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(54) **Title**: NOVEL POLYMORPHIC FORMS OF ELVITEGRAVIR AND ITS PHARMACEUTICALLY ACCEPTABLE SALTS

(57) **Abstract**: The present invention relates to amorphous Elvitegravir, amorphous Elvitegravir sodium, crystalline Elvitegravir sodium and processes for the preparation thereof. The present invention also relates to novel processes for the preparation of Elvitegravir polymorphic forms II & III.

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NOVEL POLYMORPHIC FORMS OF ELVITEGRAVIR AND ITS PHARMACEUTICALLY ACCEPTABLE SALTS

This patent application claims priority from Indian Patent Application bearing number 1114/CHE/2009 dated May 12, 2009.

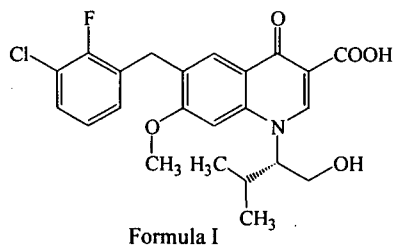
FIELD OF THE INVENTION

The present invention relates to amorphous Elvitegravir, amorphous Elvitegravir sodium, crystalline Elvitegravir sodium and processes for the preparation thereof. The present invention also relates to novel processes for the preparation of Elvitegravir polymorphic forms II & III.

BACKGROUND OF THE INVENTION

Elvitegravir, also known as GS 9137 or JTK 303, is a novel oral integrase inhibitor that is being evaluated for the treatment of HIV-1 infection. These integrase inhibitors interfere with HIV replication by blocking the ability of the virus to integrate into the genetic material of human cells.

Elvitegravir has the chemical name: 6-(3-chloro-2-fluorobenzyl)-1-[(S)-1-hydroxy -methyl-2-methylpropyl]-7-methoxy-4-oxo-1, 4-dihydroquinoline-3-carboxylic acid and has the following structural formula I:



Formula I

US Patent No 7176220 discloses Elvitegravir, solvate, stereoisomer, tautomer, pharmaceutically acceptable salt thereof or pharmaceutical composition containing them and their method of treatment.

US Patent No 7635704 discloses Elvitegravir Form II, Form III and processes for their preparation. The process for the preparation of Form II disclosed in the said patent is mainly by three methods - a) dissolution of Elvitegravir followed by seeding with Form II, b) recrystallisation of Elvitegravir, and c) anti-solvent method.

The process for the preparation of Form III in the said patent is mainly by three methods - a) dissolution of Form II in isobutyl acetate by heating followed by cooling the reaction mass, b) dissolution of Form II in isobutyl acetate by heating followed by seeding with Form III, and c) dissolving Form II in 2-propanol followed by seeding with Form III.

Amorphous materials are becoming more prevalent in the pharmaceutical industry. In order to overcome the solubility and potential bioavailability issues, amorphous solid forms are becoming front-runners. Of special importance is the distinction between amorphous and crystalline forms, as they have differing implications on drug substance stability, as well as drug product stability and efficacy.

An estimated 50% of all drug molecules used in medicinal therapy are administered as salts. A drug substance often has certain suboptimal physicochemical or biopharmaceutical properties that can be overcome by pairing a basic or acidic drug molecule with a counter-ion to create a salt version of the drug. The process is a simple way to modify the properties of a drug with ionizable functional groups to overcome undesirable features of the parent drug. Salt forms of drugs have a large effect on the drugs' quality, safety, and performance. The properties of salt-forming species significantly affect the pharmaceutical properties of a drug and can greatly benefit chemists and formulators in various facets of drug discovery and development.

In spite of the numerous advantages associated with amorphous and salt forms, their development is not available in the literature for Elvitegravir. This statement emphasizes the need to develop amorphous and various novel salt forms of Elvitegravir. The present invention includes polymorphs of Elvitegravir, Elvitegravir sodium and process for their preparation.

OBJECT OF THE INVENTION

The main object of the present invention is to provide amorphous Elvitegravir.

Another object of the present invention is to provide amorphous Elvitegravir sodium.

Yet another object of the present invention is to provide crystalline Elvitegravir sodium.

Yet another object of the present invention is to provide the process for the preparation of amorphous Elvitegravir, amorphous Elvitegravir sodium and crystalline Elvitegravir sodium.

Another object of the present invention is to provide novel processes for the preparation of Elvitegravir Form II and Form III.

SUMMARY OF THE INVENTION

One aspect of the present invention provides an amorphous Elvitegravir , having an X-ray diffraction pattern as shown in Fig. 1.

Another aspect of the present invention provides a process for the preparation of amorphous Elvitegravir comprising the steps of dissolving Elvitegravir in an organic solvent, optionally adding to an anti-solvent, and removing the solvent to isolate amorphous Elvitegravir .

Yet another aspect of the present invention provides an amorphous Elvitegravir sodium, having an X-ray diffraction pattern as shown in Fig. 3.

Yet another aspect of the present invention provides a process for the preparation of amorphous Elvitegravir sodium, comprising the steps of dissolving Elvitegravir in an organic solvent, adding a source of sodium ion, adding an anti-solvent and isolating amorphous Elvitegravir sodium.

Yet another aspect of the present invention provides a process for the preparation of amorphous Elvitegravir sodium comprising the steps of dissolving Elvitegravir in a source of sodium ion and removing the solvent to obtain amorphous Elvitegravir sodium.

Yet another aspect of the present invention provides crystalline Elvitegravir sodium, having an X-ray diffraction pattern, as shown in Fig. 5.

Yet another aspect of the present invention provides a process for the preparation of crystalline Elvitegravir sodium comprising the steps of dissolving Elvitegravir in a source of sodium ion and isolating crystalline Elvitegravir sodium.

Yet another aspect of the present invention provides a process for the preparation of crystalline Form II of Elvitegravir comprising the steps of dissolving Elvitegravir in an organic solvent, adding an anti-solvent and isolating crystalline Form II of Elvitegravir.

