

06-18322

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Solicitud de patente de invención titulada: "FORMAS DE DOSIFICACION DE LIBERACION SOSTENIDA DE ZIPRASIDONA".

Solicitante: PFIZER PRODUCTS INC

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN
EL ARTÍCULO 44 DE LA DECISION 486, GACETA No. 579

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, D.C., identificado tal como aparece al pie de mi firma, en mi condición de apoderado del solicitante, respetuosamente me permito solicitar que se examine si la invención reúne los requisitos de patentabilidad previstos en la misma, dando cumplimiento a lo establecido en el artículo 44 de la Decisión 486 de la comisión de la Comunidad Andina de Naciones. Adjunto recibo por el monto de \$404.000 pesos para cubrir la tasa correspondiente, según la Resolución 36155 del año 2006.

Atentamente,

CARLOS R. OLARTE
C.C. 79.782.747 de Bogotá
T.P. 74.295

Anexo: Recibo por \$404.000 pesos

LMB/P2006/ 000039 070913

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-18322

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **579** DE

FECHA **31 DE AGOSTO DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **28 DE NOVIEMBRE DE 2007**

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

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO X



US006046177A

United States Patent [19]
Stella et al.

[11] **Patent Number:** 6,046,177
 [45] **Date of Patent:** *Apr. 4, 2000

- [54] **SULFOALKYL ETHER CYCLODEXTRIN BASED CONTROLLED RELEASE SOLID PHARMACEUTICAL FORMULATIONS**
- [75] **Inventors:** Valentino J. Stella; Roger A. Rajewski; Venkatramana M. Rao, all of Lawrence, Kans.; James W. McGlinly, Austin, Tex.; Gerold L. Mosher, Kansas City, Mo.
- [73] **Assignee:** Cydex, Inc., Overland Park, Kans.
- [*] **Notice:** This patent is subject to a terminal disclaimer.
- [21] **Appl. No.:** 09/229,513
- [22] **Filed:** Jan. 13, 1999

Related U.S. Application Data

- [63] Continuation-in-part of application No. 08/851,006, May 5, 1997, Pat. No. 5,874,418.
- [51] **Int. Cl.⁷** A61K 31/735; C07H 13/12; C08B 37/16
- [52] **U.S. Cl.** 514/58; 514/778; 514/964; 514/965; 536/103
- [58] **Field of Search** 514/58, 778, 964, 514/965; 536/103

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[57] ABSTRACT

Sulfoalkyl ether cyclodextrin (SAE-CD) based controlled release pharmaceutical formulations are provided by the present invention. The present solid pharmaceutical formulations consist of a core comprising a physical mixture of one or more SAE-CD derivatives, an optional release rate modifier, a therapeutic agent, a major portion of which is not complexed to the SAE-CD, and an optional release rate modifying coating surrounding the core. The present formulations are advantageously easier to prepare than other SAE-CD based formulations in the art yet provide similar or improved effectiveness. The SAE-CD derivative is used to modify the bioavailability and/or rate of bioabsorption of therapeutic agents. Multi-layered, osmotic pump, coated, and uncoated tablet, minitab, pellet, micropellet, particle, powder, and granule dosage forms are disclosed herein.

95 Claims, 29 Drawing Sheets

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 302
 349

FIG. 14. Release profiles for DP from tablet formulations having a combined delayed and controlled release profile and the effect of film thickness and film composition there-upon.

FIG. 15. Release profile for methylprednisolone (MP) from tablet formulations comprising a physical mixture and preformed complex of MP and SBE- β -CD surrounded by a coating comprising a composition of EUDRAGITTM RS30D and EUDRAGITTM RL30D but no pore forming agent.

FIG. 16. Release profiles for prednisolone (PD) from tablet formulations having a core comprising a physical mixture of PD and SBE- β -CD and a rate modifier, wherein the tablet is uncoated.

FIG. 17. Release profiles for PD from tablet formulations consisting essentially of cores having different ratios of cyclodextrin to therapeutic agent.

FIG. 18. Release profiles for PD from tablet formulations comprising uncoated cores containing constant amounts of cyclodextrin and PD but different amounts of rate modifier.

FIG. 19. Release profiles for PD from tablet formulations containing uncoated cores comprising release modifiers having different viscosity and solubility characteristics as well as formulations containing different drug to rate modifier polymer ratio.

FIG. 20. Release profiles for PD from tablet formulations containing uncoated cores comprising release modifiers having different viscosity and solubility characteristics as well as formulations containing different drug to rate modifier polymer ratio.

FIG. 21. Release profiles for PD from tablet formulations having a core comprising a physical mixture of PD, a rate modifier and one of SBE- β -CD, KCl, sucrose or lactose, wherein the tablet is uncoated.

FIG. 22. Release rate profiles for PD from tablet formulations wherein the ratio of drug: SBE- β -CD is varied.

FIG. 23a depicts a first embodiment of a two-layered tablet according to the invention.

FIG. 23b depicts a first embodiment of a three-layered tablet according to the invention.

FIG. 24 depicts a second embodiment of a controlled-release tablet according to the invention.

FIG. 25 depict release profiles for testosterone (TS) and excipients from various osmotic pumps, one of which is prepared according to the invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention overcomes the disadvantages inherent in known therapeutic agent/cyclodextrin physical mixture-containing pharmaceutical formulations by providing a formulation that is easy to prepare and has a therapeutic agent solubility, dissolution profile and/or bioavailability that approximates that of its respective therapeutic agent/cyclodextrin complex-containing pharmaceutical formulation. The present invention employs sulfoalkyl ether cyclodextrin (SAE-CD) derivatives in preparing a wide range of pharmaceutical formulations as herein described. The present formulations are used for rapid, controlled, delayed, timed, pulsatile and sustained delivery of a wide range of therapeutic agents. The formulations can also be included in a wide variety of dosage forms as herein described.

Sulfoalkyl Ether Cyclodextrin Derivatives

The terms "alkylene" and "alkyl," as used herein (e.g., in the —O—(C2—C6-alkylene)SO₃-group or in the

alkylamines), include linear, cyclic, and branched, saturated and unsaturated (i.e., containing one double bond) divalent alkylene groups and monovalent alkyl groups, respectively. The term "alkanol" in this text likewise includes both linear, cyclic and branched, saturated and unsaturated alkyl components of the alkanol groups, in which the hydroxyl groups may be situated at any position on the alkyl moiety. The term "cycloalkanol" includes unsubstituted or substituted (e.g., by methyl or ethyl) cyclic alcohols.

