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(54) Titre : COMPOSITION STABLE DE DOSE ORALE A LIBERATION PROLONGEE COMPRENANT DE LA DESLORATADINE ET DE LA PSEUDOEPHEDRINE

(54) Title: STABLE EXTENDED RELEASE ORAL DOSAGE COMPOSITION COMPRISING DESLORATADINE AND PSEUDOEPHEDRINE

(57) Abrégé/Abstract:
A film-coated extended release solid oral dosage composition containing a nasal decongestant, pseudoephedrine or salt thereof, e.g., pseudoephedrine sulfate in a core effective to provide a geometric maximum plasma concentration of pseudoephedrine of about 345 ng/mL to about 365 ng/mL at a time of about 7.60 hrs to about 8.40 hrs and having two or three film-coatings on thecore, the second one containing an amount of the non-sedating antihistamine, desloratadine, effective to provide a geometric maximum plasma concentration of desloratadine of about 2.15 ng/mL to about 2.45 ng/mL at a time of about 4.0 hours to about 4.5 hours, and use of the composition for treating patients showing the signs and symptoms associated with allergic and/or inflammatory conditions of the skin and airway passages are disclosed.

ABSTRACT

A film-coated extended release solid oral dosage composition containing a nasal decongestant, pseudoephedrine or salt thereof, e.g., pseudoephedrine sulfate in a core effective to provide a geometric maximum plasma concentration of pseudoephedrine of about 345 ng/mL to about 365 ng/mL at a time of about 7.60 hrs to about 8.40 hrs and having two or three film-coatings on thecore, the second one containing an amount of the non-sedating antihistamine, desloratadine, effective to provide a geometric maximum plasma concentration of desloratadine of about 2.15 ng/mL to about 2.45 ng/mL at a time of about 4.0 hours to about 4.5 hours, and use of the composition for treating patients showing the signs and symptoms associated with allergic and/or inflammatory conditions of the skin and airway passages are disclosed.

STABLE EXTENDED RELEASE ORAL DOSAGE COMPOSITION COMPRISING DESLORATADINE AND PSEUDOEPHEDRINE

BACKGROUND OF THE INVENTION

This invention relates to a film-coated extended release solid oral dosage composition containing a nasal decongestant, e.g., pseudoephedrine in a controlled release core and a film outer coating containing the non-sedating antihistamine, desloratadine. The solid oral dosage compositions of this invention are useful for treating patients showing the signs and symptoms associated with allergic and/or inflammatory conditions such as the common cold, as well as signs and symptoms associated with allergic and/or inflammatory conditions of the skin or upper and lower airway passages such as allergic rhinitis, seasonal allergic rhinitis and nasal congestion, upper respiratory diseases, allergic rhinitis and nasal congestion.

Desloratadine, also called descarbethoxyloratadine, is disclosed in US Patent No. 4,659,716 as a non-sedating antihistamine useful as an anti-allergy agent . US Patent No. 6,100,274 discloses compositions containing desloratadine. US Patent No. 5,595,997 discloses methods and compositions for treating seasonal allergic rhinitis symptoms using desloratadine. Desloratadine, upon oral absorption, is hydroxylated at the 3 position to produce the metabolite, 3-hydroxyldesloratadine.

U. S. Patent Nos. 4,990,535 and 5,100,675 disclose a twice-a-day sustained release coated tablet wherein the tablet coating comprises descarbethoxyloratadine and a hydrophilic polymer and polyethylene glycol, and the tablet core comprises acetaminophen, pseudoephedrine or a salt thereof, a swellable hydrophilic polymer and pharmaceutically acceptable excipients.

U.S. Patent No. 5,314,697 discloses an extended release tablet containing matrix core comprising pseudoephedrine sulfate and a coating comprising loratadine.

None of the prior art discloses a once-a-day film-coated solid oral dosage composition.

The successful development of a formulation of a desloratadine-pseudoephedrine once-a-day product would be desirable, but would require achieving a release rate profile for pseudoephedrine component over an extended period in excess of twelve hours and preferably at least 16 hours while maintaining delivery of an effective once a day dose of desloratadine.

It would be desirable for increased patient compliance to have an extended release desloratadine-pseudoephedrine product effective and safe when used on a once-a-day basis for the treatment, management and/or mitigation of the signs and symptoms associated with the common cold, as well as allergic and/or inflammatory conditions of the skin or upper and lower airway passages such as seasonal, allergic rhinitis and nasal congestion.

SUMMARY OF THE INVENTION

The present invention is based on the discovery of a desloratadine-pseudoephedrine product, preferably a once-a-day product, which produces a release rate profile for pseudoephedrine over an extended period in excess of twelve hours and preferably at least 16 hours while maintaining delivery of an effective dose, more preferably a once-a-day dose of desloratadine.

Thus, the present invention provides a film-coated extended release solid oral dosage composition comprising (a) a core comprising an effective amount of pseudoephedrine or pharmaceutically acceptable salt thereof, and (b) a film coating uniformly covering the core and comprising an effective amount of desloratadine wherein the amount of pseudoephedrine or pharmaceutically acceptable salt thereof is effective to produce a geometric maximum plasma

concentration of pseudoephedrine of about 345 ng/mL to about 365 ng/mL at a time of about 7.60 hrs to about 8.40 hrs and the amount of desloratadine is effective to produce a geometric maximum plasma concentration of desloratadine of about 2.10 ng/mL to about 2.45 ng/mL at a time of about 4.0 hours to about 4.5 hours after administration of a single dose of said composition.

Preferred embodiments of the film-coated extended release solid oral dosage compositionof the present invention also produce a geometric maximum plasma concentration of 3-hydroxydesloratadine of about 0.75 ng/mL to about 1.15 ng/mL at a time of about 5.50 hours to about 6.25 hours after administration of a single dose of said composition.

More preferred embodiments of the film-coated extended release solid oral dosage composition of the present invention also produce a geometric maximum plasma concentration of desloratadine of about 2.10 ng/mL to about 2.45 ng/mL at a time of about 4.0 hours to about 4.5 hours and a geometric maximum plasma concentration of 3-hydroxydesloratadine of about 0.75 ng/mL to about 1.15 ng/mL at a time of about 5.50 hours to about 6.25 hours after administration of a single dose of said composition.

Thus, in a preferred embodiment, this invention provides a pharmaceutical composition comprising therapeutically effective amount of pseudoephedrine sulfate in a core and an effective amount of desloratadine in a film coating maintaining the desirable pharmacokinetic parameters of desloratadine, 3-hydroxydesloratadine and pseudoephedrine listed herein above and containing less than about 2 % of desloratadine decomposition products such as N-formyldesloratadine, preferably less than about 1.4% to about 1.6 % of the desloratadine decomposition products such as N-formyldesloratadine, initially, as well as when such compositions are stored at 25°C and about 60% relative humidity for periods of at least about 24 months.

We have also discovered that by placing a first coating between film-coating comprising desloratadine and the core comprising a nasal

decongestant, e.g., pseudoephedrine salt, preferably pseudoephedrine sulfate, provides release of desloratadine from the second film-coating and extended release of the nasal decongestant pseudoephedrine sulfate from the core, preferably a matrix core, over a period in excess of twelve hours while maintaining the desirable pharmacokinetic parameters of desloratadine, 3-hydroxydesloratadine and pseudoephedrine listed herein above and producing less than 2 % degradation of the desloratadine to N-formyldesloratadine.

Thus, in a preferred embodiment, the present invention provides a film-coated extended release solid oral dosage composition comprising:

(a). a matrix core comprising:

1. an extended release amount of a pharmaceutically acceptable decongestant;
2. a polymer matrix;
3. a water insoluble basic calcium, magnesium or aluminum salt;
4. a binder;
5. a lubricant; and optionally,
6. a glidant;

(b) a first film coating uniformly covering the matrix core comprising;

1. a water-swellable film-forming neutral or cationic copolymeric ester;
2. a lubricant;
3. a film-modifier; and
4. optionally, an anti-foaming agent;

(c) a second film coating uniformly covering the first coating, comprising:

1. an immediate release amount of desloratadine;
2. a water-swellable film-forming neutral or cationic copolymeric ester;
3. a lubricant;

4. a water soluble film-modifier; and optionally,

5. an anti-foaming agent.

