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(54) Title: EXTENDED RELEASE DOSAGE FORM CONTAINING OLOPATADINE FOR ORAL ADMINISTRATION

(57) Abstract: The present invention relates to extended-release dosage form for oral administration comprising olopatadine and the process of preparation of the same.

EXTENDED RELEASE DOSAGE FORM CONTAINING OLOPATADINE FOR ORAL ADMINISTRATION

Field of the Invention

The present invention relates to extended release dosage form for oral administration comprising olopatadine and the process of preparation of the same.

Background of the Invention

Drug products designed to reduce the frequency of dosing by modifying the rate of drug absorption are well known in the art as modified-release dosage forms. Many terms are used to describe modified-release dosage forms including extended-release, prolonged-release, controlled-release, slow-release and sustained-release which by definition have a reduced rate of release of active substance and hence these terms are, in general, interchangeable.

The various approaches for extended-release oral drug delivery systems; include: 1) a matrix based system, 2) a release-modifying film coated system; or 3) a multiparticulate system. The matrix system is based on hydrophilic polymers in which the drug and the hydrophilic polymers are mixed together and then formed as a tablet by a conventional compression process. The release of the drug from the matrix initializes with the diffusion of water into the matrix of the tablet which causes polymer in the matrix to swell. Thus, the drug gets dissolved and diffuses out to be absorbed. In a release-modifying film coated system the drug is formulated into a core (tablets or pellets) and is surrounded by a polymeric film. The film acts as a release rate-controlling barrier and controls the release of the drug from the core. The multiparticulate system is based on small beads, where each small bead is further composed of many layers. Some layers contain drug substance, others are rate-controlling polymers.

Extended-release pharmaceutical preparations regulate the release of the incorporated active ingredient(s) over time thereby improving therapeutic effectiveness and/or convenience objectives not offered by conventional dosage forms. It is widely known in the art that modified-release of active ingredient(s) improves patient's compliance by reducing the dosing frequency and attenuates adverse events related to fluctuations in drug plasma concentration due to immediate-release dosage forms. Hence,

it would be advantageous to formulate an extended-release dosage form for oral administration containing a drug, for example, olopatadine, or a pharmaceutically acceptable salt thereof.

Olopatadine is a selective histamine H1 receptor antagonist which has a inhibitory action on production/release of chemical mediators (leukotrienes, thromboxane and platelet aggregation factor). Olopatadine and its acid addition salt, metal salt, ammonium salt, organic amine addition salt and amino acid addition salt are disclosed in U.S. Patent No. 5,116,863. It also discloses pharmaceutical composition of olopatadine comprising a pharmaceutical carrier. European Patent No. EP 0 214 779 B1 describes olopatadine generically and a process of preparation of the same. Olopatadine is commercially available as the hydrochloride salt under the trade names Allelock® conventional tablets from Kyowa Hakko Kogyo Co., Ltd., in Japan as Pataday® ophthalmic solution for topical administration to the eyes from Alcon Laboratories Inc., USA, as Patanol® ophthalmic solution for topical administration to the eyes from Alcon Laboratories Inc., USA, and as Patanase® nasal spray, a metered-spray solution, for intranasal administration from Alcon Laboratories Inc., USA.

Allelock® conventional tablets are currently administered twice daily, in the morning and before going to bed. Hence, it would be advantageous to formulate once daily dosage regimen for olopatadine HCl as it would exhibit better patient compliance in outpatient therapy, thereby eliminating the complications and residual morbidity resulting from non-adherence with the prescribed medication. In general once daily formulation offers the advantage of patient compliance to an extent of 84%, while the twice and thrice daily regimens shows compliance only to an extent of 75% and 59%, respectively. The elimination half life of olopatadine is 8 hours to 12 hours in plasma which is entirely compatible, from the pharmacokinetic point of view, with the design of a once daily extended-release formulation. Olopatadine being a amphoteric compound with low lipophilicity, shows low incidence of CNS side effects. There are also references in the art which describe that an increased plasma concentration of olopatadine by 1.7 times, over that achieved by 5 mg twice daily formulation, do not cause a serious safety concern.

