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(54) **Title**: PHARMACEUTICAL COMPOSITIONS OF RALTEGRAVIR, METHODS OF PREPARATION AND USE THEREOF

(57) **Abstract**: Disclosed are pharmaceutical compositions comprising HIV integrase strand transfer inhibitor. More particularly, oral pharmaceutical compositions of raltegravir or its pharmaceutically acceptable salts and process for preparing and use of the same are disclosed.

PHARMACEUTICAL COMPOSITIONS OF RALTEGRAVIR, METHODS OF PREPARATION AND USE THEREOF

Priority

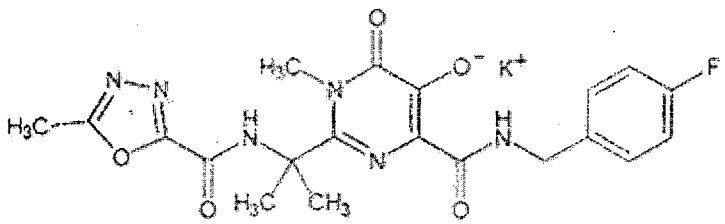
This patent application claims priority to Indian application number 1414/CHE/2011, filed on April 25, 2011, the contents of which are incorporated by reference herein in their entirety.

Field of the Invention

Disclosed herein are pharmaceutical compositions comprising HIV integrase strand transfer inhibitor. More particularly, oral pharmaceutical compositions of raltegravir or its pharmaceutically acceptable salts and process for preparing and use of the same are disclosed.

Background

Raltegravir and its pharmaceutically acceptable salt or solvate thereof were disclosed in U.S. Patent No. 7,169,780. Chemically raltegravir potassium is *N*-[(4-Fluorophenyl)methyl]-1,6-dihydro-5-hydroxy-1-methyl-2-[1-methyl-1-[[(5-methyl-1,3,4 -oxadiazol-2-yl)carbonyl]amino]ethyl]-6-oxo-4-pyrimidinecarboxamide monopotassium salt having the following structural formula:



Raltegravir potassium, a human immunodeficiency virus integrase strand transfer inhibitor, is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.

Raltegravir is commercially available as a prescription medicine from Merck; under the trade name ISENTRESS® (Raltegravir Potassium) for the treatment of HIV infections. Approved in 2007 by the U.S. Food and Drug Administration, ISENTRESS® is currently available in the form of 400 milligram (mg) oral tablets.

U.S. Patent No. 7,754,731 assigned to Merck claims anhydrous crystalline potassium salt of raltegravir.

WO2006060681 assigned to Merck claims compositions of raltegravir potassium comprising an anti-nucleating agent selected from hydroxyalkylcellulose, alkylcellulose, polyvinylpyrrolidone and polyacrylic acid.

WO2006060711 assigned to Merck claims oral formulations of raltegravir potassium comprising poloxamer as a solubilizing agent, and high viscosity hydroxypropylmethylcellulose, glyceryl behenate as gelling agent.

WO2010140156 assigned to Hetero Research Foundation discloses amorphous raltegravir potassium, and crystalline Form H1 of raltegravir potassium.

There remains a need to develop formulations of raltegravir using conventional techniques and equipment which is easy to manufacture.

Summary of the Invention

It has been found that compositions of raltegravir comprising non-gelling polymers are comparable with the marketed raltegravir potassium formulation.

In one embodiment, the pharmaceutical composition comprises raltegravir as active ingredient or its pharmaceutically acceptable salt thereof, non-gelling polymer and one or more pharmaceutically acceptable excipients.

In another embodiment, the pharmaceutical composition comprises raltegravir, non-gelling polymer selected from polymethacrylates and / or polyethylene oxide, and one or more

pharmaceutically acceptable excipients, characterized in that said composition is free of anti-nucleating agent.

In another embodiment, a process for preparing a pharmaceutical composition comprising raltegravir, non-gelling polymer and at least one pharmaceutically acceptable excipient, comprises using wet granulation, dry granulation, spray granulation, direct compression or extrusion-spheronization, wherein the composition is free of anti-nucleating agent and solubilizing agent.