This preferred embodiment of the film-coated extended release solid oral dosage composition of the present invention releases at least about 80% of the desloratadine into a 0.1N HCl solution at 37°C within about 45 minutes and about 64% of the pseudoephedrine sulfate in 6 hours and 88% of the pseudoephedrine sulfate in 12 hours in a USP Paddle Method at 100 rpm. wherein the film-coated extended release oral dosage composition contains less than about 2% of the the desloratadine decomposition products such as N-formyldesloratadine.

In preferred embodiments, the matrix core comprises about 120 to about 360 mg of pseudoephedrine sulfate.

In another preferred embodiment, the present invention provides a film-coated extended release solid oral dosage composition comprising:

(a) a matrix core comprising:

Ingredient	mg/core
Pseudoephedrine Sulfate	about 240
Hydroxypropyl Methylcellulose 2208 100,000 cps.	about 160-480
Ethylcellulose	about 40-120
Dibasic Calcium Phosphate Dihydrate	about 56-162
Povidone	about 20-60
Silicon Dioxide	about 6-12
Magnesium Stearate	about 2-6
Approximate Matrix Core Weigh Range:	**about 518-1082 mg**

and

(b) a first film coating uniformly covering the matrix core comprising:

(1) a neutral copolymer of ethyl acrylate and methyl acrylate;

(2) a lubricant selected from talc, silicon dioxide and magnesium stearate;

(3) a polyethylene glycol selected form polyethylene glycol 200 to polyethylene glycol 8000; and

(4) optionally, a pharmaceutically acceptable mixture of homologous liquid methyl siloxane polymers and silica gel; and

(c) a second film coating uniformly coating the first coating, comprising:

(1) an amount of desloratadine effective to produce a geometric maximum plasma concentration of desloratadine of about 2.10 ng/mL to about 2.45 ng/mL at a time of about 4.0 hours to about 4.5 hours after administration of a single dose of said composition;

(2) a neutral copolymer of ethyl acrylate and methyl acrylate;

(3) a lubricant selected from talc, silicon dioxide and magnesium stearate;

(4) a polyethylene glycol selected from polyethylene glycol 200 to polyethylene glycol 8000; and optionally

(5) a pharmaceutically acceptable mixture of homologous liquid methyl siloxane polymers and silica gel.

The above-listed preferred film-coated extended solid oral dosage composition may further comprise a third film coating uniformly covering the second film coating, wherein the third film coating comprises:

(1) a neutral copolymer of ethyl acrylate and methyl acrylate;

(2) a lubricant selected from talc, silicon dioxide and magnesium stearate;

(3) an effective amount of at least one a water-soluble film-modifying agent selected from low viscosity hydroxypropyl cellulose, methyl hydroxyethyl cellulose and sodium carboxymethyl cellulose, and a polyethylene glycol selected from polyethylene glycol 200 to polyethylene glycol 8000 or mixtures thereof;

(4) a pharmaceutically acceptable dye; and

(5) optionally a pharmaceutically acceptable mixture of homologous liquid methyl siloxane polymers and silica gel.

In a more preferred embodiment, the present invention provides a film-coated extended release solid oral dosage composition comprising:

(a) a matrix core comprising:

Ingredient	**mg/core**
Pseudoephedrine Sulfate	about 240
Hydroxypropyl Methylcellulose 2208 100,000 cps.	about 160-480
Ethylcellulose	about 40-120
Dibasic Calcium Phosphate Dihydrate	about 54-162
Povidone	about 20-60
Silicon Dioxide	about 6-12
Magnesium Stearate	about 2-6
Approximate (Matrix Core) Weight Range:	**about 518-1082 mg**

(b) a first film coating uniform by covering the matrix core comprising:

Ingredient	**mg/first coating**
(d) a neutral copolymer of ethyl acrylate and methyl acrylate having an average molecular weight of 800,000;	about **1.36-about 4.08**
(2) a lubricant selected from talc, silicon dioxide and magnesium stearate;	about **1.36-about 4.08**
(3) a polyethylene glycol selected from a polyethylene glycol 6000 to a polyethylene glycol 8000 and	about **0.136-about 0.408**
(4) optionally, a pharmaceutically acceptable mixture of homologous liquid methyl siloxane polymers and silica gel;	**about 0.11-about 0.33**
Total for first film coating:	**about 2.96-8.89mg**

And

(c) a second film coating uniformly coating the first coating, said second film comprising:

Ingredient	**mg/second film coating**
(1) a 24-hour amount of desloratadine;	about **5.0-about 6.0**

(2) a neutral copolymer of ethyl acrylate and methyl acrylate having an average molecular weight of 800,000; about **3.04-about 9.12;**

(3) a lubricant selected from talc, silicon dioxide and magnesium stearate; about **3.5-about 10.5**

(4) a polyethylene glycol selected from a polyethylene glycol 6000 to a polyethylene glycol 8000; about **0.915-about 2.75**

and (5) optionally, a pharmaceutically acceptable mixture of homologous liquid methyl silsoxane polymers and silica gel; about **0.14-about 042**

Total for second coating: about 12.60-about 38.79mg

In a preferred embodiment, the present invention provides a film-coated extended release oral dosage composition comprising:

a. a matrix core comprising:

Ingredient	**mg/core**
Pseudoephedrine Sulfate	about 240
Hydroxypropyl Methylcellulose 2208 100,000 cps.	about 160-480
Ethylcellulose	about 40-120

Dibasic Calcium Phosphate	about 56-162
Povidone	about 20-60
Silicon Dioxide; and	about 6-12
Magnesium Stearate	about 2-6

Approximate Matrix Core Weight Range: about 518-1082 mg

(b) a first film coating uniform by covering the matrix core comprising:

(1) a neutral copolymer of ethyl acrylate and methyl acrylate having molecular weight of 800,000;

(2) a lubricant selected from talc, silicon dioxide and magnesium stearate;

(3) a polyethylene glycol selected from a polyethylene glycol 200 to polyethylene glycol 8000; and

(4) optionally a pharmaceutically acceptable mixture of homologous liquid methyl siloxane polymers and silica gel; and

(c) a second film coating uniformly covering the first coating comprising:

(1) an amount of desloratadine effective to produce a geometric maximum plasma concentration of desloratadine of about 2.10 ng/mL to about 2.45 ng/mL at a time of about 4.0 hours to about 4.5 hours after administration of a single dose of said composition;

(2) a netural copolymer of ethyl acrylate and methyl acrylate having an average molecular weight of 800,000;

(3) a lubricant selected from talc, silicon dioxide and magnesium stearate;

(4) a polyethylene glycol selected from a polyethylene glycol 200 to a-polyethylene 8000; and

(5) optionally a pharmaceutically acceptable mixture of homogous liquid methyl siloxane and polymers and silica gel.

