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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Bogotá, D.C.

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Re.: Código 02-01-444
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Fase Nacional de Solicitud
de Patente PCT
R.P. SCHERER TECHNOLOGIES, INC.

En relación con el expediente de la referencia y con el propósito de dar respuesta a las oposiciones presentadas contra esta solicitud de patente por las sociedades Procape S.A., Lafrancol S.A. y Tecnoquímicas S.A. con fundamento de falta de novedad y nivel inventivo de la materia que mi representada desea proteger por medio de patente de invención por medio del presente escrito me permito manifestarles lo siguiente:

1. Dentro del trámite de la solicitud estadounidense No. 09/909,313 presentada el 20 de Julio de 2001 y de la cual se deriva la presente solicitud con fundamento en el ejercicio del derecho de prioridad, la Oficina de Patentes de los Estados Unidos tuvo en cuenta y analizó todas y cada una de las anterioridades mencionadas por las sociedades opositoras.
2. En ningún caso de las anterioridades citadas por las partes opositoras se consideró por parte de la Oficina de Patentes de Estados Unidos que ellas afectaban de manera alguna la novedad o el nivel inventivo requeridos para que se le otorgara protección por vía de patente a la materia de esta solicitud.

3. Con fundamento en lo expuesto en el punto anterior, la Oficina de Patentes de Estados Unidos concedió protección para esta invención cuyo número de certificado es el 6,720,002 de Abril 13 de 2004.
4. Para mayor ilustración, acompaño una copia de la citada patente en la cual se mencionan, como anterioridades y referencias citadas todas y cada una de las mencionadas en las oposiciones.
5. De otro lado, por expresas instrucciones de mi representada, me permito modificar el capítulo reivindicatorio originalmente aportado el cual es idéntico al admitido por las autoridades estadounidenses. En este sentido vale la pena resaltar que ninguna de las anterioridades reclaman una cantidad crítica de 6.3% por peso del total de la composición de loratadina y sus derivados.
6. Más aún, la especificidad de las Reivindicaciones 17 y 19 no se encuentra en las anterioridades citadas en las oposiciones.
7. Acompaño el comprobante de pago por concepto de la modificación de la solicitud, recibo No. 06-49,947

Renuncio al término faltante de traslado, y les solicito otorgar el privilegio de patente de invención aquí tramitado.

De Ustedes Atentamente,


LUIS FELIPE CASTILLO GIBSONE
T.P. No. 68.995 del C.S.J.

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(12) **United States Patent**
Lin et al.

(10) Patent No.: **US 6,720,002 B2**
(45) Date of Patent: **Apr. 13, 2004**

(54) **ANTIHISTAMINE FORMULATIONS FOR
SOFT CAPSULE DOSAGE FORMS**

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(*) Notice: **Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.**

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424/452, 455, 462, 456**

(56) **References Cited**

U.S. PATENT DOCUMENTS

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(57) **ABSTRACT**

The invention herein relates to a pharmaceutical composition containing loratadine and derivatives thereof which is suitable for use in soft capsule dosage forms. A pharmaceutical composition according to the invention comprises loratadine and derivatives thereof in a pharmaceutically effective amount; and a solvent system comprising a mixture of medium chain fatty acids. The loratadine compositions exhibit good solubility and storage stability while maintaining bioavailability of the drug. The compositions also permit high concentrations of solubilized loratadine per total fill volume and thereby permit the use of smaller capsules to deliver the same dosage of drug.

20 Claims, No Drawings

ANTI-HISTAMINE FORMULATIONS FOR SOFT CAPSULE DOSAGE FORMS

FIELD OF THE INVENTION

The invention relates to the field of pharmaceutical compositions. In particular, the invention pertains to pharmaceutical formulations containing antihistamines, such as, loratadine and its derivatives that are formulated for use in conjunction with soft gelatin capsules.

BACKGROUND OF THE INVENTION

Two identified histamine receptors are the receptors H-1 and H-2. The H-1 receptors mediate the response antagonized by conventional antihistamines. H-1 receptors are present in the mammalian skin, ileum and bronchial smooth muscle.

Non-narcotic or non-sedating hydrophobic antihistamine compounds such as loratadine and its derivatives are known. Loratadine was first described in U.S. Pat. No. 4,282,233 to Villani. Loratadine is an H-1 histamine receptor protein antagonist which binds to peripheral H-1 receptors as discussed in Quercia et al., *Hasp. Formul.*, 28, p.137-53 (1993). Loratadine is useful as an antihistamine and has little or no sedative effects. Thus, loratadine provides an antihistamine effect while still allowing the user to perform mental or physical functions requiring high levels of concentration. A variety of other therapeutic treatments using loratadine alone or in combination with other active ingredients have been suggested, such as treatment of seasonal or perennial rhinitis, allergic asthma, and motion sickness. See Aberg et al., U.S. Pat. No. 5,731,319, for example. Antiarrhythmic uses, such as treatment of atrial fibrillation (AF), have also been suggested, as described in Buckland et al., U.S. Pat. No. 6,110,927.

