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(71) Applicant *(for all designated States except US)*: **ALCON RESEARCH, LTD.** [US/US]; 6201 South Freeway, Mail Code TB4-8, Fort Worth, Texas 76134-2099 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **GAMACHE, Daniel A.** [US/US]; 5610 Hunterwood Lane, Arlington, Texas 76017 (US). **ALANI, Laman** [US/US]; 6809 Shadow Creek Court, Fort Worth, Texas 76132 (US). **GHOSH, Malay** [US/US]; 4221 Kirkland Court, Fort Worth, Texas 76109 (US). **GALÁN, Francisco Javier** [ES/ES]; c/ Dels Pins, 19, E-08329 Teià (ES). **PERDIGUER, Núria** [ES/ES]; Ametller, 9, E-08140 Calades de Montbui (ES). **SINGH, Onkar** [US/US]; 5606 Rachel Court, Arlington, Texas 76017 (US).

(74) Agents: **SCOTT A. CHAPPLE** et al.; Alcon Research, Ltd., IP Legal, Mail Code TB4-8, 6201 South Freeway, Fort Worth, Texas 76134-2099 (US).

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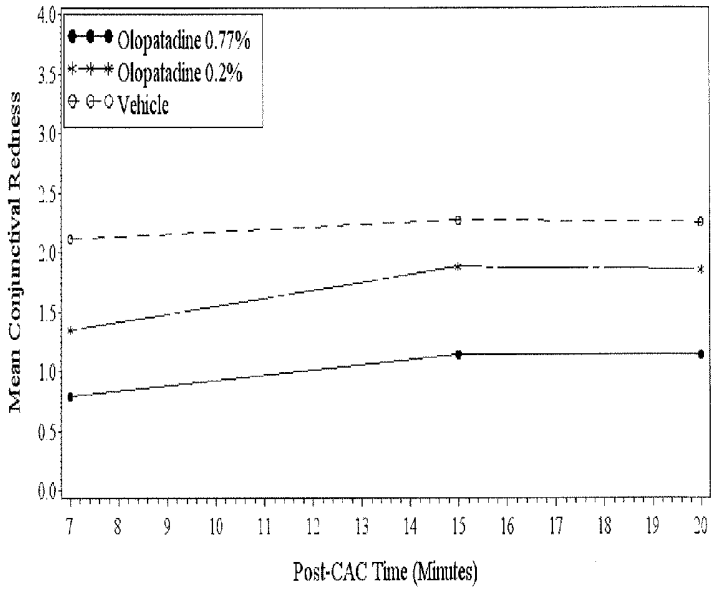

FIG. 1

(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.

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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

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