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(54) Title: A PROCESS FOR PREPARING RALTEGRAVIR POTASSIUM FORM 3

(57) Abstract: The present invention relates to a process for preparing Raltegravir potassium Form 3.



“A PROCESS FOR PREPARING RALTEGRAVIR POTASSIUM FORM 3”

PRIORITY

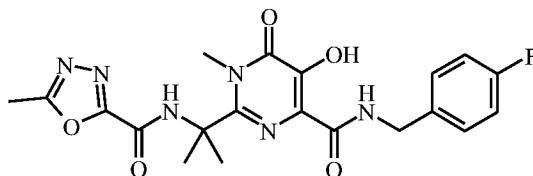
This application claims the benefit under Indian Provisional Application No(s).
5 3282/CHE/2015, filed on June 29 2015 entitled “A process for preparing raltegravir
potassium form 3”, and 201641012263 filed on Apr 07, 2016 entitled “A process for
preparing raltegravir potassium form 3” the content of each of which are incorporated
by reference herein.

FIELD OF THE INVENTION

10 The present invention generally relates to a process for the preparation of Raltegravir
potassium Form 3 and its pharmaceutical composition thereof.

BACKGROUND OF THE INVENTION

15 Raltegravir, also referred to as N-(2-(4-(4- fluorobenzylcarbamoyl)-5-hydroxy- 1 -
methyl-6-oxo-1,6-dihydropyrimidin-2-yl)propan-2-yl)-5-methyl-1,3,4-oxadiazole-2-
carboxamide, is an antiretroviral drug used to treat HIV infection and has the
following formula I;



Formula I

20

Raltegravir is an antiretroviral drug which is marketed as potassium salt under the
trade name ISENTRESS™ by Merck & Co to treat human immunodeficiency virus
(HIV) infection. It is a first line HIV-integrase strand transfer inhibitor drug that
targets Integrase, an HIV enzyme that integrates the viral genetic material into human
25 chromosomes.

N-substituted hydroxypyrimidinone carboxamide inhibitors of HIV integrase including
raltegravir or a pharmaceutically acceptable salt thereof and its preparation are
described in US Patent No. 7,169,780 and U.S. Patent No. 7,754,731 is specifically
directed to a potassium salt, particularly a crystalline potassium salt of Raltegravir.

Raltegravir exhibits poor aqueous solubility where as the potassium salt of Raltegravir is significantly more soluble in water and exhibit improved pharmacokinetics in animal models over Raltegravir free base.

- 5 Raltegravir potassium can exist in different polymorphic forms, which differ from each other in terms of stability, physical properties and pharmacokinetics. The following documents in the art are directed towards polymorphs of Raltegravir potassium, which are incorporated here by way reference.

10 U.S. Patent No. 7,754,731 (the “731 patent) disclosed polymorphic forms of raltegravir potassium namely anhydrous crystalline Form 1, Form 3; hydrated crystalline Form 2 and amorphous form including their preparation process. Raltegravir potassium form 3 is prepared by reacting raltegravir with aqueous potassium hydroxide in acetonitrile solvent, frozen drying the resulting solution at -78°C followed by freeze drying to obtain amorphous raltegravir potassium, a portion
15 of which is then crystallized from hot ethanol to yield raltegravir potassium form 3.

The above process for the preparation of raltegravir potassium form 3 suffers from the certain disadvantages in that it is not reproducible and involves preparing amorphous form of raltegravir potassium in the first step by frozen drying at -78°C followed by freeze drying which requires specialized equipment and cryogenic temperatures and
20 then converting it to form 3 in the second step, hence this process is not economical and industrially viable.

PCT Publication No. WO 2011/024192 (“the 192 publication”) disclosed preparation of raltegravir potassium amorphous form and crystalline forms 1, 2 and 3. Raltegravir potassium form 3 is being prepared in this publication by suspending raltegravir in a
25 1:1 mixture of methanol and acetone, stirring at 23-30°C to get a clear solution, treating with methanolic potassium hydroxide solution and isolating the product by adding isopropyl ether as anti-solvent. This publication uses trisolvant system for the preparation of Form 3 of raltegravir potassium, which is un-economical on commercial
30 scale.

IP.Com journal disclosure No. IPCOM000243081D disclosed a process for the preparation of raltegravir potassium form 3 by suspending or dissolving raltegravir in a solvent or mixture of solvents such as ethanol, water, methanol and the like, adding a potassium base and isolating form 3.

35 IN Publication No. 5282/CHE/2013 (“the ‘5282 application”) disclosed the preparation of Raltegravir potassium Form-3 by providing a solution or suspension of Raltegravir in ethanol, adding aq KOH, optionally seeding and isolating Form 3.

IN Publication No. 3346/DEL/2012 (“the ‘346 application”) disclosed the preparation of Raltegravir potassium Form-3 by using an alcoholic solvent.