Loratadine derivatives which share antihistamine properties of loratadine have also been developed. Active metabolites such as decarballoxyated forms of loratadine have been of interest. One such metabolite derivative is 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo-[5,6]-cyclohepta-[1,2-b] pyridine, also known as decarboethoxy-loratadine (DCL) which is described in U.S. Pat. No. 4,659,716. U.S. Pat. No. 5,595,997 to Aberg et al. discloses methods of utilizing DCL for the treatment of allergic rhinitis and other disorders without adverse side effects.

Other patents relating to loratadine or a chemically related antihistamine, including any pharmaceutically acceptable salt thereof, in various dosage forms include U.S. Pat. No. 5,100,675 to Cho et al.; U.S. Pat. No. 4,990,535 to Cho et al.; and U.S. Pat. No. 5,314,697 to Kwam et al.

Oral dosage forms, such as loratadine-containing tablets and syrups, are known and marketed under the names Claritin®, Claritin Redibags® and Claritin-D® 24-Hour etc. (commercially available from Schering-Plough Corporation, N.J.).

These commercial products are described in U.S. Pat. No. 4,282,233 to Villani; U.S. Pat. No. 4,659,716 to Villani; U.S. Pat. No. 4,863,931 to Schumacher et al.; U.S. Pat. No. 6,132,758 to Munayyer et al. U.S. Pat. No. 6,132,758 discloses an antihistaminic syrup stabilized against degradation of the active ingredient by the addition of about 0.05 to 5 mg/mL of an amino-polycarboxylic acid. This patent teaches that under certain storage conditions losses of active agent can occur.

U.S. Pat. No. 4,910,205 to Kogan et al. discloses a transdermally acceptable composition comprising an effective amount of loratadine or its decarballoxylation product, about 40-70% weight % of a volatile solvent, about 5-50% by weight of a fatty acid ester and about 2-60% of an essential oil.

While syrup, solid and fast dissolving dosage forms are available for loratadine type antihistamines, there presently exists a need for a soft capsule dosage form. The soft capsule dosage form has many advantages known to those skilled in the art, however, formulating hydrophobic drugs into solutions for encapsulation into a soft capsule can present many problems. Oral delivery systems for hydrophobic drugs are known. Lacy et al. U.S. Pat. No. 6,096,338 describes delivery systems for hydrophobic drugs including histamine H-1 receptor antagonists such as loratadine. The carrier systems discussed include a digestible oil, preferably mixtures of partial or complete esters of medium chain fatty acids, and a pharmaceutically acceptable surfactant component comprising a hydrophilic surfactant containing a transesterification product of polyoxyethylene glycol with glycerol esters of capric and/or caprylic acids. This surfactant disperses the oil in vivo without substantially inhibiting in vivo lipolysis of the oil. The reference does not, however, specifically address the problems associated with storage stability and recrystallization of loratadine and its derivatives in soft capsule dosage forms.

Hydrophobic solvents are preferred for use in soft capsules so as to reduce the hydrophilic nature of the fill, wherein migration of water through the soft capsular material into the fill composition can cause recrystallization and precipitation of the active ingredient under storage conditions. One problem associated with hydrophobic solvents, however, is that they are known to adversely affect bioavailability of the drug. Compounds such as loratadine are susceptible to recrystallization and therefore experience the solvent system challenges associated with soft capsules. Ideally, a solvent system for loratadine and its derivatives is one which is hydrophobic, protonic and water-dispersible.

There thus exists a need for improved pharmaceutical formulations containing loratadine and derivatives thereof for use in soft capsules which solubilize loratadine and exhibit long-term storage stability at ambient conditions without recrystallization. There is also a need for a solvent system which does not adversely affect bioavailability of the active ingredient. Even more desirable would be a formulation which satisfies both of these criteria and also increase the fill concentration of loratadine. This would permit the use of smaller size capsules for a given dose of active.

SUMMARY OF THE INVENTION

The invention provides for a pharmaceutical composition comprising loratadine and its derivatives together with a solvent system for use in soft capsules. Loratadine compositions of the invention exhibit unexpected and improved solubilization properties at ambient storage conditions over extended period of time without recrystallization and precipitation of loratadine. The inventive composition also permits higher concentrations of loratadine to be delivered within a given fill volume. As a result, the total amount of fill volume needed to administer the same dosage of loratadine is reduced, and smaller capsule sizes can be used thereby improving patient comfort and reducing manufacturing costs.