Yet another aspect of the present invention provides a process for the preparation of crystalline Form III of Elvitegravir comprising the steps of dissolving Elvitegravir in an organic solvent, optionally adding an anti-solvent, cooling the resultant solution and isolating crystalline form III of Elvitegravir.

Yet another aspect of the present invention also provides pharmaceutical compositions comprising Elvitegravir and salt so prepared and an excipient/carrier, known in the art.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 is a representative X-ray diffraction pattern of amorphous Elvitegravir .
FIG. 2 is a representative DSC thermogram of amorphous Elvitegravir .
FIG. 3 is a representative X-ray diffraction pattern of amorphous Elvitegravir sodium.
FIG. 4 is a representative DSC thermogram of amorphous Elvitegravir sodium.
FIG. 5 is a representative X-ray diffraction pattern of crystalline Elvitegravir sodium.
FIG. 6 is a representative DSC thermogram of crystalline Elvitegravir sodium.
FIG. 7 is a representative X-ray diffraction pattern of crystalline Form II Elvitegravir.
FIG. 8 is a representative X-ray diffraction pattern of crystalline Form III of Elvitegravir.

The X-ray powder diffraction data was collected on Bruker axs D8 ADVANCE powder diffractometer. The Copper anode is used as radiation source with scintillation counter as detector.

The Differential scanning calorimetric (DSC) was recorded on Mettler Toledo DSC 822e. The experiment was performed at a heating rate of 10°C/min. over a temperature range of 50-300°C purging with nitrogen at a flow rate of 50mL/min.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to amorphous Elvitegravir , amorphous Elvitegravir sodium, crystalline Elvitegravir sodium and processes for the preparation thereof. The present invention also relates to novel processes for the preparation of Elvitegravir polymorphic forms II & III.

In one embodiment, the present invention provides an amorphous Elvitegravir, having an X-ray diffraction pattern as shown in Fig. 1.

In yet another embodiment, the present invention provides amorphous Elvitegravir further characterized by a Differential Scanning Calorimetry (DSC) thermogram having a sharp endotherm at 152.52 ± 2°C. The typical DSC thermogram is shown in figure 2.

In another embodiment, the present invention provides a process for the preparation of amorphous Elvitegravir comprising the steps of:

a) dissolving Elvitegravir in an organic solvent,
b) optionally adding the solution of step [a] to an anti-solvent, and
c) removing the solvent to isolate amorphous Elvitegravir .

According to the present invention, Elvitegravir is dissolved in an organic solvent. Optionally, the resultant step [a] solution is added to the pre-cooled anti-solvent at 0-35°C under stirring. In case anti-solvent is used for the precipitation, the solvent is removed by filtration and thus isolating amorphous Elvitegravir . In the case where anti-solvent is not used, the solvent is removed by conventional techniques and thus isolating amorphous Elvitegravir.

The solvent used for the dissolution is selected from alcohols such as methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, iso-butanol or a mixture thereof and the anti-solvent for precipitation is water. The conventional technique is selected from spray drying, freeze drying, agitated thin film drying or distillation.

In yet another embodiment, the present invention provides amorphous Elvitegravir sodium, having an X-ray diffraction pattern as shown in Fig. 3.

In yet another embodiment, the present invention provides amorphous Elvitegravir sodium is further characterized by a Differential Scanning Calorimetry (DSC) thermogram having small exotherms in the range between 181-197°C and 209-219°C followed by a sharp endotherm at 248 ± 2°C. The typical DSC thermogram is shown in figure 4.

In yet another embodiment, the present invention provides a process for the preparation of amorphous Elvitegravir sodium comprising the steps of:

a) dissolving Elvitegravir in an organic solvent,
b) adding a source of sodium ion,
c) adding an anti-solvent, and
d) isolating amorphous Elvitegravir sodium.

According to the present invention, Elvitegravir is dissolved in an organic solvent at ambient temperature and a source of sodium ion is added under stirring. To the resultant solution, an anti-solvent is added at 0-5°C for the precipitation followed by isolating amorphous Elvitegravir sodium. The organic solvent used for the dissolution is selected from methanol, ethanol, isopropyl alcohol, 1-propanol, 1-butanol, 2-butanol, iso-butanol or a mixture thereof. The anti-solvent used is selected from toluene, xylene, hexane, heptane or a mixture thereof. The source of sodium ion is selected from sodium hydroxide, sodium bicarbonate, sodium methoxide, sodium ethoxide, sodium n-propoxide, sodium isopropoxide, sodium butoxide, sodium tertiary butoxide or a mixture thereof.

In yet another embodiment, the present invention provides a process for the preparation of amorphous Elvitegravir sodium comprising the steps of:

a) dissolving Elvitegravir in a source of sodium ion an a solvent, and
b) removing the solvent to isolate amorphous Elvitegravir sodium.

According to the present invention, Elvitegravir is dissolved in a source of sodium ion in a solvent and solvent is concentrated using conventional techniques to isolate amorphous Elvitegravir sodium. The solvent used for the dissolution is selected from methanol, ethanol, 1-propanol, isopropyl alcohol, 1-butanol, 2-butanol, iso-butanol or a mixture thereof. The

source of sodium ion is selected from sodium hydroxide, sodium bicarbonate, sodium methoxide, sodium ethoxide, sodium n-propoxide, sodium isopropoxide, sodium butoxide, sodium tertiary butoxide or a mixture thereof. The conventional techniques used to remove the solvent is selected from spray drying or freeze drying, agitated thin film drying (ATFD) or distillation.

In yet another embodiment, the present invention provides crystalline Elvitegravir sodium.

In yet another embodiment, the present invention provides crystalline Elvitegravir sodium characterized by an X-ray diffraction pattern having three or more peaks at 2θ values selected from 4.61, 8.00, 9.24, 11.02, 12.25, 12.83, 13.64, 15.82, 16.72, 18.57, 18.95, 20.26, 21.14, 22.18, 23.29, 23.60 and 24.62 ± 0.2 θ, as shown in Fig. 5.

