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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

S.

D.

REF: Expediente 11-086-183

TÍTULO SOLICITADO: COMPOSICIÓN DE LIBERACIÓN PULSATIL DE
SILDENAFIL Y PROCESO PARA PREPARARLA.

PUBLICACIÓN: Gaceta 639 de 29 de febrero de 2012, N° de
publicación 108.

SOLICITANTE: SIEGFRIED RHEIN S.A. DE C.V.

APODERADO: J. IAN RAISBECK.

TRÁMITE: SUSTENTACIÓN DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUÍMICAS S.A.**, dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2º de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar y complementar la oposición presentada el 30 de mayo de 2012, en los siguientes términos:

I. **RATIFICACIÓN.**

Comedidamente me permito insistir en los argumentos planteados en la oposición respectiva, los cuales, como se dijo en su momento, demuestran que la solicitud de la referencia incumple los requisitos de patentabilidad establecidos por los artículos 14 y 18 de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario.

- En primer lugar, y ante la reivindicación textual de concentraciones (dosis) de sildenafil, específicamente en la reivindicación 1, es importante indicar que esto contraviene lo dispuesto en la Decisión 486 de 2000 que literalmente refiere a que "No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para

el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales.” Dicha mención de dosificaciones tiene el mismo efecto que las reivindicaciones sobre métodos de tratamiento médico explícitos, dado que la concentración, en este caso directamente referido a la dosificación de la formulación farmacéutica, no pertenece a la categoría de producto o proceso, sino que hace referencia la forma en la que un producto se utiliza terapéuticamente, y por lo tanto no hace parte de las actividades industriales sino de las actividades médicas.

- La dosificación o los cambios en la dosificación dentro de un producto farmacéutico no tiene naturaleza inventiva, ya que no cumplen con el estándar de aplicabilidad industrial, dado que dichas modificaciones solo tienen efectos en el organismo (verificables a nivel clínico) y no efectos técnicos.
- No tiene naturaleza inventiva la reivindicación 10, referida a las características de disolución, puesto que no se debe determinar la novedad de dichos valores de disolución exclusivamente sobre la base de la documentación correspondiente al arte previo (si dichos perfiles de disolución o velocidades de disolución se conseguían anteriormente), sino que se debe también tener en cuenta que conseguir dichos perfiles de disolución hace parte de los conocimientos propios de una persona versada en la formulación de productos farmacéuticos. Es así como dicha persona versada en la formulación, debe reconocer que los perfiles de disolución se consiguen en relación a los ensayos rutinarios de formulación y preformulación que aplican para la elaboración de cualquier medicamento y que dichos perfiles de disolución están relacionados a la evaluación biofarmacéutica y no a las actividades industriales.
- Otra evidente prueba de la carencia absoluta de nivel inventivo de la solicitud colombiana en trámite, son los excipientes mencionados en las reivindicaciones 4 a 9 así como el papel que juegan dentro de la formulación, dado que no representan ningún efecto sorprendente, sino que por el contrario resultan ser excipientes ampliamente utilizados en el estado de la técnica para los mismos propósitos que se utilizan en la formulación reivindicada por la solicitud en cuestión.
- La croscarmelosa sódica, el almidón glicolato de sodio y la crospovidona, resultan ser ampliamente reconocidos como agentes desintegrantes o superdesintegrantes, .De la misma manera los excipientes mencionados en las reivindicaciones 5 y 8 son reconocidos por su solubilidad dependiente del pH, ; así como los copolímeros de amonio metacrilato, mencionados en la

reivindicación 6, también son ampliamente reconocidos y comercializados por su característica independencia del pH; y en general, la selección de un excipiente por sus características fisicoquímicas, por parte de una persona versada en la formulación de productos farmacéuticos, no puede comprender nivel inventivo alguno, más cuando dichas características fisicoquímicas y su utilidad dentro de la formulación se obtienen a través de los rutinarios ensayos de preformulación y formulación.

- Carecen de nivel inventivo los procedimientos descritos en las reivindicaciones 11 a 15, puesto que comprenden procedimientos convencionales para la obtención de formulaciones sólidas a través de un lecho fluidizado o por granulación y compresión (en el caso de la fracción de liberación controlada).
- Teniendo en cuenta que la solicitud se refiere a un proceso en donde a un soporte sólido inerte se le adicionan los principios activos con ayuda de una solución aglutinante, se hace evidente que dicho procedimiento se relaciona estrechamente a lo que en el estado de la técnica se reconoce como un proceso de granulación “por pulverización” o “spray-dried granulation”. La obtención de gránulos a través de este tipo de procedimiento, es una estrategia que cualquier persona versada en la formulación de productos farmacéuticos debe reconocer, y así mismo es una estrategia tecnológica que ha utilizado con bastante anterioridad en la industria farmacéutica .
- Las técnicas de formulación y el conjunto de compuestos que se pueden utilizar para desarrollar productos farmacéuticos viables en sus diferentes formas, son elementos que bien debe conocer una persona medianamente capacitada en la formulación de productos farmacéuticos. No resulta de ninguna manera inventivo el hecho de escoger una técnica de granulación reconocida en el estado de la técnica (entre las diversas técnicas de granulación existentes) y aplicarla para obtener una formulación farmacéutica, como ocurre en el caso de la solicitud colombiana en cuestión.
- En los gránulos obtenidos, que posteriormente son recubiertos a través de un “peliculado”, no representa nivel inventivo alguno aplicar las ya reconocidas técnicas para recubrimiento de formulaciones sólidas .
- La utilización de dichos soportes o “seeds” también es una estrategia tecnológica ampliamente reconocida en el estado de la técnica, es especial para obtener dispersiones sólidas, en donde dichos soportes o “seeds” son el núcleo al cual se adhieren soluciones compuestas por principios activos y otros excipientes, para formar dichas dispersiones sólidas.

- La publicación internacional WO 2008/027993 publicada el 06 de marzo de 2008 revela procedimientos para elaborar a partir de soportes sólidos o núcleos, a los cuales se les adiciona el principio activo junto con excipientes farmacéuticamente aceptables y que finalmente pueden ser recubiertos. Si bien es cierto que en esta anterioridad no se menciona sildenafil, también es cierto que lo anterior deja en evidencia la versatilidad de dicha técnica de granulación y la carencia de nivel inventivo que tiene el involucrar cualquier principio activo a través de esta técnica.
- La solicitud colombiana en trámite carece de nivel inventivo, porque las formulaciones reivindicadas y los procedimientos mediante los cuales se obtienen dichas formulaciones, son pequeñas variaciones resultantes de combinar estrategias tecnológicas ampliamente reconocidas y utilizadas en la industria farmacéutica (granulación por spray-dried, utilización de "seeds" y técnicas de recubrimiento), y cualquier persona medianamente versada en la formulación de productos farmacéuticos podría utilizar la información disponible en el estado de la técnica para obtener sin mayor inconveniente las características técnicas de las formulaciones a través de los procedimientos expuestos en el capítulo reivindicatorio de la solicitud colombiana en cuestión.

II. COMPLEMENTO DE INFORMACIÓN.

Continuando con la demostración de falta de nivel inventivo, y teniendo en cuenta que todas las estrategias tecnológicas utilizadas para la elaboración de las formulaciones farmacéuticas reivindicadas por la solicitud colombiana en trámite son convencionales y ampliamente conocidas por cualquier persona versada en la formulación de productos farmacéuticos, podemos mencionar otros documentos que refuerzan la evidencia al respecto, aportada con anterioridad, veamos:

La publicación científica ***"Pulsatile drug delivery to ileo-colonic segments by structured incorporation of disintegrants in pH-responsive polymer coatings."*** Revela: *Conventional pH-responsive coatings used for oral drug delivery to the lower parts of the gastro-intestinal tract often show a poor performance. A new system for site-specific pulsatile delivery in the ileo-colonic regions is described. The system is based on the non-percolating incorporation of disintegrants in a coating which consists further of a continuous matrix of pH-responsive polymer (Eudragit S). Extensive in vitro release studies were performed in which coatings with different concentrations and disintegrants were studied and compared to non-disintegrant containing coatings. In vitro data show that the incorporation of swelling agents in an Eudragit S-coating still allows delayed release in the simulated terminal ileum. The pulse time and the robustness could be improved compared to conventional Eudragit S-coatings. The*

augmented pH-responsiveness of the new coating was related to the swelling index of the applied disintegrant. Based on the in vitro data comparing different swelling agents, Ac-di-sol appears to be the best performing swelling agent. A proof-of-concept study in human subjects was performed to investigate the performance of the new system in vivo. Coated capsules containing the stable isotope (13)C(6)-glucose as the test compound were administered and the occurrence of (13)CO(2) in the breath of the subjects was measured. It could be shown that the coating is able to resist the environmental conditions in the stomach and duodenum and delay release until deeper parts of the intestines are reached. Furthermore, the capsule is able to maintain a pulsatile release profile. It is concluded that the structured incorporation of swelling agents in pH-responsive polymers improves the delayed, pulsatile release kinetics of coated capsules. In a proof-of-concept in vivo study it was shown that the newly developed coating enables pulsatile delivery of the content to the lower parts of the intestines.

