf	564386 86b97a07bd35685180a04786db421142c7c01924	no	7

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25	Non Patent Literature	Loftsson_1017.pdf	768460 b4bb3546559619030e2601aff8086cc41d68d917	no	9
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26	Non Patent Literature	Nandi_2003_1.pdf	176049 1cb2f950eaf707d440f6cfa61cc596c629498ab6	no	5
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27	Non Patent Literature	Patanol_Label_2002.pdf	97218 677491d80159c63b4dbb097ab9bf65393c9d0a95	no	3
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29	Non Patent Literature	Patanase_Label_2008.pdf	618083 4f07429e6ea036289838f399a0e5f0054ead90fe	no	10
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30	Non Patent Literature	Polyvinylpyrrolidone_K30_1.pdf	166483 f1c75026a728ee1551c1a6883be48419371a6e08	no	2
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31	Non Patent Literature	Proud_1989_896.pdf	1900112 84296e3e7c692b88c58f65b5a703a55e4c11d890	no	10
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33	Non Patent Literature	Swei_2003_1153.pdf	81327 8ee9abbd90296d4c5532b477c2deeb8a73e7fa0a	no	3

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34	Non Patent Literature	US_District_Court_Complaint_2015_1.pdf	178140 faacd350a4ad76fccd349c95558012e8d556c91f	no	16
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35	Non Patent Literature	US_District_Court_Defendants_Answer_2016_1.pdf	2811896 8eb35ddc85f962e6501f7680530952a8ce97d137	no	26
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36	Non Patent Literature	USPTO_Petition_For_IPR_2016_1.pdf	369376 1d8a6af561053ab71b098c1ccb2511756db8d3bc	no	68
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38	Non Patent Literature	Watson_Laboratories_Para_IV_Cert_Letter_2015_1.pdf	3298972 8733c8888b9088290091a542de3df977b36acb4f	no	29
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Information:					
			Total Files Size (in bytes):	61610570	

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
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New International Application Filed with the USPTO as a Receiving Office
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PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/304,124	Filing Date 06/13/2014	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ 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).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 05/11/2016	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 13	Minus	** 20	= 0	X $80 =	0
Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0	X $420 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	0

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					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 number found in the appropriate box in column 1.

LIE
/TRINA RIDDICK/

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	14/304,124	GAMACHE ET AL.	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 5/11/16	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:

Felicia D. Roberts

8,791,154

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1095 7590 08/09/2016

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INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 433/2
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EXAMINER	
TRAN, MY CHAU T	
ART UNIT	PAPER NUMBER
1629	

DATE MAILED: 08/09/2016

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/304,124	06/13/2014	Daniel A. Gamache	PAT903988-US-CNT	1002

TITLE OF INVENTION: HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	11/09/2016

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

1095 7590 08/09/2016
NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 433/2
EAST HANOVER, NJ 07936-1080

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

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14/304,124	06/13/2014	Daniel A. Gamache	PAT903988-US-CNT	1002

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nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	11/09/2016

EXAMINER	ART UNIT	CLASS-SUBCLASS
TRAN, MY CHAU T	1629	514-450000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): (**Please first reapply any previously paid issue fee shown above**)
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ Applicant certifying micro entity status. See 37 CFR 1.29 — NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ❑ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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
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www.uspto.gov

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Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Notice Requiring Inventor's Oath or Declaration	Application No. 14/304,124	Applicant(s) Daniel A. Gamache	
	Examiner TRAN, MY CHAU T	Art Unit 1629	

This notice is an attachment to the Notice of Allowability (PTOL-37), or the Notice of Allowability For A Design Application (PTOL-37D).

An inventor's oath or declaration in compliance with 37 CFR 1.63 or 1.64 executed by or with respect to each inventor has not yet been submitted.

An oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each inventor (for any inventor for which a compliant oath, declaration, or substitute statement has not yet been submitted) MUST be filed no later than the date on which the issue fee is paid. See 35 U.S.C. 115(f). Failure to timely comply will result in ABANDONMENT of this application.

A properly executed inventor's oath to declaration has not been received for the following inventor(s):

If applicant previously filed one or more oaths, declarations, or substitute statements, applicant may have received an informational notice regarding deficiencies therein.

The following deficiencies are noted:

INFORMAL ACTION PROBLEMS

- A properly executed inventor's oath or declaration has not been received for the following inventor(s): **Daniel A. Gamache**, **Laman Alani**, **Malay Ghosh**, **Francisco Javier Galan**, **Nuria Carreras Perdiguer**, and **Onkar N. Singh** .
  Applicant may submit the inventor's oath or declaration at any time before the Notice of Allowance and Fee(s) Due, PTOL-85, is mailed.

Questions relating to this Notice should be directed to the Application Assistance Unit at 571-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 14/304,124	Applicant(s) GAMACHE ET AL.	
	Examiner MY-CHAU T. TRAN	Art Unit 1629	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *06/10/2016*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *26-33 and 35-39*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 05/11/2016
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/MY-CHAU T TRAN/
Primary Examiner, Art Unit 1629

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14304124	GAMACHE ET AL.
	Examiner	**Art Unit**
	MY-CHAU T TRAN	1629

CPC								
Symbol							**Type**	**Version**
A61K		47	/	40			F	2013-01-01
A61K		9	/	0048			I	2013-01-01
A61K		31	/	335			I	2013-01-01
A61K		47	/	32			I	2013-01-01
A61K		9	/	08			I	2013-01-01
A61K		47	/	48969			I	2013-01-01
C08B		37	/	0015			I	2013-01-01
C08L		5	/	16			I	2013-01-01
A61K		47	/	10			I	2013-01-01
B82Y		5	/	00			I	2013-01-01
			/					
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			/					
			/					
			/					

CPC Combination Sets								
Symbol						**Type**	**Set**	**Ranking**	**Version**
			/						
			/						

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	13	
/MY-CHAU T TRAN/ Primary Examiner.Art Unit 1629	07/25/2016	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	26	NONE

U.S. Patent and Trademark Office — Part of Paper No. 20160725

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14304124	GAMACHE ET AL.
	Examiner	**Art Unit**
	MY-CHAU T TRAN	1629

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION												
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED							
514	450	A	6	1	K	31 / 335 (2006.0)								
CROSS REFERENCE(S)		A	0	1	N	43 / 02 (2006.0)								
		A	6	1	K	47 / 00 (2006.01.01)								
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)													
514	449	777	778											

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 13	
/MY-CHAU T TRAN/ Primary Examiner.Art Unit 1629 (Primary Examiner)	07/25/2016 (Date)	O.G. Print Claim(s) 26	O.G. Print Figure NONE

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14304124	GAMACHE ET AL.
	Examiner	**Art Unit**
	MY-CHAU T TRAN	1629

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1		17	8	33										
	2		18		34										
	3		19	9	35										
	4		20	10	36										
	5		21	11	37										
	6		22	12	38										
	7		23	13	39										
	8		24												
	9		25												
	10	1	26												
	11	2	27												
	12	3	28												
	13	4	29												
	14	5	30												
	15	6	31												
	16	7	32												

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 13	
/MY-CHAU T TRAN/ Primary Examiner.Art Unit 1629 (Primary Examiner)	07/25/2016 (Date)	O.G. Print Claim(s) 26	O.G. Print Figure NONE

U.S. Patent and Trademark Office Part of Paper No. 20160725

PTO/SB/08a (03-15)
Approved for use through 07/31/2016. 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	14304124
Filing Date	2014-06-13
First Named Inventor	Daniel A. Gamache
Art Unit	1629
Examiner Name	TRAN, MY CHAU T
Attorney Docket Number	PAT903988-US-CNT

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
/MCT/	1	4871865		1989-10-03	Lever, Jr. et al.	
	2	5342620		1994-08-30	Chowhan	
	3	5985310		1999-11-16	Castillo et al.	
	4	6316483		2001-11-13	Haslwanter et al.	
	5	7402609		2008-07-22	Castillo et al.	
	6	7687646		2010-03-30	Bader et al.	
	7	7977376		2011-07-12	Singh et al.	
/MCT/	8	8399508		2013-03-19	Singh et al.	

If you wish to add additional U.S. Patent citation information please click the Add button. Add

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /MCT/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14304124
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	Examiner Name	TRAN, MY CHAU T
	Attorney Docket Number	PAT903988-US-CNT

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
/MCT/	1	20050239745		2005-10-27	Abelson et al.	
	2	20080139531		2008-06-12	Yanni et al.	
	3	20090136598		2009-05-28	Chapin et al.	
	4	20090156568		2009-06-18	Hughes et al.	
/MCT/	5	20100010082		2010-01-14	CHONG et al.	

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
/MCT/	1	0214779	EP	B1	1987-03-18	Lever et al.		
/MCT/	2	0235796	EP	B2	1987-09-09	Oshima et al.		
/MCT/	3	0799044	EP	B1	1997-10-08	Yanni et al.		

EFS Web 2.1.17 ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /MCT/

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	Examiner Name	TRAN, MY CHAU T
	Attorney Docket Number	PAT903988-US-CNT

/MCT/	4	0078396	WO	A2	2000-12-28	Graff et al.		
/MCT/	5	0224116	WO	A1	2002-03-28	Shahinian		
/MCT/	6	9918963	WO		1999-04-22	Lisi		
/MCT/	7	2004024126	WO	A1	2004-03-25	Thompson et al.		
/MCT/	8	2011138801	WO	A1	2011-11-10	Khopade et al.		
/MCT/	9	2012159064	WO		2012-11-22	Alcon Research, Ltd.		