In yet another embodiment, the present invention provides crystalline Elvitegravir sodium is further characterized by a Differential Scanning Calorimetry (DSC) thermogram having small endotherm in the range between 186-213°C followed by a sharp endotherm at 265 ± 2°C. The typical DSC thermogram is shown in figure 6.

In another embodiment, the present invention provides a process for the preparation of crystalline Elvitegravir sodium comprising the steps of:

a) dissolving Elvitegravir in a source of sodium ion, and
b) isolating crystalline Elvitegravir sodium.

According to the present invention, Elvitegravir is dissolved in a source of sodium ion in a solvent at ambient temperature and stirred for 1h. The resultant solution is left overnight for crystallization thus isolating crystalline Elvitegravir sodium. The solvent is selected from methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, iso-butanol or a mixture thereof. The source of sodium ion is selected from sodium hydroxide, sodium bicarbonate, sodium methoxide, sodium ethoxide, sodium n-propoxide, sodium isopropoxide, sodium butoxide, sodium tertiary butoxide or a mixture thereof.

In yet another embodiment, the present invention provides a process for the preparation of crystalline Form II of Elvitegravir comprising the steps of:

a) dissolving Elvitegravir in an organic solvent,

b) adding an anti-solvent, and
c) isolating crystalline Form II of Elvitegravir.

According to the present invention, Elvitegravir is dissolved in an organic solvent such as dimethoxyethane at 35-80°C. To the reaction mass, an anti-solvent is added at same temperature and maintained for 30 min-2h. The resulting solution is cooled to isolate crystalline Form II of Elvitegravir. The anti-solvent is selected from methanol, ethanol, 1-propanol, 2-propanol, hexane, cyclohexane, heptane, toluene, xylene or a mixture thereof.

In yet another embodiment of the present invention, the crystalline Form II of Elvitegravir prepared according to the above method, have an X-ray diffraction pattern with peaks at 6.63, 13.27, 19.9, 20.95, 21.30 and 25.31 ± 0.2 θ, as shown in Fig.7.

In yet another embodiment, the present invention provides a process for the preparation of crystalline Form III of Elvitegravir comprising the steps of:

a) dissolving Elvitegravir in an organic solvent,
b) optionally adding an anti-solvent,
c) cooling the resultant solution, and
d) isolating crystalline form III of Elvitegravir

According to the present invention, Elvitegravir is dissolved in an organic solvent at 35-95^{0}C, optionally, added an anti -solvent, cooled to ambient temperature and stirred for over night for the crystallization. The formed wet crystals are collected by filtration and dried to obtain crystalline form III of Elvitegravir. The organic solvent is selected from methanol, ethanol, n-propanol, 2-propanol, 2-methoxyethanol, acetonitrile, nitromethane, dichloromethane, ethyl acetate, water or a mixture thereof and anti-solvent is selected from methanol, ethanol, propanol, water, hexane, cyclohexane, heptane, toluene, xylene or a mixture thereof.

In yet another embodiment of the present invention, the crystalline Form III of Elvitegravir prepared according to the above method, have an X-ray diffraction pattern with peaks at 8.51, 14.06, 15.71, 17.11, 24.17 and 25.73 ±0.2 θ, as shown in Fig. 8.

In yet another embodiment, the spray drying technique is done using a flow rate of about 150 to 250 ml/Hr. with an air inlet temperature of about 55 to 65°C and outlet temperature of about 40 to 50°C.

In yet another embodiment, the invention is further directed to pharmaceutical composition comprising: (a) a therapeutically effective amount of Elvitegravir or salt thereof of the present invention; and (b) at least one pharmaceutically acceptable carrier, diluent, vehicle or excipient.

The term "pharmaceutical composition" as used herein refers to dosage form for oral administration in the form of tablets, capsules, pills, powders, granules, particles, pellets, beads, or mini-tablets. Preferred dosage forms are tablets or capsules.

The excipients included in the composition are those which are customary and known to a person skilled in the art. These include without any limitations, diluents, fillers, binders, disintegrants, surfactants, stabilizers, glidants, lubricants etc.

The tablets or capsules can be prepared by any conventional processes known to a person skilled in the art.

The following examples are provided for illustrative purposes only and are not intended to limit the scope of the in any way.

Examples

Example 1: Preparation of amorphous Elvitegravir.

Elvitegravir (10 g, 0.022 moles) was dissolved in methanol (100 mL). In another Flask, purified water (500 mL) was charged, cooled to 0 to 5°C, above Elvitegravir solution in methanol was added over a period of 30 to 45 min and maintained for 1 h. The precipitated solid was collected by filtration at 0°C and washed with chilled methanol-water mixture (1:5, 10 mL). The wet product was vacuum dried to get amorphous Elvitegravir (9.5 g; Yield 95 %).

2: Preparation of amorphous Elvitegravir.

Elvitegravir (10 g, 0.022 moles) was dissolved in methanol (145 mL) at room temperature. The resulting solution was spray-dried under the following conditions:

Flow rate 200 mL/h, air inlet temperature between 60 to 65°C and out let temperature between 45 to 50°C to provide amorphous Elvitegravir (4.0 g, 40% yield).

Example 3: Preparation of amorphous Elvitegravir Sodium.

Elvitegravir (100 g, 0.223 moles) was dissolved in methanol (250 mL) and aqueous sodium hydroxide (2.25 N, 1000 mL) was added. The reaction mixture was stirred for about 30 min. and diluted with toluene (1000 mL). The resultant slurry was stirred for 1 h. at 0 to 5°C. The precipitated solid was filtered. The wet product was washed with chilled water (200 mL) and dried under vacuum to give the amorphous Elvitegravir sodium (90 g, yield 86%).

Example 4: Preparation of amorphous Elvitegravir sodium.

Elvitegravir (10 g, 0.022 moles) was dissolved in a solution of sodium hydroxide (0.9 g) in methanol (145 mL) at room temperature. The resulting solution was spray-dried to remove the solvent under the following conditions: Flow rate 200 mL/h., air inlet temperature between 60 to 65°C and out let temperature is in between 45 to 50°C to provide amorphous Elvitegravir sodium (3.5 g, Yield 35%).

