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(54) **OLOPATADINE COMPOSITIONS AND USES THEREOF**

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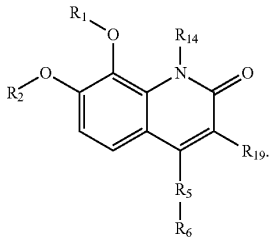
(57) **ABSTRACT**

The invention provides solution compositions comprising olopatadine and a PDE4 inhibitor compound of Formula I:

(Formula I)



The invention also provides methods for treating allergic and inflammatory diseases. More particularly, the present invention relates to formulations of olopatadine and their use for treating and/or preventing allergic or inflammatory disorders of the eye, nose, skin, and ear.

Plot of Olopatadine Free Base Solubility versus PDE4 Inhibitor Concentration (% w/v).

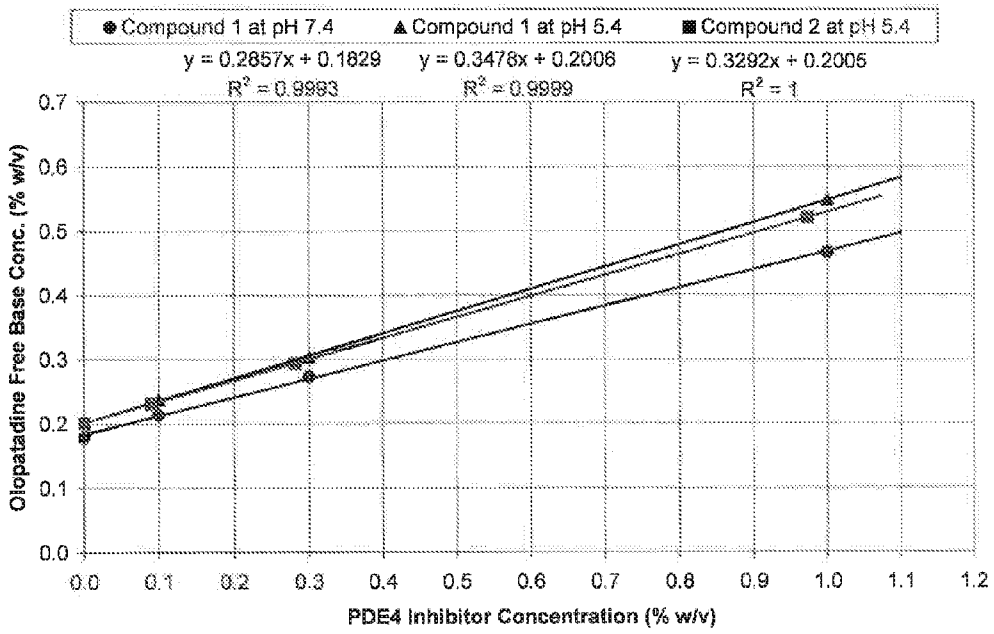


FIG. 1

Plot of Olopatadine Free Base Solubility versus PDE4 Inhibitor Concentration (milliMolar).

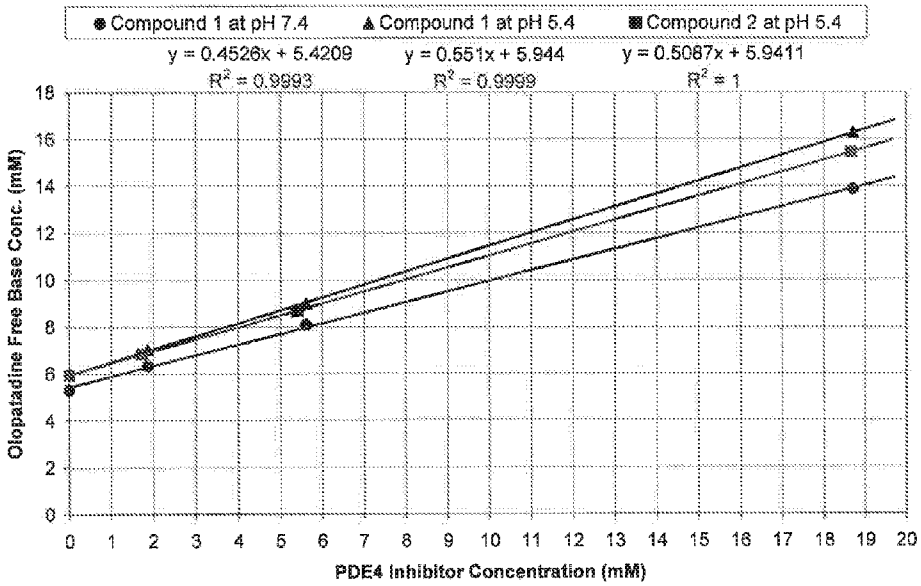


FIG. 2

OLOPATADINE COMPOSITIONS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims priority under 35 U.S.C. §119 to U.S. Provisional Patent Application No. 61/247,618 filed Oct. 1, 2009, the entire contents of which are incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to olopatadine formulations used for treating allergic and inflammatory diseases. More particularly, the present invention relates to formulations of olopatadine and their use for treating and/or preventing allergic or inflammatory disorders of the eye, ear, skin, and nose.

