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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____

SUPERINDUSTRIA Y COMERCIO
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Trámite : 002 PATENTES 0 332 PRESENTAC 411 PRESENTA
Dependencia: 2003 DIVISION DE NUEVAS CREACIONES

Ref.: Solicitud colombiana de Patente No. 00 096727
Solicitante: SCHERING CORPORATION

SUSTITUCIÓN DE PODER

CARLOS R. OLARTE, mayor y vecino de Bogotá. D.C., identificado como aparece al pie de mi firma, actuando en mi carácter de apoderado de la sociedad de la referencia, respetuosamente me permito manifestar que **SUSTITUYO** el poder a mi conferido por la mencionada sociedad en el doctor **ALVARO CORREA ORDOÑEZ**, identificado con la Cédula de Ciudadanía número 79.143.366 de Usaquén y con la Tarjeta Profesional número 20.281, para que sea él quien en adelante, asuma el trámite de la presente solicitud.

El apoderado sustituto queda con las mismas facultades del principal.

Atentamente,



CARLOS R OLARTE
C.C. No. 79.782.747 de Bogotá
T. P. No. 74.295 del Consejo Superior de la Judicatura

**DILIGENCIA DE RECONOCIMIENTO
Y PRESENTACION PERSONAL**

Ante el Notario Once del Circulo de Santafé de Bogotá, compareció [Firma]

Quien exhibió la C.C. No. 99-982-919
expedida en Bogotá el 14.195
y declaró que la firma y huella que aparece en
el presente memorial son suyas y que el con-
enido del mismo es cierto.

Memorial dirigido a interesa del

29 JUL 195

Santafé de Bogotá, D.C.

Firma del Declarante

HUELLA

Autorizó la a. Termin. Diligencia

NOTARIO ONCE DEL CIRCULO DE SANTAFÉ DE BOGOTÁ



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**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

2020/
Bogotá, D.C.,

Doctor
Álvaro Correa Ordóñez
Apoderado

Oficio N° 06986

REFERENCIA	Radicación	00 96727
	Trámite	002
	Evento	001
	Actuación	430
	Folios	010

Como resultado del examen de patentabilidad de la solicitud de patente de invención N° 00 96727, realizado según el artículo 45 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

Documentos estudiados:

- . Descripción: folios 52-83
- Ejemplos: folios 84-92
- . Capítulo reivindicatorio estudiado: folios 93-99
- . Se reivindica prioridad presentada en Estados Unidos, el 20.12.99, bajo el número 60/172836

Objeto de la Invención

Según las reivindicaciones 1 a 15 de la presente solicitud, se refiere a una composición sólida de liberación extendida que comprende (1) un núcleo que comprende pseudoefedrina y (2) un revestimiento de película que comprende desloratadina.

Clasificación Internacional de patentes A 61 K 9/22

Claridad de la solicitud

El art. 30 de la Decisión 486 contempla que *"Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción."*

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Los términos "cantidad efectiva" de la reivindicación 1, no es claro, debido a que no define de manera clara el alcance de la protección que se busca.
Las reivindicaciones 1, 2, 4, 5, 12, 14 y 15 caracterizan a una composición por un resultado a obtener, lo cual no es claro y no diferencia técnicamente a la composición; además los parámetros farmacocinéticos presentes en dichas reivindicaciones no son claros, debido a que los test in vivo también dependen del paciente y una persona versada en la materia no sabría si está trabajando dentro o fuera del alcance de dichas reivindicaciones.

Favor hacer las aclaraciones y correcciones del caso.

Determinación del estado de la técnica:

Consultadas las fuentes de información con que cuenta este despacho, se encontraron los siguientes documentos, anteriores a la fecha de prioridad de la presente solicitud - 20.12.99-, relacionados con la materia de la presente solicitud:

Nº	Documento	Título	Fecha de publicación
1	US 5314697	"Composición oral estable de liberación extendida que comprende loratadina y pseudoefedrina"	07.11.90
2	US 5100675	"Tableta de liberación sostenida que comprende loratadina, ibuprofeno y pseudoefedrina"	31.03.92

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*

En cumplimiento del artículo 14 de la decisión 486 de la comisión de la comunidad andina, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación del NIVEL INVENTIVO

El artículo 18 de la decisión 486 dispone *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica"*

La patente US 5314697 revela composiciones orales de liberación prolongada que comprenden un núcleo que contiene pseudoefedrina y una capa de loratadina.

