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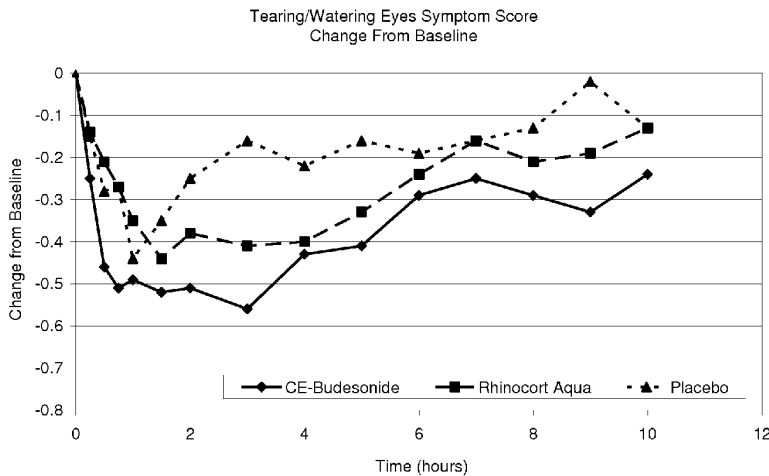
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(54) Title: NASAL AND OPHTHALMIC DELIVERY OF AQUEOUS CORTICOSTEROID SOLUTIONS

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FIG. 6E



(57) Abstract: The present invention is directed to methods of treating nasal and/or ophthalmic diseases, symptoms, or disorders that are therapeutically responsive to corticosteroid therapy by delivering aqueous solution formulations comprising a corticosteroid to nasal and ophthalmic tissues. The invention is also directed to methods, systems, devices, and compositions for delivering aqueous solution formulations comprising a corticosteroid and an antihistamine to nasal and ophthalmic tissues. watering eyes

Nasal and Ophthalmic Delivery of Aqueous Corticosteroid Solutions

FIELD OF THE INVENTION

The present invention is directed to methods of treating nasal and/or ophthalmic diseases, symptoms, or disorders that are therapeutically responsive to corticosteroid therapy by delivering aqueous solution formulations comprising a corticosteroid to nasal and ophthalmic tissues. The invention is also directed to methods, systems, devices, and compositions for delivering aqueous solution formulations comprising a corticosteroid and an antihistamine to nasal and ophthalmic tissues.

BACKGROUND OF THE INVENTION

The nasal administration of drugs allows for their deposition to the nose, sinuses, and other nasal cavities. Intranasal administration of drugs such as corticosteroids and antihistamines may be used to treat nasal symptoms including seasonal allergic rhinitis, perennial allergic rhinitis, perennial non-allergic rhinitis, nasal polyps, as well as prevention of post surgical polyps, chronic sinusitis, recurrent sinusitis, asthma, grass pollen rhinitis, hay fever, snoring, cluster headache, and other diseases and disorders.

The ophthalmic administration of drugs allows for their deposition to the eye, including the ocular mucosa, eye surface, cornea, conjunctiva, sclera, and posterior eye parts such as the retina, choroid, and vitreous and optic nerves, as well as tissues surrounding the eye. Ophthalmic administration of drugs such as corticosteroids and antihistamines may be used to treat ocular symptoms including conjunctivitis, inflammation of tissue(s) in the eye, dry eye, filamentary keratitis, delayed tear clearance, pain, keratoconjunctival dryness, keratoconjunctivitis sicca, lesions/tumors of the eye, infectious processes of the eye, bacterial infections, viral infections, glaucoma, uveitis, diabetic retinopathy, eye trauma, blepharitis, blepharoconjunctivitis, and other diseases or disorders.