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
/MCT/	1	ABELSON et al., "Combined Analysis of Two Studies Using the Conjunctival Allergen Challenge Model to Evaluate Olopatadine Hydrochloride, a New Ophthalmic Antiallergic Agent With Dual Activity," American Journal of Ophthalmology, Volume 125, Number 6, pp. 797-804.	
/MCT/	2	ABELSON and ANDERSON, "Demystifying Dumulcents," Review of Ophthalmology, November 2006, pp. 122-125.	
/MCT/	3	ANSEL, Howard C., Pharmaceutical Calculations, 13th Ed., Wolters Kluwer, 2010, pp. 82-83.	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /MCT/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14304124
	Filing Date	2014-06-13
	First Named Inventor	Daniel A. Gamache
	Art Unit	1629
	Examiner Name	TRAN, MY CHAU T
	Attorney Docket Number	PAT903988-US-CNT

/MCT/	4	CHAUDHARI et al., "Solubility enhancement of hydrophobic drugs using synergistically interacting cyclodextrins and cosolvent," Current Science, 1586 Volume 92, Number 11, 10 June 2007; pp 1586-1591.	
/MCT/	5	CHOI, et al., "Late-phase reaction in ocular allergy," Current Opinion in Allergy and Clinical Immunology, 2008, Volume 8, pp. 438–444.	
/MCT/	6	GENNARO, Alfonso R., Remington: The Science and Practice of Pharmacy, Philadelphia College of Pharmacy and Science, 1995, Volume 1, pp. 613-627.	
/MCT/	7	GENNARO, Alfonso R., Remington: The Science and Practice of Pharmacy, Philadelphia College of Pharmacy and Science, 1995, Volume 2, pp. 1563-1576.	
/MCT/	8	HARADA, A., "Preparation and structures of supramolecules between cyclodextrins and polymers," Coordination Chemistry Reviews, 148, 1996, pp. 115-133.	
/MCT/	9	JANSOOK et al., "CDs as solubilizers: Effects of excipients and competing drugs," International Journal of Pharmaceutics, 379, 2009, pp. 32-40.	
/MCT/	10	LIDE, David R., CRC Handbook of Chemistry and Physics, CRC Press, 2006, pp. 6-4 – 6-5.	
/MCT/	11	LOFTSSON et al., "Cyclodextrins in eye drop formulations: enhanced topical delivery of corticosteroids to the eye," Acta Ophthamologica Scandinavica, 2002, pp. 144-150.	
/MCT/	12	LOFTSSON et al., "The effect of water-soluble polymers on the aqueous solubility and complexing abilities of ß-cyclodextrin," International Journal of Pharmaceutics, 1998, Volume 163, pp. 115-121.	
/MCT/	13	LOFTSSON, et al., "Pharmaceutical Applications of Cyclodextrins. 1. Drug Solubilization and Stabilization," Journal of Pharmaceutical Sciences, October 1996, Volume 85, Number 10, pp. 1017-1025.	
/MCT/	14	NANDI et al., "Synergistic Effect of PEG-400 and Cyclodextrin to Enhance Solubility of Progesterone," AAPS PharmSciTech 2003; 4 (1), pp 1-5.	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14304124
	Filing Date	2014-06-13
	First Named Inventor	Daniel A. Gamache
	Art Unit	1629
	Examiner Name	TRAN, MY CHAU T
	Attorney Docket Number	PAT903988-US-CNT

/MCT/	15	PATANOL® Label, Revised August 2002.	
/MCT/	16	PATADAY® Label, Revised August 2010.	
/MCT/	17	PATANASE® Label, Revised March 2008.	
/MCT/	18	Polyvinylpyrrolidone K 30, http://www4.mpbio.com/ecom/docs/proddata.nsf/(webtds2)/102787, pp. 1-2.	
/MCT/	19	PROUD, et al., "Inflammatory mediator release on conjunctival provocation of allergic subjects with allergent provocation of allergic subjects with allergen," Mediator generation in ocular allergy, 1989, Volume 85, Number 5, pp. 896-905.	
/MCT/	20	SHARIF, et al., "Characterization of the Ocular Antiallergic and Antihistaminic Effects of Olopatadine (AL-4943A), a Novel Drug for Treating Ocular Allergic Diseases," The Journal OF Pharmacology and Experimental Therapeutics, 1996, Volume 278, Number 3, pp. 1252-1261.	
/MCT/	21	SWEI, et al., "Viscosity Correlation for Aqueous Polyvinylpyrrolidone (PVP) Solutions," Journal of Applied Polymer Science, 2003, Volume 90, pp. 1153-1155.	
/MCT/	22	United States District Court for the District of Delaware, Complaint, Alcon Research, Ltd. v. Watson Laboratories, Inc. et al., December 16, 2015, pages 1-16.	
/MCT/	23	United States District Court for the District of Delaware, Defendants' Answer, Separate Defenses, and Counterclaims, Alcon Research, Ltd. v. Watson Laboratories, Inc. et al., February 29, 2016, pages 1-26.	
/MCT/	24	United States Patent and Trademark Office Before the Patent Trial and Appeal Board, Petition for Inter Partes Review, Argentum Pharmaceuticals LLC v. Alcon Research, Ltd., U.S. Patent No. 8,791,154, February 2, 2016, pages 1-60.	
/MCT/	25	WADE et al., "Ophthalmic antihistamines and H1–H4 receptors," Current Opinion in Allergy and Clinical Immunology, 2012, Volume 12, Number 5, pp. 510–516.	

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /MCT/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14304124
	Filing Date	2014-06-13
	First Named Inventor	Daniel A. Gamache
	Art Unit	1629
	Examiner Name	TRAN, MY CHAU T
	Attorney Docket Number	PAT903988-US-CNT

/MCT/	26	WATSON LABORATORIES, INC., Notification of Certification for U.S. Patent No. 8,791,154 Pursuant to § 505(j)(2)(B)(iv) of the Federal Food, Drug, and Cosmetic Act, November 3, 2015, pages 1-25.	

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/My Chau Tran/	Date Considered	07/25/2016

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

WEST Search History for Application 14304124

Creation Date: 2016072513:30

Interference Searches

Query	DB	Hits	Op.	Plur.	Thes.	Date
(A61K31/335 | A61K47/10 | A61K47/32 | A61K47/40 | A61K47/48969 | A61K9/0048 | A61K9/08 | B82Y5/00 | C08B37/0015 | C08L5/16)![CPC, CPCL]	PGPB	16352	ADJ	YES	ASSIGNEE	07-25-2016
(olopatadine same ((mass ratio) or dos $ 4 or concentrat $ 3 or ((weight or WT) same (percent or (per cent) or "%")))) and ((A61K31/335 | A61K47/10 | A61K47/32 | A61K47/40 | A61K47/48969 | A61K9/0048 | A61K9/08 | B82Y5/00 | C08B37/0015 | C08L5/16)![CPC, CPCL])	PGPB	71	ADJ	YES	ASSIGNEE	07-25-2016
(hydroxypropyl near3 cyclodextrin) and ((olopatadine same ((mass ratio) or dos $ 4 or concentrat $ 3 or ((weight or WT) same (percent or (per cent) or "%")))) and (A61K31/335 | A61K47/10 | A61K47/32 | A61K47/40 | A61K47/48969 | A61K9/0048 | A61K9/08 | B82Y5/00 | C08B37/0015 | C08L5/16)![CPC, CPCL])	PGPB	19	ADJ	YES	ASSIGNEE	07-25-2016
(polyvinylpyrrolidone same (benzalkonium chloride) same borate) and ((hydroxypropyl near3 cyclodextrin) and (olopatadine same ((mass ratio) or dos $ 4 or concentrat $ 3 or ((weight or WT) same (percent or (per cent) or "%")))) and (A61K31/335 | A61K47/10 | A61K47/32 | A61K47/40 | A61K47/48969 | A61K9/0048 | A61K9/08 | B82Y5/00 | C08B37/0015 | C08L5/16)![CPC, CPCL])	PGPB	2	ADJ	YES	ASSIGNEE	07-25-2016
(514/449, 450, 777, 778)![CCLS]	PGPB	3841	ADJ	YES	ASSIGNEE	07-25-2016
(olopatadine same ((mass ratio) or dos $ 4 or concentrat $ 3 or ((weight or WT) same (percent or (per cent) or "%")))) and ((514/449, 450, 777, 778)![CCLS])	PGPB	28	ADJ	YES	ASSIGNEE	07-25-2016
(hydroxypropyl near3 cyclodextrin) and ((olopatadine same ((mass ratio) or dos $ 4 or concentrat $ 3 or ((weight or WT) same (percent or (per cent) or "%")))) and	PGPB	5	ADJ	YES	ASSIGNEE	07-25-2016

(514/449, 450, 777, 778)![CCLS])						
(olopatadine same ((mass ratio) or dos $ 4 or concentrat $ 3 or ((weight or WT) same (percent or (per cent) or "%")))) and (hydroxypropyl near3 cyclodextrin)	PGPB	24	ADJ	YES	ASSIGNEE	07-25-2016
(polyvinylpyrrolidone same (benzalkonium chloride) same borate) and ((olopatadine same ((mass ratio) or dos $ 4 or concentrat $ 3 or ((weight or WT) same (percent or (per cent) or "%")))) and (hydroxypropyl near3 cyclodextrin))	PGPB	2	ADJ	YES	ASSIGNEE	07-25-2016

Prior Art Searches

Query	DB	Hits	Op.	Plur.	Thes.	Date
("20020006443" | "20020150616" | "20030170309" | "20050004074" | "20050191270" | "20050244472" | "20060210645" | "20070020336" | "20080132444" | "20090118262" | "20090232763" | "20090239842" | "20100240625" | "20100249062" | "20100324031" | "3767788" | "3843782" | "3856919" | "3931319" | "3947573" | "4027020" | "4120949" | "4283393" | "4407791" | "4470965" | "4525346" | "4836986" | "4923693" | "5037647" | "5068225" | "5116863" | "5134127" | "5141961" | "5300287" | "5376645" | "5472954" | "5591426" | "5597559" | "5624962" | "5888493" | "6153746" | "6511949" | "6828356" | "7074424" | "7147844" | "7429602" | "7635773" | "5874414" | "6280745" | "6407079" | "20040198828" | "5874418" | "20110082145" | "5641805" | "20120015953" | "20030055102" | "6995186").PN.	PGPB, USPT	57	ADJ	YES	ASSIGNEE	07-25-2016
olopatadine and (("20020006443" | "20020150616" | "20030170309" | "20050004074" | "20050191270" | "20050244472" | "20060210645" | "20070020336" | "20080132444" | "20090118262" | "20090232763" | "20090239842" | "20100240625" | "20100249062" | "20100324031" | "3767788" | "3843782" | "3856919" |	PGPB, USPT	10	ADJ	YES	ASSIGNEE	07-25-2016

