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- as to the identity of the inventor (Rule 4.17(i))
- as to applicant's entitlement to apply for and be granted a
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- as to the applicant's entitlement to claim the priority of the
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(54) Title: MODIFIED RELEASE FORMULATION FOR TREATING PREMATURE EJACULATION

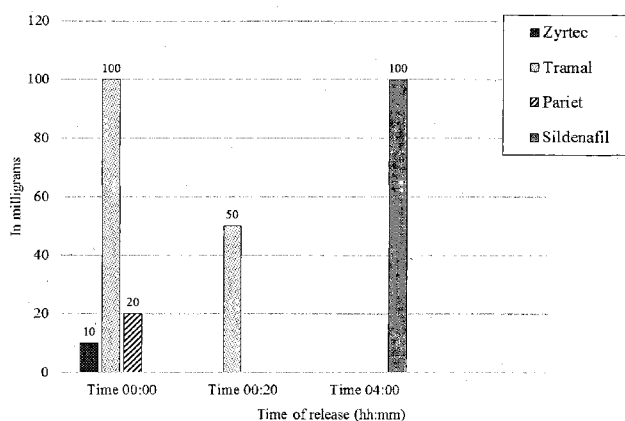


FIG. 1

(57) Abstract: A modified release pharmaceutical composition for treating premature ejaculation. The above composition comprises full quantitative timely release (FQTR) of therapeutically effective amounts of active compounds comprising tramadol, rabeprazole, cetirizine, sildenafil or their pharmaceutically acceptable salts thereof. Full quantitative timely release of the pharmaceutical composition comprises total and immediate release of the prescribed doses at the specified time and at once, for delaying the onset of ejaculation by at least 20 minutes irrespective of non-medicated time delay.



MODIFIED RELEASE FORMULATION FOR TREATING PREMATURE EJACULATION

FIELD OF THE INVENTION

[1] The present invention generally relates to the treatment of premature ejaculation, more specifically relates to a pharmaceutical composition formulated for timed release of therapeutically effective amounts of active compounds which delay the onset of ejaculation in male patients.

BACKGROUND

[2] Premature ejaculation (PME) is regarded as the most common sexual disorder in males. It is defined as a condition resulting in persistent or recurrent ejaculation before, upon, or shortly after initiation of copulation. In addition to sexual dysfunction, the condition of premature ejaculation may also result in social difficulties including asthenia, domestic discord due to loss of confidence, lack of focus and anxiety.

[3] PME is not just a medical condition, but also a psychological condition. Both men and women consider it as failure as their mutual needs are unfulfilled, especially causing a huge embarrassment for men. The above condition of PME may jeopardize relationships, resulting in loss of spouse, causes shame in social or family circle, instills fear of failure and even earns bad reputation for men. For most men, the condition will also affect their ability to work to their fullest potential or failing completely due to loss of self-esteem, self-confidence as well as their ability to focus and concentrate on their work related tasks. Due to the above reasons, there is a very strong need for more effective and reliable treatment for PME.

[4] Existing treatment options for PME includes drug therapy, behavioral therapy, psychological counselling and mechanical devices. All of these methods may have significant drawbacks. For example, use of topical local anesthetics such as lidocaine may result in loss of erection, and decrease the sensitivity of tissues. Use of antidepressants can cause side effects like nausea, dizziness and unwanted mood alterations. The improvements brought about by behavioral or psychological therapy is short lived and have a moderate success rate. Mechanical devices are relatively unpopular due to factors like embarrassment to use and physical discomfort.

[5] With the option of drug therapy, most of the existing medications for PME may result in little improvement in delaying the onset of ejaculation, especially when compared to placebo time, for example, improvement of 2-3 times than the placebo time. Moreover, the time delay in ejaculation induced by existing drug formulations highly depend on non-medicated time delay of a patient. For example, if non-medicated time delay for PME patient is 56 seconds, then the time delay for ejaculation can be increased only up to 96 seconds using existing medication. Any drug used for the treatment of PME should be reliable, providing a minimum time delay of 20 minutes before onset of ejaculation and 20 folds increase in time delay when compared to placebo time delay and should not depend on non-medicated time delay of patient.

