

Señor

SUPERINTENDENTE DELEGADO PARA LA PROPIEDAD INDUSTRIAL
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Ref: P1.-GRUNENTHAL GmbH.-Expediente No. 00-002.023.-

1. Me refiero al asunto de la referencia.
2. Por medio del presente, atentamente me permito manifestar que hubo un **cambio** de apoderado para todos los asuntos de la Propiedad Industrial en Bogotá de la sociedad **GRUNENTHAL GmbH**.
3. En consecuencia, atentamente solicito a ese Despacho reconocerme personería en este asunto, de conformidad con la sustitución de poder adjunta, otorgada a favor de la SUSCRITA.
4. Por lo tanto, ruego a usted notificarme de las providencias expedidas dentro de este expediente y notificadas al anterior apoderado, que actualmente se encuentran pendientes de cumplimiento o de respuesta.
5. Solicito a ese Despacho proceder de conformidad.

Atentamente,


ALICIA LLOREDA RICAURTE

T.P. 53215

Código 231

Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. _____ S. _____ D. _____

142

Ref: P1.-GRUNENTHAL GmbH .-Expediente No.00-002.023.-

Yo, **JOSE ANTONIO LLOREDA**, mayor de edad y vecino de esta ciudad, abogado titulado e inscrito, identificado como aparece al pie de mi firma, actuando en mi carácter de Representante Legal en Bogotá para asuntos relacionados con la propiedad industrial de **GRUNENTHAL GmbH**, sociedad organizada y existente de conformidad con las leyes de Alemania, domiciliada en Aachen, Alemania, tal y como consta en este expediente, atentamente manifiesto a usted que **SUSTITUYO** el poder a mi conferido a la doctora **ALICIA LLOREDA RICAURTE**, abogada titulada e inscrita, identificada con la cédula de ciudadanía No. 39.690.713 de Usaquén, para que continúe representando a la mencionada sociedad en el expediente de la referencia.

De conformidad con el artículo 66 del C.P.C., manifiesto bajo la gravedad de juramento que los demás apoderados citados en el documento otorgado a mi favor no desean ejercer el poder a ellos conferido.

El mencionado apoderado tendrá las mismas facultades a mi conferidas, en especial, renunciar, recibir, sustituir, desistir, presentar recursos, conciliar, transigir, y en fin, para todo lo que se encamine a la correcta defensa de los intereses de la sociedad en cuyo nombre hablo.

NOTARIA SEXTA DE BOGOTÁ
Atentamente, **JOSE ANTONIO LLOREDA**
25 AGO 2004
Ante mí **PABLO MENDEZ BARAJAS**
NOTARIO SEXTO(E) DEL CIRCULO
BOGOTÁ
Código 231

JOSE ANTONIO LLOREDA
C.C. No. 17.159.681 de Bogotá



143

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

375
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2020

Bogotá, DC, 21 de septiembre de 2004

Apoderado: Alicia Llorada Ricaurte

Oficio: 00044

ASUNTO

Radicación: 0-2023

Trámite 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:

Documentos estudiados:

- ◆ capítulo descriptivo, folios 7 a 26;
- ◆ capítulo reivindicatorio, folios 27 a 29;
- ◆ 1° examen de forma, folios 97 y 98 ;
- ◆ respuesta técnica al 1° examen de forma, folios 100 a 123;
- ◆ solicitud de la cual se reivindica prioridad, junto con la traducción mínima requerida, folios 36 a 92;
- ◆ 2° examen de forma, folio 135;
- ◆ Solicitud del examen de patentabilidad, folios 137 a 140.

Objeto de la invención:

El título de la invención es "PROCEDIMIENTO DE PREPARACIÓN DE UNA COMPOSICIÓN DE LIBERACIÓN RETARDADA, Y COMPOSICIÓN PREPARADA POR EL PROCEDIMIENTO".

El objeto de la presente solicitud se refiere a composiciones de clorhidrato de tramadol que tienen la liberación retardada, por una cubierta de etilcelulosa y un plastificante de al menos un diéster lipófilo de un ácido dicarboxílico alifático o aromático.

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	US 5645858	Multilayered controlled release pharmaceutical dosage form	08-julio-1997
D2	EP 0630646	Controlled-release formulations coated with aqueous dispersions of ethylcellulose	28-dic-94

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 con 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*

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SURELEASE and comprises ethyl cellulose, dibutyl sebacate, oleic acid, ammoniated water, and fused silica.

The multilayered controlled release pellets of the invention are preferably provided in a hard gelatin capsule but may also be provided in any other suitable oral dosage form such as a matrix comprising such pellets agglomerated with an appropriate and compatible binder to form a unitary solid dosage form which will release the intact pellets in the digestive tract after swallowing.

The film forming process of the invention can be carried out in conventional pans, preferably pans with one way air flow to provide more control over the pan environment. More preferably the coating is accomplished in a fluidized bed which is an air suspension technique known as "Wurster" coating. Most preferably the pellets are coated in a rotor granulator with a top fluid bed which provides rotation of the pellets during coating to ensure a more uniform coat of the pellets. Examples of a preferred coating apparatus of the invention is a GLATT GPCG-5 rotor granulator. Other coating materials and techniques can be applied such as those disclosed in *The Theory and Practice of Industrial Pharmacy*, Lachman et al., 3d edition, 1986.

The invention will now be illustrated by examples. The examples are not intended to be limiting of the scope of the present invention but read in conjunction with the detailed and general description above, provide further understanding of the invention and outline a process for preparing the compositions of the inventions and methods of practicing the invention.

