SUPERINDUSTRIA Y COMERCIO
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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Señor

SUPERINTENDENTE DELEGADO PARA LA PROPIEDAD INDUSTRIAL

DIVISION DE NUEVAS CREACIONES

E. S. D.

Ref: P1.-**GRUNENTHAL GmbH**.-Expediente No. **00-002.025.-**

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

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

Ref: P1.-**GRUNENTHAL GmbH** .-Expediente No.**00-002.025.-**

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.

Atentamente,

JOSE ANTONIO LLOREDA
T.P. 10784
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DILIGENCIA DE RECONOCIMIENTO Y PRESENTACION PERSONAL
Bogotá, D.C. 25 AGO 2004
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En constancia se firma esta diligencia y se imprime

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

NOTARIA SEXTA
PABLO MENDEZ BARAJAS
Notario Encargado

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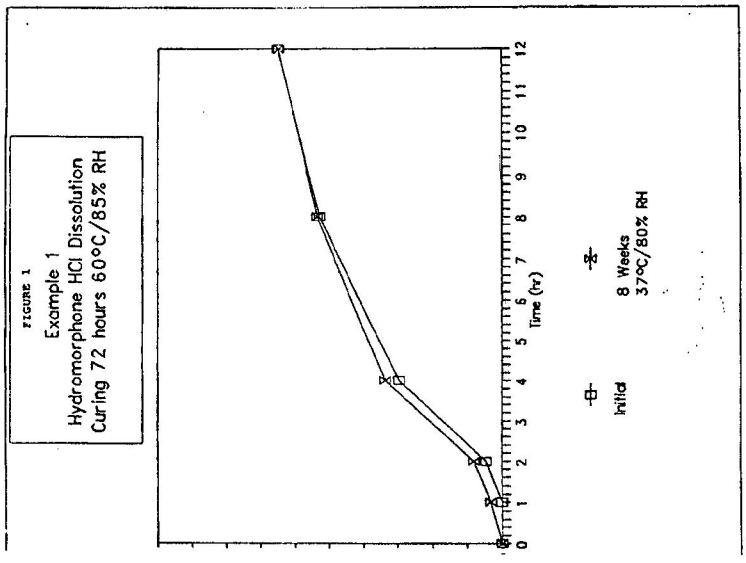
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(54) **Stabilized controlled release substrate having a coating derived from an aqueous dispersion of hydrophobic polymer.**

(57) A stabilized solid controlled release dosage form having a coating derived from an aqueous dispersion of ethylcellulose is obtained by overcoating a substrate including a therapeutically active with an aqueous dispersion of ethylcellulose and then curing the coated substrate at a temperature and relative humidity elevated to a suitable level above ambient conditions until the coated dosage form attains a stabilized dissolution profile substantially unaffected by exposure to storage conditions of elevated temperature and/or elevated relative humidity.



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BACKGROUND OF THE INVENTION

It is the aim of all controlled release preparations to provide a longer duration of pharmacological response after the administration of the dosage form than is ordinarily experienced after the administration of an immediate release dosage form. Such extended periods of response provides for many inherent therapeutic benefits that are not achieved with short acting, immediate release products.

Controlled release formulations known in the art include specially coated beads or pellets, coated tablets and ion exchange resins, wherein the slow release of the active drug is brought about through selective breakdown of, or permeation through, the coating of the preparation or through formulation with a special matrix to affect the release of the drug.

An important aspect of all forms of controlled release dosage forms is related to the stability of the same. The stability of a pharmaceutical dosage form is related to maintaining its physical, chemical, microbiological, therapeutic, pharmaceutical, and toxicological properties when stored, i.e., in a particular container and environment. Stability study requirements are covered, e.g., in the Good Manufacturing Practices (GMPs), the U.S.P., as well as in New Drug Applications (NDAs) and Investigational New Drug Applications (INDs).

The ingredients used in sustained release dosage formulations often present special problems with regard to their physical stability during storage. For example, waxes which have been used in such formulations are known to undergo physical alterations on prolonged standing, thus precautions are taken to stabilize them at the time of manufacture or to prevent the change from occurring. Fats and waxy materials when used in purified states are known to crystallize in unstable forms, causing unpredictable variations in availability rates during stability testing at the time of manufacture and during later storage.

It is known that certain strategies can be undertaken to obtain stabilized controlled release formulations in many cases, such as insuring that the individual ingredients are in a stable form before they are incorporated into the product, and that processing does not change this condition, retarding the instability by including additional additives, and inducing the individual ingredients of the dosage form to reach a stable state before the product is finally completed.

It is also recognized that the moisture content of the product can also influence the stability of the product. Changes in the porosity and/or hydration level of a polymeric film, such as the ethyl celluloses, can alter the rate of water permeation and drug availability. Also, binders such as acacia are known to become less soluble when exposed to moisture and heat. Such problems have been handled by controls in the processing method and proper packaging of the product.

Hydrophobic polymers such as certain cellulose derivatives, zein, acrylic resins, waxes, higher aliphatic alcohols, and polylactic and polyglycolic acids have been used in the prior art to develop controlled release dosage forms. Methods of using these polymers to develop controlled release dosage forms such as tablets, capsules, suppositories, spheroids, beads or microspheres are to overcoat the individual dosage units with these hydrophobic polymers. It is known in the prior art that these hydrophobic coatings can be applied either from a solution, suspension or dry. Since most of these polymers have a low solubility in water, they are usually applied by dissolving the polymer in an organic solvent and spraying the solution onto the individual drug forms (such as beads or tablets) and evaporating off the solvent.

Aqueous dispersions of hydrophobic polymers have been used in the prior art to coat pharmaceutical dosage forms for aesthetic reasons such as film coating tablets or beads or for taste-masking. However, these dosage forms are used for immediate release administration of the active drug contained in the dosage form.

The use of organic solvents in the preparation of polymer coatings is considered problematic as the formulations have inherent problems with regard to flammability, carcinogenicity, and safety in general. In addition, the use of organic solvents is disfavored due to environmental concerns.

Therefore, it is desirable to prepare a controlled release formulation prepared from an agueous dispersion of a hydrophobic polymer. However, to date, attempts to prepare stable controlled release pharmaceutical formulations using aqueous dispersions of hydrophobic polymers have been unsuccessful due to stability problems. In particular, when coating these pharmaceutical forms using aqueous polymeric dispersions to obtain a desired release profile of the active drug(s) over several hours or longer, it is known in the art that the dissolution release profile changes on ageing. It is also known that this instability problem does not exist when the polymers are applied from organic solvent solution.

For example, Dressman, et al., Proceed. Intern. Symp. Control. Rel. Bioact. Mater., 18 (1991), pp. 654-655, Controlled Release Society, Inc. reported on tests conducted which showed that phenylpropanolamine

organic solvent and then emulsifying the same 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.

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.

However, as will be demonstrated by the examples provided herein, it has been found that curing the film coating simply by utilizing a higher coating temperature or a high temperature curing step will not effectively stabilize the dissolution profile of the product upon storing.

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.

The coating formulations of the present invention should be capable of producing a strong, continuous film that is smooth and elegant, capable of supporting pigments and other coating additives, non-toxic, inert, and tack-free.

It is preferred that the aqueous dispersion of ethylcellulose used in the present invention include an effective amount of a suitable plasticizing agent, as it has been found that the use of a plasticizer will further improve the physical properties of the film. The plasticization of the ethylcellulose may be accomplished either by so-called "internal plasticization" and "external plasticization."

Internal plasticization usually pertains directly to molecular modifications of the polymer during its manufacture, e.g., by copolymerization, such as altering and/or substituting functional groups, controlling the number of side chains, or controlling the length of the polymer. Such techniques are usually not performed by the formulator of the coating solution.

External plasticization involves the addition of a material to a film solution so that the requisite changes in film properties of the dry film can be achieved.

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 (Tg) 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 Tg, the polymer chain mobility is severely restricted. Thus, for a given polymer, if its Tg 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 Tg, 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 include water insoluble plasticizers such as dibutyl sebacate, diethyl phthalate, triethyl citrate, tibutyl citrate, and triacetin, although it is possible that other water-insoluble

invention.

The stabilized controlled release formulations of the present invention slowly release the therapeutically active agent, e.g., when ingested and exposed to gastric fluids, and then to intestinal fluids. 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 ethylcellulose, altering the manner in which the plasticizer is added to the aqueous dispersion of ethylcellulose, by varying the amount of plasticizer relative to ethylcellulose, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc.

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.), anti-inflammatory agents (e.g., naproxyn, diclofenac, indomethacin, ibuprofen, acetaminophen, aspirin, sulindac), gastro-intestinals and anti-emetics (e.g., metoclopramide), anti-epileptics (e.g., phenytoin, meprobamate and nitrezepam), vasodilators (e.g., nifedipine, papaverine, diltiazem and nicardirine), antitussive agents and expectorants (e.g., codeine phosphate), anti-asthmatics (e.g. theophylline), anti-spasmodics (e.g. atropine, scopolamine), hormones (e.g., insulin, leparin), diuretics (e.g., eltacrymic acid, bendrofluazide), anti-hypotensives (e.g., propranolol, clonidine), bronchodilators (e.g., albuterol), anti-inflammatory steroids (e.g., hydrocortisone, triamcinolone, prednisone), antibiotics (e.g., tetracycline), antihemorrhoidals, hypnotics, psychotropics, antidiarrheals, mucolytics, sedatives, decongestants, laxatives, antacids, 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, dihydromorphine, morphine, buprenorphine, salts of any of the foregoing, and mixtures of any of the foregoing, and the like.

When the aqueous dispersion of ethylcellulose is used to coat inert pharmaceutical beads such as nu pariel 18/20 beads, a plurality of the resultant stabilized solid controlled release beads 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. In this embodiment, 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 ingredients are also added prior to coating the beads in order to assist the hydromorphone binding to the beads, and/or to color the solution, etc. For example, a product which includes hydroxypropyl methylcellulose, etc. 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 ethylcellulose coating. An example of a suitable barrier agent is one which comprises hydroxypropyl methylcellulose. 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 ethylcellulose. The aqueous dispersion of ethylcellulose 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 ethylcellulose. For example, color 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.

The plasticized aqueous dispersion of ethylcellulose may be applied onto the substrate comprising the therapeutically active agent by spraying using any suitable spray equipment known in the art. A sufficient amount of the aqueous dispersion of ethylcellulose to obtain a predetermined controlled release of said

dissolution upon storage under stress conditions, the degree of slowdown of release being said to be directly proportional to temperature, while the effect of relative humidity (RH) appeared to be insignificant. Munday, et al. concluded that the decreased rate of release was due to the slowing in the rate of molecular diffusion of the drug across the polymeric coating material, and suggested that the change was due to significant alterations in the permeability of the polymer which occurred during the experimental storage.

This instability problem is known to not exist when the polymers are applied from organic solvent solution.

OBJECTS AND SUMMARY OF THE INVENTION

It is therefore an object of the present invention to provide a controlled release tablet comprising a core containing an active agent, e.g. a therapeutically active agent, a disinfecting agent, a cleansing agent, a sanitizing agent and a fertilizing agent coated with an aqueous dispersion of a hydrophobic polymer, e.g. alkylcellulose or acrylic polymers such that there is a stable dissolution profile of the active agent when placed in an environment of use.

It is another object of the present invention to provide a controlled release formulation comprising a plurality of inert beads comprising an effective amount of an active agent, the beads being coated with an aqueous dispersion of a hydrophobic polymer and providing a reproducible, stable dissolution despite exposure to accelerated storage conditions.

It is another object of the present invention to provide a method of preparing a controlled release tablet comprising a core containing an active agent coated with an aqueous dispersion of a hydrophobic polymer such that there is a stable dissolution profile of the active agent when placed in an environment of use, despite exposure to accelerated storage conditions.

Still another object of the present invention is to provide a controlled release formulation comprising a substrate containing an active agent coated with an aqueous dispersion of a hydrophobic polymer such that there is a stable dissolution profile of the active agent when placed in an environment of use, even after storage for a period of time where the coated formulation may be exposed to storage conditions of temperature and/or humidity elevated above ambient conditions.

A further object of the present invention is to provide a controlled release formulation wherein the controlled release is caused by a coating on the formulation of an aqueous dispersion of a hydrophobic polymer such as ethylcellulose which coating provides a stable dissolution of an active agent contained in the formulation, despite exposure to accelerated storage conditions such that the dissolution would be deemed acceptable by a governmental regulatory agency such as the U.S. FDA for purposes of according expiration dating.

The above-mentioned objects and others are accomplished by the present invention, which relates in part to a controlled release formulation comprising a substrate containing an active agent in an amount sufficient to provide a desired effect in an environment of use, said substrate coated with an aqueous dispersion of plasticized ethylcellulose in an amount sufficient to obtain a controlled release of said active agent when said formulation is exposed to an environmental fluid. The coated substrate is cured at a temperature greater than the glass transition temperature of the aqueous dispersion of plasticized ethylcellulose and at a relative humidity from about 60% to about 100% for a sufficient period of time until a curing endpoint is reached at which said coated substrate provides a stabilized dissolution of said active agent which is unchanged after exposure to accelerated storage conditions, said 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, e.g., of one-three months at a temperature of 37°C and at a relative humidity of 80%. In certain preferred embodiments, the substrate is coated to a weight gain from about 2% to about 25%.

