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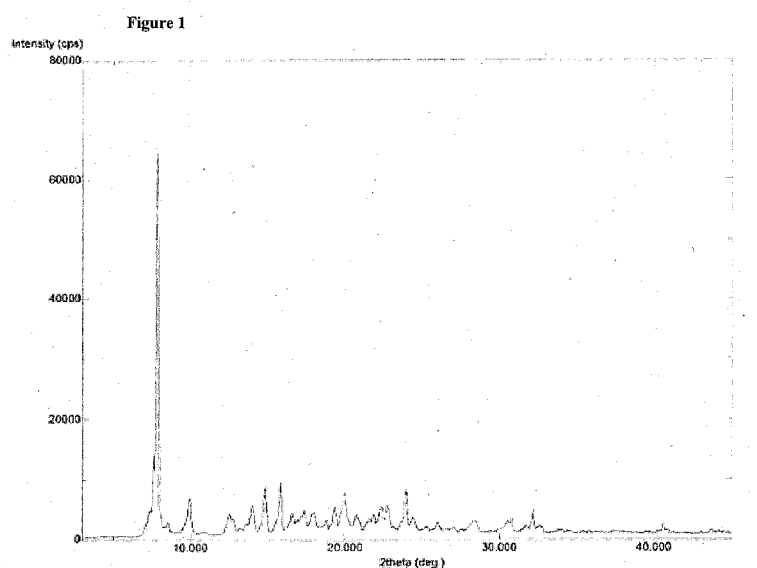
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(54) Title: SOLID FORMS OF CABAZITAXEL AND PROCESSES FOR PREPARATION THEREOF



(57) Abstract: The present invention provides solid forms of cabazitaxel, processes for its preparation and pharmaceutical compositions containing the same. The present invention also provides an amorphous form and a process for its preparation and pharmaceutical compositions thereof.



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“Solid forms of Cabazitaxel and processes for preparation thereof”**PRIORITY**

- 5 This application claims the benefit under Indian Provisional Application No. 799/CHE/2013 filed on Feb 25, 2013 entitled “Process for preparing amorphous Cabazitaxel”, and 3754/CHE/2013 filed on Aug 26, 2013 entitled “Solid Forms of Cabazitaxel and processes for preparation thereof”, the content of each of which are incorporated by reference herein.

FIELD OF THE INVNETION

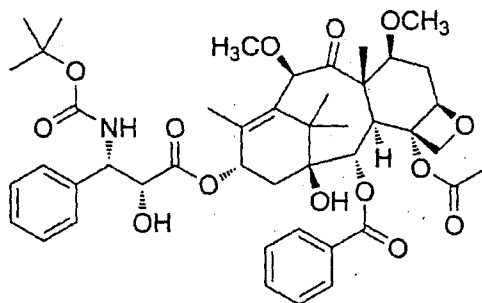
The present invention relates to solid Forms of Cabazitaxel.

- 15 The present invention also relates to process for preparation of said solid forms of cabazitaxel and pharmaceutical compositions containing the same.

The present invention also relates to amorphous cabazitaxel, processes for the preparation and pharmaceutical compositions containing the same.

BACKGROUN OF THE INVENTION

- 25 Cabazitaxel is a semi-synthetic taxoid derivative, known as 4 α -acetoxy-2 α -benzyloxy-5 β ,20-epoxy-1-hydroxy-7 β ,10 β -dimethoxy-9-oxotax-11-en-13 α -yl(2R,3S)-3-tert-butoxy carbonyl amino-2-hydroxy-3-phenylpropionate, has the following structure:



- 30 Cabazitaxel is marketed as its acetone solvate under the trade name JEVTANA[®] for the treatment of hormone-refractory prostate cancer. JEVTANA[®] is prescribed as single use vial 60 mg of cabazitaxel/1.5 ml supplied with diluents (5.7 ml).

The use of cabazitaxel in the treatment of prostate cancer is known and described in PCT publication: WO 2011/ 051894.

35 Cabazitaxel and a process for its preparation are disclosed in U.S. Patent No. 5,847,170 (“the ‘170 patent”). The ‘170 patent disclosed process involves evaporation of

cabazitaxel in a solution of methanol or ethyl acetate and dichloromethane to afford a white foamy solid.

U.S. Patent No. 7,241,907 ("the '907 patent") disclosed Cabazitaxel acetone solvate and a process for its preparation; also disclosed characterization of the acetone solvate by XRD pattern.

The '907 patent discloses process includes providing a solution of crude cabazitaxel in acetone and adding water followed by seeding the solvated crystals and then adding additional water to the suspension. The European counterpart of the '907 patent stated that cabazitaxel obtained by the process described in the '170 patent is an amorphous solid.

U.S. Patent No. 8,378,128 ("the '128 patent") disclosed other crystalline forms of Cabazitaxel, including anhydrous forms, hydrates, ethanolate solvate forms and ethanol/water hetero-solvates. Certain crystalline forms have been suggested in the '128 patent, but have not been chemically characterized except for anhydrous Form D.

PCT Publication No. WO2012/142117 discloses several crystalline forms such Form I (Toluene solvate), Form II (Methyl ter. butyl ether solvate), Form III (2-propanol solvate), Form IV (n-butanol solvate), form V (1-propanol solvate) and non-foamy amorphous form of Cabazitaxel preparation from organic solvent mixture or a mixture of water and water immiscible solvent.

PCT Publication No. WO2013/069027 disclosed cabazitaxel isopropanol solvate, process for it preparation and characterization of the same.

IN Publication No. 5464/CHE/2012 disclosed crystalline cabazitaxel ethyl acetate solvate characterized by XRD, DSC and IR and process for the preparation of the same.

IN Publication No. 35/CHE/2012 disclosed a non-solvated amorphous form having upto 2% w/w or less of volatiles measured upto 160°C and process for the preparation of the same.

PCT Publication No. WO2013/088335 disclosed cabazitaxel ethyl acetate solvate characterized by XRD and process for the preparation of the same.

PCT Publication No. WO2013/080217 disclosed crystalline forms of Cabazitaxel such as Form -1, Form-2, Form-3, Form-4, Form-5, Form-6, Form-7, Form-8, Form-9, Form-10, Form-11, Form-12 and Form-13. The crystalline Forms reported in the PCT publication characterized by XRD, DSC and TGA.

PCT Publication No. WO2013/034979 disclosed crystalline Forms of Cabazitaxel such as Form C1 (Anhydrous Isopropanol solvate), Form C2, Form C3, Form C4, Form C5, Form C6, Form C7, Form C8, Form C8b (Monohydrate DMSO solvate), Form C9 and Form C9p (Monohydrate acetic acid solvate).

PCT Publication No. WO2013/134534 disclosed crystalline Cabazitaxel alkyl acetate solvates such as ethyl acetate, isopropyl acetate, methyl acetate, butyl acetate, isobutyl acetate, crystalline Cabazitaxel ketone solvates such as methyl ethyl ketone, methyl isobutyl ketone, crystalline Cabazitaxel alcohol solvents such as 2-butanol, isobutanol, amyl alcohol and anhydrous Form XVI are characterized by XRD and process for the preparation of the same.

PCT Publication No. WO2014/015760 disclosed crystalline Cabazitaxel Form J, Form G and Form I characterized by XRD.

PCT Publication No. WO2014/022237 ("the '237 publication") disclosed amorphous Form of Cabazitaxel characterized by XRD, DSC and IR and process for the preparation of the same.

The '237 publication disclosed process involves dissolving solid Cabazitaxel in organic solvent and removing of organic solvent by concentration.

IPCOM000221343 discloses a process for the preparation of amorphous Cabazitaxel by providing a solution of Cabazitaxel in dimethyl sulfoxide, acetone, acetonitrile or mixtures thereof and isolating the product by solvent distillation followed by spray drying or freeze drying.

Polymorphism is the occurrence of different crystalline forms of a single compound and it is a property of some compounds and complexes. Thus, polymorphs are distinct solids sharing the same molecular formula, yet each polymorph may have distinct physical properties. Therefore, a single compound may give rise to a variety of polymorphic forms where each form has different and distinct physical properties, such as different solubility profiles, different melting point temperatures and/or different x-ray diffraction peaks. Since the solubility of each polymorph may vary, identifying the existence of pharmaceutical polymorphs is essential for providing pharmaceuticals with predictable solubility profiles. It is desirable to investigate all solid state forms of a drug, including all polymorphic forms and solvates, and to determine the stability, dissolution and flow properties of each polymorphic form. Polymorphic forms and solvates of a compound can be distinguished in a laboratory by X-ray diffraction spectroscopy and by other methods such as, infrared spectrometry. Additionally, polymorphic forms and solvates of the same drug substance or active pharmaceutical ingredient, can be administered by itself or formulated as a drug product (also known as the final or finished dosage form),

and are well known in the pharmaceutical art to affect, for example, the solubility, stability, flowability, tractability and compressibility of drug substances and the safety and efficacy of drug products.

5 The discovery of new polymorphic forms and solvates of a pharmaceutically useful compound, like Cabazitaxel, may provide a new opportunity to improve the performance characteristics of a pharmaceutical product. It also adds to the material that a formulation scientist has available for designing, for example, a pharmaceutical dosage form of a drug with a targeted release profile or other desired characteristic. New
10 polymorphic forms and solvates of the Cabazitaxel have now been discovered and have been designated as Cabazitaxel methyl acetate solvate, isopropyl acetate solvate and tert. butyl acetate solvate.

Further, the reported methods for amorphous cabazitaxel has certain drawbacks as it
15 involves solvent distillation under higher temperatures and drying techniques such as spray drying or freeze drying are cumbersome in to the commercial scale operations.

Hence, there is a need in the art for additional processes for preparation of cabazitaxel amorphous form.

SUMMARY OF THE INVENTION

The present invention provides solid Forms of Cabazitaxel, processes for preparation thereof and, pharmaceutical compositions containing the same.

The present invention also provides to amorphous cabazitaxel, processes for the preparation and pharmaceutical compositions containing the same.

In one embodiment, the present invention provides solid Forms of Cabazitaxel; wherein
30 the solid forms are selected from the group comprising methyl acetate solvate, isopropyl acetate solvate and tert. butyl acetate solvate.

In a second embodiment, the present invention provides Cabazitaxel methyl acetate solvate.

In a third embodiment, the present invention provides Cabazitaxel methyl acetate solvate characterized by an X-Ray diffraction (XRD) pattern substantially in accordance with Figure 1.