EXAMPLES

The following ingredients, processes and procedures for preparing the compositions of the present invention correspond to that described above. The procedure below describes with particularity the various formulation ingredients and procedures utilized. Any methods, starting materials, reagents or excipients which are not particularly described will be generally known and available to those skilled in the pharmaceutical formulation arts. All formulation percentages are provided in percent by weight by total weight of the composition.

Example 1

300 mg. tramadol sustained release capsules

A. Composition: Unit Dose.

The theoretical quantitative composition (per unit dose) for tramadol HCl 300 mg sustained release capsules is provided below:

Components	% weight/weight (theoretical)	mg/Capsule (theoretical)
Tramadol HCl	68.34	300
(OPADRY® Clear YS-3-7011) ¹	1.14	5.01
Purified Water, USP ²	—	—
Sugar Spheres, NF ³	12.5	54.87
OPADRY® Clear YS-1-7006 ³	4.48	19.66
SURELEASE® E-7-7050 ⁴ Capsules ⁵	13.54	59.44
Total	100.00%	438.98mg ⁶

6

-continued

Components	% weight/weight (theoretical)	mg/Capsule (theoretical)
¹ A mixture of hydroxypropyl methylcellulose, polyethylene glycol and propylene glycol.		
² Purified Water, USP is evaporated during processing.		
³ A mixture of hydroxypropyl methylcellulose and polyethylene glycol.		
⁴ Solid content only of a 25% aqueous dispersion of a mixture of ethyl cellulose, dibutyl sebacate, oleic acid, ammoniated water and fused silica.		
⁵ The water in the dispersion is evaporated during processing.		
⁶ White, opaque, hard gelatin capsule, size 00.		
⁶ Each batch is assayed prior to filling and the capsule weight is adjusted as required to attain 300 mg tramadol hydrochloride per capsule.		

The quantitative batch composition for tramadol hydrochloride 300 mg sustained release capsule is shown below (Theoretical batch quantity 25,741 capsules):

Components	Weight
Step 1: Preparation of Tramadol Hydrochloride Beads (bead Build-up #1)	12.000
Opadry® Clear YS-3-7011	0.200
Purified Water, USP	5.454
Sugar Spheres, NF	4.000
Total Weight Tramadol Hydrochloride Beads (Bead Build-up #1)	16.200 kg
Step 2: Clear & Sustained Release Bead coating #1	
Tramadol Hydrochloride Beads (derived from Step 1)	8.000
Opadry® Clear YS-1-7006	0.360
Purified Water, USP	5.928
Surelease® E-7-7050	0.672
Total Weight Clear Coated Sustained Release Beads	9.032 kg
Step 3: Tramadol Hydrochloride Beads (Build-up #2)	
Sustained Release Beads (derived from Step 2)	8.000
Tramadol Hydrochloride	4.320
Opadry® Clear YS-3-7011	0.072
Purified Water, USP	1.964
Total Weight Tramadol Hydrochloride Beads (Build-up #2)	12.392 kg
Step 4: Clear & Sustained Release Bead Coating #2	
Tramadol Hydrochloride Beads (derived from Step 3)	10.000
Opadry® Clear YS-1-7006	0.250
Purified Water, USP	6.450
Surelease® E-7-7050	1.050
Total Weight Tramadol Hydrochloride Sustained Release Beads	11.300 kg
Step 5: Capsule Filling	—

B. Methods of Manufacturing and Packaging

NOTE: The drug substance and excipients may be deagglomerated, if needed, by milling or screening.

Step 1: Preparation of Tramadol Hydrochloride Beads (Bead Build-up #1)

a. Preparation of Tramadol Hydrochloride Build-up Solution

i. Admix the batch quantity of Purified Water, USP and the batch quantity of Opadry® Clear YS-3-7011.

ii. Add the batch quantity of tramadol hydrochloride and mix for approximately 1.5 hours.

b. Preparation of Tramadol Hydrochloride Beads

i. Load the bowl of a suitable bead coater such as the Glatt GPCG 5 Rotor-Granulator with the batch quantity of sugar spheres, NF and heat until the bed reaches approximately 40° C.-60° C.

5,645,858

7

ii. While maintaining the bed temperature at approximately 40°-60° C., spray the entire tramadol hydrochloride/Opadry® Clear YS-3-7011 solution prepared in Step 1.a. onto the sugar spheres.

iii. Remove the tramadol hydrochloride beads from the granulator and screen to remove any agglomerates and any fine powder.

Step 2: Clear and Sustained Release Bead Coating #1

a. Preparation of Clear Coat #1

Add 54.7% of the batch quantity of Purified Water, USP (3.240 kg) and the batch quantity of Opadry® Clear YS-1-7006 (0.360 kg) and mix for approximately 1-2 hours.

b. Preparation of Sustained Release Dispersion #1

Add 11.3% of the batch quantity of Purified Water, USP (0.672 kg) and 2.688 kg of Surelease® E-7-7050 dispersion and mix for approximately 1-2 hours.

c. Preparation of Coated Beads

i. Transfer the batch quantity of the tramadol hydrochloride beads prepared in Step 1. (8.0 kg) into a suitable bead coater such as the Glatt GPCG 5 Rotor-Granulator and heat until the bed reaches approximately 40° C.-60° C.

ii. Maintain the bed temperature at the following conditions and spray:

40° C.-60° C. 88.9% of the Opadry® Clear YS-1-7006 solution prepared in Step 2.a.

42° C.-50° C. the batch quantity of the Surelease® E-7-7050 dispersion prepared in Step 2.b.

40° C.-60° C. the remaining batch quantity (11.1%) of the Opadry® Clear YS-1-7006 solution prepared in Step 2.a.

iii. Remove the tramadol sustained release beads derived in Step 2.c.ii. from the granulator and screen the beads to remove any agglomerates and any remaining fine powder.