[6] Therefore, there exists a need in the art for an effective and reliable treatment option for premature ejaculation by significantly delaying the onset of ejaculation, wherein the time delay is not influenced by non-medicated time delay of a patient.

SUMMARY OF THE INVENTION

[7] The present invention relates to a modified release pharmaceutical composition for treating premature ejaculation. The composition is formulated for timed release of therapeutically effective amounts of active compounds essentially comprises of tramadol, rabeprazole, cetirizine, sildenafil in their pharmaceutically acceptable salts thereof. The composition further comprises pharmaceutically acceptable carriers thereof. The timed release formulation of the present invention refers to modified and immediate release of the prescribed doses at the specified time.

[8] According to an embodiment, the pharmaceutical composition of the present invention comprises a timed release formulation, comprising tramadol, rabeprazole, cetirizine hydrochloride at a pharmacologically active concentration of 50 mg, 20mg and 10mg respectively formulated for immediate release, and sildenafil at active concentration of 100mg is formulated for timed release after 4 hours. The above composition is formulated for delaying the onset of ejaculation by approximately 20 minutes.

[9] In another embodiment, the pharmaceutical composition of the present invention comprises a timed release formulation comprising tramadol, rabeprazole, cetirizine hydrochloride at an active concentration 50mg, 20mg and 10mg respectively, formulated for immediate release and further tramadol 50mg formulated for timed release at 20 minutes, and sildenafil 100mg formulated for timed release at 4 hours. The above composition is formulated for delaying the onset of ejaculation by approximately 40 minutes.

[10] In another embodiment, the pharmaceutical composition of the present invention comprises a timed release formulation, comprising tramadol at 100mg, rabeprazole at 20mg, cetirizine hydrochloride at 10mg formulated for immediate release and the composition further comprises tramadol 50mg formulated for timed release at 20 minutes and , sildenafil citrate 100mg are formulated for timed release at 4 hours. The above composition is formulated for delaying the onset of ejaculation by approximately 60 minutes.

[11] The pharmaceutical composition of the present invention comprise a timed release formulation for delaying the onset of ejaculation irrespective of non-medicated time delay of a patient.

BRIEF DESCRIPTION OF SEVERAL VIEWS OF DRAWINGS

[12] FIG. 1 shows a chart illustrating timed release of different doses of Zyrtec, Tramal, Pariet and sildenafil.

[13] FIG. 2 shows a chart illustrating the minutes of delay in onset of ejaculation caused by timed release formulation of the present invention compared with other drug products at different dosage strengths.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[14] The present disclosure provides pharmaceutical compositions (combinations and formulations) comprising a plurality of dosage amounts, each comprising, together with pharmaceutical excipients suitable for oral administration, a therapeutically effective dosage amounts of tramadol, rabeprazole, cetirizine, and

sildenafil in their pharmaceutically acceptable salts thereof for the treatment of premature ejaculation in male individuals.

[15] The terms "active agent," "drug", "active compound" and "pharmacologically active agent" are used interchangeably herein to refer to a chemical material or compound which, when administered to human, induces a desired pharmacologic effect. Included are derivatives and analogs of those compounds or classes of compounds specifically mentioned which also induce the desired pharmacologic effect.

[16] "Premature ejaculation" refers to persistent or recurring ejaculation with minimal stimulation before or during sexual intercourse. The term includes both "congenital" or "lifelong" premature ejaculation and "primary" or "acquired" premature ejaculation.

[17] "Pharmaceutically acceptable salt" refers to a salt of a compound, which possesses the desired pharmacological activity of the parent compound. Such salts include: acid addition salts, formed with inorganic acids; acid addition salts formed with organic acids; or salts formed when an acidic proton present in the parent compound is replaced by a metal ion, e.g., an alkali metal ion, aluminum ion; or coordinates with an organic base such as ethanolamine, and the like.

