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(54) Title: NOVEL POLYMORPHS OF RALTEGRAVIR

(57) Abstract: The present invention relates to novel polymorphic forms of Raltegravir and processes for its preparation thereof. The present invention further relates to an improved process for preparation of amorphous and crystalline Form 1, Form 2 and Form 3 of Raltegravir Potassium salt.



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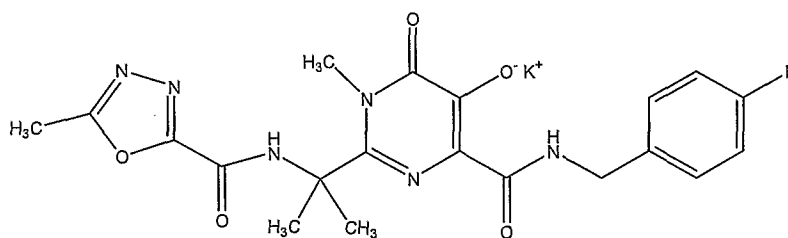
This application claims priority to Indian patent application No. 1765/CHE/2009 filed on July 27, 2009 the contents of which are incorporated by reference in their entirety.

FIELD OF INVENTION

The present invention relates to novel polymorphic forms of Raltegravir and processes for its preparation thereof. The present invention further relates to an improved process for preparation of amorphous and crystalline Form 1, Form 2 and Form 3 of Raltegravir potassium salt.

BACKGROUND OF THE INVENTION

Raltegravir is an antiretroviral drug produced by Merck & Co and marketed as potassium salt used in combination with other anti-retroviral drugs 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 chromosomes. The chemical name for Raltegravir potassium is N-[(4-fluorophenyl)methyl]-1,6-dihydro-5-hydroxy-1-methyl-2-[[[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino]ethyl]-6-oxo-4-pyrimidinecarboxamide monopotassium salt and is structurally represented by formula I. Raltegravir potassium salt is marketed under the brand name **Isentress®**.



Formula I

Raltegravir and its pharmaceutically acceptable salts are disclosed in US 7,169,780. US 2006/0122205 A1 discloses polymorphic forms of Raltegravir Potassium namely anhydrous crystalline potassium salt of Raltegravir (Form 1 and Form 3); hydrated crystalline potassium salt of Raltegravir (Form 2).

In literature, polymorphs of Raltegravir are not known and during our recent studies on polymorphic screening inventors found two novel polymorphic forms Form A and Form B of Raltegravir and also amorphous form of Raltegravir. The Raltegravir polymorphic Form B and amorphous form of Raltegravir potassium salt of the present invention is
5 having good stability and purity in different conditions and can also be prepared by an efficient, economic and reproducible process particularly in large scale preparation with free flowing nature.

OBJECT OF THE INVENTION

10 Principle object of the present invention is to provide amorphous Raltegravir and process for preparation of the same.

Another principle object of the present invention is to provide novel Raltegravir Form A and process for preparation of the same.

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Yet another principle object of the present invention is to provide novel Raltegravir Form B and process for preparation of the same.

Further principle object of the present invention is to provide amorphous Raltegravir
20 potassium salt and process for preparation of the same.

Another principle object of the present invention is to provide improved process for preparation of Raltegravir potassium Form 1.

25 Another principle object of the present invention is to provide improved process for preparation of Raltegravir potassium Form 2.

Another principle object of the present invention is to provide improved process for preparation of Raltegravir potassium Form 3.

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SUMMARY OF THE INVENTION

The main aspect of the present invention is to provide amorphous Raltegravir as shown in figure 1.

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Another aspect of the present invention is to provide process for the preparation of amorphous Raltegravir comprising the steps of a) dissolving Raltegravir in a solvent to form a clear solution; b) removing the solvent; and c) isolating amorphous Raltegravir.

10 In another aspect, the present invention provides crystalline form of Raltegravir, designated as Form A.

Another aspect of the present invention is to provide process for the preparation of crystalline Raltegravir Form A comprising the steps of: a) suspending Raltegravir in a solvent; b) heating the suspension to form clear solution; and c) crystallizing the solution
15 of step b) to isolate Raltegravir Form A.

Another aspect of the present invention is to provide alternative process for the preparation of crystalline Raltegravir Form A comprising the steps of: a) suspending Raltegravir in a solvent; b) heating the suspension to form clear solution; c) adding anti-
20 solvent; and d) isolating Raltegravir Form A.

Another aspect of the present invention is to provide alternative process for the preparation of Raltegravir Form A comprising the steps of: a) suspending Raltegravir in a polar solvent; and b) isolating Raltegravir Form A.

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In another aspect, the present invention provides crystalline form of Raltegravir, designated as Form B.

Another aspect of the present invention is to provide process for the preparation of
30 crystalline Raltegravir Form B comprising the steps of: a) suspending Raltegravir in a polar solvent or mixtures thereof; b) optionally heating the contents to form clear solution; and c) cooling the solution to isolate Raltegravir Form B.

Another aspect of the present invention is to provide alternative process for the preparation of crystalline Raltegravir Form B comprising the steps of: a) dissolving Raltegravir in a solvent; b) adding isopropyl ether as anti-solvent; and c) isolating Raltegravir Form B.

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Another aspect of the present invention is to provide alternative process for the preparation of crystalline Raltegravir Form B comprising the steps of: a) suspending amorphous Raltegravir in isopropyl ether; and b) isolating Raltegravir Form B.

In another aspect, the present invention provides amorphous Raltegravir potassium. Another aspect of the present invention is to provide process for the preparation of amorphous Raltegravir potassium salt comprising the steps of: a) dissolving Raltegravir in a polar solvent; b) adding aqueous potassium hydroxide solution; c) removing the solvent; and d) isolating amorphous Raltegravir Potassium.

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In another aspect, the present invention provides process for the preparation of Raltegravir Potassium Form 1 comprising the steps of: a) dissolving Raltegravir in a solvent; b) adding alcoholic potassium hydroxide solution; and c) isolating Raltegravir Potassium Form 1.

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Another aspect of the present invention is to provide alternative process for the preparation of Raltegravir Potassium Form 1 comprising the steps of: a) suspending amorphous Raltegravir potassium in a solvent; b) heating the suspension to get the clear solution; c) cooling the reaction mass; and d) isolating Raltegravir Potassium Form 1.

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Another aspect of the present invention is to provide alternative process for the preparation of Raltegravir Potassium Form 1 comprising the steps of: a) suspending amorphous Raltegravir potassium in solvent mixture; b) heating the suspension to get the clear solution; c) allowing the contents of step b) to evaporate slowly; and d) isolating Raltegravir potassium form 1.

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In another aspect, the present invention provides process for the preparation of Raltegravir Potassium Form 2 comprising the steps of: a) suspending amorphous Raltegravir Potassium in chlorinated solvents; and b) isolating Raltegravir potassium Form 2.

In another aspect, the present invention provides process for the preparation of Raltegravir Potassium Form 3 comprising the steps of: a) suspending Raltegravir in a solvent or mixture of solvents; b) stirring the suspension to obtain a clear solution; c) adding alcoholic potassium hydroxide solution; d) adding isopropyl ether as anti-solvent; and e) isolating Raltegravir potassium Form 3.

In another aspect, the present invention provides process for the preparation of Raltegravir Potassium Form 3 comprising the steps of: a) suspending Raltegravir in a solvent or mixture of solvents; b) stirring the suspension to obtain a clear solution; c) adding alcoholic potassium hydroxide solution; and d) isolating Raltegravir potassium Form 3.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrate the PXRD of amorphous Raltegravir

Figure 2 illustrate the DSC of amorphous Raltegravir

Figure 3 illustrate the IR of amorphous Raltegravir

Figure 4 illustrate the PXRD of Raltegravir Form A

Figure 5 illustrate the DSC of Raltegravir Form A

Figure 6 illustrate the TGA/DTA of Raltegravir Form A

Figure 7 illustrate the IR of Raltegravir Form A

Figure 8 illustrate the PXRD of Raltegravir Form B

Figure 9 illustrate the DSC of Raltegravir Form B

Figure 10 illustrate the TGA/DTA of Raltegravir Form B

Figure 11 illustrate the IR of Raltegravir Form B

Figure 12 illustrate the PXRD of amorphous Raltegravir potassium.

Figure 13 illustrate the DSC of amorphous Raltegravir potassium.

Figure 14 illustrate the IR of amorphous Raltegravir potassium.

Figure 15 illustrate the PXRD of Raltegravir potassium Form 1.

5 Figure 16 illustrate the PXRD of Raltegravir potassium Form 2.

Figure 17 illustrate the PXRD of Raltegravir potassium Form 3.

DETAILED DESCRIPTION OF THE INVENTION

0 The present invention provides novel polymorphic forms of Raltegravir designated as crystalline Form A, Form B and amorphous form. The present invention also provides novel amorphous form of Raltegravir potassium salt. The present invention further relates to processes for the preparation of the said polymorphic forms. The present invention also provides processes for the preparation of Raltegravir potassium Form 1, 2 and 3.

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In one embodiment, the present invention provides amorphous Raltegravir characterized by PXRD pattern as shown in Figure 1. The amorphous form contains the water up to approximately 1.0 to 4.0 % by weight, preferably 1.0 to 2.0 % determined by the Karl-Fisher method.

20

The DSC thermogram of amorphous Raltegravir shows three characteristic peaks (Figure 2); first endothermic peak at an extrapolated onset temperature ranging from 30 to 90°C corresponding to the moisture loss, an exothermic peak at an extrapolated onset temperature ranging from 120 to 140°C, corresponding to the transition from an amorphous phase to crystalline anhydrous phase which is identified with a peak at 25 131.7°C, and a second endothermic peak at 216.7°C (maxima), corresponding to the complete melting of the product.

Amorphous Raltegravir is further characterized by IR with absorption bands (cm^{-1}) at 30 832, 1017, 1248, 1350, 1510, 1682, 2995, and 3374 respectively; as depicted in Figure 3.

The present invention provides process for the preparation of amorphous Raltegravir comprising the steps of: a) dissolving Raltegravir in a solvent to form a clear solution; b) removing the solvent; and c) isolating amorphous Raltegravir.

5 According to the present invention, Raltegravir is suspended in a solvent selected from ketone, nitrile, halogenated solvents or mixture thereof; wherein ketone is selected from acetone, methyl isobutyl ketone (MIBK); nitrile is selected from acetonitrile; halogenated solvent is selected from dichloromethane, dichloroethane. Raltegravir suspension is maintained at 20-40°C preferably 25-30°C for 10-20 min to obtain clear solution. The
0 clear solution is subjected to distillation or spray drying to obtain amorphous Raltegravir.

In another embodiment, the present invention provides crystalline form of Raltegravir, referred to herein as Form A characterized by PXRD pattern as shown in Figure 4, having peaks at about 7.74, 8.03, 11.83, 15.11, 15.50, 16.08° ± 0.2° two theta values.

15 Crystalline Raltegravir Form A is further characterized by PXRD peaks at about 7.74, 8.03, 11.83, 13.57, 15.11, 15.50, 16.08, 16.35, 22.60, 23.03 ± 0.2° two theta values.

Crystalline Raltegravir Form A is further characterized by the DSC (Figure 5), which
20 shows two broad endothermic peaks at an extrapolated onset temperature ranging from 80 to 150°C corresponding to solvent loss with peak maxima at 117.6°C and 139.6°C, an exothermic peak at an extrapolated onset temperature ranging from 150 to 200°C, corresponding to the transition from a solvated phase to crystalline anhydrous phase which is identified with a peak at 176.6°C, and a third endothermic peak at 216.9°C
25 (maxima), corresponding to the complete melting of the product. TGA of Raltegravir Form A shows two step weight loss of about 4-7% attributing to solvent loss. Further, crystalline Raltegravir Form A contains the water up to approximately 4.0 to 6.0 % by weight, preferably 5.0 to 6.0 % determined by the Karl-Fisher method. Crystalline Raltegravir Form A is preferably a hydrate.