Several other polymorphic forms of raltegravir potassium have been reported in the art such as:

- 5 PCT Publication No(s). WO2010/140156 (“the ‘156 publication”) & WO 2011/148381 (“the ‘381 publication”) disclosed amorphous Raltegravir potassium and crystalline Raltegravir potassium Form H1 and process for preparation thereof.

- PCT Publication No. 2011/123754 disclosed crystalline Forms such as Form IV, Form V, Form VI, Form VII, Form VIII, Form IXa, Form IXb, Form X, Form XI, Form XII,
10 Form XIII, Form XIV, Form XV, and Form XVI of raltegravir potassium and preparation thereof.

PCT Publication No. WO2012/103105 disclosed the preparation of raltegravir potassium Form V.

- PCT Publication No. 2013/037731 disclosed crystalline raltegravir potassium hydrate
15 form IV and its preparation

IN Publication No. 522/MUM/2011 discloses crystalline Raltegravir potassium Form APO-I and a process for its preparation.

- 20 IP.Com journal disclosure Number IPCOM000194495D discloses an amorphous form of Raltegravir potassium.

IP.Com journal disclosure Number IPCOM000224583D discloses the preparation of Form I of Raltegravir potassium.

- 25 IP.Com journal disclosure Number IPCOM000223913D discloses a crystalline form of Raltegravir potassium characterized by X-ray powder diffraction pattern having peaks at 7.6, 11.4, 15.1, 16.7, 18.2, 19.1, 22.9, 24.3, 27.2 and 27.8°2θ.

- IP.Com journal disclosure Number IPCOM000209501D discloses a crystalline form of Raltegravir potassium characterized by X-ray powder diffraction pattern having peaks
30 at 8.0, 11.9, 14.9, 18.2, 19.8, 24.9, 26.6, 27.7 and 28.9°2θ and a process for preparing crystalline form of Raltegravir potassium by exposing amorphous Raltegravir potassium to water.

Journal of Medicinal Chemistry (2008), 51(18), 5843-5855 describes the preparation of potassium salt of Raltegravir by freeze-drying a solution of Raltegravir in acetonitrile and aqueous KOH, followed by crystallization of the freeze-dried material from ethanol. The Raltegravir potassium salt reported in this publication is
5 characterized by M.P 282°C.

Organic Process Research & Development, 2011, 15 (1), pp 73–83 reports the preparation of the potassium salt of Raltegravir by adding aqueous KOH to a solution of Raltegravir in ethanol:water (1:1 by volume) at 20°C followed by seeding at room
10 temperature with Raltegravir potassium. The Raltegravir potassium salt reported in this publication is characterized by M.P 274.2-275.2°C.

Although processes for the preparation of raltegravir potassium form 3 is known in the art, there is a need for improved methods for the preparation of raltegravir potassium form 3, which can be prepared by an efficient, economic and reproducible process
15 particularly in large scale preparation.

Therefore, the present invention fulfills the need in the art and provides a simple, commercially viable and scalable process for the preparation of Raltegravir potassium Form 3 that circumvent disadvantages associate with prior-art.

Accordingly, the present invention provides a process for preparation of Raltegravir potassium Form 3, which process reduces the number of solvent usage, avoids cryogenic temperatures and specialized equipment, thereby the process is advantageous for scale-up production, especially in terms of operating efficiency and makes the process commercially viable. The invention further provides use of tertiary alcoholic potassium base as potassium source, which process provides Raltegravir
20 potassium Form 3 consistently.
25

SUMMARY OF THE INVENTION

The main object of the present invention is to provide convenient, commercially viable, and economical process for the preparation of raltegravir potassium form 3.

30 In accordance with one embodiment, the present invention provides a process for the preparation of raltegravir potassium form 3, comprising:

- a) providing a solution or suspension of raltegravir in an organic solvent, wherein the organic solvent is selected from esters, halogenated hydrocarbons, alcohols, amides, cyclic ethers and ketonic solvents or mixtures thereof,
- 35 b) treating the step a) reaction mixture with a suitable potassium source, and
- c) isolating the raltegravir potassium Form 3.

In accordance with another embodiment, the present invention provides a process for the preparation of raltegravir potassium form 3, comprising:

- a) providing a solution or suspension of raltegravir in an organic solvent, ,
- b) treating the step a) reaction mixture with suitable potassium source, and
- 5 c) isolating the raltegravir potassium Form 3;

wherein the organic solvent is selected from ethyl acetate, dichloromethane, N,N-dimethyl acetamide, ethanol, 2-butanol and tert-butanol or mixtures thereof; wherein the potassium source is selected from potassium tertiary butoxide or potassium hydroxide.

10

In accordance with another embodiment, the present invention provides a process for the preparation of raltegravir potassium form 3, comprising:

- a) providing a solution or suspension of raltegravir in ethyl acetate at a temperature of about 25°C to reflux temperature,
- 15 b) treating the step a) reaction mixture with potassium tertiary butoxide in tertiary butanol,
- c) stirring the reaction mass at a temperature of about 25°C to 45°C,
- d) optionally, cooling the solution to less than 20°C, and
- e) filtering the raltegravir potassium Form 3.