[18] Pharmaceutically acceptable "carrier" or "carrier" is composed of materials that are present in pharmaceutical formulation other than the active ingredient. Carriers are considered safe and effective and may be administered to an individual without causing undesirable biological side effects. The term "carrier" includes, but is not limited to, diluents, binders, lubricants, disintegrators, fillers, and coating compositions.

[19] "Therapeutically effective amount" refers to the amount of an active compound that, when administered to a male patient for treating premature ejaculation, is sufficient to effect such treatment. The "therapeutically effective amount" may vary depending on the active compound, the disease and its severity and the age, weight, etc., of the patient to be treated.

[20] The term “timed release” as used herein refers to total release of the prescribed doses of active compounds at the specified time..

[21] The present invention relates to a modified release pharmaceutical composition for treating premature ejaculation. The composition is formulated for timed release of therapeutically effective amounts of active compounds essentially comprising of tramadol, rabeprazole, cetirizine, and sildenafil in their pharmaceutically acceptable salts thereof in their pharmaceutically acceptable forms thereof. One or more of the active compounds are formulated to comprise an immediate release profile, a timed release profile and its combination.

[22] Timed release formulations are created by coating a solid dosage form with a film of polymer which is insoluble in the acid environment of the stomach, and soluble in the neutral environment of small intestines. The timed 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 or 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.

[23] According to an embodiment, the pharmaceutical composition of the present invention comprises a timed release formulation, which can include pharmacologically active concentration of tramadol, rabeprazole, cetirizine hydrochloride formulated for immediate release. In addition, the composition comprises a combination of sildenafil at an active concentration formulated for timed release after 4 hours. The above composition is formulated for delaying the onset of ejaculation by approximately 20 minutes.

[24] The four active compounds present in the composition comprises different mechanism of action. For example, tramadol constitutes an opioid pain reliever which acts by binding to opioid receptor and inhibiting reuptake of serotonin and norepinephrine. Rabeprazole is selected from a class of proton pump inhibitors.

Cetirizine is an antihistamine which acts as racemic selective H1 receptor antagonist. Sildenafil acts by inhibiting cGMP-specific phosphodiesterase type 5.

[25] In another embodiment, the pharmaceutical composition of the present invention comprises a timed release formulation which contains active concentration of tramadol, rabeprazole, cetirizine hydrochloride, all three active compounds formulated for immediate release. In addition the composition further comprises tramadol formulated for timed release at 20 minutes, tramadol formulated for timed release at 40 minutes and sildenafil formulated for timed release at 4 hours. The above composition is formulated for delaying the onset of ejaculation by approximately 40 minutes.

[26] In another embodiment, the pharmaceutical composition of the present invention comprises a timed release formulation, which can include tramadol, rabeprazole, cetirizine hydrochloride formulated for immediate release. The composition further comprises tramadol formulated for timed release at 20 minutes. In addition, sildenafil citrate and cetirizine hydrochloride are formulated for timed release at once after 4 hours of dosing. The above composition is formulated for delaying the onset of ejaculation by approximately 60 minutes.

[27] The present pharmaceutical composition acts by delaying the onset of ejaculation in male patients, wherein the drug induced time delay is independent of non-medicated time delay for ejaculation. The time delay created by the present pharmaceutical composition is 20 times more than placebo induced time delay in patients with premature ejaculation. The composition is formulated in a single tablet or capsule, configured to release therapeutically effective amounts of one or more active compounds in a timed sequence. Timed release formulation of the present invention comprises full quantitative timely release (FQTR), which denotes full release of a certain dose at a specific point of time.

[28] Existing oral medication options for treating the condition of PME generally doubles the non-medicated time delay for ejaculation. For example, if the non-medicated time delay is 2 minutes and medicine induced time delay would be

approximately 4 minutes. Whereas the present pharmaceutical composition is formulated to provide a minimum time delay of at least 20 minutes irrespective of non-medicated time delay. Moreover, the present oral drug composition is formulated into different strengths as exemplified in the above embodiments, thus providing patients with different options to choose from, based on their needs.