La patente US 5100675 enseña tabletas que consisten en un núcleo de liberación sostenida que contiene pseudoefedrina e ibuprofeno y una capa de liberación inmediata con loratadina o desloratadina. La capa de liberación sostenida contiene excipientes como hidroxipropil metilcelulosa, povidona, celulosa microcristalina,

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Teniendo en cuenta el objeto de la presente solicitud, el cual es proveer una tableta recubierta que comprende pseudoefedrina y desloraradina, es obvio que una persona versada en la materia utilice las enseñanzas de los elementos citados y llegue a fabricar las composiciones que se pretenden proteger.

Además no se demuestra que las composiciones de la presente solicitud presentan efectos superiores o inesperados a las reportadas en el estado de la técnica.

Lo anterior puede afectar en nivel inventivo de la presente solicitud.

En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
1	US 5314697	1-15	Nivel Inventivo
2	US 5100675	1-15	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo 5 del título primero de la Circular Única N° 10 de 2001


Álix Carmona Céspedes de Vergel
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 6 JUL 2016

CONCEPTO TÉCNICO Número 1033	EXAMINADOR TÉCNICO Código 202024
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US005314697A

United States Patent [19]
Kwan et al.

[11] **Patent Number:** **5,314,697**
[45] **Date of Patent:** **May 24, 1994**

- [34] **STABLE EXTENDED RELEASE ORAL
DOSAGE COMPOSITION COMPRISING
LORATADINE AND PSEUDOPHEDRINE**
- [75] **Inventors:** Henry K. Kwan, Summit; Stephen M.
Lisbowitz, Neuhanic Station, both of
N.J.
- [73] **Assignee:** Schering Corporation, Kenilworth,
N.J.
- [21] **Appl. No.:** 953,470
- [22] **Filed:** Oct. 23, 1992
- [31] **Int. Cl.¹** A61K 9/36
- [32] **U.S. Cl.** 424/480; 424/463;
424/465; 424/468; 424/469; 424/470; 424/474;
424/475; 514/849; 514/853; 514/964; 514/965
- [38] **Field of Search** 424/480, 463, 465, 468,
424/469, 470, 474, 475; 514/849, 853
- [36] **References Cited**
U.S. PATENT DOCUMENTS
4,232,233 8/1981 Vilmi 424/267

4,990,335 2/1991 Cho et al. 514/556
5,100,675 3/1992 Cho et al. 424/468

OTHER PUBLICATIONS

Package Label for Claritin® (Loratadine, 5 mg, pseudoephedrine sulfate, 120 mg) Extra Repetabs Schering, Canada.

Primary Examiner—Paul R. Michl
Assistant Examiner—James M. Spear
Attorney, Agent, or Firm—Thomas D. Hoffman

[57] **ABSTRACT**

A film-coated extended release oral dosage composition containing the nasal decongestant pseudoephedrine sulfate in a unique polymer matrix core and a film-coating on such core containing the non-sedating antihistamine, loratadine, and use of the said composition for treating patients showing the signs and symptoms associated with upper respiratory diseases and nasal congestion are disclosed.

7 Claims, No Drawings

STABLE EXTENDED RELEASE ORAL DOSAGE COMPOSITION COMPRISING LORATADINE AND PSEUDOEPHEDRINE

BACKGROUND OF THE INVENTION

This invention relates to a film-coated extended release oral dosage composition containing the nasal decongestant pseudoephedrine in a unique polymer matrix core and a film-coating on such core containing the non-sedating antihistamine, loratadine. The oral dosage composition is useful for treating patients showing the signs and symptoms associated with upper respiratory diseases and nasal congestion.

Loratadine is disclosed in U.S. Pat. No. 4,282,133 as a non-sedating antihistamine and it is useful as an anti-allergy agent in, for example, the treatment of seasonal allergic rhinitis symptoms such as sneezing and itching.