The invention provides a pharmaceutical composition for use in soft capsules comprising loratadine and derivatives thereof and a solvent system comprising a mixture of mono- and diglycerides of medium chain fatty acids. In a more preferred embodiment the invention provides a pharmaceutical composition that additionally comprises a dispersant. In a most preferred embodiment the dispersant comprises povidone and Polysorbate™ 80.

There is further disclosed a pharmaceutical composition for use in soft capsule dosage form consisting essentially of:
a) loratadine and derivatives thereof present in an amount of about 6.3% by weight of the total composition;

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- b) mono- and di-glycerides of medium chain fatty acids present in an amount of about 87% by weight of the total composition;
- c) povidone present in an amount of about 6.3% by weight of the total composition; and
- d) Polysorbate™ 80 present in an amount of about 0.8% by weight of the total composition.

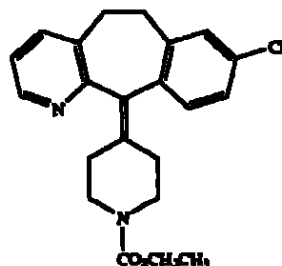
There is also disclosed a pharmaceutical composition for use in soft capsule dosage forms consisting essentially of:

- a) decarboxylated loratadine derivative in a pharmaceutically effective amount;
- b) CAPMUL™ MCM C-8;
- c) povidone; and
- d) Polysorbate™ 80.

There is further disclosed a soft capsule dosage form comprising a fill composition consisting essentially of:

- a) loratadine and derivatives thereof in a pharmaceutically effective amount;
 - b) a mixture of mono- and diglycerides of medium chain fatty acids;
 - c) povidone;
 - d) Polysorbate™ 80; and
- wherein said soft capsule has a capsule size of 5 minima or less.

Loratadine is the drug name given to the compound known as ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidinecarboxylate. A structure for this compound is:



Loratadine derivatives include compounds having the structural formula of loratadine and having substituents differing from that of loratadine and having substantially the same chemical and therapeutic properties. Loratadine derivatives include, but are not limited to, decarboxylated forms of loratadine, such as 8-chloro-5,6-dihydro-11-(4-piperidylidene)-5H-benzo-[5,6]-cyclohepta-[1,2-b]pyridine, also known as decarboxylated loratadine (DCL); and oxaloradine. As used herein and in the claims the phrase "loratadine and derivatives thereof" means loratadine or any chemically related antihistamine, including any pharmaceutically acceptable salt thereof. Chemically related antihistamines include any halogenated 11-benzo-cyclohepta-pyridine.

Loratadine and derivatives thereof can be present in an amount of about 6.3% or less by weight of the total fill composition. Typically, loratadine and derivatives thereof can be present in an amount of about 6.3% to about 3.0% by weight of the total fill composition.

Solvent systems which can be used in accordance with the invention are those which are both moderately lipophilic and have hydrogen bonding capability. Preferably, the solvent system has a hydrophilic lipophilic balance (HLB) value ranging from about 3 to about 7, more preferably ranging from about 4 to about 5. The preferred solvent system of the

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invention contains a mixture of mono- and diglycerides of medium chain fatty acids. Preferred mixtures of mono- and diglycerides are mixtures of caprylate and caprate. Most preferred as the mixture of mono- and diglyceride medium chain fatty acids is CAPMUL™ MCM-C8 (available from Ablec Corporation, Northampton, England). The mono- and diglyceride mixture can be present in an amount of about 89.0% by weight or less of the total fill composition. When CAPMUL™ MCM-C8 is used, it is preferably present in an amount ranging from about 89.0% to about 70.0%, more preferably about 89.0% to about 80%, by weight of the total fill composition.

The solvent system can further comprise a dispersant composition to enhance uniform dispersibility of the fill in water or gastric juices. The amount of the additional dispersant, however, is present in amount sufficient to enhance uniform dispersion of the fill in water or gastric juices without significantly increasing the volume of the fill. When a dispersant is used, it is preferred that the dispersant be present in an amount of 8.0% by weight of the fill or less. More preferred is a dispersant present in an amount of from about 7.5% to about 5.0%, most preferably from about 7.5% to about 7.0%, by weight of the total fill composition.

A preferred dispersant is a mixture of povidone (polyvinylpyrrolidone) and Polysorbate™ 80 (a polyoxyethylene sorbitol fatty acid esters). Mixtures of povidone and Polysorbate™ 80 can preferably be present in a weight ratio of about 10:1 to about 15:1, respectively.

Compositions according to the invention do not require the presence of additional ingredients such as additives and stabilizers typically associated with soft capsule fill formulations. Without these additional ingredients higher concentrations of loratadine and derivatives thereof can be obtained within smaller fill volumes as compared to existing formulations.