Example 5: Preparation of crystalline Elvitegravir Sodium.

Elvitegravir (10 g, 0.022 moles) was dissolved in methanolic sodium hydroxide solution (50 mL, 1.78% w/v, 0.022 moles). The reaction mixture was stirred for 1 h. and the resultant mass was left over night at room temperature. The precipitated solid was collected by filtration at room temperature and washed with chilled methanol (10 mL). The wet product was vacuum dried to give crystalline Elvitegravir sodium (8.5 g; Yield 85 %).

Example 6: Preparation of polymorphic form-II of Elvitegravir.

Elvitegravir (10 g, 0.022 moles) was dissolved in dimethoxyethane (20 mL) at 60 to 65°C. Hexane (20 mL) was slowly added to it at 55 to 65°C over a period of 30 min. and maintained for 30 min. The reaction mass was cooled to 25 to 35°C and stirred for 3 h. at ambient temperature. The solid precipitated out was collected by filtration at room temperature and washed with a mixture of dimethoxyethane - hexane (1:1, 10 mL). The wet product was vacuum dried to give polymorphic form -II of Elvitegravir (8 g; Yield 80 %).

Example 7: Preparation of crystalline form III of Elvitegravir

Elvitegravir (10 g, 0.022 moles) was dissolved in methanol (25 mL) at 50 to 55°C, maintained for 1 h. and left over night at room temperature. The solid precipitated out was collected by filtration at room temperature and washed with chilled methanol (10 mL). The wet product was vacuum dried to give crystalline form-III of Elvitegravir (7 g; Yield 70 %).

Example 8: Preparation of polymorphic form-III of Elvitegravir

Elvitegravir (10 g, 0.0223 moles) was dissolved in 2-methoxyethanol (15 mL) at 85 to 90°C and maintained for about 15 min. The reaction mixture was cooled to ambient temperature and maintained for 12 h. The obtained solid was collected by filtration at room temperature and washed with n-hexane (10 mL). The wet product was dried to give polymorphic form – III of Elvitegravir (7.0 g; Yield 70%).

Example 9: Preparation of polymorphic form-III of Elvitegravir

Elvitegravir (10 g, 0.0223 moles) was dissolved in acetonitrile (40 mL) at 60 to 65°C and maintained for about 15 min. The reaction mixture was cooled to ambient temperature and stirred for 12 h. The obtained solid was collected by filtration at room temperature and washed with n-hexane (10 mL). The wet product was dried to give polymorphic form – III of Elvitegravir (7.5 g; Yield 75%).

Example 10: Preparation of polymorphic form-III of Elvitegravir

Elvitegravir (10 g, 0.022 moles) was dissolved in nitromethane (20 mL) at 60-65°C. Hexane (20 mL) was slowly added to it over a period of 30 min. at a temperature of about 55 to 65°C and maintained for 1 h. The reaction mass was cooled to 25 to 35°C and stirred for 3 h. at ambient temperature. The solid precipitated out was collected by filtration at room temperature and washed with a mixture of nitromethane-hexane (1:1, 10 mL). The wet product was vacuum dried to give polymorphic form -III of Elvitegravir (8 g; Yield 80 %).

Example 11: Preparation of polymorphic form-III of Elvitegravir

Elvitegravir (10 g, 0.0223 moles) was dissolved in dichloromethane (80 mL) at 38 to 40°C and maintained for about 30 min. The reaction mixture was distilled at atmospheric pressure up to 2 volumes of solvent left in the reaction mass. n-Hexane (20 mL) was slowly added to the reaction mass at 38 to 45°C over a period of 1 h. The reaction mass was cooled to

ambient temperature and maintained for 12 h. The precipitated solid was collected by filtration at room temperature and washed with a mixture of dichloromethane and n-hexane (1:1, 10 mL). The wet product was dried to give polymorphic form – III of Elvitegravir (8.5 g; Yield 85%).

Example 12: Preparation of polymorphic form-III of Elvitegravir

Elvitegravir (10 g, 0.0223 moles) was dissolved in a mixture of ethyl acetate (100 mL) and water (5 mL) at 75 to 80°C and maintained for 30 min. The reaction mixture was distilled at atmospheric pressure up to 2 volumes of the solvent left in the reaction mass. n-Hexane (15 mL) was slowly added to the resultant reaction mass at 60 to 75°C over a period of 2 h. Then, the reaction mixture was cooled to 30 to 35°C. The precipitated solid was collected by filtration at room temperature and washed with a mixture of ethyl acetate and n-hexane (1:1, 10 mL). The wet product was dried to give polymorphic form – III of Elvitegravir (9.5 g; Yield 95%).

Example 13: Preparation of polymorphic form-III of Elvitegravir

Elvitegravir (10 g, 0.0223 moles) was dissolved in a mixture of ethyl acetate (100 mL) and water (5 mL) at 75 to 80°C and maintained for 30 min. The reaction mixture was distilled at atmospheric pressure up to leave 2 volumes of the solvent left in reaction mass. The resultant reaction mass was diluted with a mixture of methanol (5 mL) and n-Hexane (30 mL) at 60 to 75°C over a period of 2 h. The reaction mixture was cooled to 30 to 35°C. The precipitated solid was collected by filtration at room temperature and washed with a mixture of ethyl acetate and n-hexane (10 mL). The wet product was dried to give polymorphic form – III Elvitegravir (6.5 g; Yield 65%).