In other embodiments, the coated substrate is cured at a temperature greater than the glass transition temperature of the aqueous dispersion of plasticized ethylcellulose and at a relative humidity from about 60% to about 100% to cause individual ethylcellulose particles in said coating to coalesce and to gradually slow the release of said active agent when exposed to an environmental fluid, until an endpoint is reached at which the cured coated substrate, when subjected to in-vitro dissolution, releases said active agent in amounts which do not vary at any time point along the dissolution curve by more than about 20% of the total amount of active agent released, when compared to the in-vitro dissolution of said coated substrate prior to curing.

In yet other embodiments of the invention, the cured formulation provides a stabilized dissolution of

according expiration dating for said formulation.

Other preferred embodiments relate to controlled release dosage formulation comprising a substrate coated with an effective amount of an aqueous dispersion of ethylcellulose to obtain a controlled release of an active agent which formulation, after exposure to accelerated storage conditions of at least one month at 40 °C/75% RH, releases an amount of therapeutically active agent which does not vary at any given dissolution time point by more than about 20% of the total amount of therapeutically active agent released, when compared to in-vitro dissolution conducted prior to storage.

In other embodiments, the coated substrate, upon in-vitro dissolution testing, provides a band range after exposure to accelerated storage conditions which is not wider than about 20% at any point of time when compared to the dissolution profile prior to exposure to the accelerated storage conditions.

The active agent may be chosen for a wide variety of uses, including but not limited to systemically active therapeutic agents, locally active therapeutic agents, disinfectants, cleansing agents, fragrances, fertilizers, deodorants, dyes, animal repellents, insect repellents, pesticides, herbicides, fungicides, and plant growth stimulants.

The present invention is further related to a solid controlled release oral dosage formulation, comprising a substrate containing an systemically active therapeutic agent in an amount sufficient to provide a desired therapeutic effect when said formulation is orally administered. The substrate is coated with an aqueous dispersion of plasticized ethylcellulose and cured at a temperature greater than the glass transition temperature of the aqueous dispersion of plasticized ethylcellulose and at a relative humidity from about 60% to about 100% for a period of time sufficient to obtain a controlled release of said active agent when measured by the USP Paddle Method at 100 rpm at 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37 °C from about 5% to about 42.5% (by wt) active agent released after 1 hour, from about 15% to about 60% (by wt) active agent released after 2 hours, from about 17% to about 75% (by wt) active agent released after 4 hours, and from about 20% to about 90% (by wt) active agent released after 8 hours, said coated substrate being cured to cause individual ethylcellulose particles in said coating to coalesce and to gradually slow the release of said active agent when exposed to an environmental fluid until an endpoint is reached at which the release rate (e.g., in-vitro dissolution) obtained after exposing the cured, coated substrate to accelerated storage conditions of 37 °C and 80% relative humidity for one-three months is stable when compared to the release rate obtained immediately after curing. The dosage form preferably provides a therapeutic effect for about 24 hours. The present invention further relates to a method of preparing the dosage form.

The present invention is also related to a method for obtaining a controlled release formulation of an active agent, comprising preparing a solid substrate comprising an active agent, coating the substrate with a sufficient amount an aqueous dispersion of plasticized ethylcellulose to obtain a predetermined controlled release of the active agent when the coated substrate is exposed to an environmental fluid, and curing the coated substrate at a temperature greater than the glass transition temperature of the aqueous dispersion of plasticized ethylcellulose and at a relative humidity from about 60% to about 100% until a curing endpoint is reached at which said coated substrate provides a stabilized dissolution of said active agent which is unchanged after exposure to accelerated storage conditions. The endpoint is determined, e.g., 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, for example, one-three months at a temperature of 37 °C and at a relative humidity of 80%.

The present invention is further related to a method of treating a patient with an oral solid dosage form described above. In this method, present invention further comprises administering the oral solid dosage form comprising the cured, coated substrate to the patient to thereby obtain the desired therapeutic effect for about 12 to about 24 hours. In especially preferred embodiments, the oral solid dosage forms of the present invention provide a desired therapeutic effect for about 24 hours.

The present invention provides many benefits over prior art coatings, including, but not limited to, avoidance of organic solvents which have inherent safety concerns (flammability, carcinogenicity, environmental concerns, safety in general), and extended stability which may result in extended shelf life and expiration dating.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings are illustrative of embodiments of the invention and are not meant to limit the scope of the invention as encompassed by the claims.

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;

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;

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;

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);

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

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

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 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 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 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 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.

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"

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 (Tg) 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 Tg, the polymer chain mobility is severely restricted. Thus, for a given polymer, if its Tg 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 Tg, 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

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, tibutyl 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

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 physically 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

acceptable when considered by governmental regulatory agencies such as the U.S. FDA for stability concerns and expiration dating. Acceptable band ranges are determined by the FDA on a case-by-case basis, and any band range for a particular pharmaceutical which would be deemed acceptable by such a governmental regulatory agency would be considered to fall within the appended claims. In preferred embodiments, the aforementioned band range is not more than 15% of the total amount of active agent released. In more preferred embodiments, the band range is not more than 10% of the total amount of active agent released. In the appended Examples, the band range is often significantly less than 10%.

The release of the active agent from the controlled release formulation of the present invention can be further influenced, i.e., adjusted to a desired rate, by the addition of one or more release-modifying agents, or by providing one or more passageways through the coating.

The release-modifying agents which function as pore-formers can be inorganic or organic, and include materials that can be dissolved, extracted or leached from the coating in the environment of use.

For example, the pore-formers may comprise one or more water-soluble hydrophilic polymers in order to modify the release characteristics of the formulation. Examples of suitable hydrophilic polymers include hydroxypropylmethylcellulose, cellulose ethers, acrylic resins and protein-derived materials. Of these polymers, the cellulose ethers, especially hydroxyalkylcelluloses and carboxyalkylcelluloses, are preferred. Also, synthetic water-soluble polymers may be used, such as polyvinylpyrrolidone, cross-linked polyvinylpyrrolidone, polyethylene oxide, etc., and polysaccharides, e.g., pullulan, dextran, etc. In certain preferred embodiments of the present invention, the hydrophilic polymer comprises hydroxypropylmethylcellulose.

In addition, a water-soluble polydextrose that dissolves to a level of at least about 1% (W/W) in water at 25 °C may be incorporated into the controlled release coating.

The pore-formers further include alkali metal salts, polysaccharides, such as lithium carbonate, sodium chloride, sodium bromide, potassium chloride, potassium sulfate, potassium phosphate, sodium acetate, sodium citrate, and the like. Suitable polysaccharides include sucrose, glucose, fructose, mannitol, lactose, mannose, galactose, sorbitol and the like. The pore-forming solids may also be polymers which are soluble in the environment of use, such as Carbowaxes®, Carbopol®, and the like. The pore-formers embrace diols, polyols, polyhydric alcohols, polyalkylene glycols, polyglycols, poly(a-w)alkylenediols, and the like. The pore-formers are non-toxic and on their removal from lamina, channels and pores are formed through the lamina that fill with fluid present in the environment use.

Semipermeable polymers may also be incorporated in the controlled release coating to change the release characteristics of the formulation. Such semipermeable polymers include, for example, cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, beta-glucan acetate, acetaldehyde dimethyl acetate, cellulose acetate ethyl carbamate, polyamide, polyurethane, sulfonated polystyrene, cellulose acetate phthalate, cellulose acetate methyl carbamate, cellulose acetate succinate, cellulose acetate dimethylaminoacetate, cellulose acetate chloracetate, cellulose dipalmitate, cellulose dioctanoate, cellulose dicaprylate, cellulose dipentanlate, cellulose acetate valerate, cellulose acetate p-toluenesulfonate, cellulose acetate butyrate, and other semipermeable polymers such as those described in U.S. Patent No. 4,285,987 (hereby incorporated by reference), as well as the selectively permeable polymers formed by the coprecipitation of a polycation and a polyanion as disclosed in U.S. Pat. Nos. 3,173,876; 3,276,586; 3,541,005; 3,541,006 and 3,546,142 (hereby incorporated by reference).

The controlled release coatings of the present invention can also include other release-modifying agents such as cellulose acetate phthalate, such as those disclosed in U.S. Patent No. 2,196,768, herein incorporated by reference. Other suitable release-controlling agents which may be included in the controlled release coating of the present invention include shellac, zein, hydroxypropylmethyl cellulose phthalate, sandarac, modified shellac, etc.

The controlled release coatings of the present invention can also include released modifying agents which promote erosion (i.e., erosion promoting agents), such as starch (including, but not limited to corn starch, rice starch, α starch, carboxymethyl starch, potato starch, and other vegetable starches), modified starch, and starch derivatives. This category is also intended to include other erosion-promoting agents such as gums, including but not limited to xanthan gum, alginic acid, other alginates, bentonite, veegum, agar, guar, locust bean gum, gum arabic, quince psyllium, flax seed, okra gum, arabinoglactin, pectin, tragacanth, scleroglucan, dextran, amylose, amylopectin, dextrin, etc., cross-linked polyvinylpyrrolidone, ion-exchange resins, such as potassium polymethacrylate, carrageenan, kappa-carrageenan, lambdacarrageenan, gum karaya, biosynthetic gum, etc.

The controlled release coatings of the present invention can also include release-modifying agents which are useful for making microporous lamina in the environment of use, such as polycarbonates

microporous poly(vinylchloride), microporous polyamides such as polyhexamethylene adipamide, microporous modacrylic copolymers including those formed from poly(vinychloride) and acrylonitrile, microporous styrene-acrylic and its copolymers, porous polysulfones haying 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 nitrezepam), vasodilators (e.g., nifedipine, papaverine, diltiazem and nicardirine), 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, dihydromorphine, 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

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-flammatory 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, methysalicylate, 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, micronutrient 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,

Table 58

Hour	% APAP Dissolved
1	3.1
2	22.4
4	79.4
8	100.1

EXAMPLE 29

In Example 29, the dissolution rate of the tablets of Example 26 is increased by virtue of increasing the amount of pore former contained in the controlled release coating to 70%.

In Example 29, immediate release tablet cores are prepared in accordance with the procedure set forth with regard to Example 26. Thereafter, the immediate release cores are coated with a controlled release coating comprising an aqueous dispersion of ethylcellulose containing 70% HPMC as the pore former. The coating is contained until a weight gain of 10% is achieved. The formula for the coated APAP tablet cores is set forth in Table 59 below:

Table 59

Ingredients	mg/tab
APAP IR tablet cores	555.6
Aquacoat ECD-30 (solids)	16.668
Methocel E5 premium	38.892
Triethyl Citrate	11.112
Purified water	qs
Total:	622.272

Thereafter, the coated tablets are cured under the same conditions set forth in Example 26. In vitro dissolution is then carried out as set forth in Example 26. The results are set forth in Table 60 below:

Table 60

Hour	% APAP Dissolved
1	97.2
2	102.8

The examples provided above are not meant to be exclusive. Many other variations of the present invention would be obvious to those skilled in the art.

Claims

1. A controlled release dosage form, comprising

a solid substrate comprising an effective amount of a therapeutically active agent, said solid substrate being controlled with an aqueous dispersion of ethylcellulose in an amount effective to provide a controlled release of said therapeutically active agent when said coated substrate is exposed to gastrointestinal fluid, said coated substrate when subjected to in-vitro dissolution after exposure to accelerated storage conditions of at least one month at 40°C/75% RH releasing an amount of said therapeutically active agent which does not vary at any given dissolution time point by more than about 20% of the total amount of therapeutically active agent released when compared to in-vitro dissolution

2. The dosage form of claim 1, characterized in that said coating is sufficient to provide effective blood levels of said therapeutically active agent for at least about 12 hours, said coated substrate upon in-vitro dissolution testing providing a band range, when comparing the dissolution profile after exposure to accelerated storage conditions of at least one month at a temperature of 40 °C and a relative humidity of 75% to the dissolution profile prior to exposure to said accelerated conditions, which is not wider than about 20% of total active agent released at any point of time.

3. The dosage form of claim 2, characterized in that said coated substrate is cured at a temperature greater than the glass transition temperature of the aqueous dispersion of plasticized ethylcellulose and at a relative humidity from about 60% to about 100% to cause individual ethylcellulose particles in said coating to coalesce and to gradually slow the release of said active agent when exposed to an environmental fluid, until said band range is obtained.