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Crystalline Raltegravir Form A is further characterized by IR with absorption bands (cm^{-1}) at 641, 855, 1003, 1218, 1342, 1536, 1637, 1703, 3000, 3302, 3493 and 3582 respectively; as depicted in Figure 7.

5 The present invention provides process for the preparation of crystalline Raltegravir Form A comprising the steps of: a) suspending Raltegravir in a solvent; b) heating the suspension to form clear solution; and c) crystallizing the solution of step b) to isolate Raltegravir Form A.

0 According to the present invention, Raltegravir is suspended in solvent selected from alcohols such as methanol, nitrile such as acetonitrile, ketones such as acetone, tetrahydrofuran, dimethyl sulfoxide, N-methyl pyrrolidone. The suspension is heated to complete dissolution. The clear solution obtained is allowed for crystallization to obtain Raltegravir Form A.

15 The present invention provides alternative process for the preparation of crystalline Raltegravir Form A comprising the steps of: a) suspending Raltegravir in a solvent; b) heating the suspension to form clear solution; c) adding anti-solvent; and d) isolating Raltegravir Form A.

20 According to the present invention, Raltegravir is dissolved in suspended in solvent selected from dimethyl acetamide, dimethyl formamide, dimethyl sulfoxide, N-methyl pyrrolidone, 1,4-dioxane, acetic acid and pyridine. The suspension is heated to high temperatures preferably 30-60° to obtain clear solution. To this clear solution, water or
25 isopropyl ether is added as an anti-solvent. The obtained solid is filtered to isolate Raltegravir Form A.

The present invention provides alternative process for the preparation of Raltegravir Form A comprising the steps of: a) suspending Raltegravir in a polar solvent; and b)
30 isolating Raltegravir Form A.

According to the present invention, crystalline or amorphous Raltegravir is suspended in water and stirred at 25-30°C. The obtained solid is filtered to isolate Raltegravir Form A.

In another embodiment, the present invention provides crystalline form of Raltegravir, referred to herein as Form B characterized by powder X-ray diffraction pattern as shown in Figure 8, having peaks at about 6.36, 12.73, 19.88, 20.20, $21.64 \pm 0.2^\circ$ two theta values.

Crystalline Raltegravir Form B is further characterized by PXRD peaks at about 6.36, 8.26, 10.92, 12.73, 13.79, 15.55, 16.57, 19.88, 20.20, $21.64 \pm 0.2^\circ$ two theta values.

Crystalline Raltegravir Form B is further characterized by the DSC (Figure 9), which shows single melting endotherm at 216.5°C. TGA/DTA (Figure 10), of Raltegravir Form B shows no significant weight loss (<0.3%) attributing anhydrous form. Further, crystalline Raltegravir Form B contains less than 0.3 % as determined by the Karl-Fisher method. Crystalline Raltegravir Form B is preferably anhydrate.

Crystalline Raltegravir Form B is further characterized by IR with absorption bands (cm^{-1}) at 488, 554, 641, 837, 1006, 1216, 1355, 1566, 1679, 3242, and 3404 respectively; as depicted in Figure 11.

The present invention provides process for the preparation of crystalline Raltegravir Form B comprising the steps of: a) suspending Raltegravir in a polar solvent or mixtures thereof; b) optionally heating the contents to form clear solution; and c) cooling the solution to isolate Raltegravir Form B.

According to the present invention, Raltegravir is suspended in a solvent selected from esters such as ethyl acetate, ketones such as acetone, alcohol such as propanol or mixtures thereof. The suspension is heated to 25-30°C to obtain clear solution which is later allowed to crystallization forms Raltegravir Form B.

The present invention provides alternative process for the preparation of crystalline Raltegravir Form B comprising the steps of: a) dissolving Raltegravir in a solvent; b) adding isopropyl ether as anti-solvent; and c) drying to isolate Raltegravir Form B.

- 5 According to the present invention, Raltegravir is dissolved in solvent selected from 1,4-dioxane, acetic acid, ketones such as acetone, alcohols such as methanol, esters such as ethyl acetate, aprotic polar solvents such as dimethyl acetamide, dimethyl formamide, N-methylpyrrolidine, aromatic solvents such as pyridine. Raltegravir suspension is maintained at 20-40°C preferably 25-30°C for 10-20 min to obtain clear solution. To the
0 clear solution, anti solvent such as isopropyl ether is added and stirred for crystallization at room temperature. Product obtained is Raltegravir form B.

- The present invention provides alternative process for the preparation of crystalline Raltegravir Form B comprising the steps of: a) suspending amorphous Raltegravir in
15 isopropyl ether; and b) isolating Raltegravir Form B.

According to the present invention, amorphous Raltegravir is suspended in isopropyl ether and stirred for 12-15 hrs at 25-30°C. The product is filtered to obtain Raltegravir Form B.

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In another embodiment, the present invention provides amorphous Raltegravir potassium as shown in Figure 12. The amorphous form contains the water up to approximately 5.0 to 7.0 % by weight, preferably 6.0 to 7.0 % determined by the Karl-Fisher method.

- 25 The DSC thermogram of amorphous Raltegravir potassium shows three characteristic peaks (Figure 13); first endothermic peak at an extrapolated onset temperature ranging from 30 to 130°C corresponding to the moisture loss, an exothermic peak at an extrapolated onset temperature ranging from 185 to 255°C, corresponding to the transition from amorphous phase to an crystalline anhydrous phase which is identified
30 with a peak at 226.2°C, and a second endothermic peak at 272.2°C (maxima), corresponding to the complete melting of the product.

Amorphous Raltegravir potassium is further characterized by IR with absorption bands (cm^{-1}) at 496, 571, 640, 830, 1218, 1280, 1510, 1639, 1680, and 3393 respectively; as depicted in Figure 14.

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The present invention provides process for the preparation of amorphous Raltegravir potassium comprising the steps of: a) dissolving Raltegravir in a polar solvent; b) adding aqueous potassium hydroxide solution; c) removing the solvent; and d) isolating amorphous Raltegravir Potassium.

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According to the present invention, Raltegravir is dissolved in a solvent group selected from ketones, nitriles, wherein the ketone is selected from acetone, MIBK or mixtures thereof, nitrile is acetonitrile. To this clear solution, potassium hydroxide solution is added and stirred at 25-30°C. The resulting clear solution is subjected to known
15 distillation techniques such as vacuum distillation at 45-65°C preferably 50-60°C or spray drying in a Mini Spray Dryer (Model Buchi-290). Spray dryer is maintained in such a way that outlet temperature is 70-80°C with continuous purging of nitrogen to isolate amorphous Raltegravir potassium.

20 The present invention provides process for the preparation of Raltegravir Potassium Form 1 comprising the steps of: a) dissolving Raltegravir in a solvent; b) adding alcoholic potassium hydroxide solution; and c) isolating Raltegravir Potassium Form 1.

According to the present invention, Raltegravir is dissolved in a solvent group selected
25 from ketones, nitriles, wherein the ketone is selected from acetone, MIBK or mixtures thereof; nitrile is selected from acetonitrile and stirred for 10 min at 25-30°C. To this clear solution, methanolic potassium hydroxide solution is added. The solid obtained is filtered to get Raltegravir Potassium Form 1.

30 The present invention provides alternative process for the preparation of Raltegravir Potassium Form 1 comprising the steps of: a) suspending amorphous Raltegravir

potassium in solvent; b) heating the suspension to get a clear solution; c) cooling the reaction mass; and d) isolating Raltegravir Potassium Form 1.

5 According to the present invention, amorphous Raltegravir potassium is suspended in a solvent selected from alcohols, ketones, and nitroalkanes, wherein alcohol is selected from methanol, ethanol, isopropanol or mixtures thereof; ketone is selected from acetone, MIBK or mixtures thereof, nitro-alkane is selected from nitro methane, nitro-ethane or mixtures thereof. The suspension is cleared at 25-30°C or subjected to heating at 60-75°C preferably 65-70°C. The obtained filtrate is stirred at 25-30°C to precipitate out
0 crystalline Raltegravir potassium Form 1.

The present invention provides alternative process for the preparation of Raltegravir Potassium Form 1 comprising the steps of: a) suspending amorphous Raltegravir potassium in solvent mixture; b) heating the suspension to get the clear solution; c)
15 allowing the contents of step b) to evaporate slowly; and d) isolating Raltegravir potassium form 1.

According to the present invention, amorphous Raltegravir potassium salt is suspended in solvent selected from alcohols such as methanol, ketones such as acetone or mixtures
20 thereof. The suspension is stirred at 25-30°C to obtain clear solution which is subjected to slow evaporation to obtain Raltegravir potassium form 1.

In another embodiment, the present invention provides process for the preparation of Raltegravir Potassium Form 2 comprising the steps of: a) suspending amorphous
25 Raltegravir Potassium in chlorinated solvents; and b) isolating Raltegravir potassium Form 2.

According to the present invention, Raltegravir is suspended in chlorinated solvents such as dichloromethane and stirred at 25-30°C for 1-3 days, preferably 2 days. The resulting
30 solid is filtered to obtain Raltegravir Potassium Form 2.

In another embodiment, the present invention provides process for the preparation of Raltegravir Potassium Form 3 comprising the steps of: a) suspending Raltegravir in solvent or mixture of solvents; b) stirring the suspension to obtain a clear solution; c) adding alcoholic potassium hydroxide solution; d) adding isopropyl ether as anti-solvent; and e) isolating Raltegravir potassium Form 3.

According to the present invention, Raltegravir is suspended in a solvent selected from alcohols, ketones such as methanol, acetone or mixtures thereof. The suspension is stirred to get clear solution and to this clear mass, methanolic potassium hydroxide solution is added. Isopropyl ether is added to the solution as an anti-solvent to isolate crystalline Raltegravir Form 3.

In another embodiment, the present invention provides process for the preparation of Raltegravir Potassium Form 3 comprising the steps of: a) suspending Raltegravir in a solvent or mixture of solvents; b) stirring the suspension to obtain a clear solution; c) adding alcoholic potassium hydroxide solution; and d) isolating Raltegravir potassium Form 3.

According to the present invention, Raltegravir is suspended in a solvent selected from ester such as ethyl acetate. The suspension is stirred to get clear solution and to this clear mass, methanolic potassium hydroxide solution is added. The solid obtained is filtered to isolate Raltegravir Potassium Form 3.

Physical Stability

The physical stability of the amorphous and novel polymorphic form B of Raltegravir and amorphous form of Raltegravir potassium salt was determined by storing approximately 3.0 g of the sample at 40°C/75% Relative Humidity (RH). The samples were tested by PXRD after 15 days, 1 month and 2 months and the observed results are shown in below table.

Compound	Initial Polymorph	Indicative stability at 40°C and 75%RH as per PXRD		
		After 15 days	After 1 month	After 2 months

Raltegravir	Amorphous	Mix of Form B+A	Mix of Form B+A	Mix of Form B+A
	Form B	Form B	Form B	Form B
Raltegravir Potassium	Amorphous	Amorphous	Amorphous	Amorphous

From indicative stability data it appears that the amorphous form of Raltegravir Potassium and Raltegravir anhydrate Form B are physically stable up to two months whereas amorphous Raltegravir is converting into a mixture of crystalline Form B and Form A.

INSTRUMENTATION

Powder X-ray Diffraction (PXRD)

The said polymorphs of the present invention are characterized by their X-ray powder diffraction pattern. Thus, the X-ray diffraction patterns of said polymorphs of the invention were measured on *PANalytical, X'Pert PRO* powder diffractometer equipped with goniometer of θ/θ configuration and *X'Celerator* detector. The Cu-anode X-ray tube was operated at 40kV and 30mA. The experiments were conducted over the 2θ range of 2.0° - 50.0° , 0.030° step size and 50 seconds step time.

Differential Scanning Calorimetry (DSC)

The DSC measurements were carried out on TA Q1000 of TA instruments. The experiments were performed at a heating rate of $10.0^\circ\text{C}/\text{min}$ over a temperature range of 30°C - 300°C purging with nitrogen at a flow rate of 50ml/min. Standard aluminum crucibles covered by lids with three pin holes were used.