Example 14: Preparation of Elvitegravir dosage form

Elvitegravir prepared according to the invention is incorporated into suitable pharmaceutical dosage form. Not limited by any example, various dosage forms can be prepared using Elvitegravir according to the invention. The tablet dosage form comprising elvitegravir is prepared as disclosed below:

Unit composition

Ingredients	**mg/tab**
Intra granular	
Elvitegravir	100-250
Lactose monohydrate	50-75
Microcrystalline cellulose	75 -125
Dibasic calcium phosphate	65-95
Poloxamer	25-55
Hypromellose	25-52
Purified water	Qs
Extra granular	
Microcrystalline cellulose	60-85
Magnesium stearate	2-6
Sodium stearyl fumarate	5-15
Opadry® Coating	15-35

Brief Manufacturing Process:

1. Sift Elvitegravir, lactose monohydrate, microcrystalline cellulose and dibasic calcium phosphate separately through suitable sieve.
2. Dissolve hypromellose in purified water.
3. Load the materials of step 1 into rapid mixer granulator and granulate using the solution of step 2.
4. Dry the granulate of step 3 and mill through suitable screen.
5. Sift the remaining quantity of microcrystalline cellulose, sodium stearyl fumarate and magnesium stearate separately through suitable sieve.
6. Load the granules of step 4 and materials of step 5 into a blender and blend for suitable period of time.
7. Compress the blend of step 6 using appropriate tooling.
8. Coat the tablet with the commercially available Opadry® till the required weight build up.

Claims

1. Amorphous Elvitegravir.

2. Amorphous Elvitegravir having an X-ray diffraction pattern as shown in Fig. 1.

3. A process for the preparation of amorphous Elvitegravir comprising the steps of:
   a) dissolving Elvitegravir in an organic solvent,
   b) optionally adding the solution of step [a] to an anti-solvent, and
   c) removing said organic solvent to isolate amorphous Elvitegravir .

4. The process according to claim 3, wherein said anti-solvent is water.

5. The process according to claim 3, wherein said organic solvent is removed by using techniques such as spray drying, freeze drying, agitated thin film drying, distillation or filtration.

6. Amorphous Elvitegravir sodium.

7. Amorphous Elvitegravir sodium, having an X-ray diffraction pattern as shown in Fig. 3.

8. A process for the preparation of amorphous Elvitegravir sodium comprising the steps of:
   a) dissolving Elvitegravir in an organic solvent,
   b) adding a source of sodium ion,
   c) adding an anti-solvent, and
   d) isolating amorphous Elvitegravir sodium.

9. The process according to claim 3 and 8 , wherein said organic solvent is selected from methanol, ethanol, isopropyl alcohol, 1-propanol, 1-butanol, 2-butanol, iso-butanol or a mixture thereof.

10. The process according to claim 8, wherein an anti-solvent is selected from toluene, xylene, hexane, heptane or a mixture thereof.

11. A process for the preparation of amorphous Elvitegravir sodium comprising the steps of:
    a) dissolving Elvitegravir in a source of sodium ion in a solvent, and
    b) removing the solvent to isolate amorphous Elvitegravir sodium.

12. The process according to claim 11, wherein removal of the solvent is carried out by using techniques such as spray drying, freeze drying, agitated thin film drying or distillation.

13. Crystalline Elvitegravir sodium.

14. A crystalline Elvitegravir sodium characterized by an X-ray diffraction pattern having three or more peaks at 2θ values selected from 4.61, 8.00, 9.24, 11.02, 12.25, 12.83, 13.64, 15.82, 16.72, 18.57, 18.95, 20.26, 21.14, 22.18, 23.29, 23.60 and 24.62 ± 0.2θ, as shown in Fig. 5.

15. A process for the preparation of crystalline Elvitegravir sodium comprising the steps of:
    a) dissolving Elvitegravir in a source of sodium ion, and
    b) isolating crystalline Elvitegravir sodium.

16. The process according to claims 8, 11 and 15, wherein the sodium ion source is selected from sodium hydroxide, sodium bicarbonate, sodium methoxide, sodium ethoxide, sodium n-propoxide, sodium isopropoxide, sodium butoxide or sodium tertiary butoxide.

17. A process for the preparation of crystalline Form II of Elvitegravir comprising the steps of:
    a) dissolving Elvitegravir in dimethoxyethane,
    b) adding an anti-solvent, and
    c) isolating crystalline Form II of Elvitegravir.

18. The process according to claim 17, wherein said anti-solvent is selected from methanol, ethanol, 1-propanol, 2-propanol, hexane, cyclohexane, heptane, toluene, xylene or a mixture thereof.

19. A process for the preparation of crystalline form III of Elvitegravir comprising the steps of:
    a) dissolving Elvitegravir in a solvent,
    b) optionally adding an anti-solvent,
    c) cooling the resultant solution, and
    d) isolating crystalline form III of Elvitegravir.

20. The process according to claim 19, wherein the solvent is selected from methanol, ethanol, n-propanol, 2-propanol, 2-methoxyethanol, acetonitrile, nitromethane, dichloromethane, chloroform, ethyl acetate, water or a mixture thereof.

21. The process according to claim 19, wherein the anti-solvent is selected methanol, ethanol, propanol, water, hexane, cyclohexane, heptane, toluene, xylene or a mixture thereof.

22. A pharmaceutical composition comprising: (a) a therapeutically effective amount of Elvitegravir or its sodium salt; and (b) at least one pharmaceutically acceptable carrier.

23. The pharmaceutical composition of claim 22, wherein the Elvitegravir or its salts are used in the amorphous or crystalline form or mixtures thereof.

