ESCOBAR – URIBE ASOCIADOS
A B O G A D O S
Carrera 11A No. 94-76 - OF.305 - P.O. Box 94948, Bogotá, D.C. - Colombia
Tels: (571) 6162051 - Fax (571) 6161889
www.escobaruribe.com - info@escobaruribe.com

170
171

[illegible] Folios 1

As:2518

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO.
DOCTOR:
GIANCARLO MARCENARO JIMÉNEZ.
Superintendente Delegado Para la Propiedad Industrial

EXPEDIENTE: **03-012.637.**
ASUNTO: **Solicitud de patente a nombre de NOVARTIS AG**

Estimado Doctor:

En mi calidad de apoderada de la sociedad solicitante de la patente de la referencia manifiesto a usted lo siguiente:

1-Mediante memorial presentado ante ese despacho el **18 de noviembre de 2004**, se solicitó a la división de nuevas creaciones examinar la patente de la referencia, asunto que no ha sido atendido aún por parte de esa Superintendencia.

2-En vista de que han transcurrido **10 MESES**, desde que se solicitó dicho examen de patentabilidad, sin que hasta la fecha se haya resuelto dicha petición, ruego a usted se sirva dar las instrucciones del caso para que se proceda de inmediato a tramitar tal solicitud y se otorgue la patente de la referencia lo mas pronto posible

Cordialmente,

JIMENA ESCOBAR URIBE
CC 39.779.452 de Usaquén.
T.P. 68228

Industria y Comercio
SUPERINTENDENCIA

171

172

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. **03-12637**

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **540**, DE

FECHA **31** DE **MAYO** DE **2004**, EL TERMINO HABIL SEÑALADO POR LA LEY

EXPIRA EL **30** DE **AGOSTO** DE **2004**.

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI ____ _____ NO ____ X _____

Carrera 13 No. 27-00 Piso 5 y 10
Conmutador: 334 12 21-2-3-4
Fax: 281 31 25 e-mail: info@sic.gov.co
Santa Fe de Bogotá D.C. - Colombia

173
172

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACI NES

2020
Bogotá, D.C., 20 de octubre de 2006

Apoderado: Jimena Escobar Uribe Oficio: 12663

REFERENCIA: Radicación No. 03-12637
Tramite 002
Evento 001
Actuación 430
Folios

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados:

- Capítulo descriptivo, folios 10 a 69;
- Capitulo reivindicatorio modificado, 165 a 170;
- 1° examen de forma, folio 79;
- Respuesta técnica al primer examen de forma, folios 80 y 81;
- Solicitud de la cual se reivindica prioridad, folios 82 a 157;
- 2° examen de forma folio 159;
- Solicitud del examen de patentabilidad, folios 161 y 162;

2. Objeto de la invención:

La presente solicitud cuyo título es "GRANULOS VETERINARIOS AGRADABLES QUE CONTIENEN PARTÍCULAS DE GRANO FINO RECUBIERTAS CON UNA SUSTANCIA ACTIVA Y ADICIONALMENTE ESTÁN RECUBIERTAS CON UNA CAPA PROTECTORA QUE ENMASCARA EL SABOR "

El objeto de la solicitud es composiciones que comprenden gránulos de principio activo recubiertas.

El objeto de la invención se puede clasificar según la clasificación internacional como A61K 9/20

174

179

Claridad:

En el artículo 30 de la decisión 486 de la Comisión de la Comunidad Andina se establece: *"Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción"*.

La reivindicación 20, no es clara puesto que el encabezado no es consecuente con el resto del texto de la reivindicación, su preámbulo es referido a "las partículas doblemente recubiertas de acuerdo con la reivindicación 10" y la reivindicación 10 es un proceso; además el resto del texto es referente al uso, lo cual es inaceptable en las reivindicaciones; lo correcto es definir la composición técnicamente como tal, por sus elementos constitutivos, perfectamente definidos y delimitada la invención.
-En la reivindicación no es aceptable definir un componente mediante una marca comercial, tal como lo hace en la reivindicación 19 (shellac).

Determinación del estado de la técnica:

El artículo 16 de la Decisión 486 de la Comisión establece: *"El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.*
Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40."

No	Documento No.	Título	Fecha de Publicación
D1	Pharmazeutisc he Technologie	Pharmazeutische Technologie	1986

D2	US4708867	Minipellets	24-nov-1987
D3	WO9725066	Oral pharmaceutical dosage forms comprising a proton pump inhibitor and an antiacid agent or alginate	17-jul-1997
D4	WO0149272	Method for preparing solid delivery syste for encapsulated and non-encapsulated pharmaceutical	20-julio-2001

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina establece: *"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 de este artículo, 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 de la Novedad:

El Art.16 de la Decisión 486 de la Comisión de la Comunidad Andina establece: *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica." "El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida".*

La solicitud en estudio reclama como nuevo un medicamento para animales, el cual consiste en un sustrato en forma de un gránulo o tableta, que es atractivo para el ganado y los animales domésticos, en donde se empotran partículas de grano fino en un material de vehículo sólido de sabor neutro, fisiológicamente compatible, el cual se caracteriza porque las partículas de grano fino del material del vehículo tienen un diámetro promedio de 0.09 a 0.8 milímetros, y están recubiertas con un ingrediente activo para medicina veterinaria, y la capa de sustancia activa se encierra con una capa protectora de una matriz polimérica fisiológicamente compatible.

-La anterioridad D1 describe la tecnología de recubrimiento de las pequeñas partículas de un núcleo con un principio activo posteriormente con una cubierta

176

175

enterica, lo cual no es una tecnología nueva, tal como lo se reclama en la solicitud en estudio, los núcleos recubierto con principio activo y posterior recubrimiento con película polimérica, no son nuevos son ya conocidos en el estado de la técnica, tal como lo muestra D1.

-La anterioridad D2 describe una forma farmacéutica que comprende uno núcleos recubiertos con una mezcla especifica esteroide (principio activo) y luego una cubierta de polímero polivinilpirrolidona , resistente al ataque de la saliva y los jugos gástricos, de tal manera que lo reivindicado en la solicitud en estudio como una idea, la anterioridad lo enseña como una solución técnica especifica; por lo tanto "el medicamento" que se reclama como nuevo en la solicitud en estudio se encuentra materializado específicamente en la anterioridad D2.

-La anterioridad D3 describe una forma farmacéutica de dosificación oral, describe específicamente núcleos recubiertos de principios activos específicos, que luego son recubiertos con polímeros tales como hidroxipropilmetil celulosa, HPC, carboximetilcelulosa, PVP, azúcar, almidones. Se puede ver el ejemplo 1 donde esta un medicamento especifico, destruye categóricamente la novedad la solicitud en estudio.