Pseudoephedrine as well as pharmaceutically acceptable acid additional salts, e.g., those of HCl or H₂SO₄, 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. For example, 5 mg of loratadine and 120 mg of pseudoephedrine sulfate ("PES") in a matrix core repotab tablet product is available wherein the PES is equally distributed in the tablet coating and barrier core and all the loratadine is in the coating. The product is recommended for twice-a-day dosing for effectiveness. It would be desirable to have a once-a-day loratadine-pseudoephedrine product.

The successful development of a formulation of a loratadine-pseudoephedrine once-a-day product requires achieving a release rate profile for pseudoephedrine component over an extended period in excess of twelve hours while maintaining the safety and effectiveness of loratadine. Products containing non-sedating antihistamines in combination with pseudoephedrine such as Seldane-D, a press-coated product of terfenadine and pseudoephedrine and Hismanal-D, a combination of pseudoephedrine prills and a separate astemizole tablet are known. However, the administration of terfenadine and astemizole products to humans has been found to cause adverse effects including cardiac arrhythmias and occurrence of these arrhythmias have increased when the terfenadine or astemizole products are co-administered with other drugs such as ketoconazole and erythromycin or upon overdose of the non-sedating anti-histamine.

It would be desirable for increased patient compliance to have an extended release product effective and safe when used on a once-a-day basis.

SUMMARY OF THE INVENTION

We have discovered that a film-coating of loratadine on a core tablet containing pseudoephedrine sulfate in a specific polymer matrix provides immediate release of loratadine and extended release of pseudoephedrine sulfate from the matrix core over a period in excess of twelve hours.

Thus the present invention provides a film-coated extended release oral dosage composition comprising:

a. a matrix core comprising:

	mg/core
Pseudoephedrine Sulfate	120-360
Hydroxypropyl Methylcellulose 2208	160-480
100,000 cps	
Ethylcellulose	40-120
Dihydro Calcium Phosphate Dihydrate	56-164
Povidone	20-60
Silicon Dioxide	6-12
and	
Magnesium Stearate	2-6
Matrix Core Weight Range:	400-1200 mg

and

b. a coating on said core comprising:

	mg/tablet
Loratadine	5-15
Hydroxypropyl Methylcellulose 2910 6 cps	17-50
Polyethylene Glycol 400	0.25-5.0
Polyethylene Glycol 3350	3.4-10.15
Approximate Coating Weight	25-80.0 mg
Composition Weight Range	427-1280 mg

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

a. a matrix core comprising:

	mg/core
Pseudoephedrine Sulfate	240
Hydroxypropyl Methylcellulose 2208 100,000 cps.	160-480
Ethylcellulose	40-120
Dihydro Calcium Phosphate Dihydrate	56-164
Povidone	20-60
Silicon Dioxide	6-12
and	
Magnesium Stearate	2-6
Approximate Core Weight Range	520-1080 mg

and

b. a coating on said core comprising:

	mg/tablet
Loratadine	10
Hydroxypropyl Methylcellulose 2910 6 cps.	17-50
Polyethylene Glycol 400	0.25-5.0
Polyethylene Glycol 3350	3.4-10.15
Approximate Coating Weight Range	31-75 mg
Approximate Composition Weight Range	553-1155 mg

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

a. a matrix core

	mg/core
Pseudoephedrine Sulfate USP	240
Hydroxypropyl Methylcellulose 2208 USP 100,000 cps	320
Ethylcellulose NF Type 7	80
Dihydro Calcium Phosphate USP Dihydrate	108
Povidone USP	40
Silicon Dioxide NF	8
and	
Magnesium Stearate NF	4
Approximate Matrix Core weight	800 mg

and

b. a coating upon said core comprising:

	mg/tablet
Loratadine, Microencapsulated	10
Hydroxypropyl Methylcellulose 2910 USP 6 cps	13
Polyethylene Glycol 400 NF	0.67
Polyethylene Glycol 3350 NF	6.73
Color Dispersion (Solids)	6.25
Approximate Coating Weight	57 mg
Approximate Composition Weight	837 mg

DETAILED DESCRIPTION OF THE INVENTION

We have discovered a unique oral dosage composition containing a specific selection of ingredients including specific amounts of pseudoephedrine sulfate in a matrix core and of loratadine in an immediate release polymer film coating on the core. The oral dosage composition of this invention provides (1) immediate release (i.e., within one hour after oral administration to a patient) of the total dose of loratadine to maintain the once-a-day efficacy of Loratadine (2) the extended release of pseudoephedrine from the matrix polymer cover over a period of at least 12 preferably 12 to 16 hours and more preferably at least 16 hours from oral administration (3) reasonable dose size for enhancing patients' compliance and (4) a shelf life of at least 24 months.