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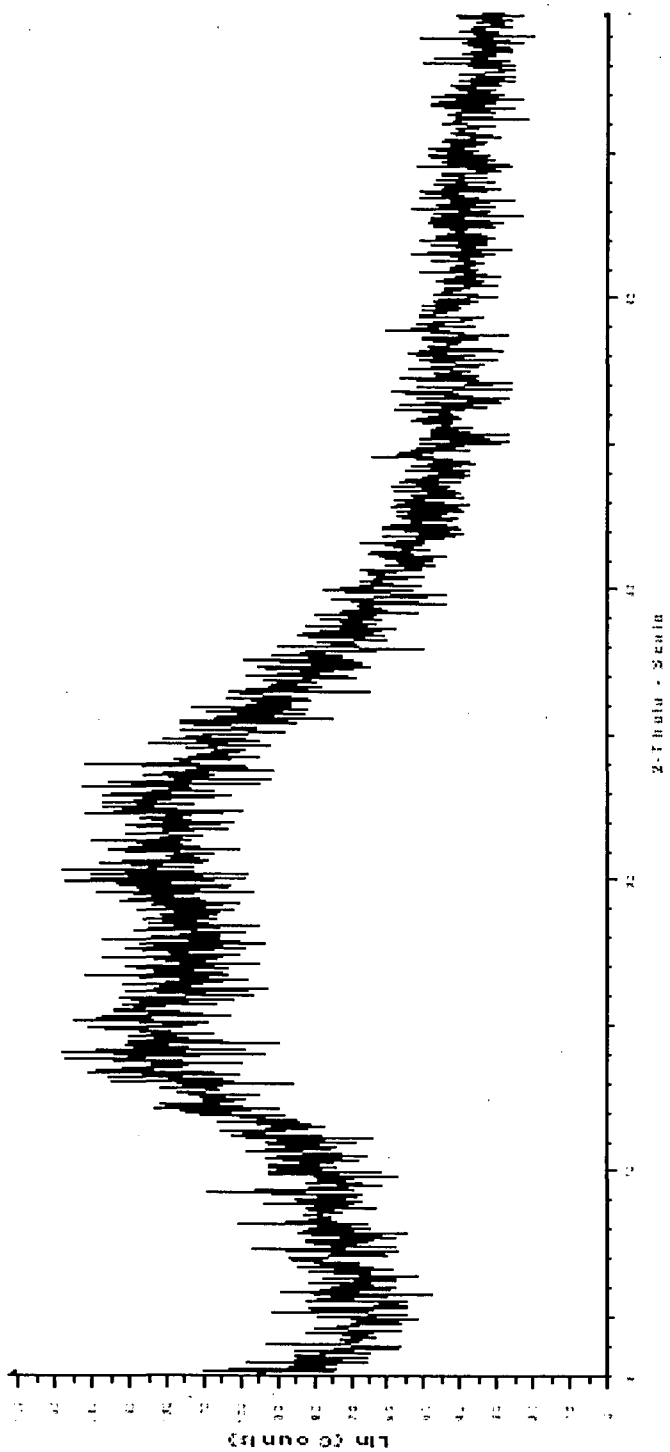

Figure 1

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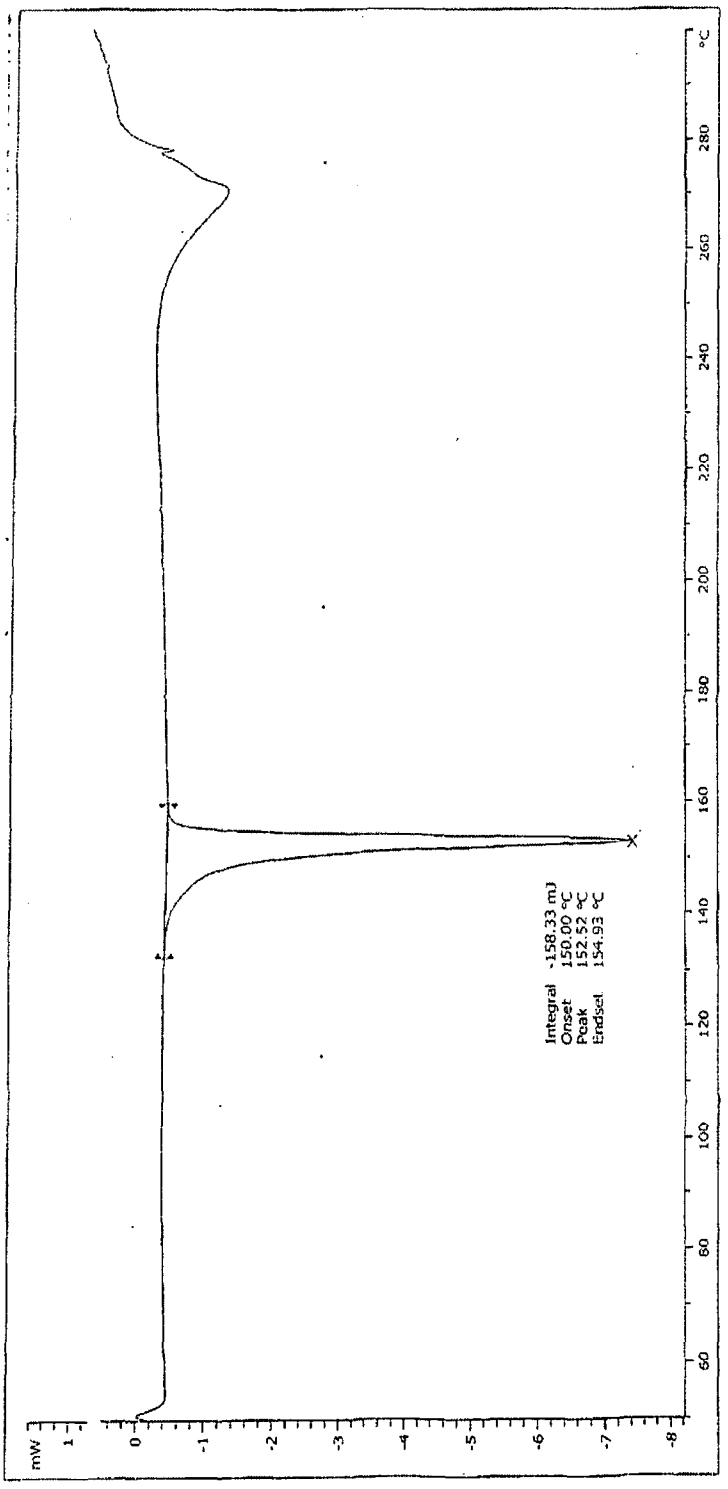