The invention further provides a soft dosage form having a pharmaceutical composition comprising loratadine and derivatives thereof and a solvent system having a mixture of medium chain mono- and diglycerides. In one embodiment, the invention includes a soft capsule comprising a storage stable composition having 10 mg of loratadine in solubilized state in a capsule size as small as 3 minima.

DETAILED DESCRIPTION OF THE INVENTION

The loratadine compounds of the invention can be prepared according to the method described in Villani U.S. Pat. No. 4,282,233, the entire text of which is incorporated herein by reference. The starting materials and reagents to prepare loratadine and its derivatives are well known in the art and readily available, and loratadine and its derivatives can be synthesized using conventional organic synthesis techniques. Metabolic derivatives of loratadine, such as decarboxylated forms of loratadine, can be prepared by removal of the carboxy moiety according to methods known in the art and as described in U.S. Pat. No. 4,659,716, the entire text of which is incorporated herein by reference. For example, loratadine can be refluxed in the presence of sodium hydroxide and ethanol to remove the carboxy moiety from the piperidine ring of the compound structure.

Solvent systems which can be used in accordance with the invention are those which are both moderately lipophilic and have hydrogen bonding capability. Preferably, the solvent system has a hydrophilic lipophilic balance (HLB) value ranging from about 3 to about 7, more preferably ranging from about 4 to about 5. Suitable solvent systems include, but are not limited to, polyglycolated glycerides (such as LABRAHIL® WL 2609HS available from Gattefosse, Blainville, U.K.), propylene glycol monolaurate (such as LAUROGLYCOL™ 90 available from Gattefosse), propy-

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less glycol monoacrylate (such as CAPRYOL™ 90 available from Janetsol), and mono- and diglyceride medium chain fatty acids. Most preferred is the mono-, diglyceride medium chain fatty acid mixture CAPMUL™ MCM C8 (commercially available from Abitec Corporation).

The solvent system can further comprise a dispersant composition to enhance uniform dispersibility of the fill in water. The amount of the additional dispersant, however, is present in amount sufficient to enhance uniform dispersion of the fill in water or gastric juices without significantly increasing the volume of the fill. When a dispersant is used, it is preferred that the dispersant be present in an amount of 8.0% by weight of the fill or less. Most preferred is a dispersant present in an amount of from about 7.5% to about 7.0% by weight of the total fill composition.

The dispersant composition used in accordance with the invention can be a combination of povidone together with a surfactant. Suitable surfactants which can be used include, but are not limited to, non-ionic surfactants having an HLB value ranging from about 14 to about 17; polyoxyethylene sorbitan fatty acid esters, such as Polysorbate™ 40, Polysorbate™ 60, Polysorbate™ 20, and Polysorbate™ 120; ethoxylated aliphatic alcohols, such as Oleth-20 (Volpo™ 20 available from Croda, Inc., Parsippany, N.J.), Ceteareth-20 (Volpo™ CS-20 available from Croda, Parsippany, N.J.); and caprylocaproyl macrogol-8 glycerides (LAUROGLYCOL™ 90 available from Gattafioro).

A preferred dispersant is a mixture of povidone and Polysorbate™ 80. Mixtures of povidone and Polysorbate™ 80 can be present in a ratio of about 10:1 to about 15:1.0, respectively.

Soft capsules containing pharmaceutical compositions can be prepared using conventional and known encapsulation techniques, such as that described in Stroud et al., U.S. Pat. No. 5,735,105, the entire text of which is incorporated herein by reference. In general, the formulation is deposited between two opposing ribbons of a gel composition. The composition of the ribbons may include gelatin, modified starches, gums, carrageenans and mixtures thereof. Those skilled in the art will appreciate what compositions are suitable. The opposing ribbons are then run between two die rollers having die pockets thereon the surface of which corresponds to the configuration of the desired soft capsule. The composition is sealed within the fused casing.

When formulated in accordance with the invention, a 10 mg loratadine dose can be accommodated by a 5 minim or less size oval soft capsule. A 10 mg loratadine dose can be contained within a capsule size as small as a 3 minim size

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oval soft capsule. Capsule size volumes of the invention are herein expressed in terms of minima. A minim is a pharmaceutical volumetric unit of measure wherein 1 minim=0.0616 cc.

Soft dosage forms, such as soft gelatin capsules, containing the loratadine compositions of the invention can be orally administered to patients in need of H1 receptor antagonist or antihistamine treatment.