In one aspect, a wet granulation process for preparing compressed tablet of raltegravir, comprising non-gelling polymer, comprises: (i) dry mixing raltegravir with one or more excipients, (ii) wet granulating the dry mix of step (i) using binder solution to form granules followed by drying, (iii) lubricating the dried granules with remaining portion of the excipients and finally compressing into tablets.

In a further aspect, the process for preparing a compressed tablet of raltegravir, comprising non-gelling polymer, by dry granulation comprises: (i) sifting and blending raltegravir with one or more excipients, (ii) compressing the blended mixture of step (i) to form slugs and then sizing the resulting slugs to form granules; (iii) blending the granules with remaining portion of the excipients; and (iv) finally compressing the granules of step (iii) into tablets.

In yet another aspect, the tablet composition comprises raltegravir potassium, non-gelling polymer selected from polymethacrylates and / or polyethylene oxide and one more pharmaceutically acceptable excipients, characterized in that said composition is free of anti-nucleating agent and solubilizing agent.

Detailed Description

By "salts" or "pharmaceutically acceptable salts", it is meant those salts and esters which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, and allergic response, commensurate with a reasonable benefit to risk ratio, and effective for their intended use.

"Free from" or "Free of" used here synonymously means that the ingredient is not intentionally added as a major ingredient during preparation of a composition; the composition can contain trace amounts of the ingredient, such as less than about 2%, or 1 %, or 0.5%, by weight.

A pharmaceutical composition comprises raltegravir or its pharmaceutically acceptable salt thereof, non-gelling polymer and one or more pharmaceutically acceptable excipients.

A pharmaceutical composition comprises raltegravir, non-gelling polymer selected from polymethacrylates and / or polyethylene oxide and one or more pharmaceutically acceptable excipients, characterized in that said composition is free of anti-nucleating agent.

"Anti-nucleating agent" means a water-soluble polymer. The term "water-soluble polymer" means any polymer which is freely soluble in water or which dissolves or solubilizes in water (e.g., in an amount of at least about 0.005 mg/ml). Exemplary water-soluble polymers include hydroxyalkylcelluloses, alkylcelluloses, polyvinylpyrrolidones, and polyacrylic acids.

"Non-gelling polymer" means a polymer that is insoluble and essentially un-swellable upon contact with an aqueous medium, specifically water. Non-gelling polymer specifically excludes water soluble (e.g., in an amount of at least about 0.005 mg/ml) and/or water swellable polymers such as hydroxyalkylcelluloses, alkylcelluloses, polyvinylpyrrolidones, and polyacrylic acids.

Suitable non-gelling polymethacrylates include by way of example and without limitation, poly (ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) polymer, poly (ethyl acrylate, methyl methacrylate) polymer, a methacrylic acid-methyl methacrylate co-polymer, a methacrylic acid-ethyl acrylate co-polymer, poly (methyl acrylate, methyl methacrylate, methacrylic acid) or combination thereof. The non-gelling polymers exclude polyacrylic acids such as carbomer polymers (Carbopol). Exemplary non-gelling polymers include Eudragit RL (poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) 1:2:0.2), and Eudragit RS (poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) 1:2:0.1), Eudragit NE 30 D (poly(ethyl acrylate-co-methyl methacrylate) 2:1), Eudragit L30 D-55 (poly(methacrylic acid-

co-ethyl acrylate) 1:1), Eudragit FS 30D (poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid) 7:3:1), Eudragit L100 55 (poly(methacylic acid-co-ethyl acrylate) 1:1), Polyethylene oxide (Sentry Polyox) or combinations thereof. It is noted that polyethylene oxide is different from polyethylene glycol. Polyethylene oxide is a high molecular weight non ionic homopolymer of ethylene oxide and having the molecular formula $(CH_2CH_2O)_n$. In comparison, polyethylene glycol is a low molecular weight addition polymer of ethyleneoxide and water, having the molecular formula $H(OCH_2CH_2)_nOH$, where n represents the average number of oxyethylene groups.