In a fourth embodiment, the present invention provides Cabazitaxel methyl acetate solvate characterized by an X-Ray diffraction (XRD) pattern having peaks at about: 7.4,

7.9, 8.6, 10, 12.5, 12.8, 14, 14.8, 15.9, 16.6, 17.4, 18, 18.8, 19.4, 19.9, 20.8, 21.9, 22.3, 22.8, 24, and $24.4 \pm 0.2^\circ 2\theta$.

5 In a fifth embodiment, the present invention provides Cabazitaxel methyl acetate solvate characterized by its DSC curve having an endothermic peak at about 171.35°C .

10 In a sixth embodiment, the present invention provides Cabazitaxel methyl acetate solvate characterized by an X-Ray diffraction (XRD) pattern substantially in accordance with Figure 1 and differential scanning calorimetry (DSC) substantially in accordance with Figure 2.

In a seventh embodiment, the present invention provides a process for preparation of Cabazitaxel methyl acetate solvate, comprising:

- 15 a) providing a solution of cabazitaxel in methyl acetate,
b) evaporating the solvent from the solution, and
c) isolating the cabazitaxel methyl acetate solvate.

20 In an eighth embodiment, the present invention provides Cabazitaxel isopropyl acetate solvate.

In a ninth embodiment, the present invention provides Cabazitaxel isopropyl acetate solvate characterized by an X-Ray diffraction (XRD) pattern substantially in accordance with Figure 4.

25 In a tenth embodiment, the present invention provides Cabazitaxel isopropyl acetate solvate characterized by an X-Ray diffraction (XRD) pattern having peaks at about: 7.9, 8.5, 10, 12.6, 14, 14.9, 15.8, 16.6, 17.2, 17.8, 18.7, 19.4, 20.1, 20.7, 21.4, 22, 22.4, 23.7, 24.2 and $25.7 \pm 0.2^\circ 2\theta$.

30 In an eleventh embodiment, the present invention provides a process for preparation of Cabazitaxel isopropyl acetate solvate, comprising:

- a) providing a solution of cabazitaxel in isopropyl acetate,
b) cooling the solution to precipitation, and
c) isolating the cabazitaxel isopropyl acetate solvate.

35 In a twelfth embodiment, the present invention provides Cabazitaxel tert. butyl acetate solvate.

40 In a thirteenth embodiment, the present invention provides Cabazitaxel tert. butyl acetate solvate characterized by an X-Ray diffraction (XRD) pattern substantially in accordance with Figure 7.

In a fourteenth embodiment, the present invention provides cabazitaxel tert. butyl acetate solvate characterized by an X-Ray diffraction (XRD) pattern having peaks at about: 7.5, 8.5, 10, 12.4, 13.3, 14, 14.8, 15.3, 15.6, 16, 16.8, 17.3, 17.6, 18.4, 19, 19.5, 20.2, 20.8, 21.6, 22.2, 23, 23.6 and $25.3 \pm 0.2^\circ 2\theta$.

5

In a fifteenth embodiment, the present invention provides cabazitaxel tert. butyl acetate solvate characterized by its DSC curve having an endothermic peak at about 156.3°C .

10

In a sixteenth embodiment, the present invention provides cabazitaxel tert. butyl acetate solvate characterized by an X-Ray diffraction (XRD) pattern substantially in accordance with Figure 7 and differential scanning calorimetry (DSC) substantially in accordance with Figure 8.

15

In a seventeenth embodiment, the present invention provides a process for preparation of Cabazitaxel tert. butyl acetate solvate, comprising:

- a) providing a solution of cabazitaxel in tert. butyl acetate,
- b) cooling the solution to precipitation, and
- c) isolating the cabazitaxel tert. butyl acetate solvate.

20

In an eighteenth embodiment, the present invention provides a process for preparing amorphous cabazitaxel, comprising:

- a) providing a solution of cabazitaxel in an organic solvent,
- b) adding the solution of step (a) into water at temperature less than 30°C ; and
- c) isolating the amorphous form.

25

In a nineteenth embodiment, the present invention provides a process for preparing amorphous cabazitaxel, comprising:

- a) providing a solution of cabazitaxel in an organic solvent;
- b) adding the solution of step (a) into water at temperature less than 30°C ; and
- c) isolating the amorphous form.

30

wherein the organic solvent is selected from acetone, isopropanol, 2-methoxy ethanol, 1,4-dioxane, N-methyl pyrrolidone, N-methyl morpholine, dimethyl formamide, dimethyl sulfoxide, dimethyl acetamide, pyridine or mixtures thereof.

35

In a twentieth embodiment, the present invention provides amorphous cabazitaxel characterized by an X-Ray diffraction (XRD) pattern substantially in accordance with Figure 10 and differential scanning calorimetry (DSC) substantially in accordance with Figure 11.

40

In a twenty-first embodiment, the present invention provides a pharmaceutical composition comprising solid forms of Cabazitaxel or amorphous cabazitaxel prepared

by the processes of the present invention and at least one pharmaceutically acceptable excipient.

BRIEF DESCRIPTION OF THE DRAWINGS

5

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.

10 Figure 1 is the characteristic powder X-ray diffraction (XRD) pattern of Cabazitaxel methyl acetate solvate.

Figure 2 is the characteristic differential scanning calorimetric (DSC) thermogram of Cabazitaxel methyl acetate solvate.

15

Figure 3 is the characteristic thermo gravimetric analysis (TGA) of Cabazitaxel methyl acetate solvate.

20 Figure 4 is the characteristic powder X-ray diffraction (XRD) pattern of Cabazitaxel isopropyl acetate solvate.

Figure 5 is the characteristic differential scanning calorimetric (DSC) thermogram of Cabazitaxel isopropyl acetate solvate.

25 Figure 6 is the characteristic thermo gravimetric analysis (TGA) of Cabazitaxel isopropyl acetate solvate.

Figure 7 is the characteristic powder X-ray diffraction (XRD) pattern of Cabazitaxel tert. butyl acetate solvate.

30

Figure 8 is the characteristic differential scanning calorimetric (DSC) thermogram of Cabazitaxel tert. butyl acetate solvate.

35 Figure 9 is the characteristic thermo gravimetric analysis (TGA) of Cabazitaxel tert. butyl acetate solvate.

Figure 10 is the characteristic powder X-ray diffraction (XRD) pattern of amorphous cabazitaxel of the present invention.

40 Figure 11 is the characteristic differential scanning calorimetric (DSC) thermogram of amorphous Cabazitaxel.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides solid Forms of Cabazitaxel, processes for preparation thereof and, pharmaceutical compositions containing the same.

The solid forms of Cabazitaxel of the present invention have advantageous properties selected from at least one of: chemical purity, flowability, solubility, morphology or crystal habit, stability - such as storage stability, stability to dehydration, stability to polymorphic conversion, low hygroscopicity, and low content of residual solvents.

The term "solvate," as used herein and unless indicated otherwise, refers to a crystal form that incorporates a solvent in the crystal structure. When the solvent is water, the solvate is often referred to as a "hydrate." The solvent in a solvate may be present in either a stoichiometric or in a non-stoichiometric amount.

The solid forms of Cabazitaxel of the present invention obtained by process of present invention are characterized by one or more analytical methods such as X-ray powder diffraction (XRPD) patterns, differential scanning calorimetry (DSC) curves and thermo gravimetric analysis (TGA).

The X-Ray powder diffraction can be measured by an X-ray powder Diffractometer equipped with a Cu-anode ($\lambda = 1.54$ Angstrom), X-ray source operated at 30kV, 15 mA and a Ni filter is used to strip K-beta radiation. 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 width=0.020°; and scan speed=2°/minute.

All DSC data reported herein were analyzed in hermitically sealed 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 2°C per minute with an Indium standard

All TGA data reported herein were analyzed using TGA Q500 V 20.8 build 34 in platinum pan with a temperature rise of about 5°C/min in the range of about 30°C to about 300°C.

In one embodiment, the present invention provides solid forms of Cabazitaxel; wherein the solid forms are selected from the group comprising methyl acetate solvate, isopropyl acetate solvate, and tert. butyl acetate solvate.

In another embodiment, the present invention provides Cabazitaxel methyl acetate solvate.

In another embodiment, the present invention provides Cabazitaxel methyl acetate solvate characterized by an X-Ray diffraction (XRD) pattern substantially in accordance with Figure 1.

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In another embodiment, the present invention provides Cabazitaxel methyl acetate solvate characterized by an X-Ray diffraction (XRD) pattern having peaks at about: 7.4, 7.9, 8.6, 10, 12.5, 12.8, 14, 14.8, 15.9, 16.6, 17.4, 18, 18.8, 19.4, 19.9, 20.8, 21.9, 22.3, 22.8, 24, and $24.4 \pm 0.2^\circ 2\theta$.

10

In another embodiment, the present invention provides Cabazitaxel methyl acetate solvate characterized by an X-Ray diffraction (XRD) pattern having peaks at about: 7.4, 7.86, 8.58, 9.98, 12.54, 12.78, 14.04, 14.84, 15.86, 16.60, 17.36, 17.98, 18.84, 19.36, 19.92, 20.78, 21.88, 22.34, 22.76, 23.98, 24.4, 25.98, 28.36, 30.82 and $32.22 \pm 0.2^\circ 2\theta$.

15

In another embodiment, the present invention provides Cabazitaxel methyl acetate solvate characterized by differential scanning calorimetry (DSC) substantially in accordance with Figure 2.

20

In another embodiment, cabazitaxel methyl acetate solvate of the present invention is further characterized by its DSC curve having an endothermic peak at about 171.35°C .

In another embodiment, the present invention provides Cabazitaxel methyl acetate solvate characterized by thermo gravimetric analysis (TGA) substantially in accordance with Figure 3.

25

In another embodiment, cabazitaxel methyl acetate solvate of the present invention is further characterized by its TGA curve corresponding to a weight loss of about 6.3%.

30

In another embodiment, the present invention provides Cabazitaxel methyl acetate solvate characterized by an X-Ray diffraction (XRD) pattern substantially in accordance with Figure 1 and differential scanning calorimetry (DSC) substantially in accordance with Figure 2.

35

In another embodiment, the present invention provides a process for preparation of Cabazitaxel methyl acetate solvate, comprising:

- a) providing a solution of cabazitaxel in methyl acetate,
- b) evaporating the solvent from the solution, and
- c) isolating the cabazitaxel methyl acetate solvate.