The invention can be further illustrated by the following Examples:

EXAMPLE 1

Process of Preparing Loratadine Formulation
CAPMUL™ MCM C8, povidone, and Polysorbate™ 80 were combined. The mixture was heated to about 60° C. until the povidone was completely dissolved. Loratadine was added to the mixture and the resulting mixture was stirred until the loratadine was completely dissolved. The mixture was cooled to room temperature. The formulations prepared are summarized in Table 1 below:

TABLE 1

Loratadine Formulations with Mono-diglyceride of Medium Chain Fatty Acid Solvent System			
Ingredient	Formula 4-1 (mg/capsule) (% w/w)	Formula 4-2 (mg/capsule) (% w/w)	Formula 4-3 (mg/capsule) (% w/w)
Capsul™	139 mg (86.9%)	201.5 mg (86.2%)	264 mg (86.2%)
MCM-C8	10 mg (6.3%)	15 mg (6.6%)	20 mg (6.8%)
Povidone	1 mg (0.6%)	1.5 mg (0.7%)	2 mg (0.7%)
Polysorbate™ 80	10 mg (6.3%)	10 mg (4.4%)	10 mg (3.4%)
Loratadine CTK	100 mg (100.0%)	228 mg (100.0%)	296 mg (100.0%)
Fill weight	2.60 minims	3.70 minims	4.60 minims

40 Density = 1.0 g/ml

EXAMPLE 2

Preparation of Comparative Loratadine Formulations
In a manner similar to that of Example 1, the following formulations were prepared in accordance with the corresponding ingredients and proportions:

TABLE 2

Loratadine Formulations with PEG (Macrogel™ 400)/Propylene Glycol Solvent System				
Ingredient	Formula 1-1 (mg/capsule) (% w/w)	Formula 1-2 (mg/capsule) (% w/w)	Formula 1-3 (mg/capsule) (% w/w)	Formula 1-4 (mg/capsule) (% w/w)
PEG 400 (Macrogel™ 400)	240 mg (87.8%)	305 mg (88.4%)	340 mg (88.7%)	408 mg (88.9%)
Propylene Glycol	26 mg (8.8%)	30 mg (8.7%)	36 mg (8.9%)	41 mg (8.9%)
Loratadine	10 mg (3.4%)	10 mg (2.9%)	10 mg (2.5%)	10 mg (2.2%)
CTK	296 mg (100.0%)	345 mg (100.0%)	406 mg (100.0%)	439 mg (100.0%)
Fill weight				

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TABLE 2-continued

Lorazepam Formulations with PEG (Macrogel™ 400)/Propylene Glycol Solvent System				
Ingredient	Formula 1-1 (mg/capsule) (% w/w)	Formula 1-2 (mg/capsule) (% w/w)	Formula 1-3 (mg/capsule) (% w/w)	Formula 1-4 (mg/capsule) (% w/w)
Capsule size (ml/min)	5 ml/min oval	6 ml/min oval	7.5 ml/min oval	8.5 ml/min oval

Density = 1.08 g/ml

TABLE 3

Lorazepam Formulations with PEG (Macrogel™ 400)/Propylene Glycol/Povidone Solvent System				
Ingredient	Formula 2-1 (mg/capsule) (% w/w)	Formula 2-2 (mg/capsule) (% w/w)	Formula 2-3 (mg/capsule) (% w/w)	Formula 2-4 (mg/capsule) (% w/w)
PEG 400 (Macrogel™ 400)	240 mg (81.8%)	235 mg (82.6%)	336 mg (82.8%)	381 mg (83.0%)
Propylene Glycol	26 mg (8.2%)	28 mg (8.1%)	34 mg (8.4%)	38 mg (8.3%)
Povidone	22 mg (6.9%)	22 mg (6.4%)	26 mg (6.4%)	30 mg (6.5%)
Lorazepam CHK	10 mg (3.1%)	10 mg (2.9%)	18 mg (2.5%)	10 mg (2.2%)
Full weight Capsule size (ml/min)	318 mg (100.0%) 5 ml/min oval	345 mg (100.0%) 6 ml/min oval	406 mg (100.0%) 7.5 ml/min oval	459 mg (100.0%) 8.5 ml/min oval

Density = 1.1 g/ml

TABLE 4

Lorazepam Formulations with PEG (Macrogel™ 400)/Propylene Glycol/Polyoxyethylene 20 sorbitan monooleate (Polysorbate 80) Solvent System				
Ingredient	Formula 3A-1 (mg/capsule) (% w/w)	Formula 3A-2 (mg/capsule) (% w/w)	Formula 3B-1 (mg/capsule) (% w/w)	Formula 3B-2 (mg/capsule) (% w/w)
PEG 400 (Macrogel™ 400)	89 mg (36.2%)	108 mg (36.5%)	96 mg (39.0%)	116 mg (39.2%)
Propylene Glycol	13 mg (5.3%)	16 mg (5.4%)	13 mg (5.3%)	15 mg (5.1%)
Polysorbate™ 80	134 mg (54.5%)	162 mg (54.7%)	127 mg (51.6%)	155 mg (52.4%)
Lorazepam CHK	10 mg (4.1%)	10 mg (3.4%)	10 mg (4.1%)	10 mg (3.4%)
Full weight Capsule size (ml/min)	246 mg (100.0%) 4 ml/min oval	296 mg (100.0%) 5 ml/min oval	246 mg (100.0%) 4 ml/min oval	296 mg (100.0%) 5 ml/min oval