Step 3: Tramadol Hydrochloride Beads (Build-up #2)

a. Preparation of the Tramadol Hydrochloride Build-up Solution

i. Add the batch quantity of Purified Water, USP and the batch quantity of Opadry® Clear YS-3-7011.

ii. Add the batch quantity of tramadol hydrochloride and mix for approximately 1-2 hours.

b. Preparation of the Tramadol Hydrochloride Beads

i. Load the bowl of a suitable bead coater such as the Glatt GPCG 5 Rotor-Granulator with the batch quantity of sustained release beads from Step 2. (8.0 kg) and heat until the bed reaches approximately 40° C.-60° C.

ii. Spray on the entire tramadol hydrochloride/Opadry® Clear YS-3-7011 solution prepared in Step 3.a. onto the heated sustained release beads, while maintaining the bed temperature at approximately 40° C.-60° C.

iii. Remove the tramadol hydrochloride beads from the granulator and screen the beads to remove any agglomerates and any fine powder.

Step 4: Clear and Sustained Release Bead Coating #2

a. Preparation of Clear Coat

Add 34.9% of the respective batch quantity of Purified Water, USP (2.250 kg) and the respective batch quantity of Opadry® Clear YS-1-7006 (0.250 kg) and mix for approximately 1-2 hours.

b. Preparation of Sustained Release Dispersion #2

Add to a suitable stainless steel mixing tank 16.3% of the batch quantity of Purified Water, USP (1.050 kg) and 4.200 kg of Surelease® E-7-7050 dispersion and mix for approximately 1-2 hours.

c. Preparation of Coated Beads

i. Transfer the batch quantity of the tramadol hydrochloride beads prepared in Step 3. (10.0 kg) into a suitable granulator such as the Glatt GPCG 5 Rotor-Granulator and heat until the bed reaches approximately 40° C.-60° C.

8

ii. Maintain the bed temperature at the following conditions and sprays:

40° C.-60° C. 80% of the Opadry® Clear YS-1-7006 solution prepared in Step 4.a.

42° C.-50° C. the batch quantity of the Surelease® E-7-7050 dispersion prepared in Step 4.b.

40° C.-60° C. the remaining batch quantity (20.0%) of the Opadry® Clear YS-1-7006 solution prepared in Step 4.a.

iii. Remove the tramadol sustained release beads derived in Step 4.c.ii. from the granulator and screen the beads to remove any agglomerates and any remaining fine powder.

iv. Dry the beads in a 45° C.-55° C. dry heat oven for approximately 24 hours.

Step 5: Capsule Filing

a. Based on the in-process assay results, calculate the fill weight of the tramadol hydrochloride sustained release beads.

b. On a suitable filling machine or by hand, fill the calculated amount of tramadol hydrochloride sustained release beads into white, opaque, hard gelatin capsules (size 00).

Example 2

Preparation of Pseudophedrine sustained Release Capsules

Follow the procedure of Example 1 but replace the tramadol HCl with pseudophedrine HCl and reduce all of the ingredients to two-thirds to produce 200 mg pseudophedrine sustained release capsules.

The present invention provides for a heretofore unrealized consistent drug release pattern for very water soluble drugs such as tramadol HCl and pseudophedrine HCl from a sustained released pellet system. The advantages obtained by the multilayered pellets of the invention are indicated in the appended graph of FIG. 1 for comparing formulations for tramadol. The graph shows that the double layer bead of the invention (i.e. two controlled release layers, i.e. 8% and 10% controlled release layer amounts, by weight of the total weight of the beads) provides a more linear (i.e., more constant or uniform) release rate as compared to single layered beads with a single controlled release layer (i.e., 12.5% and 14% controlled release layer amounts by weight of the total weight of the beads).

The scope of the present invention is not limited by the description, examples or suggested uses herein and modifications can be made without departing from the spirit of the invention. The multilayered dosage forms of the invention may, for example, have other applications and uses in addition to those described herein, e.g. for vitamin supplements or for controlled delivery of diagnostic agents.

Applications of the compositions and methods of the present invention for medical or pharmaceutical uses can be accomplished by any clinical, medical, and pharmaceutical methods and techniques as are presently or prospectively known to those skilled in the art. Thus it is intended that the invention cover any modifications and variations of this invention provided that they come within the scope of the appended claims and their equivalents.

What is claimed is:

1. A multilayered controlled release pharmaceutical dosage form for water soluble drugs comprising a plurality of coated particles each comprising: a drug active core comprising a mixture of hydroxypropyl methylcellulose, polyethylene glycol and propylene glycol which is sequentially

151

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EUROPEAN PATENT APPLICATION

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Controlled-release formulations coated with aqueous dispersions of ethylcellulose.

A stabilized solid controlled release formulation having a coating derived from an aqueous dispersion of a hydrophobic polymer is obtained by overcoating a substrate including an active agent selected from the group consisting of a systemically active therapeutic agent, a locally active therapeutic agent, a disinfecting and sanitizing agent, a cleansing agent, a fragrance agent and a fertilizing agent, with an aqueous dispersion of the plasticized hydrophobic polymer and then curing the coated substrate at a temperature above the glass transition temperature of the plasticized hydrophobic polymer, until a curing endpoint is reached at which the coated substrate provides a stabilized dissolution of the active agent which is unchanged after exposure to accelerated storage conditions, the endpoint being determined by comparing the dissolution profile of the formulation immediately after curing to the dissolution profile of the formulation after exposure to accelerated storage conditions of at least one month at a temperature of 37 °C and at a relative humidity of 80%.