The present invention provides compositions containing a mixture of cyclodextrin derivatives, having the structure set out in formula (I), where the composition overall contains on the average at least 1 and up to 3 n+6 alkylsulfonic acid moieties per cyclodextrin molecule. The present invention also provides compositions containing a single type of cyclodextrin derivative, or at least 50% of a single type of cyclodextrin derivative.

The present cyclodextrin derivatives are either substituted at least at one of the primary hydroxyl group (i.e., at least one of R₁ to R₃ is a substituent), or they are substituted at both the primary hydroxyl group and at the 3-position hydroxyl group (i.e., both at least one of R₁ to R₃ and at least one of R₄, R₆ and R₈ are a substituent). Substitution at the 2-position hydroxyl group, while theoretically possible, on the basis of the inventors' studies, does not appear to be substantial in the products of the invention.

The cyclodextrin derivatives of the present invention are obtained as purified compositions, i.e., compositions containing at least 95 wt. % of cyclodextrin derivative(s) with the substitution occurring at least on the primary hydroxyl group of the cyclodextrin molecule (i.e. R₁, R₂ or R₃ of formula (I)). In a preferred embodiment, purified compositions containing at least 98 wt. % cyclodextrin derivative(s) are obtained.

In some of the compositions of the invention unreacted cyclodextrin has been substantially removed, with the remaining impurities (i.e., <5 wt. % of composition) being inconsequential to the performance of the cyclodextrin derivative-containing composition.

The cyclodextrin derivatives used herein are generally prepared as described in U.S. Pat. No. 5,134,127, the entire disclosure of which is incorporated herein by reference. This preparation process may comprise dissolving the cyclodextrin in aqueous base at an appropriate temperature, e.g., 70° to 80° C., at the highest concentration possible. For example, to prepare the cyclodextrin derivatives herein, an amount of an appropriate alkyl sulfone, corresponding to the number of moles of primary CD hydroxyl group present, is added with vigorous stirring to ensure maximal contact of the heterogeneous phase.

The various SAE-CD derivatives evaluated include SBE- α , SBE- β , SBE- γ , and SBE- δ , which correspond to SAE-CD derivatives of the formula I wherein n=5, 5 and 6; m is 4; and there are 4, 7, 11 and 4 sulfoalkyl ether substituents present, respectively. It has been found that these SAE-CD derivatives increase the solubility of poorly water soluble drugs to varying degrees. For example, the table below summarizes the binding constant and solubility observed with several SAE-CDs (0.1 M at 25° C.) and methylprednisolone.

More specifically, agents can form weak through very strong inclusion complexes with SAE-CDs. A very weak inclusion complex would be one where the binding constant is less than about 500 M^{-1} ; a weak constant would be one where the binding constant is about 500 to about 1000 M^{-1} ; a moderate binder would have a binding constant of about $1,000$ to about $5,000 \text{ M}^{-1}$; a strong binder would be one with a binding constant of about $5,000$ to about $20,000 \text{ M}^{-1}$; and a very strong binder would have a binding constant of greater than about $20,000 \text{ M}^{-1}$.

The relative increase in the solubility of a poorly soluble drug in the presence of SAE-CDs is a product of the binding constant and the molar concentration of SAE-CD present. For a very weakly bound drug, a ratio of 100:1, on a molar basis, between SAE-CD and agent might be necessary. If this is the case, the amount of drug in the formulation might have to be as low as 1 mg. If the binding constant between SAE-CD and the agent is very strong, then a ratio of about 1:1 could be permitted. In such a case, a drug dosage as high as 50 mg can be used provided the intrinsic solubility of the drug is suitable. Consider a drug with a binding constant of $10,000 \text{ M}^{-1}$, a binding constant that is realistic for a number of drugs. In the presence of 0.1 M SAE-CD, the solubility of the drug would be increased about 1,000 fold over the solubility in the absence of the SAE-CD. If the intrinsic solubility of the drug is about 1 ng/ml, then only a solubility of about 1 $\mu\text{g/ml}$ will be possible in the presence of 0.1 M SAE-CD, however, if the intrinsic solubility of the drug is about 10 $\mu\text{g/ml}$, then a solubility of about 10 mg/ml might be possible in the presence of about 0.1 M SAE-CD.

Various therapeutic agent/SAE-CD physical mixture-containing pharmaceutical formulations are contemplated by the present invention: osmotic pump tablet, layered tablet, coated tablet, coated pellets, powder for reconstitution, capsules, coated granules and hot-melt extruded films.

The coated tablets, granules and pellets of the invention comprise an optional film coating and a solid core. The film coating comprises a film coating agent and an optional pore forming agent. The film coating can also comprise plural film forming agents and optionally pore forming agents, e.g. combinations of film forming agents are used in some embodiments of the film coating.

The terms "film forming agent" and "release controlling agent" are used interchangeably herein and are intended to include polymeric compounds (of natural, synthetic, semi-synthetic or genetically engineered sources) which will form a film coating around the solid core of the formulation and control the release or slow down the release rate of therapeutic agent or SAE-CD from said core. The film forming agents contemplated by the invention are further described and, for particular embodiments, exemplified herein.

FIG. 1, which procedure is detailed in Example 1, depicts the release profiles for two methylprednisolone (MP) containing osmotic pump tablets which differ only in the complexation of the SAE-CD and the therapeutic agent. Two compositions, the first containing methylprednisolone/SBE- β -CD physical mixture and the second containing methylprednisolone-SBE- β -CD complex, were formulated into controlled release osmotic pump tablets according to Example 1. The MP and SBE- β -CD (present in a 1:7 molar ratio) along with a pharmaceutical carrier were compressed into a solid core which was spray coated with a mixture of ethylcellulose, PEG3350, PEG400 and ethanol to form a 140 μm thick film coating around the solid core. The dissolution profile was determined using USP dissolution apparatus II

(100 rpm, 37°C) and an HPLC assay for methylprednisolone (MP). A fluorimetric assay employing 2,6-toluidino naphthalene sulfonate (2,6-TNS) was developed for quantitating the SAE-CD. The first formulation, indicated in FIG. 1 by the hollow circles, contains the separately preformed MP-SBE- β -CD freeze-dried complex. The second formulation, indicated by the filled in circles, contains a major portion of uncomplexed MP as a physical mixture with SBE- β -CD. The third formulation, indicated by the squares, contains a physical mixture of lactose, fructose and MP. It is evident by the similarity of the curves corresponding to the preformed complex and the physical mixture, that the latter has a release profile similar to or substantially similar to the former. It should be noted that, for this particular dosage form, the MP and SBE- β -CD had substantially the same release profiles. The results are depicted in FIGS. 2a and 2b for MP and SBE- β -CD, respectively.