WO 2006/057769 discloses a method of delivering a nasal spray comprising the steps of providing a sprayer having a formulation comprising olopatadine and delivering a spray of said formulation to a subject's nose.

U.S. Patent No. 5,641,805 covers a method of treating allergic eye diseases in humans by topically administering to the eye a composition comprising a therapeutically effective amount of olopatadine or a pharmaceutically acceptable salt.

U.S. Patent No. 6,995,186 discloses a topically administrable solution composition for treating allergic or inflammatory disorders of the eye and nose comprising olopatadine and a polymeric ingredient, the improvement wherein the amount of olopatadine in the solution is 0.17 to 0.62% (w/v), 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.

In the present invention, the inventors describe an extended-release dosage form for oral administration comprising an effective amount of olopatadine or a pharmaceutically acceptable salt thereof.

Summary of the Invention

In one general aspect, the present invention provides for an extended-release dosage form for oral administration, which includes a therapeutically effective amount of olopatadine or a pharmaceutically acceptable salt thereof, a rate-controlling polymer, and one or more pharmaceutically acceptable excipient(s).

Embodiments of this aspect of the present invention may include one or more of the following features. For example, the rate-controlling polymer may be one or more of methylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, hydroxypropyl methylcellulose, xanthum gum, polyethylene oxide, ethylcellulose, cellulose acetate, polyvinyl pyrollidone, cellulose acetate phthalate, hydroxypropyl methylcellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl phthalate, hydroxypropylmethyl phthalate, hydroxypropyl methylcellulose acetate succinate, enteric grades of methacrylic acid and ammoniomethacrylic acid polymers, such as Eudragit® L30D-55, Eudragit® FS30D and combinations thereof.

Suitable one or more pharmaceutically acceptable excipient(s) include diluent(s), binder(s), lubricant(s) and glidant(s).

The extended release dosage form may be formulated with:

a) a tablet core, which includes olopatadine or a pharmaceutically acceptable salt thereof, and

b) a coating containing the rate controlling polymer over said core.

The extended-release dosage form may be formulated into pellets wherein each pellet includes an inert core onto which is applied a coating containing olopatadine or a pharmaceutically acceptable salt thereof and a binder; wherein said coated core is further coated with a coating of the rate-controlling polymer.

The extended release dosage form may be manufactured by dispersing olopatadine or pharmaceutically acceptable salt thereof in the rate-controlling polymer and one or more pharmaceutically acceptable excipient(s), including diluent(s), binder(s), lubricant(s) and glidant(s) and processing into a tablet.

The manufacturing process may further include applying a coating containing rate-controlling polymer(s) over the tablet core comprising olopatadine or a pharmaceutically acceptable salt thereof. The process may also include applying over each pellet a coating comprising olopatadine or a pharmaceutically acceptable salt thereof and a binder and onto which coated core is further applied a coating containing the rate-controlling polymer.

The extended-release dosage form of olopatadine should remain available in a therapeutically affective amount for a period of up to 24 hours to a human subject in need thereof.

Detailed Description of the Invention

As used herein, the term "extended-release dosage form" refers to a dosage form which maintains the therapeutic blood concentration of the drug over a prolonged period of time thereby reducing the dosing frequency of the drug. The extended-release dosage form can be further illustrated as a dosage form wherein the drug is dispersed in a rate-controlling polymer, or which has a core containing the drug and is further coated with a

rate-controlling polymer, or which has pellets wherein each pellet has an inert core containing the drug and is coated with a rate-controlling polymer.

The term "therapeutically effective amount", as used herein, refers to the amount of olopatadine or pharmaceutically acceptable salt thereof contained in the orally administered composition is of sufficient quantity to reduce, eliminate, treat, prevent or control the symptoms of a disease or condition affecting a human. Generally, the dosage may be between 1 and 100 mg; particularly, it may be between 1 and 50 mg; more particularly it may be between 1 and 20 mg.