The non-gelling polymer can be present in the composition in an amount of about 0.5 to about 20 percent weight/weight (%w/w), specifically about 1 to about 15%w/w, and yet more specifically about 3 to about 10%w/w based on the total weight of the composition.

The pharmaceutical compositions can be made into solid dosage forms such as tablets, capsules, Multiple Unit Pellet System (MUPS), granules, solid dispersions, pellets, beads, particles, mini-tablets, orally disintegrating tablets and the like.

Accordingly, in one embodiment, the pharmaceutical oral composition comprises raltegravir, non-gelling polymers and one or more excipients selected from diluents, binders, lubricants and/or glidants.

Suitable diluents include talc, lactose, sugar, starches, modified starches, mannitol, sorbitol, inorganic salts, cellulose derivatives (e.g. microcrystalline cellulose), calcium sulfate, xylitol, lactitol, starch, pregelatinized starch, kaolin, sucrose, mannitol, sorbitol, dextrates, dextrin, maltodextrin, dextrose, calcium carbonate, calcium sulfate, dibasic calcium phosphate, tribasic calcium phosphate, magnesium carbonate, magnesium oxide and the like and mixtures thereof.

The pharmaceutically acceptable diluent can be present in the composition in an amount of about 1 to about 50 percent %w/w, specifically about 15 to about 45%w/w, and yet more specifically about 30 to about 40%w/w based on the total weight of the composition.

The term "binders" as used herein is intended to mean substances used to cause adhesion of powder particles in tablet granulations. Suitable binders include, by way of example and

without limitation, lactose, starches such as corn starch, potato starch, modified starches, sugars, guar gum, pectin, wax binders, microcrystalline cellulose, methylcellulose, carboxymethylcellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, copolyvidone, sodium alginate, acacia, alginic acid, tragacanth, carboxymethylcellulose sodium, ethyl cellulose, gelatin, liquid glucose, povidone and pregelatinized starch, and the like or mixtures thereof.

The term "lubricant" as used herein is intended to mean substances used in tablet formulations to reduce friction during tablet compression. Suitable lubricants include, by way of example and without limitation, calcium stearate, magnesium stearate, sodium stearyl fumarate, zinc stearate, stearic acid, fumaric acid, palmitic acid, talc, carnauba wax, hydrogenated vegetable oils, mineral oil, polyethylene glycols and the like or combinations thereof.

The term "glidant" as used herein is intended to mean agents used in tablet and capsule formulations to improve flow-properties during tablet compression and to produce an anti-caking effect. Such compounds include, by way of example and without limitation, colloidal silica, calcium silicate, magnesium silicate, silicon hydrogel, cornstarch, talc and the like or combinations thereof.

The tablets may be coated with an aqueous or non aqueous solution or dispersion of film forming agents. Optionally, the film coat may be an aqueous moisture barrier. The coating solution mainly comprises of film forming polymers and one or more of plasticizers, opacifiers, surfactants, anti tacking agents, coloring agents and the like.

The coating can be applied by solubilizing or suspending the excipients in solvents such as isopropyl alcohol, water, acetone, ethanol, methylene chloride and the like or mixtures thereof.

Also provided herein is a process for preparing a pharmaceutical composition comprising raltegravir, non-gelling polymer and at least one pharmaceutically acceptable excipient, using wet granulation, dry granulation, spray granulation, direct compression, or extrusion-spheronization wherein the composition is free of anti-nucleating agent and solubilizing agent.

"Solubilizing agent" means an agent that acts to prevent or minimize precipitation of raltegravir in the gastrointestinal tract by maintaining it in a solubilized form for several hours following administration; solubilizing agents include poloxamers and fatty acid macrogolglycerides.

Direct compression process for preparing raltegravir tablets comprises the steps of: (i) dry mixing raltegravir with one or more excipients followed by blending, (ii) lubricating the blend obtained in step (i), and (iii) finally compressing the blend of step (ii) into tablets.