Thermo gravimetric Analysis (TGA)

TGA was recorded using the instrument TA Q5000 of TA instruments. The experiments were performed at a heating rate of $10.0^\circ\text{C}/\text{min}$ over a temperature range of 30°C - 300°C purging with nitrogen at a flow rate of 25ml/min.

Karl-Fisher

Water content was determined on Metrohm Karl-Fisher titrator (Model: 794 Basic Titrino) using pyridine free single solution (Merck, Mumbai) with sample mass between 450mg to 550mg.

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Infrared spectroscopy

Fourier transform infrared (FT-IR) spectra were recorded with a Perkin-Elmer spectrum one spectrophotometer. The samples were prepared as 13mm thickness potassium bromide discs by triturating 1 to 2mg of sample with 300mg to 400mg of KBR by
10 applying pressure of about 1000 lbs/sq inch. Then these discs were scanned in the spectral range of 4000 to 650 cm^{-1} with a resolution of 4 cm^{-1} .

In the foregoing section embodiments are described by way of examples to illustrate the process of invention. However, these are not intended in any way to limit the scope of the
15 present invention and several variants of these examples would be evident to person ordinary skilled in the art.

Example 1: Preparation of amorphous Raltegravir

Raltegravir (2g) was dissolved in acetone (20 ml) and stirred for 10-15 min at 25-30°C.
20 The clear solution was then distilled out completely under vacuum at 40-50°C. The solid isolated was identified as amorphous Raltegravir.

Example 2: Preparation of amorphous Raltegravir

Raltegravir (2g) was suspended in acetonitrile (20 ml) and stirred for 10-15 min at 25-
25 30°C. The clear solution was then distilled out completely under vacuum at 40-50°C. The solid isolated was identified as amorphous Raltegravir.

Example 3: Preparation of amorphous Raltegravir

Raltegravir (2g) was suspended in dichloromethane (20 ml) and stirred for 10-15 min at
30 25-30°C. The clear solution was then distilled out completely under vacuum at 40-50°C. The solid isolated was identified as amorphous Raltegravir.

Example 4: Preparation of amorphous Raltegravir

Raltegravir (2g) was suspended in acetone (20 ml) and stirred at 25-30°C to get the clear solution. The resulting clear solution was subjected to spray drying in a Mini Spray Dryer (Model Buchi – 290) at the outlet temperature of 70-80°C with purging of nitrogen gas.

5 The solid obtained was identified as amorphous Raltegravir.

Example 5: Preparation of Raltegravir Form A by Crystallization

Raltegravir Form B (1 g) is suspended in indicated solvents at the indicated volumes at 25-30°C and stir for 10 minutes. This slurry is heated for complete dissolution and
0 allowed for crystallization at room temperature. The results obtained are displayed in the next table.

Process	Input	Solvents	Volume ratio	Temp (°C)	Result
Slow crystallization	Form B	MeOH	2	30-40	Form A
		ACN	1		
		Acetone	1		
		THF	1		
		DMSO	1		
		NMP	1		

Example 6: Preparation of Raltegravir Form A

1g of Raltegravir Form B is suspended in indicated solvents at the indicated volumes at
15 25-30°C and stir for 10 minutes. This slurry is optionally heated for complete dissolution followed by addition of an antisolvent and stirred for crystallization at room temperature. The results obtained are displayed in the next table.

Process	Input	Solvents	Volume ratio	Temp (°C)	Result
Anti-solvent method	Form B	1,4-dioxane/IPE	1:20	50-60	Form A
		DMA/water		25-30	
		DMF/water			
		NMP/water			

		DMSO/water			
		Acetic acid/water			
		Pyridine/water			

Example 7: Preparation of Raltegravir Form A

Raltegravir amorphous or Form B (1g) was suspended in water (20 ml) and stirred for 12-15 hrs at 25-30°C. The solid obtained was filtered and identified as Form A of Raltegravir.

Example 8: Preparation of Raltegravir Form B by Crystallization

1g of Raltegravir Form A is suspended in indicated solvents at the indicated volumes at 25-30°C and stir for 10 minutes. This slurry is heated for complete dissolution and allowed for crystallization at room temperature. The results obtained are displayed in the next table.

Process	Input	Solvents	Volume ratio	Temp (°C)	Result
Slow crystallization	Form A	EtOAc	3	50-60	Form B
		Acetone	1		
		Acetone + Propanol	1		

Example 9: Preparation of Raltegravir Form B

Raltegravir Form A (1g) is suspended in indicated solvents at the indicated volumes at 25-30°C and stir for 10 minutes. This slurry is optionally heated for complete dissolution followed by addition of an antisolvent and stirred for crystallization at room temperature. The results obtained are displayed in the next table.

Process	Input	Solvents	Volume ratio	Temp (°C)	Result
Anti-solvent method	Form A	Acetone/IPE	1:20	25-30	Form B
		DMA/IPE			
		DMF/IPE			
		NMP/IPE			

		MeOH/IPE	1:20	50-60	
		ACN/IPE	1:20	25-30	
		EtOAc/IPE	1:20	50-60	
		1,4-dioxane/IPE		50-60	
		Acetic acid/IPE	1:20	25-30	
		Pyridine/IPE		25-30	

Example 10: Preparation of Raltegravir Form B

Raltegravir (1g) was dissolved in acetonitrile (10 ml) and stirred for 15-30 min at 25-30°C. The clear solution is then added to prechilled isopropyl ether (80 ml) at -30 to -20°C. The solid precipitated was filtered and dried under vacuum at 40-50°C for 4-5 hours. The solid obtained is identified as Form B of Raltegravir.

Example 11: Preparation of Raltegravir Form B

Raltegravir amorphous (1g) was suspended in isopropyl ether (20 ml) and stirred for 12-15 hrs at 25-30°C. The solid obtained was filtered and identified as Form B of Raltegravir.

Example 12: Preparation of amorphous Raltegravir Potassium salt

Raltegravir (5gm) was dissolved in acetonitrile (196 ml) and stirred for 10 min at 25-30°C. To this clear solution 0.5N aqueous potassium hydroxide solution (22.3 ml) was added and stirred the mass for 15-20 min at 25-30°C. The resulting clear solution was then distilled out completely under vacuum at 50-60°C. The solid isolated was identified as amorphous Raltegravir Potassium salt.

Example 13: Preparation of amorphous Raltegravir Potassium salt

Raltegravir (5g) was dissolved in acetonitrile (196 ml) and stirred for 10 min at 25-30°C. To this clear solution 0.5N aqueous potassium hydroxide solution (22.3 ml) was added and stirred the mass for 15-20 min at 25-30°C. The resulting clear solution was subjected to spray drying in a Mini Spray Dryer (Model Buchi-290) at the outlet temperature of 80-

90°C with purging of nitrogen gas. The solid obtained was identified as amorphous Raltegravir Potassium salt.

Example 14: Preparation of amorphous Raltegravir Potassium salt

5 Raltegravir (5g) was dissolved in acetone (196 ml) and stirred for 10 min at 25-30°C. To this clear solution 0.5N aqueous potassium hydroxide solution (22.3 ml) was added and stirred for 15-20 min at 25-30°C. The resultant solution was subjected to spray drying in a Mini Spray Dryer (Model Buchi-290) at the outlet temperature of 70-80°C with purging of nitrogen gas. The solid obtained was identified as amorphous Raltegravir Potassium salt.

Example 15: Preparation of Raltegravir Potassium Form 1

Raltegravir (1g) was dissolved in acetonitrile (40 ml) and stirred for 10 min at 25-30°C. To this clear solution 0.5N methanolic potassium hydroxide solution (4.5 ml) was added and stirred for 15-20 min at 25-30°C. The solid obtained was filtered and identified as Form 1 of Raltegravir Potassium salt.

Example 16: Preparation of Raltegravir Potassium Form 1

20 Raltegravir (1g) was dissolved in acetone (40 ml) and stirred for 10 min at 25-30°C. To this clear solution 0.5N methanolic potassium hydroxide solution (4.5 ml) was added and stirred for 15-20 min at 25-30°C. The solid obtained was filtered and identified as Form 1 of Raltegravir Potassium salt.

Example 17: Preparation of Raltegravir Potassium Form 1

25 Amorphous Raltegravir potassium salt (1g) was suspended in nitro methane (12 ml) and heated at 65-70°C to get the clear solution. The solution is then filtered through hyflo bed to remove any undissolved particulate. The clear filtrate was then stirred for 1 hr at 25-30°C during which the solid was precipitated out. The product obtained was filtered and identified as Form 1 of Raltegravir Potassium salt.

Example 18: Preparation of Raltegravir Potassium Form 1

Amorphous Raltegravir potassium salt (1g) was suspended in 1:1 mixture of methanol and acetone (40 ml) and stirred at 25-30°C to get the clear solution. The solution is then filtered through hyflo bed to remove any undissolved particulate. The clear filtrate was then transferred to conical flask and allowed the solvent to evaporate slowly at 25-30°C.

5 The solid obtained was identified as Form 1 of Raltegravir Potassium salt.

Example 19: Preparation of Raltegravir Potassium Form 2

Amorphous Raltegravir potassium salt (1g) was suspended in dichloromethane (20 ml) and stirred at 25-30°C for 2 days. The resulting solid obtained was filtered and identified as Form 2 of Raltegravir Potassium salt.

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Example 20: Preparation of Raltegravir Potassium Form 3

Raltegravir (5g) was suspended in 1:1 mixture of methanol and acetone (40 ml) and stirred at 25-30°C to get the clear solution. To this solution 0.5N methanolic potassium hydroxide solution (4.5 ml) was added and stirred for 15-20 min at 25-30°C. To this clear solution IPE (160 ml) was added and stirred for 30 min at 25-30°C. The solid obtained was filtered and identified as Form 3 of Raltegravir Potassium salt.

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Example 21: Preparation of Raltegravir Potassium Form 3

Raltegravir (5g) was suspended in ethyl acetate (450 ml) and stirred at 25-30°C to get the clear solution. To this solution 0.5N methanolic potassium hydroxide solution (2.3 ml) was added and stirred for 15-30 min at 25-30°C. The solid obtained was filtered and identified as Form 3 of Raltegravir Potassium salt.

20

We Claim:

1. Amorphous Raltegravir.
2. A process for the preparation of amorphous Raltegravir comprising the steps of:
 - 5 a) dissolving Raltegravir in a solvent to form a clear solution;
 - b) removing the solvent; and
 - c) isolating amorphous Raltegravir.
3. Crystalline Raltegravir Form A.
4. The crystalline Raltegravir Form A according to claim 2, which is characterized by
10 powder X-ray diffraction chromatogram having peaks at about 7.74, 8.03, 11.82, 15.10, 15.50, 16.08 ± 0.20 values.
5. A process for the preparation of crystalline Raltegravir Form A comprising the steps of:
 - 15 a) suspending Raltegravir in a solvent;
 - b) heating the suspension to form clear solution; and
 - c) crystallizing the solution of step b) to isolate Raltegravir Form A.
6. A process for the preparation of crystalline Raltegravir Form A comprising the steps of:
 - 20 a) suspending Raltegravir in a solvent;
 - b) heating the suspension to form clear solution;
 - c) adding anti-solvent; and
 - d) isolating Raltegravir Form A.
7. A process for the preparation of Raltegravir Form A comprising the steps of: a) suspending Raltegravir in a polar solvent; and b) isolating Raltegravir Form A.
- 25 8. Crystalline Raltegravir Form B.
9. The crystalline Raltegravir Form B according to claim 8, which is characterized by powder X-ray diffraction chromatogram having peaks at about 6.35, 8.25, 12.72, 19.88, 20.19, 21.63 ± 0.20 values.
10. A process for the preparation of crystalline Raltegravir Form B comprising the steps of:
 - 30 a) suspending Raltegravir in a polar solvent or mixtures thereof;

- b) optionally heating the contents to form clear solution; and
- c) cooling the solution to isolate Raltegravir Form B.