EXAMPLE 1

[29] The pharmaceutical composition of the present invention comprise a timed release formulation, hereinafter referred to as first or lower strength, including tramadol 50mg, rabeprazole 20mg, cetirizine hydrochloride 10mg formulated for immediate release. In addition, the composition comprises a combination of sildenafil 100mg formulated for timed release after 4 hours. The above composition is formulated for resulting in an ejaculation time delay of approximately 20 minutes.

EXAMPLE 2

[30] The pharmaceutical composition of the present invention comprise a timed release formulation, hereinafter referred to as second or medium strength, including tramadol 50mg, rabeprazole 20mg, cetirizine hydrochloride 10mg, all three active compounds formulated for immediate release. In addition the composition further comprises tramadol 50mg formulated for timed release at 20 minutes, and sildenafil 100mg formulated for timed release at 4 hours. The above composition is formulated for resulting in an ejaculation time delay of approximately 40 minutes.

EXAMPLE 3

[31] The pharmaceutical composition of the present invention comprise a timed release formulation, hereinafter referred to as third strength, including tramadol 100mg, rabeprazole 20mg, cetirizine hydrochloride 10mg formulated for immediate release. The composition further comprises tramadol 50mg formulated for timed release at 20 minutes. In addition, sildenafil citrate 100mg is formulated for timed release at once after 4 hours of dosing. The above composition is formulated for resulting in an ejaculation time delay of approximately 60 minutes.

[32] FIG.1 shows a chart illustrating different doses of Zyrtec, Tramal, Pariet and sildenafil formulated for timed release at 0 hours, 20 minutes and 4 hours after dosing. Zyrtec 10mg, Tramal 100mg and Pariet 20mg were formulated for immediate release at 0 minutes, Tramal 50mg formulated for timed release at 20 minutes after dosing, and Sildenafil 100mg formulated for timed release at 4 hrs after dosing.

[33] FIG. 2 shows a line chart illustrating the minutes of delay in onset of ejaculation, caused by the timed release formulation in different strengths (first, second and third strengths) as given in the above examples. The chart also shows minutes of delay caused by other drug formulations.

[34] Although the invention has been described with reference to the disclosed embodiments, those skilled in the art will readily appreciate that the specific examples and studies detailed above are only illustrative of the invention. It should be understood that various modifications can be made without departing from the spirit of the invention. Accordingly, the invention is limited only by the following claims.

I Claim:

1. A modified release pharmaceutical composition for treating premature ejaculation, wherein the said composition comprises the timed release of therapeutically effective amounts of following ingredients:
 - a) 150 mg of tramadol in modified release, wherein 100mg of the tramadol is used at once and 50mg after 20 minutes; and
 - b) 20 mg of rabeprazol in immediate Release; and
 - c) 10 mg Citrizine in immediate release; and
 - d) 100 mg of sildenafil in modified release after 4 hoursin their pharmaceutically acceptable excipients, salts, carriers and spansule coatings thereof.
2. The composition of claim 1, further comprises the timed release of therapeutically effective amounts of following ingredients:
 - a) 150 mg of tramadol in modified release, wherein 100mg of the tramadol used at once and 50mg after 20 minutes; and
 - b) 20 mg of rabeprazol in immediate release; and
 - c) 10 mg Citrizine in immediate release; and
 - d) 100 mg of sildenafil in modified Release after 4 hours

in their pharmaceutically acceptable excipients, salts, carriers and spansule coatings thereof; wherein the said composition is useful for the delay the onset of ejaculation by approximately 60 minutes.