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 12 hours, preferably 12 to 16 hours and more preferably for at least 16 hours for pseudoephedrine. For example, the use of hydroxypropyl methyl cellulose 4,000 cps and 15,000 cps did not provide this desired extended release period for dose of pseudoephedrine sulfate. Only by combining four parts by weight of hydroxypropyl methyl cellulose 2208 USP, 100,000 cps with one part by weight of ethyl cellulose together with $\frac{1}{2}$ part by weight of povidone as a secondary binder was the desired extended release profile for pseudoephedrine 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 (6 mg/tablet) but it is preferred to maintain the lubricant level at 1/10 part by weight of lubricant to one part by weight of povidone as secondary binder.

The hydroxyl propyl methyl cellulose 2910 acts as a film-forming agent in the film coating, and the polyethylene glycols act as plasticizers. Other suitable film-forming polymers which may be used include hydroxypropyl cellulose, 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 packages at between 2° and 30° C. in an ambient environment.

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, 100,000 cps, ethylcellulose, and dibasic calcium phosphate are blended and granulated with the 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 oral dosage composition in the preferred form of a tablet.

The coating is normally applied to the tablet cores in the following manner:

Cores are charged into a suitable coating pan. A water dispersion of hydroxypropyl methylcellulose 2910 USP and polyethylene glycol 3350 NF is applied to the cores. These sub-coated cores are then coated with a dispersion of loratadine, hydroxypropyl methylcellulose 2910 USP, polyethylene glycol 3350 NF and white color dispersion. This is followed by an application of polishing coating dispersion containing hydroxypropyl methylcellulose and polyethylene glycol 400 NF. The coated tablets are then branded (with black ink) and packaged in plastic bottles and blisters for storage at a temperature between 2° and 30° C. in an ambient environment.

EXAMPLE I

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

1. Tablet Core

A. Method of Manufacture

1. Dissolve povidone in a mixture of alcohol and water.
2. Combine the pseudoephedrine sulfate, hydroxypropyl methylcellulose 2208, ethylcellulose and dibasic calcium phosphate, dihydrate in a suitable mixing bowl and blend.
3. Granulate the blend from Step 2 with the solution from Step 1. pass the wet granulation through a screen.
4. Dry the granulation 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 a screen.
6. Add the requisite amount of silicon dioxide and magnesium stearate to the dried, milled granules and blend.
7. Compress the blend on a suitable tablet press. During the compression operation, representative samples of the cores are taken and in-process tests are performed.

The core matrix meets the following specification:

Weight: $800 \pm 5\%$ (mg)

Thickness: 0.280 ± 0.010 inches

Hardness: 22 ± 6 Strong-Cobb Units

The cores are coated in the following manners:

A. Preparation of Coating Dispersions and Solutions

1. Sub-Coating Solution

- (1) Disperse hydroxypropyl methylcellulose USP 2910 and polyethylene glycol 3350 in a portion of hot purified water.
- (2) Add the remainder of the purified water and cool the solution to room temperature.

2. Active Coating Dispersion

- (1) Disperse hydroxypropyl methylcellulose USP 2910 and polyethylene glycol 3350 in a portion of hot purified water. Add additional water and cool the dispersion to room temperature.

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(2) Disperse Loratadine in the remaining portion of room temperature purified water. Combine with hydroxypropyl methylcellulose polyethylene glycol dispersion (Step 1).

(3) Add white color dispersion. Mix until uniform.

3. Polishing Coating Solution

(1) Disperse hydroxypropyl methylcellulose USP 2910 and polyethylene glycol 400 in a portion of hot purified water.

(2) Add the remainder of the purified water and cool the solution to room temperature.

B. Coating of Tablet Core

(1) Charge the requisite quantity of tablet cores to a suitable coating pan.

(2) Apply the sub-coating solution.