When the therapeutic agent was testosterone (TST), the physical mixture formulation of SBE- β -CD and TST exhibited the same release profile as the respective freeze dried mixture. (FIG. 8) The solid core of the tablet comprised a 1:1 molar ratio of TST and SBE- β -CD. The film coating of this tablet comprised sorbitol, PEG 400 and cellulose acetate. The release profiles of the physical mixture and complex formulation were compared to that of a baseline TST/fructose-lactose formulation.

When the thickness of the film coating, or membrane, surrounding the tablet core, which comprised either a physical mixture or a freeze dried complex of MP and SBE- β -CD, was increased to 200 μm , a slight difference was noted in the release profiles of the physical mixture versus the freeze dried complex; however, the SBE- β -CD did have a release profile substantially similar to that of the MP. The results are depicted in FIGS. 3a and 3b for MP and SBE- β -CD, respectively. Additional exemplary film coated tablets having film thicknesses of 38, 89, 137, 198 and 234 μm were prepared and evaluated as above. The results depicted in FIGS. 4a and 4b indicated that SBE- β -CD exhibited substantially the same release profile as MP in each of the dosage forms. In the 234 μm film embodiment, the freeze-dried complex appeared to release SBE- β -CD faster than MP; however, when the release rate data for the physical mixture embodiments of FIGS. 4a and 4b was plotted against the inverse of the film thickness, the results indicated that the SBE- β -CD had a release profile substantially similar to the MP (FIG. 5).

Film thickness need not have a significant impact upon the release profile of a given dosage form. FIG. 10 depicts the effect that film thickness has upon a delayed release formulation comprising an EUDRAGITTM-L/urea film coating and a dipyrindamole/SBE- β -CD physical mixture solid core. The results indicate that, for this embodiment, the release profile for DP is independent of film thickness but dependent upon solution pH.

By changing the film coating composition to EUDRAGITTM-S and urea, a delayed release formulation releasing DP at about pH 7.2 rather than at about 6.8 can be made (FIG. 11). The more basic pH corresponds to that found in the lower small intestine or the large intestine of a patient. Accordingly, one can prepare a delayed release formulation for enteric or colorectal release of a therapeutic agent comprising a solid core and a film coating, the solid core comprising a therapeutic agent and an SAE-CD and the film coating comprising a film forming agent which is a polymer with pH dependent solubility.

The film surrounding the solid core will affect the release of MP and SBE- β -CD. In the embodiments of the invention

release of the poorly water soluble drug prednisolone (PD) absent a release rate modifying coat. In the example of FIG. 16, the release rate modifier is hydroxypropyl methylcellulose (HPMC). In the absence of the cyclodextrin, only approximately 50% by weight of the PD is released after eleven hours; however, addition of the SAE-CD effects a greater than 90% delivery of the drug in approximately six hours and substantially complete delivery of the drug in eleven hours.

The effect of changing the ratio of therapeutic agent to sulfoalkyl ether cyclodextrin is exemplified in FIG. 17 wherein the amount of prednisolone and HPMC in an uncoated core is kept constant while the amount of SBE- β -CD and lactose monohydrate are varied. Specifically, the PD is kept constantly at 5% by weight of the formulation and the HPMC is kept constant at approximately 25% by weight of the formulation. The cyclodextrin and lactose amounts are varied such that they will comprise approximately 70% by weight of the formulation in the exemplary formulations of FIG. 17. Generally as the amount of SAE-CD is decreased and the amount of lactose is increased in the formulation, the rate of delivery of the PD and the overall amount of PD delivered decrease and the rate of delivery of the SAE-CD increases. Stated otherwise, as the PD/SAE-CD ratio is increased, the release rate of the drug is decreased, and the release rate of the SAE-CD is increased. Accordingly, one embodiment of a controlled release pharmaceutical formulation according to the invention includes an uncoated core comprising an SAE-CD, a therapeutic agent, and a release rate modifier. Exemplary formulations include those formulations wherein approximately 40% of the drug, preferably 60% of the drug, more preferably 80% of the drug, is delivered within four hours and 60% of the drug, preferably 80% of the drug, and more preferably 90% of the drug, respectively is delivered within eight hours after administration of the formulation.

In the controlled release formulation according to the invention wherein the core is uncoated, the ratio of release rate modifier to either one or both of the therapeutic agent or SAE-CD will have an impact upon the rate of delivery of the drug and the overall amount of drug delivered. Accordingly, FIG. 18 depicts release profiles for various formulations wherein the amount of drug and cyclodextrin in the formulation have been kept constant and the amount of release rate modifier (HPMC) and diluent (lactose) have been varied. Generally, as the ratio of release rate modifier to drug is increased, the release rate of the drug is decreased, and as the ratio of release rate modifier to cyclodextrin is increased, the release rate of the cyclodextrin is decreased. In the specific example of FIG. 18, in this embodiment, when the ratio of release rate modifier to drug is approximately 10:1, approximately 40–50% of the drug will be released in about six hours after administration and approximately 55–60% of the drug will be released 12 hours after administration. When the ratio of release rate modifier to drug is approximately 5:1, the formulation will release approximately 65–75% of the drug after about six hours and approximately 75–90% of the drug 12 hours after administration. PD comprises 5% by weight of the formulation, SAE-CD comprises 35% by weight of the formulation, and increasing the amount of HPMC in the formulation is varied from 25% by weight to 50% by weight.