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In accordance with another embodiment, the present invention provides a process for the preparation of raltegravir potassium Form 3, comprising:

- a) providing a solution of raltegravir in dichloromethane,
- b) treating the resultant solution with potassium tertiary butoxide solution, and
- 25 c) isolating the raltegravir potassium Form 3.

In another embodiment, the present invention provides a pharmaceutical composition comprising raltegravir potassium form 3 prepared by the process of the present invention and at least one pharmaceutically acceptable excipient.

30 BRIEF DESCRIPTION OF THE DRAWINGS:

The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate several embodiments of the invention and together with the description, serve to explain the principles of the invention.

35 Figure 1 is the characteristic powder XRD pattern of raltegravir potassium form 3.

Figure 2 is the characteristic DSC thermogram of raltegravir potassium form 3.

DETAILED DESCRIPTION OF THE INVENTION

The main object of the present invention is to provide convenient, commercially viable, and economical process for the preparation of Raltegravir potassium form 3 and pharmaceutical compositions comprising the same.

In accordance with one embodiment, the present invention provides a process for the preparation of raltegravir potassium form 3, comprising:

- a) providing a solution or suspension of raltegravir in an organic solvent, wherein the organic solvent is selected from esters, halogenated hydrocarbons, alcohols, amides, cyclic ethers and ketonic solvents or mixtures thereof,
- b) treating the step a) reaction mixture with a suitable potassium source, and
- c) isolating the raltegravir potassium Form 3.

The starting material raltegravir free base used in the present invention can be obtained by any of the methods known in the art, for example according to U.S. Patent No. 7,169,780 and U.S. Patent No. 7,754,731 or it may be obtained as a solution directly from a reaction mixture in which raltegravir is formed and used as such without isolation.

The step of providing a solution or suspension of raltegravir in an organic solvent may include stirring any form of raltegravir in an organic solvent in suspension state or by stirring any form of raltegravir in an organic solvent until clear solution is obtained. Alternatively, raltegravir may be obtained as a suspension or solution directly from a reaction mixture in which raltegravir is formed and used as such without isolation.

Examples of organic solvents used herein for step (a) includes but are not limited to esters such as ethyl acetate, n-butyl acetate, n-propyl acetate, t-butyl acetate, isopropyl acetate and the like; halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform and the like; amides such as N,N-dimethyl acetamide, N,N-diethylacetamide and the like; alcohols such as methanol, ethanol, n-butanol, 2-butanol, tert-butanol, and the like; cyclic ethers such as tetrahydrofuran, 1,4-dioxane, 2-methyl tetrahydrofuran and the like; ketones such as acetone, methyl ethyl ketone or mixtures thereof. Preferably, the organic solvent is selected from the group consisting of ethyl acetate, dichloromethane, N,N-dimethyl acetamide, ethanol, tert-butanol, 2-butanol or mixtures thereof.

The step a) is carried out at a temperature of about 20°C to reflux temperature, preferably at about 25°C to about 45°C. Then, the reaction mixture is treated with a suitable potassium source at a temperature of from about 10°C to about 50°C for a period of about 5 minutes to about 120 minutes.

The suitable potassium source is selected from potassium hydroxide, potassium carbonate, potassium bicarbonate, or potassium alkoxide i.e a potassium salt of an alkyl alcohol selected from potassium methoxide, potassium ethoxide, potassium propoxide, potassium isopropoxide and potassium tertiary butoxide; preferably the
5 suitable potassium source is selected from potassium tertiary butoxide or potassium hydroxide. In some embodiments potassium alkoxide such as potassium tertiary butoxide, was found to be particularly useful.

The potassium source can be used as a solid or in dissolved form in a solvent; preferably potassium tertiary butoxide or potassium hydroxide is dissolved in a solvent
10 such as alcohols selected from methanol, ethanol, isopropanol, tertiary butanol, 1-pentanol and the like; cyclic ethers such as tetrahydrofuran. Preferably the potassium source can be dissolved in ethanol, 1-pentanol, tertiary butanol or mixtures thereof.

The suitable potassium source can be added either as a solution in one or more solvents or it may be added as a solid to the solution of raltegravir in one or more
15 solvents or the solution of raltegravir in one or more solvents may be added to a solution of potassium source. The way of addition of the potassium source is not particularly critical.

The step b) reaction may typically be carried out at a temperature of about 10° C to
20 50°C and the potassium salt emission occurred during the addition of potassium source.

Typically the step b) reaction is preferably carried out at a temperature of about 25°C to about 35°C and stirred for appropriate period of time for precipitation of the product, preferably over a period from about 10 mins to about 6 hours such that the
25 resulting raltegravir potassium form 3 can be isolated by conventional techniques.