11. A process for the preparation of crystalline Raltegravir Form B comprising the steps of:

- a) dissolving Raltegravir in a solvent;
- b) adding isopropyl ether as anti-solvent; and
- c) isolating Raltegravir Form B.

12. A process for the preparation of crystalline Raltegravir Form B comprising the steps of: a) suspending amorphous Raltegravir in isopropyl ether; and

- b) isolating Raltegravir Form B.

13. A process for the preparation of amorphous Raltegravir potassium salt comprising the steps of:

- a) dissolving Raltegravir in a polar solvent;
- b) adding aqueous potassium hydroxide solution;
- c) removing the solvent; and
- d) isolating amorphous Raltegravir Potassium.

14. A process for the preparation of Raltegravir Potassium Form 1 comprising the steps of:

- a) dissolving Raltegravir in a solvent;
- b) adding alcoholic potassium hydroxide solution; and
- c) isolating Raltegravir Potassium Form 1.

15. A process for the preparation of Raltegravir Potassium Form 1 comprising the steps of:

- a) suspending amorphous Raltegravir potassium in a solvent;
- b) heating the suspension to get the clear solution;
- c) cooling the reaction mass; and
- d) isolating Raltegravir Potassium Form 1.

16. A process for the preparation of Raltegravir Potassium Form 1 comprising the steps of:

- a) suspending amorphous Raltegravir potassium in solvent mixture;
- b) heating the suspension to get the clear solution;

- c) allowing the contents of step b) to evaporate slowly; and
- d) isolating Raltegravir potassium Form 1.

17. A process for the preparation of Raltegravir Potassium Form 2 comprising the steps of:

- a) suspending amorphous Raltegravir in chlorinated solvents; and
- b) isolating Raltegravir Potassium Form 2.

18. A process for the preparation of Raltegravir Potassium Form 3 comprising the steps of:

- a) suspending Raltegravir in a solvent or mixture of solvents;
- b) stirring the suspension to obtain a clear solution;
- c) adding alcoholic potassium hydroxide solution;
- d) adding isopropyl ether as anti-solvent; and
- e) isolating Raltegravir Potassium Form 3.

19. A process for the preparation of Raltegravir Potassium Form 3 comprising the steps of:

- a) suspending Raltegravir in a solvent or mixture of solvents;
- b) stirring the suspension to obtain a clear solution;
- c) adding alcoholic Potassium hydroxide solution; and
- d) isolating Raltegravir Potassium Form 3.