EXAMPLE 3

Comparative Storage Stability Study of Lorazepam Compositions

The storage stability test was conducted on each of the above formulations by subjecting samples of each formulation to varying conditions. Each sample was prepared by either filling 3DX11B gel pouches with the formulation or a

screw-capped brown glass bottle. Some of the samples were tested using pouches that were unsealed, and some of the samples tested were sealed using fresh gel. Each pouch sample was subjected to the following conditions: 1) 22° C. under ambient humidity, 2) 30° C. under 75% relative humidity (corresponding to accelerated solution stability test conditions), and 3) 5° C. under ambient humidity.

TABLE 5

Storage Stability at 5° C./Ambient Humidity of Loratadine Formulations with PEG 400/Propylene Glycol Solvent System			
Formulation:	Container:	Storage Period:	Result:
1-1	Capped vial	8 months	Clear/no crystals
1-1	Open gel bag	8 months	Crystallization

As can be seen from the data in the above Table, no observable crystallization occurred in the conventional Macrolog™ 400 formulation in the capped vials at 5° C. and ambient humidity conditions. On the other hand, the Macrolog™ 400 formulation crystallized when stored in the open gel bag. The results demonstrate that exposure of loratadine formulations to ambient moisture causes crystallization over time.

TABLE 6

Storage Stability at 22° C./Ambient Humidity of Loratadine Formulations			
Formulation:	Container:	Storage Period:	Result:
ALL	Capped vial	80 days	Clear/no crystals
1-1	Capped vial	8 months	Clear/no crystals

As can be seen in the above Table, none of the formulations tested had observable crystallization during a storage period of 80 days when contained in the capped vial at 22° C. and ambient humidity conditions.

TABLE 7

Storage Stability at 30° C./75% Relative Humidity of Loratadine Formulations with PEG 400/Propylene Glycol Solvent System				
Formula:	1-1	1-2	1-3	1-4
Days until crystallization (sealed gel bag)	8 days	13 days	13 days	16 days
Days until crystallization (open gel bag)	5 days	10 days	Not tested	Not tested

As can be seen from the above data, storage at 30° C. and 75% relative humidity resulted in observable crystallization of the conventional loratadine formulations in the Macrolog™ 400 solvent system, and crystallization occurred in both sealed and open gel bag containment. In the case of Formulas 1-1 and 1-2, crystallization occurred more rapidly in the open gel bag than the sealed gel bag.

TABLE 8

Storage Stability at 30° C./75% Relative Humidity of Loratadine Formulations with PEG 400/Propylene Glycol/Povidone Solvent System				
Formula:	2-1	2-2	2-3	2-4
Days until crystallization (sealed gel bag)	8 days	10 days	13 days	15 days
Days until crystallization (open gel bag)	5 days	10 days	Not tested	Not tested

As the data shows, storage conditions of 30° C. and 75% relative humidity of loratadine formulations with a solvent system of Macrolog™ 400 in combination with povidone

did not prevent crystallization from occurring in either sealed or open gel bags.

TABLE 9

Storage Stability at 30° C./75% Relative Humidity of Loratadine Formulations with PEG 400/Propylene Glycol/Polyisobutyl 80 Solvent System				
Formula:	3A-1	3A-2	3B-1	3B-2
Days until crystallization (sealed gel bag)	16 days	29 days	19 days	29 days

The above data shows that loratadine formulations in a Macrolog™ 400 solvent system and Polyisobutyl™ 80 did not prevent crystallization under 30° C. and 75% relative humidity storage conditions.

TABLE 10

Storage Stability at 30° C./75% Relative Humidity of Loratadine Formulations with Mono-, Diglyceride of Medium Chain Fatty Acid Solvent Systems				
Formula:	4-1	4-2	4-3	
Days until crystallization (sealed gel bag)	No crystals after 1 year and 4 months	No crystals after 71 days	No crystals after 71 days	
Days until crystallization (open gel bag)	Not tested	No crystals after 73 days	No crystals after 92 days	

As can be seen from the above data, loratadine formulations prepared in accordance with Formula 4-1 of the invention as described above exhibited no observable crystallization even after 71 days in storage at 30° C. with 75% relative humidity conditions in either the open or sealed gel bag containment. Further yet, no observable crystals were present in Formulation 4-1 of the invention even after 16 months in the sealed gel pouch containment.