A more preferred composition of the present invention is provided herein below:

1. Matrix Core

Ingredient	**mg/core**
Pseudoephedrine Sulfate USP	240
Hydroxypropyl Methylcellulose 2208 USP I00,000 cps	320
Ethylcellulose NF Type 7	80
Dibasic Calcium Phosphate USP Dihydrate	I08
Povidone USP	40
Silicon Dioxide NF	8
Magnesium Stearate NF	4
Approximate Matrix Core Weight:	**800mg**

1. Matrix Core Coatings

1. **First Film Coating:**

Ingredient	**mg/tablet**
Simethicone	0.22
Polyethylene glycol 8000	0.27

Talc NF	2.72
Ethyl Acrytalc/Methyl	
Methacrylate neutral copolymer	
(30% dispersion in water)	2.72
Subtotal for first coating	**5.93 mg**

Second Film(Immediate Release)Coating

	mg/tablet
Desloratadine	6.0
Simethicone	0.28
Polyethylene glycol 8000	1.83
Talc NF	5.88
Ethyl Acrylate/Methyl methacrylate neutral copolymer	6.09
Subtotal for second coating	**20.08mg**

3. **Third Film Coating**

	mg/tablet
Hydroxypropyl Methylcellulose 2910 USP 6 cps	2.09
Talc NF	5.79
Ethyl Acrylate/Methyl Methacrylate	
Neutral copolymer	4.18
Polyethylene Glycol 8000 NF	0.42
Simethicone	0.11
Spectra Spray Med Blue Dye	3.65
Subtotal for third coating	**16.24**
Approximate Total of Three Coatings Weight:	**42.37mg**

Approximate Tablet (MatrixCore and Three Coatings) Weight: 842.97mg

Another more preferred composition of the present invention is provided herein below:

1. **Matrix Core**

Ingredient	**mg/core**
Pseudoephedrine Sulfate USP	240
Hydroxypropyl Methylcellulose 2208 USP l00,000 cps	320
Ethylcellulose NF Type 7	80
Dibasic Calcium Phosphate USP Dihydrate	l08
Povidone USP	40
Silicon Dioxide NF	8
Magnesium Stearate NF	4
Approximate Matrix Core Weight:	**800mg**

2. **Matrix Core Coatings**

1. **First Film Coating:**

Ingredient	**mg/tablet**
Simethicone	0.22
Polyethylene glycol 8000	0.27
Talc NF	2.72

Ethyl Acrytalc/Methyl Methacrylate neutral copolymer	
(30% dispersion in water)	2.72
Subtotal for first coating	**5.93 mg**

Second Film(Immediate Release)Coating	**mg/tablet**
Desloratadine	5.0
Simethicone	0.28
Polyethylene glycol 8000	0.61
Talc NF	5.17
Ethyl Acrylate/Methyl methacrylate neutral copolymer	6.09
Hydroxypropyl Methylcellulose 2910 USP 6 cps	3.05
Subtotal for second coating	**20.20mg**

3. Third Film Coating	**mg/tablet**
Hydroxypropyl Methylcellulose 2910 USP 6 cps	2.09
Talc NF	5.79
Ethyl Acrylate/Methyl Methacrylate	
Neutral copolymer	4.18
Polyethylene Glycol 8000 NF	0.42
Simethicone	0.11
Spectra Spray Med Blue Dye	3.65
Subtotal for third coating	**16.24**

Approximate Total of Three Coatings Weight:	**42.37mg**

Approximate Tablet (MatrixCore & Three Coatings) Weight:	**842.97mg**

Similar results would be expected if a decongestant effective amount of another pharmaceutically acceptable pseudoephedrine salt, e.g., pseudoephedrine hydrogen chloride was used in place of pseudoephedrine sulfate.

The compositions of the present invention are useful for treatment of allergic and/or inflammatory conditions of the skin (e.g. urticaria) and the upper and lower airway passages including the nasal and non-nasal symptoms of seasonal allergic rhinitis including nasal congestion in patients in need of such treating.

DETAILED DESCRIPTION OF THE INVENTION

During the course of development of the compositions of the present invention, desloratadine was found to be unstable and to discolor when stored in combination with various excipients such as those disclosed in U.S. Patent No. 5,314,697 as part of the matrix core containing pseudoephedrine sulfate. The excipients causing discoloration and instability of desloratadine include acidic excipients having a pH of less than 7 in water such as organic acids, such as stearic acid, povidone, crospovidone and carbonyl-containing materials such as lactose, and ethyl cellulose and hydroxylpropyl methylcellulose. Binders like povidone and polymers such as hydroxypropymethylcellulose are useful as a polymer matrix for the sustained release of the pseudoephedrine sulfate from the inner polymer matrix core.

We discovered that by uniformly covering the inner core matrix containing a nasal decongestant, e.g.,pseudoephedrine sulfate and hydroxypropyl methylcellulose, ethyl cellulose and povidone with a first coating comprising a water-swellable film-forming neutral or cationic copolymeric ester, a film modifier and lubricant, the desloratadine could safely be coated onto the first coating. The desloratadine was found to have an acceptable immediate release profile from the

second coating (80% release in 0.1N HCl in less than about 45 min.) and contain less than about 2% of N-formyldesloratadine, preferably aboutr 1.4% to about 1.6 % of N-formyldesloratadine even after storage for at least 24 months – preferably up to 36 months at 25° C and about 60% relative humidity ("RH").

When a third film coating comprising a water swellable film-forming neutral or cationic co-polymeric ester and polyethylene glycol as a film modifier was placed on top of the second coating, the dissolution rate of desloratadine from the second coating and pseudoephedrine from the core decreased to unacceptably low levels.

Suprisingly, addition of a low viscosity hydroxylpropyl methylcellulose to the third coating as a film-modifier, restored the dissolution rates of both active ingredients (pseudoephedrine sulfate and desloratadine) to levels approximately the same as those obtained when a core matrix was uniformly covered with two film coatings.

The phrase "allergic and inflammatory conditions of the skin and airway passages" is meant those allergic and inflammatory conditions and symptoms found on the skin and in the upper and lower airway passages from the nose to the lungs. Typical allergic and inflammatory conditions of the skin and upper and lower airway passages include seasonal and perennial allergic rhinitis, non-allergic rhinitis, asthma including allergic and non-allergic asthma, sinusitis, colds (in combination with a NSAID, e.g., aspirin, ibuprofen or acetaminophen) and/or a decongestant e.g. pseudoephedrine), dermatitis, especially allergic and atopic dermatitis, and urticaria and symptomatic dermographism as well as retinophathy, and small verssel diseases, associated with diabetes mellitus.

The amount of desloratadine effective for treating or preventing allergic and inflammatory conditions of the skin and upper and lower airway passages will vary with the age, sex, body weight and severity of the allergic and inflammatory condition of the patient. Typically, the amount of desloratadine

effective for treating or preventing such allergic and inflammatory conditions is in the range of about 2.5 mg/day to about 60 mg/day, preferably about 2.5 mg/day to about 20 mg/day, or about 4.0 mg/day to about 15 mg/day, or about 5.0 mg/day to about 10 mg/day, more preferably about 5.0 mg/day to about 10.0 mg/day, and most preferably about 5.0 mg/day to about 6.0mg/day in a single dose.

Desloratadine is a non-sedating long acting histamine antagonist with potent selective peripheral H1-receptor antagonist activity. Following oral administration, loratadine is rapidly metabolized to descarboethoxyloratadie or desloratadine, a pharmacologically active metabolite. *In vitro* and *in vivo* animal pharmacology studies have been conducted to assess various pharmacodynamic effects of desloratadine and loratadine. In assessing antihistamine activity in mice (comparison of ED_{50} value), desloratadine was relatively free of producing alterations in behavior alterations in behavior, neurologic or autonomic function. The potential for desloratadine or loratadine to occupy brain H1-receptors was assessed in guinea pigs following i.p. administration and results suggest poor access to central histamine receptors for desloratadine or loratadine.

In addition to antihistaminic activity, desloratadine has demonstrated anti-allergic and anti-inflammatory activity from numerous *in vitro* and *in vivo* tests. These *in vitro* tests (mainly conducted on cells of human origin) have shown that desloratadine can inhibit many events in the cascade of allergic inflammation. These anti-inflammatory effects for desloratadine are independent of the H1-antagonist effect of desloratadine and include:

The release of inflammatory mediators histamine, truptase, leukotriene and prostaglandin D2 from mast cells;

The release of inflammatory cytokines including IL-4, IL-6, IL-8 and IL-13;

The release of the inflammatory chemokines such as RANTES (regulated upon activation, normal T cell expressed and presumably secreted);

Superoxide anion production of polymorphonuclear neutrophils;

The expression of cell adhesion molecules such as intracellular adhesion molecules (ICAM-1) and P-selectin in endothelial cells; and

Eosinophil migration and adhesion

In vivo studies also suggest that an inhibitory effect of desloratadine on allergic bronchospasm and cough can also be expected.