Figure 2

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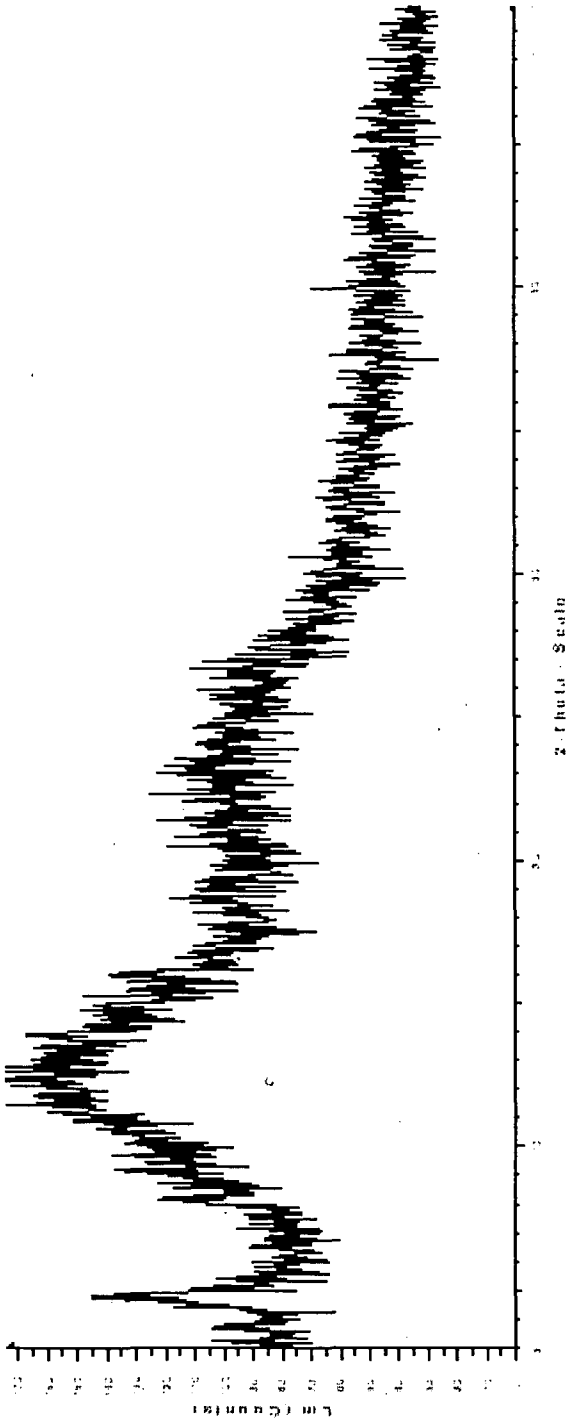
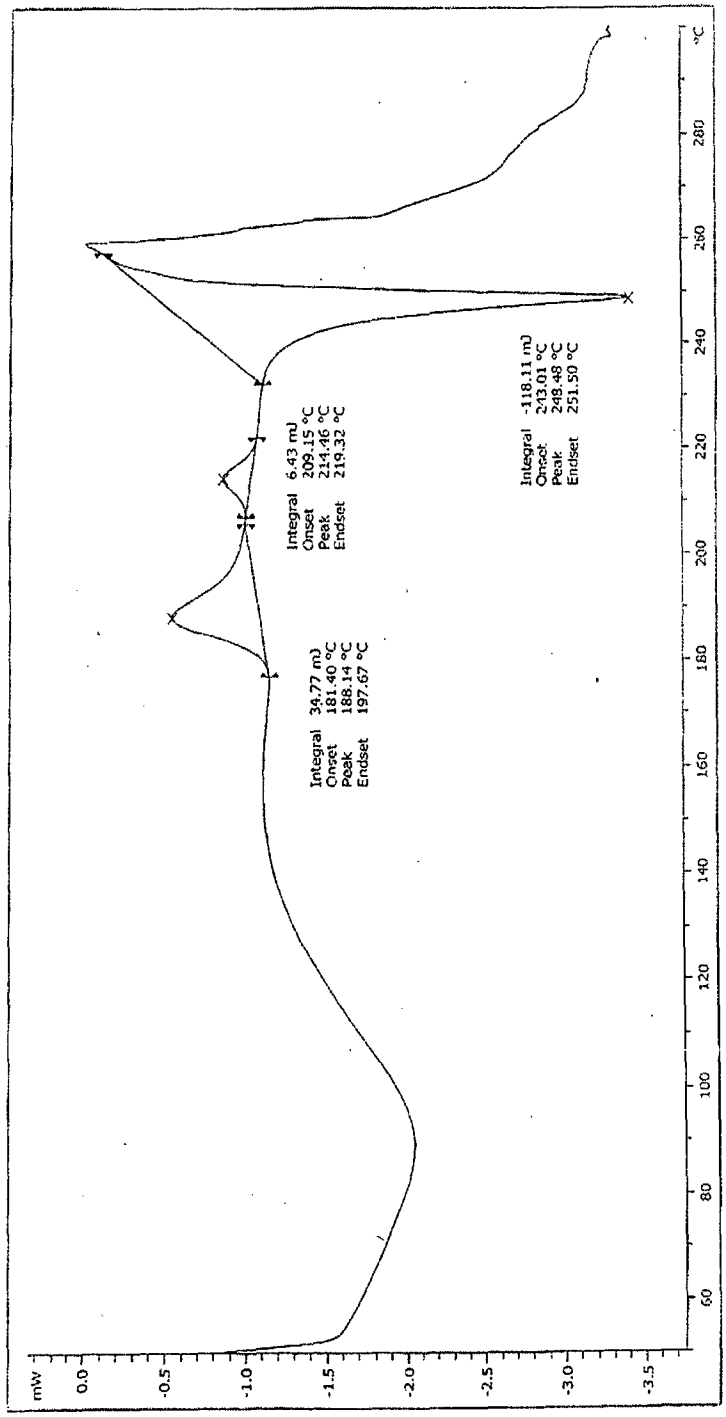


Figure 3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-1.5
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100
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140
160
180
200
220
240
260
280
°C
Integral 34.77 mJ
Onset 181.40 °C
Peak 188.14 °C
Endset 197.67 °C
Integral 6.43 mJ
Onset 209.15 °C
Peak 214.46 °C
Endset 219.32 °C
Integral -118.11 mJ
Onset 243.01 °C
Peak 248.48 °C
Endset 251.50 °C