INDUSTRIAL APPLICABILITY

The loratadine compositions of the invention provide for the use of loratadine in soft capsule dosage forms such as soft gelatin capsules by improving its solubility under storage conditions without adversely affecting its bioavailability. The compositions of the invention offer the additional benefit of increasing the concentration of solubilized loratadine per total fill volume, which permits smaller fill volumes to be used to deliver the same dosage of the drug. Accordingly, smaller capsule sizes can be used to administer the drug to patients, thereby increasing patient comfort and reducing manufacturing costs.

The complete disclosures of all patents, patent applications and publications are incorporated herein by reference as if each were individually incorporated by reference. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications can be made while remaining within the spirit and scope of the invention.

What is claimed is:

1. A pharmaceutical composition for use in soft capsule dosage forms comprising:
 - a) loratadine and derivatives thereof in a pharmaceutically effective amount; and
 - b) a solvent system comprising a mixture of medium chain fatty acids;
 wherein said loratadine and derivatives thereof is present in an amount of about 6.3% by weight of the total composition.

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2. A pharmaceutical composition for use in soft capsule dosage forms comprising:

- a) loratadine and derivatives thereof in a pharmaceutically effective amount; and
- b) a solvent system comprising a mixture of medium chain fatty acids;

wherein the mixture of medium chain fatty acids is present in an amount of about 89.0% by weight or less of the total composition;

and wherein said loratadine and derivatives thereof is present in an amount of about 6.3% by weight of the total composition.

3. A pharmaceutical composition for use in soft capsule dosage forms comprising:

- a) loratadine and derivatives thereof in a pharmaceutically effective amount; and
- b) a solvent system comprising a mixture of medium chain fatty acids;

and further comprising a dispersant;

and wherein said loratadine and derivatives thereof is present in an amount of about 6.3% by weight of the total composition.

4. The composition of claim 1 wherein said loratadine derivatives are decarboxylated forms of loratadine.

5. The composition of claim 4 wherein the decarboxylated loratadine derivative is decarboethoxyloratadine.

6. The composition of claim 1 wherein said loratadine and derivatives thereof is present in an amount of less than 6.3% of the total composition.

7. The composition of claim 1 wherein said mixture of medium chain fatty acids is a mixture of mono- and diglycerides of medium chain fatty acids.

8. The composition of claim 7 wherein said mixture of mono- and diglycerides of medium chain fatty acids comprises a mixture of caprylic acid and capric acid.

9. The composition of claim 2 wherein the mixture of medium chain fatty acids is present in an amount of from about 89.0% to about 90.0% by weight of the total composition.

10. The composition of claim 3 wherein the dispersant is present in an amount of about 8.0% by weight or less of the total fill composition.

11. The composition of claim 10 wherein the dispersant is present in an amount ranging from about 7.5% to about 7.0% by weight of the total composition.

12. The composition of claim 10 wherein the dispersant comprises povidone and polyoxyethylene sorbitan fatty acid ester.

13. The composition of claim 12 wherein the povidone to polyoxyethylene sorbitan fatty acid ester ratio is from about 10:1 to about 15:1.

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14. The composition of claim 13 wherein the ratio of povidone to polyoxyethylene sorbitan fatty acid ester is about 10:1.

15. The composition of claim 1 wherein said soft capsule dosage form is a soft gelatin capsule.

16. A pharmaceutical composition for use in soft capsule dosage forms consisting essentially of:

- a) loratadine and derivatives thereof present in an amount of about 6.3% by weight of the total composition;
- b) mono- and di-glycerides of medium chain fatty acids present in an amount of about 87% by weight of the total composition;
- c) povidone present in an amount of about 6.3% by weight of the total composition; and
- d) polyoxyethylene sorbitan fatty acid ester present in an amount of about 0.8% by weight of the total composition.

17. A pharmaceutical composition for use in soft gelatin dosage forms consisting essentially of:

- a) decarboxylated loratadine derivative in a pharmaceutically effective amount;
 - b) a mixture of mono- and di-glycerides of medium chain fatty acids comprising a mixture of caprylic and capric acid;
 - c) povidone; and
 - d) polyoxyethylene sorbitan fatty acid ester;
- wherein said loratadine derivative is present in an amount of about 6.3% by weight of the total composition.

18. The composition of claim 17 wherein the decarboxylated loratadine derivative is decarboethoxyloratadine.

19. A soft capsule dosage form comprising a fill composition consisting essentially of:

- a) loratadine and derivatives thereof in a pharmaceutically effective amount;
 - b) a mixture of mono- and diglycerides of medium chain fatty acids;
 - c) povidone;
 - d) polyoxyethylene sorbitan fatty acid ester; and
- wherein said loratadine and derivatives thereof is present in an amount of about 6.3% by weight of the total composition, and

wherein said soft capsule has a capsule size of 5 min or less.