4. A solid controlled release oral dosage form, comprising a substrate containing a systemically active therapeutic agent in an amount sufficient to provide a desired therapeutic effect when said formulation is orally administered, said substrate being coated with an aqueous dispersion of plasticized ethylcellulose to a weight gain from about 2% to about 25%, said coating being sufficient to obtain a controlled release of said active agent when measured by the USP Paddle Method at 100 rpm at 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37 °C from about 12.5% to about 42.5% (by wt) active agent released after 1 hour, from about 25% to about 55% (by wt) active agent released after 2 hours, from about 45% to about 75% (by wt) active agent released after 4 hours and from about 55% to about 85% (by wt) active agent released after 8 hours, said coated substrate, when subjected to accelerated storage conditions of at least one month at 40 °C/75% RH, releasing an amount of said therapeutically active agent upon in-vitro dissolution which does not vary at any given time point by more than about 20% of the total amount of therapeutically active agent released when compared to in-vitro dissolution conducted prior to storage.

5. The dosage form of claims 1-4, which provides therapeutically effective blood levels when administered orally for at least 24 hours.

6. The dosage form of claims 1-5, wherein said substrate is coated to a weight gain from about 2% to about 25%.

7. The dosage form of claims 1-6, wherein said therapeutically active agent is selected from the group consisting of antihistamines, analgesics, non-steroidal anti-inflammatory agents, gastro-intestinals, anti-emetics, anti-epileptics, vasodilators, anti-tussive agents, expectorants, anti-asthmatics, hormones, diuretics, anti-hypotensives, anti-hypertensives, bronchodilators, antibiotics, antivirals, antihemorrhoidals, steroids, hypnotics, psycho-tropics, antidiarrheals, mucolytics, sedatives, decongestants, laxatives, vitamins, and stimulants.

8. The dosage form of claims 1-7, wherein said substrate is a pharmaceutically acceptable bead, and a plurality of said coated, cured beads are placed in a capsule in an amount sufficient to provide an effective controlled release dose when contacted by an aqueous solution.

9. The dosage form of claims 1-8, wherein said substrate is a tablet core.

10. The dosage form of claims 1-8, wherein said therapeutically active agent is an opioid analgesic selected from the group consisting of hydromorphone, oxycodone, morphine, levorphanol, methadone, meperidine, heroin, dihydrocodeine, codeine, dihydromorphine, buprenorphine, salts of any of the foregoing, and mixtures of any of the foregoing.

11. The dosage form of claim 3, wherein said coating is cured for a time period from about 48 to about 72 hours at a relative humidity of about 85%.

12. The dosage form of claims 1-11, characterized in that said coating further comprises a release-modifying agent in an amount effective to modify the rate of release of said active agent from said

13. The dosage form of claim 12, wherein said release-modifying agent is selected from the group consisting of a hydrophilic polymer, a semi-permeable polymer, an erosion-promoting polymer, an agent capable of making microporous lamina, a pore-former, and mixtures of any of the foregoing.

14. The dosage form of claims 12-13, wherein said coating comprises from about 0.1% to about 70% of said release-modifying agent.

15. The dosage form of claim 12, wherein said coating comprises from about 0.1% to about 50% of said release-modifying agent.

16. The dosage form of claim 12, wherein said coating comprises from about 0.1% to about 25% of said release-modifying agent.

17. The dosage form of claims 1-4, wherein said coated substrate includes at least one passageway through said coating which modifies the release of said systemically active therapeutic agent.

18. The dosage form of claim 12, wherein said release-modifying agent is selected from the group consisting of hydroxypropylmethylcellulose, lactose, metal stearates, and mixtures of any of the foregoing.

19. The dosage form of claims 1-4, which provides a stabilized dissolution of said active agent which is unchanged after exposure to accelerated storage conditions of a temperature of 40 °C and a relative humidity of 75% for 3 months.

20. The dosage form of claims 4, 5, 7 and 10, wherein a portion of the amount of said active agent included in said formulation is incorporated into a coating on said substrate.

21. The dosage form of claim 2, characterized in that the band range, when comparing the dissolution profile after exposure to accelerated storage conditions of at least one month at a temperature of 40 °C and a relative humidity of 75% to the dissolution profile prior to exposure to said accelerated conditions, does not differ by more than about 15%.

22. The dosage form of claim 2, characterized in that the band range, when comparing the dissolution profile after exposure to accelerated storage conditions of at least one month at a temperature of 40 °C and a relative humidity of 75% to the dissolution profile prior to exposure to said accelerated conditions, does not differ by more than about 10%.

23. A method of treating a human patient, comprising orally administering the oral solid dosage form of claims 1-22.

24. A controlled release formulation comprising a substrate containing an active agent in an amount sufficient to provide a desired effect in an environment of use, said active agent being selected from the group consisting of a locally active therapeutic agent, a disinfecting agent, a cleansing agent, a fragrance, a fertilizing agent, a deodorant, a dye, an animal repellant, an insect repellant, a pesticide, a herbicide, a fungicide, and a plant growth stimulant, said substrate coated with an aqueous dispersion of plasticized ethylcellulose in an amount sufficient to obtain a controlled release of said active agent when said formulation is exposed to an environmental fluid, said coated substrate being cured at a temperature greater than the glass transition temperature of the aqueous dispersion of plasticized ethylcellulose and at a relative humidity from about 60% to about 100% for a sufficient period of time until a curing endpoint is reached at which said coated substrate provides a stabilized dissolution of said active agent which is unchanged after exposure to accelerated storage conditions, said 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%.

25. The formulation of claim 24, wherein said substrate is coated to a weight gain from about 2 to about

36. The method of claim 34, wherein said locally active therapeutic agent is selected from the group consisting of an antifungal agent, an antibiotic, an antiviral agent, a breath freshener, an antitussive agent, an anticariogenic agent, an analgesic agent, a local anesthetic, an antiseptic, an anti-flammatory agent, a hormonal agent, an antiplaque agent, an acidity reducing agent, and a tooth desensitizer.

37. The method of claims 33-34, characterized in that said substrate comprises pharmaceutically acceptable inert beads, further comprising coating said therapeutically active agent onto the surface of said inert beads, and preparing said oral dosage form by placing a sufficient quantity of cured coated beads into a capsule.

38. The method of claim 33, further comprising preparing said substrate for oral administration by incorporating said therapeutically active agent into a tablet.

39. The method of claims 33-34, wherein said coated substrate is cured for about 48 to about 72 hours, until said endpoint is reached.

40. The method of claims 33-34, further comprising coating said substrate to a weight gain from about 2% to about 25%.

41. The method of claims 33-34, wherein said therapeutically active agent is selected from the group consisting of antihistamines, analgesics, non-steroidal anti-inflammatory agents, gastro-intestinals, anti-emetics, anti-epileptics, vasodilators, anti-tussive agents, expectorants, anti-asthmatics, hormones, diuretics, anti-hypotensives, anti-hypertensives, bronchodilators, antibiotics, antivirals, antihemorrhoidals, steroids, hypnotics, psychotropics, antidiarrheals, mucolytics, sedatives, decongestants, laxatives, vitamins, and stimulants.

42. The method of claims 33-34, wherein said active agent is an opioid analgesic selected from the group consisting of hydromorphone, oxycodone, morphine, levorphanol, methadone, meperidine, heroin, dihydrocodeine, codeine, dihydromorphine, buprenorphine, salts thereof, and mixtures thereof.

43. The method of claims 33-34 and 37-42, wherein said oral solid dosage form provides a desired therapeutic effect for about 24 hours.

44. The method of claims 33-34, further comprising incorporating a release-modifying agent in said aqueous dispersion of ethylcellulose in an amount effective to modify the rate of release of said active agent from said cured, coated substrate.

45. The method of claim 44, wherein said release-modifying agent is selected from the group consisting of a hydrophilic polymer, a semi-permeable polymer, an erosion-promoting polymer, an agent capable of making microporous lamina, a pore-former, and mixtures of any of the foregoing.

46. The method of claim 44, wherein said release-modifying agent is selected from the group consisting of hydroxypropylmethylcellulose, lactose, metal stearates, and mixtures of any of the foregoing.

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Kotwal et al.

[11] Patent Number: 5,645,858

[45] Date of Patent: Jul. 8, 1997

[54] **MULTILAYERED CONTROLLED RELEASE PHARMACEUTICAL DOSAGE FORM**

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Related U.S. Application Data

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[58] **Field of Search** 424/490, 494, 424/495, 497, 458, 461, 472

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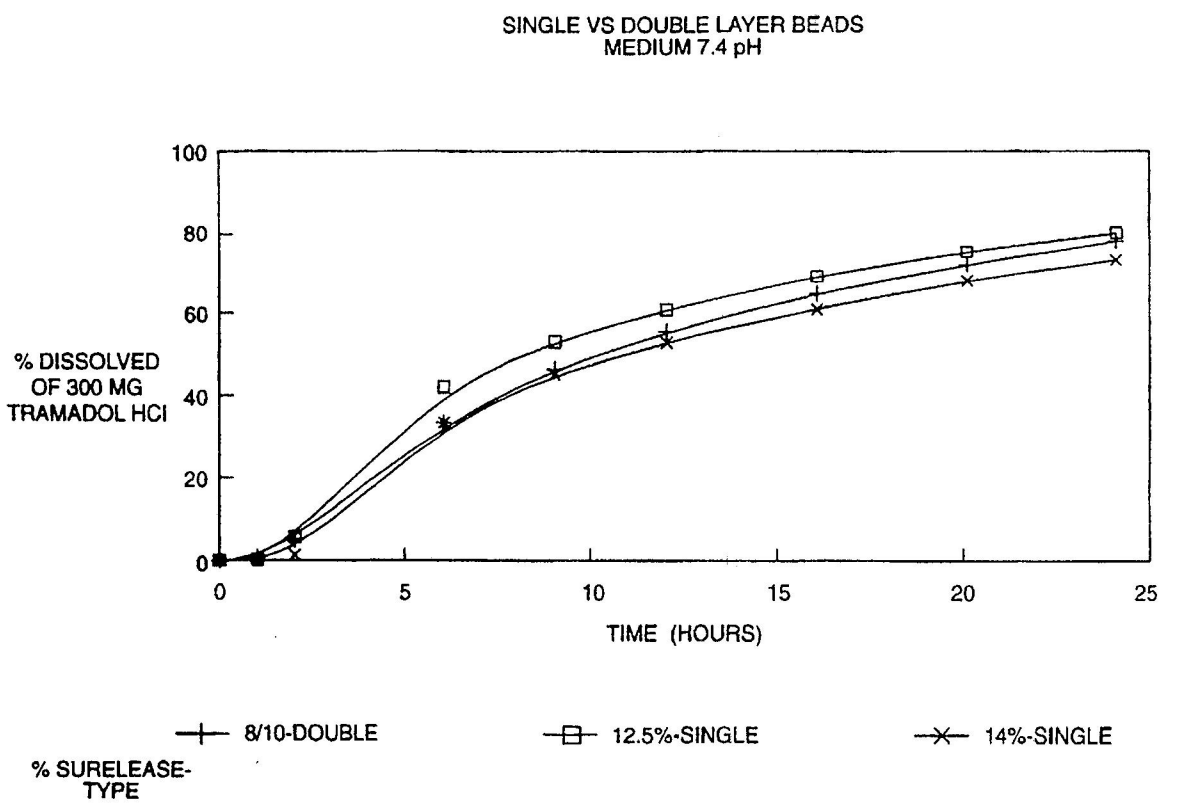
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Primary Examiner—Amy Hulina

[57] **ABSTRACT**

This invention is directed to a multilayered controlled release pharmaceutical dosage form. More particularly the dosage form is adapted for water soluble drugs and comprises a plurality of coated particles wherein each has multiple layers about a core containing a drug active whereby the drug containing core and at least one other layer of drug active is overcoated with a controlled release barrier layer and preferably an outer layer of additional drug is adapted for immediate release to preferably provide one immediate releasing layer and at least two controlled releasing layers of a water soluble drug from the multilayered coated particle.

10 Claims, 1 Drawing Sheet



MULTILAYERED CONTROLLED RELEASE PHARMACEUTICAL DOSAGE FORM

This is a division of application Ser. No. 08/319,186, filed Oct. 6, 1994, which is hereby incorporated by reference, U.S. Pat. No. 5,474,786.

FIELD OF THE INVENTION

This invention is directed to a multilayered controlled release pharmaceutical dosage form. More particularly, the dosage form is adapted for controlled release of water soluble drugs and comprises a plurality of multilayered coated particles, wherein each particle has multiple layers about a core containing a drug active. The drug containing core and at least one other layer of drug active is overcoated with a controlled release barrier layer and an outer layer of additional drug may be adapted for immediate release.

BACKGROUND OF THE INVENTION

Controlled release pharmaceutical dosage forms are well known and provide distinct advantages for delivery of certain chemotherapies. Controlled release dosage forms are particularly useful for drugs which act optimally at certain levels of plasma concentration over extended periods of time. Controlled release systems may also avoid the presence of ineffective or toxic levels of drugs which result from periodic administration of immediate release dosage forms which provide high initial levels of drug but may leave only ineffectively small amounts of drugs in the plasma near the end of the administration periods (i.e. cycles) prior to subsequent administration of drug. Controlled release dosage forms are also desirable for providing continuous chemotherapy for chronic conditions or those with a long duration of therapy by providing drugs in a sustained released manner that only requires administration either once or twice daily instead of every four to six hours as may be indicated for a particular drug.