Por su parte la patente Americana US 2008/0200508 publicada el 21 de agosto de 2008 revela:

[0042] A pulsatile release dosage form is one that mimics a multiple dosing profile without repeated dosing and allows at least a twofold reduction in dosing frequency as compared to that drug presented as a conventional dosage form (e.g. as a solution or prompt drug-releasing, conventional solid dosage form). A pulsatile release profile is characterized by a time period of no release (lag time) followed by rapid drug release.

(...)

acetate phthalate, acrylic acid polymers and copolymers, and methacrylic resins that are commercially available under the trade name Lucragin® (Roth Pharma, Westerstadt, Germany), Zein, shellac, and polysaccharides.

(...)

cesses. Beads containing the active agent may also be prepared by any one of a number of conventional techniques, typically starting from a fluid dispersion. For example, a

(...)

7.2 Pulsatile Release Dosage Form

[0084] Pulsatile release of active ingredients may be achieved by coating the active ingredients with polymers chosen to release the second and any further pulses at specific time points. This embodiment of the invention allows for the administration of a dosage form which provides a first release (pulse) of active ingredient, followed by a desired delay before a second pulse of active ingredient. The polymers are chosen in such a way as to deliver the secondary pulses at chosen time intervals. The time intervals may be chosen based on the pharmacokinetics of the desired plasma level of the active ingredient, and/or may be chosen based on the release site of the second pulse.

(...)

[0088] In one aspect, a dosage form comprising a closed capsule housing at least two drug-containing dosage units is used. Each dosage unit comprises two or more compressed tablets or may be comprised of a plurality of beads, granules or particles, providing that each dosage unit has a different drug release profile. The immediate release dosage unit

(...)

[0097] Preferred polymers for coating the embodiments of the invention include Eudragit L 100, Eudragit S 100, and their mixtures, which can have a 1:1 to 100:0 Eudragit S:100 ratio, i.e., in approximately 95:5 to approximately 75:25 (w/w), more preferably 90:10 to 80:20 (w/w) in order to achieve a second pulse at about 2-8 hours. A combination of

(...)

®. In further preferred embodiments, the acrylic polymer comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the Tradename Eudragit®. RL 300 and Eudragit®. RS 300, respectively. Eudragit®. RL 300 and Eudragit®. RS 300 are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit®. RL 300 and 1:40 in Eudragit®. RS 300. The mean molecular weight is about 50,000. Eudragit®. RL and Eudragit®. RS 100 are also preferred. The code designator RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit®. RL/RS mixtures are insoluble in water and in digestive fluids. However, multiparticulate systems formed to include the same are swellable and permeable in aqueous solutions and digestive fluids.

(...)

Delayed Release Ondansetron Dosage Form

[0142] In this example, a tablet of the form similar to that shown in FIG. 1 is constructed as follows. A delayed release ondansetron tablet described in the Examples 2, 4-6 is further coated with an ondansetron containing layer. Such a tablet when administered to a patient provides for two pulses of ondansetron at the desired absorption sites. The first pulse is released in the stomach and the second pulse is released in the intestines. The first to second pulse ondansetron ratio is in the range from approximately 5/95 to approximately 95/5 (w/w), preferably from approximately 20/80 to approximately 80/20 (w/w), and the most preferably from approximately 30/70 to approximately 70/30 (w/w). Ondansetron total dose is approximately between 1 and 100 mg. In the preferred embodiment ondansetron total dose is between 1 and 24 mg. Optionally, ondansetron multi-layer tablet is further coated with an enteric polymer.

Si bien los anteriores documentos no revelan explícitamente a sildenafil, si dejan claro la versatilidad de las formas de liberación pulsátiles, así como los métodos y excipientes indispensables para obtenerlas.

Ahora bien, la patente americana US 6964780 publicada el 15 de noviembre de 2005, revela:

The invention provides controlled-release formulations for oral administration containing a cGMP PDE-5 inhibitor. The formulations are useful, inter alia, in the treatment or prevention of sexual dysfunction.

(...)

Controlled-release formulations may be divided into sustained-release and pulsatile-release formulations (also known as delayed-release formulations). In general, such formulations are known to those skilled in the art or are available using conventional methods.

(...)

Pulsatile-release formulations release the active compound after a sustained period of time following administration of the dosage form to the patient. The release may then be in the form of immediate- or sustained-release. This delay may be achieved by releasing the drug at particular points in the gastro-intestinal tract or by releasing drug after a pre-determined time. Pulsed-release formulations may be in the form of tablets or multiparticulates or a combination of both. Particular dosage forms include:

1. osmotic potential triggered release (see U.S. Pat. No. 3,952,741);
2. compression coated two layer tablets (see U.S. Pat. No. 5,464,633);
3. capsules containing an erodible plug (see U.S. Pat. No. 5,474,784);
4. sigmoidal releasing pellets (referred to in U.S. Pat. No. 5,112,621); and

(...)

Como se puede apreciar, en esta anterioridad se revela la posibilidad de la inclusión de inhibidores PDE5 (como sildenafil) en este tipo de formulaciones pulsátiles. En consecuencia y sin más explicaciones, queda demostrada la ausencia de Nivel inventivo de la solicitud en trámite.

Por todo lo anterior, le solicito Señor Superintendente, que analice los argumentos citados tanto en este complemento de información como en el escrito de oposición presentado en su momento, con el rigor y detenimiento habituales y que decrete, además de la negación de la solicitud en comento, el archivo del citado expediente.

III. ANEXOS.

- ❖ Copia de todos los documentos mencionados en el acápite de Complemento de información.

Señor Superintendente,



JOSÉ LUIS REYES VILLAMIZAR

C.C. 79'152.473 de Usaquén

T.P.A. 44.655 del C.S.J.

PubMed

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ELSEVIER
FULL-TEXT ARTICLEJ Control Release. 2008 Dec 8;132(2):91-8. Epub 2008 Aug 23.

Pulsatile drug delivery to ileo-colonic segments by structured incorporation of disintegrants in pH-responsive polymer coatings.

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Abstract

Conventional pH-responsive coatings used for oral drug delivery to the lower parts of the gastrointestinal tract often show a poor performance. A new system for site-specific pulsatile delivery in the ileo-colonic regions is described. The system is based on the non-percolating incorporation of disintegrants in a coating which consists further of a continuous matrix of pH-responsive polymer (Eudragit S). Extensive in vitro release studies were performed in which coatings with different concentrations and disintegrants were studied and compared to non-disintegrant containing coatings. In vitro data show that the incorporation of swelling agents in an Eudragit S-coating still allows delayed release in the simulated terminal ileum. The pulse time and the robustness could be improved compared to conventional Eudragit S-coatings. The augmented pH-responsiveness of the new coating was related to the swelling index of the applied disintegrant. Based on the in vitro data comparing different swelling agents, Ac-di-sol appears to be the best performing swelling agent. A proof-of-concept study in human subjects was performed to investigate the performance of the new system in vivo. Coated capsules containing the stable isotope (13)C(6)-glucose as the test compound were administered and the occurrence of (13)CO(2) in the breath of the subjects was measured. It could be shown that the coating is able to resist the environmental conditions in the stomach and duodenum and delay release until deeper parts of the intestines are reached. Furthermore, the capsule is able to maintain a pulsatile release profile. It is concluded that the structured incorporation of swelling agents in pH-responsive polymers improves the delayed, pulsatile release kinetics of coated capsules. In a proof-of-concept in vivo study it was shown that the newly developed coating enables pulsatile delivery of the content to the lower parts of the intestines.

PMID: 18775755 [PubMed - indexed for MEDLINE]

MeSH Terms, Substances**LinkOut - more resources**



US 20080200508A1

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(19) **United States**

(12) **Patent Application Publication**

Rariy et al.

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(43) **Pub. Date: Aug. 21, 2008**

(54) **PHARMACEUTICAL COMPOSITIONS FOR SLEEP DISORDERS**

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(86) PCT No.: **PCT/US05/46049**

§ 371 (c)(1),
(2), (4) Date: **Jun. 19, 2007**

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A61K 31/4164 (2006.01)
A61P 25/00 (2006.01)
A61P 43/00 (2006.01)

(52) **U.S. Cl.** **514/321; 514/385**

(57) **ABSTRACT**

Pharmaceutical compositions are provided for the pharmacological treatment of breathing disorders and, more specifically, to compositions containing agents having serotonin receptor modulating activity for the alleviation of sleep apnea (central and obstructive) and other sleep-related breathing disorders wherein the active ingredients are released such as to extend effective blood plasma concentrations across the period of sleep.

prematurity, congenital central hypoventilation syndrome, obesity hypoventilation syndrome, central sleep apnea syndrome, Cheyne-Stokes respiration, and snoring.

[0039] A serotonin receptor antagonist can be used in its free base form or as a quaternary ammonium salt form. The quaternization of these serotonin receptor antagonists occurs by conversion of tertiary nitrogen atom into a quaternary ammonium salt with reactive alkyl halides such as, for example, methyl iodide, ethyl iodide, or various benzyl halides. Some quaternary forms of a serotonin antagonist, specifically, methylated zatosetron, has been shown to lack the ability to cross the blood-brain barrier (Gidda et al., *J. Pharmacol. Exp. Ther.* 273:695-701 (1995)), and thus only works on the peripheral nervous system. A serotonin receptor antagonist is defined by the chemical compound itself and one of its pharmaceutically acceptable salts.