20. The soft capsule of claim 19 wherein the capsule size is a 3 min oval.

* * * * *

REIVINDICACIONES:

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1. Una composición farmacéutica para uso en formas de dosificación de cápsula blanda, que comprende:

- a) loratadina y sus derivados, en una cantidad farmacéuticamente efectiva; y
- b) un sistema de solvente que comprende una mezcla de ácidos grasos de cadena mediana;

en la cual, dichos loratadina y sus derivados están presentes en una cantidad aproximada de 6,3% por peso de la composición total.

2. Una composición farmacéutica para uso en formas de dosificación de cápsulas blandas, que comprende:

- a) loratadina y sus derivados, en una cantidad farmacéuticamente aceptable; y
- b) un sistema de solvente que comprende una mezcla de ácidos grasos de cadena mediana;

en la cual, la mezcla de ácidos grasos de cadena mediana están presentes en una cantidad aproximada de 89,0% por eso o menos de la composición total;

y en la cual dichos loratadina y sus derivados están presentes en una cantidad aproximada de 6,3% por peso de la composición.

3. Una composición farmacéutica para uso en formas de dosificación de cápsulas blandas, que comprende:

- a) loratadina y sus derivados, en una cantidad farmacéuticamente aceptable;
y
- b) un sistema de solvente que comprende una mezcla de ácidos grasos de cadena mediana;

y que además comprende un dispersante;

y en donde dichos loratadina y sus derivados están presentes en una cantidad aproximada de ,3% por peso de la composición total.

4. La composición de la reivindicación 1, en la cual dichos derivados de

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6. La composición de la reivindicación 1, en la cual dicha loratadina y sus derivados están presentes en una cantidad no menor 6,3% de la composición total.

7. La composición de la reivindicación 1, en la cual dicha mezcla de ácidos grasos de cadena mediana es una mezcla de mono y di-glicéridos de ácidos grasos de cadena mediana.

8. La composición de la reivindicación 7, en la cual dicha mezcla de mono y di-glicéridos de ácidos grasos de cadena mediana comprende una mezcla de ácido caprílico y ácido cáprico.

9. La composición de la reivindicación 2, en la cual la mezcla de ácidos grasos de cadena mediana está presente en una cantidad entre 89,0% y 90,0% por peso de la composición total.

10. La composición de la reivindicación 3, en la cual el dispersante está presente en una cantidad aproximada de 8,0% por peso o menos de la composición completa de relleno.

11. La composición de la reivindicación 10, en la cual el dispersante está presente en una cantidad que varía de 7,5% a 7,0% por peso de la composición total.

12. La composición de la reivindicación 10, en la cual el dispersante comprende povidona y éster de ácido graso de sorbitán y polioxietilén.

13. La composición de la reivindicación 12, en la cual la relación povidona a éster de ácido graso de sorbitán polietoxietilén es entre 10:1 a 15:1

14. La composición de la reivindicación 13, en la cual la relación de povidona a éster de ácido graso de sorbitán polioxietilén es de aproximadamente 10:1

15. La composición de la reivindicación 1, en la cual dicha forma de dosificación de cápsula blanda es una cápsula de gelatina blanda.

16. Una composición farmacéutica para uso en formas de dosificación de cápsula blanda, la cual consiste esencialmente de:

a) loratadina y sus derivados presentes en una cantidad aproximada de 6,3% por peso de la composición total;

b) mono y di-glicéridos de ácidos grasos de cadena mediana presentes en

- d) éster de ácido graso de sorbitan polioxietilén en una cantidad aproximada de 0,8% por peso de la composición total.

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17. Una composición farmacéutica para uso en formas de dosificación de gelatina blanda consistente esencialmente de:

18. La composición de la reivindicación 17, en la cual el derivado de loratadina descarbalcoxilada es un descarboetoxi loratadina.

19. Una forma de dosificación de cápsula blanda que comprende una composición de relleno que consiste esencialmente de:

- a) loratadina y sus derivados en una cantidad farmacéuticamente efectiva;
- b) una mezcla de mono y di-glicéridos de ácidos grasos de cadena mediana;
- c) povidona;
- d) éster de ácido graso de sorbitan polioxietilén, y

en donde dicha loratadina y sus derivados están presentes en una cantidad aproximada de 6,3% por peso de la composición total, y

en donde dicha cápsula blanda tiene un tamaño de cápsula de 5 mínimas o menos.

20. La cápsula blanda de la reivindicación 19, en la cual el tamaño de la cápsula es de 3 mínimas ovalada.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 06 - 49,947
FECHA : JUNIO 30 DE 2006

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PBO	Vr. PAGO
CASTILLO BRAU Y ASOCIADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	53780427	30/06/2006	95,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03	CAMBIO DE MODALIDAD Y MODIFICA	
		12 MARCAS Y LENAS COMERCIALES	95,000.00
		TOTAL :	\$ 95,000.00

SON: NOVENTA Y CINCO MIL PESOS



RESPONSABLE : _____