The embodiments of the formulation according to the invention which comprise an uncoated core for releasing a drug at a controlled rate are generally affected by the molecular weight and/or the viscosity of a release rate modifier used to comprise the core. It is generally accepted

that an increase in viscosity for a polymer can correspond to an increase in the molecular weight of the polymer, an increase in the branching of the polymer or an increase in the degree of substitution of the polymer. For example, FIG. 19 depicts an uncoated core formulation wherein the core comprises 5% by weight of PD, 70% by weight of SAE-CD and 25% by weight of HPMC. The HPMC includes either HPMC K100M (having a viscosity of 100,000 cps) or HPMC K15M (having a viscosity of 15,000 cps). As the viscosity of the release rate modifier is increased, the rate of release of the PD is increased. The control sample which includes HPMC K100M and no cyclodextrin releases approximately 30% by weight of the PD in six hours and approximately 50% by weight of the PD in eleven hours. Surprisingly, as the viscosity of the HPMC is increased from 15,000 to 100,000, the rate of delivery of the PD and the overall amount of PD delivered increases; whereas, the rate of delivery of the cyclodextrin and the overall amount of the cyclodextrin delivered decreases. This behavior is quite unexpected as it is generally expected in the art that the rate of delivery of components in a controlled release matrix will decrease as the viscosity of the release rate modifier increases. Accordingly, this embodiment of the invention provides a controlled release formulation wherein the release rate modifier is present in an amount sufficient to render the release rate of the drug dependent upon the viscosity of the release rate modifier.

FIG. 20 includes release profiles for uncoated controlled release core formulations comprising 5% by weight of PD, 35% by weight of SAE-CD, 50% by weight of HPMC and 10% by weight of lactose wherein the HPMC viscosity has been increased from 15,000 to 100,000 cps. In this particular example, which includes a high concentration of HPMC relative to the cyclodextrin and the drug, the rate of delivery and the overall amount delivered of the drug and SAE-CD appear to be substantially independent of the viscosity of the HPMC. Accordingly, the controlled release uncoated core formulation according to the invention can provide release of a therapeutic agent wherein about 60% of the therapeutic agent has been released within about four hours and about 80% of the drug has been released within about 10 hours or wherein about 80% of the formulation has been released within about 4 hours and greater than 90% of the formulation has been released within about 10 hours. The invention can also provide a controlled release uncoated formulation wherein approximately 40% of the drug is released within four hours and approximately 50% of the drug is released within 8 hours. Stated otherwise, one embodiment of the formulation comprises a release rate modifier present in an amount sufficient to render the release rate of the drug substantially independent of the viscosity of the release rate modifier.

FIGS. 19 and 20 indicate that when higher concentrations of the release rate modifier are present in the formulation, the release rate of the drug in the formulation will be substantially independent of the viscosity of the release rate modifier; whereas, when lower concentrations of the release rate modifier are present in the core, the release rate of the drug from the core will be substantially dependent upon the viscosity of the release rate modifier. Stated otherwise, increasing the amount of release rate modifier in the core generally decreases the dependence of the release rate of the drug upon the molecular weight or viscosity of the release rate modifier.

Another aspect of the invention provides a multi-layered controlled release solid pharmaceutical formulation or dosage form comprising at least a first layer comprising a

physical mixture of a therapeutic agent and an SAE-CD and at least a second layer comprising a release rate modifier. In this embodiment as with all the others of the present invention, a major portion of the therapeutic agent is not complexed with the SAE-CD. The components of the at least first and second layers will cooperate to provide a controlled delivery of the therapeutic agent. In the present embodiment, the formulation can comprise two, three, four or more layers which are compressed individually, simultaneously, sequentially or otherwise to form a formulation have a desired release profile of the therapeutic agent. In a preferred embodiment, the multi-layered formulation will comprise a middle first layer comprising a therapeutic agent and SAE-CD sandwiched between two second layers, each comprising a release rate modifier. The first and second layers according to the invention can comprise additional pharmaceutical excipients and components known to those of ordinary skill in the art.

While it is an object of the invention to provide controlled release solid pharmaceutical formulations comprising a combination of a SAE-CD and therapeutic agent wherein a major portion of the therapeutic agent is not complexed with the SAE-CD, the present formulations can further include additional compositions wherein the therapeutic agent is complexed with the SAE-CD. For example, one embodiment of the invention can comprise a core containing a first composition and a second composition, wherein the first composition comprises a physical mixture of an SAE-CD and a therapeutic agent, wherein a major portion of the therapeutic agent is not complexed with the SAE-CD, and the second composition comprises a preformed complex of the SAE-CD and the therapeutic agent.

Example 8 details a method of preparing an exemplary embodiment of a multi-layered tablets according to the invention comprising at least one immediate release layer adjacent a controlled release layer. FIG. 23a depicts a bilayered tablet (1) comprising an immediate release layer (3) containing a predetermined amount of drug and SAE-CD, together present as a physical mixture, and a rapid release matrix and a controlled release layer (2) containing a predetermined amount of a physical mixture of a drug, an SAE-CD and a release rate modifier. The immediate release layer readily disintegrates and releases the drug into the surrounding milieu following administration to the patient or addition of the tablet to a dissolution medium. FIG. 23b depicts a three-layered tablet wherein a controlled release layer (6), prepared as described in Example 8, is sandwiched between two immediate release layers (5a, 5b), prepared as described in Example 8. Note that the immediate release layers of FIG. 23b comprise a preformed indomethacin/SAE-CD complex. The bi-layered and three-layered tablets can be coated with a finish, enteric or controlled release coating if desired.

In another embodiment, the multi-layered controlled release formulation comprises at least first, second and third layers wherein the first layer contains a first composition comprising a physical mixture of an SAE-CD and a therapeutic agent, wherein a major portion of the therapeutic agent is not complexed with the SAE-CD, the second layer contains a second composition comprising a preformed complex of the SAE-CD and a therapeutic agent, and the third layer comprises a release rate modifier. In this particular embodiment, the third layer can cover either one or both of the first and second layers.

FIG. 24 depicts another embodiment of the controlled release formulation (7) of the invention wherein a controlled release core (8), containing a physical mixture of drug and

SAE-CD, is surrounded by a compression coating (9) containing a preformed complex of drug and SAE-CD.

The controlled release formulations of the invention also include physical mixture particulate or granular formulations wherein a first group of particles contains a physical mixture of a first therapeutic agent, a first sulfoalkyl ether cyclodextrin and a release rate modifier and a second group of particles contains an inclusion complex of a first therapeutic agent and a second sulfoalkyl ether cyclodextrin. The first group of particles will preferably deliver the first therapeutic agent in a controlled manner, and the second group of particles will preferably deliver the second therapeutic agent in a rapid manner. The first and second therapeutic agents can be the same or different. Likewise, the first and second sulfoalkyl ether cyclodextrins can be the same or different. The particulates will preferably include additional pharmaceutically acceptable excipients. If a delayed and controlled delivery of the second therapeutic agent is desired, the particles of the second group will be coated with a delayed release coating. The delayed release can be pH, erosion, or solubility controlled. Delayed release coatings include those described herein as well as other coatings known to those of ordinary skill in the art.