"3931319" | "3947573" | "4027020" | "4120949" | "4283393" | "4407791" | "4470965" | "4525346" | "4836986" | "4923693" | "5037647" | "5068225" | "5116863" | "5134127" | "5141961" | "5300287" | "5376645" | "5472954" | "5591426" | "5597559" | "5624962" | "5888493" | "6153746" | "6511949" | "6828356" | "7074424" | "7147844" | "7429602" | "7635773" | "5874414" | "6280745" | "6407079" | "20040198828" | "5874418" | "20110082145" | "5641805" | "20120015953" | "20030055102" | "6995186").PN.)						
GAMACHE-DANIEL-A$.in.	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	500	ADJ	YES	ASSIGNEE	07-25-2016
ALANI-LAMAN$.in.	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	324	ADJ	YES	ASSIGNEE	07-25-2016
GHOSH-MALAY$.in.	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	143	ADJ	YES	ASSIGNEE	07-25-2016
GALAN-FRANCISCO-JAVIER$.in.	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	43	ADJ	YES	ASSIGNEE	07-25-2016
PERDIGUER-NURIA-CARRERAS$.in.		14	ADJ	YES	ASSIGNEE	07-25-2016

	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS					
SINGH-ONKAR-N$.in.	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	101	ADJ	YES	ASSIGNEE	07-25-2016
(GAMACHE-DANIEL-A$.in.) and (ALANI-LAMAN$.in.) and (GHOSH-MALAY$.in.) and (GALAN-FRANCISCO-JAVIER$.in.) and (PERDIGUER-NURIA-CARRERAS$.in.) and (SINGH-ONKAR-N$.in.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	1	ADJ	YES	ASSIGNEE	07-25-2016
(GAMACHE-DANIEL-A$.in.) and (ALANI-LAMAN$.in.) and (GHOSH-MALAY$.in.) and (GALAN-FRANCISCO-JAVIER$.in.) and (PERDIGUER-NURIA-CARRERAS$.in.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	1	ADJ	YES	ASSIGNEE	07-25-2016
(GAMACHE-DANIEL-A$.in.) and (ALANI-LAMAN$.in.) and (GHOSH-MALAY$.in.) and (GALAN-FRANCISCO-JAVIER$.in.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	10	ADJ	YES	ASSIGNEE	07-25-2016
(GAMACHE-DANIEL-A$.in.) and (ALANI-LAMAN$.in.) and (GHOSH-MALAY$.in.) and (GALAN-FRANCISCO-JAVIER$.in.) and (SINGH-ONKAR-N$.in.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD,	3	ADJ	YES	ASSIGNEE	07-25-2016

	FPRS					
olopatadine.clm. and (GAMACHE-DANIEL-A$.in.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	11	ADJ	YES	ASSIGNEE	07-25-2016
olopatadine.clm. and (ALANI-LAMAN$.in.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	3	ADJ	YES	ASSIGNEE	07-25-2016
olopatadine.clm. and (GHOSH-MALAY$.in.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	3	ADJ	YES	ASSIGNEE	07-25-2016
olopatadine.clm. and (GALAN-FRANCISCO-JAVIER$.in.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	3	ADJ	YES	ASSIGNEE	07-25-2016
olopatadine.clm. and (PERDIGUER-NURIA-CARRERAS$.in.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	1	ADJ	YES	ASSIGNEE	07-25-2016
olopatadine.clm. and (SINGH-ONKAR-N$.in.)	PGPB, USPT, USOC, EPAB, JPAB,	11	ADJ	YES	ASSIGNEE	07-25-2016

	DWPI, TDBD, FPRS					
ALCON RESEARCH$.as.	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	583	ADJ	YES	ASSIGNEE	07-25-2016
olopatadine.clm. and (ALCON RESEARCH$.as.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	12	ADJ	YES	ASSIGNEE	07-25-2016
(ophthalmic (formulation or composition)).clm. and (olopatadine.clm. and GAMACHE-DANIEL-A$.in.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	3	ADJ	YES	ASSIGNEE	07-25-2016
(ophthalmic (formulation or composition)).clm. and (olopatadine.clm. and SINGH-ONKAR-N$.in.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	2	ADJ	YES	ASSIGNEE	07-25-2016
(ophthalmic (formulation or composition)).clm. and (olopatadine.clm. and ALCON RESEARCH$.as.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	1	ADJ	YES	ASSIGNEE	07-25-2016
(A61K47/40 or B82Y5/00 or A61K47/10 or C08L5/16 or C08B37/0015 or A61K9/08 or A61K47/48969 or A61K47/32 or	PGPB, USPT, USOC	27110	ADJ	YES	ASSIGNEE	07-25-2016

A61K31/335 or A61K9/0048)![CPC, CPCL]						
(A61K31/335 | A61K47/40 | A61K9/0048 | A61K9/08)![CPC, CPCL]	PGPB, USPT, USOC	9095	ADJ	YES	ASSIGNEE	07-25-2016
(olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and ((A61K47/40 or B82Y5/00 or A61K47/10 or C08L5/16 or C08B37/0015 or A61K9/08 or A61K47/48969 or A61K47/32 or A61K31/335 or A61K9/0048)![CPC, CPCL])	PGPB, USPT, USOC	100	ADJ	YES	ASSIGNEE	07-25-2016
(hydroxypropyl near3 cyclodextrin) and ((olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and (A61K47/40 or B82Y5/00 or A61K47/10 or C08L5/16 or C08B37/0015 or A61K9/08 or A61K47/48969 or A61K47/32 or A61K31/335 or A61K9/0048)![CPC, CPCL])	PGPB, USPT, USOC	24	ADJ	YES	ASSIGNEE	07-25-2016
(polyvinylpyrrolidone same (benzalkonium chloride) same borate) and ((hydroxypropyl near3 cyclodextrin) and (olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and (A61K47/40 or B82Y5/00 or A61K47/10 or C08L5/16 or C08B37/0015 or A61K9/08 or A61K47/48969 or A61K47/32 or A61K31/335 or A61K9/0048)![CPC, CPCL])	PGPB, USPT, USOC	3	ADJ	YES	ASSIGNEE	07-25-2016
(olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and ((A61K31/335 | A61K47/40 | A61K9/0048 | A61K9/08)![CPC, CPCL])	PGPB, USPT, USOC	86	ADJ	YES	ASSIGNEE	07-25-2016
(hydroxypropyl near3 cyclodextrin) and ((olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and (A61K31/335 | A61K47/40 | A61K9/0048 | A61K9/08)![CPC, CPCL])	PGPB, USPT, USOC	24	ADJ	YES	ASSIGNEE	07-25-2016
(polyvinylpyrrolidone same (benzalkonium chloride) same borate) and	PGPB, USPT,	3	ADJ	YES	ASSIGNEE	07-25-2016

((hydroxypropyl near3 cyclodextrin) and (olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and (A61K31/335 | A61K47/40 | A61K9/0048 | A61K9/08)![CPC, CPCL])	USOC					
(((514/449) | (514/450)))![CCLS]	PGPB, USPT, USOC	4590	ADJ	YES	ASSIGNEE	07-25-2016
(((514/777) | (514/778)))![CCLS]	PGPB, USPT, USOC	2302	ADJ	YES	ASSIGNEE	07-25-2016
(olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and ((((514/449) | (514/450)))![CCLS])	PGPB, USPT, USOC	35	ADJ	YES	ASSIGNEE	07-25-2016
(hydroxypropyl near3 cyclodextrin) and ((olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and (((514/449) | (514/450)))![CCLS])	PGPB, USPT, USOC	6	ADJ	YES	ASSIGNEE	07-25-2016
(polyvinylpyrrolidone same (benzalkonium chloride) same borate) and ((hydroxypropyl near3 cyclodextrin) and (olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and (((514/449) | (514/450)))![CCLS])	PGPB, USPT, USOC	3	ADJ	YES	ASSIGNEE	07-25-2016
(olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and ((((514/777) | (514/778)))![CCLS])	PGPB, USPT, USOC	2	ADJ	YES	ASSIGNEE	07-25-2016
(olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and (hydroxypropyl near3 cyclodextrin)	EPAB, JPAB, DWPI, TDBD, FPRS	3	ADJ	YES	ASSIGNEE	07-25-2016
(olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and (hydroxypropyl near3 cyclodextrin)	PGPB, USPT, USOC	32	ADJ	YES	ASSIGNEE	07-25-2016
(polyvinylpyrrolidone same (benzalkonium chloride) same borate) and ((olopatadine same ((mass ratio) or dos$4	PGPB, USPT, USOC	3	ADJ	YES	ASSIGNEE	07-25-2016

or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and (hydroxypropyl near3 cyclodextrin))						
(CAC model) and ((olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and (hydroxypropyl near3 cyclodextrin))	PGPB, USPT, USOC	3	ADJ	YES	ASSIGNEE	07-25-2016
((CAC model) and (olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and (hydroxypropyl near3 cyclodextrin)) and @pd > 20160208	PGPB, USPT, USOC	0	ADJ	YES	ASSIGNEE	07-25-2016
("20050239745" | "20080139531" | "20090136598" | "20090156568" | "20100010082" | "4871865" | "5342620" | "5985310" | "6316483" | "7402609" | "7687646" | "7977376" | "8399508").PN.	PGPB, USPT	13	ADJ	YES	ASSIGNEE	07-25-2016
(olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and (("20050239745" | "20080139531" | "20090136598" | "20090156568" | "20100010082" | "4871865" | "5342620" | "5985310" | "6316483" | "7402609" | "7687646" | "7977376" | "8399508").PN.)	PGPB, USPT	5	ADJ	YES	ASSIGNEE	07-25-2016
(hydroxypropyl near3 cyclodextrin) and ((olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and ("20050239745" | "20080139531" | "20090136598" | "20090156568" | "20100010082" | "4871865" | "5342620" | "5985310" | "6316483" | "7402609" | "7687646" | "7977376" | "8399508").PN.)	PGPB, USPT	0	ADJ	YES	ASSIGNEE	07-25-2016

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CONFIRMATION NO. 1002

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
14/304,124	06/13/2014 RULE	514	1629	PAT903988-US-CNT

APPLICANTS
Alcon Research, Ltd., Fort Worth, TX;

INVENTORS
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Laman Alani, Fort Worth, TX;
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Francisco Javier Galan, Teia, SPAIN;
Nuria Carreras Perdiguer, Barcelona, SPAIN;
Onkar N. Singh, Arlington, TX;

**** CONTINUING DATA **************************
This application is a CON of 13/475,607 05/18/2012 PAT 8791154
which claims benefit of 61/548,957 10/19/2011
and claims benefit of 61/487,789 05/19/2011

**** FOREIGN APPLICATIONS **************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****
06/24/2014

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☐ No Verified and Acknowledged /MY-CHAU T TRAN/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		TX	5	25	4

ADDRESS
NOVARTIS PHARMACEUTICAL CORPORATION
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UNITED STATES

TITLE
HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION

FILING FEE RECEIVED		
2560	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

BIB (Rev. 05/07).