1. Definitions

[0040] A “delayed release dosage form” is one that releases a drug (or drugs) at a time other than promptly after administration.

[0041] An “extended release dosage form” is one that allows at least a twofold reduction in dosing frequency as compared to the drug presented as a conventional dosage form (e.g. as a solution or prompt drug-releasing, conventional solid dosage form).

[0042] A “pulsatile release dosage form” is one that mimics a multiple dosing profile without repeated dosing and allows at least a twofold reduction in dosing frequency as compared to that drug presented as a conventional dosage form (e.g. as a solution or prompt drug-releasing, conventional solid dosage form). A pulsatile release profile is characterized by a time period of no release (lag time) followed by rapid drug release.

[0043] A “modified release dosage form” is one for which the drug release characteristics of time, course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms. Delayed release and extended release dosage forms and their combinations are types of modified release dosage forms. The pharmaceutical combination of the invention may have any or all of its constituents in a modified release dosage form. A “modified release pharmaceutical composition” has at least one of its components in modified release dosage form.

[0044] As used herein “active compounds” in addition to their free base and quaternized forms also encompasses pharmaceutically acceptable, pharmacologically active derivatives of active compounds including individual enantiomers and their pharmaceutically acceptable salts, mixtures of enantiomers and their pharmaceutically acceptable salts, and active metabolites of active compounds and their pharmaceutically acceptable salts, unless otherwise noted. It is understood that in some cases dosages of enantiomers, derivatives, and metabolites may need to be adjusted based on relative activity of the racemic mixture of active compound.

[0045] As used herein, “pharmaceutically acceptable salts” refer to derivatives of the disclosed compounds wherein the parent 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. 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 acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, and isethionic.

[0046] The pharmaceutically acceptable salts of the compounds can be synthesized from the parent compound, which contains a basic or acidic moiety, by conventional chemical methods.

[0047] Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 20th ed., Lippincott Williams & Wilkins, Baltimore, Md., 2000, p. 704.

[0048] The phrase “pharmaceutically acceptable” is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problems or complications commensurate with a reasonable benefit/risk ratio.

[0049] As used herein, the term “stereoisomers” refers to compounds made up of the same atoms bonded by the same bonds but having different spatial structures which are not interchangeable. The three-dimensional structures are called configurations. As used herein, the term “enantiomers” refers to two stereoisomers whose molecules are nonsuperimposable mirror images of one another. As used herein, the term “optical isomer” is equivalent to the term “enantiomer”. The terms “racemate”, “racemic mixture” or “racemic modification” refer to a mixture of equal parts of enantiomers. The term “chiral center” refers to a carbon atom to which four different groups are attached. The term “enantiomeric enrichment” as used herein refers to the increase in the amount of one enantiomer as compared to the other. Enantiomeric enrichment is readily determined by one of ordinary skill in the art using standard techniques and procedures, such as gas or high performance liquid chromatography with a chiral column. Choice of the appropriate chiral column, eluent and conditions necessary to effect separation of the enantiomeric pair is well within the knowledge

of one of ordinary skill in the art using standard techniques well known in the art, such as those described by J. Jacques, et al., “Enantiomers, Racemates, and Resolutions”, John Wiley and Sons, Inc., 1981. Examples of resolutions include recrystallization of diastereomeric salts/derivatives or preparative chiral chromatography.

2. Serotonin Receptor Antagonists Exemplary serotonin receptor antagonists include, but are not limited to, the free base form or a quaternized form of zatosetron, tropisetron, dolasetron, hydrodolasetron, mescaline, oxetorone, homochlorcyclizine, perlapine, ondansetron, ketanserin, loxapine, olanzapine, chlorpromazine, haloperidol, (+) ondansetron, cisapride, norcisapride, (+) cisapride, (–) cisapride, (+) nor-

[0081] The delayed release dosage units can be prepared, for example, by coating a drug or a drug-containing composition with a selected coating material. The drug-containing composition may be, e.g., a tablet for incorporation into a capsule, a tablet for use as an inner core in a "coated core" dosage form, or a plurality of drug-containing beads, particles or granules, for incorporation into either a tablet or capsule. Preferred coating materials include bioerodible, gradually hydrolyzable, gradually water-soluble, and/or enzymatically degradable polymers, and may be conventional "enteric" polymers. Enteric polymers, as will be appreciated by those skilled in the art, become soluble in the higher pH environment of the lower gastrointestinal tract or slowly erode as the dosage form passes through the gastrointestinal tract, while enzymatically degradable polymers are degraded by bacterial enzymes present in the lower gastrointestinal tract, particularly in the colon. Suitable coating materials for effecting delayed release include, but are not limited to, cellulosic polymers such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxymethyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl methyl cellulose acetate succinate, hydroxypropylmethyl cellulose phthalate, methylcellulose, ethyl cellulose, cellulose acetate, cellulose acetate phthalate, cellulose acetate trimellitate and carboxymethylcellulose sodium; acrylic acid polymers and copolymers, preferably formed from acrylic acid, methacrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate and/or ethyl methacrylate, and other methacrylic resins that are commercially available under the tradename Eudragit®. (Rohm Pharma; Westerstadt, Germany), including Eudragit® L30D-55 and L100-55 (soluble at pH 5.5 and above), Eudragit® L-100 (soluble at pH 6.0 and above), Eudragit® S (soluble at pH 7.0 and above, as a result of a higher degree of esterification), and Eudragits NE, RL and RS (water-insoluble polymers having different degrees of permeability and expandability); vinyl polymers and copolymers such as polyvinyl pyrrolidone, vinyl acetate, vinylacetate phthalate, vinylacetate crotonic acid copolymer, and ethylene-vinyl acetate copolymer; enzymatically degradable polymers such as azo polymers, pectin, chitosan, amylose and guar gum; zein and shellac. Combinations of different coating materials may also be used. Multi-layer coatings using different polymers may also be applied. Polymer blends can be used to achieve the desired delay in drug release.

[0082] The preferred coating weights for particular coating materials may be readily determined by those skilled in the art by evaluating individual release profiles for tablets, beads and granules prepared with different quantities of various coating materials. It is the combination of materials, method and form of application that produce the desired release characteristics, which one can determine only from the clinical studies.

[0083] The coating composition may include conventional additives, such as plasticizers, pigments, colorants, stabilizing agents, glidants, etc. A plasticizer is normally present to reduce the fragility of the coating, and will generally represent about 10 wt. % to 50 wt. % relative to the dry weight of the polymer. Examples of typical plasticizers include polyethylene glycol, propylene glycol, triacetin, dimethyl phthalate, diethyl phthalate, dibutyl phthalate, dibutyl sebacate, triethyl citrate, tributyl citrate, triethyl acetyl citrate, castor oil and acetylated monoglycerides. A stabilizing agent is preferably used to stabilize particles in the dispersion. Typical stabilizing agents are nonionic emulsifiers such as sorbitan esters, polysorbates and polyvinylpyrrolidone. Glidants are recommended to reduce sticking effects during film forma-

tion and drying, and will generally represent approximately 25 wt. % to 100 wt. % of the polymer weight in the coating solution. One effective glidant is talc. Other glidants such as magnesium stearate and glycerol monostearates may also be used. Pigments such as titanium dioxide may also be used. Small quantities of an anti-foaming agent, such as a silicone (e.g., simethicone), may also be added to the coating composition.

7.2 Pulsatile Release Dosage Forms

[0084] Pulsatile release of active ingredients may be achieved by coating the active ingredients with polymers chosen to release the second and any further pulses at specific time points. This embodiment of the invention allows for the administration of a dosage form which provides a first release (pulse) of active ingredient, followed by a desired delay before a second pulse of active ingredient. The polymers are chosen in such a way as to deliver the secondary pulses at chosen time intervals. The time intervals may be chosen based on the pharmacokinetics of the desired plasma level of the active ingredient, and/or may be chosen based on the release site of the second pulse.

[0085] The composition provides an initial rapid release of a therapeutically effective dose of ondansetron followed by so-called "delayed release" pulses such that a second and optional third delayed dose of the active agent is released from the dosage form. By incorporating both an immediate release dosage unit and one or more delayed release dosage units of the active agent, the dosage form mimics a multiple dosing profile without repeated dosing, i.e., with only a single administration. For example, the dosage form provides a twice daily dosing profile when the dosage form contains both an immediate release dosage unit and a single delayed release dosage unit. Alternatively, the dosage form provides a three times daily dosing profile when the dosage form contains an immediate release dosage unit and two delayed release dosage units. The formulation provides a pulsatile release dosage form, wherein the dosage form comprises an immediate release dosage unit, a delayed release dosage unit and an optional second delayed release dosage unit. The immediate release dosage unit comprises a first dose of an active agent that is released substantially immediately following oral administration of the dosage form to a patient. The delayed release dosage unit comprises a second dose of the active agent and a means for delaying release of the second dose until approximately 3 hours to less than 14 hours following oral administration of the dosage form. The second delayed release dosage unit, when present, comprises a third dose of the active agent and a means for delaying release of the third dose until at least 5 hours to approximately 18 hours following oral administration of the dosage form.