-La anterioridad D4 describe método para la preparación de un sistema sólido de de liberación de un principio activo, que comprende un núcleo el cual se recubre con un principio activo específico, y luego se recubre con una cubierta polimérica, para modificarle la palatabilidad y el tiempo de liberación, a la composición final, lo cual nos muestra claramente que "el medicamento" reclamado en la presente solicitud no nuevo, ni es la primera vez que se recubre núcleos de con el principio activo y posteriormente se recubren con un polímero, tal y como lo reclama la solicitud en estudio.

No.	Documento	Reivindicaciones Afectadas	Requisito que afecta
D1	Pharmazeutische Technologie	1 A 20	Novedad
D2	US4708867	1 A 20	Novedad
D3	WO9725066	1 A 20	Novedad
D4	WO0149272	1 A 20	Novedad

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

177

176

denegará la patente.

Notifíquese conforme a lo dispuesto en el numeral 5.2, literal e), del capitulo 5° del titulo 1° de la Circular Única n°.10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL.
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 02 NOV. 2006

CONCEPTO TÉCNICO No.	EXAMINADOR TÉCNICO Código: 202012

177

Thieme
Taschenlehrbuch
Pharmazie

Kurt H Bauer Karl Heinz Frömmung
Claus Führer

D1

Pharmazeutische Technologie

Unter Mitarbeit von

Engelbert Graf Tübingen
Hans Leuenberger Basel
Hans Peter Merkle, Bonn
Jobst B Mielck, Hamburg
Heinz Schlicher Berlin
Karl Heinz Wallhäußer Frankfurt

276 Abbildungen 64 Tabellen

1986
Georg Thieme Verlag Stuttgart New York

179

Prof. Dr. Kurt H. Bauer
Pharmazeut. Institut
der Universität Freiburg
Hermann-Herder-Str. 9
7800 Freiburg

Prof. Dr. K.-H. Frömming
Institut für Pharmazie
der Freien Universität Berlin
Königin-Luise-Str. 2+4
1000 Berlin 33

Prof. Dr. Claus Führer
Institut für Pharmaz. Technologie der Techn. Universität
Mendelssohnstr. 1
3300 Braunschweig

CIP-Kurztitelaufnahme der Deutschen Bibliothek

Bauer, Kurt H.:
Pharmazeutische Technologie / Kurt H. Bauer ; Karl-Heinz Frömming ; Claus Führer. –
Stuttgart ; New York : Thieme, 1986
(Thieme-Taschenlehrbuch Pharmazie)
NE: Frömming, Karl-Heinz; Führer, Claus:

Wichtiger Hinweis: Medizin als Wissenschaft ist ständig im Fluß. Forschung und klinische Erfahrung erweitern unsere Kenntnisse, insbesondere was Behandlung und medikamentöse Therapie anbelangt. Soweit in diesem Werk eine Dosierung oder eine Applikation erwähnt wird, darf der Leser zwar darauf vertrauen, daß Autoren, Herausgeber und Verlag größte Mühe darauf verwandt haben, daß diese Angabe genau dem Wissensstand bei Fertigstellung des Werkes entspricht. Dennoch ist jeder Benutzer aufgefordert, die Beipackzettel der verwendeten Präparate zu prüfen, um in eigener Verantwortung festzustellen, ob die dort gegebene Empfehlung für Dosierungen oder die Beachtung von Kontraindikationen gegenüber der Angabe in diesem Buch abweicht. Das gilt besonders bei selten verwendeten oder neu auf den Markt gebrachten Präparaten und bei denjenigen, die vom Bundesgesundheitsamt (BGA) in ihrer Anwendbarkeit eingeschränkt worden sind.

Satz: Tutte Druckerei GmbH, 8391 Salzweg/Passau
Druck: Appl, Wemding

ISBN 3-13-692301-7 1 2 3 4 5 6

Vorwort

Die pharmazeutische Technologie hat sich unter den pharmazeutischen Wissenschaften einen festen Platz erobert. Als angewandtes Fach basiert sie in erster *Linie* auf physikalischen, physikalisch-chemischen und chemischen Grundlagen sowie auf der *Pharmakokinetik* und Biopharmazie. Das *Lehrbuch* versucht dies auch durch die Wahl von drei Autoren als *Herausgeber* zu berücksichtigen, deren fachliche Interessengebiete unterschiedlich gelagert sind. So werden auch die industriellen Belange der Herstellung von Arznei- und Darreichungsformen angemessen berücksichtigt. Durch Hinzuziehung einiger weiterer Mitarbeiter wird vorhandenes *spezielles* Fachwissen genutzt.
Das Buch ist in erster Linie als Lehrbuch für die pharmazeutisch-technologische Ausbildung der Pharmaziestudenten gedacht. Es setzt Grundkenntnisse der chemischen, physikalischen, physikalisch-chemischen Grundvorlesungen sowie die Absolvierung der propädeutischen Lehrveranstaltungen voraus. Es soll dem Studenten das Verständnis für die Belange der Arzneimittelherstellung in der pharmazeutischen Industrie, in der Offizin- und in der Krankenhausapotheke vermitteln. Es wird versucht, Zusammenhänge zwischen unterschiedlichen Arznei- und Darreichungsformen aufzuzeigen. Daher sind zum Beispiel wichtige, für mehrere *Arzneiformen* benötigte *Hilfsstoffe* in einem gesonderten *Kapitel* beschrieben. Es sollen aber auch Hinweise für die zukünftige Arzneimittel-Entwicklung aufgezeigt werden, um so dem Studenten vielleicht Anregungen für eine spätere Beschäftigung mit pharmazeutisch-technologischen Problemen zu geben. Darüber hinaus soll das Buch aber auch dem in der Praxis stehenden Apotheker sowie anderen Naturwissenschaftlern, die sich mit der pharmazeutischen Technologie beschäftigen, die Möglichkeit geben, sich über Grundlagen und den aktuellen Stand dieses Fachgebietes zu informieren.
Die Verfasser möchten allen, die durch Anregungen, Materialüberlassung, Herstellung von Zeichnungsvorlagen und der Manuskripterstellung usw. zum Gelingen dieses Buches beigetragen haben, danken. Ein besonderer Dank gilt den Herren Dr. P. Fuchs und Prof. Dr. H. Sucker als Beratern des Georg Thieme Verlags für anregende Diskussionen.