40

The starting material cabazitaxel is known in the art and can be prepared by any known method. The cabazitaxel in the solution may be any crystalline or other form of

cabazitaxel, including various solvates and hydrates, as long as cabazitaxel methyl acetate solvate is produced during the process of the invention or cabazitaxel obtaining an existing solution from a previous processing step.

- 5 The solution may be heated to dissolve the cabazitaxel. Typically, the solution is heated at a temperature of at about 25°C to about reflux temperature. Preferably, the solution is heated at about 25°C to about 35°C.

- 10 Then the resultant reaction solution can be isolated by conventional techniques known in the art such as concentrated by subjecting the solution to heating, spray drying, freeze drying, evaporation on rotary evaporator under vacuum, agitated thin film evaporator (ATFE) and the like; preferably evaporation under vacuum. The cabazitaxel methyl acetate solvate can be recovered by any conventional techniques known in the art, for example filtration. Typically, if stirring is involved, the temperature during stirring can
15 range from about 0°C to about 35°C, preferably at about 20°C to about 35°C.

- The resultant product 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
20 about 50°C. The drying can be carried out for any desired time until the required product purity is achieved, e.g., a time period ranging from about 1 hour to about 10 hours.

- In another embodiment, the present invention provides Cabazitaxel isopropyl acetate solvate.
25

- In another embodiment, the present invention provides Cabazitaxel isopropyl acetate solvate characterized by an X-Ray diffraction (XRD) pattern substantially in accordance with Figure 4.

- 30 In another embodiment, the present invention provides Cabazitaxel isopropyl acetate solvate characterized by an X-Ray diffraction (XRD) pattern having peaks at about: 7.9, 8.5, 10, 12.6, 14, 14.9, 15.8, 16.6, 17.2, 17.8, 18.7, 19.4, 20.1, 20.7, 21.4, 22, 22.4, 23.7, 24.2 and $25.7 \pm 0.2^\circ 2\theta$.

- 35 In another embodiment, the present invention provides Cabazitaxel isopropyl acetate solvate characterized by an X-Ray diffraction (XRD) pattern having peaks at about: 7.88, 8.5, 9.9, 12.58, 13.96, 14.86, 15.76, 16.56, 17.2, 17.8, 18.75, 19.42, 20.1, 20.7, 21.42, 22, 22.44, 23.74, 24.24, 25.72, 26.78, 27.14, 28.08, 29.98, 30.78 and $32.32 \pm 0.2^\circ 2\theta$.
40

In another embodiment, the present invention provides Cabazitaxel isopropyl acetate solvate characterized by differential scanning calorimetry (DSC) substantially in accordance with Figure 5.

- 5 In another embodiment, cabazitaxel isopropyl acetate solvate of the present invention is further characterized by its DSC curve having an endothermic peak at about 159.47°C.

10 In another embodiment, the present invention provides Cabazitaxel isopropyl acetate solvate characterized by thermo gravimetric analysis (TGA) substantially in accordance with Figure 6.

In another embodiment, cabazitaxel isopropyl acetate solvate of the present invention is further characterized by its TGA curve corresponding to a weight loss of about 11.5%.

- 15 In another embodiment, the present invention provides a process for preparation of Cabazitaxel isopropyl acetate solvate, comprising:
- a) providing a solution of cabazitaxel in isopropyl acetate,
 - b) cooling the solution to precipitation, and
 - c) isolating the cabazitaxel isopropyl acetate solvate.

20 The starting material cabazitaxel is known in the art and can be prepared by any known method. The cabazitaxel in the solution may be any crystalline or other form of cabazitaxel, including various solvates and hydrates, as long as cabazitaxel isopropyl acetate solvate is produced during the process of the invention or cabazitaxel obtaining
25 an existing solution from a previous processing step.

The solution may be heated to dissolve the cabazitaxel. Typically, the solution is heated at a temperature of at about 35°C to about reflux temperature. Preferably, the solution is heated at about 80°C to about 90°C.

30 Then the resultant reaction solution can be isolated by conventional techniques known in the art such as isolated by crystallization, solvent precipitation, concentrated by subjecting the solution to heating, spray drying, freeze drying, evaporation on rotary evaporator under vacuum, agitated thin film evaporator (ATFE) and the like; preferably
35 crystallization by cooling the solution temperature to about 30°C. The cabazitaxel isopropyl acetate solvate can be recovered by any conventional techniques known in the art, for example filtration. Typically, if stirring is involved, the temperature during stirring can range from about 0°C to about 35°C, preferably at about 20°C to about 35°C.

40 The resultant product 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 50°C. The drying can be carried out for any desired time until the required product purity is achieved, e.g., a time period ranging from about 1 hour to about 10 hours.

- 5 In another embodiment, the present invention provides Cabazitaxel tert. butyl acetate solvate.

In another embodiment, the present invention provides Cabazitaxel tert. butyl acetate solvate characterized by an X-Ray diffraction (XRD) pattern substantially in accordance
10 with Figure 7.

In another embodiment, the present invention provides Cabazitaxel tert. butyl acetate solvate characterized by an X-Ray diffraction (XRD) pattern having peaks at about: 7.5, 8.5, 10, 12.4, 13.3, 14, 14.8, 15.3, 15.6, 16, 16.8, 17.3, 17.6, 18.4, 19, 19.5, 20.2, 20.8,
15 21.6, 22.2, 23, 23.6 and $25.3 \pm 0.2^\circ 2\theta$.

In another embodiment, the present invention provides Cabazitaxel tert. butyl acetate solvate characterized by an X-Ray diffraction (XRD) pattern having peaks at about: 7.54, 8.46, 9.96, 12.44, 13.3, 14, 14.78, 15.32, 15.58, 16.08, 16.82, 17.28, 17.64, 18.36,
20 18.92, 19.5, 20.2, 20.8, 21.56, 22.18, 23.08, 23.64, 25.26, 25.94, 26.62, 27.2, 27.76, 29.66, 30.34 and $31.02 \pm 0.2^\circ 2\theta$.

In another embodiment, the present invention provides Cabazitaxel tert. butyl acetate solvate characterized by differential scanning calorimetry (DSC) substantially in
25 accordance with Figure 8.

In another embodiment, cabazitaxel tert. butyl acetate solvate of the present invention is further characterized by its DSC curve having an endothermic peak at about 156.3°C.

30 In another embodiment, the present invention provides cabazitaxel tert. butyl acetate solvate characterized by an X-Ray diffraction (XRD) pattern substantially in accordance with Figure 7 and differential scanning calorimetry (DSC) substantially in accordance with Figure 8.

35 In another embodiment, the present invention provides Cabazitaxel tert. butyl acetate solvate characterized by thermo gravimetric analysis (TGA) substantially in accordance with Figure 9.

In another embodiment, cabazitaxel tert. butyl acetate of the present invention is further
40 characterized by its TGA curve corresponding to a weight loss of about 11.4%.

In another embodiment, the present invention provides a process for preparation of Cabazitaxel tert. butyl acetate solvate, comprising:

- a) providing a solution of cabazitaxel in tert. butyl acetate,
- b) cooling the solution to precipitation, and
- 5 c) isolating the cabazitaxel tert. butyl acetate solvate.

The starting material cabazitaxel is known in the art and can be prepared by any known method. The cabazitaxel in the solution may be any crystalline or other form of cabazitaxel, including various solvates and hydrates, as long as cabazitaxel tert. butyl acetate solvate is produced during the process of the invention or cabazitaxel obtaining an existing solution from a previous processing step.

The solution may be heated to dissolve the cabazitaxel. Typically, the solution is heated at a temperature of at about 35°C to about reflux temperature. Preferably, the solution is heated at about 90°C to about 100°C.

Then the resultant reaction solution can be isolated by conventional techniques known in the art such as isolated by crystallization, solvent precipitation, concentrated by subjecting the solution to heating, spray drying, freeze drying, evaporation on rotary evaporator under vacuum, agitated thin film evaporator (ATFE) and the like; preferably crystallization by cooling the solution temperature to about 30°C. The cabazitaxel tert. butyl acetate solvate can be recovered by any conventional techniques known in the art, for example filtration. Typically, if stirring is involved, the temperature during stirring can range from about 0°C to about 35°C, preferably at about 20°C to about 35°C.

The resultant product 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 50°C. The drying can be carried out for any desired time until the required product purity is achieved, e.g., a time period ranging from about 1 hour to about 10 hours.

In another embodiment, the present invention provides solid forms of cabazitaxel, having a chemical purity of 96% or more as measured by HPLC, preferably 99% or more, more preferably 99.5% or more. Moreover, the solid forms of cabazitaxel, particularly cabazitaxel methyl acetate solvate, cabazitaxel isopropyl acetate solvate or cabazitaxel tert. butyl acetate solvate may be obtained substantially free of any unknown impurity, e.g., a content of less than about 0.1% of impurities.

In another embodiment, the present invention provides amorphous cabazitaxel characterized by an X-Ray diffraction (XRD) pattern substantially in accordance with Figure 10.

In another embodiment, the present invention provides amorphous cabazitaxel characterized by an X-Ray diffraction (XRD) pattern substantially in accordance with Figure 10 and differential scanning calorimetry (DSC) substantially in accordance with Figure 11.

In another embodiment, the present invention provides a process for preparing amorphous cabazitaxel, comprising:

- a) providing a solution of cabazitaxel in an organic solvent,
- b) adding the solution of step (a) into water at temperature less than 30°C; and
- c) isolating the amorphous form.

The cabazitaxel in the step a) may be any crystalline or other form of cabazitaxel, including various solvates, hydrates, as long as amorphous cabazitaxel is produced during the process of the invention or cabazitaxel obtaining as existing solution from a previous processing step.

The step of providing a solution of cabazitaxel may include dissolving any form of cabazitaxel, in an organic solvent. The organic solvent include, but is not limited to acetone, isopropanol, 2-methoxy ethanol, 1,4-dioxane, N-methyl pyrrolidone, N-methyl morpholine, dimethyl formamide, dimethyl sulfoxide, dimethyl acetamide, pyridine or mixtures thereof.

Preferably, the solvent contains less than about 20% water by volume, more preferably, less than about 10% water by volume, and, most preferably, less than about 2% water by volume. Cabazitaxel can be present in any amount that will produce the amorphous form upon the process of the present invention. Preferably, the cabazitaxel is present in an amount of about 1% to about 50% by weight of the solvent, more preferably about 1% to about 30% by weight, more preferably about 1% to about 20% by weight, and most preferably about 2% to about 10% by weight. One skilled in the art would understand that depending on the choice of solvent, the amount of cabazitaxel used may be varied.