[0086] Each dosage form contains a therapeutically effective amount of active agent. For dosage forms that mimic the twice daily dosing profile, approximately 30 wt. % to 80 wt. %, preferably 40 wt. % to 70 wt. %, of the total amount of active agent in the dosage form is released in the initial pulse, and, correspondingly approximately 70 wt. % to 20 wt. %, preferably 60 wt. % to 30 wt. %, of the total amount of active agent in the dosage form is released in the second pulse. For dosage forms mimicking the twice daily dosing profile, the second pulse is preferably released approximately 3 hours to less than 14 hours, and most preferably approximately 5 hours to 12 hours, following administration.

[0087] For dosage forms mimicking the three times daily dosing profile, approximately 25 wt. % to 40 wt. % of the total amount of active agent in the dosage form is released in the initial pulse, and approximately 25 wt. % to 40 wt. % of the total amount of active agent in the dosage form is released in each of the second and third pulses. For dosage forms that mimic the three times daily dosing profile, release of the second pulse preferably takes place approximately 3 hours to 10 hours, and most preferably approximately 4 to 9 hours, following oral administration. Release of the third pulse occurs about 2 hours to about 8 hours following the second pulse, and is typically about 5 hours to approximately 18 hours following oral administration.

[0088] In one aspect, a dosage form comprising a closed capsule housing at least two drug-containing dosage units is used. Each dosage unit comprises two or more compressed tablets, or may be comprised of a plurality of beads, granules or particles, providing that each dosage unit has a different drug release profile. The immediate release dosage unit releases drug substantially immediately following oral administration to provide an initial dose. The delayed release dosage unit releases drug approximately 3 hours to 14 hours following oral administration to provide a second dose. Finally, an optional second delayed release dosage unit releases drug about 2 hours to 8 hours following the release of the second dose, and is typically 5 hours to 18 hours following oral administration.

[0089] Another dosage form comprises a compressed tablet having a drug-containing immediate release dosage unit, a delayed release dosage unit and an optional second delayed release dosage unit. In this dosage form, the immediate release dosage unit comprises a plurality of beads, granules or particles that release drug substantially immediately following oral administration to provide an initial dose. The delayed release dosage unit comprises a plurality of coated beads or granules, which release drug approximately 3 hours to 14 hours following oral administration to provide a second dose.

[0090] An optional second delayed release dosage unit comprises coated beads or granules that release drug about 2 to 8 hours following administration of the initial delayed release dose, typically 5 to 18 hours following oral administration. The beads or granules in the delayed release dosage unit(s) are coated with a bioerodible polymeric material. This coating prevents the drug from being released until the appropriate time, i.e., approximately 3 hours to less than 14 hours following oral administration for the delayed release dosage unit and at least 5 hours to approximately 18 hours following oral administration for the optional second delayed release dosage unit. In this dosage form the components may be admixed in the tablet or may be layered to form a laminated tablet.

[0091] Another dosage form is a tablet having a drug-containing immediate release dosage unit, a delayed release dosage unit, and an optional second delayed release dosage unit, wherein the immediate release dosage unit comprises an outer layer that releases the drug substantially immediately following oral administration. The arrangement of the remaining delayed release dosage(s), however, depends upon whether the dosage form is designed to mimic twice daily dosing or three times daily dosing.

[0092] In the dosage form mimicking twice daily dosing, the delayed release dosage unit comprises an inner core that is coated with a bioerodible polymeric material. The coating is applied such that release of the drug occurs approximately 3

hours to less than 14 hours following oral administration. In this form, the outer layer completely surrounds the inner core. In the dosage form mimicking three times a day dosing, the (first) delayed release dose comprises an internal layer that releases drug approximately 3 hours to less than 14 hours following oral administration. This internal layer is surrounded by the outer layer. The second delayed release dosage unit generally comprises an inner core that releases the drug at least 5 hours to approximately 18 hours following oral administration. Thus, the layers of this tablet (starting from the external surface) comprise an outer layer, an internal layer and an inner core. The inner core comprises delayed release beads or granules. Furthermore, the internal layer comprises the drug coated with a bioerodible polymeric material. Alternatively, in this particular dosage form mimicking three times a day dosing, both the delayed release dosage unit and second delayed release dosage units are surrounded by an inner layer. This inner layer is free of active agent. Thus, the layers of this tablet (starting from the external surface) comprise an outer layer, inner layer and an admixture of the delayed release dosage units. The first delayed release pulse occurs once the inner layer is substantially eroded thereby releasing the admixture of the delayed release dosage units. The dose corresponding to the (first) delayed release dosage unit is released immediately since the inner layer has prevented access to this dose for the appropriate time, e.g., from approximately 3 hours to 10 hours. The second delayed release dose, however, is formulated to effectively delay release for at least 5 hours to approximately 18 hours following oral administration.

[0093] Alternatively, each dosage unit in the capsule may comprise a plurality of drug-containing beads, granules or particles. As is known in the art, drug-containing "beads" refer to beads made with drug and one or more excipients or polymers. Drug-containing beads can be produced by applying drug to an inert support, e.g., inert sugar beads coated with drug or by creating a "core" comprising both drug and one or more excipients. As is also known, drug-containing "granules" and "particles" comprise drug particles that may or may not include one or more additional excipients or polymers. In contrast to drug-containing beads, granules and particles do not contain an inert support. Granules generally comprise drug particles and require further processing. Generally, particles are smaller than granules, and are not further processed. Although beads, granules and particles may be formulated to provide immediate release, beads and granules are generally employed to provide delayed release.

[0094] In still another embodiment, a dosage form comprises a coated core-type delivery system wherein the outer layer is comprised of an immediate release dosage unit, such that active agent therein is immediately release following oral administration, an intermediate layer thereunder surrounds a core, and the core is comprised of immediate release beads or granules and delayed release beads or granules, such that the second dose is provided by the immediate release beads or granules and the third dose is provided by the delayed release beads or granules.

[0095] For the compositions of the present invention, where the second pulse is intended to be delivered, a delay of 3-8 hours is desired between the time of administration and the release of the second pulse. Appropriate polymers are chosen which release the second pulse at 3-8 hours. In this way, a series of pulses may be achieved over specific time intervals or specific release sites. The aforementioned polymers can be

used to construct delayed release portion(s) of pulsatile release composition. Polymer blends can be used to achieve the desired release profile.

[0096] Thus, in one embodiment, a serotonin receptor antagonist is present in a tablet form in both an outer portion of the tablet (to achieve the first release pulse) and an inner core (to achieve a second release pulse). A preferred embodiment comprises ondansetron in the core, coated with polymers, and further coated with a composition comprising ondansetron.

[0097] Preferred polymers for coating all embodiments of the invention include Eudragit L-100, Eudragit S-100, and their mixtures wherein Eudragit L-100 to Eudragit S-100 ratio is from approximately 95/5 to approximately 75/25(w/w), more preferably 90/10 to 80/20(w/w), in order to achieve a second pulse at about 3-8 hours. A combination of ondansetron tablet and fluoxetine tablet in a hard gelatin capsule, wherein fluoxetine tablet is optionally coated with polymers, is depicted in FIG. 4. It is understood that by varying polymer composition used for tablet coating, fluoxetine release can occur either simultaneously with the release of second pulse of ondansetron or at a different time.

[0098] Another preferred embodiment adds a dose of fluoxetine to the inner core, such that upon administration of the tablet to a patient, a first pulse of ondansetron is followed by a pulse of ondansetron and fluoxetine 3-8 hours later. A tablet dosage form of this embodiment is depicted in FIG. 1. This embodiment releases ondansetron upon administration, followed 3-8 hours later by a release of fluoxetine and a second pulse of ondansetron. Such a form allows for the pulsatile release of ondansetron as well as the time delayed release of fluoxetine, thereby minimizing sleep disturbances related to fluoxetine administration shortly before bedtime.

[0099] Additional examples of such pulsatile release dosage forms are readily constructed based on these principles.

7.3 Extended Release Dosage Forms

[0100] The extended release formulations are generally prepared as diffusion or osmotic systems, for example, as described in "Remington—The science and practice of pharmacy" (20th ed., Lippincott Williams & Wilkins, Baltimore, Md., 2000). A diffusion system typically consists of two types of devices, a reservoir and a matrix, and is well known and described in the art. The matrix devices are generally prepared by compressing the drug with a slowly dissolving polymer carrier into a tablet form. The three major types of materials used in the preparation of matrix devices are insoluble plastics, hydrophilic polymers, and fatty compounds. Plastic matrices include, but not limited to, methyl acrylate-methyl methacrylate, polyvinyl chloride, and polyethylene. Hydrophilic polymers include, but are not limited to, cellulosic polymers such as methyl and ethyl cellulose hydroxyalkyl-celluloses such as hydroxypropylcellulose, hydroxypropyl-methylcellulose, sodium carboxymethylcellulose, and carbopol 934, polyethylene oxides and mixtures thereof. Fatty compounds include, but are not limited to, various waxes such as carnauba wax and glyceryl tristearate and wax-type substances including hydrogenated castor oil or hydrogenated vegetable oil, or mixtures thereof.

[0101] In certain preferred embodiments, the plastic material is a pharmaceutically acceptable acrylic polymer, including but not limited to, acrylic acid and methacrylic acid copolymers, methyl methacrylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl meth-

acrylate, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer poly(methyl methacrylate), poly(methacrylic acid)(anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.