Herbst 1986 *K. H. Bauer, K. H. Frömming, C. Führer*

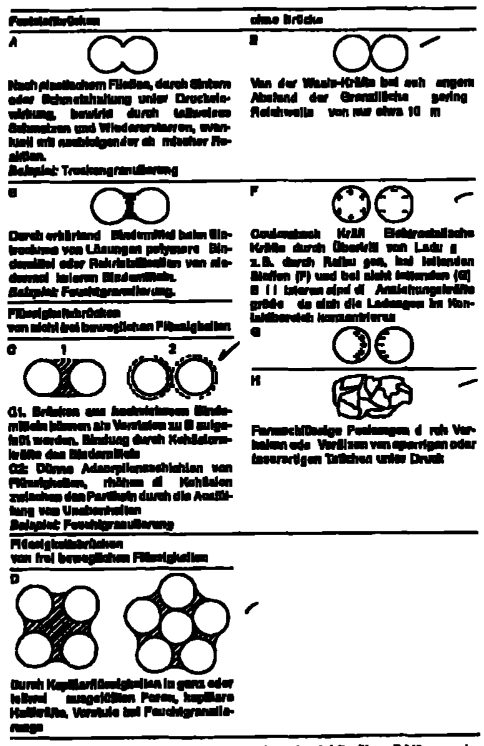


Abb. 12.15 Bindungsmechanismen in Granulaten (nach [illegible]); nähere Erklärungen im Text

In Knetern mit starkem Kneteffekt entstehen Granulate hoher Dichte, in Wirbelschichtgranulatoren dagegen eher lockere Granulate. Bei der Verwendung von *Lösungsmitteldämpfen* anstelle von Lösungen werden hochporöse Instantgranulate aufgebaut, die beim Einbringen in Flüssigkeiten wegen ihrer hohen Porosität außerordentlich rasch dispergieren (s. Abb. 12.16).

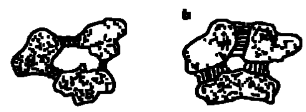


Abb. 12.16 Feststoffbrücken bei lockeren und dichten Granulaten: a punktuelle Verbindungen, lockere, poröse Granulate, kurze Zerfallszeiten, [illegible] nach Löslichkeit und Klebkraft der Bindemittel; b breitere Überbrückungen: höhere Dichten, weniger Poren

Die Bindungstypen B, F, G und H kommen als alleinige Bindungsmechanismen praktisch kaum vor. Die Reichweite der Van der Waals-Kräfte erstreckt sich nur über etwa 10 nm. So nahe lassen sich Feststoffpartikeln beim Granulieren meist *nicht* zusammenpressen. Erlauben Oberflächenrauhigkeiten auch unter hohen Druckanwendungen keine genügend Annäherung, können die Haftkräfte verstärkt werden, indem entweder nicht vollkommen getrocknet wird oder indem das Granulat einer feuchten Atmosphäre ausgesetzt wird. Hierbei bilden sich dünne Filme von adsorbierter, nicht beweglicher Feuchtigkeit (s. Abb. 12.15, Flüssigkeitsbrücken C). Ähnliches wird erreicht, wenn zwischen zwei leicht plangeschliffene Glasplättchen etwas Wasser gegeben wird.

Die wichtigsten Bindemittel bei der Herstellung von Granulaten in der pharmazeutischen Technologie und ihre üblichen Anwendungskonzentrationen sind:

Stärkekleister	5–15%
Gelatine	1–3%
Polyvinylpyrrolidon	3–5%
Celluloseether	1–5%

Die erforderlichen Anwendungskonzentrationen ergeben sich aus der Effektivität der Bindemittel. Von stark wirkenden Bindemitteln müssen geringere Mengen eingesetzt werden.

Diese Prozentangaben beziehen sich auf Feststoffanteile der Bindemittel pro trockenes Granulatgewicht

D2 182 180

United States Patent [19]

Hsiao

[11] **Patent Number: 4,708,867**

[45] **Date of Patent: Nov. 24, 1987**

[54] **MINIPELLETS**

[75] Inventor: **Charles H. Hsiao, Cooper City, Fla.**

[73] Assignee: **Key Pharmaceuticals, Inc., Miami, Fla.**

[21] Appl. No.: **587,536**

[22] Filed: **Mar. 8, 1984**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 564,852, Dec. 19, 1983, abandoned.

[51] Int. Cl.[4] A61K 9/28; A61K 9/32; A61K 9/58

[52] U.S. Cl. 424/80; 424/458; 424/470; 424/474; 424/482; 424/489

[58] Field of Search 424/81, 33, 80, 458, 424/470, 474, 482, 489

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,715,537	11/1973	Lehmann et al.	424/33
3,939,540	5/1976	Leiberich et al.	424/33
4,101,651	7/1978	Kobayashi et al.	424/81
4,150,110	4/1979	Yoshida et al.	424/81
4,341,759	7/1982	Bogentoft et al.	424/33

OTHER PUBLICATIONS

Eudragit E Data Sheet (Info E-3/e), Eudragit E Application in the Production of Pharmaceutical Preparations.

Primary Examiner—Shep K. Rose
Attorney, Agent, or Firm—Anita W. Magatti; James R. Nelson; Stephen I. Miller

[57] **ABSTRACT**

A minipellet dosage form of prednisone or prednisolone, resistant to attack by saliva but readily dissolvable in gastric juice, which comprises a mixture of prednisone or prednisolone and polyvinylpyrrolidone coated onto a nonpareil seed, and further coated with a layer of dimethylaminoethyl and methyl methacrylate copolymer.

5 Claims, No Drawings

MINIPELLETS

This application is a continuation-in-part of my copending application Ser. No. 564,852, filed on Dec. 19, 1983 now abandoned.

BACKGROUND OF THE INVENTION

The present invention relates to an improved dosage form for prednisone or prednisolone. More particularly, it relates to minipellets coated to mask the unpleasant taste of those compounds.

Prednisone, 17α, 21-dihydroxypregna-1,4-diene-3,11,20-trione, also named 1,4-pregnadiene-17α, 21-diol-3,11,20-trione, and prednisolone, also named of 11β,17,21-trihydroxypregna-1,4-diene-3,20-dione, are well known adrenocortical steroids. They are available as 1 to 50 mg tablets; and the usual oral dose is from 5 to 50 mg per day. Both are described as having a very bitter taste, unpleasant to adults and particularly unpleasant to children. While it is possible to administer prednisone or prednisolone in a conventional gelatin capsule, children are often unwilling to swallow capsules and older adults may be unable to swallow them. Accordingly, it would be desirable to provide these medicaments in minipellet form coated to mask their unpleasant taste. However, the United States Pharmacopeia requires that dosage forms containing prednisone or prednisolone be almost completely dissolved within 30 minutes after administration; prednisone or prednisolone coated with the usual tablet coatings would not meet that test.

The present invention provides a prednisone or prednisolone minipellet which, when ingested, does not exhibit a bitter taste in the mouth but is rapidly dissolved in the stomach.

In its broadest aspect, the present invention is a minipellet comprising prednisone or prednisolone admixed with polyvinylpyrrolidone coated on a nonpareil seed, and further coated with a copolymer of dimethylaminoethyl and methyl methacrylate.