Aqueous formulations containing a corticosteroid and a solubilizing agent have been prepared: Saidi et al. (U.S. Patent No. 6,241,969); Keller et al. (Respiratory Drug

Delivery IX (2004) 221-231); Lintz et al. (AAPS Annual Meeting and Exposition, Baltimore, Nov. 8, 2004; Poster M1128); Schuepp et al. (ATS 99th International Conference, Seattle, May 16th-21st, 2003; poster 1607); Russian Patent No. 2180217 to Chuchalin; U.S. Publication No. 2006/0045850; and Waldrep et al. (*J. Aerosol Med.* 5 (1994), 7(2), 135-145); PCT International Publications No. WO 06/108556, No. WO 03/35030, and No. WO 06/37246 and European Publications No. EP1894559 and No. EP1712220 to PARI Pharma GmbH.

Cyclodextrins have been included in nasal or ophthalmic compositions: Kaur et al. (*Curr. Drug Deliv.* (2004), 1(4), 351-360); Shimpi et al. (*Acta Pharm.* (2005), 55(2), 139-10 56); Viegas et al. (U.S. Patents No. 6,136,334, No. 5,587,175, and No. 5,958,443); Pate et al. (U.S. Patent No. 5,977,180); Loftsson et al. (*Acta Ophthalmol. Scand.* (2002), 80(2), 144-50).

Underivatized and derivatized cyclodextrins can be used to prepare aqueous formulations containing a corticosteroid: U.S. Patents No. 5,376,645 and No. 5,134,127 to 15 Stella et al.; U.S. Patent No. 5,914,122 to Otterbeck et al.; Worth et al. (*24th International Symposium on Controlled Release of Bioactive Materials* (1997)); Kinnarinen et al. (*11th International Cyclodextrin Symposium CD*, (2002)); U.S. Patent No. 5,472,954; U.S. patent No. 5,089,482; Zimmerer et al. in *Respiratory Drug Delivery IX* (2004) 461 – 464); Singh et al. (U.S. Patents No. 7,128,928 and No. 6,696,426); Loftsson (U.S. Patents No. 20 7,115,586, No. 5,472,954, and No. 5,324,718); Chang et al. (U.S. Patent No. 6,969,706); Beck et al. (U.S. Patents No. 6,723,353 and No. 6,358,935); Buchanan et al. (U.S. Patent No. 6,610,671); Pitha (U.S. Patents No. 6,576,261 and No. 5,935,941); Kis (U.S. Patent No. 6,468,548); Müller et al. (U.S. Patent No. 6,407,079); Wiebe et al. (U.S. Patent No. 5,739,121); Guy (U.S. Patent No. 5,576,311); Babcock et al. (U.S. Patent No. 5,538,721); 25 Folkman et al. (U.S. Patent No. 5,227,372); Lipari (U.S. Patent No. 4,383,992); PCT International Publication No. WO 2004/087043 to Sun Pharmaceutical Industries Ltd.; Saari et al. (*Graefes Arch. Clin. Exp. Ophthalmol.* (2006), 244(5), 620-6); Kristinsson et al. (*Invest. Ophthalmol. Vis. Sci.* (1996), 37(6), 1199-203); Usayapant et al. (*Pharm. Res.* (1991), 8(12), 1495-9); Bary et al. (*Eur. J. Pharm. Biopharm.* (2000), 50(2), 237-244); 30 U.S. Publication No. 2006/0193783; U.S. Publication No. 2002/0198174; European Publication No. EP 0435682; Lyons et al. (abstract in *AAPS Annual Meeting and Exposition*, Denver, CO USA, October 1-25, 2001); Amselem et al. (U.S. Patent No. 5,747,061).