The raltegravir potassium isolated using the process of the present invention is substantially in polymorph form 3. The resultant raltegravir potassium form 3 can be isolated by any conventional technique known in the art, for example, filtration and the resultant raltegravir potassium may optionally be further dried. Drying can be suitably
30 carried out in a tray dryer, vacuum oven, air oven, fluidized bed drier, spin flash dryer, flash dryer and the like. The drying can be carried out at a temperature ranging from about 30°C to about 150°C for a time period ranging from about 1 hour to about 20 hours.

35 In another embodiment, the present invention provides a process for the preparation of raltegravir potassium form 3, comprising:

- a) providing a solution or suspension of raltegravir in ethyl acetate at a temperature of about 25°C to reflux temperature,

- b) treating the step a) reaction mixture with potassium tertiary butoxide in tertiary butanol;
- c) stirring the reaction mass at a temperature of about 25°C to 45°C,
- d) optionally, cooling the solution to less than 20°C, and
- 5 e) filtering the raltegravir potassium Form 3.

The step a) is carried out at a temperature of about 20°C to reflux temperature, preferably at about 25°C to about 45°C. Then, the reaction mixture is treated with potassium tertiary butoxide in tertiary butanol at a temperature of from about 10°C to about 50°C for a period of about 5 minutes to about 120 minutes.

The potassium tertiary butoxide solution can be added to the solution or suspension of raltegravir in ethyl acetate or the solution or suspension of raltegravir in ethyl acetate may be added to a potassium tertiary butoxide solution. The way of addition of the potassium source is not particularly critical; preferably the potassium source is added to the suspension of raltegravir in ethyl acetate.

The addition of potassium tertiary butoxide solution typically carried out at a temperature of about 25° C to 35°C and the potassium salt emission occurred during the addition of potassium source.

Then, the reaction is stirred for a period of about 10 mins to about 6 hours at a temperature of about 25°C to about 35°C and the reaction mass may optionally be cooled to less than 20°C and the resulting raltegravir potassium form 3 can be isolated by filtration. The resultant raltegravir potassium may optionally be further dried. Drying can be suitably carried out in a tray dryer, vacuum oven, air oven, fluidized bed drier, spin flash dryer, flash dryer and the like. The drying can be carried out at a temperature ranging from about 30°C to about 150°C for a time period ranging from about 1 hour to about 20 hours.

In accordance with another embodiment, the present invention provides a process for the preparation of raltegravir potassium Form 3, comprising:

- a) providing a solution or suspension of raltegravir in dichloromethane at a temperature of about 20°C to reflux temperature,
- b) treating the step a) reaction mixture with potassium tertiary butoxide in tetrahydrofuran,
- c) stirring the reaction mass at a temperature of about 25°C to 45°C, and
- 35 d) isolating the raltegravir potassium Form 3.

The step a) is carried out at a temperature of about 20°C to reflux temperature. At this stage, the step a) solution or suspension optionally treated with charcoal at the same temperature.

The step b) reaction may typically be carried out at a temperature of about 20° C to 65°C and the potassium salt emission occurred during the addition of potassium tert-butoxide solution.

- 5 Then, the reaction is stirred for a period of about 10 mins to about 6 hours at a temperature of about 25°C to about 45°C and the reaction mass may optionally be cooled to less than 20°C and the resulting raltegravir potassium form 3 can be isolated by filtration. The resultant raltegravir potassium may optionally be further dried. Drying can be suitably carried out in a tray dryer, vacuum oven, air oven, fluidized bed
10 drier, spin flash dryer, flash dryer and the like. The drying can be carried out at a temperature ranging from about 30°C to about 150°C for a time period ranging from about 1 hour to about 20 hours.

- The reported process for the preparation of raltegravir potassium form 3 involves a two-step process of preparing amorphous form of raltegravir potassium in the first step
15 and then converting it to form 3 in the second step. Further, the reported process involves the techniques such as frozen drying and freeze drying which are not commercially viable and requires specialized equipment and cryogenic temperatures. In contrast, the process of the present invention involves a simple and economical process and does not require any specialized equipment and cryogenic temperatures
20 and is conveniently carried out at room temperature in one step. According to the present inventive process raltegravir potassium Form 3 can be prepared consistently.

The raltegravir potassium form 3 can be characterized by one or more of the techniques such as PXRD and DSC techniques.

- 25 The X-Ray powder diffraction can be measured using PANalytical X'per³pro X-ray powder Diffractometer equipped with a Cu-anode ($[\lambda] = 1.54$ Angstrom), X-ray source operated at 45kV, 40 mA. Two-theta calibration is performed using an NIST SRM 640c Si standard. The sample was analyzed using the following instrument parameters: measuring range=3-45°2 θ ; step size=0.01°; and Time per step=43 sec.

- 30 The DSC data reported herein were analyzed in hermitically sealed pinhole aluminium pan, with a blank hermitically sealed aluminium pan as the reference and were obtained using DSC (DSC Q200, TA instrumentation, Waters) at a scan rate of 10°C per minute to 350°C with an Indium standard.