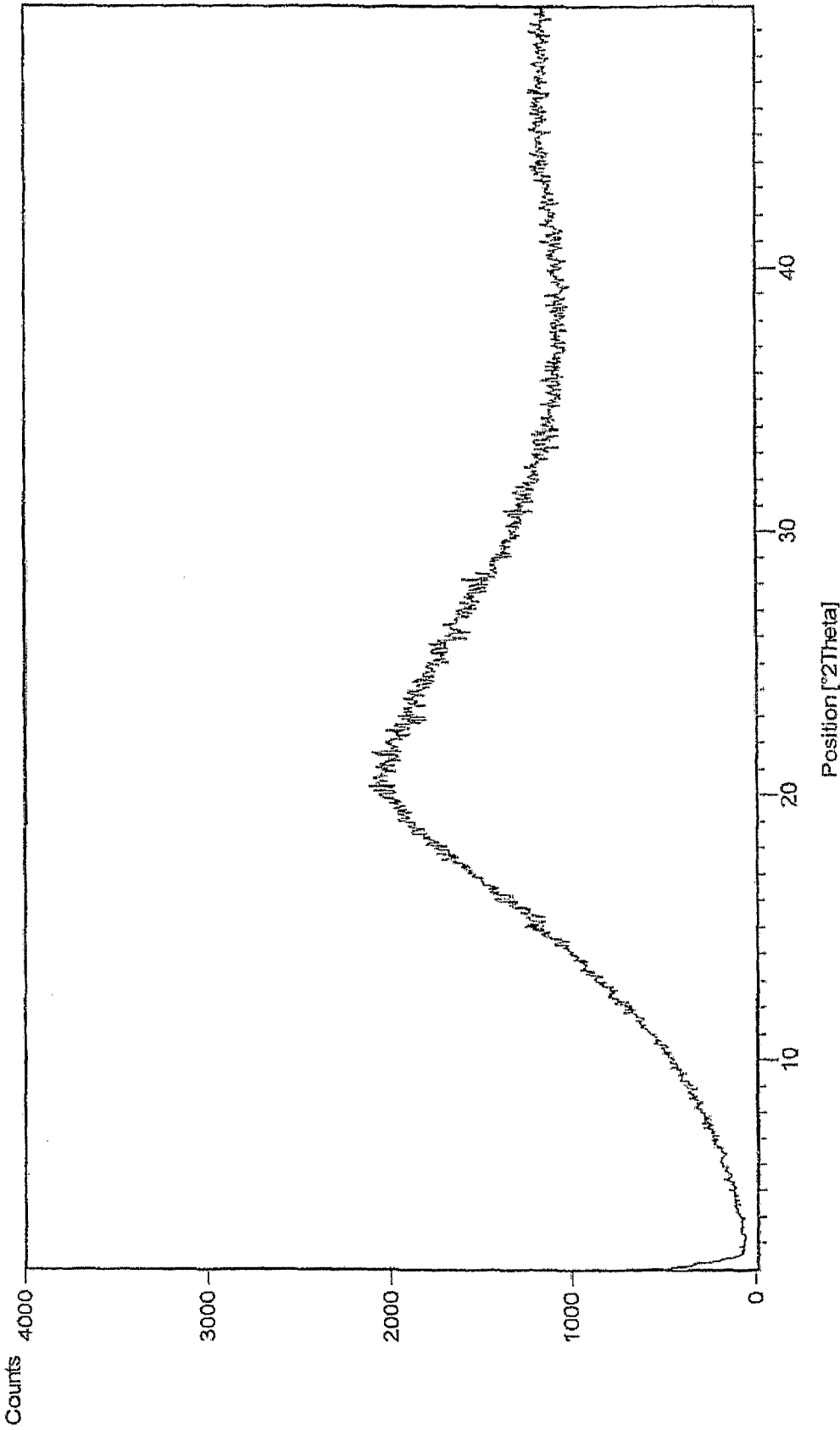


Figure 1

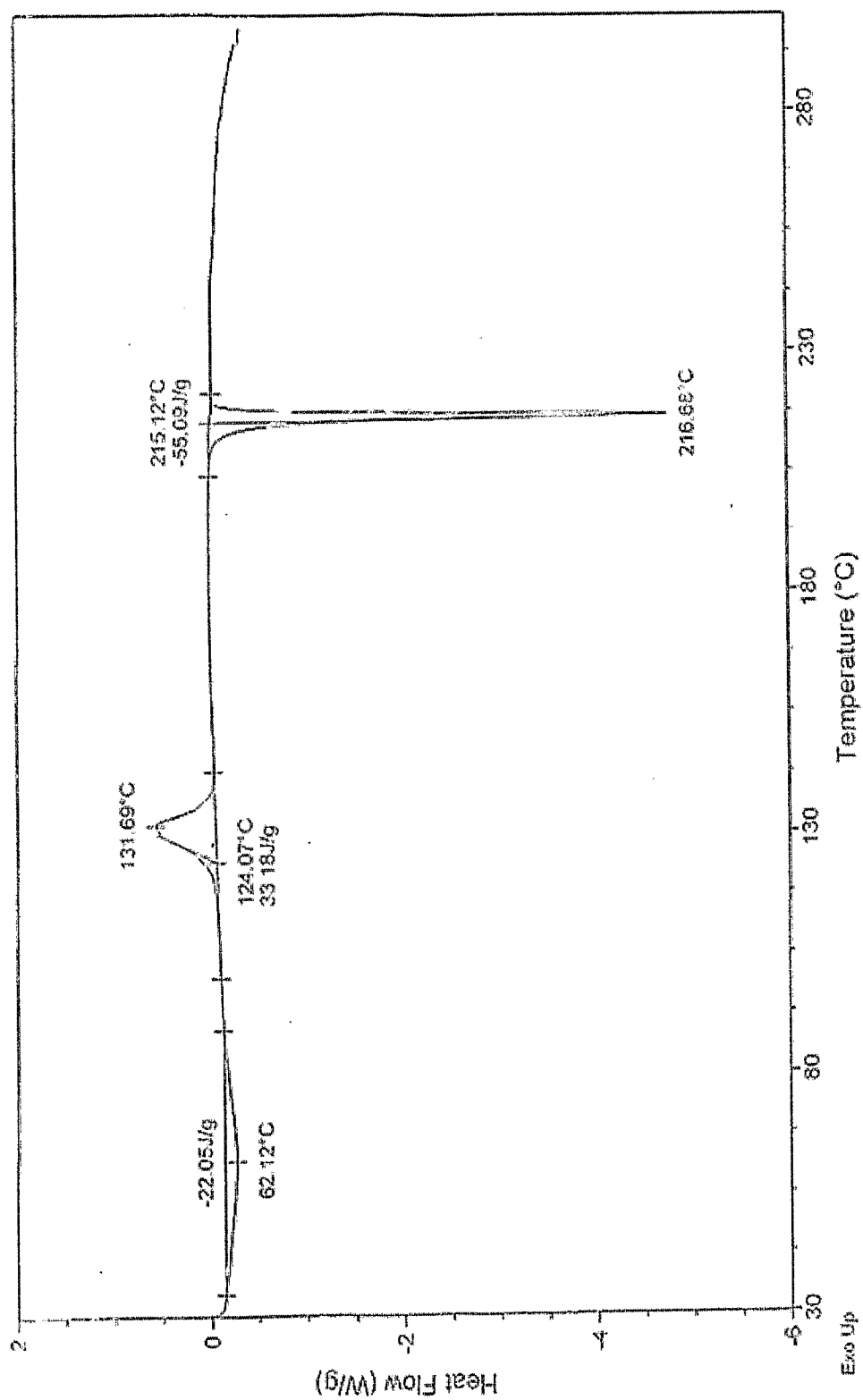


Figure 2



Figure 3

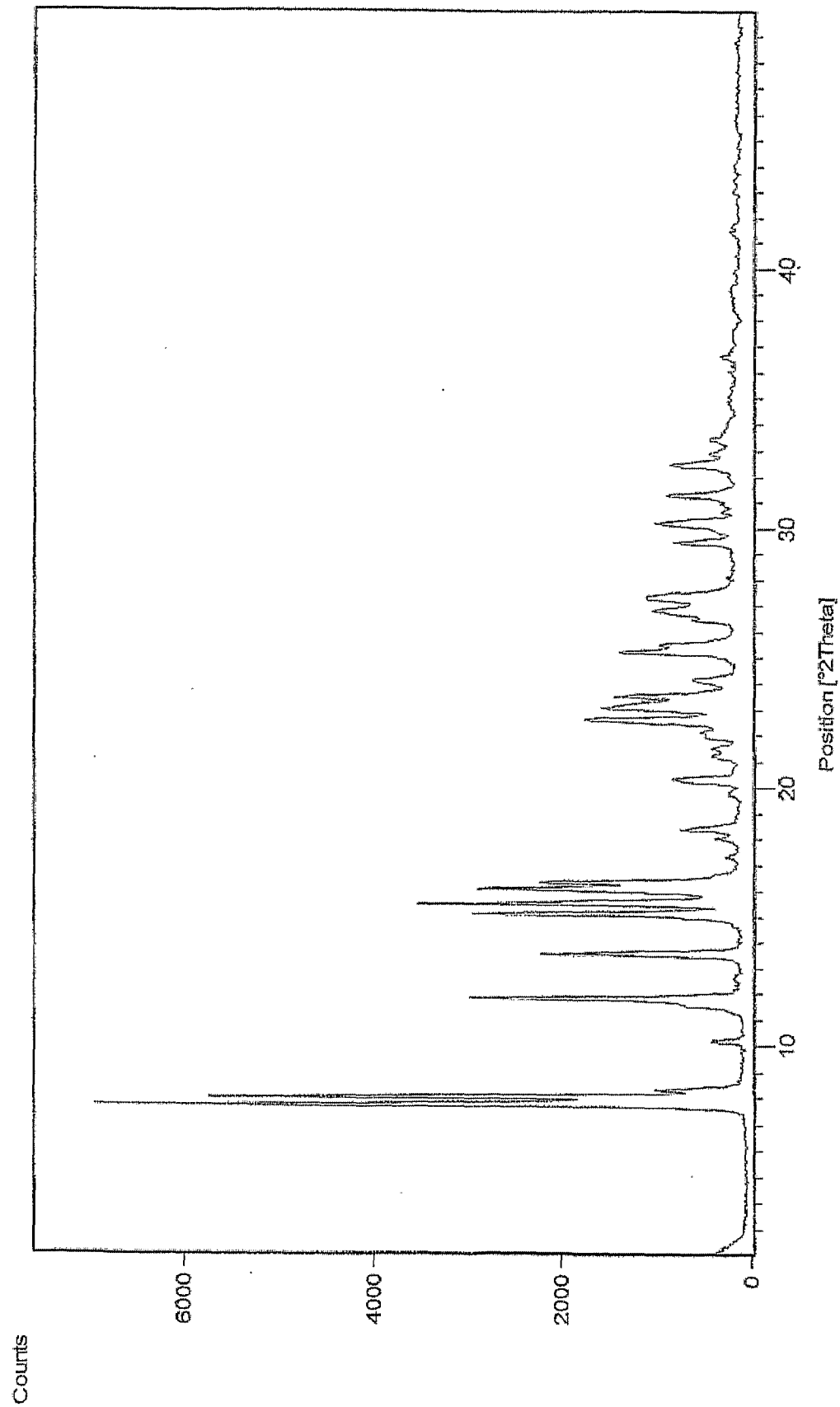


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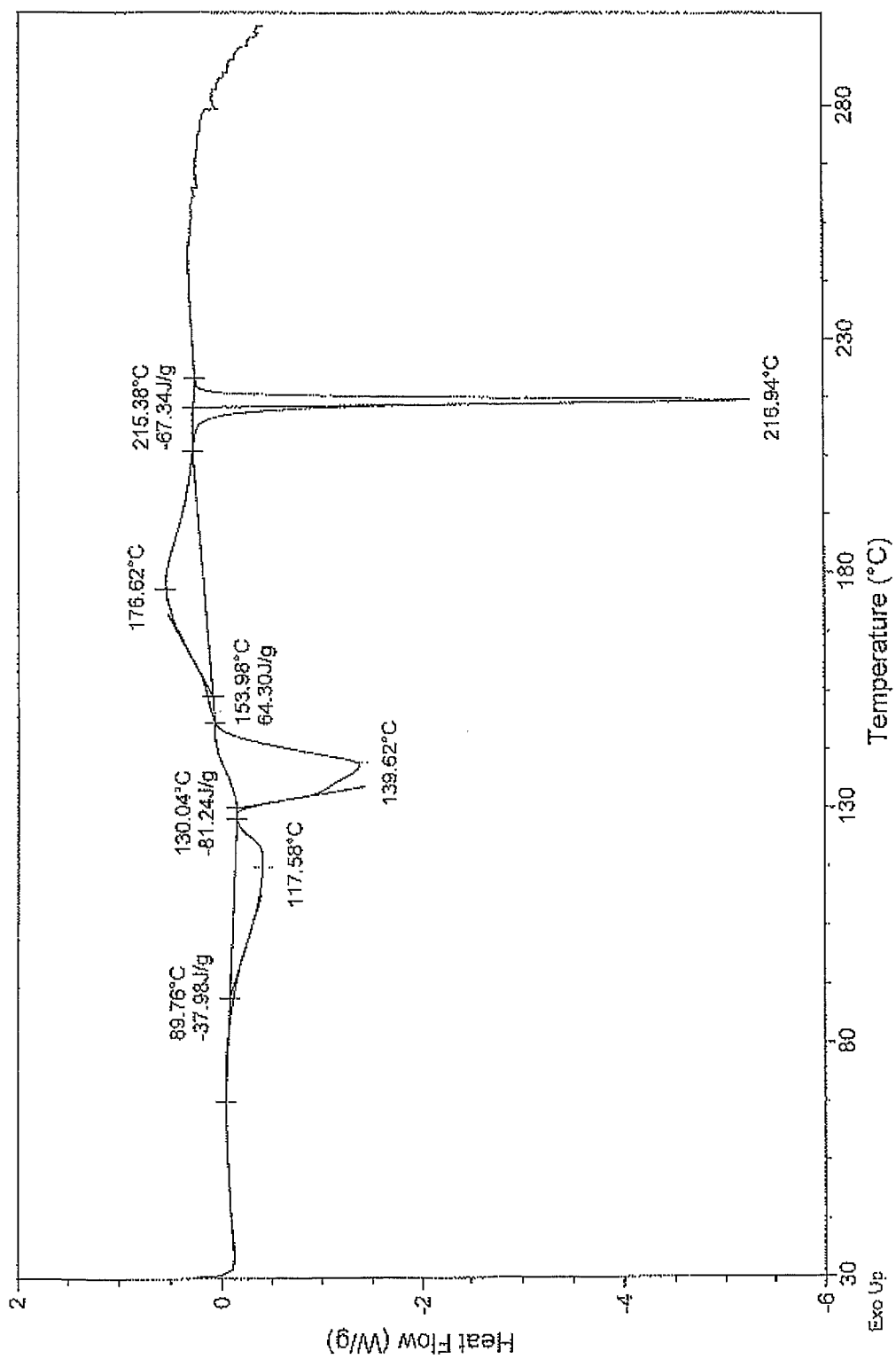


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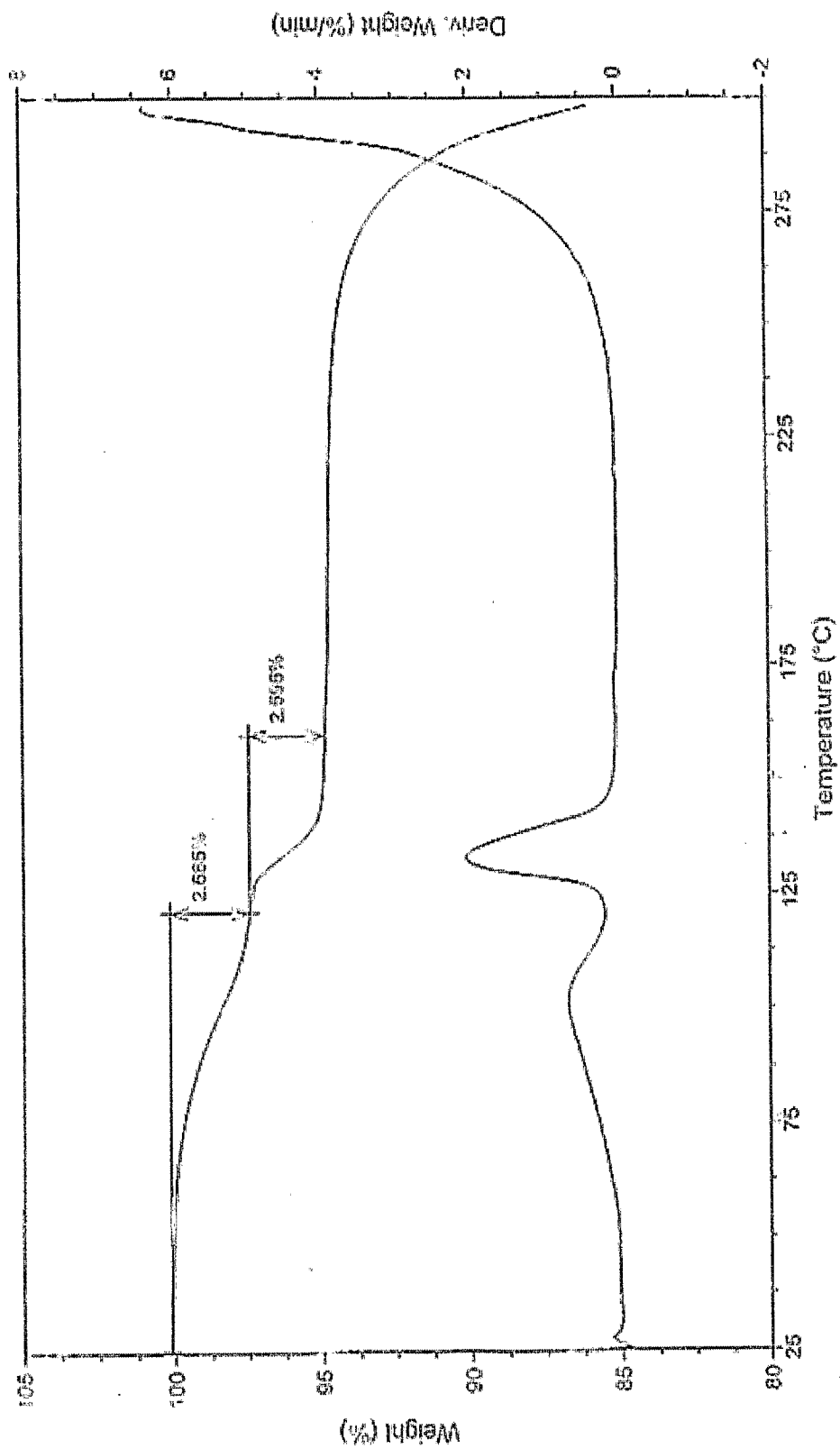