[0102] In certain preferred embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well known in the art, and are described in NF XVII as fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups.

[0103] In one preferred embodiment, the acrylic polymer is an acrylic resin lacquer such as that which is commercially available from Rohm Pharma under the Tradename Eudragit.®. In further preferred embodiments, the acrylic polymer comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the Tradenames Eudragit.®. RL30D and Eudragit.®. RS30D, respectively. Eudragit.®. RL30D and Eudragit.®. RS30D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit.®. RL30D and 1:40 in Eudragit.®. RS30D. The mean molecular weight is about 150,000. Eudragit.®. and Eudragit.®. L-100 are also preferred. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit.®. RL/RS mixtures are insoluble in water and in digestive fluids. However, multiparticulate systems formed to include the same are swellable and permeable in aqueous solutions and digestive fluids.

[0104] The polymers described above such as Eudragit.®. RL/RS may be mixed together in any desired ratio in order to ultimately obtain a sustained-release formulation having a desirable dissolution profile. Desirable sustained-release multiparticulate systems may be obtained, for instance, from 100% Eudragit.®. RL, 50% Eudragit.®. RL and 50% Eudragit.®. RS, and 10% Eudragit.®. RL:Eudragit.®. 90% RS. One skilled in the art will recognize that other acrylic polymers may also be used, such as, for example, Eudragit.®. L.

[0105] Alternatively, extended release formulations can be prepared using osmotic systems or by applying a semi-permeable coating to the dosage form. In the latter case, the desired drug release profile can be achieved by combining low permeable and high permeable coating materials in suitable proportion.

[0106] The devices with different drug release mechanisms described above can be combined in a final dosage form comprising single or multiple units. Examples of multiple units include multilayer tablets, capsules containing tablets, beads, granules, etc.

[0107] An immediate release portion can be added to the extended release system by means of either applying an immediate release layer on top of the extended release core using a coating or compression process or in a multiple unit system such as a capsule containing extended and immediate release beads.

[0108] Extended release tablets containing hydrophilic polymers are prepared by techniques commonly known in the art such as direct compression, wet granulation, or dry granulation processes. Their formulations usually incorporate polymers, diluents, binders, and lubricants as well as the

used. The samples with the various delayed release coating levels (weight gain, w/w) were collected.

Example 7

Pulsatile Release Ondansetron Dosage Form

[0142] In this example, a tablet of the form similar to that shown in FIG. 1 is constructed as follows. A delayed release ondansetron tablet described in the Examples 2, 4-6 is further coated with an ondansetron containing layer. Such a tablet when administered to a patient provides for two pulses of ondansetron at the desired absorption sites. The first pulse is released in the stomach and the second pulse is released in the intestines. The first to second pulse ondansetron ratio is in the range from approximately 5/95 to approximately 95/5 (w/w), preferably from approximately 20/80 to approximately 80/20 (w/w), and the most preferably from approximately 30/70 to approximately 70/30 (w/w). Ondansetron total dose is approximately between 1 and 100 mg. In the preferred embodiment ondansetron total dose is between 1 and 24 mg. Optionally, ondansetron multi-layer tablet is further coated with an enteric polymer.

Example 8

Pulsatile Release Ondansetron Dosage Form (Version 2)

[0143] In this example, a delayed release ondansetron tablet described in the Examples 2, 4-6 is combined with an immediate release ondansetron tablet described in the Example 1. Such a capsule when administered to a patient provides for two pulses of ondansetron at the desired absorption sites. The first pulse is released in the stomach and the second pulse is released in the intestines. The first to second pulse ondansetron ratio is in the range from approximately 5/95 to approximately 95/5 (w/w), preferably from approximately 20/80 to approximately 80/20 (w/w), and the most preferably from approximately 30/70 to approximately 70/30 (w/w). Ondansetron total dose is approximately between 1 and 100 mg. In the preferred embodiment ondansetron total dose is between 1 and 24 mg.

[0144] An immediate release tablet is optionally coated with an enteric release polymer resulting in no drug being released in the acidic environment of the stomach. Alternatively, the capsule is optionally further coated with an enteric polymer resulting in no drug being released in the acidic environment of the stomach.

Example 9

Immediate Release Ondansetron-Fluoxetine Tablet

[0145] Ondansetron HCl dihydrate USP from Natco Pharma Ltd (India) was used to manufacture immediate release (IR) ondansetron-fluoxetine tablet. Prior to tablet manufacturing Ondansetron HCl dihydrate was milled to the following particle size: 10% particles below 1.7 microns, 50% particles below 8.6 microns, and 90% particles below 32.2 microns. Fluoxetine HCl from Divis Pharmaceuticals (India) was used as received and had the following particle size distribution: 10% particles below 1.9 microns, 50% particles below 8.4 microns, and 90% particles below 31.9 microns.

[0146] The first step of tablet manufacturing process was sifting Ondansetron HCl, Fluoxetine HCl, Lactose, Prosolv

50, Ac-Di-Sol, and SDS through 40 mesh sieve. The second step consisted of dry mixing of sifted material in V-cone blender for 20 minutes. Aerosil and Mg stearate sifted through 40 mesh sieve were then added and the resultant blend further mixed for 10 minutes. The final blend was compressed into tablets with average tablet weight of 75 mg using 4.76 mm round standard concave punch at a hardness of 10-12 Kp.

[0147] Batch size was 1,000 tablets and each tablet contained Ondansetron HCl dihydrate equivalent to 8 mg Ondansetron and Fluoxetine HCl equivalent to 10 mg Fluoxetine. Tablet composition of Lot#3 is given below.

Tablet composition of Lot# 3			
No.	Ingredient	Source	Amount per tablet
1	Ondansetron HCl dihydrate USP	Natco Pharma	9.98 mg
2	Fluoxetine HCl	Divis Parma	11.18 mg
3	Lactose (Pharmatose DCL 14)	DMV	23.55 mg
4	Prosolv 50	JRS Pharma	23.55 mg
5	Ac-Di-Sol	FMC	3.75 mg
6	SDS	Himedia	1.5 mg
7	Aerosil	Degussa	0.75 mg
8	Mg stearate	Aceto Corp.	0.75 mg
Tablet weight			75 mg

[0148] Dissolution of IR tablet was examined in 900 ml of pH 6.8 phosphate buffer containing 1% (w/w) SDS in USP dissolution apparatus 2 (paddles) at 50 rpm and 37° C. Surfactant was added in order to facilitate drug dissolution. HPLC method was used to analyze the dissolution samples. Dissolution data obtained for three tablets is presented below.

Incubation time, hours	Ondansetron released, % total			
	Tablet# 1	Tablet# 2	Tablet# 3	Average
1	86	84	87	86
2	97	96	93	95

Incubation time, hours	Fluoxetine released, % total			
	Tablet# 1	Tablet# 2	Tablet# 3	Average
1	82	79	83	81
2	94	95	93	94

[0149] The scale-up 12,000-tablet batch of ondansetron-fluoxetine tablet was manufactured (Lot#4). The manufacturing procedure and a tablet composition was the same as for Lot#3. Lot#4 tablets were evaluated for tablet weight variation, thickness, friability, and disintegration time. Tablet weight variation analysis was performed as follows. 10 tablets were selected at random and weighed individually. The weight of all the tablets was in the range of 74.5 mg to 78.1 mg. The average weight was 75.9 mg and the relative standard deviation was 2.63%. The thickness of the tablets ranged



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(12) **United States Patent**
King et al.

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(45) **Date of Patent:** **Nov. 15, 2005**

(54) **CONTROLLED-RELEASE
PHARMACEUTICAL FORMULATIONS**

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(30) **Foreign Application Priority Data**

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A61K 9/32; A61K 9/36

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Arznei-formenlehre; Ein Lehrbuch der galenick fur Theorie and Praxis; Von Dr. Ursula Schoffling, Trier, 1998, 199-205 (English Translation).

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Primary Examiner—James M. Spear

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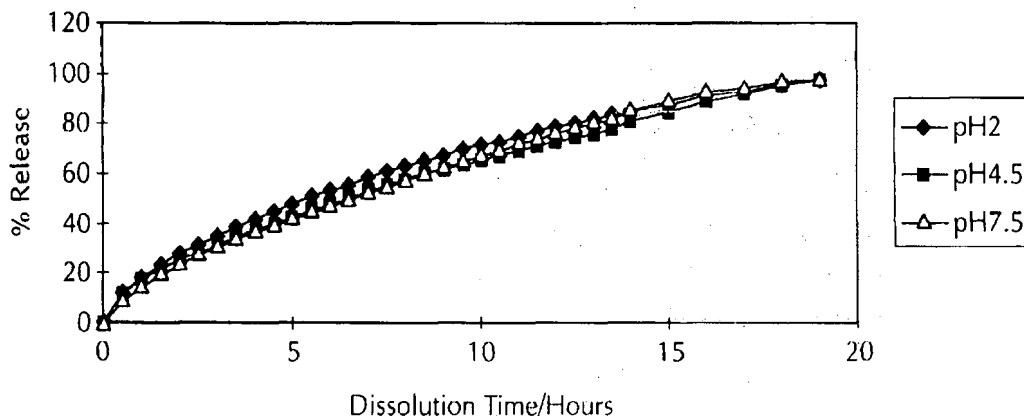
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(57) **ABSTRACT**

The invention provides controlled-release formulations for oral administration containing a cGMP PDE-5 inhibitor. The formulations are useful, inter alia, in the treatment or prevention of sexual dysfunction.