- 35 In another embodiment, the present invention provides a pharmaceutical composition comprising the raltegravir potassium form 3 prepared according to the process of the present invention and at least one or more pharmaceutically acceptable excipients.

EXAMPLES

The present invention is further illustrated by the following examples, which are provided by way of illustration only and should not be construed to limit the scope of the invention.

5 EXAMPLE 1: Preparation of raltegravir potassium form 3:

Raltegravir (500 mg) was suspended in a mixture of tert-butanol (4 ml), ethanol (8 ml) containing potassium tertiary butoxide solution (1M, 1.2 ml) in tert-butanol at 25-35°C. The reaction mass was stirred for 4 hours at 25-35°C, filtered, washed with ethanol (2 ml) and suck dried the solids under nitrogen for 30 mins. The obtained
10 compound was dried at 53°C under vacuum for 4 hours to obtain 501 mg of raltegravir potassium form 3.

EXAMPLE 2: Preparation of raltegravir potassium form 3:

Raltegravir (5 gms) was suspended in ethanol (100 ml) and charged potassium tertiary butoxide solution (1M, 12 ml) in tert-butanol at 25-35°C. The reaction mass was
15 stirred for 4 hours at 25-35°C, filtered, washed with ethanol (25 ml) and suck dried the solids under nitrogen for 30 mins. The obtained compound was further dried at 53°C under vacuum for 6 hours to obtain 4.9 gms of raltegravir potassium form 3.

EXAMPLE 3: Preparation of raltegravir potassium form 3:

Raltegravir (10 gms) was dissolved in DCM (100ml), filtered and distilled DCM
20 completely under vacuum at 35°C. Co-distilled two times with ethanol (50 ml each) at 65°C and ethanol (200 ml) was added to the resulting residue. The reaction mixture was cooled to 25°C and charged potassium tertiary butoxide solution (1M, 24 ml) in tert-butanol at 25°C. The reaction mass was stirred for 3 hours at room temperature, filtered, washed with ethanol (50 ml) and suck dried the solids for 15 mins under
25 nitrogen. The obtained compound was dried at 75°C under vacuum for 16 hours to obtain 9.5 gms of raltegravir potassium form 3.

EXAMPLE 4: Preparation of raltegravir potassium form 3:

Raltegravir (500 mg) was dissolved in N,N-dimethyl acetamide (2 ml) and alcoholic potassium hydroxide solution (70 mg potassium hydroxide dissolved in a mixture of
30 ethanol (4 ml) and 1-pentanol(4 ml)) was added at 25°C. The resulting suspension was stirred for 4 hours at 25-35°C, filtered, washed with ethanol (2 ml) and suck dried the solids for 30 mins under nitrogen. The obtained compound was dried at 53°C under vacuum for 6 hours to obtain 356 mg of raltegravir potassium form 3.

EXAMPLE 5: Preparation of raltegravir potassium form 3:

Raltegravir (300 mg) was suspended in 2-butanol (2 ml) and ethanolic potassium hydroxide solution (42 mg potassium hydroxide dissolved in ethanol (0.5 ml)) was added at 25-35°C. Further, ethanol (4 ml) was added to the reaction mass and the resulting suspension was stirred at 25-35°C for 2 hours. The reaction mass was
5 filtered, washed with ethanol (1 ml) and suck dried the solids for 30 mins under nitrogen to obtain 130 mg of raltegravir potassium form 3.

EXAMPLE 6: Preparation of Raltegravir potassium Form-3:

Raltegravir (100 g) was suspended in dichloromethane (1000 ml) at room temperature (25-35°C). The solution was stirred under N₂ atmosphere for 15-30 min at 25-35°C,
10 decolorized with charcoal, filtered and washed with dichloromethane. The resulting filtrate was allowed to cool to 20-25°C. This clear solution was added to a solution of pre-filtered 1.0 M potassium tertiary butoxide (183 g) in THF over a period of 5-10 min at 20-35°C, stirred the reaction mass for 10 min at 25-35°C, filtered and washed with dichloromethane (100 ml) and suck dried. The obtained wet material was dried
15 initially at 50-55°C for 1 hour, cooled to 35-40°C and milled under nitrogen at room temperature. The semidried raltegravir potassium further dried for 12 hours under vacuum at 120-125°C to obtain 105 gms of the title compound.

EXAMPLE 7: Preparation of Raltegravir potassium Form-3:

Raltegravir (100 gms) was dissolved in DCM (1 Ltr) at 25-35°C and stirred for 10 min
20 at 25-35°C under nitrogen. The obtained solution was decolorized with charcoal (5 gms), filtered and washed with DCM (200 mL). The resulting filtrate was distilled completely under vacuum at below 35°C and co-distilled with ethyl acetate (200 mL) at below 45°C. Ethyl acetate (2 Ltr) was added to the residue followed by pre-filtered 1.0 M potassium tertiary butoxide (172.73 gms) in tert butanol over a period 5-15 min
25 at 25-35°C. The reaction mass was stirred for 30 min at 30°C, filtered the reaction mass, washed with ethyl acetate (100 mL) and suck dried. The obtained wet material was dried initially at 50-55°C for 4 hr under vacuum, cooled to 35-40°C and milled under nitrogen at room temperature followed by further drying for 16 hrs under vacuum at 95-105°C and cooled to 25-30°C to obtain 85 gms of raltegravir potassium
30 form 3.