The solution may be heated to dissolve the cabazitaxel. The temperature suitable for dissolving cabazitaxel depends on the solvent used and the amount of cabazitaxel in the solution. Typically, the solution is heated at a temperature of at least about 25°C to about reflux. The solution may be prepared at other suitable temperatures as long as the cabazitaxel is sufficiently dissolved. Increasing the amount of cabazitaxel would generally require the use of higher temperatures. Routine experimentation will provide the approximate range of suitable temperatures for a given solvent and amount of cabazitaxel.

Step b) of the aforementioned process involves adding cabazitaxel solution obtained from step (a) into water at less than 30°C to obtain the amorphous cabazitaxel, preferably, less than about 10°C.

5 Water can be taken in any amount that will produce the amorphous form upon the process of the present invention. Preferably, the water quantity may be about 1 to about 50 by volumes of the solvent, more preferably about 1 to about 30 by volumes and most preferably about 1 to about 20 by volumes. One skilled in the art would understand that depending on the choice of solvent, the amount of water used may be varied.

10

The addition of the solution into water is carried out for a suitable period of time, preferably about 5 minutes to about 3 hours.

15

The step of isolating the amorphous form is accomplished by, for example isolated by crystallization and the like. The amorphous cabazitaxel can be recovered by any conventional technique known in the art, for example filtration. Typically, if stirring is involved, the temperature during stirring can range from about -10°C to about +20°C, preferably at about -10°C to about +10°C, more preferably at temperature between about 0°C to about 5°C.

20

The cabazitaxel substantially in an amorphous form obtained by the above process may be further dried in, for example, a Vacuum Tray Dryer, Rotocon Vacuum Dryer, Vacuum Paddle Dryer or pilot plant Rota vapor.

25

The present invention provides a composition comprising cabazitaxel, wherein at least about 80% by weight of the solid cabazitaxel is an amorphous form of cabazitaxel, preferably at least about 90%, more preferably about 95%, most preferably at least about 99%.

30

In another embodiment, the present invention provides amorphous cabazitaxel, having a chemical purity of 96% or more as measured by HPLC, preferably 99% or more, more preferably 99.5% or more. Moreover, the highly purified amorphous cabazitaxel may be obtained substantially free of any unknown impurity, e.g., a content of less than about 0.1% of impurities.

35

In another embodiment, the present invention provides a pharmaceutical composition either solid forms of Cabazitaxel selected from Cabazitaxel methyl acetate solvate, Cabazitaxel isopropyl acetate solvate or Cabazitaxel tert. butyl acetate solvate; or an amorphous cabazitaxel, disclosed herein and at least one pharmaceutically acceptable excipient. Such pharmaceutical composition may be administered to a mammalian patient in any dosage form, e.g., liquid, powder, elixir, injectable solution, etc.

40

EXAMPLES

The following non limiting examples illustrate specific embodiments of the present invention. They are not intended to be limiting the scope of the present invention in any way.

5

EXAMPLE 1:

Preparation of Cabazitaxel methyl acetate solvate.

- 10 Cabazitaxel (1 g) was dissolved in methyl acetate (20 ml) at 25-35°C and stirred to get a clear solution. The resultant solution was partly evaporated under vacuum at below 45°C upto 3 vol remains in the flask. The reaction mass was allowed to cool to 25-35°C and stirred for 30 minutes at same temperature. The obtained solid was filtered, washed with methyl acetate (2 vol), suck dried and dried under vacuum at 40-45°C for 4 h to yield
- 15 Cabazitaxel methyl acetate solvate. (0.75g).

HPLC purity: 99.7%

The XRPD is set forth in Figure-1

The DSC is set forth in Figure-2

The TGA is set forth in Figure-3

20

EXAMPLE 2:

Preparation of Cabazitaxel isopropyl acetate solvate.

- 25 Cabazitaxel (1g) was dissolved in isopropyl acetate (50 ml) at 25-35°C and heated to about 85-90°C. The reaction mass was stirred for 30 minutes at same temperature to get a clear solution. The resultant solution was allowed to cool to 25-35°C and stirred for 30 minutes at same temperature. The obtained solid was filtered, washed with isopropyl acetate (2 vol), suck dried and dried under vacuum at 40-45°C for 4h to yield
- 30 Cabazitaxel isopropyl acetate solvate. (0.85g)

HPLC purity: 99.64%

The XRPD is set forth in Figure-4

The DSC is set forth in Figure-5

The TGA is set forth in Figure-6

35

EXAMPLE 3:

Preparation of Cabazitaxel tert. butyl acetate solvate.

- 40 Cabazitaxel (1g) was dissolved in tert. butyl acetate (50 ml) at 25-35°C and heated to about 95-98°C. The reaction mass was stirred for 30 minutes at same temperature to get a clear solution. The resultant solution was allowed to cool to 25-35°C and stirred for 30

minutes at same temperature. The obtained solid was filtered, washed with tert. butyl acetate (2 vol), suck dried and dried under vacuum at 40-45°C for 4h to yield Cabazitaxel tert. butyl acetate solvate. (0.85g)

HPLC purity: 99.52%

5 The XRPD is set forth in Figure-7

The DSC is set forth in Figure-8

The TGA is set forth in Figure-9

EXAMPLE 4:

10

Preparation of amorphous form of Cabazitaxel (acetone + water)

Cabazitaxel (0.5 g) was dissolved in acetone (2.5 ml) at 25-30°C. The acetone solution was added to pre-cooled water (30 ml) at 0-3°C over 15 min. The reaction mixture was stirred for 5 min at 0-3°C. The obtained solid was filtered, washed with water, suck dried under vacuum at 45-50°C for 2 h to yield Cabazitaxel amorphous form. (0.29g)

15

The XRPD is set forth in Figure-10

The DSC is set forth in Figure-11

20

EXAMPLE 5:

Preparation of amorphous form of Cabazitaxel (dimethyl formamide + water)

Cabazitaxel (0.5g) was dissolved in dimethyl formamide (5ml) at 25-35°C and stirred to get a clear solution. The dimethyl formamide solution was added to pre-cooled water slowly at 0-8°C over 15 min. The reaction mixture was stirred for 1h at 0-8°C. The obtained solid was filtered, washed with water, suck dried under vacuum at 50°C for 4h to yield Cabazitaxel amorphous form. (0.3g)

25

The XRPD is set forth in Figure-10

30

The DSC is set forth in Figure-11

EXAMPLE 6:

Preparation of amorphous form of Cabazitaxel (dimethyl sulfoxide + water)

35

Cabazitaxel (0.5g) was dissolved in dimethyl sulfoxide (4ml) at 25-35°C and stirred to get a clear solution. The dimethyl sulfoxide solution was added to pre-cooled water slowly at 0-8°C over 15 min. The reaction mixture was stirred for 1h at 0-8°C. The obtained solid was filtered, washed with water, suck dried under vacuum at 50°C for 4h to yield Cabazitaxel amorphous form. (0.5g).

40

The XRPD is set forth in Figure-10

The DSC is set forth in Figure-11

We Claim:

Claim 1: Cabazitaxel methyl acetate solvate.

5 Claim 2: The cabazitaxel methyl acetate solvate of claim 1, characterized by X-Ray diffraction (XRD) pattern having peaks at about 7.4, 7.9, 8.6, 10, 12.5, 12.8, 14, 14.8, 15.9, 16.6, 17.4, 18, 18.8, 19.4, 19.9, 20.8, 21.9, 22.3, 22.8, 24, and $24.4^{\circ} 2\theta \pm 0.2^{\circ} 2\theta$.

10 Claim 3: The cabazitaxel methyl acetate solvate of claim 1, characterized by an X-Ray diffraction (XRD) pattern substantially in accordance with Figure 1.

Claim 4: The cabazitaxel methyl acetate solvate of claim 1, characterized by a DSC thermogram substantially in accordance with Figure 2.

15 Claim 5: The cabazitaxel methyl acetate solvate of claim 1, characterized by a DSC curve having an endothermic peak at about 171.35°C .

Claim 6: A process for preparing cabazitaxel methyl acetate solvate, comprising:

- 20 a) providing a solution of cabazitaxel in methyl acetate,
b) evaporating the solvent from the solution, and
c) isolating the cabazitaxel methyl acetate solvate.

25 Claim 7: The process of claim 6, wherein the solution in step a) is formed at a temperature of about 25°C to about reflux temperature.

Claim 8: The process of claim 6, wherein the step b) is carried out by removing the solvent under vacuum.

30 Claim 9: The process of claim 6, wherein the isolation is carried out by cooling the solution to less than 35°C and then filtration.

Claim 10: Cabazitaxel isopropyl acetate solvate.

35 Claim 11: The cabazitaxel isopropyl acetate solvate of claim 10, characterized by an X-Ray diffraction (XRD) pattern having peaks at 7.9, 8.5, 10, 12.6, 14, 14.9, 15.8, 16.6, 17.2, 17.8, 18.7, 19.4, 20.1, 20.7, 21.4, 22, 22.4, 23.7, 24.2 and $25.7 \pm 0.2^{\circ} 2\theta$.

40 Claim 12: The cabazitaxel isopropyl acetate solvate of claim 10, characterized by an X-Ray diffraction (XRD) pattern substantially in accordance with Figure 4.

Claim 13: The cabazitaxel isopropyl acetate of claim 10, characterized by a DSC thermogram substantially in accordance with Figure 5.

Claim 14: The cabazitaxel isopropyl acetate solvate of claim 10, characterized by a DSC curve having an endothermic peak at about 159.47°C.

5 Claim 15: A process for preparing Cabazitaxel isopropyl acetate solvate, comprising:

- a) providing a solution of cabazitaxel in isopropyl acetate,
- b) cooling the solution to precipitation, and
- c) isolating the cabazitaxel isopropyl acetate solvate.

10

Claim 16: The process of claim 15, wherein the solution in step a) is formed at a temperature of about 35°C to about reflux temperature.

15 Claim 17: The process of claim 15, wherein the step b) is carried out at a temperature below about 35°C.

Claim 18: The process of claim 15, wherein the step c) is carried out by filtration.