More specifically, the present invention is a minipellet dosage form of prednisone or prednisolene resistant to attack by saliva but readily dissolvable in gastric juice which comprises a mixture of prednisone or prednisolone and polyvinylpyrrolidone coated onto a nonpareil seed, and further coated with a copolymer of dimethylaminoethyl and methyl methacrylate.

In another aspect, the invention contemplates a unit dosage of said minipellets in a readily opened container such as an unsealed capsule.

The copolymer utilized in practicing the present invention is a cationic copolymer available under the trade name Eudragit E 100. That copolymer forms a coating resistant to saliva and effectively masks any unpleasant taste in the mouth, but becomes water soluble in the stomach very quickly by forming a salt with the hydrochloric acid present in the gastric juice.

In preparing minipellets according to the present invention, micronized prednisone or prednisolone is suspended in a solution of polyvinylpyrrolidone dissolved in a suitable organic solvent, preferably isopropyl alcohol. The suspension and/or solution is coated onto nonpareil sugar seeds, preferably 30–60 mesh in size, using conventional equipment. The minipellets coated with prednisone or prednisolone and polyvinylpyrrolidone are further coated with an organic solvent solution of dimethylaminoethyl and methyl methacrylate. While not required, the addition of separation substances, such as talc, magnesium stearate and pigments, decreases the tendency of the polymer to agglutinate and produces a more uniform surface on the resultant minipellet. After drying, an appropriate number of minipellets are placed in a capsule to provide the desired dosage. The capsule should be readily openable by an elderly person to avoid unintentional spilling and loss of minipellets. Typically, the capsule is opened just before use and the minipellets sprinkled onto a food which is then eaten as part of a meal or snack.

My invention is further illustrated by means of the following non-limiting example.

500 gm nonpareil sugar seeds, mesh size of between 35–40, were placed in a preheated air suspension coating column (4"–6" Wurster column manufactured by Glatt, West Germany). The seeds were coated with 80 gm of prednisone suspended in a solution containing 40 gm of polyvinylpyrrolidone in 800 ml of isopropyl alcohol and dried. The dried pellets were further coated with a solution containing 288 gm of dimethylaminoethyl and methyl methacrylate copolymer (Eudragit E 100) in 1600 ml of acetone and 1600 ml of isopropyl alcohol. After the polymer solution/suspension had been applied, the resultant minipellets were dried and hand-filled into No. 3 size clear gelatin capsules. Each capsule contained about 200 minipellets or 10 mg of prednisone.

Minipellets as prepared in the previous example were suspended in various food preparations which were given to a four-person panel for taste testing. The results are summarized in the table which follows:

TABLE

Time in	Beef		Chicken		Pudding			Vegetable		Apple			Pear		
Minutes	5	10	5	10	5	10	26	5	10	2	4	5	2	4	5
I	O	T	O	O	O	O	O	O	O	O	O	T	O	O	T
II	O	O	O	O	O	O	O	O	O	O	O	T	O	O	T
III	O	O	O	O	O	O	O	O	O	O	O	T	O	O	T
IV	O	O	O	O	O	O	O	O	O	O	O	T	O	O	T

O indicates no taste detected
T indicates taste detected

Almost no taste was detected in non-acid food preparations (beef, chicken, pudding and vegetables). Taste was detected in acid fruit products (apple and pear) after 5 minutes.

Minipellets produced in accordance with the procedure of Example I, when tested in the simulated gastric juice test procedure described in U.S.P. XI, dissolved within 30 minutes.

I claim:

1. A minipellet dosage form of prednisone or prednisolone, resistant to attack by saliva but readily dissolvable in gastric juice, consisting essentially of a nonpareil seed having coated thereon a first layer comprising a mixture of a prednisone or prednisolone and polyvinylpyrrolidone and a second layer of dimethylaminoethyl and methyl methacrylate copolymer, the minipellet

being substantially dissolved in 30 minutes on contact with gastric juice.

2. A dosage form according to claim 1 wherein the minipellets are approximately 25–35 mesh in size.

3. A dosage form according to claim 1 wherein a unit dosage of minipellets is contained in an unsealed capsule.

4. A dosage form according to claim 1 which contains prednisone.

5. A dosage form according to claim 1 which contains prednisolone.

* * * * *

185 D3

183

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 45/06, 31/44, 33/08, 33/10, 9/20, 9/26 — A1

(11) International Publication Number: WO 97/25066

(43) International Publication Date: 17 July 1997 (17.07.97)

(21) International Application Number: PCT/SE96/01737

(22) International Filing Date: 20 December 1996 (20.12.96)

(30) Priority Data:
9600071-6 8 January 1996 (08.01.96) SE

(71) Applicant *(for all designated States except US)*: ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: DEPUI, Helene [FR/SE]; Wrangelsgatan 7B, S-416 62 Göteborg (SE). HALLGREN, Agneta [SE/SE]; Hälsingegatan 2C, S-431 38 Mölndal (SE).

(74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).

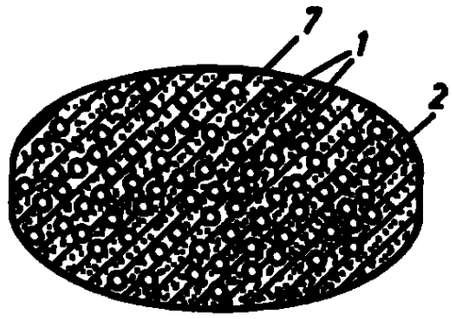
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: ORAL PHARMACEUTICAL DOSAGE FORMS COMPRISING A PROTON PUMP INHIBITOR AND AN ANTACID AGENT OR ALGINATE

(57) Abstract

An oral pharmaceutical dosage form comprising an acid susceptible proton pump inhibitor and one or more antacid agents or an alginate in a fixed formulation, wherein the proton pump inhibitor is protected by an enteric coating layer and an optional separating layer in between the proton pump inhibitor and the enteric coating. The fixed formulation is in the form of multilayered tablets, sachets or multiple unit tableted dosage forms. The multiple unit dosage form is most preferred. The new fixed formulation is especially useful in the treatment of disorders associated with dyspepsia such as heartburn.



expression "individual units" is meant small beads, granules or pellets, in the following referred to as pellets of the proton pump inhibitor.

The compaction process (compression) for formulating the multiple unit tableted dosage form must not significantly affect the acid resistance of the enteric coating layered pellets. In other words the mechanical properties, such as the flexibility and hardness as well as the thickness of the enteric coating layer(s), must secure that the requirements on enteric coated articles in the United States Pharmacopeia are accomplished in that the acid resistance does not decrease more than 10% during the compression of the pellets into tablets.