EXAMPLE 8: Preparation of Raltegravir potassium Form-3:

Raltegravir (100 mg) was suspended in ethyl acetate (2 Ltr) at 25-35°C and 1.0 M potassium tertiary butoxide (172.73 gms) in tert butanol was added over a period 5-15 min at 25-35°C. The reaction mass was stirred for 30 min at 30°C, filtered the reaction
35 mass, washed with ethyl acetate (100 mL) and suck dried. The obtained wet material was dried initially at 50-55°C for 1 hr under vacuum, cooled to 35-40°C and milled

under nitrogen at room temperature followed by further drying for 16 hrs under vacuum at 95-105°C and cooled to 25-30°C to obtain 87 gms of raltegravir potassium form 3.

EXAMPLE 9: Preparation of Raltegravir potassium Form-3:

5 Raltegravir (100 g) was suspended in dichloromethane (1000 ml) at room temperature (25-35°C). The solution was stirred under N₂ atmosphere for 15-30 min at 25-35°C, decolorized with charcoal, filtered and washed with dichloromethane. The resulting filtrate was allowed to cool to 20-25°C. This clear solution was added to a solution of
10 pre-filtered 1.0 M potassium tertiary butoxide (183 g) in tetrahydrofuran over a period of 5-10 min at 20-35°C, stirred the reaction mass for 10 min at 25-35°C, filtered and washed with dichloromethane (100 ml) and suck dried. The obtained wet material was dried initially at 50-55°C for 1 hour, cooled to 35-40°C and milled under nitrogen at room temperature. The semidried raltegravir potassium further dried for 12 hours under vacuum at 120-125°C to obtain 105 gms of raltegravir potassium form 3.

15 EXAMPLE 10:

Preparation of Raltegravir potassium Form-3:

Raltegravir (10 g) was suspended in dichloromethane (100 ml) at room temperature (25-35°C). The solution was stirred under N₂ atmosphere for 15-30 min at 25-35°C, decolorized with charcoal, filtered and washed with dichloromethane. The resulting
20 filtrate was cooled to 20-25°C. This clear solution was added to a solution of pre-filtered 1.0 M potassium tertiary butoxide (18.3 g) in tetrahydrofuran over a period of 5-10 min at 20-35°C, stirred the reaction mass for 10 min at 25-35°C, filtered and washed with dichloromethane (10 ml) and suck dried. The obtained wet material was dried initially at 50-55°C for 1 hour, cooled to 35-40°C and milled under nitrogen at
25 room temperature followed by further dried for 12 hours under vacuum at 120-125°C to obtain 10 gms of raltegravir potassium form 3.

While the invention has been described with reference to above detailed description and the preferred examples, it is not intended to be limited thereto. Therefore the above description should not be construed as limiting, but merely as exemplifications
30 of preferred embodiments. For example, the functions described above and implemented as the best mode for operating the present invention are for illustration purposes only. Other arrangements and methods may be implemented by those skilled in the art without departing from the scope and spirit of this invention. Moreover, those skilled in the art will envision other modifications within the scope and spirit of
35 the specification appended hereto.

WE CLAIM

Claim 1: A process for the preparation of raltegravir potassium Form 3, comprising:

- 5 a) providing a solution or suspension of raltegravir in an organic solvent, ,
 b) treating the step a) reaction mixture with a suitable potassium source, and
 c) isolating the raltegravir potassium Form 3; wherein the organic solvent is
 selected from esters, halogenated hydrocarbons, alcohols, amides, cyclic ethers
 and ketonic solvents or mixtures thereof.

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Claim 2: The process of claim 1, wherein the organic solvent is selected from the group consisting of ethyl acetate, dichloromethane, N,N-dimethyl acetamide, ethanol, 2-butanol and tert-butanol or mixtures thereof.

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Claim 3: The process of claim 1, wherein the step a) is carried out at a temperature of about 20°C to reflux temperature.

Claim 4: The process of claim 1, wherein the suitable potassium source is used as a solvent containing potassium source.

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Claim 5: The process of claim 4, wherein the suitable potassium source is potassium hydroxide or potassium tertiary butoxide.

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Claim 6: The process of claim 4, wherein the solvent is selected from the alcohols selected from methanol, ethanol, isopropanol, tertiary butanol, 1-pentanol and the like; cyclic ethers such as tetrahydrofuran.

Claim 7: The process of claim 4, wherein the suitable potassium source used is potassium tertiary butoxide in tertiary butanol or tetrahydrofuran.

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Claim 8: The process of claim 4, wherein the suitable potassium source used is potassium hydroxide in ethanol, or a combination of ethanol and 1-pentanol.