EP 0 630 646 A1

antiinflammatoris (NSAID) →

Figure B is an SEM of the coated bead depicted in Figure A after curing in accordance with the present invention;

Figure 1 is a graphical representation of the dissolution stability results obtained with Example 1;

Figure 2 is a graphical representation of the dissolution stability results of Comparative Example 1A;

5 Figure 3 is a graphical representation of the dissolution stability results of Comparative Example 1B;

Figure 4 is a graphical representation of the dissolution stability results of Comparative Example 1C;

Figure 5 is a graphical representation of the dissolution stability results of Example 1, comparing the dissolution profiles obtained under various conditions;

10 Figure 6 is a graphical representation of the initial dissolution profiles obtained under various curing conditions;

Figure 7 is a graphical representation of the results obtained for Comparative Example 18A;

Figure 8 is a graphical representation of the results obtained for Example 18;

Figure 9 is a graphical representation of the results obtained for Example 19;

Figure 10 is a graphical representation of the results obtained for Example 21;

15 Figure 11 is a graphical representation comparing the in-vitro release of Examples 22 and 23 versus a commercially available reference (MS Contin);

Figure 12 is a graphical representation of the blood levels obtained for the controlled release formulation of Examples 22 and 23 versus a commercially available reference (MS Contin);

20 Figure 13 is a graphical representation of the blood levels obtained when two 30 mg capsules of Example 23 are administered, in comparison to one 30 mg MS Contin tablet;

Figure 14 is a graphical representation comparing the in-vitro release of Examples 23 and 24 versus MS Contin;

Figure 15 is a graphical representation of the blood levels obtained for Examples 23 and 24 versus MS Contin; and

25 Figure 16 is a graphical representation of the blood levels obtained when two 30 mg capsules of Example 24 are administered at the same time, in comparison to one 30 mg MS Contin tablet.

DETAILED DESCRIPTION

30 The aqueous dispersions of hydrophobic polymers used as coatings in the present invention may be used to coat substrates such as tablets, spheroids (or beads), microspheres, seeds, pellets, ion-exchange resin beads, and other multi-particulate systems in order to obtain a desired controlled release of the active agent. Granules, spheroids, or pellets, etc., prepared in accordance with the present invention can be presented in a capsule or in any other suitable dosage form. The tablets of the present invention may be
35 any suitable shape, such as round, oval, biconcave, hemispherical, any polygonal shape such as square, rectangular, and pentagonal, and the like.

In order to obtain a controlled release formulation, it is usually necessary to overcoat the substrate comprising the active agent with a sufficient amount of the aqueous dispersion of hydrophobic polymer e.g., ethylcellulose, to obtain a weight gain level from about 2 to about 25 percent, although the overcoat may be
40 lesser or greater depending upon the physical properties of the active agent and the desired release rate, the inclusion of plasticizer in the aqueous dispersion and the manner of incorporation of the same, for example.

The cured, coated substrates of the present invention provide a stable dissolution profile (e.g., release of the active agent in the environment of use) when stored for extended periods of time at room
45 temperature and ambient humidity (e.g., long term (real time) testing), and when tested under accelerated storage conditions.

The terms "stable dissolution profile" and "curing endpoint" are defined for purposes of the present invention as meaning that the cured, coated substrate reproducibly provides a release of the active agent when placed in an environment of use which is unchanged, even after exposing the cured, coated substrate
50 to accelerated storage conditions. Those skilled in the art will recognize that by "unchanged" it is meant that any change in the release of the active agent from the cured, coated formulation would be deemed insignificant in terms of the desired effect. For pharmaceutical formulations, stability is determined by, e.g., a regulatory agency such as the Food & Drug Administration (FDA) in the U.S., for the purpose of according an expiration date for the formulation.

55 By the phrase "accelerated storage conditions" it is meant, e.g., storage conditions of elevated temperature and/or elevated relative humidity. Preferably, the phrase "accelerated storage conditions" refers to storage conditions to which the final drug formulation is subjected for the purpose of obtaining regulatory approval (e.g., FDA approval in the U.S.) and an expiration date.

153

The term "expiration date" is defined for purposes of the present invention as the date designating the time during which a batch of the product (e.g., the cured, coated substrate) is expected to remain within specification if stored under defined conditions, and after which it should not be used.

The term "band range" for purposes of the present invention is defined as the difference in in-vitro dissolution measurements of the controlled release formulations when comparing the dissolution profile (curve) obtained by the formulation upon completion of the manufacturing of the coated product (prior to storage) and the dissolution profile obtained after the coated product is exposed to accelerated storage conditions, expressed as the change in percent of the active agent released from the coated product at any dissolution time point along the dissolution curves.

In general, the length of the studies and the storage test conditions required by regulatory agencies such as the FDA for pharmaceutical formulations are sufficient to cover storage, shipment, and subsequent use. Allowable storage test conditions may vary depending upon the particulars of the product. For example, temperature sensitive drug substances should be stored under an alternative, lower temperature condition, which is then deemed to be the long term testing storage temperature. In such cases, it is generally accepted that the accelerated testing should be carried out at a temperature at least 15°C above this designated long term storage temperature, together with appropriate relative humidity conditions for that temperature.