The term "pharmaceutically acceptable salt", as used herein, refers to inorganic acid salts, such as hydrochloride, hydrobromide, sulfate and phosphate; organic acid salts, such as acetate, maleate, fumarate, tartrate and citrate. In one of the embodiments the salt form of olopatadine may be olopatadine hydrochloride.

The rate-controlling polymer may be both hydrophilic and hydrophobic polymers selected from one or more of methylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, hydroxypropyl methylcellulose, xanthum gum, polyethylene oxide, ethylcellulose, cellulose acetate, polyvinyl pyrollidone, and enteric polymers selected from one or more of cellulose acetate phthalate, hydroxypropyl methylcellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl phthalate, hydroxypropylmethyl phthalate, hydroxypropyl methylcellulose acetate succinate; enteric grades of methacrylic acid and ammoniomethacrylic acid polymers, such as Eudragit® L30D-55, Eudragit® FS30D, and combinations thereof.

Other pharmaceutically acceptable excipient(s) may be selected from diluent(s), binder(s), glidant(s), and lubricant(s).

The diluent(s) used may be selected from lactose, microcrystalline cellulose, starch, pregelatinized starch, calcium sulphate, calcium carbonate, kaolin, powered cellulose, polyols such as mannitol, sorbitol, xylitol, lactitol, dicalcium phosphate, tricalcium phosphate or combinations thereof.

The binder(s) used may be selected from carboxymethyl cellulose, methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, starch and its

derivative such as corn starch and pregelatinized starch, polyvinylpyrrolidone, polyethylene glycols, polyvinyl acetate, polyvinyl alcohol, or combinations thereof.

The glidant(s) used may be selected from colloidal silica, magnesium trisilicate, powdered cellulose, talc, tribasic calcium phosphate and the like. Colloidal silica may be colloidal silica anhydrous.

The lubricant(s) used may be selected from magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, powdered stearic acid, magnesium oleate, calcium palmitate, potassium laureate, and the like.

Suitable solvents for granulation or coating processes may include aqueous or non-aqueous solvent or mixtures thereof selected from one or more of methylene chloride, isopropyl alcohol, polyvinyl alcohol, acetone, methanol, ethanol, water, and combination thereof.

The extended-release dosage form may be prepared by employing conventional techniques known in the art, including dry granulation, wet granulation, direct compression and combinations thereof. The extended-release dosage form may be prepared by mixing a therapeutically effective amount of olopatadine or a pharmaceutically acceptable salt and rate-controlling polymer and other pharmaceutically acceptable excipients; further granulating the blend or directly compressing into a dosage form. The extended-release dosage form may also be obtained by coating the core or pellets containing olopatadine or pharmaceutically acceptable salt thereof with a rate-controlling coating containing the rate-controlling polymer wherein the coating excipient may further comprise of one or more of other film forming polymer(s) and plasticizer(s).

The film forming polymer(s) may be selected from one or more of hydroxypropyl methyl cellulose, hydroxypropyl cellulose, methyl hydroxyethyl cellulose, ethylcellulose and sodium carboxymethyl cellulose.

The plasticizer(s) may be selected from acetyltributyl citrate, acetyltriethyl citrate, castor oil, diacetylated monoglycerides, dibutyl sebacate, diethyl phthalate, glycerin, polyethylene glycol, triacetin, tributyl citrate, or triethyl citrate.

The pellets used for extended-release may be selected from one or more of non pareils seeds comprising sugar and corn starch, MCC pellet, starch pellet, glass pellets, and the like. In one of the embodiments the pellets may be sugar spheres.