26 Claims, 1 Drawing Sheet



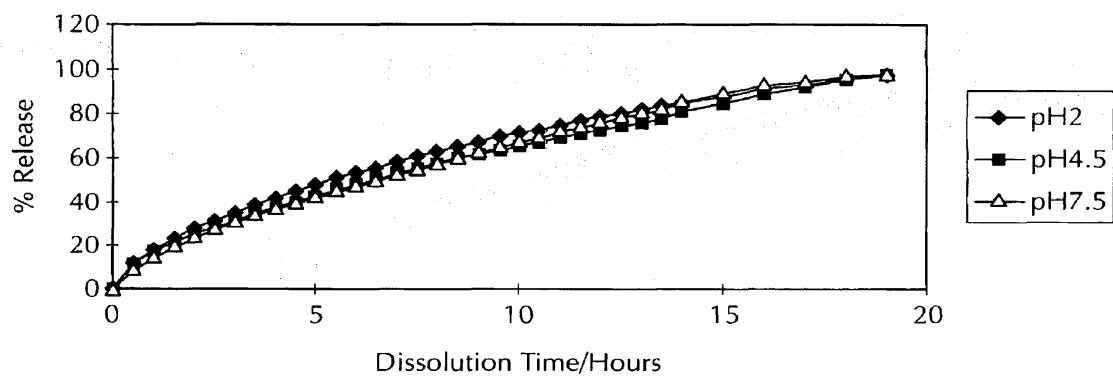


FIG. 1

CONTROLLED-RELEASE PHARMACEUTICAL FORMULATIONS

This invention relates to controlled-release oral pharmaceutical formulations of cGMP PDE-5 inhibitors, and to methods of treatment involving them.

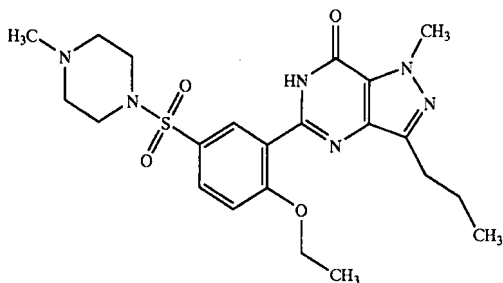
Controlled-release oral pharmaceutical formulations are known. Their purpose is to modify the rate of drug release, for example to produce a constant rate of release of a drug into the gastrointestinal tract of a patient, or to delay the release of a drug into the gastrointestinal tract of a patient (see 'Sustained and Controlled Release Drug Delivery Systems', pp 3-6, edited by J R Robinson, published by Marcel Dekker Inc).

Cyclic nucleotide phosphodiesterases (PDEs) are a family of enzymes that catalyse the degradation of cyclic nucleotides. Cyclic nucleotides, particularly cAMP (i.e. cyclic adenosine 3',5'-monophosphate), are important intracellular second messengers. PDEs are one cellular component that regulates the concentration of cyclic nucleotides. In recent years, at least seven PDE enzymes (such as PDE-1-PDE-7), as well as many subtypes of these enzymes, have been defined based on substrate affinity and cofactor requirements (J A Beavo and D H Reifsnyder, Trends Pharmacol Sci 11:150 [1990]; and J Beavo, in 'Cyclic Nucleotide Phosphodiesterases: Structure, Regulation and Drug Action', (Editors J Beavo and M D Housley). Wiley, Chichester, pp. 3-15 [1990]).

PDE-5 is a cGMP (i.e. cyclic guanosine 3',5'-monophosphate) specific PDE. It has been shown that PDE-5 is an important enzyme in regulating the physiological response to sexual stimulation, and that inhibitors of the enzyme are useful in the treatment of sexual dysfunction.

In males, sexual dysfunction may be defined as the inability to obtain or sustain a penile erection adequate for satisfactory sexual intercourse. In females, sexual dysfunction may be defined as deficient physiological response to sexual stimulation and/or a deficient subjective feeling of arousal.

A cGMP PDE-5 inhibitor of particular interest is sildenafil {5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1,6-dihydro-1-methyl-3-propylpyrazolo[4,3-d]pyrimidin-7-one}, which has the following structure:



The compound was first disclosed in European Patent Application 463756, and its use in the treatment of sexual dysfunction was disclosed in International Patent Application WO 94/28902. A formulation of the citrate salt (VIA-GRATM) was made available for the treatment of male erectile dysfunction in a number of countries including the USA in 1998. VIA-GRATM is an immediate release tablet that is administered about 1 hour before an effect is required, and the half-life of the drug in human plasma is about 4 hours after administration.

The main interest in the art so far has been to provide a fast-acting treatment of sexual dysfunction, which can provide an effect as soon as possible after administration. For example, International Patent Application WO 98/30209 discloses a rapidly releasing formulation of sildenafil citrate.

International Patent Application WO 97/18814 discloses controlled-release pharmaceutical formulations for oral administration consisting essentially of an active ingredient, low molecular weight polyethylene oxide, hydroxypropylmethyl cellulose, tableting excipients, and optionally one or more enteric polymers. It is suggested therein that sildenafil could be delivered using the disclosed formulations. However, the advantages given below for controlled-release formulations of cGMP PDE-5 inhibitors were not mentioned.

International Patent Application WO 98/48781 (published on 5 Nov. 1998, after the priority date of the present application) discloses compositions providing "relatively slow release" of compounds including apomorphine (which is not a cGMP PDE-5 inhibitor). The formulations are indicated in the treatment of sexual dysfunction.

According to the present invention, there is provided a controlled-release formulation for oral administration containing a cGMP PDE-5 inhibitor; provided that the formulation does not consist essentially of sildenafil, low molecular weight polyethylene oxide, hydroxypropylmethyl cellulose, tableting excipients, and optionally one or more enteric polymers.

Usually, formulations according to the invention will be tablets or capsules that are swallowed. However, the invention also includes buccal formulations (which may be tablets, ointments, gels or patches).

Controlled-release formulations may be divided into sustained-release and pulsatile-release formulations (also known as delayed-release formulations). In general, such formulations are known to those skilled in the art or are available using conventional methods.

Sustained-release dosage forms release their active ingredient into the gastro-intestinal tract of a patient over a sustained period of time following administration of the dosage form to the patient. Particular dosage forms include:

- those in which the active ingredient is embedded in a matrix from which it is released by diffusion or erosion (see Example 1 below);
- those in which the active ingredient is present in a core which is coated with a release rate-controlling membrane (see Example 3 below);
- those in which the active ingredient is present in a core provided with an outer coating impermeable to the active ingredient, the outer coating having an aperture (which may be drilled) for release of the active ingredient;
- those in which the active ingredient is released through a semi-permeable membrane, allowing the drug to diffuse across the membrane or through liquid filled pores within the membrane; and
- those in which the active ingredient is present as an ion exchange complex.

The dosage forms mentioned in (a), (b) and (c) above are of particular interest.

When several cores are present, for example coated cores in the dosage forms mentioned in (b) and (c), such formulations are sometimes referred to as "multiparticulates".

It will be apparent to those skilled in the art that some of the above means of achieving sustained-release may be combined, for example a matrix containing the active compound may be formed into a multiparticulate and/or coated with an impermeable coating provided with an aperture.

Pulsatile-release formulations release the active compound after a sustained period of time following administration of the dosage form to the patient. The release may then be in the form of immediate- or sustained-release. This delay may be achieved by releasing the drug at particular points in the gastro-intestinal tract or by releasing drug after a pre-determined time. Pulsed-release formulations may be in the form of tablets or multiparticulates or a combination of both. Particular dosage forms include:

1. osmotic potential triggered release (see U.S. Pat. No. 3,952,741);
2. compression coated two layer tablets (see U.S. Pat. No. 5,464,633);
3. capsules containing an erodible plug (see U.S. Pat. No. 5,474,784);
4. sigmoidal releasing pellets (referred to in U.S. Pat. No. 5,112,621); and
5. formulations coated with or containing pH-dependent polymers including shellac, phthalate derivatives, polyacrylic acid derivatives and crotonic acid copolymers.

Dual release formulations can combine the active ingredient in immediate release form with additional active ingredient in controlled-release form. For example, a bilayer tablet can be formed with one layer containing immediate release active ingredient and the other layer containing the active ingredient embedded in a matrix from which it is released by diffusion or erosion. Alternatively, one or more immediate release beads can be combined with one or more beads which are coated with a release rate-controlling membrane in a capsule to give a dual release formulation. Sustained release formulations in which the active ingredient is present in a core provided with an outer coating impermeable to the active ingredient, the outer coating having an aperture (which may be drilled) for release of the active ingredient, can be coated with drug in immediate release form to give a dual release formulation. Dual release formulations can also combine drug in immediate release form with additional drug in pulsed release form. For example, a capsule containing an erodible plug could liberate drug initially and after a predetermined period of time further drug in immediate- or sustained-release form.

Thus, according to the invention, there is further provided a dual release formulation for oral administration having a first portion comprising a controlled-release formulation as defined above, but without proviso, and a second portion comprising a cGMP PDE-5 inhibitor in immediate release form. The invention also provides products containing a controlled-release formulation as defined above, but without proviso, and a cGMP PDE-5 inhibitor in immediate release form, as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of sexual dysfunction.