The acid resistance is defined as the amount of proton pump inhibitor in the tablets or pellets after being exposed to simulated gastric fluid USP, or to 0,1 M HCl (aq) relative to that of unexposed tablets and pellets, respectively. The test is accomplished in the following way. Individual tablets or pellets are exposed to simulated gastric fluid of a temperature of 37°C. The tablets disintegrate rapidly and release the enteric coating layered pellets to the medium. After two hours the enteric coating layered pellets are removed and analyzed for content of the proton pump inhibitor using High Performance Liquid Chromatography (HPLC).

Further specific components used in the fixed unit dosage forms of the present invention are defined below.

<u>Core material - for enteric coating layered pellets comprising a proton pump inhibitor</u>

The core material for the individually enteric coating layered pellets can be constituted according to different principles. Seeds layered with the proton pump inhibitor, optionally mixed with alkaline substances, can be used as the core material for the further processing.

The seeds which are to be layered with the proton pump inhibitor can be water insoluble seeds comprising different oxides, celluloses, organic polymers and other materials, alone or

in mixtures or water-soluble seeds comprising different inorganic salts, sugars, non-pareils and other materials, alone or in mixtures. Further, the seeds may comprise the proton pump inhibitor in the form of crystals, agglomerates, compacts etc. The size of the seeds is not essential for the present invention but may vary between approximately 0.1 and 2 mm. The seeds layered with the proton pump inhibitor are produced either by powder or solution/suspension layering using for instance granulation or spray coating layering equipment.

Before the seeds are layered, the proton pump inhibitor may be mixed with further components. Such components can be binders, surfactants fillers, disintegrating agents, alkaline additives or other and/or pharmaceutically acceptable ingredients alone or in mixtures. The binders are for example polymers such as hydroxypropyl methylcellulose (HPMC), hydroxypropyl-cellulose (HPC), carboxymethylcellulose sodium, polyvinyl pyrrolidone (PVP), sugars, starches or other pharmaceutically acceptable substances with cohesive properties. Suitable surfactants are found in the groups of pharmaceutically acceptable non-ionic or ionic surfactants such as for instance sodium lauryl sulfate.

Alternatively, the proton pump inhibitor optionally mixed with alkaline substances and further mixed with suitable constituents can be formulated into a core material. Said core material may be produced by extrusion/spheronization, balling or compression utilizing conventional process equipment. The size of the formulated core material is approximately between 0.1 and 4 mm and preferably between 0.1 and 2 mm. The manufactured core material can further be layered with additional ingredients comprising the proton pump inhibitor and/or be used for further processing.

The proton pump inhibitor is mixed with pharmaceutical constituents to obtain preferred handling and processing properties and a suitable concentration of the substance in the final mixture. Pharmaceutical constituents such as fillers, binders, lubricants, disintegrating agents, surfactants and other pharmaceutically acceptable additives.

Further, the proton pump inhibitor may also be mixed with an alkaline, pharmaceutically acceptable substance (or substances). Such substances can be chosen among, but are not restricted to substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminium hydroxide/sodium bicarbonate coprecipitate; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $Al_2O_3.6MgO.CO_2.12H_2O$, $(Mg_6Al_2(OH)_{16}CO_3.4H_2O)$, $MgO.Al_2O_3.2SiO_2.nH_2O$ or similar compounds; organic pH-buffering substances such as trihydroxymethyl-aminomethane, basic amino acids and their salts or other similar, pharmaceutically acceptable pH-buffering substances.

Alternatively, the aforementioned core material can be prepared by using spray drying or spray congealing technique.

Enteric coating layer(s)

Before applying the enteric coating layer(s) onto the core material in the form of individual pellets or tablets, the pellets or tablets may optionally be covered with one or more separating layer(s) comprising pharmaceutical excipients optionally including alkaline compounds such as pH-buffering compounds. This/these separating layer(s), separate(s) the core material from the outer layers being enteric coating layer(s). The separating layer(s) protecting the proton pump inhibitor should be water soluble or rapidly disintegrating in water.

The separating layer(s) can be applied to the core material by coating or layering procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating process. As an alternative the separating layer(s) can be applied to the core material by using powder coating technique. The materials for the separating layers are pharmaceutically acceptable compounds such as, for instance, sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl

acetate, hydroxypropyl cellulose, methylcellulose, ethyl-cellulose, hydroxypropyl methyl cellulose, carboxymethylcellulose sodium and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers anti-tacking and anti-static agents, such as for instance magnesium stearate, titanium dioxide, talc and other additives may also be included into the separating layer(s).

When the optional separating layer, is applied to the core material it may constitute a variable thickness. The maximum thickness of the separating layer(s) is normally only limited by processing conditions. The separating layer may serve as a diffusion barrier and may act as a pH-buffering zone. The pH-buffering properties of the separating layer(s) can be further strengthened by introducing into the layer(s) substances chosen from a group of compounds usually used in antacid formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds such as, for instance $Al_2O_3.6MgO.CO_2.12H_2O$, ($Mg_6Al_2(OH)_{16}CO_3.4H_2O$), $MgO.Al_2O_3.2SiO_2.nH_2O$, aluminium hydroxide/sodium bicarbonate coprecipitate or similar compounds; or other pharmaceutically acceptable pH-buffering compounds such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, carbonic, citric or other suitable, weak, inorganic or organic acids; or suitable organic bases, including basic amino acids and salts thereof. Talc or other compounds may be added to increase the thickness of the layer(s) and thereby strenghten the diffusion barrier. The optionally applied separating layer(s) is not essential for the invention. However, the separating layer(s) may improve the chemical stability of the active substance and/or the physical properties of the novel multiple unit tableted dosage form.

Alternatively, the separating layer may be formed in situ by a reaction between an enteric coating polymer layer applied on the core material an alkaline reacting compound in the core material. Thus, the separating layer formed comprises a salt formed between the enteric coating layer polymer(s) and an alkaline reacting compound which is in the position to form a salt.

The separating layer may also be used to separate two different layers of a tablet, as described in Fig. 2.

One or more enteric coating layers are applied onto the core material or onto the core material covered with separating layer(s) by using a suitable coating technique. The enteric coating layer material may be dispersed or dissolved in either water or in suitable organic solvents.As enteric coating layer polymers one or more, separately or in combination, of the following can be used, e.g. solutions or dispersions of methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylethylcellulose, shellac or other suitable enteric coating polymer(s).

The enteric coating layers may contain pharmaceutically acceptable plasticizers to obtain the desired mechanical properties, such as flexibility and hardness of the enteric coating layers. Such plasticizers are for instance, but not restricted to triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols, polysorbates or other plasticizers.