Figure 6



Figure 7

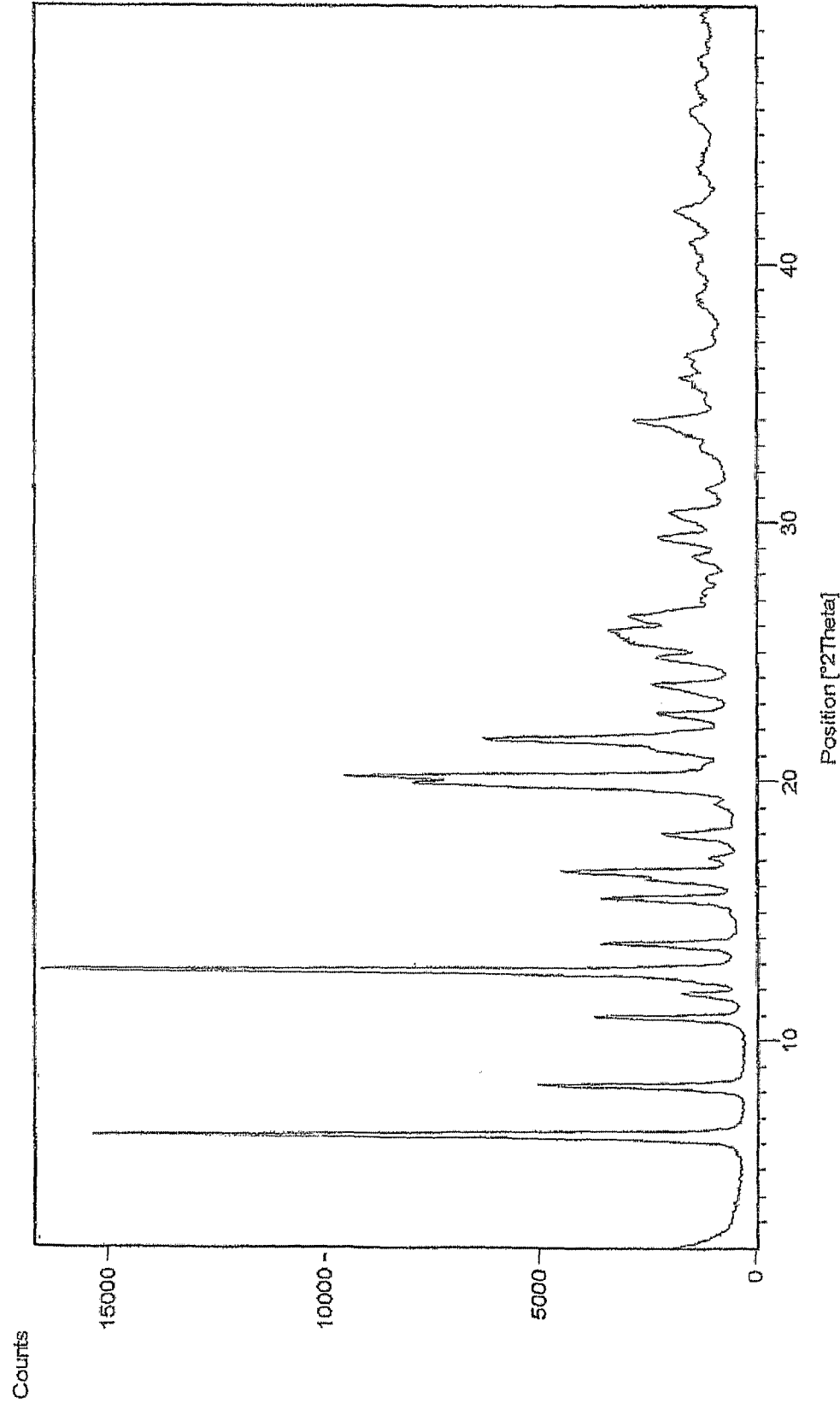


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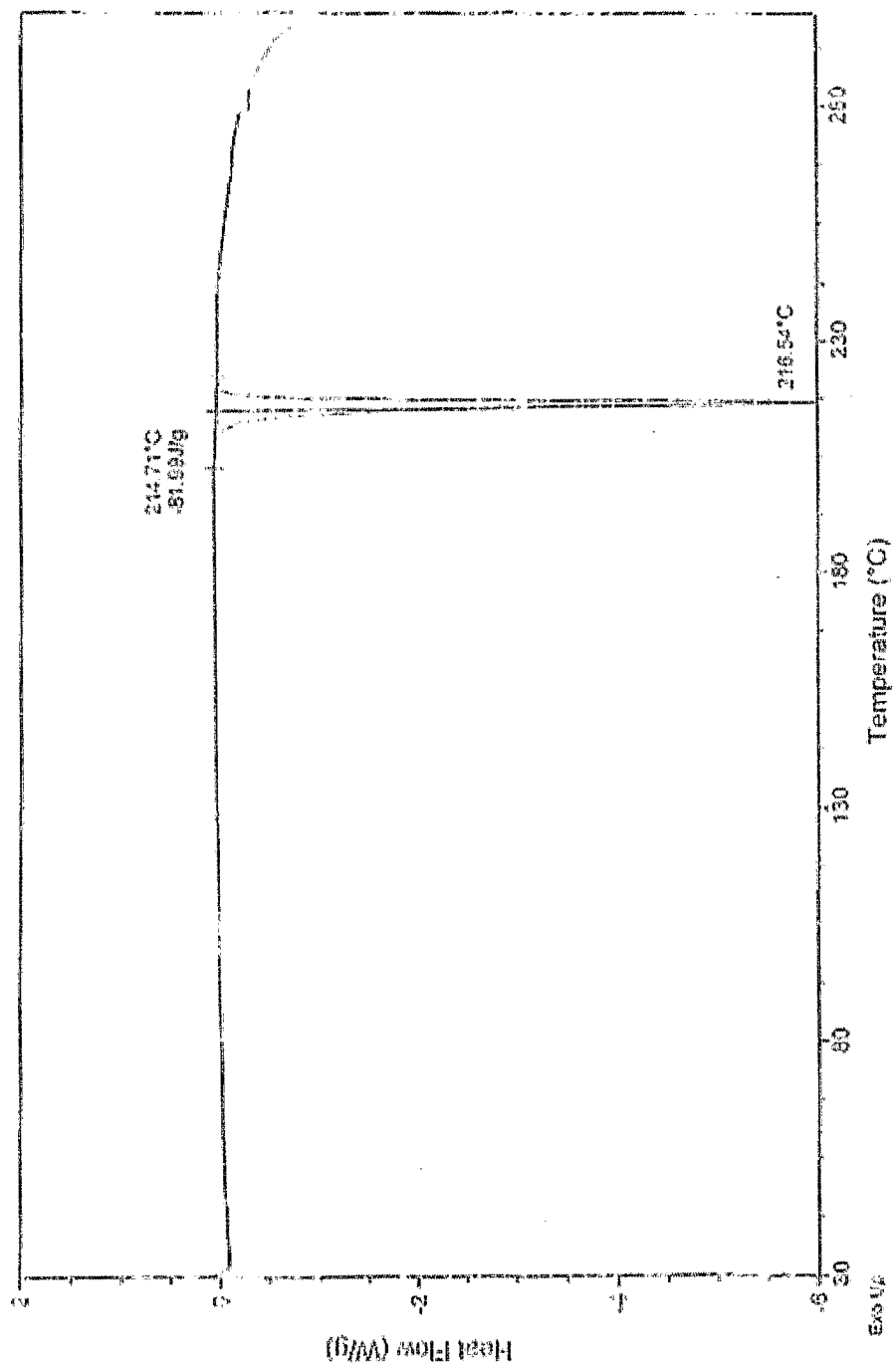


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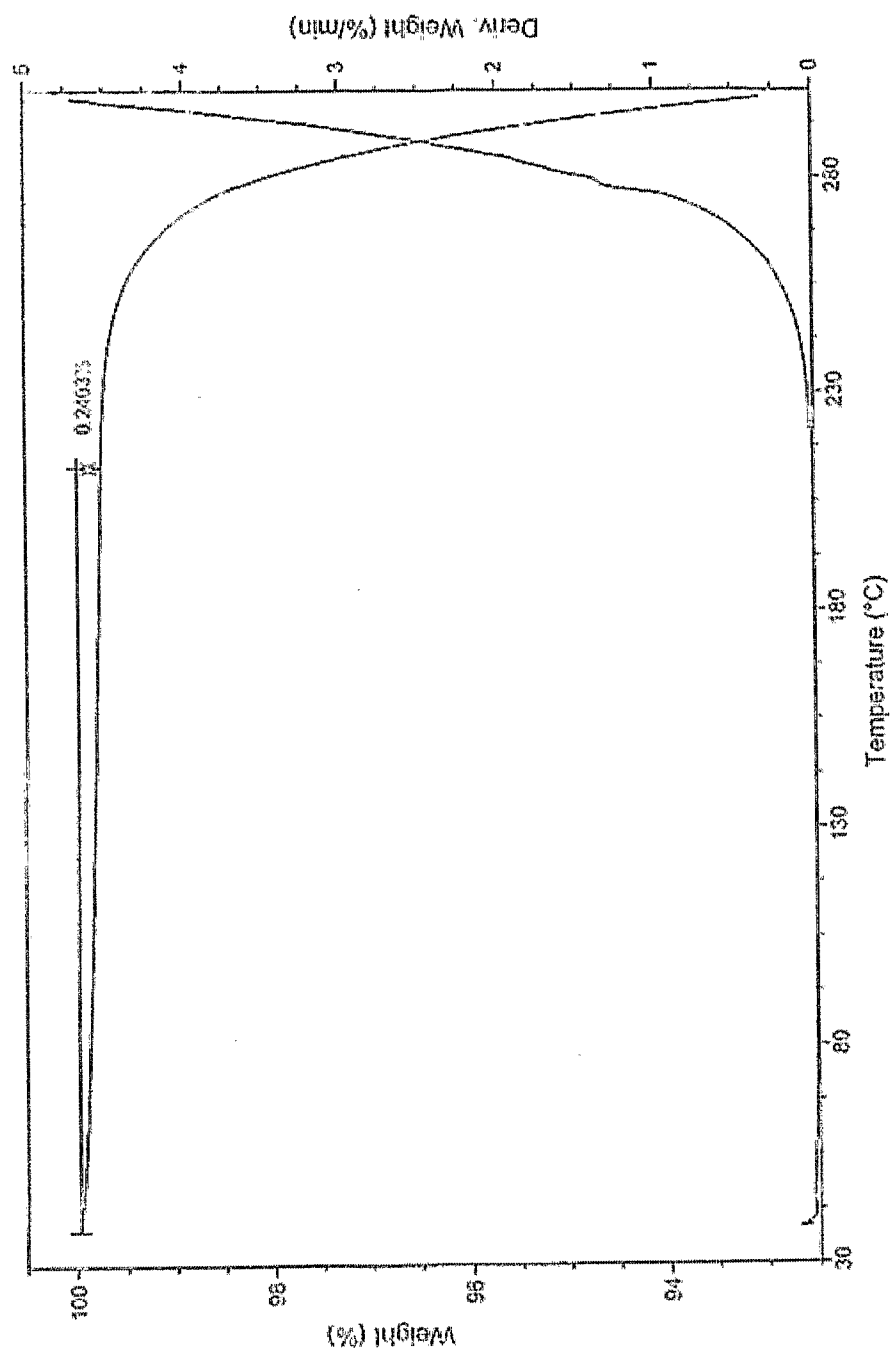