Dry granulation involves; (a) sifting and blending raltegravir with one or more excipients (b) compressing the blended mixture of step (a) to form slugs and then sizing the resulting slugs to form granules; (c) blending the granules with all or none or remaining portion of the excipients; and (d) finally compressing the granules of step (c) in to tablets.

Alternatively, dry granulation involves; compacting raltegravir and other excipients in a roller compactor; and the compacts obtained were passed through ASTM Sieve # 20 to obtain granules. The granules were lubricated and compressed into tablets on a rotary compression machine and the tablets were optionally coated with Opadry.

In one embodmient, the tablet composition comprises raltegravir, non-gelling polymer and one more pharmaceutically acceptable excipients, wherein the composition is free of anti-nucleating agent and solubilizing agent; wherein the tablet is prepared by either direct compression or dry granulation.

In another embodiment, the tablet composition of raltegravir comprising polyethylene oxide, a non-gelling polymer and one or more pharmaceutically acceptable excipients, free of anti-nucleating agent and solubilizing agent.

Tablet composition comprising raltegravir, non-gelling polymethacrylates such as poly (ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) polymer, poly (ethyl acrylate, methyl methacrylate) polymer, a methacrylic acid-methyl methacrylate co-polymer, a methacrylic acid-ethyl acrylate co-polymer, poly (methyl acrylate, methyl methacrylate, methacrylic acid) or combination thereof and one more pharmaceutically

acceptable excipients, wherein the composition is free of anti-nucleating agent and solubilizing agent.

Compositions of raltegravir comprising non-gelling polymers will improve the pharmacokinetic parameters by delaying the drug release in acidic pH and thereby delaying the T_{max}.

The term "raltegravir" as used herein includes raltegravir in the form of free base, pharmaceutically acceptable salt, amorphous raltegravir potassium, raltegravir potassium crystalline Form H1, crystalline raltegravir potassium monohydrate, crystalline raltegravir potassium dihydrate or any isomer, derivative, hydrate, solvate, or prodrug or combinations thereof.

In one embodiment, a method of treating a patient in need of raltegravir treatment comprises administering to a patient a pharmaceutical composition comprising raltegravir or a pharmaceutically acceptable salt thereof, a non-gelling polymer, and one or more pharmaceutically acceptable excipients.

The invention is further exemplified with following examples and is not intended to limit the scope of the invention. Those skilled in the art can determine the composition for other dosage forms and substitute the equivalent excipients as described in this specification or with those known to the industry without undue experimentation.

Examples 1-4

Compositions of Raltegravir tablets prepared by dry granulation:

S. No	Ingredients	Example -1 Mg / tablet	Example - 2 Mg / tablet	Example - 3 Mg / tablet	Example - 4 Mg / tablet
Intragranular portion					
1	Raltegravir potassium	434.4	434.4	434.4	434.4
2	Microcrystalline cellulose	231.5	297.4	261.3	211.5
3	Lactose monohydrate	50	15	25	40
4	Eudragit RL PO	26.1	--	--	--

5	Polyethylene oxide	17.4	17.4	43.5	78.3
6	Magnesium stearate	7	7	7	7
7	Sodium stearyl fumarate	4	4	4	4
Extragranular portion					
8	Microcrystalline cellulose	93.6	86.1	86.1	86.1
9	Magnesium stearate	6	8.7	8.7	8.7
	Core tablet weight	**870**	**870**	**870**	**870**
Coating					
10	Opadry II Pink	21.75	21.75	21.75.	21.75
11	Purified water	q.s	q.s	q.s	q.s
	Total weight	**891.75**	**891.75**	**891.75**	**891.75**

Brief manufacturing process:

i) Intragranular materials were sifted and blended together,

ii) the blended material of step no (i) was slugged/ compacted and the resulted slugs/ compacts were milled using multimill or cone mill,

iii) milled granules of step (ii) were sifted through # 30 mesh completely,

iv) extra granular materials were sifted together through # 40 mesh,

v) extra granular magnesium stearate was sifted through # 60 mesh,

vi) materials of step (iii), (iv) and (v) were blended together and compressed into tablets,

vii) compressed tablets were optionally coated with opadry II pink.