In one embodiment, the process for preparing an extended-release dosage form for oral administration comprising of a therapeutically effective amount of olopatadine or a pharmaceutically acceptable salt thereof, a rate-controlling polymer, and other pharmaceutically acceptable excipients comprises of the following steps:

i. olopatadine or a pharmaceutically acceptable salt thereof and one or more of the pharmaceutically acceptable excipient(s) selected from diluent(s), binder(s) and glidant(s) are mixed in a suitable blender;

ii. the blended material of step (i) is roll compacted and sized in a suitable mesh to form granules;

iii. the granules of step (ii) are mixed with one or more of rate-controlling polymers and one or more of other pharmaceutical excipient(s); and

iv. the blend of step (iii) is lubricated with a suitable lubricant and compressed into a tablet using appropriate tooling.

In another embodiment, the process for preparing an extended-release dosage form for oral administration comprising of a therapeutically effective amount of olopatadine or a pharmaceutically acceptable salt thereof, a rate-controlling polymer, and other pharmaceutically acceptable excipients comprises of the following steps:

i. olopatadine or a pharmaceutically acceptable salt thereof, one or more of rate-controlling polymers; and one or more of the pharmaceutically acceptable excipient(s) selected from diluent(s), binder(s) and glidant(s) are mixed in a suitable blender;

ii. the blended material of step (i) is roll compacted and sized in a suitable mesh to form granules;

iii. the granules of step (ii) are optionally mixed with one or more of other pharmaceutical excipient(s); and

iv. the blend of step (iii) is lubricated with a suitable lubricant and compressed into a tablet using appropriate tooling.

In another embodiment, the process for preparing an extended-release dosage form for oral administration comprising of a therapeutically effective amount of olopatadine or a pharmaceutically acceptable salt thereof, a rate-controlling polymer, and other pharmaceutically acceptable excipients comprises of the following steps:

i. olopatadine or a pharmaceutically acceptable salt thereof, and one or more of the pharmaceutically acceptable excipient(s) selected from diluent(s) and binder(s) are mixed in a suitable blender;

ii. the blended material of step (i) is granulated with a suitable solvent;

iii. the granules of step (ii) are dried and sized;

iv. the dried granules of step (iii) are mixed with one or more of rate-controlling polymer; and one or more of other pharmaceutical excipient(s);

v. the granules of step (iv) are lubricated with a suitable lubricant and compressed into a tablet using appropriate tooling.

In another embodiment, the process for preparing an extended release dosage form for oral administration comprising of a therapeutically effective amount of olopatadine or a pharmaceutically acceptable salt thereof, a rate-controlling polymer, and other pharmaceutically acceptable excipients comprises of the following steps;

i. olopatadine or a pharmaceutically acceptable salt thereof, one or more of rate-controlling polymer, and one or more of the pharmaceutically acceptable excipient(s) selected from diluent(s) and binder(s) are mixed in a suitable blender;

ii. the blended material of step (i) is granulated with a suitable solvent;

iii. the granules of step (ii) are dried and sized;

iv. the dried granules of step (iii) are optionally mixed with one or more of other pharmaceutical excipient(s); and

v. the granules of step (iv) are lubricated with a suitable lubricant and compressed into a tablet using appropriate tooling.

In another embodiment, the process for preparing an extended-release dosage form for oral administration comprising of a therapeutically effective amount of olopatadine or a pharmaceutically acceptable salt thereof, a rate-controlling polymer, and other pharmaceutically acceptable excipients comprises of the following steps:

i. olopatadine or a pharmaceutically acceptable salt thereof and one or more of the pharmaceutically acceptable excipient(s) selected from diluent(s), and binder(s) are mixed in a suitable blender;

ii. the blend of step (i) is mixed with one or more of rate-controlling polymers, and one or more of other pharmaceutical excipient(s); and

iii. the blend of step (ii) is lubricated with a suitable lubricant and compressed into a tablet using appropriate tooling.

In yet another embodiment, the process for preparing an extended-release dosage form for oral administration comprising of a therapeutically effective amount of olopatadine or a pharmaceutically acceptable salt thereof, a rate-controlling polymer, and other pharmaceutically acceptable excipients comprises of the following steps:

i. olopatadine or a pharmaceutically acceptable salt thereof, one or more of rate-controlling polymer and one or more of the pharmaceutically acceptable excipient(s) selected from diluent(s) and binder(s) are mixed in a suitable blender;

ii. the blend of step (i) is optionally mixed with one or more of other pharmaceutical excipient(s); and

iii. the blend of step (ii) is lubricated with a suitable lubricant and compressed into a tablet using appropriate tooling.