(3) Quantitatively apply the active coating dispersion

(4) Apply the polishing coating solution

C Branding

(1) Brand the coated tablets with black imprinting ink.

The preferred composition of the tablet core and coating is given below

Tablet Core	mg/core
Pseudoephedrine Sulfate USP	240
Hydroxypropyl Methylcellulose 2208 USP 100,000 cps	320
Ethylcellulose NF Type 7	80
Dibasic Calcium Phosphate USP Dihydrate	108
Povidone USP	40
Silicon Dioxide NF	8
Magnesium Stearate NF	4
Approximate Core Weight	800 mg

Tablet Coating	mg/tablet
Loratadine, Microencapsulated	10
Hydroxypropyl Methylcellulose 2910 USP 6 cps	33
Polyethylene Glycol 400 NF	0.67
Polyethylene Glycol 3350 NF	6.75
Color Dispersion (Solids)	6.25
Imprinting Ink	—
Approximate Coating Weight	57 mg
Approximate Tablet Weight	857 mg

The in vitro dissolution profile of the tablet of Example 1 was measured in a stirred 0.1N HCl solution at 37° C. The loratadine in the coating was dissolved within the first hour and the total dose of pseudoephedrine sulfate in the core was slowly released via erosion and dissolution mechanisms over a 12 to 16 hour period.

What is claimed is:

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

a. a matrix core comprising:

	mg/core
Pseudoephedrine Sulfate	120-360
Hydroxypropyl Methylcellulose 2208 100,000 cps	160-480
Ethylcellulose	40-120
Dibasic Calcium Phosphate USP Dihydrate	56-164
Povidone	20-60
Silicon Dioxide	6-12
and	
Magnesium Stearate	2-6
Matrix Core Weight Range:	400-1200 mg

and

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b. a coating on said core comprising:

	mg/tablet
Loratadine	5-15
Hydroxypropyl Methylcellulose 2910 6 cps	17-50
Polyethylene Glycol 400	0.25-5.0
Polyethylene Glycol 3350	3.4-10.15
Approximate Coating Weight Range:	26-80.9 mg
Approximate Composition Weight Range:	427-1280 mg

2. A method of treating patients showing the signs and symptoms associated with upper respiratory diseases which comprises administering to such a patient the oral dosage composition of claim 1.

3. The oral dosage composition of claim 1 wherein 240 mg. of pseudoephedrine sulfate is in the core and 10 mg. of loratadine is in the coating.

4. A film-coated extended release oral dosage composition comprising:

a. a matrix core comprising:

	mg/core
Pseudoephedrine Sulfate	240
Hydroxypropyl Methylcellulose 2208 100,000 cps	160-480
Ethylcellulose	40-120
Dibasic Calcium Phosphate Dihydrate	56-164
Povidone	20-60
Silicon Dioxide	6-12
and	
Magnesium Stearate	2-6
Approximate Core Weight Range:	320-1080 mg

and

b. a coating on said core comprising:

	mg/tablet
Loratadine	10
Hydroxypropyl Methylcellulose 2910 6 cps	17-50
Polyethylene Glycol 400	0.25-5.0
Polyethylene Glycol 3350	3.4-10.15
Approximate Coating Weight Range:	31-75 mg
Approximate Composition Weight Range:	352-1155 mg

5. A method of treating a patient showing the signs and/or symptoms associated with upper respiratory diseases which comprises administering to such a patient the oral dosage form of claim 4.

6. A film-coated extended release oral dosage composition comprising:

a. a matrix core comprising:

	mg/core
Pseudoephedrine Sulfate USP	240
Hydroxypropyl Methylcellulose 2208 USP 100,000 cps	320
Ethylcellulose NF Type 7	80
Dibasic Calcium Phosphate USP Dihydrate	108
Povidone USP	40
Silicon Dioxide NF	8
and	
Magnesium Stearate NF	4
Approximate Core weight	800 mg

and

b. a coating upon said core comprising:

United States Patent [19]
Cho et al.

US005100675A

[11] **Patent Number:** 5,100,675
[45] **Date of Patent:** Mar. 31, 1992

[54] **SUSTAINED RELEASE TABLET
COMPRISING LORATADINE, IBUPROFEN
AND PSEUDOEPHEDRINE**

[75] **Inventors:** Wing-Kee P. Cho, Princeton;
Winston A. Vadino, Whitehouse
Station; Imtiaz A. Chandry, Denville,
all of N.J.