The clinical efficacy and safety of desloratadine has been documented in over 3,200 seasonal allergic rhinitis patients in 4 double-blind, randomized clinical trials

The results of these chemical studies demonstrated the efficacy of desloratadine in the treatment of adult and adolescent patients with seasonal rhinitis.

The nasal decongestants useful in the present invention include phenylpropanolamine, phenylephrine and and pseudoephedrine. Pseudoephedrine as well as pharmaceutically acceptable acid additional salts, e.g., those of HCl or H_2SO_4, is a sympathomimetic drug recognized by those skilled in the art as a safe therapeutic agent effective for treating nasal congestion and is commonly administered orally and concomitantly with an antihistamine for treatment of nasal congestion associated with allergic rhinitis. The use of pseudoephedrine as a nasal decongestant in the present invention is preferred; the use of pseudoephedrine sulfate is more preferred.

In the course of development of the oral dosage composition of this invention, it was discovered that the selection of the polymers for the polymer matrix core

was critical to achieve the desired extended release period of at least l2 hours, preferably l2 to l6 hours and more preferably for at least l6 hours for pseudoephedrine sulfate. For example, the use of hydroxypropyl methyl cellulose 4,000 cps or l5,000 cps as polymers in the matrix core did not provide this more preferred extended release period of at least 16 hours for dose of pseudoephedrine sulfate. We discovered that only by selecting for inclusion into the matrix core of specific weight ratios of three specific polymers was the desired pseudoephedrine release profile achieved. Only by combining (1) four parts by weight of hydroxypropyl methyl cellulose 2208 USP, l00,000 cps with (2) one part by weight of ethyl cellulose together with (3) l/2 part by weight of povidone as a secondary binder was the more preferred extended release profile of at least 16 hours for pseudoephedrine sulfate from the matrix core achieved. The matrix core also contains specific amounts of silicon dioxide as a glidant and magnesium stearate as a lubricant. The tablet hardness 22 ± 6 Strong-Cobb Units (SCU) is not greatly affected by the higher level of lubricant (6mg/tablet) but it is preferred to maintain the lubricant level at l/l0 part by weight of lubricant to one part by weight of povidone as secondary binder.

The term "lubricant' as used herein refers to a substance added to the dosage form to enable the dosage form, e.g., a tablet, after it has been compressed to releases from the mold or die.

Suitable lubricants include talc, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oils and the like. Preferably, magnesium stearate or talc is used.

The term "glidants" as used herein refers to a substance, such as an anti-caking agent, which improves the flow characteristics of a powder mixture.

Suitable glidants include silicon dioxide and talc. Preferably, silicon dioxide is used.

The term "binders" as used herein means any material that is added to pharmaceutical compositions to help hold such compositions together and release the medicament therefrom.

Suitable binders are selected from the group consisting of: croscarmellose sodium, a cross-linked polymer of carboxymethylcellulose sodium, povidone, crospovidone, starches, celluloses, alginates, and gums;see also USP XXII page 1858 (1990). Preferably, povidone is used.

Typically suitable antifoaming agents include mixtures of homologous liquid methylsiloxane and silica gel available under the Simethecone tradename.

The term "water-swellable film-forming neutral or cationic copolymeric ester," as used herein means neutral and cationic copolymers of ethyl acrylate and substituted unsubstituted methyl or ethyl methacrylate esters.

Typically suitable water swellable film-forming neutral copolymeric esters include neutral copolymers of ethyl acrylate and methyl metharylate such as are available from Pharma Poloymers, a company of the Hüls Group under the EUDRAGIT® Tradename; EUDRAGIT NE30D. and Kollicoat available from BASF, Mt Olive, New Jersey An aqueous dispersion containing 30% by weight of a neutral copolymer based on ethyl crylate and methyl methoacrylate (average molecular weight of approximately 800,000) is preferred.

Typically suitable water-swellable film-forming cationic co-polymeric esters include cationic co-polymerers based on dimethylaminoethylmethacrylate and a neutral methacrylic ester such as the EUDRAGIT E copolymers available from Pharma Polymers as a 12.5% solution (EUDRAGIT E 12.5) or as solid (EUDRAGIT E 100) and quaternay ammonium copolymers described in USP/NF as "Amononio methacrylate copolymer, Type A" and Type "B". Such copolymers are available as aqueous dispersions of copolymers of acrylic and methacrylic acid esters with a low (substitution) content of quaternary ammonium groups present as salts, (e.g., quaternary ammonium chlorides). Type A and Type B are available as 30% aqueous dispersions under the EUDRAGIT RL 30D and EUDRAGIT RS 30D tradenames, respectively. Use of the water-swellable film-from neutral co-polymeric esters based on ethyl acrylate and methacrylate is preferred.

The term "water soluble film modifier" as used herein means a film-forming agent which modifies the water-swellable characteristics of the film-forming neutral or cationic copolymeric esters useful in the compositions of the present invention. A typically suitable water soluble film-modifying agent is a low viscosity (≤ 20 cps) cellulose such as low viscosity hydroxypropyl methyl cellulose, low viscosity hydroxylethyl methyl cellulose; low viscosity sodium carboxymethyl cellulose or a polyethylene glycol selected from polyethylene glycol 200 to polyethylene glycol 8000.

Use of a polyethylene glycol 6000 to polyethylene glycol 8000 as a film modifier is preferred in the first and second coatings; the use of polyethylene glycol 8000 in each coating is more preferred.

Use of polyethylene glycol in combination with a low viscosity hydroxypropyl methylcellulose in the third coating is preferred. Use of a mixture of polyethylene glycol 8000 and hydroxypropyl methylcellulose 2910 cps in the third or outermost fim coating is more preferred.

The term "water insoluble basic calcium, magnesium and aluminium salts" as used herein means the pharmaceutically acceptable carbonates, phosphates, silicates and sulfates of calcium, magnesium and aluminum or mixtures thereof. Typically suitable pharmaceutically acceptable basic salts include calcium sulfate anhydrous, hydrates of calcium sulfate, such as calcium sulfate dihydrate, magnesium sulfate anhydrous, hydrates of magnesium sulfate, dibasic calcium phosphate, dibasic calcium silicate, magnesium trisilicate, magnesium phosphate, aluminum silicate, and hydrates of magnesium phosphate, aluminum phosphate; and calcium phosphate is more preferred. The use of dibasic calcium phosphate dihydrate is most preferred.

The hydroxylpropyl methylcellulose 29l0 acts as a film-forming agent in the film coating, and the polyethylene glycols act as film modifier. Other suitable film-

forming polymers which may be used include low viscosity (720 cps) hydroxypropyl celluloses, methyl hydroxyethyl cellulose and sodium carboxymethyl cellulose.

The oral dosage composition of this invention also provides a shelf life of more than 24 months, e.g., up to 36 and 48 months so long as the tablets are stored in standard package at between 2° and 30° C in an ambient environment of 60% relative humidity.

In the preparation of the tablet core, the povidone is dissolved in a mixture of alcohol and water. The pseudoephedrine sulfate, hydroxypropyl methylcellulose 2208 USP, l00,000 cps, ethylcellulose, and dibasic calcium phosphate are blended and granulated with an alcoholic water solution containing povidone. The granulation is milled, and dried to a loss on drying between 0.5 to 2.0%.

The dried granulation is milled and blended with requisite amounts of silicon dioxide and magnesium stearate. The final blend is compressed to produce the inner polymer matrix core composition.

The coatings are normally applied to the inner polymer matrix cores in the following manner.