In another embodiment, the process for preparing an extended-release dosage form for oral administration comprising of a therapeutically effective amount of olopatadine or a pharmaceutically acceptable salt thereof, a rate-controlling polymer, and other pharmaceutically acceptable excipients comprises of the following steps:

i. olopatadine or a pharmaceutically acceptable salt thereof and one or more of the pharmaceutically acceptable excipient(s) selected from diluent(s), binder(s), and glidant(s) are mixed in a suitable blender;

ii. the blend of step (i) is lubricated with a suitable lubricant and compressed into tablet with appropriate tooling; and

iii. to the compressed tablets of step (ii) a coating solution is applied comprising one or more of rate-controlling polymer(s) and other pharmaceutically acceptable excipient(s) in suitable solvent(s).

In a final embodiment, the process for preparing an extended-release dosage form for oral administration comprising of a therapeutically effective amount of olopatadine or a pharmaceutically acceptable salt thereof, a rate-controlling polymer, and other pharmaceutically acceptable excipients comprises of the following steps:

Step a.

i. olopatadine or its pharmaceutically acceptable salt thereof and one or more of polymeric binder(s) are dissolved or suspended in a suitable solvent and coated on sugar pellets to give a first type of pellets; and

ii. the drug layered pellets of step (i) are optionally seal coated with a film forming polymer.

Step b.

i. olopatadine or its pharmaceutically acceptable salt thereof and one or more of polymeric binder(s) are dissolved or suspended in a suitable solvent and coated on sugar pellets; and

ii. the coated pellets of step (i) are further coated with enteric polymer dissolved in a suitable solvent to give second type of pellets.

These two types of pellets can be mixed in different weight ratios to provide a desired dissolution profile or in-vivo profile.

The process for the preparation of an extended-release dosage form for oral administration comprising an effective amount of olopatadine or pharmaceutically

acceptable salt thereof is further illustrated by the following examples but should not be construed as limiting the invention.

Example 1

S. No.	Ingredients	mg/tab
Intra Granular		
1	Olopatadine HCl	10.00
2	Lactose Anhydrous	70.00
3	Silica, Colloidal Anhydrous	2.00
4	Povidone	2.00
5	Talc	0.50
6	Magnesium Stearate	0.50
Granule Weight		**85.00**
Extra Granular		
7	Lactose Anhydrous	7.00
8	Hyperomellose	85.00
9	Hydroxypropylcellulose	155.00
10	Povidone	13.00
11	Silica, Colloidal Anhydrous	1.00
12	Talc	2.00
13	Magnesium Stearate	2.00
Total Weight		**350.00**

Procedure:

Olopatadine hydrochloride and the other intra granular materials were dispensed in quantities as per the formula and then sifted through a suitable sieve. The shifted intra granular materials were mixed in a polybag for few minutes. The mixed material thus obtained were compacted in a roller compactor and suitably sized by passing through a suitable mesh to form granules. The shifted extra granular materials (except magnesium stearate) were mixed with the granules. Magnesium stearate was then added to the above mixed material and mixed for few minutes. The lubricated blend thus obtained was compressed into tablets using a suitable tooling.

Example 2

S. No.	Ingredients	mg/tab
Intra Granular		
1	Olopatadine HCl	10.00
2	Hypromellose	25.00
3	Lactose Monohydrate	30.00
4	Polyethylene Glycol	18.00
5	Microcrystalline Cellulose	50.00
6	Polyvinyl Alcohol	15.00
7	Purified Water	QS
Granule Weight		**148.00**
Extra Granular		
8	Magnesium Stearate	2.00
Total Weight		**150.00**

Procedure:

Olopatadine hydrochloride and the other intra granular materials were dispensed in quantities as per the formula and then sifted through a suitable sieve. Polyvinyl alcohol was dissolved in purified water under constant stirring to obtain polyvinyl alcohol solution. The shifted intra granular material obtained was granulated with polyvinyl alcohol solution and the wet mass was dried. The dried material was suitably sized by passing through a suitable mesh to form granules. The granules thus obtained were mixed with magnesium stearate. The lubricated blend thus obtained was compressed into tablets using a suitable tooling.