20 Claim 19: Cabazitaxel tert. butyl acetate solvate.

Claim 20: The cabazitaxel tert. butyl acetate solvate of claim 19, characterized by an X-Ray diffraction (XRD) pattern having peaks at about: 7.5, 8.5, 10, 12.4, 13.3, 14, 14.8, 15.3, 15.6, 16, 16.8, 17.3, 17.6, 18.4, 19, 19.5, 20.2, 20.8, 21.6, 22.2, 23, 23.6 and 25.3± 0.2° 2θ.

25

Claim 21: The cabazitaxel tert. butyl acetate solvate of claim 19, characterized by an X-Ray diffraction (XRD) pattern substantially in accordance with Figure 7.

30 Claim 22: The cabazitaxel tert. butyl acetate solvate of claim 19, characterized by a differential scanning calorimetry (DSC) substantially in accordance with Figure 8.

Claim 23: The cabazitaxel tert. butyl acetate solvate of claim 19, characterized by a DSC curve having an endothermic peak at about 156.3°C.

35 Claim 24: A process for preparing Cabazitaxel tert. butyl acetate solvate, comprising:

- a) providing a solution of cabazitaxel in tert. butyl acetate,
- b) cooling the solution to precipitation, and
- c) isolating the cabazitaxel tert. butyl acetate solvate.

40

Claim 25: The process of claim 24, wherein the solution in step a) is formed at a temperature of about 35°C to about reflux temperature.

Claim 26: The process of claim 24, wherein the step b) is carried out at a temperature below about 35°C.

Claim 27: The process of claim 24, wherein the step c) is carried out by filtration.

5

Claim 28: An amorphous cabazitaxel, characterized by an X-Ray diffraction (XRD) pattern substantially in accordance with Figure 10 and differential scanning calorimetry (DSC) substantially in accordance with Figure 11.

10 Claim 29: A process for preparing amorphous Form of cabazitaxel, comprising:

- a) providing a solution of cabazitaxel in an organic solvent,
- b) adding the solution of step (a) into water at temperature less than 30°C; and
- c) isolating the amorphous form.

15 Claim 30: A process of claim 29, wherein the organic solvent in step a) is selected from the group consisting of acetone, isopropanol, 2-methoxy ethanol, 1,4-dioxane, N-methyl pyrrolidone, N-methyl morpholine, dimethyl formamide, dimethyl sulfoxide, dimethyl acetamide, pyridine and mixtures thereof.

20 Claim 31: The process of claim 29, wherein the solution of step a) is formed at a temperature of about 25°C to about reflux temperature.

Claim 32: The process of claim 31, wherein the temperature is about 25°C to 35°C.

25 Claim 33: The process of claim 29, wherein the step b) is carried out at a temperature less than 30°C.

Claim 34: The process of claim 33, wherein the temperature is less than 10°C.

30 Claim 35: The process of claim 29, wherein the addition of step a) solution into water is carried out for a period of about 5 minutes to about 3 hours.

Claim 36: The process of claim 29, wherein the isolation is carried out by crystallization, solvent precipitation or filtration.

35

Claim 37: A pharmaceutical composition comprising one or more solid forms of Cabazitaxel or amorphous cabazitaxel according to claim 1 to 36, and at least one pharmaceutically acceptable excipient.