Cores are charged into a suitable coating pan. A water dispersion of talc, Simethicone, polyethylene glycol 8000 and EUDRAGIT NE30D is applied to the matrix cores as a first coating. These coated matrix cores are then coated with a dispersion of desloratadine, Simethicone, EUDRAGIT NE 30D, polyethylene glycol 8000 NF and talc dispersion. This is followed by an application of third coating containing a dispersion of FD & C Blue No. 2 Aluminum lake containing EDTA as a chelating agent, talc, Simethicone, EUDRAGIT NE30D, containing hydroxy-propyl methylcellulose 2910 cps. and polyethylene glycol 8000 NF. The coated tablets are then branded (with black ink) and packaged in plastic bottles and blisters for storage at a temperature between 2° C and 30°C in an ambient environment

During the course of development of the formulations of the present invention, we discovered that the *in vitro* dissolution studies showed a decrease in both the desloratadine release rate and in desloratadine concentration at increased pH, especially pH values > 7.0, compared to those for a 5 mg tablet of desloratadine. The *in vivo* studies showed the Tmax was greater than 4 hours and that a significant part of the absorptive desloratadine process occurs in the small intestine which has an alkaline pH (pH values > 7.0).

We discovered we could increase the release of desloratadine by increasing the level of hydroxypropyl methylcellulose and lowering the levels of the plasticizing agent, e.g., polyethylene glycol 8000, and of the lubricant, e.g., talc, in the second film coating containing desloratadine. See Example 4.

In another preferred embodiment, the effective amount of desloratadine in the second film coating was increased to 6.0 mg and amount of talc was reduced (by about 1.12 mg) to produce an acceptable pharmacokinetic profile.See Example 3 and Table 3.

For the solid oral dosage formulations of the present invention, the geometric mean maximum plasma concentration of pseudoephedrine (PES) is about 345 ng/mL to about 365 ng/mL at a time (Tmax) of about 7.60 hours to about 8.40 hours; the geometric mean maximum plasma concentrate of desloratadine (DL) is about 2.10 ng/mL to about 2.45 ng/mL , preferably 2.15 ng/mL to about 2.35 ng/mL at a time (Tmax), of about 4.0 hours to about 4.5 hours and the geometric mean maximum plasma concentrate of 3-hydroxydesloratadine (3-OH-DL) is about 0.75 ng/mL to about 1.15 ng/mL, preferably about 0.85 ng/mL to about 1.05 ng/mL , and more preferably preferably about 0.88 ng/mL to about 1.02 ng/mL at a time (Tmax) of about 5.50 hours to about 6.25 hours after administration of a single dose of said composition to healthy subjects.

Pharmacokinetic Study No. 1:

The pharmacokinetic objective of this study was to determine the bioavailability and bioequivalence of desloratadine (DL), 3-OH DL and pseudoephedrine(PES) from the formulation of Example 2 (5 mg of DL/240 mg of PES) of this application relative to that of a 5 mg of Example 11 of USP No..6,100,274 (USP '274) and an extended-release pseudoephedrine core as references. This study was a Phase I, open-label, single-dose, randomized, three-way crossover study with a seven-day washout period between each treatment. Thirty-six healthy male and female subjects received each of the following treatments in the order assigned by a computer-generated random code:

Treatment A:	One 5 mg DL/240 mg PES tablet of Example 2.
Treatment B:	One DL 5 mg tablet of Example 11 of USP.'274.
Treatment C:	One 240 mg pseudoephedrine sulphate (oval extended-release pseudoephedrine cores from Claritin® D-24 coated with placebo Claritin® D-24 coat).

The tablets were administered with 180 mL (6 fluid ounces) of non-carbonated room temperature water. The tablet was swallowed whole, not chewed or crushed. After dosing, the oral cavity was inspected to assure that the subject had swallowed the tablet. Subjects continued fasting until the four-hour study procedures were complete. Water was permitted throughout the fasting period, except for two hours post-dose. The subjects remained awake and seated upright/ambulatory for four hours post-dose. All subjects were confined to the study site until the 120-hour blood samples, vital signs and laboratory tests were obtained.

Serial blood samples (10 mL) were to be collected into tubes containing heparin as an anticoagulant at the following time points: 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 5, 6,8, 10, 12, 16, 20, 24, 36, 48, 48, 72, 96 and 120 hours post-dose. No

food was allowed for four hours after dosing. Drinking water was not allowed from one hour pre-dose to one hour postdose, except for the 120 mL administered with the treatment. Plasma concentrations of pseudoephedrine were determined using a validated liquid chromatography with tandem mass spectrometric (LC/MS/MS) method with a lower limit of quantitation (LOQ) of 10.0 ng/mL, and a linear range of 10.0-400 ng/mL. The associated mean pharmacokinetic parameters are provided in Table 1.

The mean DL Cmax following administration of DL tablet of Example 2 of the present invention or a 5 mg desloratadine tablet of Example 11 of USP 6,100,274 were 1.79 and 2.23 ng/mL, respectively, and were reached at mean Tmax values of 6.78 and 5.10 hours, respectively.

Table 1 Mean (%CV[a]) Pharmacokinetic Parameters of DL, and 3-OH DL in Healthy Subjects Following Single-Dose Oral Administration of DL D-24 and DL

	DL			
	Example 2- 5 mg/240 mg (Treatment A)		Example 11 of USP'274-5 mg (Treatment B)	
Parameter (units)	Mean	%CV	Mean	%CV
Cmax(ng/mL)	1.79	35.8	2.23	34.8
Tmax(hr)	6.78	57.3	5.10	52.5
	3-OH DL			
	Example 2- D-24 5 mg/240 mg (Treatment A)		Example 11 of USP'274-5 mg (Treatment B)	
	Mean	%CV	Mean	%CV
Cmax(ng/mL)	0.695	59.4	0.832	55.2
Tmax(hr)	6.09[b]	32.7	4.96[b]	31.4

a: %CV is percent coefficient of variation, which is a relative measure of variability. See Steele and Torrie, "Principles and Procedures of Statistics", (1980) 2nd Edition, McGraw-Hill, NY, at page 27.

b: n=35

The mean 3-OH DL Cmax following administration of 5 mgDL/240 mgPES tablet of Example 2 of this application and a 5 mg desloratadine tablet of Example 11 of USP 6,100,274 were 0.695 and 0.832 ng/mL, respectively, and were reached at mean Tmax values of 6.09 and 4.96 hours, respectively. The peak plasma concentration of 3-OH DL decreased slowly with half-life of 29.6 hours following administration of 5 mgDL/240 mgPES tablet of Example 2 of this application, and 29.5 hours following administration of the 5 mg DL tablet of USP 6,100,274.

Statistical comparisons of Cmax and AUC(tf) following administration of tablet of Example 2 of this application and 5 mg desloratadine tablet of USP 6,100,274were performed for DK and 3-OH DL plasma concentrations.

The results showed that the 90% confidence intervals for DL and 3-OH DL did not meet the 80-125% bioequivalence guidelines for both Cmax and AUC(tf). For those subjects where AUC(I) could be determined, the confidence intervals of DL for AUC(I) did not meet the 80-125 bioequivancy guidelines. However, the confidence intervals of 3-OH DL for AUC(I) did meet the 80-125 bioequivances guidelines.

The mean pharmacokinetic parameters of pseudoephedrine are provided in Table 2.

Table 2. Mean (%CV[a]) Pharmacokinetic Parameters of Pseudoephedrine in Healthy Subjects Following Single-Dose Oral Administration of DL D-24 and 240 mg Pseudoephedrine Sulphate (Oval Extended-Release Pseudoephedrine Cores from Claritin® D-24 Coated with Placebo Claritin® D-24 Coat) Tablets (n=36)

	Pseudoephedrine			
	Example 2 of this application 5 mg/240 mg		Pseudoephedrine Sulphate (Oval-Extended Release Pseudoephedrine Cores from Claritin D-24)	
	Mean	%CV	Mean	%CV
Cmax(ng/mL)	328	25	349	18.1
Tmax(hr)	8.42	34	7.36	36.3
AUC(tf)(ng-hr/mL)	6438	42	6225	38.5
tf(hr)	44.0	37	40.0	25.8
AUC(I)(ng-hr/mL)	6780	40	6452	37.3
t½(hr)	10.3	148	7.25	21.6

a.%CV is percent coefficient of variation, which is a relative measure of variability. See Steele and Torrie, "Principles and Procedures of Statistics", (1980) 2nd Edition, McGraw-Hill, NY, at page 27.