The amount of plasticizer is optimized for each enteric coating layer formula, in relation to selected enteric coating layer polymer(s), selected plasticizer(s) and the applied amount of said polymer(s), in such a way that the mechanical properties, i.e. flexibility and hardness of the enteric coating layer(s), for instance exemplified as Vickers hardness, are adjusted so that the acid resistance of the pellets covered with enteric coating layer(s) does not decrease significantly during compression of pellets into tablets. The amount of plasticizer is usually above 10 % by weight of the enteric coating layer polymer(s), preferably 15 - 50 % and more preferably 20 - 50 %. Additives such as dispersants, colorants, pigments polymers e.g. poly (ethylacrylat, methylmethacrylat), anti-tacking and anti-foaming agents may also be included into the enteric coating layer(s). Other compounds may be added to increase film thickness and to decrease diffusion of acidic gastric juices into the acid susceptible material.

To protect the acid susceptible substance, the proton pump inhibitor, and to obtain an acceptable acid resistance of the dosage form according to the invention, the enteric coating layer(s) constitutes a thickness of approximately at least 10 µm, preferably more than 20 µm. The maximum thickness of the applied enteric coating is normally limited by processing conditions and the desired dissolution profile.

Alternatively, the enteric coating layer described above may also be used for enteric coating of conventional tablets comprising an acid susceptible proton pump inhibitor. Said enteric coating layered tablet is thereafter presscoated with antacid granules and pharmaceutical excipients.

Over-coating layer

Pellets covered with enteric coating layer(s) may further be covered with one or more over-coating layer(s). The over-coating layer(s) should be water soluble or rapidly disintegrating in water. The over-coating layer(s) can be applied to the enteric coating layered pellets by coating or layering procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating or layering process. The materials for over-coating layers are chosen among pharmaceutically acceptable compounds such as, for instance sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methyl cellulose, carboxymethylcellulose sodium and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers, anti-tacking and anti-static agents, such for instance magnesium stearate, titaniumdioxide, talc and other additives may also be included into the over-coating layer(s). Said over-coating layer may further prevent potential agglomeration of enteric coating layered pellets, further protect the enteric coating layer towards cracking during the compaction process and enhance the tableting process. The maximum thickness of the applied over-coating layer(s) is normally limited by processing conditions and the desired dissolution profile.

The above described over-coating layer may also be used as a tablet filmcoating layer to obtain tablets of good appearance.

Antacid agent(s) or alginate preparation

The active substance in form of one or more antacid agent(s) are dry mixed with inactive excipients such as fillers, binders, disintegrants, and other pharmaceutically acceptable additives.The mixture is wet massed with a granulation liquid. The wet mass is dried preferably to a loss on drying of less than 3% by weight. Thereafter the dry mass is milled to a suitable size for the granules, such as smaller than 4 mm, and preferably smaller than 1 mm. Suitable inactive excipients are for instance mannitol, corn starch, potato starch, low substituted hydroxypropylcellulose, microcrystalline cellulose and crosslinked polyvinylpyrrolidone. The dry mixture comprising antacid agent(s) is mixed with a suitable granulation liquid comprising for instance hydroxypropylcellulose or polyvinylpyrrolidone dissolved in purified water or alcohol or a mixture thereof.

Alternatively, the antacid agent(s) are dry mixed with pharmaceutically acceptable excipients according to the above. The alginate preparation should also be prepared by dry mixing with pharmaceutically acceptable excipients.

Multiple unit tablets

The enteric coating layered pellets comprising a proton pump inhibitor are mixed with the prepared antacid granules or with the prepared dry mixture comprising the antacid agent(s). The mixture is admixed with lubricant(s) and compressed into a multiple unit tableted dosage form. Suitable lubricants for the tableting process are for instance sodium stearyl fumarate, magnesium stearate and talc.The compressed tablet is optionally covered with a filmforming agent(s) to obtain a smooth surface of the tablet and further enhance the stability of the tablet during packaging and transport. Such a coating layer may further

Use of the preparation

The dosage forms according to the invention are especially advantageous in the treatment of dyspepsia and other gastrointestinal disorder to provide an immidiate symtom relief and a long-lasting symtom resolution. The dosage forms are administered one to several times a day, preferably once or twice daily. The typical daily dose of the active substances varies and will depend on various factors such as the individual requirements of the patients, the mode of administration and disease. In general each dosage form will comprise 0.1-200 mg of the proton pump inhibitor and 0.1-1000 mg of the antacid agent(s)/alginate. Preferably, each dosage form will comprise 5-80 mg of the proton pump inhibitor and 100-900 mg of the antacid agent(s)/alginate, and more preferably 10-40 mg of proton pump inhibitor and 250 - 650 mg of the antacid agent(s)/alginate, respectively.

The multiple unit tablet preparation is also suitable for dispersion in an aqueous liquid with slightly acidic pH-value before being orally administered or fed through a naso-gastric tube.

The invention is illustrated more in detail in the following examples.

Examples

Example 1:

Multiple unit tableted dosage form comprising magnesium omeprazole and antacid agents (batch size 400 tablets).

Core material

Magnesium omeprazole	5.0	kg
Sugar sphere seeds	10.0	kg
Hydroxypropyl methylcellulose	0.75	kg
Water purified	20.7	kg

<u>Separating layer</u>		
Core material (acc. to above)	10.2	kg
Hydroxypropyl cellulose	1.02	kg
Talc	1.75	kg
Magnesium stearate	0.146	kg
Water purified	21.4	kg
<u>Enteric coating layer</u>		
Pellets covered with separating layer (acc. to above)	11.9	kg
Methacrylic acid copolymer (30 % suspension)	19.8	kg
Triethyl citrate	1.79	kg
Mono- and diglycerides (NF)	0.297	kg
Polysorbate 80	0.03	kg
Water purified	11.64	kg
<u>Over-coating layer</u>		
Enteric coating layered pellets (acc. to above)	20.0	kg
Hydroxypropyl methylcellulose	0.238	kg
Magnesium stearate	0.007	kg
Water purified	6.56	kg
<u>Tablets</u>		
Prepared pellets comprising omeprazole Mg-salt (acc. to above)	31.3	g
Microcrystalline cellulose	140.0	g
Calcium carbonate	100.0	g
Aluminium hydroxide/magnesium carbonate	100.0	g
Potato starch	46.4	g
Water purified	314	g
Polyvidone crosslinked	38.0	g
Sodium stearyl fumarate	4.6	g

Suspension layering was performed in a fluid bed apparatus. Magnesium omeprazole was sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder. The size of sugar sphere seeds were in the range of 0.25 to 0.35 mm.

The prepared core material was covered with a separating layer of a hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides, triethyl citrate and polysorbate was sprayed onto the pellets covered with a separating layer in a fluid bed apparatus. In a fluid bed apparatus enteric coating layered pellets were coated with a hydroxypropyl methylcellulose containing magnesium stearate. The over-coating layered pellets were classified by sieving.

A small amount of the potato starch was dissolved in purified hot water to form the granulation liquid. Calcium carbonate, aluminium hydroxide/magnesium carbonate, potato starch and microcrystalline cellulose are dry-mixed. The granulation liquid was added to the dry mixture and the mass was wet-mixed. The wet mass was dried in a steamoven at 50°C. The prepared granulation was milled through sieve 1 mm in an oscillating mill equipment.