40

Figure 1

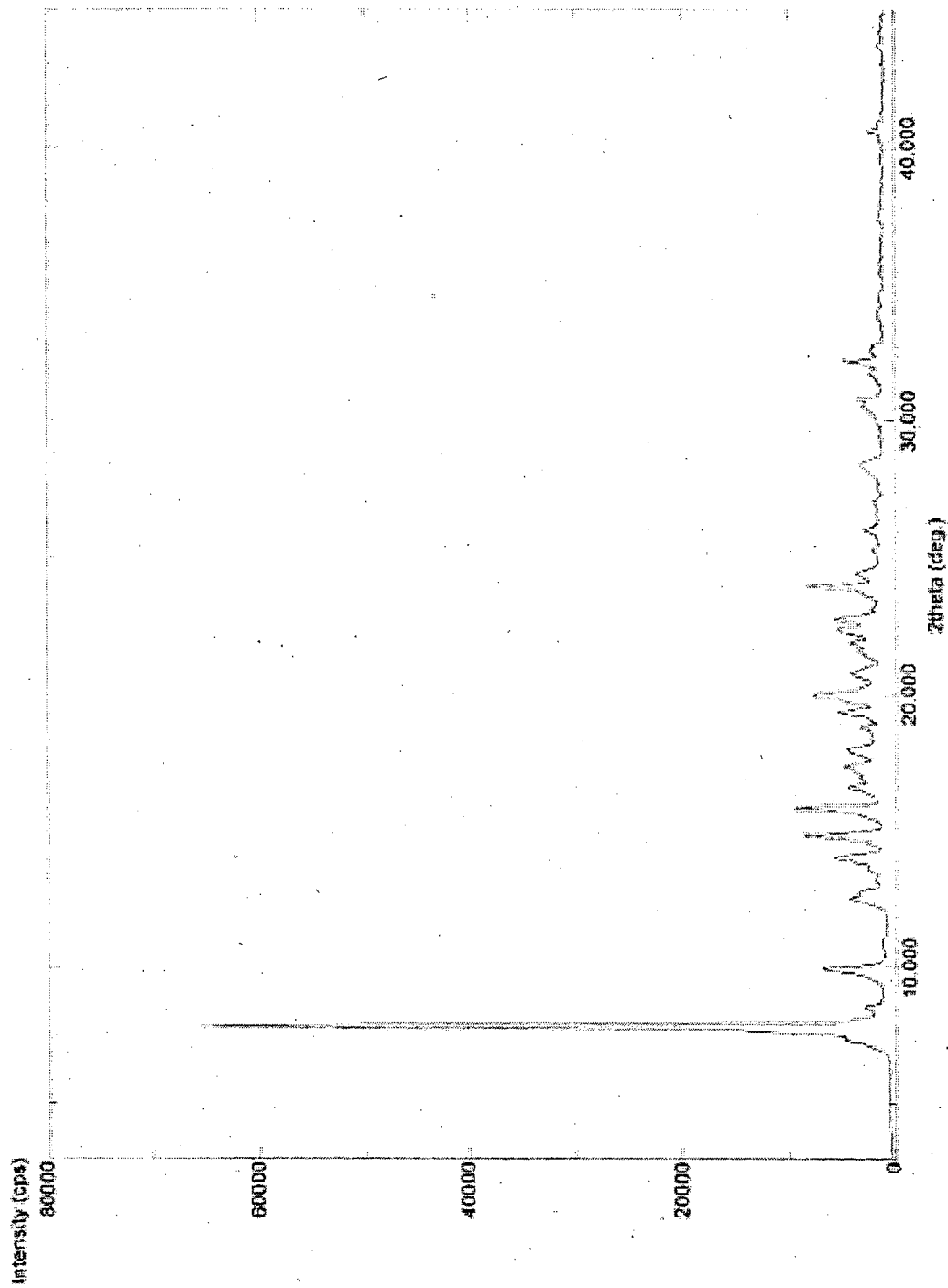


Figure 2

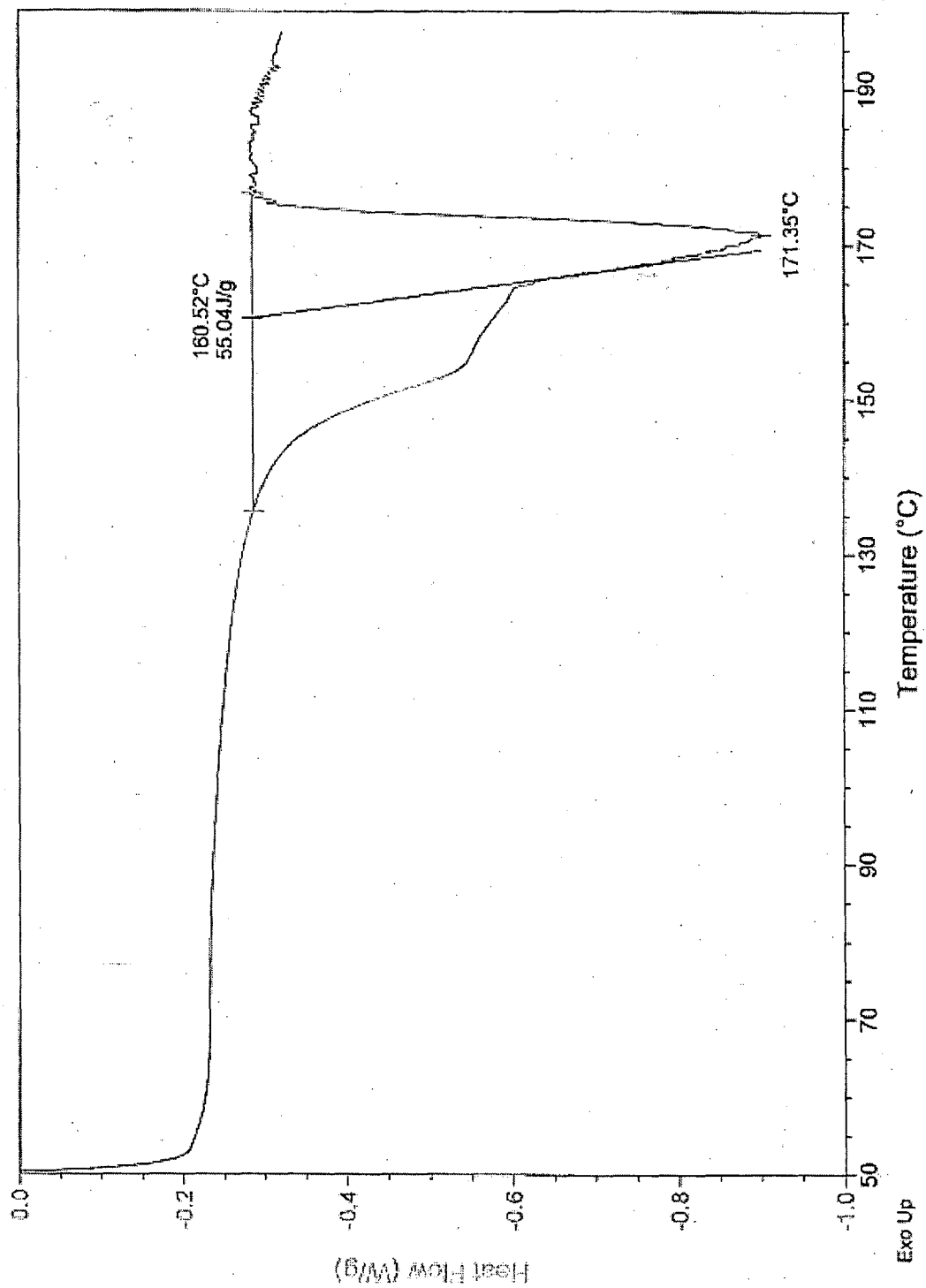


Figure 3

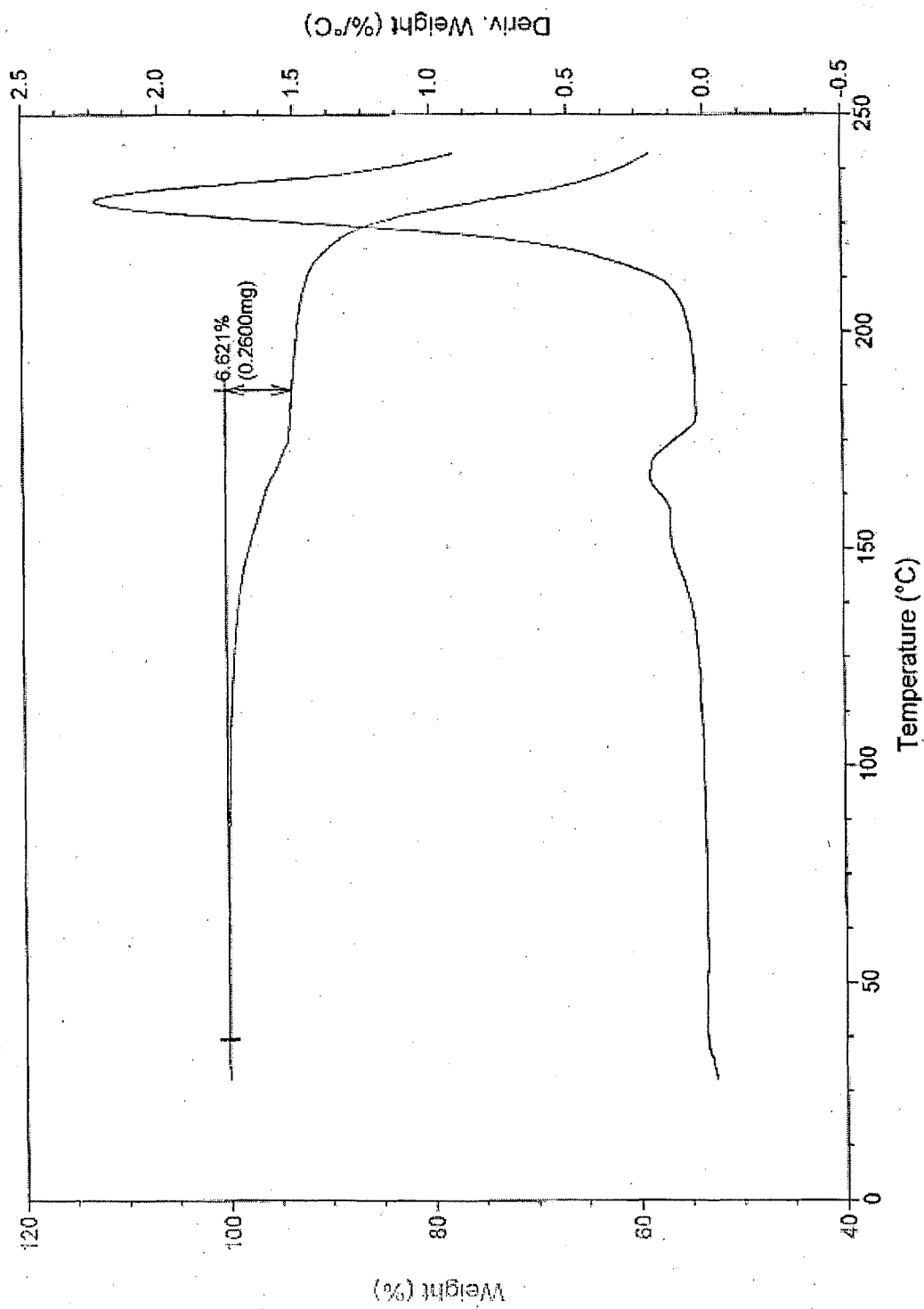


Figure 4