The administration of highly water soluble drugs in a controlled release dosage form presents particular problems. The introduction of such highly water soluble drugs in controlled release dosage forms into a patient's digestive system has met with limited success due to the normally unpredictable leaching out of the very water soluble drug active into the digestive system when using conventional sustained release techniques. It is also challenging to provide a substantially zero or constant rate of release for drugs that are highly water soluble for extended periods of time.

It is therefore an object of the present invention to provide a multilayered controlled release pharmaceutical dosage form system, particularly for very water soluble drugs. This system provides desirable plasma levels of drugs with a substantially constant rate of release of the drugs from controlled release layers over a preselected period of time.

SUMMARY OF THE INVENTION

To achieve the objects and objectives in accordance with the invention the present invention provides a multilayered controlled release pharmaceutical dosage form, preferably for water soluble drugs, comprising a plurality of coated particles each comprising: a drug active core which is sequentially overcoated with a first controlled release barrier layer; at least one additional layer containing drug active which is overcoated with an additional controlled release layer; and preferably an outer layer containing drug active which is intended for immediate release; whereby, the amount of drug active in the controlled release barrier material utilized in each coating layer thereof is provided in amounts effective to achieve a desirable plasma level of drug active in a patient over a preselected time period. In particularly preferred embodiments the time period is twelve or twenty-four hours (i.e. corresponding to once or twice daily administration).

In preferred embodiments of the invention the multilayered controlled release pharmaceutical dosage form for water soluble drugs comprises a plurality of coated particles each comprising:

a core comprising an inert material which is coated or granulated with a water soluble drug active;

a first coating layer over the drug containing core comprising a water soluble film forming polymer, preferably the film forming mixture additionally comprises a plasticizer;

a second coating layer over the first coating layer comprising a film forming dispersion or solution which forms a controlled release layer over the coated drug core, preferably a water-based dispersion;

a third coating layer comprising a water soluble film forming polymer and preferably a plasticizer;

a fourth coating layer comprising additional water soluble drug active;

a fifth coating layer comprising a water soluble film forming polymer and preferably a plasticizer;

a sixth coating layer comprising a film forming dispersion or solution which forms a controlled release layer over the coated drug core, preferably a water-based dispersion; and

a final coating layer of a water soluble film forming polymer and preferably a plasticizer.

In preferred embodiments of the invention the water soluble film forming polymer is hydroxypropyl methylcellulose and the plasticizer is polyethylene glycol.

HPMC
PEG.

Preferably the film forming polymer which forms the controlled release layer is provided as a water-based dispersion and comprises ethyl cellulose. Preferably the dispersion additionally comprises at least one of dibutyl sebacate, oleic acid, and sodium lauryl sulfate.

In preferred embodiments of the invention the water soluble drug active is selected from the group consisting of tramadol, pseudoephedrine and phenylpropanolamine and salts thereof. More preferably the drug active is very water soluble and is tramadol HCl or pseudoephedrine HCl. Most preferably the drug active is tramadol HCl. The invention is also intended to cover substantially pure active enamtiomers of these drug actives.

In a particularly preferred embodiment of the invention the controlled release layers of the second and sixth coating layers are provided at levels to obtain a substantially constant release profile of the drug active over about a twenty-four hour period.

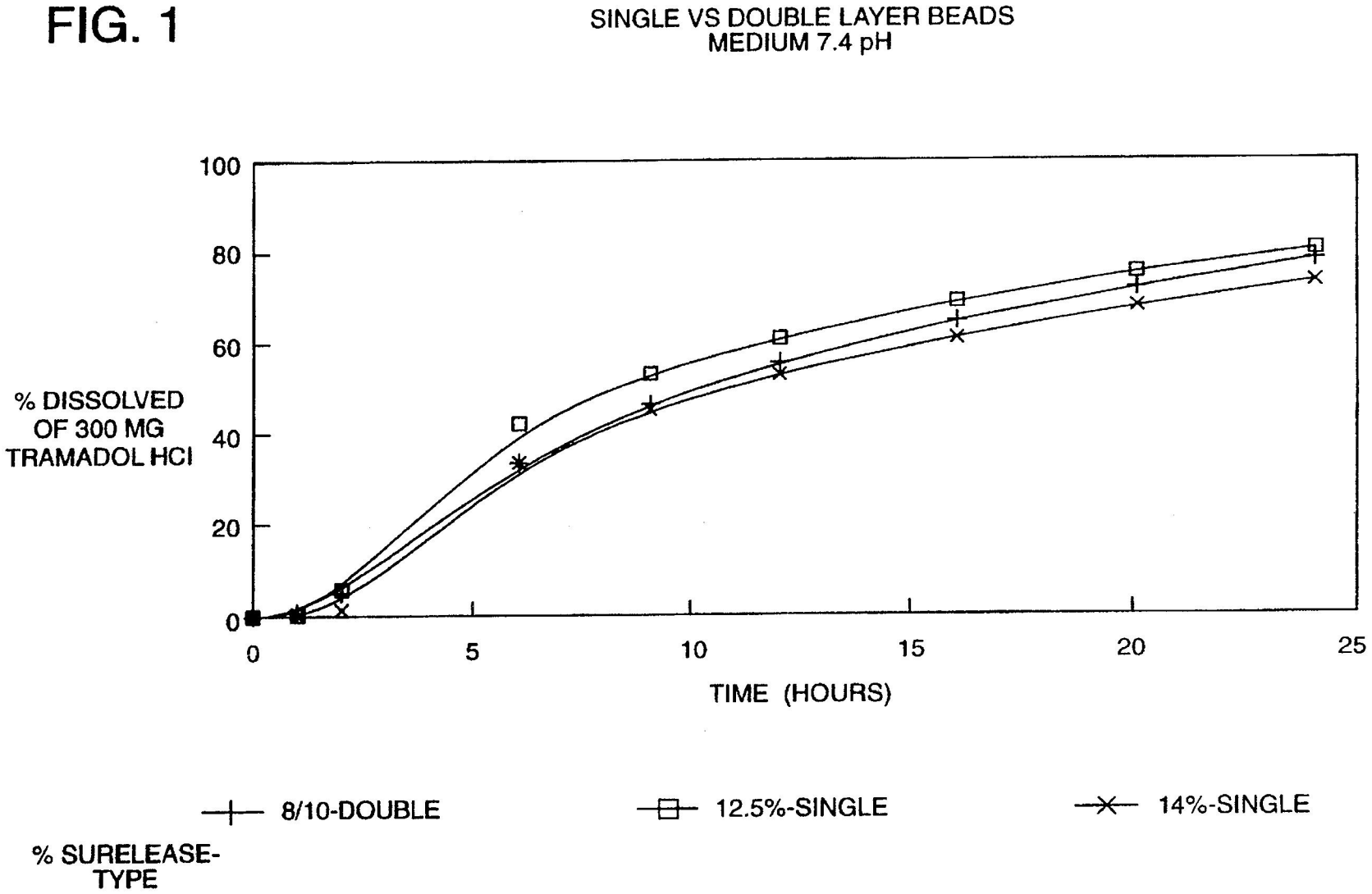
In other embodiments the invention provides a method of achieving a desirable plasma level of a water soluble drug over a twenty-four hour period in a patient comprising the steps of:

preparing a multilayered controlled release dosage form by sequentially overcoating a drug active containing core with a first controlled release barrier layer;

providing at least one additional layer containing drug active over said first controlled release barrier layer which in turn is overcoated by an additional controlled release layer; and

providing an outer layer containing drug active which is intended for immediate release; whereby, the amount of drug

FIG. 1


SINGLE VS DOUBLE LAYER BEADS
MEDIUM 7.4 pH
% DISSOLVED OF 300 MG TRAMADOL HCl
100
80
60
40
20
0
0
5
10
15
20
25
TIME (HOURS)
8/10-DOUBLE
12.5%-SINGLE
14%-SINGLE
% SURELEASE-TYPE

active and the controlled release barrier material utilized in each coating layer thereof is provided in an amount effective to achieve a desirable plasma level of drug active in a patient over a twenty-four hour period.

In preferred embodiments of the method of the invention the drug is tramadol HCl or pseudoephedrine HCl.

In other preferred embodiments of the method of the invention the sequential coatings are all applied in aqueous systems.

In particularly preferred embodiments of the method of the invention the multilayered dosage form comprises at least one additional coating layer of a water soluble film forming polymer interposed between one or more of the controlled release layers and the adjoining layer containing drug active to assure uniformity of the dosage form.

In other embodiments of the invention two or more drug actives may be provided in one or more of the drug containing layers of the multilayered dosage forms.

BRIEF DESCRIPTION OF THE DRAWING

FIG. 1 is a graph showing percent dissolved over time of single and double layer (controlled release layer) coated beads of the drug tramadol HCl.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS OF THE INVENTION

Reference will now be made in detail to preferred embodiments of the invention. Examples of the preferred embodiments are illustrated in the following example section.

As used herein the term water soluble refers to those compounds and compositions which range from slightly soluble to very soluble in water. Actives which are moderately to highly water soluble are particularly preferred for use in this invention because the multilayered approach taken herein provides barriers to premature leaching of water soluble actives which may, in clinical use, undesirably speed up the rate of release of such actives from conventional sustained release dosage forms. Examples of very or highly water soluble actives include tramadol HCl, pseudoephedrine HCl and phenylpropanolamine HCl.

The multilayered controlled release pharmaceutical dosage form of the invention is well suited for water soluble and very water soluble drugs. The plurality of coating layers including at least two controlled release layers and various sealing layers provide a dosage form which permits effective and desirable controlled release of drug substance from a plurality of coated pellets in a dosage form by providing at least two diffusion barriers through which drug active is slowly released. The multilayered coated particles of the invention are particularly well suited for very water soluble drugs since the multicontrol release barrier approach of the present invention mitigates the possibility of premature leaching out of very water soluble drug active in aqueous systems such as the digestive tract. While the present invention can be used for non-water soluble drugs it is particularly advantageous when applied to more water soluble drugs which are more prone to leaching as described above. The multilayered dosage form may contain more than one drug active in any or all of the drug containing layers thereof.

The drug active core of the multilayered controlled release pharmaceutical dosage form is generally a sugar sphere which is coated with a drug active. This core may however be a combination of a drug active and binder which is granulated into a sphere or the core may be some other non-active substance besides sugar. Each time drug active is provided in a layer it is first overcoated with a water soluble film forming polymer to inhibit the leaching of such drug active during processing into the next applied layer, e.g. controlled release layer. Such leaching into the controlled release layer may have the effect of contaminating the controlled release layer to provide for inconsistent results from layer to layer and/or batch to batch of the drug dosage form because the presence of the leached active would provide for premature release of the active as well as opening up excess space in the controlled release layer for further premature diffusion of the drug active therefrom. The inclusion of such a protective layer over the drug active is particularly indicated in the present invention because of the aqueous nature of the preferred water based polymer controlled release layer which is to be provided over each drug containing core. Further, in cases where the drug is particularly water soluble, undesirable leaching is a probable result absent provision of a protective coating of a water soluble film forming polymer over the drug containing layer.

It is preferred that the water soluble film forming polymer comprises a plasticizer to assure adequate flexibility of the film forming polymer layer. If the film forming polymer layer is comprised of a substance which inherently has adequate flexibility then a plasticizer may not be necessary. The water soluble film forming polymer is preferably hydroxypropyl methylcellulose but may be other suitable polymers such as hydroxypropyl cellulose or povidone and more preferably additionally comprises polyethylene glycol and or propylene glycol as plasticizer. Preferably this polymer is in a liquid solution. Other water soluble polymers may be applied as would be known to those skilled in the art.

The controlled release layer of the multilayered drug dosage form of the invention is a diffusion layer through which drug is released in a controlled manner. It is particularly desirable that the controlled release diffusion layer be water based for ease of processing and environmental concerns. The use of a water based dispersion to form a controlled release layer indicates the use of a protective undercoating as described above to protect against premature leaching of the underlying drug into the subsequently applied controlled release layer which may provide inconsistent release patterns for the drug. While the present invention preferably provides for two controlled released layers; three or more controlled release layers are contemplated and are a part of the present invention. The use of two or more controlled release layers and the underlying drug layers may also provide for customization of the multilayered drug pellets controlled release profile of one drug or for the release of a mixture of drug actives from the pellet.

In preferred embodiments of the invention an immediate release layer of drug is provided on the outside core of the multilayered pellet to provide for the immediate introduction of an effective amount of drug active to a patient. An effective level of drug active is then maintained through the gradual release of additional drug active by diffusion through the controlled release layers of the drug while it remains in the digestive system.