BACKGROUND OF THE INVENTION

[0003] As taught in U.S. Pat. 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 olopatadine (chemical name: Z-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepine-2-acetic 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, including nasal spray and ophthalmic formulations. See, for example, Col. 7, lines 7-26, and Examples 8 (H) and 8 (I) of the '865 patent.

[0004] U.S. Pat. No. 5,116,863, assigned to Kyowa Hakko Kogyo Co., Ltd., ("the Kyowa patent"), teaches that acetic acid derivatives of doxepin and, in particular, olopatadine, have anti-allergic and anti-inflammatory activity. 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.

[0005] U.S. Pat. No. 5,641,805, assigned to Alcon Laboratories, Inc. and Kyowa Hakko Kogyo Co., Ltd., teaches topical ophthalmic formulations containing olopatadine for treating allergic eye diseases. According to the '805 patent, the topical formulations may be solutions, suspensions or gels. The formulations contain olopatadine, an isotonic agent, and "if required, a preservative, a buffering agent, a stabilizer, a viscous vehicle and the like." See Col. 6, lines 30-43. "[P]olyvinyl alcohol, polyvinylpyrrolidone, polyacrylic acid or the like" are mentioned as the viscous vehicle. See Col. 6, lines 55-57.

[0006] Phosphodiesterase type-IV (PDE4 or PDE-IV) is the predominant cyclic nucleotide hydrolyzing enzyme found in inflammatory leukocytes, such as mast cells, neutrophils, monocytes and T-lymphocytes. PDE4 inhibitor compounds are known to be useful as anti-inflammatory and anti-allergy agents.

[0007] In general, it is more desirable for active ingredients [illegible] ture, easier to handle, provide better penetration to a target site of action, and provide better dosage consistency.

[0008] A formulation comprising both olopatadine and PDE4 inhibitor compounds is desirable because the combination addresses both the early and late phases of the allergic response. In addition, a formulation comprising compounds that enhance the solubility of olopatadine is desirable, because it assures that the olopatadine will not precipitate during a desired shelf life, and allows for an increased concentration of solubilized olopatadine.

SUMMARY OF THE INVENTION

[0009] The invention provides pharmaceutical aqueous solution compositions comprising olopatadine and a PDE4 inhibitor compound of Formula I, as provided herein. The invention also provides methods for treating allergic and inflammatory conditions of the eye, ear, skin, and nose. In one aspect, the concentration of olopatadine is at least 0.17% w/v, and the concentration of the PDE4 inhibitor compound of Formula I is at least 0.05% w/v in a solution composition.

[0010] Specific preferred embodiments of the invention will become evident from the following more detailed description of certain preferred embodiments and the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] FIG. **1** is a graph showing Olopatadine Free Base Solubility versus PDE4 Inhibitor Concentration (% w/v).

[0012] FIG. **2** is a graph showing Olopatadine Free Base Solubility versus PDE4 Inhibitor Concentration (milliMolar).

DETAILED DESCRIPTION OF THE INVENTION

[0013] The particulars shown herein are by way of example and for purposes of illustrative discussion of the preferred embodiments of the present invention only and are presented in the cause of providing what is believed to be the most useful and readily understood description of the principles and conceptual aspects of various embodiments of the invention. In this regard, no attempt is made to show structural details of the invention in more detail than is necessary for the fundamental understanding of the invention, the description taken with the drawings and/or examples making apparent to those skilled in the art how the several forms of the invention may be embodied in practice.

[0014] As used herein and unless otherwise indicated, the terms "a" and "an" are taken to mean "one", "at least One" or "one or more". Unless otherwise required by context, singular terms used herein shall include pluralities and plural terms shall include the singular.

[0015] Unless indicated otherwise, all component amounts provided herein are presented on a % (w/v) basis and all references to olopatadine are to olopatadine free base.

[0016] In certain embodiments, the invention provides solution compositions comprising a therapeutically effective amount of olopatadine and a PDE4 inhibitor compound of [illegible]

[0017] The term "therapeutically effective amount" refers to the amount of a solution composition of the invention, olopatadine, or a PDE4 inhibitor compound of Formula I determined to produce a therapeutic response in a mammal. Such therapeutically effective amounts are readily ascertained by one of ordinary skill in the art and using methods as described herein.