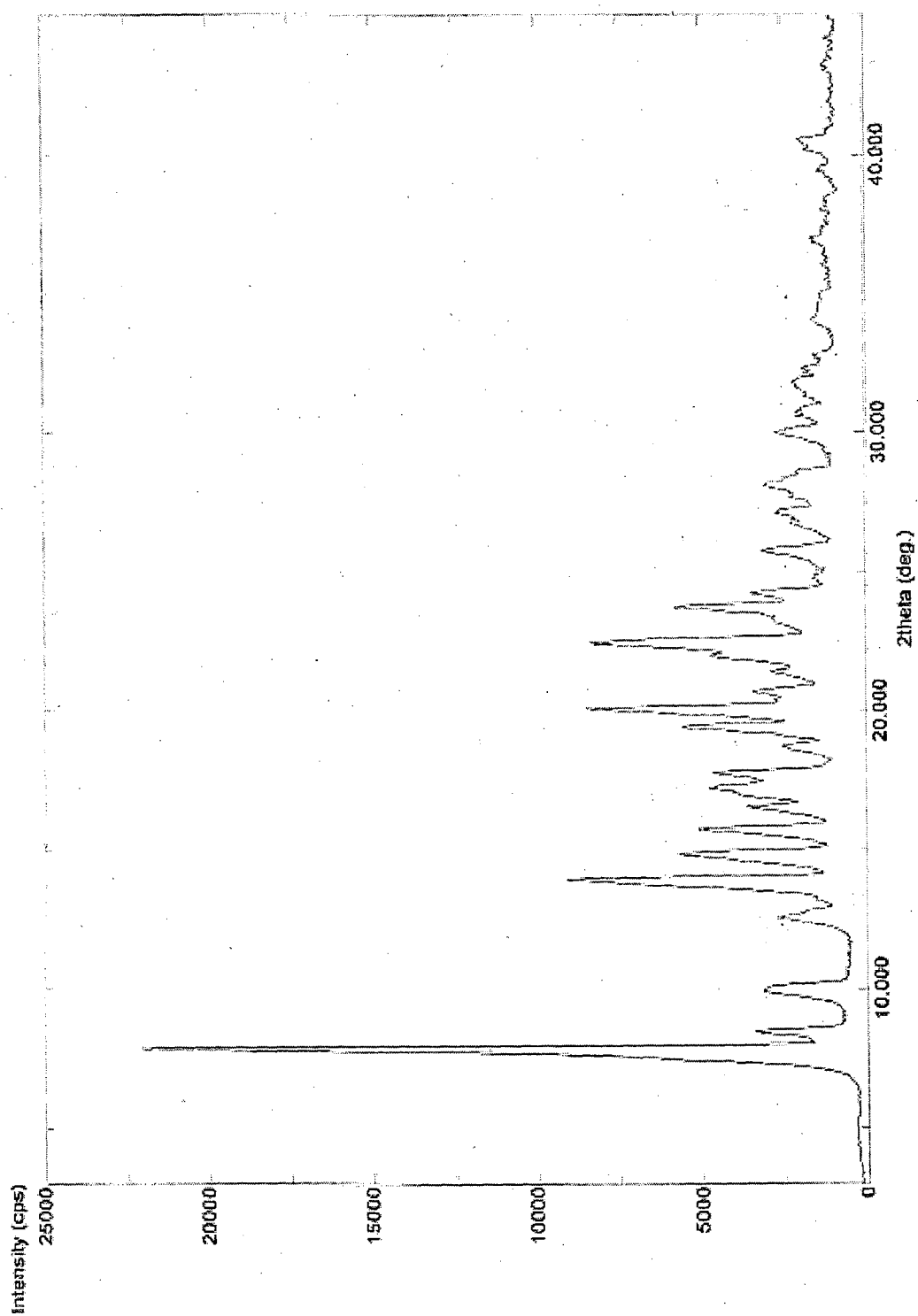


Figure 5

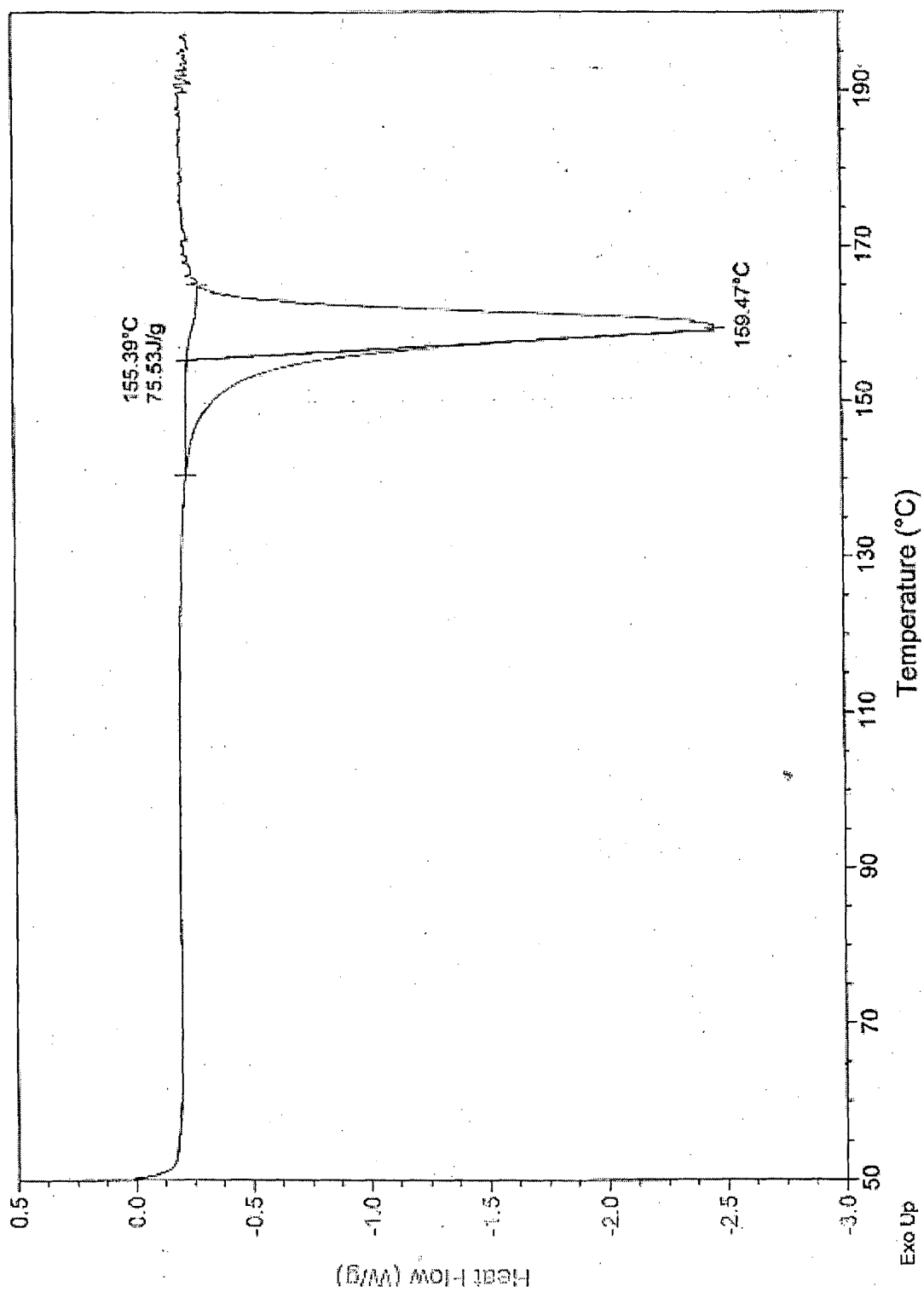


Figure 6

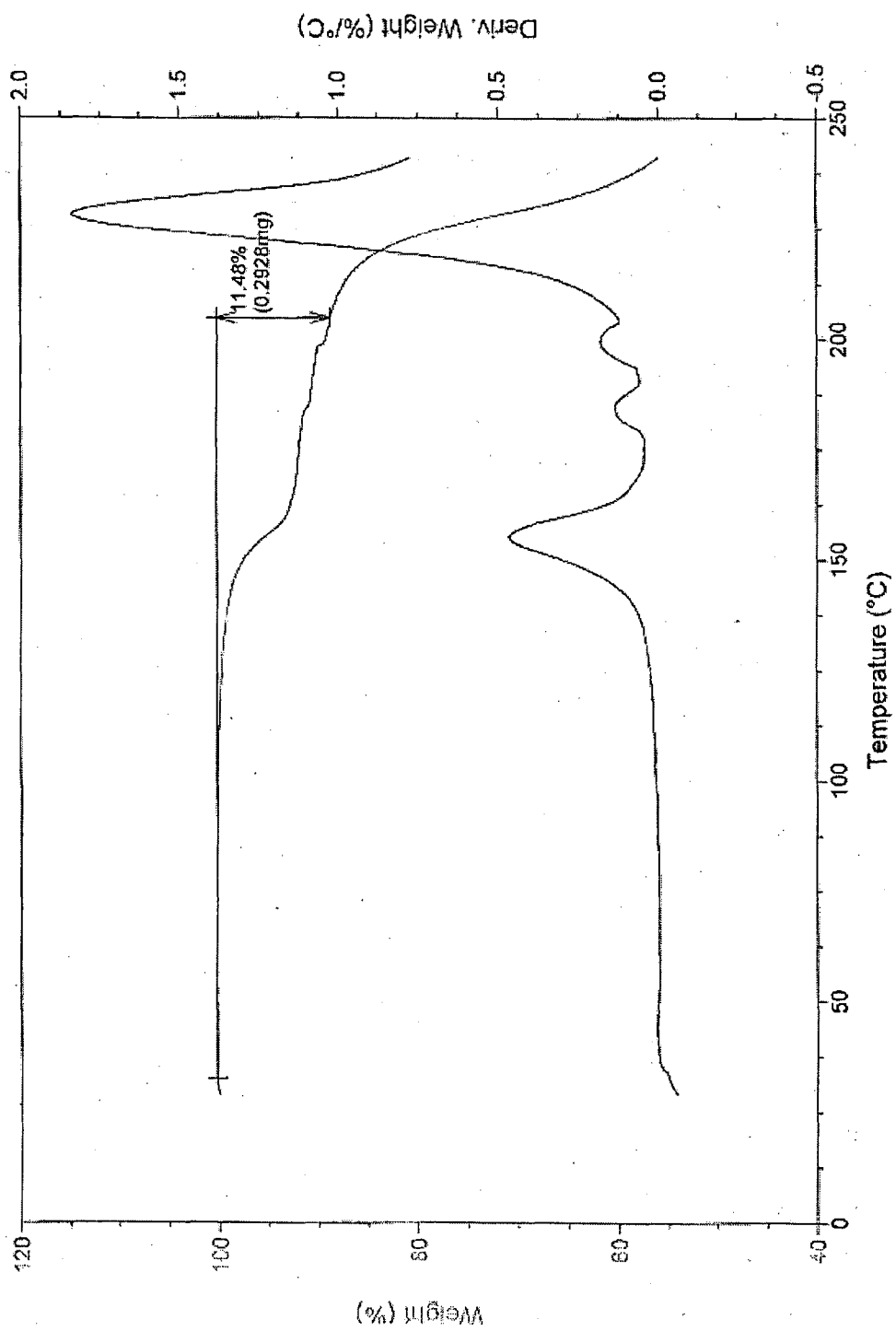


Figure 7

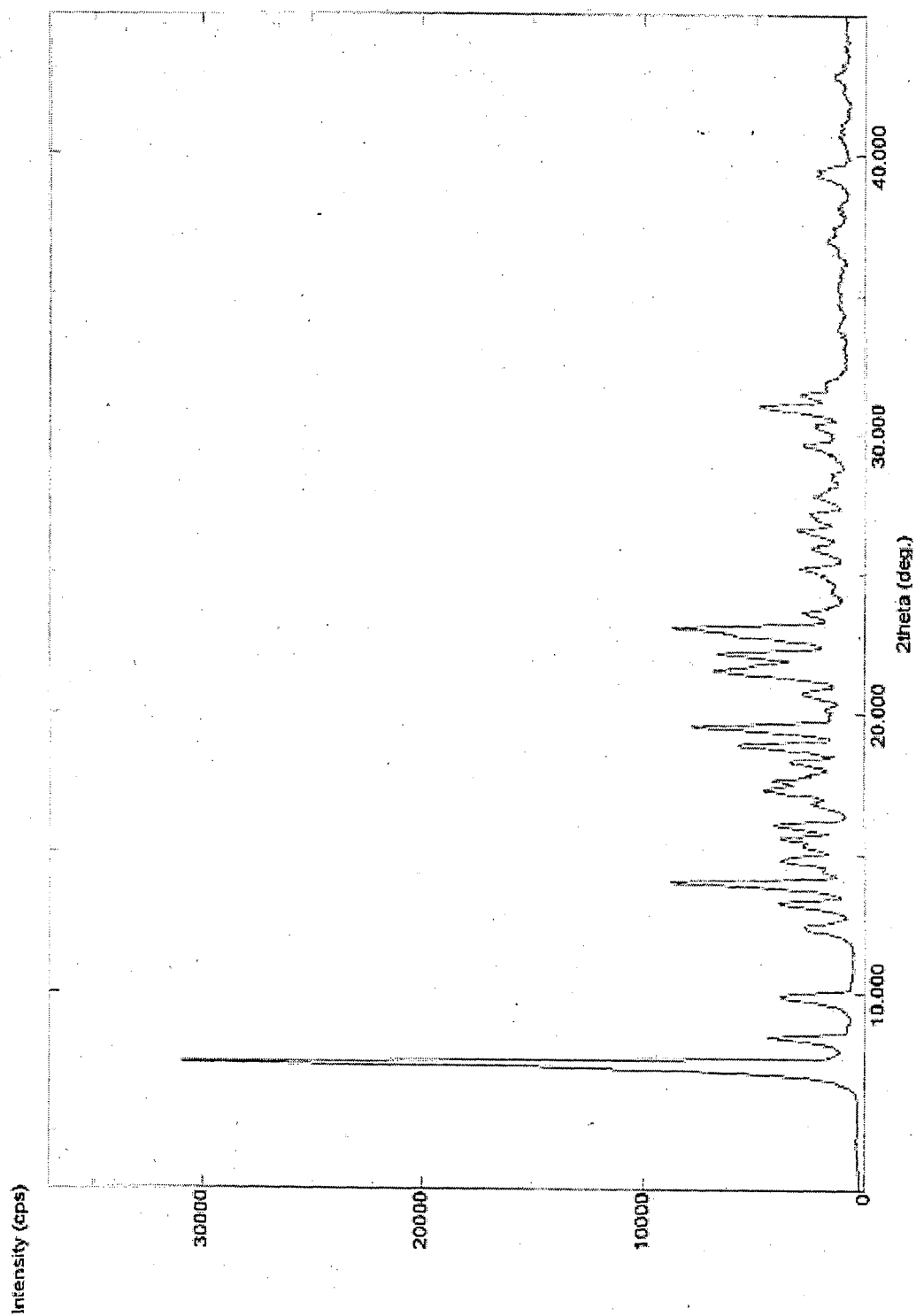