Sulfoalkyl ether cyclodextrin derivatives can be used to prepare aqueous formulations containing a corticosteroid: U.S. Publication No. 2007/0020336; U.S. Publication No. 2006/0120967; U.S. Publication No. 2002/0150616 to Van de Cruys; U.S. Publications No. 20070249572, No. 20070197487, No. 20070197486, No. 20070191599, 5 No. 20070191327; No. 20070191323, No. 20070185066, No. 20070178050, No. 20070178049, and No. 20070160542 and PCT International Publications No. WO 07/95342, No. WO 07/95341, No. WO 07/95339, No. WO 07/75963, No. WO 07/75859, No. WO 07/75801, No. WO 07/75800, No. WO 07/75799, and No. WO 07/75798 to Hill; U.S. Publications No. 20070202054, No. 20070020299, No. 20070020298, and No. 10 20070020196, and PCT International Publications No. WO 08/05692, No. WO 08/05691, No. WO 08/05053, No. WO 05/065651, No. WO 05/065649, No. WO 05/065435 to Pipkin et al.; U.S. Publication No. 20060120967 and No. 20060045850 to Namburi et al.; and U.S. Publications No. 2005085446 and No. 20070049552 to Babu.

Corticosteroid-containing formulations for ophthalmic use have been described: 15 Pflugfelder et al. (U.S. Patent No. 6,153,607), Sackeyfio et al. (U.S. Patent No. 6,995,815), Guo et al. (U.S. Patent Nos. 6,548,078 and 6,217,895), Sher (U.S. Patent No. 6,117,907), Clarke et al. (U.S. Patent Nos. 5,358,943 and 4,945,089), Schwartz (U.S. Patent Nos. 5,212,168 and 4,904,649), and Saidi et al. (U.S. Patent No. 6,241,969).

The nasal and/or ophthalmic delivery of an aqueous solution formulation 20 comprising a corticosteroid as a therapeutic agent alone or in combination with another therapeutic agent, such as an antihistamine, for the treatment of allergy-related disorders or symptoms would be useful and especially desirable if it could provide an improved clinical benefit over the delivery of other formulations, such as suspension-based formulations.

25 **SUMMARY OF THE INVENTION**

The invention provides a method of treating, preventing or ameliorating in a subject a corticosteroid-responsive disease or disorder, meaning a disease or disorder in a subject that can be treated with a therapeutically effective amount of corticosteroid to provide a clinical or therapeutic benefit to the subject. In some embodiments, the 30 corticosteroid-responsive disease or disorder is a disease, disorder, symptom, or condition of the nose or eye.

The invention provides a method for treating an allergic symptom or disorder in a subject in need thereof, comprising:

nasally administering to the subject a corticosteroid solution comprising a therapeutically effective amount of a corticosteroid, SAE-CD, and a pharmaceutically acceptable aqueous liquid carrier,

wherein the corticosteroid solution provides more rapid relief from an allergic symptom or disorder compared to a corticosteroid suspension at the same unit dose.

In some embodiments, the allergic symptom or disorder includes a non-nasal symptom selected from the group consisting of itchy/gritty eyes, tearing/watery eyes, red/burning eyes, itchy eyes and palate, and combinations thereof.

The invention also provides a method for treating an ocular symptom or disorder in a subject in need thereof, comprising:

nasally administering to the subject a corticosteroid solution comprising a therapeutically effective amount of a corticosteroid, SAE-CD, and a pharmaceutically acceptable aqueous liquid carrier,

wherein the ocular symptom or disorder is itchy/gritty eyes, tearing/watery eyes, red/burning eyes, or a combination thereof.

The invention also provides a system for treating an allergic symptom or disorder in a subject in need thereof, comprising:

a corticosteroid solution comprising a therapeutically effective amount of a corticosteroid, a therapeutically effective amount of an antihistamine, SAE-CD, and a pharmaceutically acceptable aqueous liquid carrier, and

a metered dose device for nasal administration of the corticosteroid solution to the subject, wherein the corticosteroid solution is provided in the device.

In some embodiments, the system is for treating an ocular symptom or disorder in a subject in need thereof.

The invention also provides a metered dose device for nasal administration comprising a corticosteroid solution comprising a therapeutically effective amount of a corticosteroid, a therapeutically effective amount of an antihistamine, SAE-CD, and a pharmaceutically acceptable aqueous liquid carrier.

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