3. The composition of claim 1, further comprises the timed release of therapeutically effective amounts of following ingredients:

- a) 100 mg of tramadol in modified release, wherein 50mg of the tramadol used at once and 50mg after 20 minutes; and
- b) 20 mg of rabeprazol in immediate Release; and
- c) 10 mg Citrizine in immediate Release; and
- d) 100 mg of sildenafil in modified release after 4 hours

in their pharmaceutically acceptable excipients, salts, carriers and spansule coatings thereof; wherein the said composition is useful for the delay the onset of ejaculation by approximately 40 minutes.

4. The composition of claim 1, further comprises the timed release of therapeutically effective amounts of following ingredients:

- a) 50 mg of tramadol in modified release, wherein 50 mg of the tramadol used at once; and
- b) 20 mg of rabeprazol in immediate Release; and
- c) 10 mg Citrizine in immediate Release; and

d) 100 mg of sildenafil in modified release after 4 hours
in their pharmaceutically acceptable excipients, salts, carriers and spansule
coatings thereof; wherein the said composition is useful for the delay the onset of
ejaculation by approximately 20 minutes.

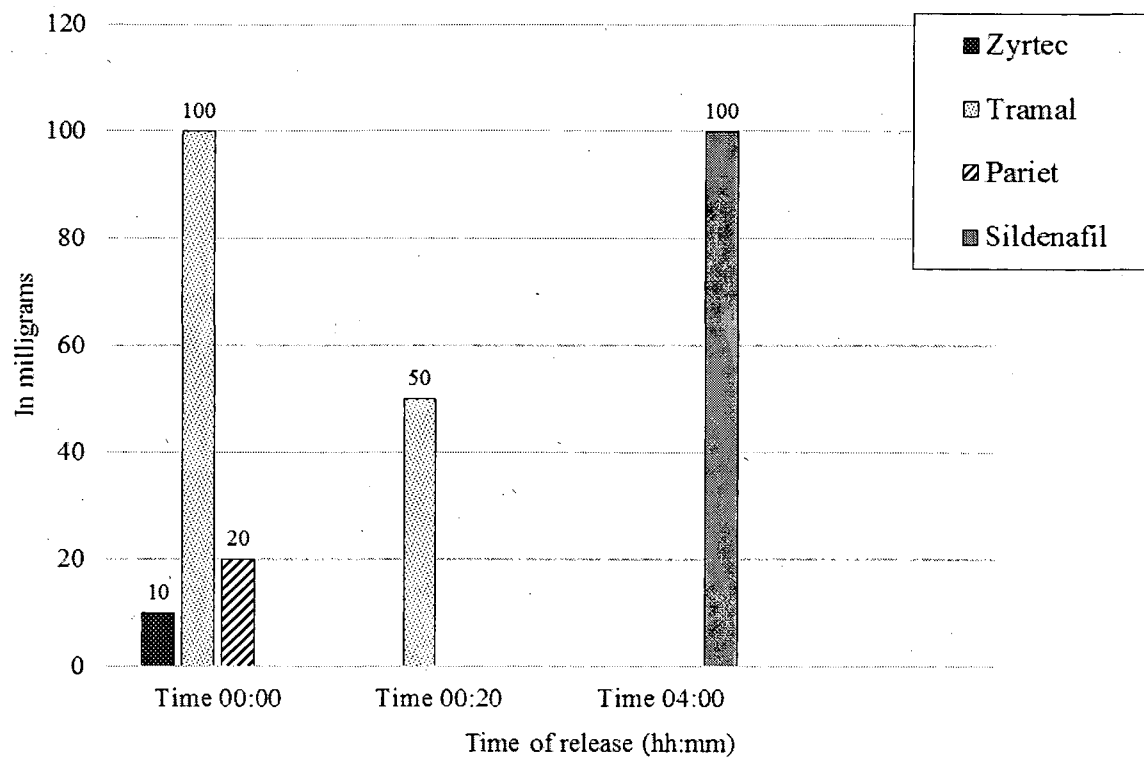


FIG. 1

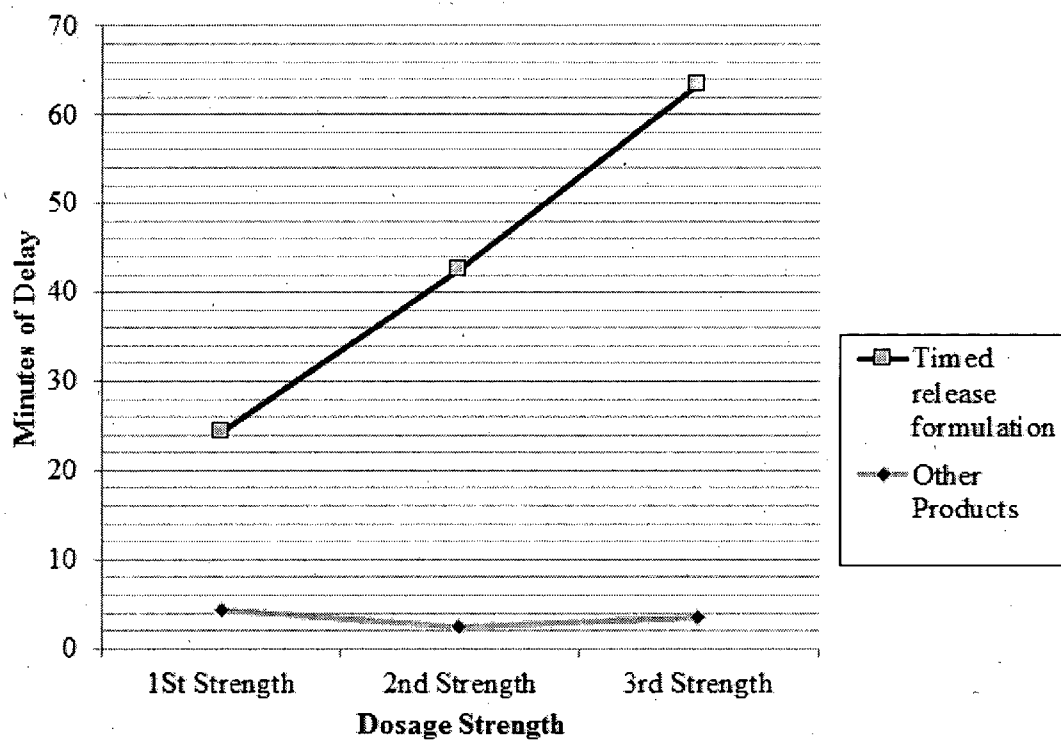