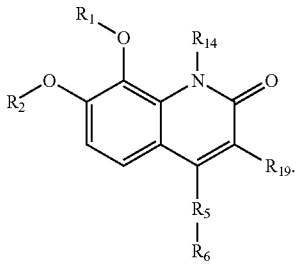
[0018] The terms "pharmaceutical aqueous solution composition" and "solution composition" as used herein refer to a composition comprising olopatadine or a pharmaceutically acceptable salt thereof, a PDE4 inhibitor compound of Formula I or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier (such as an ophthalmologic or nasal or otic carrier, or carrier suitable for delivery to the skin), excipient, or diluent as described herein that is capable of inducing a desired therapeutic effect (e.g. reducing, preventing, and/or eliminating allergies or allergy symptoms or inflammation) when properly administered to a patient. As used herein, the terms "pharmaceutical aqueous solution composition" and "solution composition" include compositions in which olopatadine (or a pharmaceutically acceptable salt thereof) and a PDE4 inhibitor compound of Formula I (or a pharmaceutically acceptable salt) are in solution, and wherein the overall composition is a solution, suspension, or semi-solid (for example cream, gel, or emulsion), depending on the presence or absence of any excipients in the composition.

[0019] As used herein, the term "pharmaceutically acceptable ophthalmologic or nasal or otic carrier" refers to those carriers that cause at most, little to no ocular, otic, or nasal irritation, provide suitable preservation if needed, and deliver olopatadine and a compound of Formula I in a homogenous dosage.

[0020] As used herein, the term "patient" includes human and animal subjects.

[0021] In one embodiment, a solution composition of the invention comprises a PDE4 inhibitor compound having structural Formula I:

(Formula I)



[0022] In certain embodiments:

[0023] R^1 and R^2 are independently selected from the group consisting of $—(CH_2)_sG^1G^2G^3$, acyl, acylalkyl, carboxyalkyl, cyanoalkyl, alkoxy, alkoxyalkyl, amidoalkyl, amino, alkyl, alkylalkoxy, aminoalkyl, alkenyl, alkynyl, carboxyl, carboxyalkyl, ether, heteroalkyl, heteroaryl, heteroaralkyl, and hydroxyalkyl, any of which may be optionally substituted;

[0024] s is 1-8;

[0025] G^1 is selected from the group consisting of alkoxy, amino, amido, carbonyl, hydroxy, ether, an amino acid, and null;

[0026] G^2 is selected from the group consisting of alkyl, alkoxy, amino, aryl, halo, haloalkyl, heterocycloalkyl, heteroaryl, carboxylalkylamino, guanidine, an amino acid, and null, any of which may be optionally substituted;

[0027] G^3 is selected from the group consisting of alkyl, alkoxy, amino, hydroxy, ether, carboxyl, hydroxamic acid, an amino acid, phosphonate, phosphoamide, and null, any of which may be optionally substituted;

[0028] R^5 is selected from the group consisting of $—(CR^8R^9)_mW(CR^{10}R^{11})_n—$ and $—(CR^{12}R^{13})_p—$;

[0029] W is selected from the group consisting of O, $N(R^7)$, $C(O)N(R^7)$, and SO_q;

[0030] m, n, and q are independently 0, 1 or 2;

[0031] p is 1 or 2;

[0032] R^6 is selected from the group consisting of carboxyl, alkylcarboxy, amido, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, acyl, and hydroxamic acid, any of which may be optionally substituted;

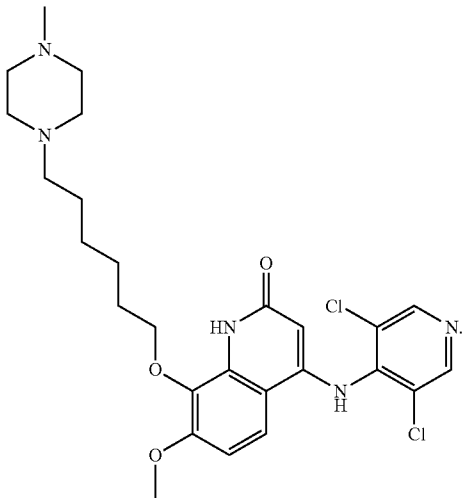
[0033] R^7 and R^{14} are independently selected from the group consisting of hydrogen, halogen, hydroxyl, lower alkyl, hydroxyalkyl, haloalkyl, and aminoalkyl;

[0034] R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} are independently selected from the group consisting of hydrogen and optionally substituted lower alkyl;

[0035] and R^{19} is selected from the group consisting of hydrogen, halogen, lower alkyl and haloalkyl; and

[0036] a pharmaceutically acceptable carrier or excipient.

[0037] In one embodiment, the PDE4 inhibitor compound of Formula I is (4-(3,5-Dichloropyridin-4-ylamino)-7-methoxy-8-(6-(4-methylpiperazin-1-yl)hexyloxy)quinolin-2 (1H)-one):



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