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(54) **Title:** INCLUSION COMPLEX

(57) **Abstract:** The invention relates to an inclusion complex of olopatadine or its pharmaceutically acceptable salt and hydroxyalkyl-ß-cylcodextrin, preferably hydroxypropyl-ß-cylcodextrin. The present invention also relates to an aqueous topical solution comprising a therapeutically effective amount of olopatadine or its pharmaceutically acceptable salt; hydroxyalkyl-ß-cylcodextrin, preferably hydroxypropyl-ß-cylcodextrin and hydroxypropyl methylcellulose in an amount sufficient to enhance the physical stability of the solution.

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INCLUSION COMPLEX

FIELD OF THE INVENTION

The present invention relates to inclusion complex of olopatadine in cyclodextrin and to aqueous solutions of olopatadine or its pharmaceutically acceptable salt for topical administration and process for preparation thereof.

BACKGROUND OF THE INVENTION

Olopatadine hydrochloride is a carboxylic acid derivative of doxepin, chemically described as (Z)-11-[3-(Dimethylamino) propylidene]-6,11-dihydrodibenz [b,e]oxepin-2-acetic acid hydrochloride [$C_{21}H_{23}NO_3$ .HCl], as disclosed in U.S. Pat Nos.4,871,865 and 4,923,892, both assigned to Burroughs Wellcome. Olopatadine has antihistaminic and antiasthmatic activity.

Olopatadine hydrochloride is commercially available in the U.S as 0.1% and 0.2% sterile ophthalmic solutions under the brand names PATANOL® and PATADAY® respectively, both marketed by Alcon. PATANOL® is indicated for the treatment of signs and symptoms of allergic conjunctivitis and the approved ophthalmic solution contains olopatadine hydrochloride equivalent to 0.1% olopatadine, 0.01% benzalkonium chloride as preservative, dibasic sodium phosphate, sodium chloride, hydrochloric acid and / or sodium hydroxide (to adjust the pH) and purified water. It has a pH of about 7, and osmolality of about 300mOsm/kg. PATADAY® is indicated for the treatment of ocular itching associated with allergic conjunctivitis and the approved ophthalmic solution contains olopatadine hydrochloride equivalent to 0.2% olopatadine, 0.01% benzalkonium chloride as preservative, povidone, dibasic sodium phosphate, sodium chloride, edetate disodium, hydrochloric acid and / or sodium hydroxide (to adjust the pH) and purified water. It has a pH of about 7, and osmolality of about 300mOsm/kg.

One obstacle for preparing olopatadine hydrochloride aqueous solutions for topical delivery is the stability of the aqueous solutions of olopatadine hydrochloride over the storage period. Olopatadine aqueous solutions having a concentrations of 0.17%w/v or higher were found to be

unstable over extended storage periods. The olopatadine hydrochloride precipitates or crystallizes out of the solution when used in concentrations higher than 0.17%w/v. Hence, there is a need for preparing aqueous solutions of olopatadine hydrochloride containing olopatadine in concentrations of about 0.17%w/v or greater, which are stable when stored over the shelf life of the product.

United States Patent No.6,995,186 (Alcon Inc., 2006, the '186 patent) discloses topically administrable solution composition for treating allergic or inflammatory disorders of the eye and nose comprising olopatadine and a polymeric ingredient, where the polymeric ingredient is a polymeric physical stability enhancing ingredient consisting essentially of polyvinylpyrrolidone or polystyrene sulfonic acid in an amount sufficient to enhance the physical stability of the solution, and wherein the composition does not contain polyvinyl alcohol, polyvinyl acrylic acid, hydroxypropyl methyl cellulose, sodium carboxymethyl cellulose, xanthan gum. Polyvinyl alcohol, polyvinyl acrylic acid, hydroxypropyl methylcellulose, sodium carboxy methyl cellulose and xanthan gum have been disclosed in the '186 patent to cause physical instability of olopatadine solutions.