[73] **Assignee:** Schering Corporation, Kenilworth,
N.J.

[21] **Appl. No.:** 612,633

[22] **Filed:** Nov. 13, 1990

Related U.S. Application Data

[62] **Division of Ser. No. 346,687, May 3, 1989, Pat. No.**
4,990,333.

[51] **Int. Cl.³** A01N 37/30; A01N 37/00;
A61K 9/22

[52] **U.S. Cl.** 424/468; 514/557;
514/964; 514/290; 514/556

[58] **Field of Search** 514/356, 290, 964, 557;
424/468

[56]

References Cited

U.S. PATENT DOCUMENTS

4,382,233	8/1981	Villani	514/290
4,540,566	9/1983	Devh et al.	424/22
4,659,716	4/1987	Villani et al.	514/290
4,738,966	4/1988	Sunshine et al.	514/277
4,780,322	10/1988	Martini et al.	424/501
4,783,465	11/1988	Sunshine et al.	514/233
4,829,064	5/1989	Sunshine et al.	514/290
4,871,733	10/1989	Sunshine	514/212
4,999,189	3/1991	Kogan et al.	424/79

Primary Examiner—Frederick E. Waddell

Assistant Examiner—T. J. Cifares

Attorney, Agent, or Firm—John J. Maitner, Anita W.
Magatti, Eric S. Dicker

[57]

ABSTRACT

Pharmaceutical compositions for use in the treatment of
cough/cold symptoms comprising loratadine, ibuprofen
and pseudoephedrine are disclosed.

10 Claims, No Drawings

SUSTAINED RELEASE TABLET COMPRISING LORATADINE, IBUPROFEN AND PSEUDOEPHEDRINE

This is a division of application Ser. No. 07/346,687, filed May 3, 1989, now U.S. Pat. No. 4,990,535.

BACKGROUND OF THE INVENTION

The present invention relates generally to novel pharmaceutical compositions of matter comprising the non-sedating antihistamine loratadine or the decarbalcoxylation product thereof (i.e. 6-chloro-6, 11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta [1,2-b]pyridine), in combination with the non-steroidal anti-inflammatory drug ibuprofen, the decongestant pseudoephedrine, and suitable pharmaceutically acceptable non-toxic carriers or excipients, and to methods of using said compositions in the treatment, management or mitigation of cough, cold, cold-like and/or flu symptoms and the discomfort, pain, fever and general malaise associated therewith.

Non-narcotic analgesics, most of which are also known as non-steroidal anti-inflammatory drugs, such as ibuprofen, are widely administered orally in the treatment of mild to severe pain, and have been disclosed as useful in treating cough/cold symptoms in combination with certain antihistamines and decongestants. See, for example U.S. Pat. Nos. 4,352,899, 4,619,334 and 4,783,465, all to Sumakine et al.

SUMMARY OF THE INVENTION

It is a primary object of the present invention to provide a novel sustained release pharmaceutical composition of matter comprising a combination of an analgesically effective amount of ibuprofen, an antihistaminically effective amount of loratadine and a decongestant-effective amount of pseudoephedrine in a pharmaceutically acceptable carrier.

It is a further object of the present invention to provide methods for the symptomatic relief of cough, cold, cold-like and flu symptoms by the administration of preselected dosages of the pharmaceutical compositions of the present invention. Cold-like symptoms as used herein refers to coryza, nasal congestion, upper respiratory infections, allergic rhinitis, otitis, sinusitis, etc.

DETAILED DESCRIPTION OF THE INVENTION

A combination dosage form especially suitable for administration of a combination comprising ibuprofen, loratadine or its decarbalcoxylation product, and pseudoephedrine or a pharmaceutically acceptable salt thereof is disclosed. The dosage form provides for the sustained release of ibuprofen and pseudoephedrine or a salt thereof, preferably the sulfate, and the immediate release of loratadine or its decarbalcoxylation product, since the latter are inherently long-acting. Release of ibuprofen and pseudoephedrine takes place over 2 to 16 hours, preferably 5 to 12 hours. One or two, preferably two tablets are administered at a time. Concentration ranges for the actives are as follows: pseudoephedrine salt, 30-240 mg/tablet; ibuprofen, 100-800 mg/tablet; and loratadine or its decarbalcoxylation product, 0.5-10 mg/tablet. The concentration ranges represent about 3 to about 25% of coated tablet weight for pseudoephedrine salt, about 10 to about 55% for ibuprofen, and about 0.05 to about 1.5% for loratadine.