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14304124	GAMACHE ET AL.
	Examiner	Art Unit
	MY-CHAU T TRAN	1629

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	02/08/2016	07/25/2016							
	1	-								
	2	-								
	3	-								
	4	-								
	5	-								
	6	-								
	7	-								
	8	-								
	9	-								
	10	-								
	11	-								
	12	-								
	13	-								
	14	-								
	15	-								
	16	-								
	17	-								
	18	-								
	19	-								
	20	-								
	21	-								
	22	-								
	23	-								
	24	-								
	25	-								
	26	✓	=							
	27	✓	=							
	28	✓	=							
	29	✓	=							
	30	✓	=							
	31	✓	=							
	32	O	=							
	33	✓	=							
	34	✓	-							
	35	✓	=							
	36	✓	=							

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14304124	GAMACHE ET AL.
	Examiner	**Art Unit**
	MY-CHAU T TRAN	1629

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	02/08/2016	07/25/2016							
	37	✓	=							
	38	✓	=							
	39	O	=							

Session Began July 25, 2016 at 01:32 PM

Task Began July 25, 2016 01:33 PM

Explore references by patent: (ID 1)

Patent Number: US20140296328
Answer Type: *References*
Result Count: *1*

Detailed display

From ID: 1
Type: High concentration olopatadine ophthalmic composition

Retrieve substance information in 1 reference (ID 2)

From ID: 0
Uses
Answer Type: *Substances*
Result Count: *6*

Retrieve reference information in 6 substances (ID 3)

From ID: 2
Uses
Answer Type: *References*
Result Count: *247525*

Refine by research topic (ID 4)

Research Topic: olopatadine
From ID: 3
Answer Type: *References*
Result Count: *670*

Refine by research topic (ID 5)

Research Topic: polyvinylpyrrolidone
From ID: 4
Answer Type: *References*
Result Count: *38*

Refine by research topic (ID 6)

Research Topic: cyclodextrin
From ID: 5
Answer Type: *References*
Result Count: *7*

Refine by research topic (ID 7)

Research Topic: PEG
From ID: 6
Answer Type: *References*
Result Count: *5*

Detailed display

From ID: 7
Type: High concentration olopatadine ophthalmic composition

Detailed display

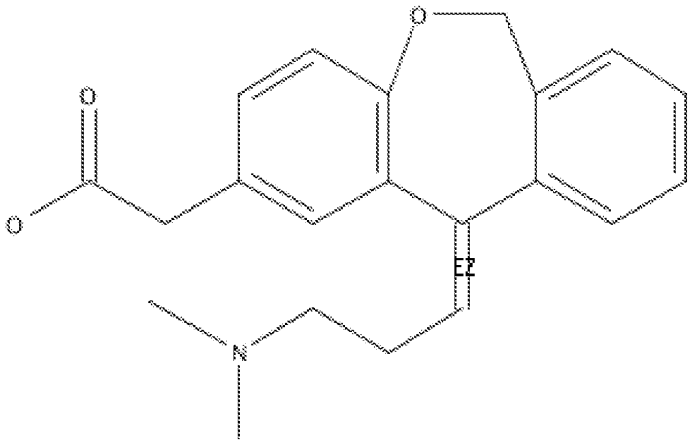
From ID: 7
Type: Ophthalmic formulation of a selective cyclooxygenase-2 inhibitory drug

Detailed display

From ID: 7
Type: Composition and method for topical treatment of tar-responsive dermatological disorders

Task Began July 25, 2016 01:37 PM

Explore substances by SUBSTRUCTURE



Candidates: *3*

Candidates Selected (ID 9)

Double bond geometry as drawn
No stereo in answer structure
Answer Type: *Substances*
Result Count: *188*

Retrieve reference information in 188 substances (ID 10)

From ID: 9
Uses
Answer Type: *References*
Result Count: *824*

Refine by research topic (ID 11)

Research Topic: olopatadine
From ID: 10
Answer Type: *References*
Result Count: *669*

Refine by research topic (ID 12)

Research Topic: polyvinylpyrrolidone
From ID: 11
Answer Type: *References*
Result Count: *37*

Refine by research topic (ID 13)

Research Topic: cyclodextrin
From ID: 12
Answer Type: *References*
Result Count: *7*

Detailed display

From ID: 13

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14304124	GAMACHE ET AL.
	Examiner	Art Unit
	MY-CHAU T TRAN	1629

CPC- SEARCHED		
Symbol	Date	Examiner
A61K47/40; B82Y5/00; A61K47/10; C08L5/16; C08B37/0015; A61K9/08; A61K47/48969; A61K47/32; A61K31/335; A61K9/0048	02/08/2016	MCT
UPDATED - see printout	07/25/2016	MCT

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
514	449, 450, 777, 778	02/08/2016	MCT
UPDATED	UPDATED - see printout	07/25/2016	MCT

SEARCH NOTES		
Search Notes	Date	Examiner
PALM Inventors; WEST - see printout; SciFinder - see printout	02/05/2016	MCT
Reviewed for ODP the following Patent(s) and/or Application(s): US 8,791,154 B2	02/07/2016	MCT
UPDATED - see printout	07/25/2016	MCT

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
514	449, 450, 777, 778; see printout	07/25/2016	MCT
A61K	47/40; 47/10; 9/08; 47/48969; 47/32; 31/335; 9/0048; see printout	07/25/2016	MCT
B82Y	5/00; see printout	07/25/2016	MCT
C08L	5/16; see printout	07/25/2016	MCT
C08B	37/0015; see printout	07/25/2016	MCT

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 NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/304,124	06/13/2014	Daniel A. Gamache	PAT903988-US-CNT	1002

7590 08/18/2016

NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 433/2
EAST HANOVER, NJ 07936-1080

EXAMINER	
TRAN, MY CHAU T	
ART UNIT	**PAPER NUMBER**
1629	
NOTIFICATION DATE	**DELIVERY MODE**
08/18/2016	ELECTRONIC

Letter Withdrawing a Notice Requiring Inventor's Oath or Declaration

The Notice Requiring Inventor's Oath or Declaration mailed on 8/9/16 was sent in error, and is hereby withdrawn. The time period set forth in the Notice of Allowance and Fee(s) Due to file a reply and pay the required fees continues to run from the mailing date of the Notice of Allowance and Fee(s) Due. Any time period set forth in the Notice of Allowability continues to run from the mailing date of the Notice of Allowability.

Questions relating to this Notice should be directed to the Application Assistance Unit at 571-272-4200.

(571)-272-4200 or 1(888)-786-0101
Patent Publication Branch
Office of Data Management

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14304124	GAMACHE ET AL.
	Examiner	**Art Unit**
	MY-CHAU T TRAN	1629

CPC							
Symbol						**Type**	**Version**
A61K		47	/	40		F	2013-01-01
A61K		9	/	0048		I	2013-01-01
A61K		31	/	335		I	2013-01-01
A61K		47	/	32		I	2013-01-01
A61K		9	/	08		I	2013-01-01
A61K		47	/	48969		I	2013-01-01
C08B		37	/	0015		I	2013-01-01
C08L		5	/	16		I	2013-01-01
A61K		47	/	10		I	2013-01-01
B82Y		5	/	00		I	2013-01-01
			/				
			/				
			/				
			/				
			/				

CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
			/					
			/					

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	13	
/MY-CHAU T TRAN/ Primary Examiner.Art Unit 1629	08/24/2016	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	26	NONE

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14304124	GAMACHE ET AL.
	Examiner	**Art Unit**
	MY-CHAU T TRAN	1629

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION	
CLASS	SUBCLASS	CLAIMED	NON-CLAIMED
514	450	A 61K 31 / 335 (2006.0)	
		A 01N 43 / 02 (2006.0)	
CROSS REFERENCE(S)		A 61K 47 / 00 (2006.0)	

CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				
514	449	777	778		

NONE	Total Claims Allowed:	
(Assistant Examiner) (Date)	13	
/MY-CHAU T TRAN/ Primary Examiner.Art Unit 1629 08/24/2016	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner) (Date)	26	NONE

U.S. Patent and Trademark Office Part of Paper No. 20160824

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14304124	GAMACHE ET AL.
	Examiner	**Art Unit**
	MY-CHAU T TRAN	1629

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1		17	8	33										
	2		18		34										
	3		19	9	35										
	4		20	10	36										
	5		21	11	37										
	6		22	12	38										
	7		23	13	39										
	8		24												
	9		25												
	10	1	26												
	11	2	27												
	12	3	28												
	13	4	29												
	14	5	30												
	15	6	31												
	16	7	32												

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 13	
/MY-CHAU T TRAN/ Primary Examiner.Art Unit 1629 (Primary Examiner)	08/24/2016 (Date)	O.G. Print Claim(s) 26	O.G. Print Figure NONE

U.S. Patent and Trademark Office Part of Paper No. 20160824

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/304,124	06/13/2014	Daniel A. Gamache	PAT903988-US-CNT	1002

1095 7590 09/06/2016

NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 433/2
EAST HANOVER, NJ 07936-1080

EXAMINER	
TRAN, MY CHAU T	

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
09/06/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

phip.patents@novartis.com

Supplemental Notice of Allowability	**Application No.** 14/304,124	**Applicant(s)** GAMACHE ET AL.	
	Examiner MY-CHAU T. TRAN	**Art Unit** 1629	**AIA (First Inventor to File) Status** No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *08/22/2016*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *26-33 and 35-39*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☒ Interview Summary (PTO-413), Paper No./Mail Date *08/24/2016* .
5. ☒ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/MY-CHAU T TRAN/
Primary Examiner, Art Unit 1629

EXAMINER'S AMENDMENT

1. The present application is being examined under the pre-AIA first to invent provisions.

2. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in an interview with Scott A. Chapple on 08/24/2016.