The extended-release compositions may also be prepared as coated tablet such as given below:

Example 3

S. No.	Name Of the Excipient	mg /tablet
Core		
1.	Olopatadine Hydrochloride	10.00
2.	Lactose Monohydrate	60.00
3.	Microcrystalline Cellulose	20.00
4.	Pregelatinised Starch	9.00
5.	Magnesium stearate	1.00
Core Tablet Weight		100.00
Coating Composition		
6.	Ethyl Cellulose	12.28
7.	Polyvinyl Pyrrolidone	6.05
8.	Dibutyl Sebacate	1.23
9.	Ethyl Alcohol	154.24
10.	Isopropyl Alcohol	8.12
Coated Tablet Weight		119.56

Procedure:

Olopatadine hydrochloride, lactose monohydrate, microcrystalline cellulose and pregelatinized starch are dispensed and shifted through a sieve of 40 mesh size. The shifted materials are mixed in a polybag. The blend is lubricated with shifted magnesium stearate. The lubricated blend is compressed into tablets using suitable tooling. The compressed tablets are applied with a coat with coating materials as per the formula given above.

Further, the extended-release compositions may also be prepared as pellets filled in a suitable capsule such as given below:

Example 4

S. No.	Name Of Excipient	mg/Capsule
Step I		
1.	Sugar Spheres (#18/22)	36.25
2.	Olopatadine	3.00
5.	Crospovidone	6.25
6.	Hypromellose	3.75
7.	Purified Water	QS
8.	Hypromellose	6.0
9.	Purified Water	QS
Step II		
1.	Sugar Spheres (#18/22)	36.25
2.	Olopatadine	3.00
3.	Crospovidone	6.25
4.	Hypromellose	3.75
5	Purified Water	QS
6.	Hypromellose Phthalate	4.325
7.	Diethyl Phthalate	0.425
8.	Acetone	QS
Step III		
1.	Sugar Spheres (#18/22)	36.25
2.	Olopatadine	4.00
3.	Crospovidone	6.25
4.	Hypromellose	3.75
5.	Purified Water	QS
6.	Eudragit® FS 30D	11.25
7.	Purified Water	QS

Procedure:

Step I:

Olopatadine hydrochloride, crospovidone and hypromellose solution or suspension in purified water is prepared and coated on sugar spheres. The drug layered pellets are seal coated with a coating containing hypromellose in purified water.

Step II:

Olopatadine hydrochloride, crospovidone and hypromellose solution or suspension in purified water are prepared and coated on sugar spheres. The drug layered pellets are seal coated with a coating containing hypromellose in purified water. Enteric coating containing hypromellose phthalate and diethyl phthalate dissolved in acetone, is applied over the seal coated pellets.

Step III:

Olopatadine hydrochloride, crospovidone and hypromellose solution or suspension in purified water is prepared and coated on sugar spheres. The drug layered pellets are seal coated with a coating containing hypromellose in purified water. Enteric coating containing Eudragit® FS 30D dissolved in purified water is applied over the hyperomellose seal coat.

Step IV:

The pellets obtained from Step I, II and III are mixed and filled in suitable capsules.

Example 5

S. No.	Ingredients	mg/tab
Intra Granular		
1	Olopatadine Hcl	10.00
2	Hypromellose	25.00
3	Lactose Monohydrate	66.00
4	Microcrystalline Cellulose	35.00
5	Povidone	10.00
6	Purified Water	QS
Granule Weight		**146.00**
Extra Granular		
7	Colloidal Silicon Dioxide	2.00
8	Magnesium Stearate	2.00
Total Weight		**150.00**

Procedure:

Olopatadine hydrochloride, lactose monohydrate, microcrystalline cellulose, hypromellose and povidone were sifted through suitable mesh screen and mixed in a rapid mixer granulator and granulated with purified water. The granules were dried and mixed with colloidal silicon dioxide and magnesium stearate. The final blend was compressed into tablets using a suitable tooling.