The preferred dosage form is a coated tablet, wherein loratadine or its decarbalcoxylation product is present in the tablet coating and ibuprofen and the pseudoephedrine salt are present in the tablet core, which core also comprises a swellable hydrophilic polymer as a binder. When the dosage form comes into contact with gastric or aqueous media, the coating dissolves rapidly to release loratadine and the core hydrates and slowly releases ibuprofen and pseudoephedrine by erosion of the hydrated layer and/or by diffusion of drug through the core. The rate and duration of release is controlled by the relative concentration of the hydrophilic polymer, as well as by the particular characteristics of the hydrophilic polymer selected.

Loratadine, the USAN chemical name of which is ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-11-piperidinecarboxylate, is claimed in U.S. Pat. No. 4,282,233, and its decarbalcoxylation product, 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo [5,6]cyclohepta[1,2-b]pyridine, claimed in U.S. Pat. No. 4,659,716. Pharmaceutically acceptable salts of loratadine and its decarbalcoxylation product are also contemplated for use in the present invention. The dosage range for both loratadine and its decarbalcoxylation product is about 0.5 to about 10 mg per day, preferably about 5 to about 10 mg/day, depending on the age, weight, condition, etc. of the patient.

Typical swellable hydrophilic polymers include cellulose ethers such as methylcellulose, hydroxypropylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, carboxymethylcellulose and carboxyethylcellulose, or mixtures thereof, with hydroxypropylmethylcellulose (HPMC) being preferred. Particularly useful HPMC polymers are HPMC USP 2910 and USP 2208, for example The Dow Chemical Company's METHOCCEL E4M, E15M and K100M, wherein the designation "E" refers to USP 2910 and the designation "K" refers to USP 2208, and wherein the number designation refers to the viscosity in a 2% aqueous solution (e.g. 4M designates a viscosity of 4000 cps) and indicates the number average molecular weight (Mn) of the polymers (E4M has Mn 86,000, E15M has Mn 120,000, and K100M has Mn 246,000). The hydrophilic polymer or polymer mixture is present at a concentration of about 5 to about 15% of the tablet core weight.

The tablet core optionally further comprises excipients such as insoluble polymers, soluble or insoluble fillers, antiadherents, lubricants and additional binders. Typical fillers include dibasic calcium phosphate and the dihydrate thereof, microcrystalline cellulose and lactose, with microcrystalline cellulose being preferred. Fillers are present at a concentration of about 10% to about 20% of the tablet core weight. Antiadherents, used to prevent tablets from sticking to the tablet press, typically include silicas such as silicon dioxide and talc, and are present at a concentration of 0 to about 5% of the tablet core weight. Typical lubricants are magnesium stearate and stearic acid, present at a concentration of about 0.25 to about 5% of the tablet core weight. Additional binders used in the granulation of the drug-polymer mixture typically include povidone and cornstarch. Such binders are present at a concentration of about 0.5 to about 3% of the tablet core weight.

The tablet coating comprises, in addition to the active, a hydrophilic polymer as described above, preferably HPMC, and a plasticizer such as polyethylene glycol (PEG). A preferred HPMC for tablet coating is

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HPMC 2910 having a viscosity of 4-60 cps in a 2% aqueous solution, more preferably having a viscosity of 6 cps. The PEG preferably has a molecular weight of 300-6000. The ratio of polymer to plasticizer is about 2:1 to about 5:1, with 5:1 being preferred.

For preferred compositions of the present invention, either the ibuprofen or the pseudoephedrine (or salt thereof) is also coated with HPMC-PEG as described for the tablet coating in order to avoid stability problems arising from the physical incompatibility of ibuprofen and pseudoephedrine.