Osmotic pump formulations made according to the examples below will generally comprise a semipermeable coating surrounding a core comprising a physical mixture of a therapeutic agent, an SAE-CD, and a pharmaceutically acceptable carrier, wherein a major portion of the therapeutic agent is not complexed with the SAE-CD and the membrane has a passageway therethrough for communicating the core to an environment of use. The core can also include an osmagent and pharmaceutically acceptable excipients. The semipermeable membrane can include one or more pore forming agents to render the membrane porous thereby permitting diffusion of therapeutic agent through the membrane and resulting in a dual function osmotic pump.

In the examples detailed below wherein a formulation comprises a film coating around a core, the film can also include a passageway therethrough for communicating the core to an environment of use. For example, a passageway is formed in the film by drilling with a laser or drill bit. If the film is porous, i.e. permits diffusion of a drug therethrough, and also includes a passageway, the formulation will deliver drug by combined osmotic and diffusional means. If the film is semipermeable, i.e. does not permit diffusion of a drug therethrough, and includes a passageway, the formulation will deliver drug by osmotic means.

The term "osmagent" means a compound or group of compounds that generate an osmotic pressure across the membrane of an osmotic pump when included within the core of the osmotic pump and when exposed to water imbibed from an environment of use. Such osmotic agents include, for example, salts, water soluble compounds, sugars and other such agents known to those of ordinary skill in the art. The SAE-CD and other hydrophilic or ionized compounds or polymers can also serve as osmagents.

Example 11 describes the preparation of an osmotic pump which delivers testosterone (TS) into an environment of use by combined diffusional and osmotic means. FIG. 25 depicts the comparative release profiles of TS, sugar, hydroxypropyl- β -cyclodextrin (HP- β -CD) and (SBE) $_{7m}$ - β -CD from various osmotic pump formulations. The first formulation contained a physical mixture of TS (○) and a mixture of sugar (●, lactose and fructose, 1/1); the second formulation contained TS (□) and (SBE) $_{7m}$ - β -CD (■); and the third formulation contained TS (◇) and HP-P-CD (◆).

ordinary skill that a therapeutic agent used in the formulations of the present invention is independently selected at each occurrence from any of the therapeutic agents disclosed herein.

The amount of therapeutic compound incorporated into the present formulations are selected according to known principles of pharmacy, clinical medicine and pharmacology. A therapeutically effective amount of therapeutic compound is specifically contemplated. By the term "therapeutically effective amount," it is understood that, with respect to, for example, pharmaceuticals, a pharmaceutically effective amount is contemplated. A pharmaceutically effective amount is the amount or quantity of a drug or pharmaceutically active substance which is sufficient to elicit the required or desired therapeutic response, or in other words, the amount which is sufficient to elicit an appreciable biological response when administered to a patient. As used with reference to a vitamin or mineral, the term "effective amount" means an amount at least about 10% of the United States Recommended Daily Allowance ("RDA") of that particular ingredient for a patient. For example, if an intended ingredient is vitamin C, then an effective amount of vitamin C would include an amount of vitamin C sufficient to provide 10% or more of the RDA. Typically, where the tablet includes a mineral or vitamin, it will incorporate higher amounts, preferably about 100% or more of the applicable RDA. The therapeutic compound is generally used in finely divided form, i.e. powder or granulate so as to increase the dissolution rate. It is preferable to use a finely powdered therapeutic compound to increase the dissolution rate, more preferably, the therapeutic compound being capable of allowing not less than 80%, desirably not less than 90%, of it to pass through a 100 mesh (150 microns) screen. The amount of therapeutic compound to be incorporated ranges usually from about 0.1 to 50%, preferably about 1 to 25% by weight based on the composition, and the ratio may be suitably modified depending on the therapeutic compound employed.

Exemplary therapeutic agents include synthetic antibacterial agents of hardly water-soluble pyridone-carboxylic acid type such as benofloxacin, nalidixic acid, enoxacin, ofloxacin, amifloxacin, flumequine, tosifloxacin, piromidic acid, pipemidic acid, miloxacin, oxolinic acid, cinoxacin, norfloxacin, ciprofloxacin, pefloxacin, lomefloxacin, enrofloxacin, danofloxacin, binfloxacin, sarafloxacin, ibafloxacin, difloxacin and salts thereof. Other therapeutic agents include penicillin, tetracycline, cephalosporins and other antibiotics, antibacterial substances, antihistamines and decongestants, anti-inflammatories, antiparasitics, antivirals, local anesthetics, antifungal, amoebicidal, or trichomonocidal agents, analgesics, antiarthritics, antiasthmatics, anticoagulants, anticonvulsants, antidepressants, antidiabetics, antineoplastics, antipsychotics, antihypertensives and muscle relaxants. Representative antibacterial substances are beta-lactam antibiotics, tetracyclines, chloramphenicol, neomycin, gramicidin, bacitracin, sulfonamides, nitrofurazone, nalidixic acid and analogs and the antimicrobial combination of fludalanine/pentizidone. Representative antihistamines and decongestants are perilamine, chlorpheniramine, tetrahydrozoline and antazoline.

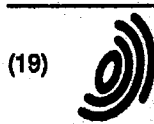
Representative anti-inflammatory drugs are cortisolone, hydrocortisone, betamethasone, dexamethasone, fluocortolone, prednisolone, triamcinolone, indomethacin, sulindac and its salts and corresponding sulfide. A representative antiparasitic compound is ivermectin.

Representative antiviral compounds are acyclovir and interferon. Representative analgesic drugs are diflunisal,

aspirin or acetaminophen. Representative antiarthritics are phenylbutazone, indomethacin, silindac, its salts and corresponding sulfide, dexamethasone, ibuprofen, allopurinol, oxyphenbutazone or probenecid. Representative antiasthma drugs are theophylline, ephedrine, beclomethasone dipropionate and epinephrine. Representative anticoagulants are bishydroxycoumarin, and warfarin. Representative anticonvulsants are diphenylhydantoin and diazepam. Representative antidepressants are amitriptyline, chlordiazepoxide, perphenazine, protriptyline, imipramine and doxepin. Representative antidiabetics are insulin, somatostatin and its analogs, tolbutamide, tolazamide, acetohexamide and chlorpropamide. Representative antineoplastics are adriamycin, fluorouracil, methotrexate and asparaginase. Representative antipsychotics are prochlorperazine, thioridazine, molindone, fluphenazine, trifluoperazine, perphenazine, amitriptyline and trifluopromazine. Representative antihypertensives are spironolactone, methyldopa, hydralazine, clonidine, chlorothiazide, deserpidine, timolol, propranolol, metoprolol, prazosin hydrochloride and reserpine. Representative muscle relaxants are succinylcholine-chloride, danbrolene, cyclobenzaprine, methocarbamol and diazepam.