Preferably, formulations according to the present invention are sustained-release formulations. For example, it is preferred that up to 75% by weight of the active ingredient is released from the formulation into the gastrointestinal tract (or in a model of the GI tract) after a period of time in the range 1-24 hours following administration, for example 6-18 hours. A suitable model of the GI tract is described in Example 2 below.

Dual release formulations as defined above are also of particular interest. It is preferred that the first portion of such formulations is a sustained-release formulation.

An advantage of controlled-release, particularly sustained-release formulations according to the present invention is that a patient receiving them would have improved sexual function for a sustained period of time following administration (such as 6-24 hours, for example 12-18

hours), and so be ready for sexual activity at almost any time. This would allow a more spontaneous sex-life to be pursued.

In addition, it is thought that in male patients at risk of developing sexual dysfunction (for example diabetic patients or patients having undergone nerve sparing radical prostatectomy), the prevalence of nocturnal erections is diminished. Nocturnal erections may play an important role in preserving normal erectile function by providing regular tissue oxygenation thus preventing tissue fibrosis and erectile degeneration. Thus, a cGMP PDE-5 inhibitor delivered to a patient during sleep will increase the ability of at-risk individuals to have nocturnal erections, increase tissue oxygenation, prevent penile fibrosis and thus preserve erectile function or slows its decline. Controlled-release formulations may be of particular use in this instance, providing cGMP PDE-5 inhibition throughout the sleeping period.

A further advantage of formulations according to the present invention is that side effects may be reduced. For example, although sildenafil offers a safe, effective and generally very well tolerated oral treatment for male erectile dysfunction, dose-related reversible side effects such as headache or visual disturbance at high dosage may limit its use in a minority of patients. Such effects are mediated by systemic exposure to sildenafil following oral administration: thus a formulation with a sustained release profile, which avoids initial high plasma concentrations, could be of great value to these patients.

Preferably, the cGMP PDE-5 inhibitor is sildenafil, or a pharmaceutically acceptable salt thereof (such as the citrate salt).

Other cGMP PDE-5 inhibitors (previously mentioned in WO 94/28902) that may be mentioned include:

- 5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.
- 5-(5-morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
- 5-[2-allyloxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
- 5-{2-ethoxy-5-[4-(2-propyl)-1-piperazinylsulphonyl]phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
- 5-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
- 5-{5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]-2-n-propoxyphenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
- 5-[2-ethoxy-5-(4-methyl-1-piperazinylcarbonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one; and
- 5-[2-ethoxy-5-(1-methyl-2-imidazolyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

The following cGMP PDE-5 inhibitors (previously mentioned in WO 97/03675 to Laboratoire Glaxo Wellcome SA) may also be mentioned:

- (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphe-nyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione; and
- (3S,6R,12aR)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-6-(3,4-methylenedioxyphe-nyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione.

When the formulation includes a matrix in which the active ingredient is embedded (such as a matrix tablet), it preferably contains hydroxypropylmethyl cellulose. Preferably, the hydroxypropylmethyl cellulose has a number average molecular weight in the range 80,000-250,000. Preferably, the hydroxypropylmethyl cellulose has a degree of

methyl substitution in the range 19–30%. Preferably, the hydroxypropylmethyl cellulose has a degree of hydroxy substitution in the range 7–12%. A number of hydroxypropylmethyl cellulose polymers are available commercially under the brand name Methocel™, and some of those suitable for use in formulations according to the invention are given in the table below:

Methocel™ grade	Number average MW	Degree of methyl substitution	Degree of hydroxy substitution	Nominal viscosity of a 2% aqueous solution	USP designation
K4M	89000	19–24%	7–12%	4000 cps	2208
K15M	125000	"	"	15000 cps	"
K100M	215000	"	"	100000 cps	"
E4M	93000	28–30%	7–12%	4000 cps	2910
E10M	113000	"	"	10000 cps	"
F4M	90000	27–30%	4–7.5%	4000 cps	2906

Methocel™ K4M has characteristics of particular interest.

It will be apparent to those skilled in the art that the hydroxypropylmethyl cellulose may consist of molecules of different chain lengths, but that the average chain length gives a molecular weight in the range stated.

Matrix formulations according to the present invention may contain a buffering agent. This is particularly useful when the formulation contains sildenafil citrate. A buffering agent of particular interest is aspartic acid. When it forms part of a matrix tablet, aspartic acid acts as a buffering agent to maintain a low pH at the surface of the tablet. Because sildenafil citrate has a low solubility at pH values greater than 6, the acid keeps the drug relatively soluble during the transit of the tablet through the GI tract. When present, aspartic acid will typically make up 15–30% by weight of the formulation.

The formulations of the present invention may include tableting excipients, for example colloidal anhydrous silica, polyvinylpyrrolidone, lactose and magnesium stearate. Lactose is of particular interest, and when present it will typically make up 10–40% by weight of the formulation.

Formulations according to the invention may be provided additionally with a cosmetic coating: for example a coating comprising a pigment, a plasticizer and a polymer such as OPADRY™ (manufactured by Colorcon), or a sugar coating. Such coatings do not substantially affect the performance of the formulation, but enhance its presentation. Such coatings may be applied by spraying tablet cores with a solution of the components, using conventional techniques.

Preferably, in matrix formulations according to the present invention, the hydroxypropylmethyl cellulose makes up 10–50% by weight of the formulation.

When the formulation has a core comprising the active ingredient which is coated with a release rate-controlling membrane, it is preferred that several such coated cores are present (i.e. the formulation is multiparticulate). For example, 100 or more coated cores may be filled into a capsule. Preferably, the core also includes a buffering agent (such as succinic acid). The release rate-controlling membrane may comprise an ammonio methacrylate copolymer and a plasticizer.

Preferably, in formulations according to the present invention, the cGMP PDE-5 inhibitor makes up 5–50% by weight of the formulation.

Preferably, in formulations according to the present invention, the rate at which the cGMP PDE-5 inhibitor is released therefrom is substantially independent of the pH of the surroundings.

The present invention also provides processes for the production of the sustained release pharmaceutical formulations set out in (a), (b) and (c) above, which include the steps of:

- (a) mixing the cGMP PDE-5 inhibitor with a matrix material, and pressing into tablets;

- (b) forming a core comprising the cGMP PDE-5 inhibitor and then coating the core with a release rate-controlling membrane; or

- (c) forming a core containing the cGMP PDE-5 inhibitor and then coating the core with a coating impermeable to the cGMP PDE-5 inhibitor:

respectively.

The invention further provides the use of a cGMP PDE-5 inhibitor in the manufacture of a formulation for the treatment or prevention of sexual dysfunction; characterized in that, following administration, the formulation releases the inhibitor over or after a sustained period of time. Consequently, following administration, the mammal's sexual function will be substantially improved for or after a sustained period of time.

Usually, the mammal will be a human, but administration to other mammals, such as horses, is contemplated.

A "sustained period of time" in relation to the improvement in sexual function is a period of time such as $6 \geq 24$ hours, for example $12 \geq 18$ hours.

It will be appreciated by those skilled in the art that the formulations of the present application may also be administered to patients suffering from or at risk of suffering from disorders other than sexual dysfunction, but in which cGMP PDE-5 inhibitors may be useful therapeutically.

The invention further provides a method of treating or preventing sexual dysfunction, which comprises administering a controlled-release formulation of a cGMP PDE-5 inhibitor, as defined above, but without proviso, to a mammal in need of such treatment or prevention. Consequently, the mammal's sexual function is substantially improved for or after a sustained period of time.

The invention further provides a method of improving sexual function in a mammal (not suffering from sexual dysfunction), which comprises administering a controlled-release formulation of a cGMP PDE-5 inhibitor, as defined above, but without proviso, to the mammal. Consequently, the mammal's sexual function is substantially improved for or after a sustained period of time.

The invention further provides a method of increasing the probability of a nocturnal erection in a male mammal, which comprises administering a controlled-release formulation, as defined above, but without proviso, to the male mammal.

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Formulations according to the invention will usually be administered once a day, or possibly twice a day. The total daily dosage of a cGMP PDE-5 inhibitor (such as sildenafil citrate) is usually in the range 25–400 mg, preferably 50–200 mg. Thus, a once daily formulation according to the invention will usually contain 25–400 mg of drug substance (such as sildenafil citrate), preferably 50–200 mg.

BRIEF DESCRIPTION OF THE DRAWING

The invention is illustrated by the following examples with reference to the accompanying drawing, in which FIG. 1 shows the percentage of drug compound released v time from a formulation prepared according to Example 1 under three different pH conditions.