Examples 5-8

Compositions of Raltegravir tablets prepared by wet granulation:

S. No	Ingredients	Example-5 Mg/ tablet	Example -6 Mg / tablet	Example -7 Mg / tablet	Example -8 Mg / tablet
Intragranular portion					
1	Raltegravir potassium	434.4	434.4	434.4	434.4
2	Microcrystalline cellulose	300	300	300	280
3	Lactose monohydrate	25	25	25	25

Binder Solution					
4	Eudragit RL PO	8.7	--	--	--
5	Eudragit NE 30 D	--	9	--	--
6	Eudragit FS 30 D	--	--	9	--
7	Eudragit L 100 55	--	--	--	10
8	Isopropyl Alchohol	q.s	--	--	q.s
9.	Acetone	q.s	--	--	q.s
10	Purified Water	--	q.s	q.s	--
Extragranular portion					
11	Microcrystalline cellulose	93.2	92.9	92.9	111.9
12	Magnesium stearate	8.7	8.7	8.7	8.7
	Core tablet weight	**870**	**870**	**870**	**870**
Coating					
13	Opadry II Pink	21.75	21.75	21.75	21.75
14	Purified water	q.s	q.s	q.s	q.s
	Total weight	**891.75**	**891.75**	**891.75**	**891.75**

Brief manufacturing process:

i) Intragranular materials were sifted and blended together,

ii) the blended material of step no (i) was granulated using binder solution and the resulted granules were dried and milled using multimill or cone mill,

iii) milled granules of step (ii) were sifted through # 20 mesh completely,

iv) extra granular materials were sifted together through # 40 mesh,

v) extra granular magnesium stearate was sifted through # 60 mesh,

vi) materials of step (iii), (iv) and (v) were blended together and compressed into tablets,

vii) compressed tablets were optionally coated with opadry II pink.

Example 9

Tablet compositions of Raltegravir prepared by extrusion -spheronization method:

S. No	Ingredients	Mg / tablet
Intragranular		
1	Raltegravir potassium	434.40
2	Microcrystalline cellulose	254.30
3	Lactose monohydrate	25.00
4	Eudragit RL PO	8.70
5	Purified water	q.s

6	Isopropyl Alchohol	q.s
Extragranular		
7	Microcrystalline cellulose	138.90
8	Magnesium stearate	8.70
Core tablet weight		**870.00**
6	Opadry pink	21.75
7	Purified water	q.s
Total tablet weight		**891.75**

Brief manufacturing process:

i) Intragranular materials were sifted and granulated with purified water using rapid mixer granulator,

ii) the wet granules of step no (i) was extruded and the resulted extrudes were spheronized using spherodizer to obtain spherical granules,

iii) spherical granules of step (ii) were dried completely,

iv) extra granular materials were sifted together through # 40 mesh,

v) extra granular magnesium stearate was sifted through # 60 mesh,

vi) materials of step (iii), (iv) and (v) were blended together and compressed into tablets,

vii) compressed tablets were optionally coated with opadry II pink.

Example 10

Comparison of a Raltegravir tablet prepared with a non-gelling polymer to a Raltegravir tablet prepared without a non-gelling polymer:

Raltegravir potassium is highly sensitive in acidic pH as it may get precipitated or degraded. The use of a non-gelling polymer in a raltegravir formulation will not allow release, or slightly delays the active agent release, from the formulation in the acidic pH range such as found in the stomach, thereby extending the formulation's T_{max} and decreasing the C_{max}. Furthermore, dose dumping and inter-intra subject variation is minimized. Additionally, there is no need for a solubilizer in the raltegravir formulation when the non-gelling polymer is used.