Some other examples of therapeutic agents include, but are not limited to, adiphenine, allobarbitol, aminobenzoic acid, amobarbital, ampicillin, anethole, aspirin, azopropazone, azulene barbituric acid, beclomethasone, beclomethasone dipropionate, bencyclane, benzaldehyde, benzocaine, benzodiazepines, benzothiazide, betamethasone, betamethasone 17-valerate, bromobenzoic acid, bromoisovalerylurea, butyl-p-aminobenzoate, chloralhydrate, chlorambucil, chloramphenicol, chlorobenzoic acid, chlorpromazine, cinnamic acid, clofibrate, coenzyme A, cortisolone, cortisolone acetate, cyclobarbitol, cyclohexyl anthranilate, deoxycholic acid, dexamethasone, dexamethasone acetate, diazepam, digitoxin, digoxin, estradiol, flufenamic acid, fluocinolone acetonide, 5-fluorouracil, flurbiprofen, griseofulvin, guaiazulene, hydrocortisone, hydrocortisone acetate, ibuprofen, indicin, indomethacin, iodine, ketoprofen, lankacidin-group antibiotics, mefenamic acid, menadione, mephobarbital, metharbitol, methicillin, metronidazole, mitomycin, nitrazepam, nitroglycerin, nitrosureas, paramethasone, penicillin, pentobarbital, phenobarbital, phenobarbitone, phenyl-butyric acid, phenyl-valeric acid, phenytoin, prednisolone, prednisolone acetate, progesterone, propylparaben, proscillaridin, prostaglandin A series, prostaglandin B series, prostaglandin E series, prostaglandin F series, quinolone antimicrobials, reserpine, spironolactone, sulfacetamide sodium, sulfonamide, testosterone, thalidomide, thiamine dilaurylsulphate, thiamphenicolpalmitate, thiopental, triamcinolone, VIAGRA™, vitamin A, vitamin D3, vitamin E, vitamin K3, and warfarin.

The therapeutic compound(s) contained within the pharmaceutical formulation are formulated as its pharmaceutically acceptable salts when necessary. As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the therapeutic compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic



(19)

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(54) **Ziprasidone formulations**

(57) Compositions comprising crystalline ziprasidone free base or crystalline ziprasidone hydrochloride particles having a mean particle size less than 85 µm, and a pharmaceutically acceptable carrier, are substantially bioequivalent and can be used to treat psychoses such as schizophrenia.

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and therefore appears to be largely independent of it. Thus ziprasidone free base or ziprasidone hydrochloride can be formulated in a composition having a reasonable particle size which is easily manageable using conventional formulations methodology and equipment, it not being necessary to use extreme measures or specialized technology to achieve and maintain relatively tiny particles to facilitate dissolution.

5 [0008] Formulations according to this invention, when dissolution tested *in vitro* preferably exhibit the following dissolution criteria. That is, the formulation exhibits dissolution properties such that, when an amount of the formulation equivalent to 100 mgA ("mgA" being an abbreviation designating active ziprasidone in the form of the free base, molecular weight 412.9) or less of active ziprasidone (100 mgA as free base being equivalent to 113.2 mg as ziprasidone hydrochloride monohydrate) is placed in a USP-2 apparatus containing 900 ml of 0.05 M NaH₂PO₄ buffer, adjusted to
10 pH 7.5, containing 2% (w/w) sodium dodecyl sulfate, the apparatus being equipped with paddles stirring at 75 rpm, at least 70% of the ziprasidone free base or hydrochloride therein dissolves within 45 minutes. Usually the test result is established as an average for a pre-determined number of dosages (e.g., capsules, tablets, suspensions, or other dosage form), usually six. The dissolution media is typically maintained at 37°C during the test. It is noted that if the dosage form being tested is a capsule, 1% (w/w) of pancreatin or other source of trypsin may need to be added to the phosphate buffer dissolution medium so that the capsule shell does not interfere with the test. The amount of dissolved ziprasidone can be determined conventionally by HPLC, as hereinafter described.

[0009] The term "particles" refers to individual particles whether the particles exist singly or are agglomerated. Thus, a composition comprising particulate ziprasidone hydrochloride may contain agglomerates that are well beyond the size limit of about 85µm specified herein. However, if the mean size of the primary drug substance particles (i.e., ziprasidone
20 free base or ziprasidone hydrochloride) comprising the agglomerate are less than about 85µm individually, then the agglomerate itself is considered to satisfy the particle size constraints defined herein and the composition is within the scope of the invention.

[0010] Reference to ziprasidone free base or to ziprasidone hydrochloride particles having "a mean particle size" (herein also used interchangeably with "VMD" for "volume mean diameter") equal to or less than a given diameter or
25 being within a given particle size range means that the average of all ziprasidone particles in the sample have an estimated volume, based on an assumption of spherical shape, less than or equal to the volume calculated for a spherical particle with a diameter equal to the given diameter. Particle size distribution can be measured by Malvern light scattering as known to those skilled in the art and as further disclosed and discussed below.

[0011] "Bioequivalent" as employed herein means that if a dosage form comprising crystalline ziprasidone particles and a pharmaceutically acceptable carrier, said particles having a given mean particle size, is tested in a crossover study (usually comprising a cohort of at least 10 or more human subjects), the average Area under the Curve (AUC) and/or the C_{max} for each crossover group is at least 80% of the (corresponding) mean AUC and/or C_{max} observed when the same cohort of subjects is dosed with an equivalent formulation differing only in that the ziprasidone particle size is 20 microns (µm), preferably with a D₉₀ of about 40 µm. The 20 µm particle size is, in effect, a standard against which
35 other different formulations can be compared. AUCs are plots of serum concentration of ziprasidone along the ordinate (Y-axis) against time for the abscissa (X-axis). Generally, the values for AUC represent a number of values taken from all the subjects in a patient population and are, therefore, mean values averaged over the entire test population. C_{max}, the observed maximum in a plot of serum level concentration of ziprasidone (Y-axis) versus time (X-axis) is likewise an average value.