The application has been amended as follows:

In claim 35, the phrase '*claim 34*' has been replaced with the phrase --"**claim 33**"--.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MY-CHAU T. TRAN whose telephone number is 571-272-0810. The examiner can normally be reached on Monday - Friday: 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey S. Lundgren can be reached on 571-272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. If you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MY-CHAU T. TRAN/
Primary Examiner, Art Unit 1629

August 31, 2016

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	14/304,124	GAMACHE ET AL.	
	Examiner	Art Unit	
	MY-CHAU T. TRAN	1629	

All participants (applicant, applicant's representative, PTO personnel):

(1) *MY-CHAU T. TRAN*. (3)_____.

(2) *SCOTT A. CHAPPLE*. (4)_____.

Date of Interview: *24 August 2016*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *35*.

Identification of prior art discussed: *NONE*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

The examiner called Mr. Chapple to request permission to correct the dependency of instant claim 35, which is currently depends on cancelled claim 34. That is claim 35 will be amended to depend on claim 33 via an Examiner's amendment. Mr. Chapple agree with the amendment proposal.

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/MY-CHAU T TRAN/ Primary Examiner, Art Unit 1629	

PTO/SB/30 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Request for Continued Examination (RCE) Transmittal

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	14/304124
Filing Date	June 13, 2014
First Named Inventor	Carreras Perdiguer , Nuria et al.
Art unit	1629
Examiner Name	TRAN, MY CHAU T
Attorney Docket Number	PAT903988-US-CNT

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant must request non-entry of such amendment(s).
   - a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.
     - i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
     - ii. ☐ Other _____
   - b. ☒ Enclosed
     - i. ☐ Amendment/Reply
     - ii. ☐ Affidavit(s)/Declaration(s)
     - iii. ☒ Information Disclosure Statement (IDS)
     - iv. ☐ Other _____
2. Miscellaneous
   - a. ☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)
   - b. ☐ Other _____
3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.
   - a. ☒ The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. .
     - i. ☒ RCE fee required under 37 CFR 1.17(e)
     - ii. ☐ Extension of time fee (37 CFR 1.136 and 1.17)
     - iii. ☐ Other _____
   - b. ☐ Check in the amount of $_____ enclosed
   - c. ☐ Payment by credit card (Form PTO-2038 enclosed)

WARNING: Information on this form may become public. Credit Card information should not be included on this form. Provide credit card information and authorization on PTO-2038

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED			
Signature	/ Scott Chapple, 46,287 /	Date	12 October 2016
Name (Print/Type)	Scott A. Chapple	Registration No.	46,287

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

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
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	14304124
Filing Date	2014-06-13
First Named Inventor	Daniel A. Gamache
Art Unit	1629
Examiner Name	TRAN, MY CHAU T
Attorney Docket Number	PAT903988-US-CNT

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					

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

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FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

EFS Web 2.1.17

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14304124
	Filing Date	2014-06-13
	First Named Inventor	Daniel A. Gamache
	Art Unit	1629
	Examiner Name	TRAN, MY CHAU T
	Attorney Docket Number	PAT903988-US-CNT

	1	Petition for Inter Partes Review, Against Patent 8,791,154 by Argentum Pharmaceuticals LLC February 02 ,2016	
	2	Petition for Inter Partes Review, Against Patent 8,791,154 by Apotex Inc. and Apotex Corp. August 18 ,2016	
	3	Inter Partes Review No.2016-00544. Exhibit 1002: Declaration of Dr.Erning Xia.	
	4	Inter Partes Review No.2016-00544. Exhibit 1003: Declaration of Dr.Leonard Bielory.	
	5	Inter Partes Review No.2016-00544. Exhibit 1024: Curriculum Vitae for Dr.Erning Xia.	
	6	Inter Partes Review No.2016-00544. Exhibit 1025: Curriculum Vitae for Dr.Leonard Bielory.	
	7	Inter Partes Review No.2016-00544. Exhibit 1030: Alcon Research, Ltd. V. Apotex Inc., 687 F.3d 1362 (Fed. Cir. 2012).	
	8	Inter Partes Review No.2016-00544. Exhibit 1031: Alcon Research, Ltd. V. Apotex Inc., 790 F. Supp. 2d 868 (S.D. Ind. 2011).	
	9	Inter Partes Review No.2016-00544. Exhibit 1057: 21.C.F.R. § 349.12.	
	10	Inter Partes Review No.2016-00544. Exhibit 1060: 68 Fed. Reg. 106, 32981-32983	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14304124
	Filing Date	2014-06-13
	First Named Inventor	Daniel A. Gamache
	Art Unit	1629
	Examiner Name	TRAN, MY CHAU T
	Attorney Docket Number	PAT903988-US-CNT

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14304124
	Filing Date	2014-06-13
	First Named Inventor	Daniel A. Gamache
	Art Unit	1629
	Examiner Name	TRAN, MY CHAU T
	Attorney Docket Number	PAT903988-US-CNT

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/ Scott Chapple, 46,287 /	Date (YYYY-MM-DD)	2016-10-12
Name/Print	Scott Chapple	Registration Number	46,287

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	14304124
Filing Date:	13-Jun-2014
Title of Invention:	HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION
First Named Inventor/Applicant Name:	Daniel A. Gamache
Filer:	Scott Chapple/Ralph Falen
Attorney Docket Number:	PAT903988-US-CNT

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

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

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
RCE- 1st Request	1801	1	1200	1200
		Total in USD ($)		**1200**

Electronic Acknowledgement Receipt	
EFS ID:	27215088
Application Number:	14304124
International Application Number:	
Confirmation Number:	1002
Title of Invention:	HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION
First Named Inventor/Applicant Name:	Daniel A. Gamache
Customer Number:	1095
Filer:	Scott Chapple/Ralph Falen
Filer Authorized By:	Scott Chapple
Attorney Docket Number:	PAT903988-US-CNT
Receipt Date:	14-OCT-2016
Filing Date:	13-JUN-2014
Time Stamp:	12:06:12
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1200
RAM confirmation Number	101416INTEFSW00009157190134
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Continued Examination (RCE)	PAT903988_US_CNT_RCE.pdf	206912 f7eb1203d3fa507f7642b8ffe2b96f633688ae82	no	1
Warnings:					
This is not a USPTO supplied RCE SB30 form.					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	PAT903988_US_CNT_IDS.pdf	612704 fe1396266a17f0bd1ad864f0247a714522899fcf	no	5
Warnings:					
Information:					
A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
3	Non Patent Literature	Petition_IPR_Argentum.pdf	342233 66b47dc17d43e46aefad8b58b1af2d2291ee231	no	68
Warnings:					
Information:					
4	Non Patent Literature	Petition_IPR_ApotexINC_ApotexCorp.pdf	357545 d14862c891e998dc0a20418f59b13ea31b255dfe	no	68
Warnings:					
Information:					
5	Non Patent Literature	Declaration_Xia_1002_2016_.pdf	391392 a3f52158b60c28df63e175558b7e54335341c356	no	52
Warnings:					
Information:					

6	Non Patent Literature	Declaration_Bielory_1003_2016.pdf	1339712 4ae0673ef1bd348197e4acc9f63403e8e7473f68	no	43
Warnings:					
Information:					
7	Non Patent Literature	CV_Xia_1024_2016_.pdf	491920 017f6a20db34d001a4f81de5eb45be721d24989b	no	17
Warnings:					
Information:					
8	Non Patent Literature	CV_Bielory_1025_2016.pdf	1844906 4412de5cfe37d4622003de33512e29efd0d25b0f	no	45
Warnings:					
Information:					
9	Non Patent Literature	Alcon_Apotex_1030_2016_00544.pdf	560148 b378ba86fb7b41f36b0dd75eda1e6c6b1334a2d6	no	8
Warnings:					
Information:					
10	Non Patent Literature	Alcon_Apotex_1031_790F_2016_00544.pdf	1165179 eb5e4e54dd5befec480878f23b792f762850c8d1	no	60
Warnings:					
Information:					
11	Non Patent Literature	21_CFR_349_12_1057_2016_00544.pdf	1449916 400daac11c6df65c2d659428e7c2c258ca518e08	no	1
Warnings:					
Information:					
12	Non Patent Literature	68_Fed_Reg_1060_2016_00544.pdf	578104 8b0292e13a1b43f6a9f4489029f52735c375bc30	no	3
Warnings:					
Information:					

13	Fee Worksheet (SB06)	fee-info.pdf	30285 1addf0653bcc74e5b08561d724360b9fad6d50b8	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	9370956	

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

NOTICE OF ALLOWANCE AND FEE(S) DUE

1095 7590 11/16/2016

NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 433/2
EAST HANOVER, NJ 07936-1080

EXAMINER	
TRAN, MY CHAU T	
ART UNIT	PAPER NUMBER
1629	

DATE MAILED: 11/16/2016

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/304,124	06/13/2014	Daniel A. Gamache	PAT903988-US-CNT	1002

TITLE OF INVENTION: HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	02/16/2017

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (Rev. 02/11)

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

1095 7590 11/16/2016

NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 433/2
EAST HANOVER, NJ 07936-1080

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/304,124	06/13/2014	Daniel A. Gamache	PAT903988-US-CNT	1002

TITLE OF INVENTION: HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	02/16/2017

EXAMINER	ART UNIT	CLASS-SUBCLASS
TRAN, MY CHAU T	1629	514-450000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): (**Please first reapply any previously paid issue fee shown above**)

❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

❑ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

❑ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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 NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/304,124	06/13/2014	Daniel A. Gamache	PAT903988-US-CNT	1002

1095 7590 11/16/2016

NOVARTIS PHARMACEUTICAL CORPORATION
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ONE HEALTH PLAZA 433/2
EAST HANOVER, NJ 07936-1080

EXAMINER	
TRAN, MY CHAU T	
ART UNIT	PAPER NUMBER
1629	

DATE MAILED: 11/16/2016

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 02/11)

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 14/304,124	Applicant(s) GAMACHE ET AL.	
	Examiner MY-CHAU T. TRAN	Art Unit 1629	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *10/14/2016*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *26-33 and 35-39*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 10/14/2016
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☒ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/MY-CHAU T TRAN/
Primary Examiner, Art Unit 1629

EXAMINER'S COMMENT(S)

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 08/22/2016 has been entered.