The mean pseudoephedriine Cmax following administration of the (5 mg DL /240 mgPES) tablet of Example 2 or a 240 mg pseudoephedrine sulphate extended-release core were 328 and 349 ng/mL, respectively. Statistical comparisons of Cmax and AUC(tf) values for DL D-24 (5 mg/240 mg) versus 240 mg pseudoephedrine sulphate (extended-release core) were performed. The power to detect a 20% difference in treatment means

at an α-level of 0.05 (two-tailed) for the log-transformed Cmax and AUC(tf) were 100 and 93%, respectively.

The 90% confidence intervals for pseudoephedrine met the 80-125% bioequivalence guidelines for both Cmax and AUC(tf). For those subjects were AUC(I) could be determined, the confidence intervals for AUC(I) also met the 80-125 guidelines.

Pharmacokinetic Study No. 2

Subjects were confined at the study site at least 12 hours prior to each treatment (Day – 1). In the morning of Day 1, following a ten-hour overnight fast, each subject received one of the following treatments based on his/her subject number and the study period:

Treatment A:One (5 mg DL/240 mgPES) tablet of Example 2 of this application
Treatment B:One (6 mgDL/240 mgPES) tablet of Example 3 of this application
Treatment C:One 5 mg DL tablet of Example 11 of USP'274 plus one 120mg PES tablet (oval extended-release pseudoephedrine core)

The study procedures, blood collection times and the analytical methodologies summarized in Study No. 1 were employed.

The mean pharmacokiinetic parameters are shown in Table 3. The power to detect a 20% difference in treatment means of DL at an α-leval of 0.05 (two tailed) for the log-transformed AUC(tf), AUC(I), and Cmax values were 89%, 90% and 88% respectively.

Table 3 Mean (%CV[1]) Pharmacokinetic Parameters of DL, 3-OH DL and Pseudoephedrine in Healthy Adult Volunteers (n=42) Following Single-Dose Oral Administration of DI Tablets of Examples 2 (5 DL/240PES mg), Example 3 (6DL/240PES mg) or a 5 mg DL Tablet of USP'274 Plus One 240 mg PES Tablet.

Treatment	DL			
	Cmax(ng/mL)/CV		Tmax(hr)/CV	
A[2]	1.91	44	4.69	52
B[3]	2.35	43	4.33	50
C[4]	2.28	40	3.87	67
Treatment	3-OH DL			
	Cmax(ng/mL)/CV		Tmax(hr)/CV	
A[2]	0.77	28	6.67	52
B[3]	1.00	39	6.12	48
C[4]	0.93	31	5.68	58
Treatment	Pseudoephedrine			
	Cmax(ng/mL)/CV		Tmax(hr)/CV	
A[2]	353	30	7.71	45
B[3]	362	28	8.14	46
C[4]	349	22	8.31	47

1%CV is percent coefficient of variation, which is a relative measure of variability. See Steele and Torrie, "Principles and Procedures of Statistics", (1980) 2nd Edition, McGraw-Hill, NY, at page 27.

2.Treatment A = One (5 mg/240 mg) tablet of Example 2.

3.Treatment B = One (6 mg/240 mg) tablet of Example 3.

4.Treatment C = One 5 mg DL tablet of Example II of USP 6,100,274 plus one 240 mg pseudoephedrine tablet.

The results show that, based on plasma 3-OH DL concentrations, the (5 mg/240 mg) of Example 2 is not equivalent to the 5 mg DL tablet of Example 11 of USP '274 and that the 6 mgDL/240 PESmg of Example 3 and 5 mg DL tablet of Example II of USP ',274 are bioequivalent.

The results show that, the bioequivalence of pseudoephedrine from the formulations of Examples 2 &3 was established relative to the reference product.

Pharmacokinetic Study No. 3:

Forty health volunteers were enrolled in this open lable, randomized, three-way cross-over, single-dose study. The subjects were randomized to receive, following a ten hour over-night fast:

Treatment A: 5 mg DL/240mg PES of Example 4 of this appln

Treatment B: DL 5 mg of Example11of USP '274 plus pseudoephedrine sulfate 240 mg.

The procedures of Study No. 1 were followed using the above-listed treatments. The mean pharmacokinetic parameters for DL, 3-OH DL and pseudoephedrine are provided in Table 4.

Table 4: Mean (%CV[1]) Pharmacokiinetic Parameters of DL, 3-OH DL and Pseudoephedrine in Healthy Adult Volunteers (n=40) Following Single-Dose Oral Administration of One 5 mg D-24 Tablet of Example 4or One 5 mg DL Tablet of USP'274 Plus One 240 mg Pseudoephedrine Tablet

Treatment	DL			
	Cmax(ng/mL)/CV		Tmax(hr)/CV	
A[2]	2.15	41	4.13	66
B[3]	2.30	44	4.83	62
Treatment	3-OH DL			
	Cmax(ng/mL)		Tmax(hr)	
A[2]	0.89	48	5.60	42
B[2]	1.07	36	6.10	37
Treatment	Pseudoephedrine			
	Cmax(ng/mL)		Tmax(hr)	
A[2]	382	34	7.83	29
B[2]	399	32	8.43	36

1.%CV is percent coefficient of variation, which is a relative measure of variability. See Steele and Torrie, "Principles and Procedures of Statistics", (1980) 2nd Edition, McGraw-Hill, NY, at page 27.

2.Treatment A= One (5 mgDL/240 mgPES) tablet of Example 4 of this application.

3.Treatment B= One 5 mg DL tablet of Example 11 of USP 6,100,274 plus one 240 mg pseudoephedrine tablet.

EXAMPLE 1

This example illustrates preparation of the preferred oral dosage composition of this invention. The ingredients and specific amounts thereof are listed below.

I. Matrix Core

A. Method of Manufacture:

1. Dissolve povidone in a mixture of 3 parts of alcohol and 1 part of purified water.
2. Combine the pseudoephedrine sulfate, hydroxypropyl methylcellulose 2208, ethylcellulose and dibasic calcium phosphate, dihydrate in a suitable mixing bowl and blend under a nitrogen overlay.
3. Granulate the blend from Step 2 with the solution from Step. I. pass the wet granulation through suitable milling equipment to breakup large lumps.
4. Dry the wet granulation at about 70°C in a siutable fluid bed processor to a loss on drying between 0.5 to 2.0% as determined by a moisture balance or equivalent.
5. Pass the dried granules through suitable milling equipment.
6. Add the requisite amounts of silicon dioxide and magnesium stearate to the dried, milled granules and blend.
7. Compress the blend on a suitable tablet press.

The matrix cores are coated in the following manners:

A. Preparation of Coating Dispersions and Solutions

I. First Film Coating Solution

(I) Disperse Simethicone and polyethylene glycol 8000 in a portion of purified water and agitate until completely dissolved.

(2) To the product of step 1, add the remainder of the purified water and the talc; stir the so-formed suspension at room temperature until homogeneous.

(3) Slowly add the so-formed homogeneous suspension of step 2 to the stirred EUDRAGIT NE30D dispersion and continue to mix the so-formed mixture until a homogeneous dispersion is formed. Pass the dispersion through a screen.

(4) Spray the dispersion onto the matrix cores maintained at 40°C± 5°C on a rotating pan.

(5) Dry the cooled matrix cores on the rotating pan.

2. <u>Second Film Coating Dispersion</u>

(I) Disperse the Simethicone and polyethylene glycol 8000 in a portion of purified water. Add additional water and stir the dispersion at room temperature until completely dissolved.

(2) Slowly add desloratadine to the dispersion of step 1 and mix until a uniform dispersion is formed. Combine with the talc with the so-formed uniform dispersion, and continue agitation until a homogenous suspension is formed.

(3) Add dispersion of step 2 to the EUDRAGIT NE 30D dispersion and mix until a uniform dispersion is formed. Pass the dispersion through a screen.