The controlled release layer may be a solution or dispersion of a film forming polymer. Preferably, the controlled release layer is applied as a water based dispersion comprising ethyl cellulose. More preferably, the dispersion additionally comprises plasticizer ingredients such as dibutyl sebacate and oleic acid. A particularly preferred water based controlled release dispersion is sold under the trademark

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	12.5	54.87
OPADRY ® Clear YS-1-7006[3]	4.48	19.66
SURELEASE ® E-7-7050[4]	13.54	59.44
Capsules[5]	—	—
Total	100.00%	438.98mg[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 fumed silica. The water in the dispersion is evaporated during processing.
[5]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)	
Opadry ® Clear YS-3-7011	12.000
Purified Water, USP	0.200
Sugar Spheres, NF	5.454
	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 Weigh 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.

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.

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

overcoated with a first controlled release barrier layer comprising ethyl cellulose; and at least one additional layer containing drug active comprising a mixture of hydroxypropyl methylcellulose, polyethylene glycol and propylene glycol which is overcoated with an additional controlled release layer comprising ethyl cellulose; whereby, the amount of drug active and the controlled release barrier material utilized in each coating layer thereof is provided in amounts effective to achieve a desirable plasma level of drug active in a patient over a preselected twelve to twenty-four hour period.

2. The multilayer dosage form of claim **1** additionally comprising an outer layer containing drug active which is intended for immediate release.

3. The multilayer dosage form of claim **1** comprising at least one additional coating layer of a water soluble film forming polymer interposed between one or more of the controlled release layers and the adjoining layer containing drug active.

4. A method of achieving a desired plasma level of a water soluble drug over a desired time period in a patient comprising the steps of:

preparing a multilayered controlled release dosage form by sequentially overcoating a drug active containing core comprising a mixture of hydroxypropyl methylcellulose, polyethylene glycol and propylene glycol with a first controlled release barrier layer comprising ethyl cellulose; and

providing at least one additional layer containing drug active comprising a mixture of hydroxypropyl methylcellulose, polyethylene glycol and propylene glycol over said first controlled release barrier layer which is overcoated by an additional controlled release layer comprising ethyl cellulose; whereby, the amount of drug active and the controlled release barrier material utilized in each coating layer thereof is provided in an amount effective to achieve a desirable plasma level of drug active in a patient over a desired period of time.

5. The method of claim **4** additionally comprising an outer layer containing drug active which is intended for immediate release.

6. The method of claim **4** wherein the desired time period is about twelve or twenty-four hours.

7. The method of claim **4** wherein the drug is tramadol HCl or pseudoephedrine HCl.

8. The method of claim **4** wherein the sequential coatings are all applied in aqueous systems.

9. The method of claim **4** wherein the multilayered dosage form comprises at least one additional coating layer of a water soluble film forming polymer interposed between one or more of the controlled release layers and the adjoining layer containing drug active.

10. The method of claim **4** wherein two or more different drug actives are provided in the dosage form.

* * * * *

D4 108 105

requerida para mantener un nivel sanguíneo constante de la droga. Es importante reconocer que si bien en teoría puede ser conveniente una liberación de orden cero, la de orden no cero puede ser clínicamente equivalente a la liberación constante en muchos casos. Aparte del grado de variación intraindividual e interindividual, se observa que, para muchas drogas, cambios modestos de sus niveles tisulares no determinan un mejoría del rendimiento clínico. Así, desde el punto de vista clínico un nivel no constante puede ser indistinguible de uno constante.

Para lograr rápidamente un nivel terapéutico y mantenerlo durante un determinado período, la administración consta de dos partes: una dosis de ataque inicial, D_i, que libera de inmediato la droga, y una dosis de mantenimiento o sostenida, D_m. Así, la dosis total, W, requerida para el sistema es:

$$W = D_i + D_m \qquad (2)$$

Para un sistema en el que la dosis de mantenimiento libera droga mediante un proceso de orden cero durante un período especificado, la dosis total[2] es:

$$W = D_i + k_r^0 T_d \qquad (3)$$

donde k_r^0 es la constante de velocidad de orden cero para la liberación de la droga y T_d es el período total deseado para la liberación sostenida de una dosis. Si la dosis de mantenimiento inicia la liberación de la droga en el momento de la dosificación ($t = 0$), se sumará a la provista por la dosis inicial, lo que aumenta el nivel inicial de la droga. En este caso, se necesita un factor de corrección para tener en cuenta la droga adicional de la dosis de mantenimiento:

$$W = D_i + k_r^0 T_d - k_r^0 T_p \qquad (4)$$

El factor de corrección, $k_r^0 T_p$, es la cantidad de droga provista durante el período desde $t = 0$ hasta el momento del nivel pico de la droga, T_p. No se requiere factor de corrección si la forma farmacéutica se elabora de manera tal que la dosis de mantenimiento no comienza a liberar droga hasta el momento T_p.

Ya se ha mencionado que el objetivo ideal de un sistema de liberación sostenida es un nivel tisular o sanguíneo perfectamente invariable en función del tiempo. La manera de lograrlo, en el caso más sencillo, es mediante una dosis de mantenimiento que libere la droga según una cinética de orden cero. Sin embargo, se pueden obtener aproximaciones satisfactorias de un nivel constante de droga mediante combinaciones adecuadas de la dosis inicial y la de mantenimiento, que libere su droga por un proceso de primer orden. La dosis total para un sistema de este tipo es:

$$W = D_i + (k_e C_d / k_r) V_d \qquad (5)$$

donde k_r es la constante de velocidad de primer orden para la liberación de la droga (tiempo^{-1}), y k_e, C_d y V_d son como se definió antes. Si la dosis de mantenimiento comienza a liberar droga a $t = 0$, se requiere un factor de corrección como en el caso de orden cero. En esta circunstancia, la expresión correcta es:

$$W = D_i + (k_e C_d / k_r) V_d - D_m k_e T_p \qquad (6)$$

Con el fin de mantener los niveles sanguíneos de la droga dentro del rango terapéutico, durante todo el curso de tratamiento, la mayoría de los sistemas de liberación sostenida se administran, al igual que las formas convencionales, en dosis múltiples en lugar de únicas. Para un sistema de liberación sostenida ideal que libera la droga según una cinética de orden cero, el esquema de dosis múltiples es análogo al indicado para una infusión intravenosa constante, como se analizó en el capítulo 42. En los sistemas de liberación sostenida con cinética de liberación distinta del orden cero el esquema de dosis múltiples es más complejo y su análisis escapa al alcance de este capítulo; Welling y Dobrinska[3] brindan una exposición más detallada.

Ventajas posibles de la farmacoterapia sostenida

Todos los productos de liberación sostenida tienen el objetivo de mejorar la farmacoterapia en comparación con sus homólogos de liberación no sostenida. Esta mejoría del tratamiento farmacológico depende de varias ventajas potenciales de los sistemas de liberación sostenida, expuestas en el cuadro 94-1.

Se ha reconocido que el cumplimiento del paciente es un componente necesario e importante para el éxito de la farmacoterapia administrada por el paciente. La minimización o la eliminación de los problemas de cumplimiento es una ventaja obvia del tratamiento de liberación sostenida. Dada la naturaleza de su cinética de liberación, un sistema de este tipo será capaz de utilizar menor cantidad total de droga en el curso de tratamiento que un preparado convencional. Las ventajas de esto son la disminución o la eliminación de efectos colaterales locales o sistémicos, menor potenciación o reducción de la actividad de la droga con la administración crónica y minimización de la acumulación del agente en tejidos orgánicos durante el tratamiento crónico.

Sin duda, la razón más importante de la farmacoterapia sostenida es la mejor eficiencia del tratamiento; es decir, tratamiento óptimo. El resultado de contar con niveles sanguíneos constantes de droga con un sistema de liberación sostenida es alcanzar pronto el efecto deseado y mantenerlo por un período prolongado. La reducción o la eliminación de las fluctuaciones de los niveles sanguíneos permiten un mejor manejo de la patología. Además, el método por el que se logra la liberación sostenida puede mejorar la biodisponibilidad de algunas drogas. Por ejemplo, los agentes susceptibles de inactivación enzimática o de descom-

Cuadro 94-1. *Ven terapia sostenida*

1. Evita los problema
2. Administra menos
   a. Minimiza o elin
   b. Minimiza o elin
   c. Se logra menos dad de la droga
   d. Minimiza la acu ción crónica
3. Mejora la eficienci
   a. Cura o controla
   b. Mejora el contr la fluctuación d
   c. Mejora la biodis
   d. Aprovecha efec beración sosteni tomando la dosi
4. Economía

posición bacteriana sulamiento en siste la liberación soste "ventana específic mayor biodisponib beración sostenida to gastrointestinal. tratamiento puede especial que no se farmacéutica conv

La última venta dro 94-1, la de la dos puntos de vista dad de la mayor p sostenida suele ser farmacéuticas con cial, el costo prom un período prolong logra economizar enfermería y de in jo perdido, etcéter

Propiedades r para la formul sostenida

El desarrollo d nida está sujeto a ble importancia. E administración, el enfermedad tratad miento y las propie riables están inter limitaciones a la el al diseño del siste del tratamiento. L propiedades de la ra el científico que

GENNARO, Alfonso R. "Remington Farmacia" 19ava ed. Editorial Médica Panamericana. Buenos Aires. 1995.

Cuadro 94-1. *Ventajas potenciales de la farmacoterapia sostenida*

1. Evita los problemas de cumplimiento del paciente
2. Administra menos cantidad total de droga
   a. Minimiza o elimina los efectos colaterales locales
   b. Minimiza o elimina los efectos colaterales sistémicos
   c. Se logra menos potenciación o reducción de la actividad de la droga con el uso crónico
   d. Minimiza la acumulación de la droga con la dosificación crónica
3. Mejora la eficiencia del tratamiento
   a. Cura o controla la enfermedad con más rapidez
   b. Mejora el control de la enfermedad; es decir, reduce la fluctuación del nivel de droga
   c. Mejora la biodisponibilidad de algunas drogas
   d. Aprovecha efectos especiales; por ej., aspirina de liberación sostenida para el alivio matinal de la artritis, tomando la dosis antes de acostarse
4. Economía

posición bacteriana pueden ser protegidos por encapsulamiento en sistemas de polímeros adecuados para la liberación sostenida. En las drogas que tienen una "ventana específica" de absorción, se puede lograr mayor biodisponibilidad localizando el sistema de liberación sostenida en determinadas regiones del tracto gastrointestinal. Asimismo, la mayor eficiencia del tratamiento puede depender de un efecto terapéutico especial que no se podría conseguir con una forma farmacéutica convencional (véase cuadro 94-1).

La última ventaja potencial enumerada en el cuadro 94-1, la de la economía, puede analizarse desde dos puntos de vista. Aunque el costo inicial por unidad de la mayor parte de los sistemas de liberación sostenida suele ser más elevado que el de las formas farmacéuticas convencionales, por su carácter especial, el costo promedio del tratamiento a lo largo de un período prolongado puede ser menor. También se logra economizar con la disminución del tiempo de enfermería y de internación, menos tiempo de trabajo perdido, etcétera.

Propiedades relevantes de las drogas para la formulación de liberación sostenida

El desarrollo de los sistemas de liberación sostenida está sujeto a numerosas variables de considerable importancia. Entre ellas se encuentran la vía de administración, el tipo de sistema de suministro, la enfermedad tratada, el paciente, la duración del tratamiento y las propiedades de la droga. Todas estas variables están interrelacionadas y esto impone ciertas limitaciones a la elección de la vía de administración, al diseño del sistema de suministro y a la duración del tratamiento. Las limitaciones impuestas por las propiedades de la droga son de particular interés para el científico que desarrolla el sistema. Esas propiedades son las que más influyen en el comportamiento de la droga en el sistema de suministro y en el organismo. A los fines de esta exposición, conviene describirlas como fisicoquímicas o biológicas. Es obvio que no hay una distinción nítida entre esas dos categorías, dado que las propiedades biológicas son una función de las propiedades fisicoquímicas. De todos modos, a los efectos de este análisis, se considerarán propiedades fisicoquímicas los atributos que pueden determinarse por experimentos in vitro. Se incluirá como propiedades biológicas las que deriven de estudios farmacocinéticos típicos sobre las características de absorción, distribución, metabolismo y excreción (ADME) de una droga, y las resultantes de estudios farmacológicos.

Propiedades fisicoquímicas

Solubilidad en agua y pK_a. Es bien sabido que para que una droga se absorba primero se debe disolver en la fase acuosa que rodea el sitio de administración y después se debe hacer la partición en la membrana absorbente. Dos de las propiedades fisicoquímicas más importantes de una droga, que inciden en su comportamiento absortivo, son su hidrosolubilidad y, si se trata de un ácido o una base débiles (como la mayor parte de las drogas), su pK_a. Estas propiedades influyen en el desempeño de los productos de liberación no sostenida, pero su participación es aun mayor en los sistemas de liberación sostenida.