The table below provides the results of a comparative dissolution profile of a raltegravir potassium tablet formulation prepared with a non-gelling polymer and a comparative raltegravir potassium tablet formulation prepared without a non-gelling polymer. The dissolution

conditions: 0.001N HCl, 900 ml, USP-II, 100 rpm. As can be seen, the formulation containing non-gelling polymer releases less raltegravir active at the low pH conditions used in the study. The delay will help prevent undue precipitation and degradation of the active. In comparison, the formulation without the non-gelling polymer exhibits a decrease in concentration of the active over time due to the active ingredient getting degraded.

Time in Minutes	% Cumulative Drug Release	
	With Non-gelling Polymer	Without Non-gelling Polymer
15	41	59
30	60	76
45	75	71
60	82	48
90	85	31

We claim:

1. A pharmaceutical composition, comprising:
raltegravir or a pharmaceutically acceptable salt thereof,
a non-gelling polymer, and
one or more pharmaceutically acceptable excipients.

2. The pharmaceutical composition of claim 1, wherein the non-gelling polymer comprises a polymethacrylate, a polyethylene oxide, or a combination thereof.

3. The pharmaceutical composition of claim 2, wherein the polymethacrylate is poly (ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride), poly (ethyl acrylate, methyl methacrylate), a methacrylic acid-methyl methacrylate co-polymer, a methacrylic acid-ethyl acrylate co-polymer, poly (methyl acrylate, methyl methacrylate, methacrylic acid), or combination thereof.

4. The pharmaceutical composition of any one of claims 1-3, wherein the non-gelling polymer is present in an amount of about 0.5 to about 20 %w/w based on the total weight of the composition.

5. The pharmaceutical composition of any one of claims 1-4, wherein the composition is free of an anti-nucleating agent, a solubilizing agent, or a combination thereof.

6. A pharmaceutical composition, comprising:
raltegravir or a pharmaceutically acceptable salt thereof,
a non-gelling polymer, wherein the non-gelling polymer comprises a polymethacrylate, a polyethylene oxide, or a combination thereof, and
one or more pharmaceutically acceptable excipients,
wherein the composition is free of an anti-nucleating agent, a solubilizing agent, or a combination thereof.

7. The pharmaceutical composition of any one of clams 1-6, wherein the composition is in the form of a tablet, capsule, Multiple Unit Pellet System, granules, pellets, beads, particles, or mini-tablets.

8. A tablet composition, comprising:
raltegravir or a pharmaceutically acceptable salt thereof,
a non-gelling polymer, wherein the non-gelling polymer is a polyethylene oxide, and
one or more pharmaceutically acceptable excipients,
wherein the tablet composition is free of an anti-nucleating agent, a solubilizing agent, or a combination thereof.

9. A tablet composition, comprising:
raltegravir or a pharmaceutically acceptable salt thereof,
a non-gelling polymer, wherein the non-gelling polymer is poly (ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride), poly (ethyl acrylate, methyl methacrylate), a methacrylic acid-methyl methacrylate co-polymer, a methacrylic acid-ethyl acrylate co-polymer, poly (methyl acrylate, methyl methacrylate, methacrylic acid), or a combination thereof, and
one or more pharmaceutically acceptable excipients,
wherein the composition is free of an anti-nucleating agent, a solubilizing agent, or a combination thereof.

10. The composition of any one of claims 1-9 wherein the raltegravir is in the form of amorphous raltegravir potassium, raltegravir potassium crystalline Form H1, crystalline raltegravir potassium monohydrate, crystalline raltegravir potassium dihydrate or a combination thereof.

11. A process for preparing a pharmaceutical composition comprising raltegravir or a pharmaceutically acceptable salt thereof, a non-gelling polymer, and one or more pharmaceutically acceptable excipients, comprising:
using wet granulation, dry granulation, spray granulation, direct compression, or extrusion-spheronization,
wherein the composition is free of anti-nucleating agent and solubilizing agent.

12. A method of treating a patient in need of raltegravir treatment, comprising:
administering a composition of any one of claims 1-10 to a patient.