(4) Spray the requisite amount of the dispersion from step 3 onto the matrix core with the first coating in a rotating pan at 25-27°C.

(5) Dry the coated matrix cores on the rotating pan.

3. The Third Film Coating Solution

(1) Add the hydroypropyl methylcellulose 2910 to hot purified water (75°C) and agitate until a solution forms. Cool the so-formed solution to room temperature.

(2) To a separate container, add Simethicone and polyethylene glycol 8000 to purified water and continue to mix until a solution is formed.

(3) Add talc to solution of step 2 and continue to mix until a uniform dispersion is formed.

(4) Add the solution of step 1 to the dispersion of step 3 and continue to mix until

(5) Add FD&C Blue No. 2 aluminum lake containing EDTA as a chelating agent to purified water in a third container and

(6) Add the Blue lake solution of step 5 to the dispersion of step 4 and mix until a homogeneous mixture is formed.

(7) Slowly add the mixture of step 6 to a dispersion of EUDRAGIT NE30D and continue to mix until homogeneous.

(8) Pass dispersion of step 6 through 60 mesh screen.

(9) Spray the requisite amount of the dispersion of step 8 onto the twice-coated matrix cores in a rotating pan at 35° - 45°C. Dry the thrice-coated matrix cores in the form of tablets in rotating pan.

(10) Remove the so-formed tablets from pan and further dry at 40° for 16 hours.

EXAMPLE 2

The following more preferred composition of the present invention was made in accordance with the above procedure of Example 1.

1. Matrix Core

Ingredient	mg/core
Pseudoephedrine Sulfate USP	240
Hydroxypropyl Methylcellulose 2208 USP I00,000 cps	320
Ethylcellulose NF Type 7	80
Dibasic Calcium Phosphate USP Dihydrate	I08
Povidone USP	40
Silicon Dioxide NF	8
Magnesium Stearate NF	4
Approximate Matrix Core Weight:	**800mg**

3. Matrix Core Coatings

1. **First Film Coating:**

Ingredient	mg/tablet
Simethicone	0.22
Polyethylene glycol 8000	0.27
Talc NF	2.72
Ethyl Acrytalc/Methyl Methacrylate neutral copolymer (30% dispersion in water)	2.72
Subtotal for first coating	5.93 mg

2. **Second Film(Immediate Release)Coating**

	mg/tablet
Desloratadine	5.0
Simethicone	0.28
Polyethylene glycol 8000	1.83
Talc NF	7.00
Ethyl Acrylate/Methyl methacrylate neutral copolymer	6.09

Subtotal for second coating	**20.20mg**
3. <u>Third Film Coating</u>	**mg/tablet**
Hydroxypropyl Methylcellulose 2910 USP 6 cps	2.09
Talc NF	5.79
Ethyl Acrylate/Methyl Methacrylate Neutral copolymer	4.18
Polyethylene Glycol 8000 NF	0.42
Simethicone	0.11
Spectra Spray Med Blue Dye	<u>3.65</u>
Subtotal for third coating	**16.24**
Approximate Total of Three Coatings Weight:	**42.37mg**
Approximate Tablet (MatrixCore & Three Coatings) Weight:	**842.97mg**

The <u>in vitro</u> dissolution profile of the tablet of Example 1 was measured in a stirred 0.1<u>N</u> HCl solution at 37°C (1st hour) and thereafter in a stirred phosphate buffer having a pH of 7.5 at 37°C. The 80% of desloratadine in the coating was dissolved within the first 45 minutes and the total dose of pseudoephedrine sulfate in the matrix core was slowly released via erosion and dissolution mechanisms over a period of at least 16 hours.

<u>Example 3</u>

The following more preferred composition of the present invention was made in accordance with the above procedure of Example 1.

1. Matrix Core

Ingredient	mg/core
Pseudoephedrine Sulfate USP	240
Hydroxypropyl Methylcellulose 2208 USP l00,000 cps	320
Ethylcellulose NF Type 7	80
Dibasic Calcium Phosphate USP Dihydrate	l08
Povidone USP	40
Silicon Dioxide NF	8
Magnesium Stearate NF	4
Approximate Matrix Core Weight:	**800mg**

4. Matrix Core Coatings

1. **First Film Coating:**

Ingredient	mg/tablet
Simethicone	0.22
Polyethylene glycol 8000	0.27
Talc NF	2.72
Ethyl Acrytalc/Methyl Methacrylate neutral copolymer (30% dispersion in water)	2.72
Subtotal for first coating	**5.93 mg**

Second Film(Immediate Release)Coating	mg/mL
Desloratadine	6.0
Simethicone	0.28

Polyethylene glycol 8000	1.83
Talc NF	5.88
Ethyl Acrylate/Methyl methacrylate neutral copolymer	6.09
Subtotal for second coating	**20.08mg**

3. Third Film Coating	**mg/tablet**
Hydroxypropyl Methylcellulose 2910 USP 6 cps	2.09
Talc NF	5.79
Ethyl Acrylate/Methyl Methacrylate Neutral copolymer	4.18
Polyethylene Glycol 8000 NF	0.42
Simethicone	0.11
Spectra Spray Med Blue Dye	3.65
Subtotal for third coating	**16.24**
Approximate Total of Three Coatings Weight:	**42.37mg**

Approximate Tablet (MatrixCore and Three Coatings) Weight: 842.97mg

Example 4

The following more preferred composition of the present invention was made in accordance with the above procedure of Example 1.

1. Matrix Core

Ingredient	**mg/core**
Pseudoephedrine Sulfate USP	240
Hydroxypropyl Methylcellulose 2208 USP I00,000 cps	320
Ethylcellulose NF Type 7	80
Dibasic Calcium Phosphate USP Dihydrate	I08
Povidone USP	40

Silicon Dioxide NF	8
Magnesium Stearate NF	4
Approximate Matrix Core Weight:	**800mg**

Matrix Core Coatings

1. **First Film Coating:**

Ingredient	**mg/tablet**
Simethicone	0.22
Polyethylene glycol 8000	0.27
Talc NF	2.72
Ethyl Acrytalc/Methyl Methacrylate neutral copolymer (30% dispersion in water)	2.72
Subtotal for first coating	**5.93 mg**

5. Matrix Core Coatings

1. **First Film Coating:**

Ingredient	**mg/tablet**
Simethicone	0.22
Polyethylene glycol 8000	0.27
Talc NF	2.72
Ethyl Acrytalc/Methyl Methacrylate neutral copolymer (30% dispersion in water)	2.72
Subtotal for first coating	**5.93 mg**

Second Film(Immediate Release)Coating	**mg/core**
Desloratadine	5.0
Simethicone	0.28
Polyethylene glycol 8000	0.61
Talc NF	5.17
Ethyl Acrylate/Methyl methacrylate neutral copolymer	6.09
Hydroxypropyl Methylcellulose 2910 USP 6 cps	3.05
Subtotal for second coating	**20.20mg**
3. Third Film Coating	**mg/tablet**
Hydroxypropyl Methylcellulose 2910 USP 6 cps	2.09
Talc NF	5.79
Ethyl Acrylate/Methyl Methacrylate Neutral copolymer	4.18
Polyethylene Glycol 8000 NF	0.42
Simethicone	0.11
Spectra Spray Med Blue Dye	3.65
Subtotal for third coating	**16.24**
Approximate Total of Three Coatings Weight:	**42.37mg**
Approximate Tablet (MatrixCore&Three Coatings) Weight:	**842.97mg**

Similar results would be expected if a decongestant effective amount of another pharmaceutically acceptable pseudoephedrine salt, e.g., pseudo-ephedrine hydrogen chloride was used in place of pseudoephedrine sulfate.

The compositions of the present invention are useful for treatment of allergic and/or inflammatory conditions of the skin (e.g. urticaria) and the upper and lower airway passages including the nasal and non-nasal symptoms of seasonal allergic rhinitis including nasal congestion in patients in need of such treating. The precise dosage and dosage regimen may be varied by the attending clinician in view of the teachings herein depending upon the requirements of the patient, e.g., the patient's age, sex and the severity of the allergic and/or inflammatory condition being treated. Determination of the proper dosage and dosage regimen for a particular patient will be within the skill of the attending clinician.