The enteric coating layered pellets with an over-coating layer, prepared granules, polyvidone crosslinked and sodium stearyl fumarate were mixed and compressed into tablets using a tableting machine equipped with 9x20 mm oval punches. The amount of omeprazole in each tablet was approx. 10 mg and the amount of antacid agents were approx. 500 mg in total. Tablet hardness was measured to 110N.

Optionally the obtained tablets were covered with a tablet coating layer.

Results

"Acid resistance" i.e. % left after exposure to 0.1 N HCl for 2 hrs	
	Tablets
Ex 1	93%

Example 2:

Multiple unit tableted dosage form comprising magnesium omeprazole and antacid agents (batch size 500 tablets).

Core material	
Magnesium omeprazole	10.0 kg
Sugar sphere seeds	10.0 kg
Hydroxypropyl methylcellulose	1.5 kg
Water purified	29.9 kg
Separating layer	
Core material (acc. to above)	20.0 kg
Hydroxypropyl cellulose	2.0 kg
Talc	3.43 kg
Magnesium stearate	0.287 kg
Water purified	41.0 kg
Enteric coating layer	
Pellets covered with separating layer (acc. to above)	24.5 kg

197D4 195

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 July 2001 (12.07.2001)

PCT

(10) International Publication Number
WO 01/49272 A2

(51) International Patent Classification[7]: A61K 9/50, 9/10

(21) International Application Number: PCT/US00/34776

(22) International Filing Date:
20 December 2000 (20.12.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/476,483 30 December 1999 (30.12.1999) US
09/656,297 6 September 2000 (06.09.2000) US

(71) Applicant *(for all designated States except US)*: SHEAR/KERSHMAN LABORATORIES, INC. [US/US]; Suite P, 701 Crown Industrial Court, Chesterfield, MO 63005 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: SHEAR, Jeff [US/US]; 1421 Wildhorse Parkway Drive, Chesterfield, MO 63005 (US). KERSHMAN, Al [US/US]; 1220 Woodbridge Crossing Drive, Chesterfield, MO 63005 (US).

(74) Agent: ROBBINS, Glenn, K., II; Greensfelder, Hemker & Gale, P.C., 2000 Equitable Building, 10 South Broadway, St. Louis, MO 63102-1774 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/49272 A2

(54) Title: METHOD FOR PREPARING SOLID DELIVERY SYSTEM FOR ENCAPSULATED AND NON-ENCAPSULATED PHARMACEUTICALS

(57) Abstract: The present invention is an oral drug delivery system for delivering unpalatable pharmaceuticals, wherein the pharmaceutical delivery system comprises a lipid, dry particles including at least one pharmaceutical and at least one filler, and a surfactant, wherein the dry particles are continuously coated by the lipid and form a suspension with the lipid, making the pharmaceutical more palatable.

METHOD FOR PREPARING SOLID DELIVERY SYSTEM FOR ENCAPSULATED AND NON-ENCAPSULATED PHARMACEUTICALS

Field of the Invention

Cross Reference to Related Application

The invention is a continuation-in-part of U.S. Patent Application Serial No. 09/476,483 filed December 30, 1999 and claims priority of said application.

The present invention relates to oral delivery systems suitable for human and veterinary applications. More specifically, the present invention relates to an oral delivery system for cats, dogs and horses, wherein the normally unpalatable pharmaceutical, such as a drug, vitamin, mineral or food supplement, is made palatable, and therefore easily administered. The pharmaceutical is administered in a solid dosage form, wherein the pharmaceutical is carried in a lipid suspension.

Background of the Invention

It is known by those skilled in the art that orally administering pharmaceuticals to animals, specifically cats, dogs and horses, can be exceedingly difficult. The animal may reject the entire dose, or parts of the dose, leaving the vet or the owner frustrated in trying to administer the proper amount.

The true test of a delivery system for animals is whether the pharmaceutical is successfully administered repeatedly. As is often the case, when treating an illness or even a permanent condition of an animal, doses are repeated daily or even several times a day. Once an animal has tasted the unpalatable pharmaceutical that the vet or owner has attempted to hide or disguise, it becomes uncooperative when the administration is repeated. Applicants have discovered a delivery system that presents the pharmaceutical

in a palatable form such that the drug can be successfully and easily administered repeatedly.

Heretofore, attempts to alleviate the problem of administering pharmaceuticals have been made a number of ways, including hiding the drug in food. Usually the keen smell of the animal will allow it to detect and reject the pharmaceutical hidden therein. The taste and smell of pharmaceuticals can be masked through the use of flavorings and/or masking agents. Typically, this is only partially successful, as the taste and smell are not completely eliminated.

The pharmaceutical may be microencapsulated, and administered in a gel capsule, but the animal will usually chew the capsule, rupture it, taste the unpalatable pharmaceutical and reject it. Future administrations of the encapsulated pharmaceuticals are thwarted. The use of gel capsules has the additional disadvantages of being costly for delivering large doses of pharmaceuticals. The microencapsulated pharmaceutical may be tabletted using a conventional tablet press. However, such a process invariably damages or ruptures the capsules, defeating the benefits of encapsulation.

The present invention is an oral delivery system, wherein the system delivers microencapsulated pharmaceuticals, wherein the microencapsulation is intact and the pharmaceutical is delivered in a palatable form. Further, the present invention provides the pharmaceutical in a low cost, concentrated form that is easily administered. The delivery system comprises at least one lipid, dry particles including at least one pharmaceutical and at least one filler, and a surfactant, wherein the dry particles are continuously coated by the lipid and form a suspension with the lipid. The suspension exhibits thixotropic or pseudoplastic flow properties. The fillers include cellulose, starch and whey, and comprise from about 60 to 80 % of the system (all percentages stated herein are weight percent, unless otherwise indicated). Optionally, flavorings can be added to the dry particles and include cheese, butter, cream, and egg flavorings. Optionally, the pharmaceutical can comprise all of the dry particles, and serve as filler as well as pharmaceutical.

The process for preparing the present delivery system comprises melting the lipid and mixing with the surfactant, blending the dry particles

which include the pharmaceutical, filler and, optionally, flavorings with the melted lipid, and pouring or molding the suspension to provide the dose.

U.S. patent 4,327,076 discloses a compressed chewable antacid tablet which contains from about 10 to 50 % active ingredient, from about 2 to 45 % fat, from about 25 to 75% fat-sorbing materials, such as starch, and from about 20 to 60% tablet bonders, such as sugars, and surfactants and flavors. The process disclosed by 4,327,076 involves a pretreatment step wherein the fat is melted and is mixed with fat-sorbing material, tablet bonders and flavorings, forming a fatty powder. The second step involves mixing the active ingredient and surfactant with the pretreated fat and forming a free flowing powder wherein each active ingredient particle is coated with the pretreated fat. The powder thus produced is compressed into chewable pellets.