A generally accepted accelerated test employed in FDA guidelines relates to the storage of a drug product (e.g., in its container and package) at 80% Relative Humidity (RH) and 37°C (1985 FDA guidelines). If the product holds up for, e.g., three months under these conditions (chemical stability, dissolution, and physical characteristics), then the drug product will be accorded, e.g., a two year expiration date. This accelerated test is also now also considered to be acceptable if conducted at 75% RH and 40°C (FDA 1987 guidelines). It has recently been proposed that long-term storage testing be conducted for pharmaceutical formulations at 25°C ± 2°C at not less than 60% RH ± 5% for a minimum time period of 12 months. It has been further proposed that accelerated testing be conducted for pharmaceutical formulations at 40°C ± 2°C at 75% RH ± 5% for a minimum time period of 6 months. All of the above-mentioned accelerated testing criteria and others are deemed equivalent for purposes of the present invention, with regard to the determination of stability and the determination of the curing endpoint.

The controlled release coatings of the present invention comprise aqueous dispersions of hydrophobic polymers. Although ethylcellulose is an especially preferred hydrophobic polymer for use in the controlled release coatings of the present invention, other hydrophobic cellulosic derivatives (including other alkyl celluloses) may be also be used, and are deemed to be encompassed by the appended claims.

The inclusion of an effective amount of a plasticizer in the aqueous dispersion of hydrophobic polymer will further improve the physical properties of the film. For example, because ethylcellulose has a relatively high glass transition temperature and does not form flexible films under normal coating conditions, it is necessary to plasticize the ethylcellulose before using the same as a coating material.

The plasticization of the ethylcellulose may be accomplished either by so-called "internal plasticization" and "external plasticization." The suitability of a plasticizer depends on its affinity or solvating power for the polymer and its effectiveness at interfering with polymer-polymer attachments. Such activity imparts the desired flexibility by relieving molecular rigidity. Generally, the amount of plasticizer included in a coating solution is based on the concentration of the film-former, e.g., most often from about 1 to about 50 percent by weight of the film-former. Concentration of the plasticizer, however, can only be properly determined after careful experimentation with the particular coating solution and method of application.

An important parameter in the determination of a suitable plasticizer for a polymer is related to the glass transition temperature (T_g) of the polymer. The glass transition temperature is related to the temperature or temperature range where there is a fundamental change in the physical properties of the polymer. This change does not reflect a change in state, but rather a change in the macromolecular mobility of the polymer.

Below the T_g, the polymer chain mobility is severely restricted. Thus, for a given polymer, if its T_g is above room temperature, the polymer will behave as a glass, being hard, non-pliable and rather brittle, properties which could be somewhat restrictive in film coating since the coated dosage form may be subjected to a certain amount of external stress.

Incorporation of suitable plasticizers into the polymer matrix effectively reduces the T_g, so that under ambient conditions the films are softer, more pliable and often stronger, and thus better able to resist mechanical stress.

Other aspects of suitable plasticizers include the ability of the plasticizer to act as a good "swelling agent" for the ethylcellulose, and the insolubility of the plasticizer in water.

Examples of suitable plasticizers for the hydrophobic polymers useful in the present invention (e.g., ethylcellulose) include water insoluble plasticizers such as dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl citrate, and triacetin, although it is possible that other water-insoluble plasticizers (such as acetylated monoglycerides, phthalate esters, castor oil, etc.) may be used. Triethyl citrate is an especially preferred plasticizer for the aqueous dispersions of ethyl cellulose of the present invention.

It has further been found that the addition of a small amount of talc reduces the tendency of the aqueous dispersion to stick during processing, and acts as a polishing agent.

In one commercially available product, Aquacoat® (aqueous dispersion of ethylcellulose available from FMC Corp., Philadelphia, Pennsylvania, U.S.A.), the ethylcellulose is dissolved in a water-immiscible organic solvent and then emulsified in water in the presence of a surfactant and a stabilizer. After homogenization to generate submicron droplets, the organic solvent is evaporated under vacuum to form a pseudolatex. The plasticizer is not incorporated in the pseudolatex during the manufacturing phase. Thus, prior to using the same as a coating, it is necessary to intimately mix the Aquacoat® with a suitable plasticizer prior to use. Another aqueous dispersion of ethylcellulose is commercially available as Surelease® (Colorcon, Inc., West Point, Pennsylvania, U.S.A.). This product is prepared by incorporating plasticizer into the dispersion during the manufacturing process. A hot melt of a polymer plasticizer (dibutyl sebacate) and stabilizer (oleic acid) is prepared as a homogeneous mixture, which is then diluted with an alkaline solution to obtain an aqueous dispersion which can be applied directly onto substrates.

With respect to handling and storage conditions, FMC states that Aquacoat® will undergo a rise in viscosity upon prolonged exposure to temperatures below 15°C or above 35°C, and that viscosity can be reduced to less than 100 cps by applying shear (e.g., propeller type mixer). FMC further states that a continuous film may be formed through a process known as gradual coalescence wherein the individual latex particles coalesce to form a continuous film of plasticized ethylcellulose polymer. After this period, the properties are said to remain constant. Higher coating temperatures, or a high temperature "curing" step is said by FMC to accelerate the process. If the coalescence process is not complete, FMC states that variability in release rates will result.

The stabilized controlled release formulations of the present invention slowly release the active agent, e.g., when placed in an environmental fluid in an environment of use. By "environmental fluid", it is meant that the formulation is placed in an aqueous solution (e.g., in-vitro dissolution), in simulated gastric fluid (e.g., in accordance with the USP Basket Method (i.e., 37°C, 100 RPM, first hour 700 ml gastric fluid at pH 1.2, then changed to 900 ml at pH 7.5), or in gastrointestinal fluid (in-vivo).

The controlled release profile of the formulations of the invention can be altered, for example, by varying the amount of overcoating with the aqueous dispersion of hydrophobic polymer, altering the manner in which the plasticizer is added to the aqueous dispersion of hydrophobic polymer, by varying the amount of plasticizer relative to hydrophobic polymer, by the inclusion of additional agents or excipients, by altering the method of manufacture, etc.