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Claim 9: The process of claim 1, wherein the step b) is carried out at a temperature of about 25°C to about 35°C.

Claim 10: The process of claim 1, wherein suitable potassium source is added at a temperature of about 20°C to about 65°C.

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Claim 11: The process of claim 1, wherein the isolation is carried out by filtration.

Claim 12: The process of claim 1, wherein step c) further comprises drying the raltegravir potassium at a temperature ranging from about 30°C to about 150°C.

5 Claim 13: A process for the preparation of raltegravir potassium Form 3, comprising:

- a) providing a solution or suspension of raltegravir in ethyl acetate at a temperature of about 25°C to reflux temperature,
- b) treating the step a) reaction mixture with potassium tertiary butoxide in tertiary butanol;
- 10 c) stirring the reaction mass at a temperature of about 25°C to 45°C,
- d) optionally, cooling the solution to less than 20°C, and
- e) filtering the raltegravir potassium Form 3.

15 Claim 14: The process of claim 13, wherein the step b) is carried out at a temperature of about 25°C to about 35°C.

Claim 15: The process of claim 13, wherein the potassium tertiary butoxide solution in tertiary butanol is added to the suspension of raltegravir in ethyl acetate.

20 Claim 16: The process of claim 13, wherein step e) further comprises of drying the raltegravir potassium at a temperature ranging from about 30°C to about 150°C.