La hidrosolubilidad incide en su velocidad de disolución, que a su vez, establece su concentración en solución y, por ende, la fuerza propulsora para la difusión a través de las membranas. La velocidad de disolución se relaciona con la hidrosolubilidad, como muestra la ecuación de Noyes-Whitney que, en condiciones de sumersión, es:

$$dC/dt = k_D A C_s \qquad (7)$$

donde dC/dt es la velocidad de disolución, k_D es la constante de velocidad de disolución, A es la superficie total de las partículas de la droga y C_s es la hidrosolubilidad de su saturación. La velocidad de disolución es constante sólo si la superficie A se mantiene constante, pero lo importante es que la velocidad inicial es directamente proporcional a C_s. Por lo tanto, la hidrosolubilidad de una droga se puede utilizar como primera aproximación a su velocidad de disolución. Las drogas con escasa hidrosolubilidad tienen velocidades de disolución bajas y suelen presentar problemas de biodisponibilidad oral.

Se recordará, por el capítulo 16, que la hidrosolubilidad de ácidos y bases débiles depende del pK_a del compuesto y del pH del medio. Para un ácido débil:

$$S_t = S_0(1 + K_a/[H^+]) = S_0(1 + 10^{pH-pK_a}) \qquad (8)$$

donde S_t es la solubilidad total (tanto de las formas ionizadas como no ionizadas) del ácido débil, S_0 es la

síntomas tóxicos, hasta varios miles. Las drogas muy "potentes", cuyo rango de concentración terapéutica es estrecho, tienen un valor de IT bajo. Por lo general, cuanto mayor es el valor del IT, más segura es la sustancia. Las drogas con valores muy pequeños de IT suelen ser malos candidatos a la formulación en productos de liberación sostenida, sobre todo por las limitaciones técnicas para controlar con precisión la velocidad de liberación. Se considera que una droga es relativamente segura si su valor de *IT* supera 10. El aprobarbital, la digitoxina, el fenobarbital y la digoxina son ejemplos de sustancias con IT < 10.

Magnitud de la dosis. Como el sistema de liberación sostenida está diseñado para evitar las dosis repetitivas, es natural que contenga mayor cantidad de droga que la forma convencional respectiva. La dosis administrada típica de una droga convencional dará alguna indicación de la cantidad total requerida en el preparado de liberación sostenida. En los casos en que se requieren grandes dosis convencionales, el volumen de la dosis sostenida puede ser tan grande que no resulta práctico o es inaceptable, según la vía de administración. Lo mismo es válido para cuando se precisa una gran velocidad de liberación a partir del sistema de liberación sostenida, como ocurre con las drogas de vida media corta. Para la vía oral, el volumen del producto está limitado por la aceptación del paciente, mientras que en las vías intramuscular, intravenosa o subcutánea, la limitación depende de la tolerancia en el sitio de inyección. También se debe mencionar que para las drogas con un bajo índice terapéutico, la incorporación de cantidades superiores a DT_{50} puede ser potencialmente peligrosa si el sistema falla.

Formas farmacéuticas orales

Para los sistemas de liberación sostenida, la vía de administración oral es la que recibió la mayor atención. Esto se debe en parte a que hay más flexibilidad para diseñar la forma farmacéutica por vía oral que por vía parenteral. La aceptación de la primera por parte del paciente es bastante alta. Se trata de una vía de administración relativamente segura respecto de la mayor parte de las vías parenterales, y las limitaciones que imponen la esterilidad y la posible lesión en el sitio de administración son mínimas. En esta sección, se analizan los métodos más comunes utilizados para lograr liberación sostenida de drogas administradas por vía oral.

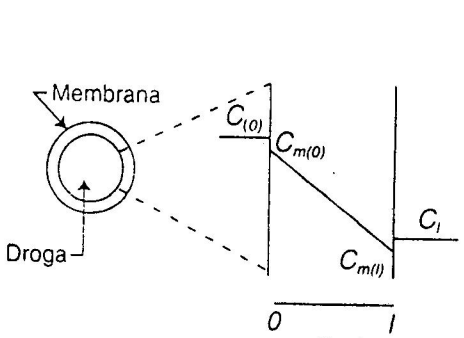


Fig. 94-6. Representación esquemática de un dispositivo de difusión a partir de un reservorio. $C_{m(0)}$ y $C_{m(l)}$ representan concentraciones de la droga en las superficies internas de la membrana, y $C_{(0)}$ y C_l representan concentraciones en las regiones adyacentes. (Reproducido con autorización.[9])

Sistemas de difusión

En estos sistemas, la velocidad de liberación depende de la difusión de la droga a través de un polímero insoluble en agua. Hay dos tipos de dispositivos de difusión: *dispositivos de reservorio*, en los que un centro de droga está rodeado de una membrana polimérica, y *dispositivos de matriz*, en los que la droga disuelta o dispersa se distribuye con uniformidad por una matriz polimérica inerte. Corresponde mencionar que en la práctica actual, muchos dispositivos de difusión también se basan en cierto grado de disolución para determinar la velocidad de liberación. Los sistemas que emplean disolución se tratarán luego en esta sección.

Dispositivos de reservorio. La liberación a partir de un dispositivo de reservorio está regida por la primera ley de difusión de Fick:

$$J = -D\, dC_m/dx \qquad (18)$$

donde J es el flujo de droga a través de una membrana en la dirección de la concentración descendente (cantidad/área-tiempo), D es el coeficiente de difusión de la droga en la membrana (área/tiempo) y dC_m/dx es el cambio de concentración de la droga en la membrana a lo largo de una distancia x. Si se asume que la sustancia a cada lado de la membrana está en equilibrio con la respectiva capa superficial de ésta, como muestra la figura 94-6,[9] entonces la concentración que se encuentra inmediatamente dentro de la superficie de la membrana se puede relacionar con aquella ubicada en la región adyacente mediante las expresiones

$$K = C_{m(0)}/C_{(0)} \text{ en } x = 0 \qquad (19)$$

$$K = C_{m(l)}/C_{(l)} \text{ en } x = l \qquad (20)$$

donde K es el coeficiente de partición. Asumiendo que D y K son constantes, la ecuación 18 puede ser integrada para tener:

$$J = DK\Delta C/l \qquad (21)$$

donde ΔC es la diferencia de concentración a través de la membrana.

Si la actividad de la droga dentro del reservorio se mantiene constante y el valor de K es menor que 1, se puede lograr una liberación de orden cero. Esto sucede cuando la droga existe como un sólido; es decir, su actividad es la unidad. La ecuación que describe la li-

beración variará según la forma del dispositivo. Sólo presentaremos aquí la geometría más simple, que corresponde a una placa rectangular o "emparedado". Para la geometría de la placa, la ecuación que describe la liberación es:

$$dM_t/dt = ADK\Delta C/l \qquad (22)$$

donde M_t es la masa de droga liberada después del tiempo t, dM/dt es la velocidad de liberación en estado estable en el momento t, A es la superficie del dispositivo, y D, K y l corresponden a las definiciones previas. Se pueden escribir ecuaciones similares para dispositivos geométricos cilíndricos o esféricos. Con el fin de obtener una velocidad de liberación constante, se deben mantener constantes el área, la longitud del trayecto de difusión, la concentración y el coeficiente de difusión; es decir, todos los términos de la derecha de la ecuación 22. A menudo, esto no sucede en la práctica real, porque uno o más de los términos anteriores se modificarán en el producto; por ende, se suele observar una liberación de orden no cero.

Los métodos comunes para desarrollar dispositivos tipo reservorio son la microencapsulación de partículas y la cobertura a presión de los comprimidos que contienen centros de droga. En la mayoría de los casos, las partículas revestidas por microencapsulación forman un sistema en el que la droga está contenida en la película de revestimiento, así como en el otro. Por lo general, la liberación implica una combinación de disolución y difusión, en la que la primera es la que controla la velocidad de liberación. Si se elige de manera correcta el material de encapsulación, la difusión será el proceso controlador. Se analizará mejor la microencapsulación en relación con los sistemas que emplean disolución. Algunos materiales utilizados como revestimiento de barrera de membrana, solos o en combinación, son gelatina endurecida, metil y etilcelulosa, polihidroximetacrilato, hidroxipropilcelulosa, polivinilacetato y diversas ceras. El cuadro 94-2 presenta ejemplos de algunos productos comercializados que usan un reservorio de droga encapsulado. Es probable que la liberación a partir de estos productos se base sobre todo en la difusión, pero también puede haber disolución.

Dispositivos de matriz. Higuchi describió la velocidad de liberación de una droga dispersa como un

Cuadro 94-2. *Productos de difusión de reservorio*

Producto	*Componente(s) activo(s)*	*Fabricante*
Plateau CAPS cápsulas		
Nico-400	Ácido nicotínico	Jones
Nitro-Bid	Nitroglicerina	Marion
Cerespan cápsulas	Clorhidrato de papaverina	Rhone-Poulenc Rorer
Histaspan cápsulas	Maleato de clorfeniramina, clorhidrato de fenilefrina, nitrato de metilescopolamina	Rhone-Poulenc Rorer
Nitrospan cápsulas	Nitroglicerina	Rhone-Poulenc Rorer
Measurin comprimidos	Ácido acetilsalicílico	Sanofi-Winthrop
Bronkodyl S-R cápsulas	Teofilina	Sanofi-Winthrop

1. Durante la liberación se mantiene un estado seudoestable.
2. La cantidad total de droga presente por unidad de volumen en la matriz, C_0, es sustancialmente mayor que la solubilidad de saturación de la droga por unidad de volumen en la matriz C_s; es decir, hay exceso de soluto.
3. El medio de liberación es una cubeta perfecta en todo momento.
4. Las partículas de droga tienen un diámetro mucho más pequeño que la distancia promedio de difusión.
5. El coeficiente de difusión se mantiene constante.
6. No hay interacción entre la droga y la matriz.

De acuerdo con la figura 94-7, el cambio en la cantidad de droga liberada por unidad de superficie, dM, ante el cambio de espesor de la zona agotada, dh, es:

$$dM = C_0 dh - (C_s/2)dh \qquad (23)$$

donde C_0 y C_s corresponden a las definiciones previas. Sin embargo, según la primera ley de Fick:

$$dM = (D_m C_s/h)dt \qquad (24)$$

donde D_m es el coeficiente de difusión en la matriz. Si se igualan las ecuaciones 23 y 24, se las resuelve para h y se sustituye ese valor de h de nuevo en la for-

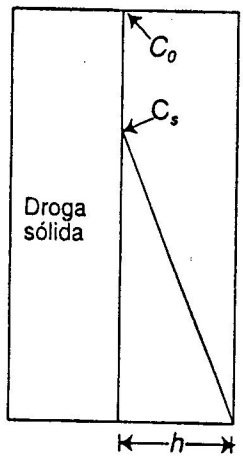


Fig. 94-7. Representación esquemática del modelo físico empleado para un dispositivo de difusión de una matriz de placa planar.

liberación y D_s es su coeficiente de difusión en el mismo medio. En este sistema, la droga se filtra de la matriz circulando por canales o poros.

Para el tratamiento de los datos, conviene reducir las ecuaciones 25 y 26 a

$$M = kt^{1/2} \qquad (27)$$

donde k es una constante, de modo que un gráfico de la cantidad de droga liberada versus la raíz cuadrada del tiempo será lineal si la liberación a partir de la matriz es controlada por la difusión. La velocidad de liberación desde un dispositivo de este tipo no es de orden cero, porque disminuye con el tiempo pero, como se mencionó, esto puede ser clínicamente equivalente a la liberación constante para numerosas drogas.

Los tres tipos principales de materiales utilizados en la preparación de dispositivos de matriz son plásticos insolubles, polímeros hidrófilos y compuestos grasos. Las matrices plásticas investigadas son metilacrilato-metilmetacrilato, cloruro de polivinilo y polieno. El comprimido Gradumet (*Abbott*) es un ejemplo de una forma farmacéutica que emplea una matriz plástica. Los polímeros hidrófilos son metilcelulosa, hidroxipropilmetilcelulosa, carboximetilcelulosa sódica y carbopol 934. Los compuestos grasos comprenden diversas ceras como la de carnauba y triestereato de glicerilo. Un ejemplo de una forma farmacéutica que utiliza una matriz de cera es el comprimido Lontab (*Ciba*).

El método más común de preparación consiste en mezclar la droga con el material de la matriz y después unir la mezcla en comprimidos. En el caso de matrices de cera, la droga se suele dispersar en cera fundida, que después se congela y se comprime en centros. En todo sistema de liberación sostenida es necesario que una parte de la droga esté disponible de inmediato como dosis de ataque, y que el resto se libere en forma lenta. Esto se consigue al colocar la dosis de ataque en una capa de la unidad. La capa se puede aplicar por cobertura a presión o en una pala convencional, o mediante suspensión aérea. El cuadro 94-3 enumera algunos productos de difusión en matriz existentes en el mercado.