FIG. 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2016/000223**A. CLASSIFICATION OF SUBJECT MATTER****A61K 31/137(2006.01)i, A61K 31/4439(2006.01)i, A61K 31/495(2006.01)i, A61K 31/519(2006.01)i, A61K 9/20(2006.01)i, A61K 9/48(2006.01)i, A61P 15/00(2006.01)i**

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K 31/137; A61K 31/135; A61K 9/22; A61K 9/20; A61K 31/138; A61P 15/00; A61K 9/58; A61K 31/485; A61K 31/4439; A61K 31/495; A61K 31/519; A61K 9/48

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal) & keywords: tramadol, rabeprazol, citrizine, sildenafil, premature ejaculation, modified release, immediate release, full quantitative timely release (FQTR)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2009-0215810 A1 (SINGH, C. U.) 27 August 2009 See paragraph [0043]; examples 2, 7; and claims 1-20.	1-4
A	US 2010-0047343 A1 (HASLAM, J. L. et al.) 25 February 2010 See abstract; and claims 1-32.	1-4
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A	US 8158147 B2 (SETH, P. et al.) 17 April 2012 See abstract; and claims 1-11.	1-4
A	MARTYN-ST JAMES, M. et al., "Tramadol for premature ejaculation: a systematic review and meta-analysis", BMC Urology, 30 January 2015, Vol. 15, No. 6, internal pages 1-11 See abstract.	1-4



Further documents are listed in the continuation of Box C.



See patent family annex.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

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