Figure 8

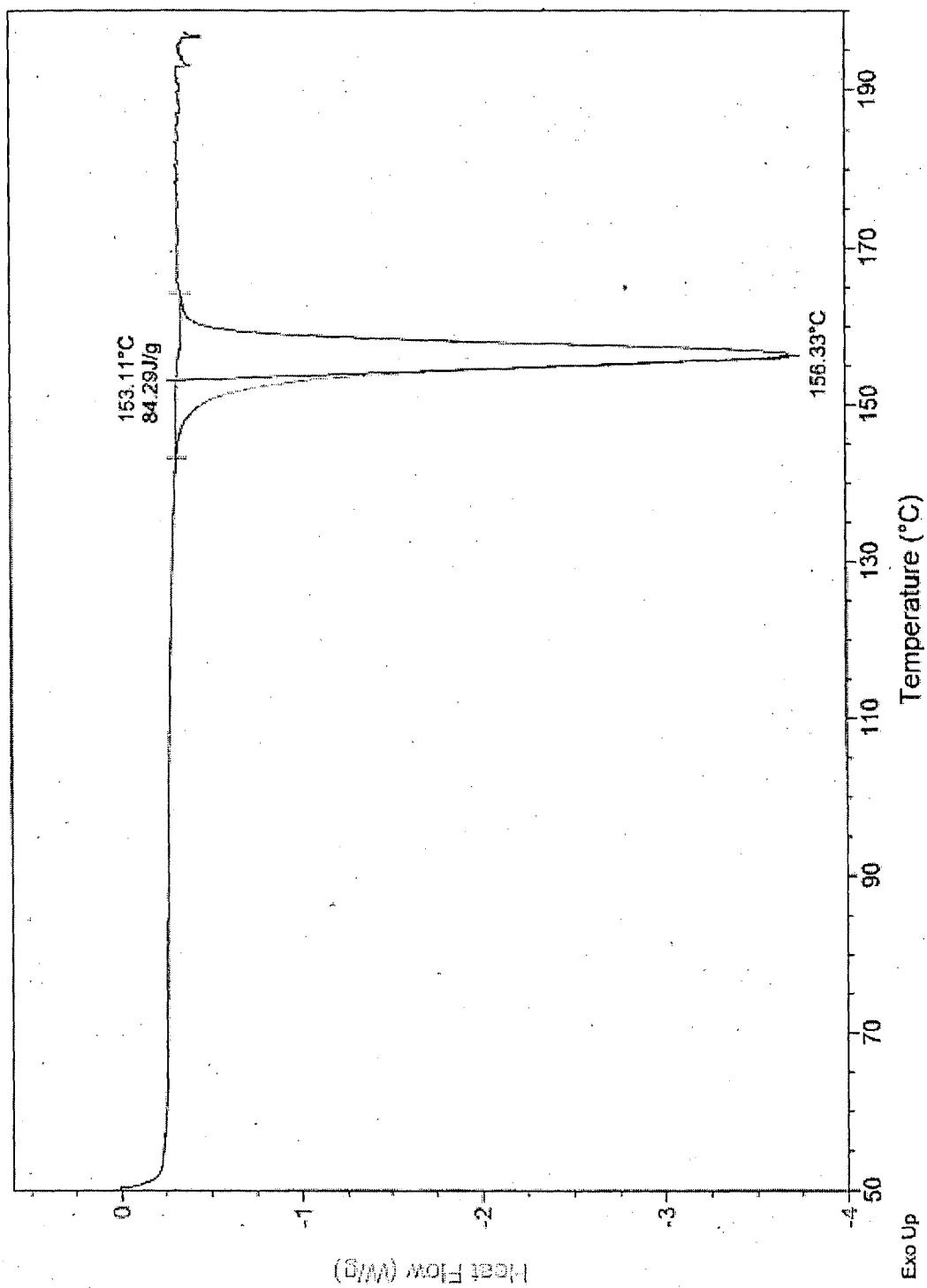


Figure 9

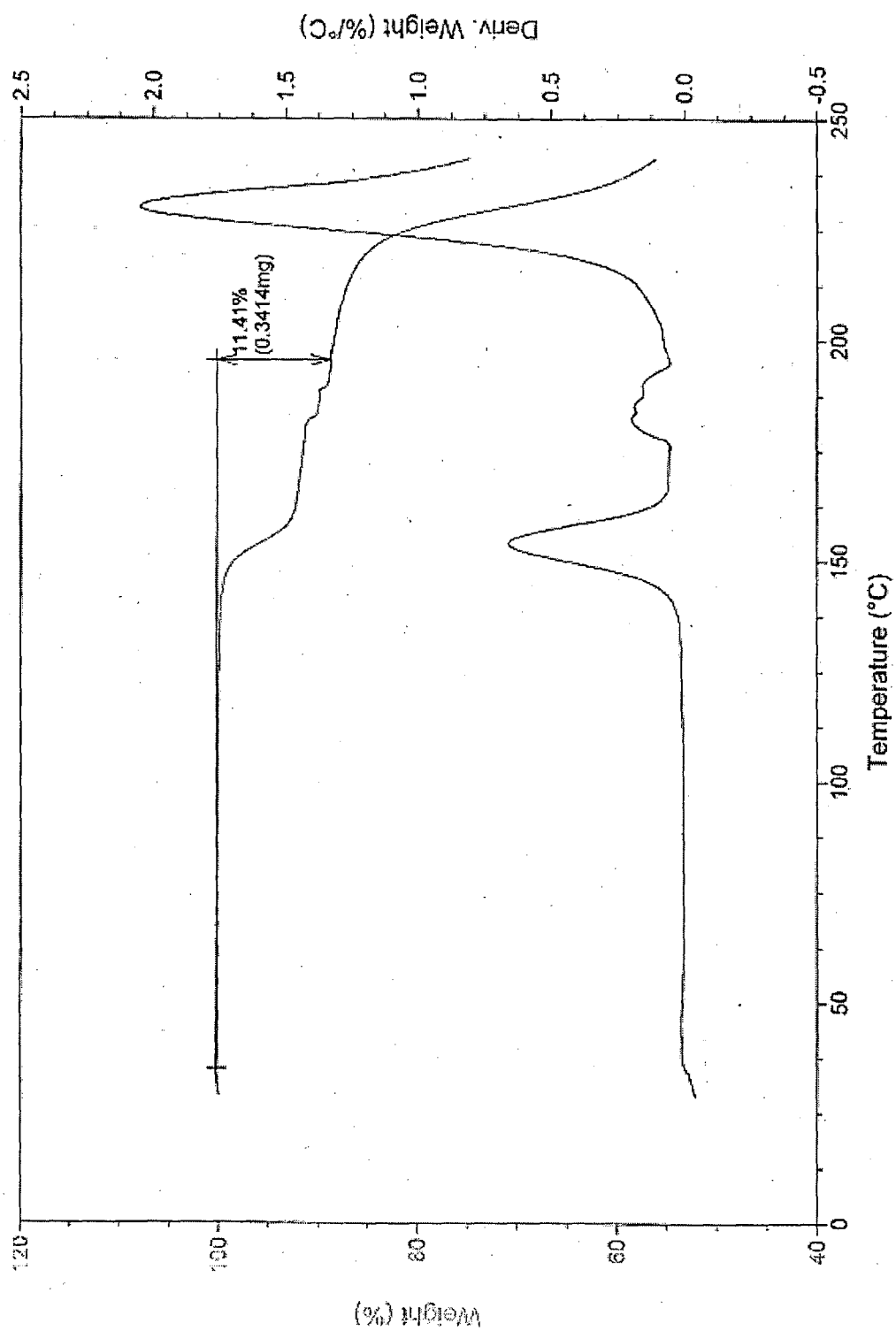


Figure 10

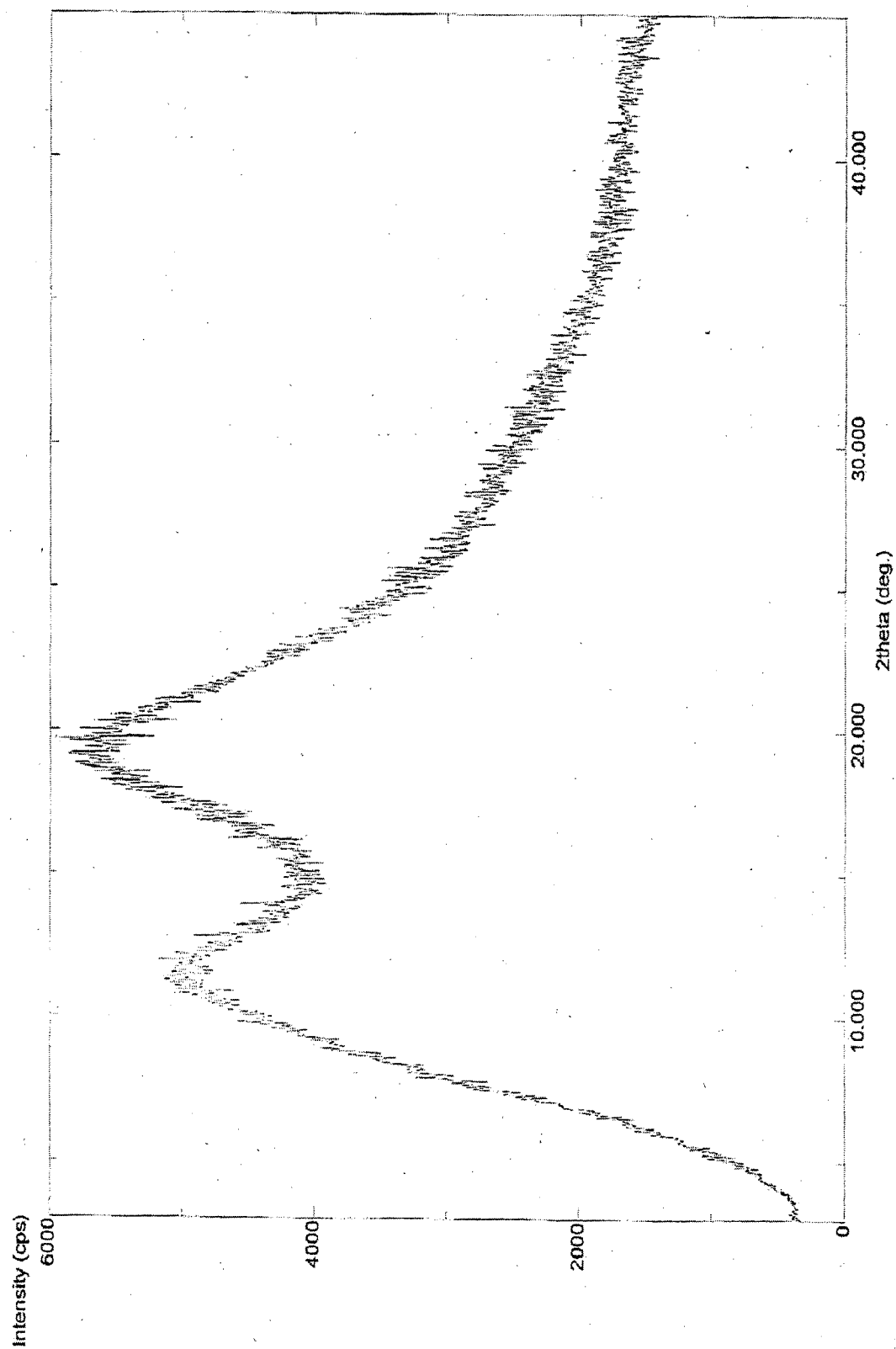


Figure 11