In one preferred embodiment of the present invention, the controlled release dosage form comprises pharmaceutically acceptable beads (e.g., spheroids) containing the active ingredient coated with a controlled release coating. The term spheroid is known in the pharmaceutical art and means, e.g., a spherical granule having a diameter of between 0.2 mm and 2.5 mm, especially between 0.5 mm and 2 mm. A suitable commercially available example of such beads are nu pariel 18/20 beads.

A plurality of the cured, coated (stabilized) controlled release spheroids may thereafter be placed in a gelatin capsule in an amount sufficient to provide an effective controlled release dose when ingested and contacted by gastric fluid.

Spheroids or beads coated with a therapeutically active agent are prepared, e.g., by dissolving the therapeutically active agent in water and then spraying the solution onto a substrate, for example, nu pariel 18/20 beads, using a Wurster insert. Optionally, additional agents are also added prior to coating the beads in order to assist the hydromorphone binding to the beads, and/or to color the solution, and the like. For example, a product which includes hydroxypropyl methylcellulose, and the like with or without colorant may be added to the solution and the solution mixed (e.g., for about 1 hour) prior to application of the same onto the beads. The resultant coated substrate, in this example beads, may then be optionally overcoated with a barrier agent, to separate the therapeutically active agent from the hydrophobic controlled release coating. An example of a suitable barrier agent is one which comprises hydroxypropyl methylcellulose (HPMC). However, any film-former known in the art may be used. It is preferred that the barrier agent does not affect the dissolution rate of the final product.

The hydromorphone, HPMC protected (optional) beads may then be overcoated with an aqueous dispersion of the hydrophobic polymer. The aqueous dispersion of hydrophobic polymer preferably further includes an effective amount of plasticizer, e.g., triethyl citrate. Pre-formulated aqueous dispersions of

ethylcellulose, such as Aquacoat® or Surelease®, may be used. If Surelease® is used, it is not necessary to separately add a plasticizer.

The coating solutions of the present invention preferably contain, in addition to the film-former, plasticizer, and solvent system (i.e., water), a colorant to provide elegance and product distinction. Color may be added to the solution of the therapeutically active agent instead, or in addition to the aqueous dispersion of hydrophobic polymer. For example, color can be added to Aquacoat® via the use of alcohol or propylene glycol based color dispersions, milled aluminum lakes and opacifiers such as titanium dioxide by adding color with shear to water soluble polymer solution and then using low shear to the plasticized Aquacoat®. Alternatively, any suitable method of providing color to the formulations of the present invention may be used. Suitable agents for providing color to the formulation when an aqueous dispersion of an acrylic polymer is used include titanium dioxide and color pigments, such as iron oxide pigments. The incorporation of pigments, may, however, increase the retardant effect of the coating.

The plasticized aqueous dispersion of hydrophobic polymer may be applied onto the substrate comprising the active agent by spraying using any suitable spray equipment known in the art. In a preferred method, a Wurster fluidized-bed system is used in which an air jet, injected from underneath, fluidizes the core material and effects drying while the hydrophobic polymer coating is sprayed on. A sufficient amount of the aqueous dispersion of hydrophobic polymer to obtain a predetermined controlled release of said active agent when said coated substrate is exposed to an environment of use, is preferably applied, taking into account considerations such as the physical characteristics of the active agent, the manner of incorporation of the plasticizer. After coating with the hydrophobic polymer, a further overcoat of a film-former, such as Opadry®, is optionally applied to the beads. This overcoat is provided, if at all, in order to substantially reduce agglomeration of the beads.

Next, the coated beads are cured in order to obtain a stabilized release rate of the active agent.

The optimum curing values for temperature, humidity and time for the particular formulation is determined experimentally. In certain embodiments of the present invention wherein the substrate is a pharmaceutically acceptable beads having the drug coated thereon, the beads which have been overcoated with the aqueous dispersion of plasticized ethylcellulose are stabilized via an oven curing conducted at a temperature of about 60°C and a relative humidity from about 60% to about 100% for a time period from about 48 to about 72 hours. This is demonstrated with respect to the hydromorphone beads described in the examples provided below.

However, one skilled in the art will recognize that necessary curing conditions will be affected by the particular drug incorporated in the formulation, as well as by the thickness of the controlled release coating, the size of the substrate (e.g., beads as compared to tablets).

It is especially contemplated that the time period needed for curing to an endpoint as described above may actually be longer or shorter than the 48-72 hour time period mentioned above. Such curing times which achieve the intended result of a stabilized formulation are considered to be encompassed by the appended claims. Additionally, it will be appreciated by those skilled in the art that it may be possible to cure the aqueous dispersion coated substrates of the present invention in other manners in order to reach the endpoint at which the coated substrate provides a stable dissolution profile. Such additional curing methods which achieve the intended result of a stabilized formulation are also considered to be encompassed by the appended claims.

The curing endpoint may be determined by comparing the dissolution profile of the cured, coated substrate (e.g., the "formulation") immediately after curing (hereinafter referred to as "the initial dissolution profile") to the dissolution profile of the formulation after exposure to accelerated storage conditions. Generally, the curing endpoint may be determined by comparing the dissolution profile of the formulation after exposure to accelerated storage conditions of, e.g., 37°C/80% RH or 40°C/75% RH for a time period of one month to the initial dissolution profile. However, the curing endpoint may be further confirmed by continuing to expose the cured, coated formulation to accelerated storage conditions for a further period of time and comparing the dissolution profile of the formulation after further exposure of, e.g., two months and/or three months, to the initial dissolution profile obtained.