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Figure 1

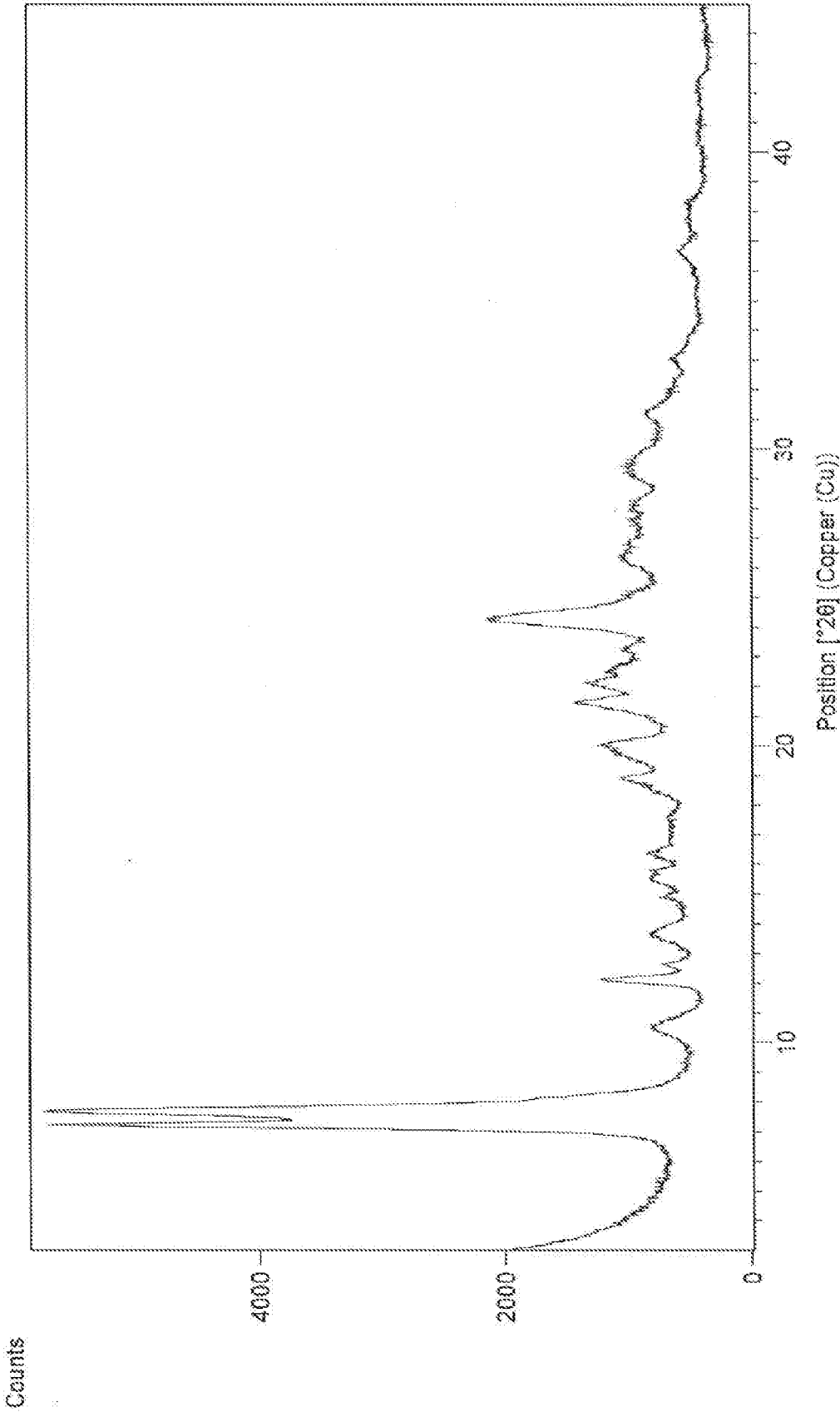
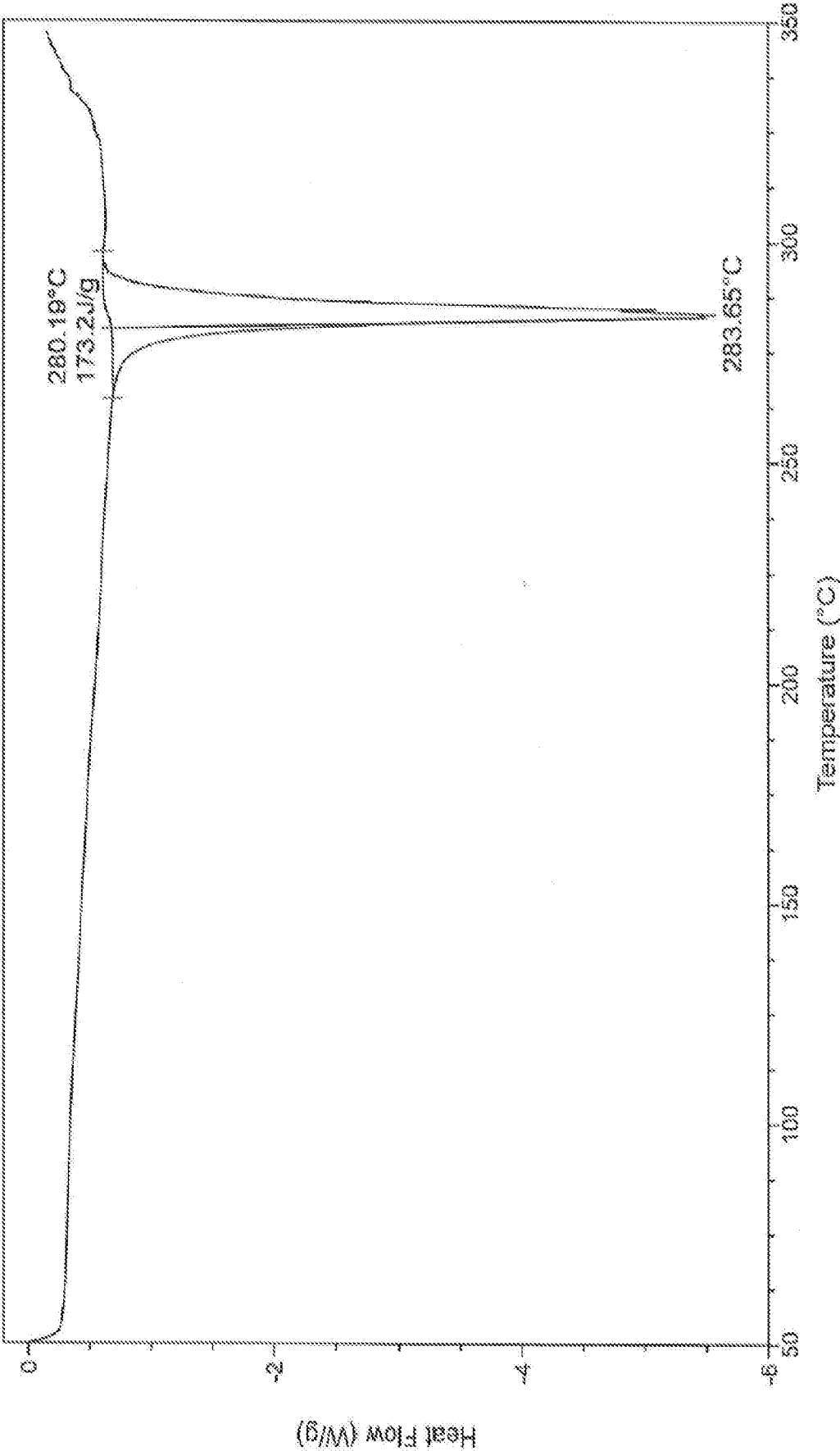


Figure 2



INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2016/053819

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/00 Version=2016.01

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

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

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

Patseer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	D1: IN2012MA000003019 OR IN3019/CHE/2012 (MYLAN LABORATORIES LTD) 07 Mar 2014 (07.03.2014) Example 3, page 11 and claim 5	1-16
Y	D2: CA2795157 A1 (TEVA PHARMACEUTICAL INDUSTRIES LTD) 06 Oct 2011 (06.10.2011) Example 29	1-16

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

17-10-2016

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2016/053819

Citation	Pub.Date	Family	Pub.Date
CA 2795157 A1	06-10-2011	US 20130079360 A1	28-03-2013
		EP 2545048 A1	16-01-2013