In order to overcome the physical stability problems associated with olopatadine aqueous solutions, we have tried various ingredients selected from hydroxypropyl-β-cyclodextrin (HPβCD), polysorbate 20, polysorbate 80, propylene glycol, hydroxypropyl methylcellulose 2910 (HPMC E4M premium), polyvinylpyrrolidone K-30, xanthan gum, sodium carboxymethylcellulose (Sodium CMC), carbopol 934P, polyvinyl alcohol and mixtures thereof.

We have now surprisingly found that stable aqueous topical solutions of olopatadine hydrochloride can be prepared by forming an inclusion complex with a hydroxyalkyl clodextrin, preferably hydroxypropyl-β-cyclodextrin (HPβCD). Optionally, hydroxypropyl methylcellulose (HPMC') may be used to stabilize the inclusion complex in the pharmaceutical composition.

SUMMARY OF THE INVENTION

In one aspect of the invention, there is provided an inclusion complex of olopatadine or its pharmaceutically acceptable salt and a hydroxyalkyl cyclodextrin, preferably hydroxypropyl-β-cyclodextrin.

In another aspect of the invention, there is provided an aqueous topical solution comprising a therapeutically effective amount of olopatadine or its pharmaceutically acceptable salt; hydroxyalkyl β-cylcodextrin, preferably hydroxypropyl β-cylcodextrin and hydroxypropyl methyl cellulose in amount sufficient to enhance the physical stability of the solution.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides an inclusion complex of olopatadine or its pharmaceutically acceptable salt and hydroxyalkyl-β-cyclodextrin, particularly hydroxypropyl-β-cyclodextrin. The present invention also provides an aqueous topical solution, comprising a therapeutically effective amount of olopatadine or its pharmaceutically acceptable salt; hydroxyalkyl-β-cyclodextrin, particularly hydroxypropyl-β-cyclodextrin and hydroxypropyl methylcellulose in an amount sufficient to enhance the physical stability of the solution.

Unless indicated otherwise, all component concentrations are presented on a %(w/v) basis and all reference to olopatadine are to olopatadine free base.

The term "in an amount sufficient to enhance the physical stability of the solution", as used herein means that the amount of hydroxyalkyl-β-cyclodextrin, particularly hydroxypropyl-β-cyclodextrin is sufficient to form a complex with olopatadine or its pharmaceutically acceptable salt and thus keep it in solution, i.e. Prevent its precipitation or crystallization.

According to one embodiment of the present invention, the aqueous topical solution contains olopatadine or its pharmaceutically acceptable salts. 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. In a preferred embodiment of the present invention, the olopatadine for use in the aqueous topical solution is a hydrochloride salt. In a most preferred embodiment of the present invention, the olopatadine hydrochloride salt may be used in concentrations such that it is equivalent to the olopatadine free base in amount ranging from about 0.17% to about 0.62%. Preferably, the solution formulations intended for use in the eye contain about 0.17% to about 0.25% olopatadine and the solution formulations intended for use in the nose contain about 0.35% to about 0.62% olopatadine.

According to one embodiment of the present invention, the aqueous topical solution comprises cyclodextrin to enhance the physical stability of the solution. Cyclodextrins are a group of structurally related saccharides which are formed by enzymatic cyclization of starch by a group of amylases termed glycosyltransferases. Cyclodextrins are cyclic oligosaccharides, consisting of (alpha-1,4)-linked alpha-D-glucopyranose units, with a lipophilic central cavity and a hydrophilic outer surface. In aqueous solutions, cyclodextrins form inclusion complexes with many drugs through a process in which the water molecules located in the central cavity are replaced by either the whole drug molecule, or more frequently, by some lipophilic portion of the drug structure. Once included in the cyclodextrin cavity, the drug molecules may be dissociated through complex dilution, by replacement of the included drug by some other suitable molecule or, the drug may be transferred to the matrix for which it has the highest affinity. Importantly, since no covalent bonds are formed or broken during the drug-cyclodextrin complex formation, the complexes are in dynamic equilibrium with free drug and cyclodextrin molecules. In solution, the complexes are usually prepared by addition of an excess amount of the drug to an aqueous cyclodextrin solution. The most common naturally occurring cyclodextrins are alpha-

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