[0012] Use of AUCs, C_{max}, and crossover studies is, of course otherwise well understood in the art. The invention can indeed be viewed in alternative terms as a composition comprising crystalline ziprasidone particles having a mean particle size equal to or less than about 85µm, as measured by Malvern light scattering, and a pharmaceutically acceptable carrier, said composition exhibiting a mean AUC and/or mean C_{max} which are at least 80% of the corresponding mean AUC and/or C_{max} values exhibited by a composition equivalent thereto (i.e., in terms of excipients employed and the
45 amount of ziprasidone hydrochloride) but having a ziprasidone mean particle size of 20µm. Use of the term "AUC" for purposes of this invention implies crossover testing within a cohort of at least 10 healthy subjects for all compositions tested, including the "standard" 20µm particle size composition.

Detailed Description

50 [0013] As previously stated, ziprasidone free base or ziprasidone hydrochloride in any form which will crystallize can be used in this invention, including anhydrous or, in the case of the hydrochloride, ziprasidone hydrochloride monohydrate. The ziprasidone hydrochloride employed herein, including the examples, was ziprasidone hydrochloride monohydrate, and is generally referred to throughout simply as ziprasidone hydrochloride for convenience. Crystalline
55 ziprasidone free base itself can be formed from the hydrochloride by adding or titrating a base (for example an alkali metal hydroxide such as sodium hydroxide) to a suspension of the acid addition salt in water, usually with stirring. Base is added at a rate such that the pH preferably rises to at least about 5. A preferred pH range within which to conduct the neutralization is from about 5 to about 7. The neutralization reaction can take up to several hours or more, depending

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[0020] Compositions comprising ziprasidone free base or ziprasidone hydrochloride having a mean particle size less than 85 μm can be formulated into conventional, usually dry, pharmaceutical dosage forms such as tablets, powders for oral suspension, unit dose packets, and capsules for oral administration, and such dosage forms can be made by conventional methodology. Ziprasidone free base can also be incorporated into a pre-constituted oral suspension as described in (Pfizer Docket 10509JTJ), filed provisionally in the US of even date herewith, and herein incorporated by reference.

[0021] The compositions, in addition to ziprasidone free base or ziprasidone hydrochloride, can contain conventional pharmaceutically acceptable excipients such as, for example: fillers and diluents such as starches and sugars; binders such as carboxymethyl cellulose and other cellulose derivatives, alginates, gelatine, and polyvinyl pyrrolidone; disintegrating agents such as agar-agar, calcium carbonate and sodium bicarbonate, pregelatinized starch, sodium croscarmellose, sodium starch glycolate and crosslinked poly(vinyl pyrrolidone); lubricants such as talc, sodium lauryl sulfate, stearic acid, calcium and magnesium stearate, and solid polyethyl glycols. Some excipients can serve more than one function; for example, a disintegrant can also serve as a filler.

[0022] In a preferred manufacturing process embodiment, ziprasidone free base or ziprasidone hydrochloride monohydrate, lactose monohydrate and pregelatinized starch are first sieved or gently milled using common stainless steel sieves or mechanical mills in order to ensure that all components are de-lumped. The mixture is then blended for 30 minutes to ensure good homogeneity, for example using a tumbling blender such as a V-blender or a bin blender. Following blending, magnesium stearate (0.75% w/w) is added and blending is continued for five more minutes. The blended mixture is then added into the hopper of a roller compactor, then compacted and milled to form a granulation. The granulation is then further blended as described above for 10 minutes. Following blending additional lubricant (magnesium stearate, 0.5% w/w) is added and blending continued for an additional five minutes. The mixture can then be sampled if desired prior to, for example, encapsulating conventionally using, for example, an H&K or Bosch encapsulation machine.

[0023] Tablets can be made by conventional methodology and employing conventional equipment.

[0024] The amount of ziprasidone free base or ziprasidone hydrochloride contained in a tablet, capsule, or other dosage form containing a composition of this invention will usually be between 5 and 100 mg, usually administered orally twice a day, although amounts outside this range and different frequencies of administration are feasible for use in therapy as well. As previously mentioned, such dosage forms are useful, *inter alia*, in the treatment of psychotic disorders, for example of the schizophrenic type, as disclosed in U.S. 4,831,031.

[0025] As noted, average particle size can be determined by Malvern light scattering, a laser light scattering technique. In the examples below, the particle size for ziprasidone HCl monohydrate drug substance was measured using a Malvern Mastersizer Model MS1 particle size analyzer (Malvern Instruments Inc., 10 Southville Rd., Southborough MA 01772) with a Small Volume Recirculating unit attached. A 300RF mm lens and a beam length of 2.4 mm was used. A recirculating speed set to 11 o'clock was used to ensure that the sample remained suspended. Samples for analysis were prepared by adding a weighed amount of ziprasidone hydrochloride (500 $\pm$ 10mg) to a 16 mL glass vial. To this vial was added 10 mL of suspending media, specifically a previously prepared mixture of hexanes (ACS reagent grade) containing 1% Span 85. The ziprasidone hydrochloride was suspended by shaking well for approximately 5 seconds. 60 second sonication can be implemented to effectively break agglomerates and help suspend particles, if necessary. Prior to analysis of the sample, a background count was achieved by filling the measurement cell with 100 mL of the suspending media. For sample analysis, a disposable Pasteur pipette was used to first withdraw and empty portions of the suspension several times to ensure representative sampling of the sample vial contents. Then the pipette was filled and a few drops of the vial contents were added to the suspending medium in the measurement cell until an obscuration value of roughly 20% was obtained. This sampling procedure was performed while continuously shaking the vial to avoid settling of the suspension during sampling. Volume distributions were obtained and, for characterization, the values for D_{10} , D_{50} , D_{90} and Volume Mean Diameter ($VMD=D[4,3]$) were specifically listed (NOTE: Mean particle size values mentioned herein refer to measured VMD values). Upon measurement completion, the sample cell was emptied and cleaned, refilled with suspending medium, and the sampling procedure repeated for a total of three measurements.