We claim:

1. A extended-release dosage form for oral administration comprising of a therapeutically effective amount of olopatadine or a pharmaceutically acceptable salt thereof, a rate-controlling polymer, and one or more pharmaceutically acceptable excipient(s).

2. The extended-release dosage form according to claim 1, wherein the rate-controlling polymer comprises one or more of methylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, hydroxypropyl methylcellulose, xanthum gum, polyethylene oxide, ethylcellulose, cellulose acetate, polyvinyl pyrollidone, cellulose acetate phthalate, hydroxypropyl methylcellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl phthalate, hydroxypropylmethyl phthalate, hydroxypropyl methylcellulose acetate succinate, enteric grades of methacrylic acid and ammoniomethacrylic acid polymers, such as Eudragit® L30D-55, Eudragit® FS30D and combinations thereof.

3. The extended-release dosage form according to claim 1, wherein the one or more pharmaceutically acceptable excipient(s) comprises diluent(s), binder(s), lubricant(s) and glidant(s).

4. The extended-release dosage form according to claim 1, wherein the extended release dosage form comprises of:

a) a tablet core, which comprises olopatadine or a pharmaceutically acceptable salt thereof, and

b) a coating containing the rate controlling polymer over said core.

5. The extended-release dosage form according to claim 1, wherein the extended-release dosage form comprises pellets wherein each pellet comprises an inert core onto which is applied a coating containing olopatadine or a pharmaceutically acceptable salt thereof and a binder and the said coated core is further coated with a coating containing the rate-controlling polymer.

6. A process of preparing an extended release dosage according to claim 1, wherein the process comprises of dispersing olopatadine or pharmaceutically acceptable salt thereof in the rate-controlling polymer and one or more pharmaceutically

acceptable excipient(s) selected from diluent(s), binder(s), lubricant(s) and glidant(s) and processing into a tablet.

7. A process of preparing an extended release dosage according to claim 4, wherein the process comprises of applying a coating containing rate-controlling polymer(s) over the tablet core comprising olopatadine or a pharmaceutically acceptable salt thereof.

8. A process of preparing an extended release dosage form according to claim 5, wherein the process comprises applying over each pellet a coating comprising olopatadine or a pharmaceutically acceptable salt thereof and a binder and onto which coated core is further applied a coating containing the rate-controlling polymer.

9. The extended-release dosage form according to claim 1, wherein the olopatadine remains available in a therapeutically affective amount for a period of up to 24 hours to a human subject in need thereof.

10. An extended-release dosage form for oral administration comprising of a therapeutically effective amount of olopatadine or a pharmaceutically acceptable salt thereof, a rate-controlling polymer, and other pharmaceutically acceptable excipients substantially as described and exemplified herein.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2010/053962

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K31/335
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

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)
EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/002093 A1 (ALCON INC [CH]; CASTILLO ERNESTO J [US]; HAN WESLEY WEHSIN [US]; ZHANG) 9 January 2003 (2003-01-09) claims 1-14 tables 1-12	1-10
X	DE 10 2005 005446 A1 (GRUENENTHAL GMBH [DE]) 10 August 2006 (2006-08-10) paragraph [0040] - paragraph [0056] claims 1-15	1-10
X	WO 2007/125545 A2 (PANACEA BIOTEC LTD [IN]; SINGH AMARJIT [IN]; SINGH SARABJIT [IN]; PUTH) 8 November 2007 (2007-11-08) claims 1-22 examples 1,2	1-10

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[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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"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

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"&" 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 November 2010	01/12/2010

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	Schifferer, Hermann

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2010/053962

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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