Sistemas de disolución

Como se mencionó en este capítulo, una droga con una velocidad de disolución lenta determina de por sí un nivel sanguíneo sostenido. En principio, sería posible entonces preparar este tipo de productos disminuyendo la velocidad de disolución de drogas muy hidrosolubles. Esto se puede lograr con una sal o un derivado apropiado, al cubrir la droga con un material que se disuelva con lentitud o al incorporarla en un comprimido con un vehículo que tarde en disolverse. En condiciones ideales, la superficie disponible para la disolución debe permanecer constante para obtener una velocidad de liberación constante. Sin embargo, esto es difícil de lograr en la práctica.

Se puede considerar que el proceso de disolución es controlado por la capa de difusión, donde la tasa de difusión a partir de la superficie sólida hacia la solución a granel a través de una película líquida no agitada es el paso que determina la velocidad. En este caso, el proceso de disolución en estado estable se cumple según la ecuación de Noyes-Whitney:

$$dC/dt = k_D A(C_s - C) = (D/h)A(C_s - C) \qquad (28)$$

donde dC/dt es la velocidad de disolución, k_D es la constante de velocidad de disolución, A es la superficie total, C_s es la solubilidad de saturación del sólido y C es la concentración del soluto en la solución a granel. La constante de disolución k_D es igual al coeficiente de difusión D dividido por el espesor de la capa de difusión h. Esta ecuación predice una velocidad de disolución constante si la superficie, el coeficiente de difusión, el espesor de la capa de difusión y

Cuadro 94-3. *Productos de difusión de matriz*

Producto	*Componente(s) activo(s)*	*Fabricante*
Gradumet comprimidos		Abbott
Desoxyn	Metanfetamina HCl	
Fero-Gradumet	Sulfato ferroso	
Fero-Grad-500	Sulfato ferroso, ascorbato de sodio	
Tral	Metilsulfato de hexociclium	
Lontab comprimidos		Ciba
PBZ-SR	Tripelenamina HCl	
Procan SR comprimidos	Procainamida HCl	Parke-Davis
Choledyl SA com-	Oxtrifilina	Parke-Davis

la diferencia de concentración se mantienen constantes. Sin embargo, a medida que prosigue la disolución, todos estos parámetros se pueden modificar, sobre todo la superficie. En el caso de partículas esféricas, el cambio de superficie se puede relacionar con el peso de la partícula y, asumiendo condiciones de sumersión, la ecuación 28 se transforma en la raíz cúbica de la ecuación de disolución:

$$w_0^{1/3} - w^{1/3} = k_D' t \qquad (29)$$

donde k_D' es la raíz cúbica de la constante de velocidad de disolución, y w_0 y w son el peso inicial y que se mantiene en el tiempo t, respectivamente.

La figura 94-8 muestra dos formulaciones comunes que dependen de la disolución para determinar la velocidad de liberación. La mayor parte de los productos caen dentro de dos categorías: sistemas de disolución encapsulados y sistemas de disolución de matriz.

Los sistemas de disolución encapsulados se pueden preparar cubriendo partículas o gránulos de la droga con polímeros de diverso espesor que se disuelven con lentitud, o por microencapsulación. Esta última se puede efectuar por métodos de separación de fase, polimerización de la interfase, fusión por calor o evaporación del solvente. Los materiales de revestimiento pueden ser seleccionados de una amplia variedad de polímeros sintéticos y naturales, lo que depende de la droga que se va a cubrir y de las características de liberación deseadas. Los materiales de cobertura utilizados con más frecuencia son gelatina, cera de carnauba, lacas, etilcelulosa, ftalato acetato de celulosa o butirato acetato de celulosa. La liberación de la droga de las microcápsulas es un fenómeno de transporte en masa, y puede ser controlado ajustando el tamaño de las microcápsulas, el espesor de los materiales de cobertura y la capacidad de difusión de los materiales del centro. El espesor del revestimiento de las microcápsulas es, en general, muy delgado, y para una relación cobertura-centro dada, disminuye con rapidez a medida que se reduce el tamaño de la microcápsula. El espesor se puede variar desde menos de 1 µm a 200 µm modificando la cantidad de material de cobertura del 3 al 30% del peso total. Si sólo se emplean unos pocos espesores diferentes, por lo general tres o cuatro, las drogas serán liberadas en distintos momentos predeterminados para lograr un efecto de liberación retardada; es decir, de acción repetida. Si se utiliza un espectro de espesores diferentes, es posible obtener un nivel de la droga en sangre más uniforme. Las microcápsulas se suelen colocar en cápsulas, rara vez se las formula en comprimidos, dado que las coberturas tienden a romperse durante la compresión. El cuadro 94-4 presenta una enumeración parcial de productos de liberación sostenida existentes en el mercado que dependen fundamentalmente de la disolución encapsulada.

Los dispositivos de disolución de matriz se preparan al comprimir la droga en un vehículo polimérico

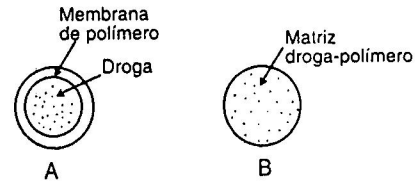


Fig. 94-8. Representación esquemática de sistemas que utilizan disolución. **A.** Formulación encapsulada en la que la liberación de la droga depende del espesor y de la velocidad de disolución de la membrana de polímero. **B.** Formulación de matriz en la que la liberación de la droga está determinada por la velocidad de disolución del polímero.

de disolución lenta para formar un comprimido. Hay dos métodos generales para preparar partículas de droga-cera: de congelación y de dispersión acuosa. En el primero, la sustancia se mezcla con un material céreo y se congela por rocío, o se lo congela y se lo tamiza. En el segundo, la mezcla droga-cera simplemente es rociada o colocada en agua, y se recogen las partículas resultantes. Los comprimidos de matriz también se preparan por compresión directa de una mezcla de droga, polímero y excipientes. El cuadro 94-5 presenta ejemplos de productos comercializados que dependen sobre todo de disolución de la matriz.

Sistemas osmóticos

La presión osmótica se puede emplear como fuerza propulsora para generar una liberación constante, siempre que se mantenga una presión osmótica constante, y que se limiten algunas otras características del sistema físico. Consideremos un comprimido formado por un centro de droga osmóticamente activa, o un centro de una droga sin actividad osmótica, combinada con una sal osmóticamente activa rodeada de una membrana semipermeable con un pequeño

Cuadro 94-4. *Productos de disolución encapsulados*

Producto	*Componente(s) activo(s)*	*Fabricante*
Spansule cápsulas		SmithKline
Dexedrine	Sulfato de dextroanfetamina	Beecham
Hispril	Difenilpiralina HCl	
Ornade	Fenilpropanolamina HCl, maleato de clorfeniramina	
Thorazine	Clorpromazina HCl	
Contac cápsulas	Fenilpropanolamina HCl, maleato de clorfeniramina	SmithKline Beecham
Sequel cápsulas		Lederle
Artane	Trihexifenidil HCl	
Diamox	Acetazolamida	
Ferro-sequels	Fumarato ferroso, docusato sódico	

Cuadro 94-5. *Productos de disolución de matriz*

Producto	*Componente(s) activo(s)*	*Fabricante*
Extentab comprimidos		Robins
Dimetane	Maleato de bromfeniramina	
Dimetapp	Maleato de bromfeniramina, fenilpropanolamina HCl	
Donnatal	Fenobarbital, sulfato de hiosciamina, sulfato de atropina, bromhidrato de escopolamina	
Quinidex	Sulfato de quinidina	
Timespan comprimidos		Roche
Mestinon	Bromuro de piridostigmina	
Dospan comprimidos		Lakeside
Tenuate	Dietilpropión HCl	
Chronotab comprimidos		Schering
Disophrol	Maleato de dexbromfeniramina, sulfato de seudoefedrina	
Tempule cápsulas		Rhone-Poulenc Rorer
Nicobid	Ácido nicotínico	
Pentritol	Tetranitrato de pentaeritritol	
Repetab comprimidos		Schering
Chlor-trimeton	Maleato de clorfeniramina	
Demazin	Maleato de clorfeniramina, fenilefrina HCl	
Polaramine	Maleato de dexclorfeniramina	
Trilafon	Perfenazina	

orificio, como muestra la figura 94-9. La membrana permitirá la libre difusión de agua, pero no de droga. Cuando el comprimido es expuesto al agua o a cualquier líquido orgánico, ingresará agua en él debido a la diferencia de presión osmótica; el volumen del flujo, dV/dt, hacia el comprimido es:

$$dV/dt = (kA/h)(\Delta\pi - \Delta P) \qquad (30)$$

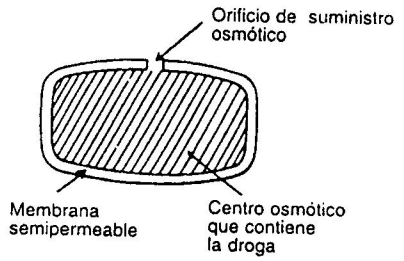


Fig. 94-9. Representación esquemática de un comprimido osmótico. (Reproducido con autorización.[12])

donde k, A y h corresponden a la permeabilidad, la superficie y el espesor de la membrana, respectivamente, $\Delta\pi$ es la diferencia de presión osmótica y ΔP es la diferencia de presión hidrostática. Si el orificio es bastante grande, la diferencia de presión hidrostática será pequeña respecto de la de presión osmótica, y la ecuación 30 se convierte en:

$$dV/dt = (kA/h)\Delta\pi \qquad (31)$$

Así, la magnitud del flujo de agua hacia el comprimido está determinada por la permeabilidad, la superficie y el espesor de la membrana. La droga será bombeada hacia el exterior del comprimido a través del orificio con una velocidad controlada, dM/dt, igual a la velocidad del flujo de agua hacia el comprimido multiplicada por la concentración de la droga, C_s:

$$dM/dt = (dV/dt)C_s \qquad (32)$$

La velocidad de liberación será constante hasta que la concentración de la droga dentro del comprimido caiga por debajo del punto de saturación.

Se desarrollaron varias modificaciones del sistema de suministro de drogas controlado por presión. Se puede aplicar una capa de polímero erosionable a la superficie externa de la membrana semipermeable. Otro sistema consiste en dos compartimientos separados por una partición móvil, como ilustra la figura 94-10. En los sistemas que no tienen un orificio, a medida que ingresa líquido GI, aumenta la presión hidráulica dentro de ellos hasta que la pared se rompe y el contenido se libera al medio.

La ventaja del sistema osmótico es que sólo requiere la acción de la presión osmótica para ser efectivo y es, en esencia, independiente del ambiente. La velocidad de liberación se puede predeterminar con precisión más allá del cambio de pH a través del tracto GI. Algunos materiales utilizados como membrana semipermeable son alcohol polivinílico, poliuretano, acetato de celulosa, etilcelulosa y cloruro de polivinilo. Las drogas que demostraron velocidad de liberación efectiva in vivo a partir de un sistema osmó-

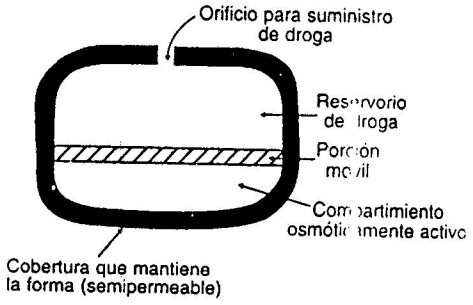


Fig. 94-10. Sistema de suministro de droga controlada por presión osmótica con dos compartimientos separados por una porción móvil.[13]

tico después de la dosificación oral son el cloruro de potasio y la acetazolamida.

Resinas de intercambio iónico

Las resinas de intercambio iónico son polímeros con enlaces cruzados insolubles en agua que contienen grupos formadores de sal en posiciones repetidas en la cadena del polímero. La droga se une a la resina por exposición reiterada de ésta a aquélla en una columna cromatográfica, o por contacto prolongado de la resina con la solución de la droga. Después, la droga-resina se lava para eliminar los iones contaminantes y se seca para formar partículas o glóbulos. La liberación a partir del complejo droga-resina depende del ambiente iónico; es decir, del pH y de la concentración de electrólitos dentro del tracto GI, así como de las propiedades de la resina.

Las moléculas de la droga fijadas a la resina se liberan por intercambio con iones del tracto GI con la carga apropiada, como muestra la figura 94-11, seguido de difusión de la molécula de droga libre hacia el exterior de la resina. La velocidad de difusión se controla por la superficie y la distancia de difusión, y la cantidad de enlaces cruzados en la resina. Se puede modificar la velocidad de liberación si se reviste el complejo droga-resina. Una mejoría adicional de este modelo de suministro de intercambio iónico se denomina sistema Penn Kinetic. En este caso, los gránulos de resina que contienen droga son tratados primero con un polímero impregnante como PEG 4000 para retardar la liberación de tumefacción en agua y se los cubre además con un polímero insoluble en agua, como etilcelulosa, para que actúe como barrera limitante de la velocidad con el fin de controlar la liberación.

En la actualidad, la mayor parte de las resinas de intercambio iónico empleadas en productos de liberación sostenida contienen grupos de ácido sulfónico que intercambian drogas catiónicas, como las que tienen función amina. El cuadro 94-6 brinda algunos ejemplos como anfetamina, fenil *t*-butilamina (fentermina), feniltoloxamina e hidrocodona.