Figure 10

11/17

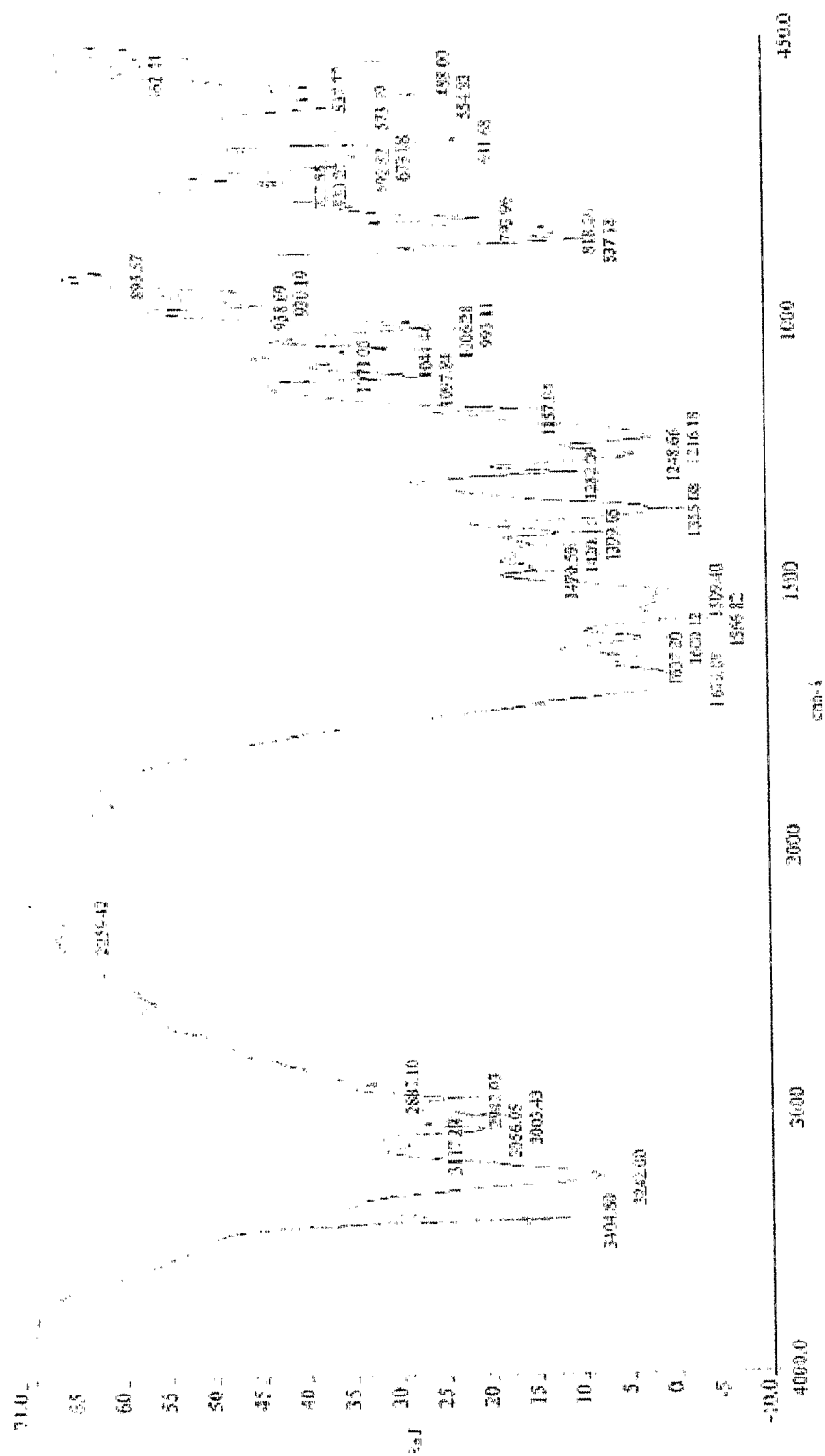


Figure 11

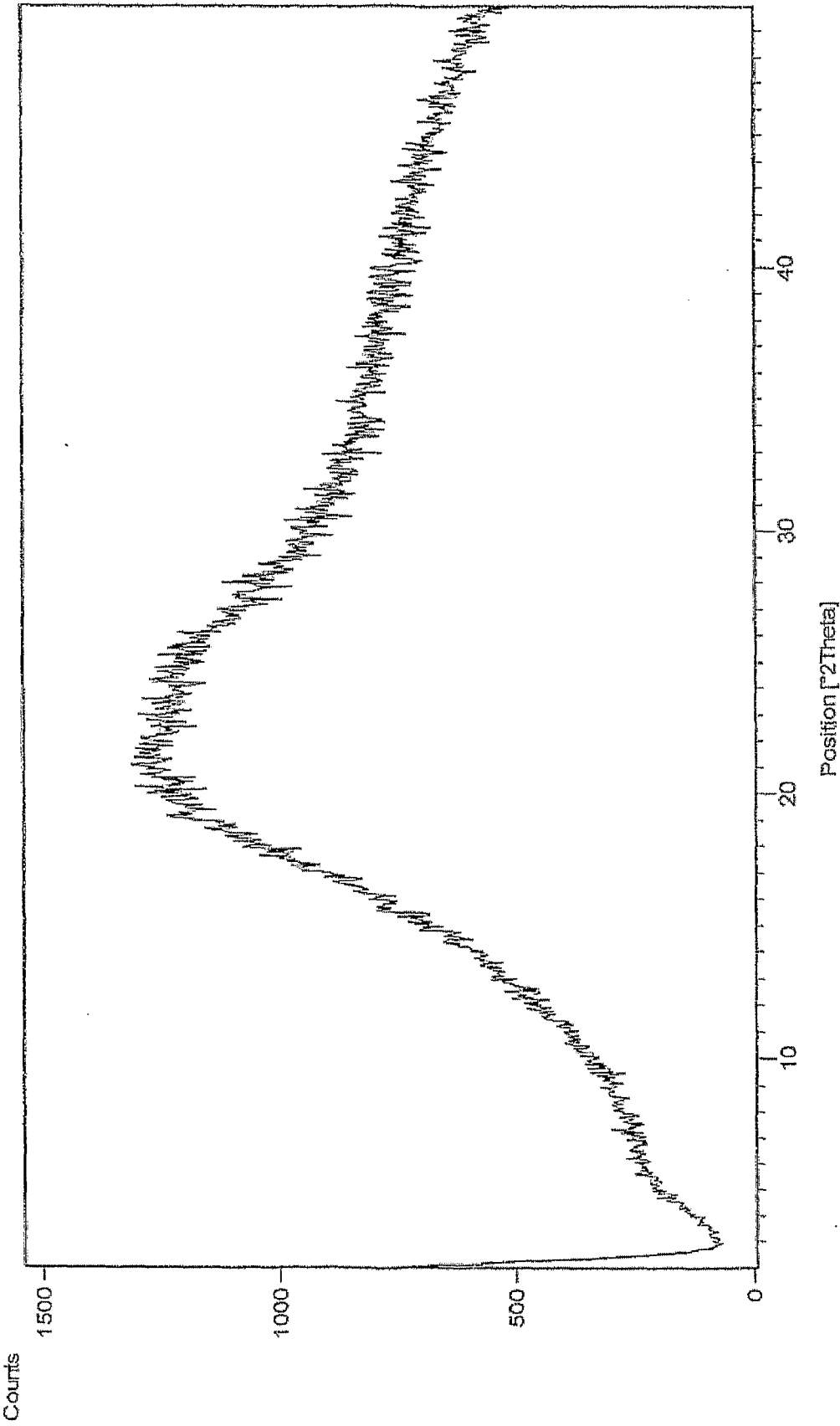


Figure 12

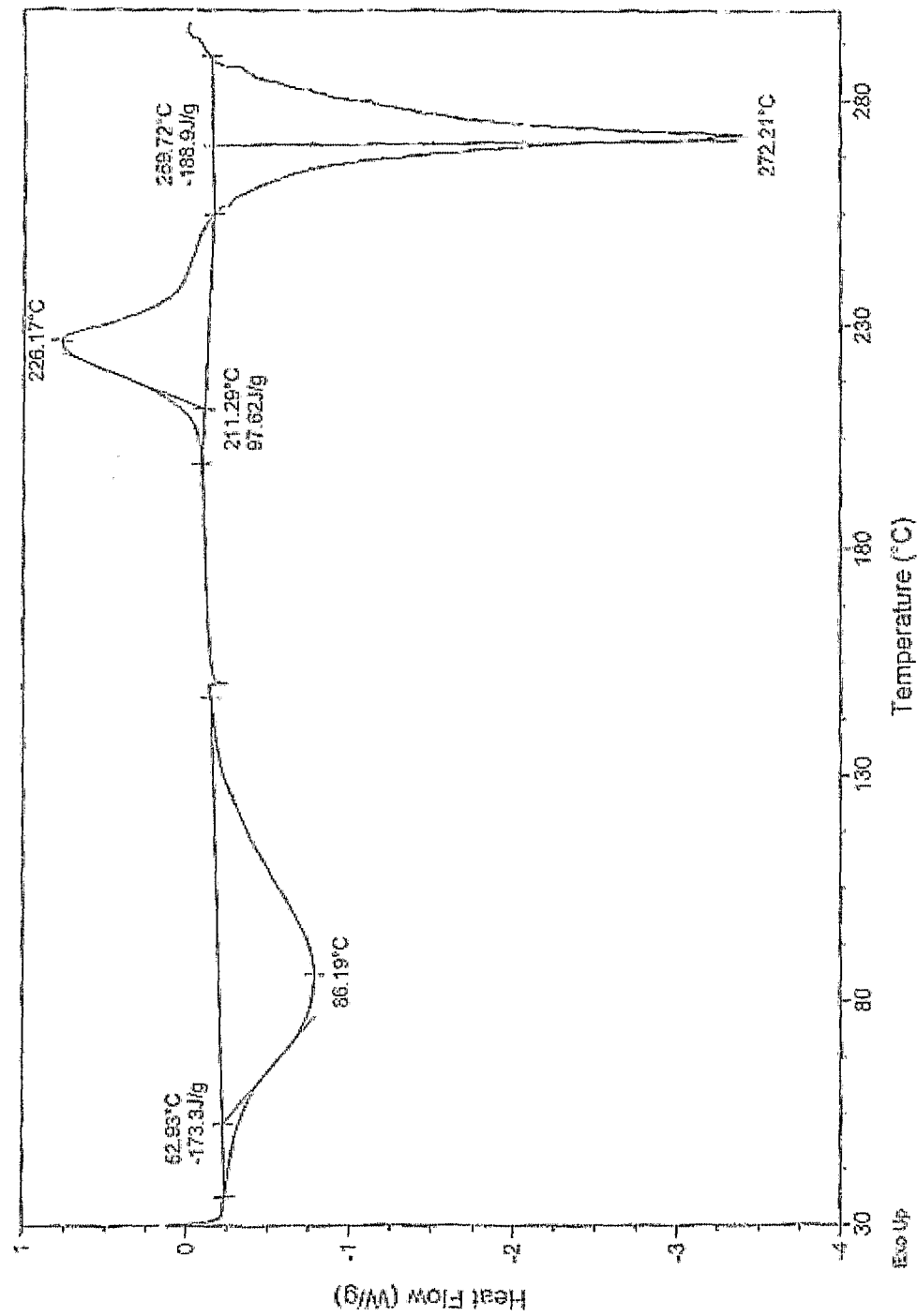


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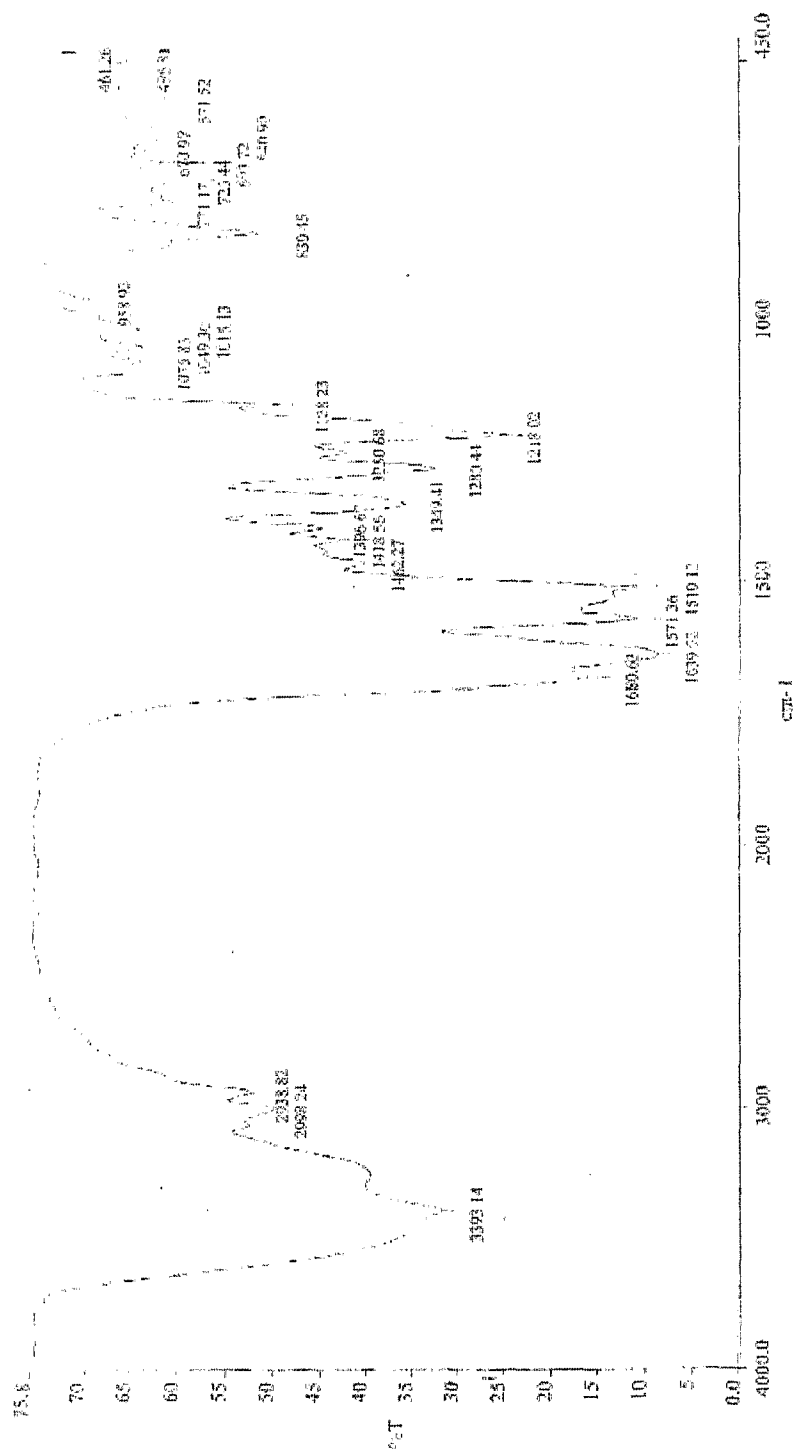