While we have hereinabove presented a number of preferred embodiments of this invention by way of example, it is apparent that the scope of the invention is to be defined by the scope of the appended claims.

CLAIMS:

1. A film-coated extended release solid, oral dosage composition comprising:

(a) a core comprising an effective extended release amount of pseudoephedrine or pharmaceutically acceptable salt thereof, and

(b) a film coating uniformly covering the core and comprising an effective amount of desloratadine;

wherein the amount of pseudoephedrine or pharmaceutically acceptable salt thereof is effective to produce a geometric maximum plasma concentration of pseudoephedrine of about 345 ng/mL to about 365 ng/mL at a time of about 7.60 hrs to about 8.40 hrs and the amount of desloratadine is effective to produce a geometric maximum plasma concentration of desloratadine of about 2.10 ng/mL to about 2.45 ng/mL at a time of about 4.0 hours to about 4.5 hours after administration of a single dose of said composition;

wherein the core is a matrix core and said film coating comprises a first film coating uniformly covering the matrix core and a second film coating uniformly covering the first coating, said second film coating comprising said effective amount of desloratadine;

and wherein:

(i) the core further comprises:

(1) a polymer matrix;

(2) a water insoluble basic calcium, magnesium or aluminum salt;

(3) a binder;

(4) a lubricant; and optionally,

(5) a glidant;

and wherein:

(ii) the first film coating uniformly covering the matrix core comprises:

(1) a water-swellable film-forming neutral or cationic co-polymeric ester;

(2) a lubricant;

(3) film-modifier; and optionally,

(4) an anti-foaming agent;

and wherein:

(iii) the second film coating uniformly covering the first coating further comprises:

1) a water-swellable film-forming neutral or cationic co-polymeric ester;
2) a lubricant;
3) water soluble film-modifier; and optionally
4) an anti-foaming agent.

2. The film-coated extended release solid, oral dosage composition of claim 1, wherein the amount of desloratadine is effective to produce a geometric maximum plasma concentration of 3-hydroxydesloratadine of about 0.75 ng/mL to about 1.15 ng/mL at a time of about 5.50 hours to about 6.25 hours after administration of a single dose of said composition.

3. The film-coated extended release solid, oral dosage composition of claim 1 or 2, wherein the film-coated extended release oral dosage composition contains less than about 2% of N-formyldesloratadine.

4. The film-coated extended release solid, oral dosage composition of claim 1, 2 or 3, which further comprises a third film coating uniformly coating the second film coating, said third coating comprising:

1) a pharmaceutically acceptable dye;
2) a water-swellable film-forming neutral or cationic copolymeric ester;
3) a lubricant;
4) at least one water soluble film-modifier; and optionally,
5) an anti-foaming agent.

5. The film-coated extended release solid, oral dosage composition of claim 4, wherein the water-soluble film-modifier is a low viscosity hydroxypropyl methylcellulose, hydroxyethyl methyl cellulose or sodium carboxymethyl cellulose or a polyethylene glycol selected from polyethylene glycol 200 to a polyethylene 8000, or mixtures thereof.

6. The film-coated extended release solid, oral dosage composition of claim 1, 2, 3, 4 or 5, wherein the water-insoluble calcium, magnesium or aluminum salt in the matrix core is a carbonate, phosphate, silicate or sulfate of calcium, magnesium or aluminum or mixtures thereof.

7. The film-coated extended release solid, oral dosage composition of claim 1, wherein the matrix core comprises:

Ingredient	mg/core
Pseudoephedrine Sulfate	about 120 to about 360
Hydroxypropyl Methylcellulose 2208, 100,000 cps	about 160 to about 480
Ethylcellulose	about 40 to about 120
Dibasic Calcium Phosphate Dihydrate	about 56 to about 162
Povidone	about 20 to about 60
Silicon Dioxide	about 6 to about 12
Magnesium Stearate	about 2 to about 6
Matrix Core Weight Range:	about 400 to about 1200mg.

8. The film-coated extended release solid, oral dosage composition of claim 1, wherein the first film coating comprises:

(1) a neutral copolymer of ethyl acrylate and methyl acrylate;

(2) a lubricant selected from talc and magnesium stearate;

(3) a polyethylene glycol selected from polyethylene glycol 200 to polyethylene glycol 8000; and optionally

(4) a pharmaceutically acceptable mixture of homologous liquid methyl siloxane polymers and silica gel.

9. The film-coated extended release solid, oral dosage composition of claim 1, wherein the second film coating comprises:

(1) an amount of desloratadine effective to produce a geometric maximum plasma concentration of desloratadine of about 2.10 ng/mL to about 2.45 ng/mL at a time of about 4.0 hours to about 4.5 hours after administration of a single dose of said composition;

(2) a neutral copolymer of ethyl acrylate and methyl acrylate;

(3) a lubricant selected from talc, silicon dioxide and magnesium stearate;

(4) a polyethylene glycol selected from polyethylene glycol 200 to a polyethylene glycol 8000; and optionally

(5) a pharmaceutically acceptable mixture of homologous liquid methyl siloxane polymers and silica gel.

10. The film-coated extended release solid, oral dosage composition of claim 4, wherein in said third film coating: said ester (2) is a neutral copolymer of ethyl acrylate and methyl acrylate; said lubricant (3) is selected from talc, silicon dioxide and magnesium stearate; said water-soluble film-modifier (4) is a low viscosity hydroxypropyl methylcellulose, hydroxyethyl methylcellulose or sodium carboxymethyl cellulose, or a polyethylene glycol selected from polyethylene glycol 200 to a polyethylene glycol 8000, or mixtures thereof; and said anti-foaming agent (5) is a pharmaceutically acceptable mixture of homologous liquid methyl siloxane polymers and silica gel.

11. The film-coated extended release solid, oral dosage composition of claim 9, wherein the amount of desloratadine is effective to produce a geometric maximum plasma concentration of 3-hydroxydesloratadine of about 0.75 ng/mL to about 1.15 ng/mL at a time of about 5.50 hours to about 6.25 hours after administration of a single dose of said composition.

12. A film-coated extended release solid, oral dosage composition comprising:

(a) a core comprising an effective amount of pseudoephedrine or pharmaceutically acceptable salt thereof, and

(b) a first film coating uniformly covering the core; and

(c) a second film coating uniformly covering the first coating

comprising an effective amount of desloratadine; wherein the amount of pseudoephedrine or pharmaceutically acceptable salt thereof is effective to provide a geometric maximum plasma concentration of pseudoephedrine of about 345 ng/mL to about 365 ng/mL at a time of about 7.60 hrs to about 8.40 hrs and the amount of desloratadine is effective to provide a geometric maximum plasma concentration of desloratadine of about 2.10 ng/mL to about 2.45 ng/mL at a time of about 4.0 hours to about 4.5 hours and to produce a geometric maximum plasma concentration of 3-hydroxydesloratadine of about 0.75 ng/mL to about 1.15 ng/mL at a time of about 5.50 hours to about 6:25 hours after administration of a single dose of said composition;

and wherein:

(i) the core further comprises:

(1) a polymer matrix;

(2) a water insoluble basic calcium, magnesium or aluminum salt;

(3) a binder;

(4) a lubricant; and optionally,

(5) a glidant;

and wherein:

(ii) the first film coating uniformly covering the matrix core comprises:

(1) a water-swellable film-forming neutral or cationic co-polymeric ester;

(2) a lubricant;

(3) film-modifier; and optionally,

(4) an anti-foaming agent;

and wherein:

(iii) the second film coating uniformly covering the first coating further comprises:

1) a water-swellable film-forming neutral or cationic co-polymeric ester;

2) a lubricant;

3) water soluble film-modifier; and optionally

4) an anti-foaming agent.

13. The film-coated extended release solid, oral dosage composition of any one of claims 1 to 12 for use once a day.