In certain preferred embodiments of the present invention in which the cured coated substrate is a pharmaceutical formulation, the curing endpoint is attained when the data points plotted along a graph of the dissolution curve obtained after, e.g., exposure to accelerated conditions of 1-3 months, show a release of the active agent which does not vary at any given time point by more than about 20% of the total amount of active agent released when compared to in-vitro dissolution conducted prior to storage. Such a difference in the in-vitro dissolution curves, referred to in the art as a "band range" or a "band width" of, e.g., 20%. In general, where the in-vitro dissolution prior to storage and after exposure to accelerated conditions varies by not more than, e.g., about 20% of the total amount of active agent released, the formulation is considered

microporous poly(vinylchloride), microporous polyamides such as polyhexamethylene adipamide, microporous modacrylic copolymers including those formed from poly(vinylchloride) and acrylonitrile, microporous styrene-acrylic and its copolymers, porous polysulfones having a diphenylene sulfone in a linear chain thereof, halogenated poly(vinylidene), polychloroethers, acetal polymers, polyesters prepared by esterification of a dicarboxylic acid or anhydride with an alkylene polyol, poly(alkylenesulfides), phenolics, polyesters, microporous polysaccharides having substituted an hydroglucose units exhibiting a decreased permeability to the passage of water and biological fluids, asymmetric porous polymers, cross-linked olefin polymers, hydrophobic or hydrophilic microporous homopolymers, copolymers or interpolymers having a reduced bulk density, and materials described in U.S. Pat. Nos. 3,595,752; 3,643,178; 3,654,066; 3,709,774; 3,718,532; 3,803,601; 3,852,224; 3,852,388; and 3,853,601 (all of which are hereby incorporated by reference); in British Pat. No. 1,126,849; and in Chem. Abst. Vol. 71, 427F, 22573F, 1969.

Additional microporous materials for forming microporous lamina include poly(urethane), cross-linked chain-extended poly(urethane), poly(imides), poly(benzimidazoles), collodion, regenerated proteins, semi-solid cross-linked poly(vinylpyrrolidone), microporous materials prepared by diffusion of multivalent cations into polyelectrolyte sols, microporous derivatives of poly(styrene) such as poly(sodium-styrenesulfonate), poly(vinyl benzyl trimethylammonium chloride), microporous cellulosic acrylates and the like microporous polymers such as those described in U.S. Pat. Nos. 3,524,753; 3,565,259; 3,276,589; 3,541,055; 3,541,006; 3,546,142; 3,615,024; 3,646,178, and 3,852,224 (all of which are hereby incorporated by reference).

In certain preferred embodiments of the present invention, the release-modifying agent is hydroxypropylmethylcellulose, lactose, metal stearates, or mixtures thereof.

In general, the amount of release-modifying agent included in the controlled release coatings of the present invention may be from about 0.1% to about 80%, by weight, relative to the combined weight of hydrophobic polymer (e.g., ethylcellulose) and release-modifying agent. In general, the ratio of hydrophobic polymer to hydrophilic polymer is from about 99:1 to about 20:80, by weight. In certain preferred embodiments, the controlled release formulations of the present invention include from about 0.1% to about 50%, and in most preferred embodiments from about 0.1% to about 25%, by weight, relative to the combined weight of the hydrophobic polymer and release-modifying agent.

The controlled release coatings of the present invention may also include an exit means comprising at least one passageway, orifice, or the like. The passageway may be formed by such methods as those disclosed in U.S. Patent Nos. 3,845,770; 3,916,889; 4,063,064; and 4,088,864 (all of which are hereby incorporated by reference). The passageway can have any shape such as round, triangular, square, elliptical, irregular, etc.

The active agent(s) included in the controlled release formulations of the present invention include systemically active therapeutic agents, locally active therapeutic agents, disinfecting agents, chemical impregnants, cleansing agents, deodorants, fragrances, dyes, animal repellents, insect repellents, a fertilizing agents, pesticides, herbicides, fungicides, and plant growth stimulants, and the like.

A wide variety of therapeutically active agents can be used in conjunction with the present invention. The therapeutically active agents (e.g., pharmaceutical agents) which may be used in the compositions of the present invention include both water-soluble and water-insoluble drugs. Examples of such therapeutically active agents include antihistamines (e.g., dimenhydrinate, diphenhydramine, chlorpheniramine and dexchlorpheniramine maleate), analgesics (e.g., aspirin, codeine, morphine, dihydromorphone, oxycodone, etc.), non-steroidal anti-inflammatory agents (e.g., naproxyn, diclofenac, indomethacin, ibuprofen, sulindac), anti-emetics (e.g., metoclopramide), anti-epileptics (e.g., phenytoin, meprobamate and nitrazepam), vasodilators (e.g., nifedipine, papaverine, diltiazem and nicardipine), anti-tussive agents and expectorants (e.g., codeine phosphate), anti-asthmatics (e.g. theophylline), antacids, anti-spasmodics (e.g. atropine, scopolamine), antidiabetics (e.g., insulin), diuretics (e.g., ethacrynic acid, bendrofluazide), anti-hypotensives (e.g., propranolol, clonidine), antihypertensives (e.g. clonidine, methyldopa), bronchodilators (e.g., albuterol), steroids (e.g., hydrocortisone, triamcinolone, prednisone), antibiotics (e.g., tetracycline), antihemorrhoidals, hypnotics, psychotropics, antidiarrheals, mucolytics, sedatives, decongestants, laxatives, vitamins, stimulants (including appetite suppressants such as phenylpropanolamine). The above list is not meant to be exclusive.