Figure 14

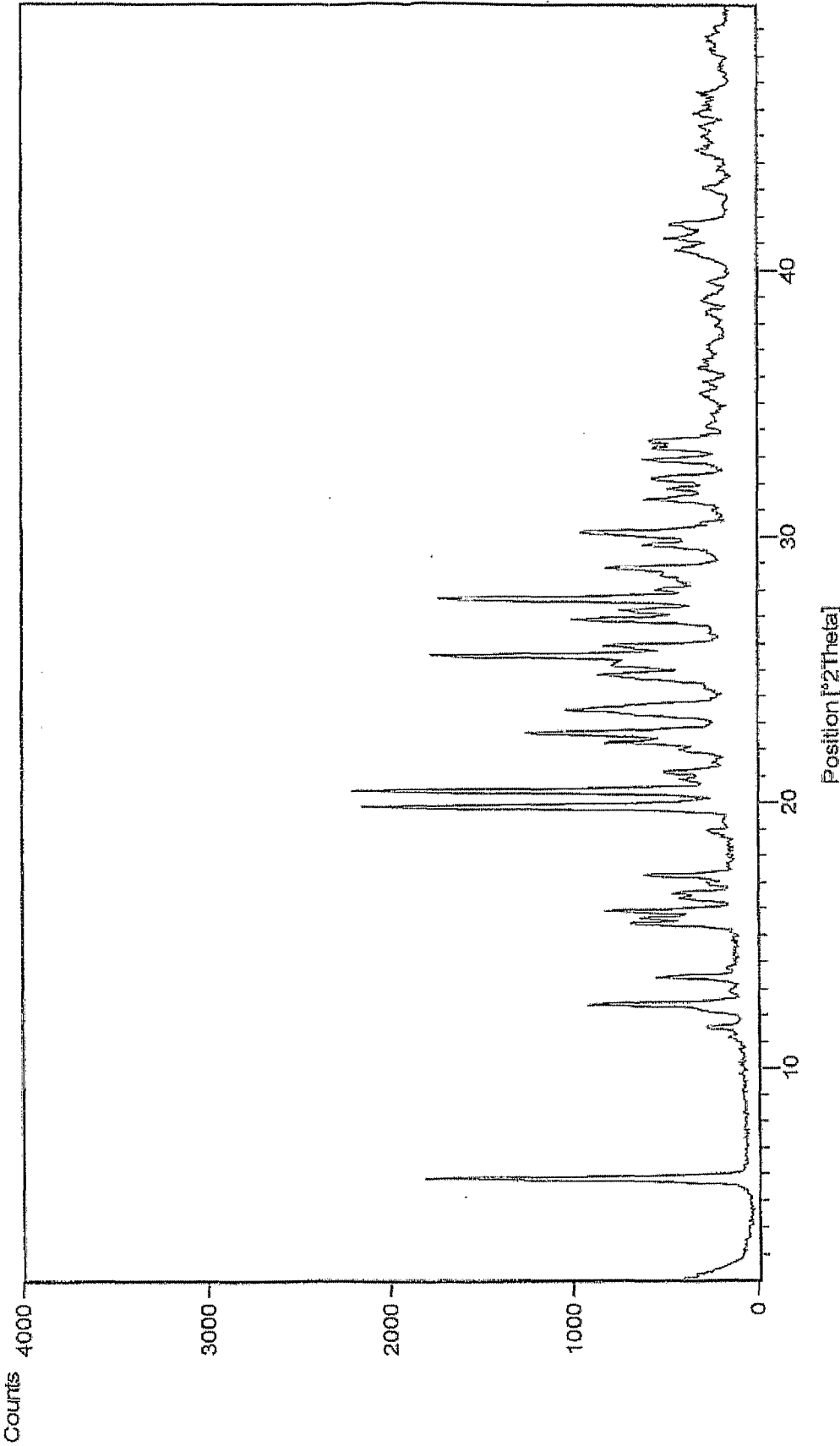


Figure 15

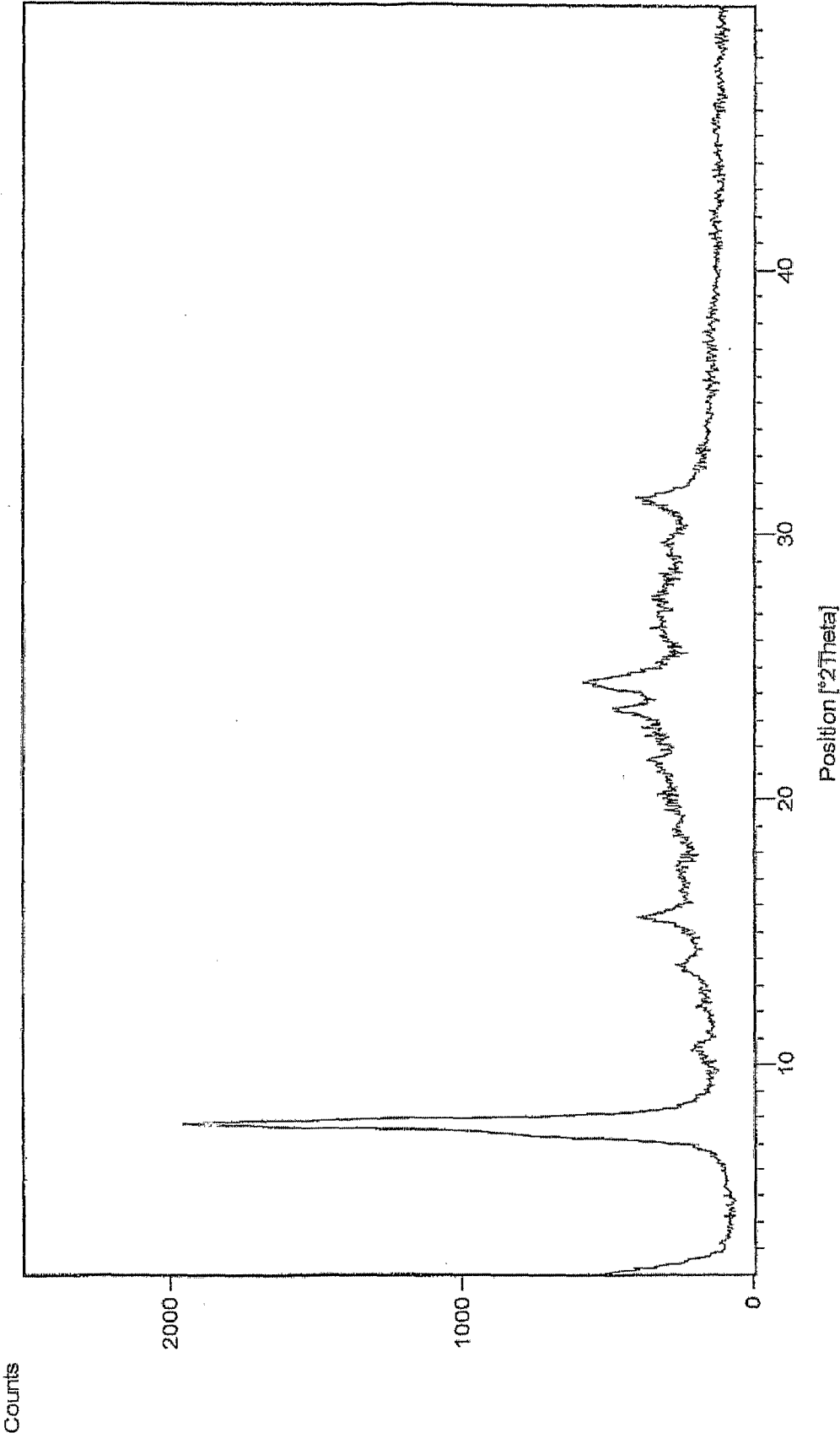


Figure 16

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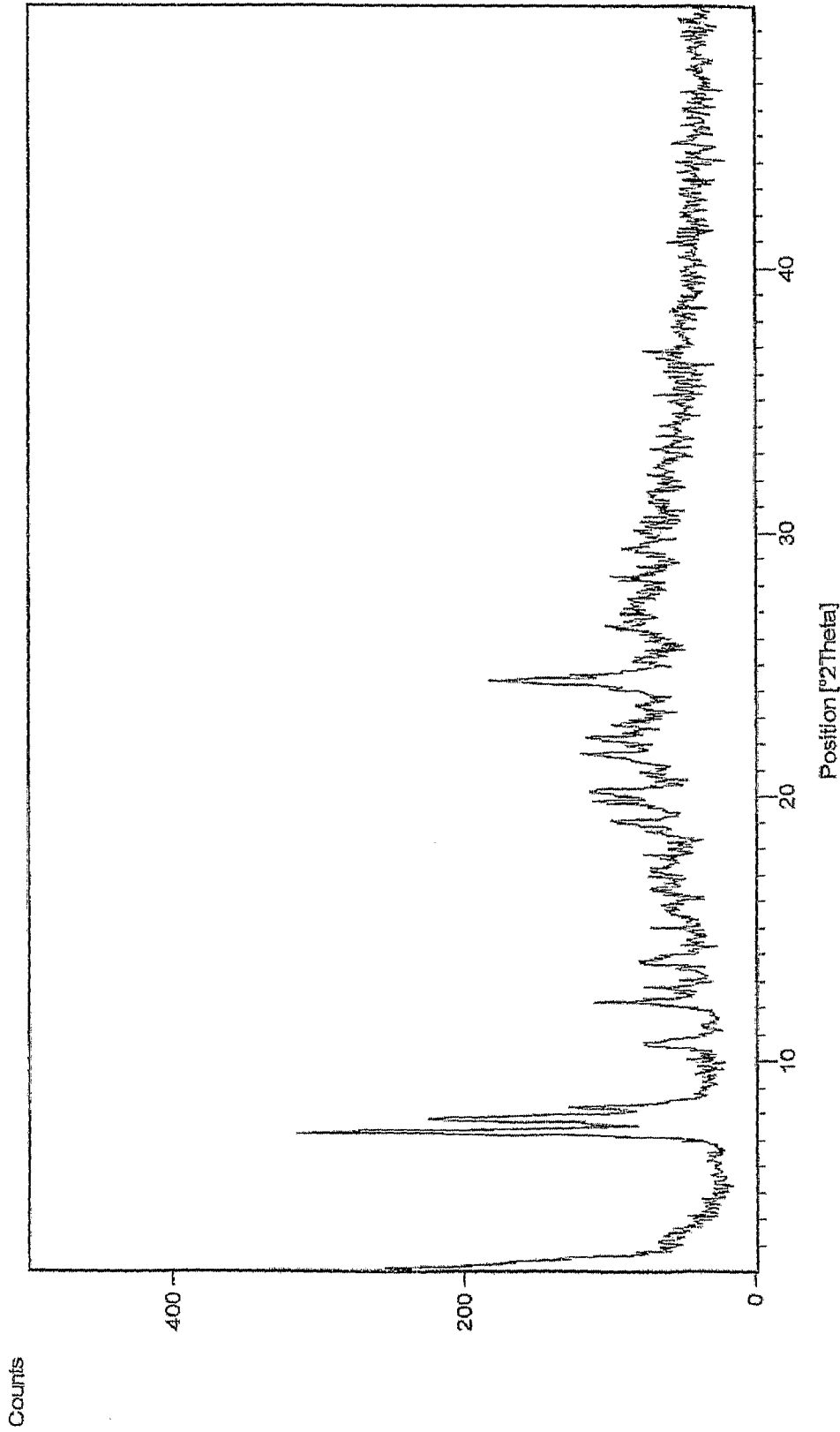


Figure 17