Prodrogas

Una prodroga es un compuesto formado por modificación química de otro biológicamente activo que será liberado in vivo por degradación enzimática o hidrolítica. La finalidad principal del empleo de una prodroga para la administración oral es aumentar la absorción intestinal o reducir los efectos colaterales locales, como la irritación GI que provoca la aspirina. Sobre esta base, en general, una prodroga no se clasifica como una forma farmacéutica de liberación sostenida. Sin embargo, la capacidad de modificar de manera biorreversible las propiedades fisicoquímicas de una droga mejora las propiedades de transporte intestinal y, por ende, influye sobre el perfil del nivel

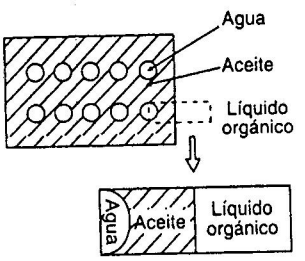


Fig. 94-11. Esquema de liberación de una droga a partir de una resina de intercambio iónico.

sanguíneo de la sustancia en función del tiempo. Así, se puede recurrir a prodrogas para favorecer las estrategias de liberación sostenida y, en un sentido limitado, la liberación puede ser sostenida "por derecho propio".

Como ejemplo del uso de una prodroga como mecanismo de liberación sostenida, consideremos una hidrosoluble que se modifica para convertirla en una prodroga insoluble en agua. La prodroga tendrá una velocidad de disolución más lenta en un medio acuoso que la droga madre y, por ende, se lentificará su aparición en plasma. Esto se observa en el caso de la teofilina y de su prodroga 7,7'-succinilditeofilina. De manera alternativa, se puede hacer que una prodroga hidrosoluble de una droga madre insoluble en agua se convierta en un sustrato de las enzimas del ribete en cepillo de las microvellosidades. La prodroga hidrosoluble forma un complejo con la enzima inmediatamente antes de alcanzar la superficie de la membrana, es metabolizada y aumenta su coeficiente de partición membrana/agua. Esto determina un aumento del nivel sanguíneo de la droga. Véase capítulo 28.

Formas farmacéuticas parenterales

Los tipos más comunes de formas farmacéuticas para farmacoterapia de liberación sostenida parenteral son las inyecciones intramusculares (IM), los implantes para tejidos subcutáneos y diversas cavidades corporales, y los dispositivos transdérmicos. Debido a las limitaciones fisiológicas y anatómicas, muchas de las otras vías parenterales de administración; por ej., intravenosa, intraarterial, intratecal e

Cuadro 94-6. *Productos de intercambio iónico*

Producto	*Componente(s) activo(s)*	*Fabricante*
Biphetamine cápsulas	Anfetamina, dextroanfetamina	Pennwalt
Tussionex cápsulas, comprimidos, suspensión	Hidrocodona, clorfeniramina	Pennwalt
Ionamin cápsulas	Fentermina	Pennwalt

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

375
2005 02 24

DIVISION DE NUEVAS CREACIONES

2020
Bogotá, D.C., Febrero 8 de 2005

Doctora
ALICIA LLOREDA RICAURTE

ASUNTO	Radicación No.	00 002 025
	Trámite	002
	Evento	001
	Actuación	430
	Oficio No.	12251
	Folios	0

Como resultado del examen de patentabilidad de la solicitud de patente de invención, realizado según lo establece el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se notifica el siguiente concepto técnico:

1. Documentos estudiados

Para el presente estudio se tuvieron en cuenta el nuevo capítulo descriptivo comprendido en los folios 7 a 20 y el capítulo reivindicatorio de los folios 21 a 23 de la solicitud en estudio.

2. Objeto de la Invención

El objeto de la presente solicitud de patente de invención consiste en:

Las reivindicaciones 1 a 20 se refieren a una composición oral (en cápsula o tableta) de liberación controlada de al menos un analgésico (opioide: hidromorfona, oxicodona, morfina, levorfanol, metadona, dihidrocodeina, fentanil, codeina, dihidromorfina, petidina, piritramida, buprenorfina, tilidina ó tramadol) caracterizada porque está constituida por microtabletas de menos de 3 mm donde el analgésico está uniformemente distribuido en una matriz retardante (de un polímero como EC, HPMC, HPC, HMC, glicéridos de ácidos grasos; una cera , aceite, grasa, ácido graso, alcohol graso ó éster), las microtabletas están recubiertas (con cera o resinas acrílicas de polímero de poliacrilato, polimetacrilato, alquilcelulosa ó EC).

El problema planteado en esta solicitud es la necesidad de proporcionar un medicamento que contiene un analgésico que permite dosificación individual.

Para resolver este problema técnico la solicitud en estudio proporciona una composición oral con liberación controlada de al menos un analgésico, consistente en una microtableta de menos de 3mm de diámetro.

El objeto de la invención definido anteriormente se clasificó de acuerdo con la IPC: A 61 K 9/22.

También se reivindica prioridad de la Solicitud de Patente de Alemania No. 19901683.6 del 18 de enero de 1999, con respecto a la cual la fecha de presentación de la actual solicitud cumple el plazo máximo permitido.

3. Unidad de Invención

El Art 25 de la D 486 estable que *"la solicitud de patente solo podrá comprender una invención o un grupo de invenciones relacionadas entre sí, de manera que conformen un único concepto inventivo".*

Se observa que el objeto de la reivindicación 18 menciona que las microtabletas pueden ser extraidas con una unidad dosificadora, lo cual no caracteriza a la composición y no mantiene el principio de la unidad de invención. Debe hacerse la corrección necesaria.

4. Claridad de la Solicitud

La descripción divulga la invención de manera suficientemente clara y completa para su comprensión, tal como lo establece el Art 28 de la decisión 486 de la Comisión Andina. Menciona el sector tecnológico al que pertenece, los antecedentes de la técnica, la divulgación del problema técnico, la solución propuesta y la ventaja frente a la tecnología anterior.

Pero en cuanto a la reivindicación 20, se observa que no se puede caracterizar una composición por el efecto o resultado a alcanzar, como lo es el tiempo de liberación del principio activo. Debe hacerse la corrección necesaria.

5. Determinación del Estado de la Técnica

El artículo 16 de la decisión 486 de la comisión de la Comunidad Andina que establece que "*El estado de la técnica comprenderá todo lo que haya sido accesible al publico 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.*

Solo 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 articulo 40".

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es 18 de enero de 1999, se consultaron las bases de datos y los archivos con que cuenta la entidad con fecha de publicación anterior y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

No.	Documento	Título	Fecha de Publicación
D1	EP 0 548 448	Sustrato de liberación controlada estabilizado que tiene una cubierta derivada de una dispersión acuosa de polímero hidrofóbico	Jun 30, 1993
D2	EP 0 630 646	Formulaciones de liberación	Dic 28, 1994

		controlada con dispersiones acuosas de etilcelulosa	
D3	US 5 645 858	Formas de dosis farmacéuticas de liberación controlada multicapa	Jul 8, 1997
D4	US 5 502 078	Compuestos Químicos	Mar 26, 1996
D5	Libro (*)	Remington Farmacia	1995

(*) GENNARO, Alfonso R. "Remington Farmacia". 19 ava. ed. Editorial Médica Panamericana.

6. Evaluación de los requisitos de Patentabilidad

El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "*Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial*".

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

Evaluación del Nivel Inventivo

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

Las reivindicaciones 1 a 20 se refieren a una composición oral (en cápsula o tableta) de liberación controlada de al menos un analgésico (opioide: hidromorfona, oxicodona, morfina, levorfanol, metadona, dihidrocodeina, fentanil, codeina, dihidromorfina, petidina, piritramida, buprenorfina, tilidina ó tramadol) caracterizada porque está constituida por microtabletas de menos de 3 mm donde el analgésico está uniformemente distribuido en una matriz retardante (de un polímero como EC, HPMC, HPC, HMC, glicéridos de ácidos grasos; una cera , aceite, grasa, ácido graso, alcohol graso ó éster), las microtabletas están recubiertas (con cera o resinas acrílicas de polímero de poliacrilato, polimetacrilato, alquilcelulosa ó EC).

D1 enseña formas de dosis de liberación controlada como cápsulas, tabletas, supositorios, esferoides, microesferas recubiertas con polímeros como derivados de celulosa, resinas acrílicas, ceras, alcoholes alifáticos superiores y ácidos poliláctico y poliglicólico. El principio activo puede ser analgésico como aspirina, codeína, morfina, dihidromorfona, oxicodona, etc. Los microgránulos recubiertos se colocan dentro de una cápsula o una tableta (ver pág 21).

D2 enseña formas de dosis de liberación controlada como cápsulas, tabletas, supositorios, esferoides, microesferas recubiertas con polímeros como derivados de celulosa, resinas acrílicas, ceras, alcoholes alifáticos superiores y ácidos poliláctico y poliglicólico, HPMC, PVP, PEO (ver folio 94). El principio activo puede ser analgésico como aspirina, codeína, morfina, dihidromorfona, oxicodona, hidromorfona, levorfanol, metadona, meperidina, dihidrocodeina, heroina, buprenorfina, tramadol, etc. (ver folios 95, 98). Los microgránulos recubiertos se colocan dentro de una cápsula o una tableta (ver folio 100).

D3 enseña una forma de dosificación de liberación controlada. Las partículas están recubiertas con películas de HPMC y plastificante PEG. Agrega (columna 5) que los pellets de liberación controlada prefertiblemente se proveen en una cápsula de gelatina dura ó cualquier otra forma de dosis oral apropiada tal como una matriz que comprende los pellets aglomerados con un aglutinante apropiado y compatible para formar una forma de dosis sólida unitaria.

D4 enseña composiciones para terapia simultánea o secuencial de dos ó más ingredientes activos como agentes hipoglicémicos tales como sulfonilúreas, biguanidinas y tiazolidindionas. Pueden ser formuladas para administración oral en una composición de liberación sostenida (o retardada), por ej.una formulación en tableta de matriz que contiene un relleno polimérico insoluble ó hinchable o una formulación esferoide recubierta. (ver columna 3).

D5 enseña que los productos se pueden recubrir con una película para modificar la liberación de la droga. Aclara que los productos de liberación prolongada tienen por objeto extender la liberación de la droga durante un período, resultado que se puede alcanzar al aplicar una cubierta con película de *liberación sostenida o controlada*. Las ventajas son alcanzar pronto el efecto deseado y mantenerlo por un tiempo prolongado, disminución de efectos colaterales y minimizar la acumulación del agente en tejidos durante el tratamiento y reducir las fluctuaciones de los niveles sanguíneos.

Se observa que lo enseñado las anterioridades es: D1: formas de dosis de liberación controlada como, esferoides, microesferas recubiertas con polímeros donde el principio activo puede ser analgésico opioide y los microgránulos recubiertos se colocan dentro de una cápsula o una tableta; D2: formas de dosis de liberación controlada como esferoides, microesferas recubiertas con polímeros donde el principio activo puede ser analgésico opioide y los microgránulos recubiertos se colocan dentro de una cápsula o una tableta; D3: una forma de dosificación de liberación controlada y las partículas están recubiertas para liberación controlada, se proveen en cápsula ó una matriz; D4: composiciones para terapia simultánea o secuencial de dos o más ingredientes activos para administración oral en una composición de liberación sostenida (o retardada), por ej. una formulación en tableta de matriz o una formulación esferoide recubierta; y D5: los productos de liberación prolongada se logran al aplicar una cubierta con película de *liberación sostenida o controlada,* y las ventajas son alcanzar pronto el efecto deseado, mantenerlo por un tiempo prolongado, disminución de efectos colaterales, minimizar la acumulación del agente en tejidos durante el tratamiento y reducir las fluctuaciones de los niveles sanguíneos. Se observa que la combinación de tan solo dos de estas anterioridades sugiere la composición oral, en cápsula o tableta, de liberación controlada de al menos un analgésico opioide caracterizada porque está constituida por microtabletas donde el analgésico está uniformemente distribuido en una matriz retardante y están recubiertas que es objeto de esta solicitud. Las reivindicaciones no mencionan una característica que conceda un efecto diferente o especial a la composición, así que esta es obvia y evidente para una persona versada en la materia. De manera que no tienen **nivel inventivo**.

7. Conclusión

En conclusión, los requisitos de patentabilidad de la presente solicitud están afectados así:

Item	Documento	Reivindicaciones	Requisito que afecta

		afectadas	
D1	EP 0 548 448	1 a 20	Nivel Inventivo
D2	EP 0 630 646	1 a 20	Nivel inventivo
D3	US 5 645 858	1 a 20	Nivel inventivo
D4	US 5 502 078	1 a 20	Nivel inventivo
D5	Libro (*)	1 a 20	Nivel inventivo

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

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No. 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 24 FEB. 2005

CONCEPTO TÉCNICO No. 224	EXAMINADOR TÉCNICO Código 202007