[0026] A dosage form can be tested to assess its dissolution profile by dissolution testing it in a USP-2 apparatus. As previously described, the apparatus is implemented to contain 900 ml of 0.05 M NaH_2PO_4 buffer, pH 7.5, containing 2% (w/w) sodium dodecyl sulfate. 1% pancreatin may be added if the dosage form being tested is a capsule, as previously noted. The pH can be adjusted as appropriate using, for example, 5N NaOH or concentrated phosphoric acid. The USP-2 apparatus is equipped with paddles stirring at 75 rpm. The dosage form (e.g., tablet or capsule) is added directly to the aqueous dissolution medium. If the dosage form is a capsule, it is inserted into a plastic clip (of the type available commercially as a Vankel, Part No. T-1045-8) to maintain the capsule at the bottom of the vessel during initial dissolution. The dissolution medium is typically maintained at 37 $^{\circ}\text{C}$ during the test. A dosage form is within the scope of the invention if at least 70% of the ziprasidone hydrochloride, preferably 75%, dissolves in the phosphate solution within 45 minutes.

[0027] The amount of dissolved ziprasidone can be determined conventionally by HPLC. As an example of an HPLC

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

2020
Bogotá, D.C.,

Abogado
CARLOS R. OLARTE
Apoderado

ASUNTO

Radicación 06-18322
Trámite 011
Evento 379
Actuación 430
Oficio 873
Folios 361

Patente de Invención

☒

Patente de Modelo de Utilidad

☐

Vía Nacional

☐

Vía PCT (fase nacional)

☒

Cap. I

☐

Cap. II

☒

No. Sol. Internacional

PCT/US2004/028304

Fecha de Presentación Internal.

2004/08/31

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

1. Documentos estudiados

Descripción: Folios: 101 a 289

Reivindicaciones: Folios 285 a 296

Prioridad: Fecha: 2003/09/02, país: US y número: 60/499.484

2. Objeto de la invención

- Título de la solicitud: Formas de dosificación de liberación sostenida de ziprasidona y número de folio: 1

El problema planteado en esta solicitud es la necesidad de formas de dosificación oral sólida de liberación sostenida para el tratamiento de un trastorno psicótico para obtener niveles del medicamento en sangre por mas tiempo.

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Para solucionar este problema técnico la solicitud en estudio proporciona una forma de dosificación oral de liberación sostenida que comprende ziprasidona.

Clasificación Internacional de Patentes (IPC.): A61K 09/20

3. De la solicitud de Patente

Reivindicaciones (*artículo 30 D 486*)

Una vez revisado el capítulo reivindicatorio esta dependencia encuentra:

- Reivindicaciones 1 – 2, 4 – 26, 28 – 29, 42 - : Se está caracterizando una forma de dosificación por su C_{min} en sangre, $C_{máx}$, en sangre, porcentaje en peso de liberación, relación de estado estable entre la C_{min} y $C_{máx}$, biodisponibilidad relativa, diámetro de partícula promedio y solubilidad, lo cual es inaceptable ya que son los resultados a esperar o las ventajas de la misma no las características esenciales de la forma de dosificación que se pretende reivindicar.

4. Excepción a la patentabilidad (*artículo 20 D486 literal a)-d*)

Reivindicaciones 46 -50: Se refiere a un método para tratamiento de un paciente por lo tanto están exceptuadas de patentabilidad según la legislación vigente.

5. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud prioritaria 2003/09/02

Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud encontrándose los siguientes documentos más relevantes:

Nº	Documento	Título	Fecha de publicación*
D ₁	US 6046177	SULFOALKYL ETHER CYCLODEXTRIN BASED CONTROLLED RELEASE SOLID PHARMACEUTICAL FORMULATIONS	2000/04/4
D ₂	EP 0965343	ZIPRASIDONE FORMULATIONS	1999/12/22

6. Análisis de patentabilidad (*artículo 14 D486*)

Nivel inventivo (*artículo 18 D486*)

La presente Solicitud de Patente reivindica:

EXP 2006 18322

Reivindicación 1: Una forma de dosificación oral de liberación sostenida que comprende:

- a) Ziprasidona
- b) Un medio de liberación sostenida para liberar una parte de dicha ziprasidona

Reivindicación 3: Una forma de dosificación oral de liberación sostenida que comprende:

- c) Ziprasidona
- d) Un medio de liberación sostenida para liberar una parte de dicha ziprasidona, en donde dicho medio es una parte de ziprasidona cristalina y ziprasidona combinada con una ciclodextrina.

Dicha forma de dosificación oral está afectada por los siguientes documentos más cercanos del Estado de la Técnica:

D₁ que enseña formulaciones farmacéuticas de liberación controlada tales como liberación rápida, controlada, retardada, temporizada, pulsátil, sostenida (ver abstract folio 302, 303) basadas en ciclodextrina sulfoalquil eter las cuales consisten en un núcleo que comprende una mezcla física de uno o más derivados de ciclodextrina sulfoalquil eter, opcionalmente un modificador de la rata de liberación y un agente terapéutico antipsicótico (folio 307). El derivado de ciclodextrina sulfoalquil eter es utilizado para modificar la biodisponibilidad y la rata de bioabsorción de los agentes terapéuticos.

D₂ que enseña formulaciones con ziprasidona cristalina base o ziprasidona cristalina cloruro con tamaño de partícula menor a 85 µm en un vehículo aceptable y sustancialmente bioequivalente, puede ser usada para tratar psicosis tal como esquizofrenia.

La única **diferencia con D₁** es que esta solicitud **menciona explícitamente la ziprasidona** pero esta diferencia no parece conceder un efecto técnico inesperado.

El **efecto técnico** logrado por esta diferencia es que la formulación de ziprasidona es de liberación sostenida.

El Problema Técnico Objetivo se puede definir en como lograr **formulaciones de ziprasidona de liberación sostenida alternativas a las previamente conocidas**.

Por consiguiente resultaría obvio el diseño de este tipo de formulaciones para un experto en la materia que conozca el estado de la técnica ya que D₂ sugería previamente las formulaciones con ziprasidona cristalina cloruro o base para tratar las psicosis por lo tanto haría una combinación de éstos documentos llegando de tal manera a la propuesta de la presente solicitud.

En conclusión, no se considera que la presente solicitud merezca reconocimiento de nivel inventivo.

6. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D ₁	US 6046177	1, 3	NIVEL INVENTIVO
D ₂	EP 0965343	1, 3	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 60 días contados a partir de la fecha de 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 Única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Directora de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha
29 ENE. 2010.

CONCEPTO TÉCNICO No. 06	EXAMINADOR TÉCNICO Código No. 202087
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