The methods of preparing compositions of the present invention, e.g. granulation, table compression and table coating, are all well known to those skilled in the art.

EXAMPLE 1

	mg/tablet
A. Core Tablet	
Pseudoephedrine Sulfate	120
Ibuprofen 90%*	225
HPMC K100M	100
Povidone	10
Microcrystalline Cellulose	154
HPMC/PEG	28
Magnesium Stearate	5
	972
B. Active Coating	
Loratadine	5
HPMC/PEG	10

*Equivalent to 200 mg ibuprofen

Method of Manufacture

A. Core

1. Blend pseudoephedrine sulfate, microcrystalline cellulose and HPMC K100M for 5-30 minutes in a suitable mixer.
2. Dissolve povidone in a hydroalcoholic mixture and use it to granulate the powder mix.
3. Dry and mill the pseudoephedrine sulfate granulation using suitable size screen.
4. Coat ibuprofen with HPMC/PEG solution in a suitable coater (see part B below).
5. Blend the screened pseudoephedrine sulfate granulation with coated ibuprofen and remaining ingredients for 3-15 minutes.
6. Compress into suitable size tablets.

B. Ibuprofen coating

1. Dissolve HPMC and PEG in suitable amount of water.
2. Coat ibuprofen with the HPMC/PEG solution in a suitable coater.

C. Active Loratadine Coating

1. Dissolve HPMC/PEG in suitable amount of water or a water/alcohol mixture.
2. Disperse loratadine in the HPMC/PEG solution.
3. Coat tablets with the dispersion and polish the coated tablets using standard procedures.

EXAMPLE 2

	mg/tablet
A. Core	
Pseudoephedrine Sulfate	120

-continued

	mg/tablet
Ibuprofen 90%*	225
HPMC E4M	150
Povidone	7.5
Microcrystalline Cellulose	148.5
Silicon Dioxide	14
Magnesium Stearate	5
	1000
B. Coating	
Loratadine	5
HPMC/PEG	10

*Equivalent to 200 mg ibuprofen

Method of Manufacture

A. Core

1. Blend pseudoephedrine sulfate, microcrystalline cellulose and HPMC E4M for 5-30 minutes in a suitable mixer.
2. Dissolve povidone in a hydroalcoholic mixture and use it to granulate the powder blend.
3. Dry and mill the pseudoephedrine sulfate granulation using suitable size screen.
4. Blend the pseudoephedrine sulfate granulation, ibuprofen and remaining ingredients for 3-15 minutes.
5. Compress into suitable size tablets.

B. Active Loratadine Coating

- 1 Dissolve HPMC and PEG in suitable amount of water.
2. Disperse loratadine in the HPMC/PEG solution.
3. Coat tablets with the dispersion and polish the coated tablets using standard procedures.
- 4 A similar dosage form comprising the non-steroidal anti-inflammatory drug acetaminophen in place of ibuprofen is also a part of the present invention. The dosage form releases acetaminophen and pseudoephedrine over 2 to 16 hours, preferably 5 to 12 hours, and immediately releases loratadine. Concentration ranges for the actives are as follows: pseudoephedrine salt, 30-240 mg/tablet; acetaminophen, 100-300 mg/tablet; and loratadine or its decarboxylation product, 0.5-10 mg/tablet. The concentration ranges represent about 3 to about 35% of coated tablet weight for pseudoephedrine salt, about 10 to about 65% for acetaminophen and about 0.05 to about 1.5% for loratadine.

The hydrophilic polymers are present at a concentration of about 5 to about 15%, fillers at about 10 to about 20%, surfactants at 0 to about 5%, lubricants at 0.25 to about 5%, and binders at 0 to about 3%, all percentages being relative to the tablet core weight.

The tablet coating comprises the loratadine or its decarboxylation product, a hydrophilic polymer and a plasticizer as described above, i.e. a preferred polymer is HPMC USP 2910 and a preferred plasticizer is PEG, present in a preferred ratio of 5:1.

The following example is directed to a loratadine, acetaminophen and pseudoephedrine sulfate combination dosage form.

EXAMPLE 3

	mg/tablet
A. Core Tablet	
Pseudoephedrine Sulfate	60
Acetaminophen 90%*	225
Dibutyl sebacate dihydrate	90