The above patent fails to disclose the claimed delivery system, wherein the pellets are not compressed into tablets but molded or poured.

U.S. patent 4,581,381 discloses a chewable antacid pill or pellet containing solid antacid particles having a particle size under 100 millimicrons coated with a fatty material, a surfactant, and a flavoring. The pill or pellet is formed by molding and provides a non-chalky, non-gritty pellet. The antacid particles are coated by melting the fatty material and mixing in the surfactant, the antacid and the flavorings.

The above patent requires very small particles (100 millimicrons), which are not required in the present process.

Neither of the above-referenced patents disclosed the present invention as disclosed and claimed herein.

also includes synthetic and natural food supplements, such as glucosamine, chondroitin, bee pollin, St. John's wort, echninacsia, etc. Additional pharmaceuticals are contemplated for the present invention, and are disclosed in U.S. patent 4,369,172, which is hereby incorporated by reference.

Optionally, the dry particles include flavorings that make the device taste and smell appealing to humans or animals. The flavorings can be natural or synthetic, and can include butter, milk, cream, egg or cheese. The flavorings are typically present in the device in the range of about 0.05 to 50.0%.

The delivery device may also include other pharmaceutically acceptable agents, such as sweetening agents, including hydrogenated starch hydrolysates, synthetic sweeteners such as sorbitol, xylitol, saccharin salts, L-aspartyl-L-phenylalanine methyl ester, as well as coloring agents, other binding agents, lubricants, such as calcium stearate, stearic acid, magnesium stearate, antioxidants such as butylated hydroxy toluene, antiflatuants such as simethicone and the like.

Optionally, rupturing agents are used to rapidly deliver the pharmaceutical into the recipient's system. A typical rupturing agent is a starch that swells in the presence of water. A preferred rupturing agent is sodium starch glycolate. When ingested, the capsule or pellet swells in the presence of gastric juices and ruptures. In one embodiment of the present invention, the rupturing agent is present inside the microcapsule. As water penetrates the microcapsule, it swells the starch and ruptures the capsule, rapidly delivering the pharmaceutical to the system.

In another embodiment, the rupturing agent is present in the lipid suspension, which ruptures the pellet, but leaves the microcapsules intact. This allows the delayed delivery of the drug farther along in the digestive system, or in the intestines. The present invention is particularly effective in this embodiment, in that the ingested pellet is chewable, yet the pellet cleaves in the lipid suspension when chewed, leaving the microcapsules intact. Tablets or gel capsules, when chewed, typically result in damage to or rupturing of the microcapsules defeating the effectiveness of the microcapsules.

Forming the Suspension

The first lipid (vegetable stearines sold under the trademark Duratex®) was heated in a Hobart 5 Quart planetary mixer jacketed with a heating mantle in the range of about 140 to 150°F and melted. The second lipid (98°F vegetable hard butter sold under the trademark Kalomel®) was added to the jacketed mixer and melted with mixing. The surfactant, lecithin, was added to the lipids with mixing, and the mixture was allowed to cool to about 135°F.

The dry particles, including the microencapsulated pharmaceutical, the flavorings, and the filler (whey) were screened to a particle size in the range of about 200 and 500 microns and dry-blended. The dry particles were slowly added incrementally to the lipid/surfactant mixture with mixing over a period of about 1 hour, to provide a smooth suspension with no lumps or agglomerations. The suspension was molded and cooled to about 70°F. The suspension shrank as it cooled, and easily released from the mold when inverted.

EXAMPLE I

TABLE A
Microencapsulation of Carprofen

BATCH FORMULA		
Ingredient	**Weight (grams)**	**%**
Carprofen (Pharmaceutical)	7.580	18.95%
Ethycellulose (30gm of 4% ethanol solution)	1.200	3.00%
Sodium starch gluconate	31.220	78.05%
Totals	**40**	**100.00%**

TABLE B
Forming a Suspension of
Carprofen in a 100mg Dose

BATCH FORMULA		
Ingredient	**Weight (grams)**	**%**
Vegetable stearine	0.4536	25.20%
Vegetable hard butter	0.1944	10.80%
Lecithin	0.0108	0.60%
Chedlong #1 (flavoring)	0.2430	13.50%
Cheese flavor 2517	0.0090	0.50%
Cheese flavor 1200s	0.0270	1.50%
Salt	0.0180	1.00%
Whey	0.2642	14.68%
Microencapsulated carprofen (drug from table A)	0.5800	32.22%
Totals	**1.8**	**100.00%**

EXAMPLE II

TABLE A
Microencapsulation of Enalapril Maleate

BATCH FORMULA		
Ingredient	**Weight (grams)**	**%**
Enalapril maleate (Pharmaceutical)	1.460	3.65%
Ethylcellulose (20gm of 4% ethanol solution)	0.800	2.00%
Sodium starch glycolate	37.740	94.35%
Totals	**40**	**100.00%**

TABLE B
Forming a Suspension of Enapril in a 5mg Dose

BATCH FORMULA		
Ingredient	**Weight (grams)**	**%**
Vegetable stearines	0.3780	25.20%
Vegetable hard butter	0.1620	10.80%
Sodium starch glycolate	0.2535	16.90%
Lecithin	0.0090	0.60%
Chedlong #1 (flavoring)	0.2025	13.50%
Cheese flavor 2517	0.0075	0.50%
Cheese flavor 1200s	0.0225	1.50%
Salt	0.0150	1.00%
Whey	0.3000	20.00%
Microencapsulated enapril (From Table A)	0.1500	10.00%
Totals	**1.5**	**100.00%**

EXAMPLE III

TABLE A
Microencapsulation of Furosemide

BATCH FORMULA		
Ingredient	**Weight (grams)**	**%**
Furosemide (Pharmaceutical)	3.66	9.15%
Ethylcellulose (20gm of 4% ethanol solution)	0.80	2.00%
Sodium starch glycolate	35.54	88.85%
Totals	**40**	**100.00%**

TABLE B
Forming a Suspension of Furosemide in a 12.5mg Dose

BATCH FORMULA		
Ingredient	**Weight (grams)**	**%**
Vegetable stearines	0.3780	25.20%
Vegetable hard butter	0.1620	10.80%
Sodium starch glycolate	0.2535	16.90%
Lecithin	0.0090	0.60%
Chedlong #1 (flavoring)	0.2025	13.50%
Cheese flavor 2517	0.0075	0.50%
Cheese flavor 1200s	0.0225	1.50%
Salt	0.0150	1.00%
Whey	0.3000	20.00%
Microencapsulated furosemide (From Table A)	0.1500	10.00%
Totals	**1.5**	**100.00%**