Application and Claims Status

2. Claims 6-21, 23, 24, 26, 28, and 31 were pending and allowed. No claims have been amended, cancelled, and/or added. Therefore, claims 6-21, 23, 24, 26, 28, and 31 are currently pending and allowable.

3. The present application is being examined under the pre-AIA first to invent provisions.

Information Disclosure Statement

4. The information disclosure statement (IDS) that was filed on 10/14/2016 has been reviewed, and the references that have been considered are initialed as recorded in PTO-1449 forms.

REASONS FOR ALLOWANCE

5. The following is an examiner's statement of reasons for allowance:

a. Claims 26-32 are allowable for the reason that the cited prior arts submitted on 10/14/2016 in the Information Disclosure Statement (IDS) do not teach or suggest the claimed composition of claim 26.

b. Claims 33 and 35-39 are allowable for the reason that the cited prior arts submitted on 10/14/2016 in the Information Disclosure Statement (IDS) do not teach or suggest the claimed composition of claim 26.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MY-CHAU T. TRAN whose telephone number is 571-272-0810. The examiner can normally be reached on Monday - Friday: 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey S. Lundgren can be reached on 571-272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. If you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MY-CHAU T. TRAN/
Primary Examiner, Art Unit 1629

November 10, 2016

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14304124	GAMACHE ET AL.
	Examiner	**Art Unit**
	MY-CHAU T TRAN	1629

CPC									
Symbol								**Type**	**Version**
A61K		47	/	40				F	2013-01-01
A61K		9	/	0048				I	2013-01-01
A61K		31	/	335				I	2013-01-01
A61K		47	/	32				I	2013-01-01
A61K		9	/	08				I	2013-01-01
A61K		47	/	48969				I	2013-01-01
C08B		37	/	0015				I	2013-01-01
C08L		5	/	16				I	2013-01-01
A61K		47	/	10				I	2013-01-01
B82Y		5	/	00				I	2013-01-01
			/						
			/						
			/						
			/						
			/						

CPC Combination Sets									
Symbol								**Type**	**Set**	**Ranking**	**Version**
			/								
			/								

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	13	
/MY-CHAU T TRAN/ Primary Examiner.Art Unit 1629	10/31/2016	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	26	NONE

U.S. Patent and Trademark Office — Part of Paper No. 20161031

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14304124	GAMACHE ET AL.
	Examiner	**Art Unit**
	MY-CHAU T TRAN	1629

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION	
CLASS	SUBCLASS	CLAIMED	NON-CLAIMED
514	450	A 61K 31 / 335 (2006.0)	
		A 01N 43 / 02 (2006.0)	
CROSS REFERENCE(S)		A 61K 47 / 00 (2006.0)	

CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				
514	449	777	778		

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	13	
/MY-CHAU T TRAN/ Primary Examiner.Art Unit 1629	10/31/2016	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	26	NONE

U.S. Patent and Trademark Office — Part of Paper No. 20161031

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14304124	GAMACHE ET AL.
	Examiner	**Art Unit**
	MY-CHAU T TRAN	1629

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1		17	8	33										
	2		18		34										
	3		19	9	35										
	4		20	10	36										
	5		21	11	37										
	6		22	12	38										
	7		23	13	39										
	8		24												
	9		25												
	10	1	26												
	11	2	27												
	12	3	28												
	13	4	29												
	14	5	30												
	15	6	31												
	16	7	32												

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	13	
/MY-CHAU T TRAN/ Primary Examiner.Art Unit 1629	10/31/2016	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	26	NONE

U.S. Patent and Trademark Office Part of Paper No. 20161031

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14304124	GAMACHE ET AL.
	Examiner	Art Unit
	MY-CHAU T TRAN	1629

CPC- SEARCHED		
Symbol	Date	Examiner
A61K47/40; B82Y5/00; A61K47/10; C08L5/16; C08B37/0015; A61K9/08; A61K47/48969; A61K47/32; A61K31/335; A61K9/0048	02/08/2016	MCT
UPDATED - see printout	07/25/2016	MCT
UPDATED - see printout	10/31/2016	MCT

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
514	449, 450, 777, 778	02/08/2016	MCT
UPDATED	UPDATED - see printout	07/25/2016	MCT
UPDATED	UPDATED - see printout	10/31/2016	MCT

SEARCH NOTES		
Search Notes	Date	Examiner
PALM Inventors; WEST - see printout; SciFinder - see printout	02/05/2016	MCT
Reviewed for ODP the following Patent(s) and/or Application(s): US 8,791,154 B2	02/07/2016	MCT
UPDATED - see printout	07/25/2016	MCT
UPDATED - see printout	10/31/2016	MCT

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
514	449, 450, 777, 778; see printout	07/25/2016	MCT
A61K	47/40; 47/10; 9/08; 47/48969; 47/32; 31/335; 9/0048; see printout	07/25/2016	MCT

INTERFERENCE SEARCH			
US Class/ CPC Symbol	**US Subclass / CPC Group**	**Date**	**Examiner**
B82Y	5/00; see printout	07/25/2016	MCT
C08L	5/16; see printout	07/25/2016	MCT
C08B	37/0015; see printout	07/25/2016	MCT
UPDATED	UPDATED - see printout	10/31/2016	MCT

WEST Search History for Application 14304124

Creation Date: 2016103112:49

Interference Searches

Query	DB	Hits	Op.	Plur.	Thes.	Date
(A61K31/335 | A61K47/10 | A61K47/32 | A61K47/40 | A61K47/48969 | A61K9/0048 | A61K9/08 | B82Y5/00 | C08B37/0015 | C08L5/16)![CPC, CPCL]	PGPB	17156	ADJ	YES	ASSIGNEE	10-31-2016
(olopatadine same ((mass ratio) or dos $ 4 or concentrat $ 3 or ((weight or WT) same (percent or (per cent) or "%")))) and ((A61K31/335 | A61K47/10 | A61K47/32 | A61K47/40 | A61K47/48969 | A61K9/0048 | A61K9/08 | B82Y5/00 | C08B37/0015 | C08L5/16)![CPC, CPCL])	PGPB	74	ADJ	YES	ASSIGNEE	10-31-2016
(hydroxypropyl near3 cyclodextrin) and ((olopatadine same ((mass ratio) or dos $ 4 or concentrat $ 3 or ((weight or WT) same (percent or (per cent) or "%")))) and (A61K31/335 | A61K47/10 | A61K47/32 | A61K47/40 | A61K47/48969 | A61K9/0048 | A61K9/08 | B82Y5/00 | C08B37/0015 | C08L5/16)![CPC, CPCL])	PGPB	19	ADJ	YES	ASSIGNEE	10-31-2016
(polyvinylpyrrolidone same (benzalkonium chloride) same borate) and ((hydroxypropyl near3 cyclodextrin) and (olopatadine same ((mass ratio) or dos $ 4 or concentrat $ 3 or ((weight or WT) same (percent or (per cent) or "%")))) and (A61K31/335 | A61K47/10 | A61K47/32 | A61K47/40 | A61K47/48969 | A61K9/0048 | A61K9/08 | B82Y5/00 | C08B37/0015 | C08L5/16)![CPC, CPCL])	PGPB	2	ADJ	YES	ASSIGNEE	10-31-2016
((514/449 | 514/450 | 514/777 | 514/778))![CCLS]	PGPB	3838	ADJ	YES	ASSIGNEE	10-31-2016
(olopatadine same ((mass ratio) or dos $ 4 or concentrat $ 3 or ((weight or WT) same (percent or (per cent) or "%")))) and (((514/449 | 514/450 | 514/777 | 514/778))![CCLS])	PGPB	28	ADJ	YES	ASSIGNEE	10-31-2016
(hydroxypropyl near3 cyclodextrin) and ((olopatadine same ((mass ratio) or dos $ 4	PGPB	5	ADJ	YES	ASSIGNEE	10-31-2016

or concentrat $ 3 or ((weight or WT) same (percent or (per cent) or "%")))) and ((514/449 | 514/450 | 514/777 | 514/778))![CCLS])						
(olopatadine same ((mass ratio) or dos $ 4 or concentrat $ 3 or ((weight or WT) same (percent or (per cent) or "%")))) and (hydroxypropyl near3 cyclodextrin)	PGPB	24	ADJ	YES	ASSIGNEE	10-31-2016
(polyvinylpyrrolidone same (benzalkonium chloride) same borate) and ((olopatadine same ((mass ratio) or dos $ 4 or concentrat $ 3 or ((weight or WT) same (percent or (per cent) or "%")))) and (hydroxypropyl near3 cyclodextrin))	PGPB	2	ADJ	YES	ASSIGNEE	10-31-2016
((polyvinylpyrrolidone same (benzalkonium chloride) same borate) and (olopatadine same ((mass ratio) or dos $ 4 or concentrat $ 3 or ((weight or WT) same (percent or (per cent) or "%")))) and (hydroxypropyl near3 cyclodextrin)) and @ pd > 20160725	PGPB	0	ADJ	YES	ASSIGNEE	10-31-2016