In certain preferred embodiments, the therapeutically active agent comprises hydromorphone, oxycodone, dihydrocodeine, codeine, dihydromorphone, morphine, buprenorphine, salts of any of the foregoing, mixtures of any of the foregoing, and the like.

In another preferred embodiment of the present invention, the active agent is a locally active therapeutic agent and the environment of use may be, e.g., the gastrointestinal tract, or body cavities such as the oral cavity, periodontal pockets, surgical wounds, the rectum or vagina.

The locally active pharmaceutical agent(s) include antifungal agents (e.g., amphotericin B, clotrimazole, nystatin, ketoconazole, miconazol, etc.), antibiotic agents (penicillins, cephalosporins, erythromycin, tetracycline, aminoglycosides, etc.), antiviral agents (e.g., acyclovir, idoxuridine, etc.), breath fresheners (e.g. chlorophyll), antitussive agents (e.g., dextromethorphan hydrochloride), anti-cariogenic compounds (e.g. metallic salts of fluoride, sodium monofluorophosphate, stannous fluoride, amine fluorides), analgesic agents (e.g., methylsalicylate, salicylic acid, etc.), local anesthetics (e.g., benzocaine), oral antiseptics (e.g., chlorhexidine and salts thereof, hexylresorcinol, dequalinium chloride, cetylpyridinium chloride), anti-inflammatory agents (e.g., dexamethasone, betamethasone, prednisone, prednisolone, triamcinolone, hydrocortisone, etc.), hormonal agents (oestriol), anti-plaque agents (e.g. chlorhexidine and salts thereof, octenidine, and mixtures of thymol, menthol, methylsalicylate, eucalyptol), acidity reducing agents (e.g., buffering agents such as potassium phosphate dibasic, calcium carbonate, sodium bicarbonate, sodium and potassium hydroxide, etc.), and tooth desensitizers (e.g., potassium nitrate). This list is not meant to be exclusive.

When the controlled release coating of the present invention is to be applied to tablets, the tablet core (e.g. the substrate) may comprise the active agent along with any pharmaceutically accepted inert pharmaceutical filler (diluent) material, including but not limited to sucrose, dextrose, lactose, microcrystalline cellulose, xylitol, fructose, sorbitol, mixtures thereof and the like. Also, an effective amount of any generally accepted pharmaceutical lubricant, including the calcium or magnesium soaps may be added to the above-mentioned agents of the excipient prior to compression of the tablet core agents. Most preferred is magnesium stearate in an amount of about 0.2-3% by weight of the solid dosage form.

In another preferred embodiment of the present invention, the active agent is disinfecting agent, e.g. a chlorine compound such as calcium hypochlorite, and the environment of use is a surrounding body of water, e.g. a recreational pool.

In still another preferred embodiment of the present invention, the active agent comprises at least one of a cleansing agent, a germicide, a deodorant, a surfactant, a fragrance, a perfume, a sanitizer, and/or a dye, and the environment of use is an aqueous solution, e.g. a urinal or toilet bowl.

In yet another preferred embodiment of the present invention, the active agent is a chemical impregnant, e.g. fertilizer, animal repellents, insect repellents, pesticides, herbicides, fungicides, plant growth stimulants, and the environment of use is, e.g., anywhere around the home, e.g. soil, trees etc. The fertilizer may be, for example, a nitrogen containing compound such as urea, urea formaldehyde composites, potassium nitrate, potassium sulfate, potassium chloride, ammonium nitrate, ammonium sulfate, monoammonium phosphate, dibasic ammonium phosphate, ammoniated super-phosphoric acid, micro-nutrient ingredients such as trace elements of iron, zinc, manganese, copper, boron, molybdenum, and mixtures of any of the foregoing. The fertilizer may be, e.g., in granular form.

For example, when the coated substrate is a coated chlorine tablet for combatting bacterial and algaecidal contamination of swimming pools and the like, the substrate may comprise commercial grade calcium hypochlorite, with or without trichloroisocyanuric acid, sodium dichlorocyanurate, lithium hypochlorite, powdered lime, and/or the like.

For example, the substrate may comprise about 98.5% commercial grade calcium hypochlorite and about 1.5% powdered lime, by weight. The substrate may also comprise commercial granular calcium hypochlorite, up to 20% by weight chloride of lime, and 1% zinc stearate having an available chlorine percentage of about 69% and a mass of about 57 g and a diameter of about 40 mm, as described in U.S. Patent No. 4,192,763, hereby incorporated by reference. The substrate is then coated with the aqueous dispersion of plasticized hydrophobic polymer to a weight gain from about 3 to about 30 percent, depending upon the desired rate of dissolution, and the coated tablet is then cured in accordance with the present invention until an endpoint is reached at which the cured coated tablet provides a reproducibly stable dissolution profile.

When the active agent comprises a composition suitable for cleaning and preventing the staining of toilet bowls, the substrate may include a well-known disinfectant such as calcium hypochlorite and/or trichloroisocyanuric acid. The active agent may alternatively comprise an alkali metal salt of dichloroisocyanuric acid and a chloride salt such as calcium chloride and barium chloride, such as that which is described in U.S. Patent No. 4,654,341, hereby incorporated by reference.

One possible example of such a product might include a substrate comprising 0.5-5% fragrance, 1-10% dye, 10-40% surfactant (which may be nonionic, cationic, anionic or zwitterion surfactants), and other optional components such as germicides, disinfectants, processing aids, and other commonly included ingredients known to those skilled in the art. Such active agents may be incorporated into a substrate comprising a tablet, along with other well-known ingredients such as detergents, surfactants, perfumes, dyes, and any necessary fillers.