EXAMPLE 1

Sustained Release Matrix Formulation of Sildenafil Citrate

Component	Weight per 450 mg matrix tablet (mg)
Sildenafil citrate	144.72 ^a
L-Aspartic acid	100
Hydroxypropylmethyl cellulose ^b	67.5 (15%)
Lactose ^c	133.28
Magnesium Stearate	4.5

^aDrug equivalent to 100 mg active substance based on actual activity of 69.1%.
^bMethocel™ grade K4M
^cLactose fastflo

Method

1. Blend components, less magnesium stearate, for 10 minutes in a turbula
2. Screen through a 500 μm sieve
3. Add 26% water (by weight) with blending
4. Screen through a 1.7 mm sieve
5. Dry resulting granules in a vacuum oven at 40° C. 2070 kPa (300 psi) until the moisture level is returned to original value
6. Screen through a 1.0 mm sieve
7. Add magnesium stearate and blend for 5 minutes
8. Press into tablets using 11 mm normal concave tablet tooling

EXAMPLE 2

Dissolution Studies

Formulations prepared in Example 1 were dissolved using Apparatus 1 (baskets) described in United States Pharmacopeia 23 (1995), page 1791, in an aqueous buffer of pH 2 (composition 0.01M HCl and 0.12M NaCl), an aqueous buffer of pH 4.5 (composition 0.06M KCl, 0.03M NaCl and 0.006M KH₂PO₄) and in an aqueous buffer of pH 7.5 (composition 0.06M KCl, 0.03M NaCl, 0.006M KH₂PO₄ and 0.005M NaOH). The dissolution fluid volume was 11 in the case of pH 2 and pH 4.5, but 5 l in the case of pH 7.5 (also replaced periodically), the temperature was 37° C., the rotation speed of the baskets was 100 rpm, and the drug compound released was detected by UV spectroscopy. The percentage of drug compound released v time is shown in FIG. 1.

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It can be seen that the release profiles at the three pH values are almost identical, indicating that the formulation is likely to give a steady, sustained rate of release of drug over a sustained period of time when administered orally to a patient.

EXAMPLE 3

Sustained-Release Coated Multiparticulate Core Formulation of Sildenafil Citrate

The formulation is prepared by applying a polymer coat onto core beads. These are then encapsulated.

Step 1 : Preparation of Multiparticulate Cores

Ingredient	Composition mg/50 mg dose
Sildenafil citrate	71.9 ^a
Microcrystalline cellulose ^b	73.5
Lactose ^c	73.5
Succinic acid (Water) ^d	93.8 (109.5)
Total:	312.7

^aDrug equivalent to 50 mg active substance based on theoretical activity of 69.5%.
^bAvicel™ PH101.
^cLactose fastflo.
^dRemoved during drying. Quantity varied with batch size.

All of the dry ingredients are blended together in a Turbula blender for 20 minutes. The mixture is then screened using a 500 μm (30 mesh) screen followed by reblending for a further 20 minutes. Wet granulation is performed in a planetary mixer by carefully adding water to the mixture while continuously blending at a low speed. Cores are produced from the wet granules by a conventional extrusion and spheronisation process. The formed cores are then dried in a standard fluidised-bed drier.

Step 2: Coating of Multiparticulate Cores

Ingredient	Composition mg/50 mg dose
Cores from step 1	312.7
Ammonio methacrylate copolymer type B ^a	31.27
Ammonio methacrylate copolymer type A ^b	7.82
Triethyl citrate	7.82
Talc	19.55
(Water) ^d	(332.3)
Total:	379.16

^aEudragit™ RS 30 D.
^bEudragit™ RL 30 D.

To prepare the coating, all of the ingredients except the active cores are mixed together to form a uniform dispersion. The mixture is applied to the cores by a conventional fluidised-bed spray coating technique to give the final coated cores. Typically, these coated cores may then be cured at 40° C. for 18 hours. They are then filled into gelatin capsule shells using conventional encapsulating equipment.

What is claimed is:

- 1. A sustained-release formulation for oral administration containing a cGMP PDE-5 inhibitor, which comprises a core containing the cGMP PDE-5 inhibitor and an outer coating impermeable to the cGMP PDE-5 inhibitor, the outer coating having an aperture for release of the cGMP PDE-5 inhibitor, provided that the formulation does not consist essentially of sildenafil, low molecular weight polyethylene oxide, hydroxypropylmethyl cellulose, tableting excipients, and optionally one or more enteric polymers.
- 2. A sustained-release formulation for oral administration containing hydroxypropylmethyl cellulose and containing a cGMP PDE-5 inhibitor embedded in a matrix from which it is released by diffusion or erosion; provided that the formulation does not consist essentially of sildenafil, low molecular weight polyethylene oxide, hydroxypropylmethyl cellulose, tableting excipients, and optionally one or more enteric polymers.
- 3. A sustained-release formulation for oral administration containing a buffering agent and a cGMP PDE-5 inhibitor embedded in a matrix from which it is released by diffusion or erosion, provided that the formulation does not consist essentially of sildenafil, low molecular weight polyethylene oxide, hydroxypropylmethyl cellulose, tableting excipients, and optionally one or more enteric polymers.
- 4. A formulation as claimed in claim 2, wherein the hydroxypropylmethyl cellulose has a number average molecular weight in the range 80,000–250,000.
- 5. A formulation as claimed in claim 2, wherein the hydroxypropylmethyl cellulose has a degree of methyl substitution in the range 19–30%.
- 6. A formulation as claimed in claim 2, wherein the hydroxypropylmethyl cellulose has a degree of hydroxy substitution in the range 7–12%.
- 7. A formulation as claimed in claim 2, wherein the hydroxypropylmethyl cellulose makes up 10–50% by weight of the formulation.
- 8. A sustained-release formulation for oral administration containing a cGMP PDE-5 inhibitor, wherein the cGMP PDE-5 inhibitor is present in a core which is coated with a release rate-controlling membrane, provided that the formulation does not consist essentially of sildenafil, low molecular weight polyethylene oxide, hydroxypropylmethyl cellulose, tableting excipients, and optionally one or more enteric polymers, wherein the release rate-controlling membrane comprises an ammonio methacrylate copolymer and a plasticizer.
- 9. A process for the production of a sustained-release formulation comprising a cGMP PDE-5 inhibitor embedded in a matrix from which it is released by diffusion or erosion, which comprises the steps of:
 - (a) mixing the cGMP PDE-5 inhibitor with a matrix material, and pressing into tablets;
 - (b) forming a core comprising the cGMP PDE-5 inhibitor and then coating the core with a release rate-controlling membrane; or
 - (c) forming a core containing the cGMP PDE-5 inhibitor and then coating the core with a coating impermeable to the cGMP PDE-5 inhibitor;respectively.
- 10. A method of treating sexual dysfunction, which comprises administering a sustained-release formulation, as defined in claim 1, to a mammal in need of such treatment.
- 11. The method of claim 10, characterized in that, following administration, the mammal's sexual function is substantially improved for or after a sustained period of time.

- 12. A method of improving sexual function in a mammal, which comprises administering a sustained-release formulation, as defined in claim 1, to the mammal.
- 13. The method of claim 12, characterized in that, following administration, the mammal's sexual function is substantially improved for or after a sustained period of time.
- 14. A method of increasing the probability of a nocturnal erection in a male mammal, which comprises administering a sustained-release formulation, as defined in claim 1, to the male mammal.
- 15. A dual release formulation for oral administration having a first portion comprising a controlled-release formulation comprising a cGMP PDE-5 inhibitor and a second portion comprising a cGMP PDE-5 inhibitor in immediate release form.
- 16. A product containing a controlled-release formulation comprising a cGMP PDE-5 inhibitor and a cGMP PDE-5 inhibitor in immediate release form, as a combined preparation for simultaneous, separate or sequential use in the treatment of sexual dysfunction.
- 17. A formulation as claimed in claim 1, wherein the cGMP PDE-5 inhibitor is sildenafil or a pharmaceutically acceptable salt thereof.
- 18. A formulation as claimed in claim 1, wherein the cGMP PDE-5 inhibitor is sildenafil citrate.
- 19. A formulation as claimed in claim 15, wherein the cGMP PDE-5 inhibitor is sildenafil or a pharmaceutically acceptable salt thereof.
- 20. A formulation as claimed in claim 15, wherein the cGMP PDE-5 inhibitor is sildenafil citrate.
- 21. A product as claimed in claim 16, wherein the controlled release formulation comprises sildenafil or a pharmaceutically acceptable salt thereof and wherein the immediate release formulation comprises sildenafil or a pharmaceutically acceptable salt thereof.
- 22. A product as claimed in claim 16, wherein the controlled release formulation comprises sildenafil citrate and wherein the immediate release formulation comprises sildenafil citrate.
- 23. A dual release formulation for oral administration as claimed in claim 15, having a first portion comprising a sustained release formulation comprising sildenafil or a pharmaceutically acceptable salt thereof and a second portion comprising sildenafil or a pharmaceutically acceptable salt thereof in immediate release form.
- 24. A dual release formulation for oral administration as claimed in claim 15, having a first portion comprising a sustained release formulation comprising sildenafil citrate and a second portion comprising sildenafil citrate in immediate release form.
- 25. A dual-release formulation for oral administration as claimed in claim 15, having a first portion comprising a controlled release formulation comprising sildenafil or a pharmaceutically acceptable salt thereof and a second portion comprising sildenafil or a pharmaceutically acceptable salt thereof in immediate release form, wherein a multiplicity of coated cores is present in the first portion.
- 26. A dual-release formulation for oral administration as claimed in claim 15, having a first portion comprising a controlled release formulation comprising sildenafil citrate and a second portion comprising sildenafil citrate in immediate release form, wherein a multiplicity of coated cores is present in the first portion.

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