Prior Art Searches

Query	DB	Hits	Op.	Plur.	Thes.	Date
("20020006443" | "20020150616" | "20030170309" | "20050004074" | "20050191270" | "20050244472" | "20060210645" | "20070020336" | "20080132444" | "20090118262" | "20090232763" | "20090239842" | "20100240625" | "20100249062" | "20100324031" | "3767788" | "3843782" | "3856919" | "3931319" | "3947573" | "4027020" | "4120949" | "4283393" | "4407791" | "4470965" | "4525346" | "4836986" | "4923693" | "5037647" | "5068225" | "5116863" | "5134127" | "5141961" | "5300287" | "5376645" | "5472954" | "5591426" | "5597559" | "5624962" | "5888493" | "6153746" | "6511949" | "6828356" | "7074424" | "7147844" | "7429602" | "7635773" | "5874414" | "6280745" | "6407079" | "20040198828" | "5874418" | "20110082145" | "5641805" | "20120015953" | "20030055102" | "6995186").PN.	PGPB, USPT	57	ADJ	YES	ASSIGNEE	10-31-2016

olopatadine and (("20020006443" | "20020150616" | "20030170309" | "20050004074" | "20050191270" | "20050244472" | "20060210645" | "20070020336" | "20080132444" | "20090118262" | "20090232763" | "20090239842" | "20100240625" | "20100249062" | "20100324031" | "3767788" | "3843782" | "3856919" | "3931319" | "3947573" | "4027020" | "4120949" | "4283393" | "4407791" | "4470965" | "4525346" | "4836986" | "4923693" | "5037647" | "5068225" | "5116863" | "5134127" | "5141961" | "5300287" | "5376645" | "5472954" | "5591426" | "5597559" | "5624962" | "5888493" | "6153746" | "6511949" | "6828356" | "7074424" | "7147844" | "7429602" | "7635773" | "5874414" | "6280745" | "6407079" | "20040198828" | "5874418" | "20110082145" | "5641805" | "20120015953" | "20030055102" | "6995186").PN.)	PGPB, USPT	10	ADJ	YES	ASSIGNEE	10-31-2016
GAMACHE-DANIEL-A$.in.	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	507	ADJ	YES	ASSIGNEE	10-31-2016
ALANI-LAMAN$.in.	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	332	ADJ	YES	ASSIGNEE	10-31-2016
GHOSH-MALAY$.in.	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	154	ADJ	YES	ASSIGNEE	10-31-2016
GALAN-FRANCISCO-JAVIER$.in.		43	ADJ	YES	ASSIGNEE	10-31-2016

	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS					
PERDIGUER-NURIA-CARRERAS$.in.	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	14	ADJ	YES	ASSIGNEE	10-31-2016
SINGH-ONKAR-N$.in.	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	105	ADJ	YES	ASSIGNEE	10-31-2016
(GAMACHE-DANIEL-A$.in.) and (ALANI-LAMAN$.in.) and (GHOSH-MALAY$.in.) and (GALAN-FRANCISCO-JAVIER$.in.) and (PERDIGUER-NURIA-CARRERAS$.in.) and (SINGH-ONKAR-N$.in.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	1	ADJ	YES	ASSIGNEE	10-31-2016
(GAMACHE-DANIEL-A$.in.) and (ALANI-LAMAN$.in.) and (GHOSH-MALAY$.in.) and (GALAN-FRANCISCO-JAVIER$.in.) and (PERDIGUER-NURIA-CARRERAS$.in.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	1	ADJ	YES	ASSIGNEE	10-31-2016
(GAMACHE-DANIEL-A$.in.) and (ALANI-LAMAN$.in.) and (GHOSH-MALAY$.in.) and (GALAN-FRANCISCO-JAVIER$.in.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD,	10	ADJ	YES	ASSIGNEE	10-31-2016

	FPRS					
(GAMACHE-DANIEL-A$.in.) and (ALANI-LAMAN$.in.) and (GHOSH-MALAY$.in.) and (GALAN-FRANCISCO-JAVIER$.in.) and (SINGH-ONKAR-N$.in.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	3	ADJ	YES	ASSIGNEE	10-31-2016
olopatadine.clm. and (GAMACHE-DANIEL-A$.in.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	11	ADJ	YES	ASSIGNEE	10-31-2016
olopatadine.clm. and (ALANI-LAMAN$.in.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	3	ADJ	YES	ASSIGNEE	10-31-2016
olopatadine.clm. and (GHOSH-MALAY$.in.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	3	ADJ	YES	ASSIGNEE	10-31-2016
olopatadine.clm. and (GALAN-FRANCISCO-JAVIER$.in.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	3	ADJ	YES	ASSIGNEE	10-31-2016
olopatadine.clm. and (PERDIGUER-NURIA-CARRERAS$.in.)	PGPB, USPT, USOC, EPAB, JPAB,	1	ADJ	YES	ASSIGNEE	10-31-2016

	DWPI, TDBD, FPRS					
olopatadine.clm. and (SINGH-ONKAR-N$.in.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	11	ADJ	YES	ASSIGNEE	10-31-2016
ALCON RESEARCH$.as.	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	611	ADJ	YES	ASSIGNEE	10-31-2016
olopatadine.clm. and (ALCON RESEARCH$.as.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	12	ADJ	YES	ASSIGNEE	10-31-2016
(ophthalmic (formulation or composition)).clm. and (olopatadine.clm. and GAMACHE-DANIEL-A$.in.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	3	ADJ	YES	ASSIGNEE	10-31-2016
(ophthalmic (formulation or composition)).clm. and (olopatadine.clm. and SINGH-ONKAR-N$.in.)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	2	ADJ	YES	ASSIGNEE	10-31-2016
(ophthalmic (formulation or composition)).clm. and (olopatadine.clm. and ALCON RESEARCH$.as.)	PGPB, USPT, USOC,	1	ADJ	YES	ASSIGNEE	10-31-2016

	EPAB, JPAB, DWPI, TDBD, FPRS					
(A61K47/40 or B82Y5/00 or A61K47/10 or C08L5/16 or C08B37/0015 or A61K9/08 or A61K47/48969 or A61K47/32 or A61K31/335 or A61K9/0048)![CPC, CPCL]	PGPB, USPT, USOC	28332	ADJ	YES	ASSIGNEE	10-31-2016
(A61K31/335 | A61K47/40 | A61K9/0048 | A61K9/08)![CPC, CPCL]	PGPB, USPT, USOC	9674	ADJ	YES	ASSIGNEE	10-31-2016
(olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and ((A61K47/40 or B82Y5/00 or A61K47/10 or C08L5/16 or C08B37/0015 or A61K9/08 or A61K47/48969 or A61K47/32 or A61K31/335 or A61K9/0048)![CPC, CPCL])	PGPB, USPT, USOC	104	ADJ	YES	ASSIGNEE	10-31-2016
(hydroxypropyl near3 cyclodextrin) and ((olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and (A61K47/40 or B82Y5/00 or A61K47/10 or C08L5/16 or C08B37/0015 or A61K9/08 or A61K47/48969 or A61K47/32 or A61K31/335 or A61K9/0048)![CPC, CPCL])	PGPB, USPT, USOC	26	ADJ	YES	ASSIGNEE	10-31-2016
(polyvinylpyrrolidone same (benzalkonium chloride) same borate) and ((hydroxypropyl near3 cyclodextrin) and (olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and (A61K47/40 or B82Y5/00 or A61K47/10 or C08L5/16 or C08B37/0015 or A61K9/08 or A61K47/48969 or A61K47/32 or A61K31/335 or A61K9/0048)![CPC, CPCL])	PGPB, USPT, USOC	3	ADJ	YES	ASSIGNEE	10-31-2016
(olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and ((A61K31/335 | A61K47/40 | A61K9/0048 | A61K9/08)![CPC, CPCL])	PGPB, USPT, USOC	89	ADJ	YES	ASSIGNEE	10-31-2016

(hydroxypropyl near3 cyclodextrin) and ((olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and (A61K31/335 | A61K47/40 | A61K9/0048 | A61K9/08)![CPC, CPCL])	PGPB, USPT, USOC	26	ADJ	YES	ASSIGNEE	10-31-2016
(polyvinylpyrrolidone same (benzalkonium chloride) same borate) and ((hydroxypropyl near3 cyclodextrin) and (olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and (A61K31/335 | A61K47/40 | A61K9/0048 | A61K9/08)![CPC, CPCL])	PGPB, USPT, USOC	3	ADJ	YES	ASSIGNEE	10-31-2016
((((514/449)) | ((514/450))))![CCLS]	PGPB, USPT, USOC	4588	ADJ	YES	ASSIGNEE	10-31-2016
((((514/777)) | ((514/778))))![CCLS]	PGPB, USPT, USOC	2300	ADJ	YES	ASSIGNEE	10-31-2016
(olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and (((((514/449)) | ((514/450))))![CCLS])	PGPB, USPT, USOC	35	ADJ	YES	ASSIGNEE	10-31-2016
(hydroxypropyl near3 cyclodextrin) and ((olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and ((((514/449)) | ((514/450))))![CCLS])	PGPB, USPT, USOC	6	ADJ	YES	ASSIGNEE	10-31-2016
(polyvinylpyrrolidone same (benzalkonium chloride) same borate) and ((hydroxypropyl near3 cyclodextrin) and (olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and ((((514/449)) | ((514/450))))![CCLS])	PGPB, USPT, USOC	3	ADJ	YES	ASSIGNEE	10-31-2016
(olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and (((((514/777)) | ((514/778))))![CCLS])	PGPB, USPT, USOC	2	ADJ	YES	ASSIGNEE	10-31-2016
(olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and (hydroxypropyl near3 cyclodextrin)	EPAB, JPAB, DWPI, TDBD, FPRS	3	ADJ	YES	ASSIGNEE	10-31-2016

(olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and (hydroxypropyl near3 cyclodextrin)	PGPB, USPT, USOC	33	ADJ	YES	ASSIGNEE	10-31-2016
(polyvinylpyrrolidone same (benzalkonium chloride) same borate) and ((olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and (hydroxypropyl near3 cyclodextrin))	PGPB, USPT, USOC	3	ADJ	YES	ASSIGNEE	10-31-2016
(CAC model) and ((olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and (hydroxypropyl near3 cyclodextrin))	PGPB, USPT, USOC	3	ADJ	YES	ASSIGNEE	10-31-2016
((CAC model) and (olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and (hydroxypropyl near3 cyclodextrin)) and @pd > 20160208	PGPB, USPT, USOC	0	ADJ	YES	ASSIGNEE	10-31-2016
("20050239745" | "20080139531" | "20090136598" | "20090156568" | "20100010082" | "4871865" | "5342620" | "5985310" | "6316483" | "7402609" | "7687646" | "7977376" | "8399508").PN.	PGPB, USPT	13	ADJ	YES	ASSIGNEE	10-31-2016
(olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and (("20050239745" | "20080139531" | "20090136598" | "20090156568" | "20100010082" | "4871865" | "5342620" | "5985310" | "6316483" | "7402609" | "7687646" | "7977376" | "8399508").PN.)	PGPB, USPT	5	ADJ	YES	ASSIGNEE	10-31-2016
(hydroxypropyl near3 cyclodextrin) and ((olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and ("20050239745" | "20080139531" | "20090136598" | "20090156568" | "20100010082" | "4871865" | "5342620" | "5985310" | "6316483" | "7402609" | "7687646" | "7977376" | "8399508").PN.)	PGPB, USPT	0	ADJ	YES	ASSIGNEE	10-31-2016
((hydroxypropyl near3 cyclodextrin) and (olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and	PGPB, USPT	0	ADJ	YES	ASSIGNEE	10-31-2016

("20050239745" | "20080139531" | "20090136598" | "20090156568" | "20100010082" | "4871865" | "5342620" | "5985310" | "6316483" | "7402609" | "7687646" | "7977376" | "8399508").PN.) and @pd > 20160725						
((CAC model) and (olopatadine same ((mass ratio) or dos$4 or concentrat$3 or ((weight or WT) same (percent or (per cent) or "%")))) and (hydroxypropyl near3 cyclodextrin)) and @pd > 20160725	PGPB, USPT	0	ADJ	YES	ASSIGNEE	10-31-2016

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United States Patent and Trademark Office
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BIB DATA SHEET

CONFIRMATION NO. 1002

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
14/304,124	06/13/2014 RULE	514	1629	PAT903988-US-CNT

APPLICANTS
Alcon Research, Ltd., Fort Worth, TX;

INVENTORS
Daniel A. Gamache, Arlington, TX;
Laman Alani, Fort Worth, TX;
Malay Ghosh, Fort Worth, TX;
Francisco Javier Galan, Teia, SPAIN;
Nuria Carreras Perdiguer, Barcelona, SPAIN;
Onkar N. Singh, Arlington, TX;

**** CONTINUING DATA ***************************
This application is a CON of 13/475,607 05/18/2012 PAT 8791154
which claims benefit of 61/548,957 10/19/2011
and claims benefit of 61/487,789 05/19/2011

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****
06/24/2014

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☐ No Verified and Acknowledged /MY-CHAU T TRAN/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		TX	5	25	4

ADDRESS
NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 433/2
EAST HANOVER, NJ 07936-1080
UNITED STATES

TITLE
HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION

FILING FEE RECEIVED		
2560	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

BIB (Rev. 05/07).

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	14304124
Filing Date	2014-06-13
First Named Inventor	Daniel A. Gamache
Art Unit	1629
Examiner Name	TRAN, MY CHAU T
Attorney Docket Number	PAT903988-US-CNT

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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
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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							

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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /MCT/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14304124
	Filing Date	2014-06-13
	First Named Inventor	Daniel A. Gamache
	Art Unit	1629
	Examiner Name	TRAN, MY CHAU T
	Attorney Docket Number	PAT903988-US-CNT

/MCT/	1	Petition for Inter Partes Review, Against Patent 8,791,154 by Argentum Pharmaceuticals LLC February 02 ,2016	
/MCT/	2	Petition for Inter Partes Review, Against Patent 8,791,154 by Apotex Inc. and Apotex Corp. August 18 ,2016	
/MCT/	3	Inter Partes Review No.2016-00544. Exhibit 1002: Declaration of Dr.Erning Xia.	
/MCT/	4	Inter Partes Review No.2016-00544. Exhibit 1003: Declaration of Dr.Leonard Bielory.	
/MCT/	5	Inter Partes Review No.2016-00544. Exhibit 1024: Curriculum Vitae for Dr.Erning Xia.	
/MCT/	6	Inter Partes Review No.2016-00544. Exhibit 1025: Curriculum Vitae for Dr.Leonard Bielory.	
/MCT/	7	Inter Partes Review No.2016-00544. Exhibit 1030: Alcon Research, Ltd. V. Apotex Inc., 687 F.3d 1362 (Fed. Cir. 2012).	
/MCT/	8	Inter Partes Review No.2016-00544. Exhibit 1031: Alcon Research, Ltd. V. Apotex Inc., 790 F. Supp. 2d 868 (S.D. Ind. 2011).	
/MCT/	9	Inter Partes Review No.2016-00544. Exhibit 1057: 21.C.F.R. § 349.12.	
/MCT/	10	Inter Partes Review No.2016-00544. Exhibit 1060: 68 Fed. Reg. 106, 32981-32983	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14304124
	Filing Date	2014-06-13
	First Named Inventor	Daniel A. Gamache
	Art Unit	1629
	Examiner Name	TRAN, MY CHAU T
	Attorney Docket Number	PAT903988-US-CNT

EXAMINER SIGNATURE			
Examiner Signature	/My Chau Tran/	Date Considered	10/31/2016

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14304124	GAMACHE ET AL.
	Examiner	**Art Unit**
	MY-CHAU T TRAN	1629

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	02/08/2016	07/25/2016	10/31/2016						
	1	-								
	2	-								
	3	-								
	4	-								
	5	-								
	6	-								
	7	-								
	8	-								
	9	-								
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	26	✓	=	=						
	27	✓	=	=						
	28	✓	=	=						
	29	✓	=	=						
	30	✓	=	=						
	31	✓	=	=						
	32	O	=	=						
	33	✓	=	=						
	34	✓	-							
	35	✓	=	=						
	36	✓	=	=						

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14304124	GAMACHE ET AL.
	Examiner	**Art Unit**
	MY-CHAU T TRAN	1629

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	02/08/2016	07/25/2016	10/31/2016						
	37	✓	=	=						
	38	✓	=	=						
	39	O	=	=						

PART B - FEE(S) TRANSMITTAL

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P.O. Box 1450
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or Fax | **(571)-273-2885**

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I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/304,124	06/13/2014	Daniel A. Gamache	PAT903988-US-CNT	1002

TITLE OF INVENTION: HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	02/16/2017

EXAMINER	ART UNIT	CLASS-SUBCLASS
TRAN, MY CHAU T	1629	514-450000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 Scott A. Chapple
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Alcon Research, Ltd.
(B) RESIDENCE: (CITY and STATE OR COUNTRY): Fort Worth, TX

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☑ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
- ☑ Issue Fee
- ☐ Publication Fee (No small entity discount permitted)
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5. **Change in Entity Status** (from status indicated above)
- ☐ Applicant certifying micro entity status. See 37 CFR 1.29
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- ☐ Applicant changing to regular undiscounted fee status.
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Authorized Signature Scott A. Chapple
Typed or printed name Scott A. Chapple
Date 22 November 2016
Registration No. 46287

Electronic Patent Application Fee Transmittal	
Application Number:	14304124
Filing Date:	13-Jun-2014
Title of Invention:	HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION
First Named Inventor/Applicant Name:	Daniel A. Gamache
Filer:	Scott Chapple/Cindy Klepacky
Attorney Docket Number:	PAT903988-US-CNT
Filed as Large Entity	
Filing Fees for Utility under 35 USC 111(a)	

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
UTILITY APPL ISSUE FEE	1501	1	960	960
PUBL. FEE- EARLY, VOLUNTARY, OR NORMAL	1504	1	0	0
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**960**

Electronic Acknowledgement Receipt	
EFS ID:	27585365
Application Number:	14304124
International Application Number:	
Confirmation Number:	1002
Title of Invention:	HIGH CONCENTRATION OLOPATADINE OPHTHALMIC COMPOSITION
First Named Inventor/Applicant Name:	Daniel A. Gamache
Customer Number:	1095
Filer:	Scott Chapple/Cindy Klepacky
Filer Authorized By:	Scott Chapple
Attorney Docket Number:	PAT903988-US-CNT
Receipt Date:	22-NOV-2016
Filing Date:	13-JUN-2014
Time Stamp:	12:25:03
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$960
RAM confirmation Number	112216INTEFSW00011588190134
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1	Issue Fee Payment (PTO-85B)	PAT903988_US_CNT_Notice_Allowance.pdf	66193 ff49a963982b0e2c1c6453eaef77cb5c14b4ccdd	no	1
Warnings:					
The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	32483 890a1bd7b9cdd8a9fc33b001b3200c6a917a844f	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	98676		

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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.

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Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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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	Tran, My Chau T.
Attorney Docket Number	PAT903988-US-NP

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
/MCT/ Change(s) applied to document, /K.S.S./ 8/22/2016	1	5874418 ~~5874414~~		1999-02-23	Stella et al. ~~Cydex, Inc.~~	
/MCT/	2	6280745	B1	2001-08-28	Flore et al. ~~Alliance Pharmaceutical Corp.~~	
/MCT/	3	6407079	B1	2002-06-18	Muller et al. ~~Janssen Pharmaceutica N.V.~~	

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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	1							☐

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/304,124	01/03/2017	9533053	PAT903988-US-CNT	1002

1095 7590 12/14/2016

NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 433/2
EAST HANOVER, NJ 07936-1080

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 117 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Daniel A. Gamache, Arlington, TX;
Alcon Research, Ltd., Fort Worth, TX;
Laman Alani, Fort Worth, TX;
Malay Ghosh, Fort Worth, TX;
Francisco Javier Galan, Teia, SPAIN;
Nuria Carreras Perdiguer, Barcelona, SPAIN;
Onkar N. Singh, Arlington, TX;

AO 120 (Rev. 08/10)

TO:	Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	3/24/2017	for the District of Delaware

PLAINTIFF	DEFENDANT
ALCON RESEARCH, LTD.	LUPIN LTD. and LUPIN PHARMACEUTICALS, INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	9,533,053 B2	1/3/2017	Alcon Research, Ltd.
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

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