Figure 4

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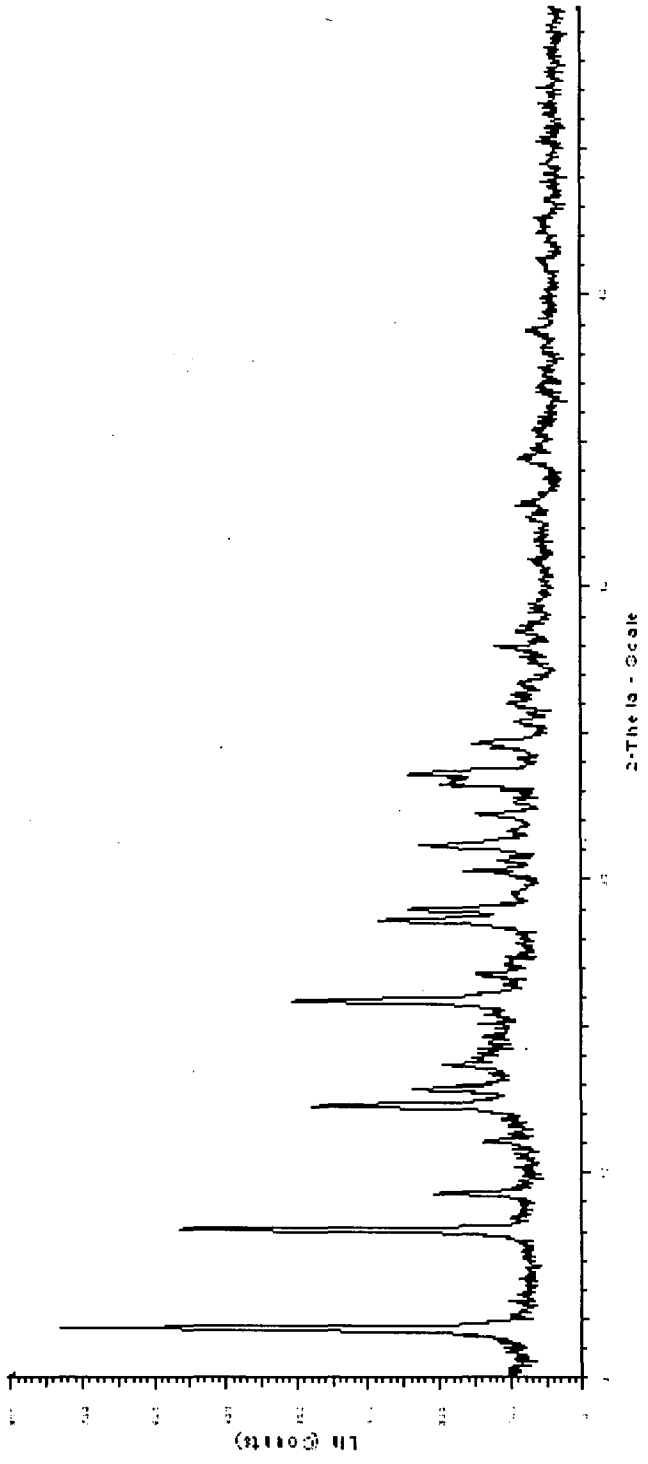

Figure 5

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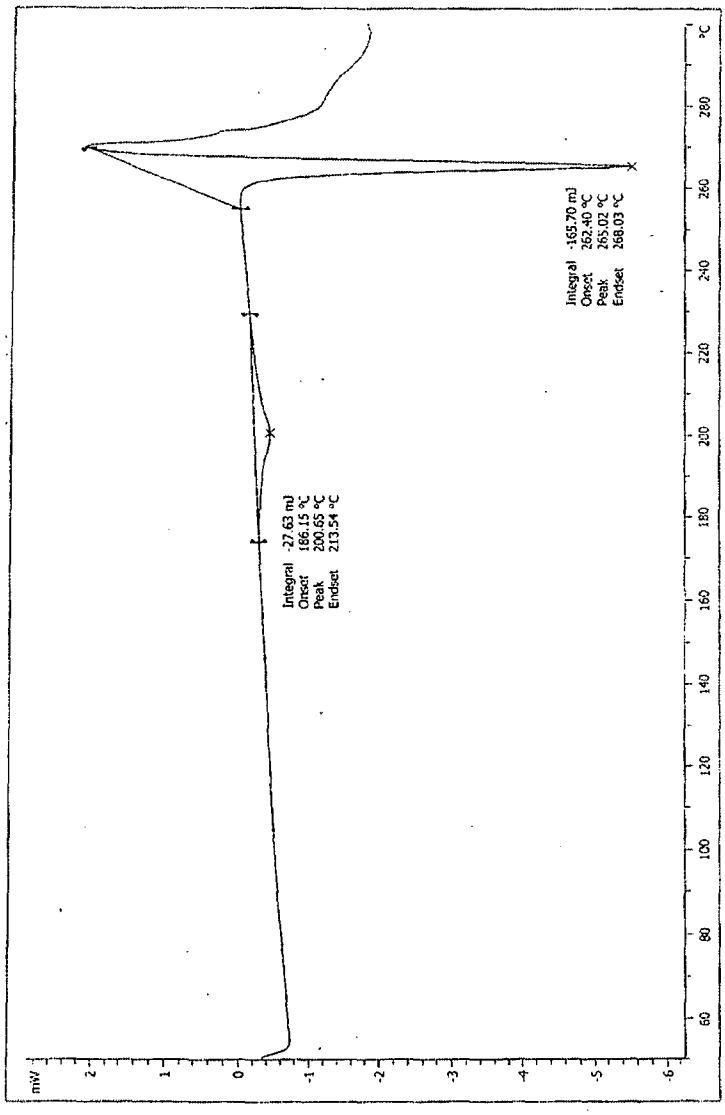

Figure 6

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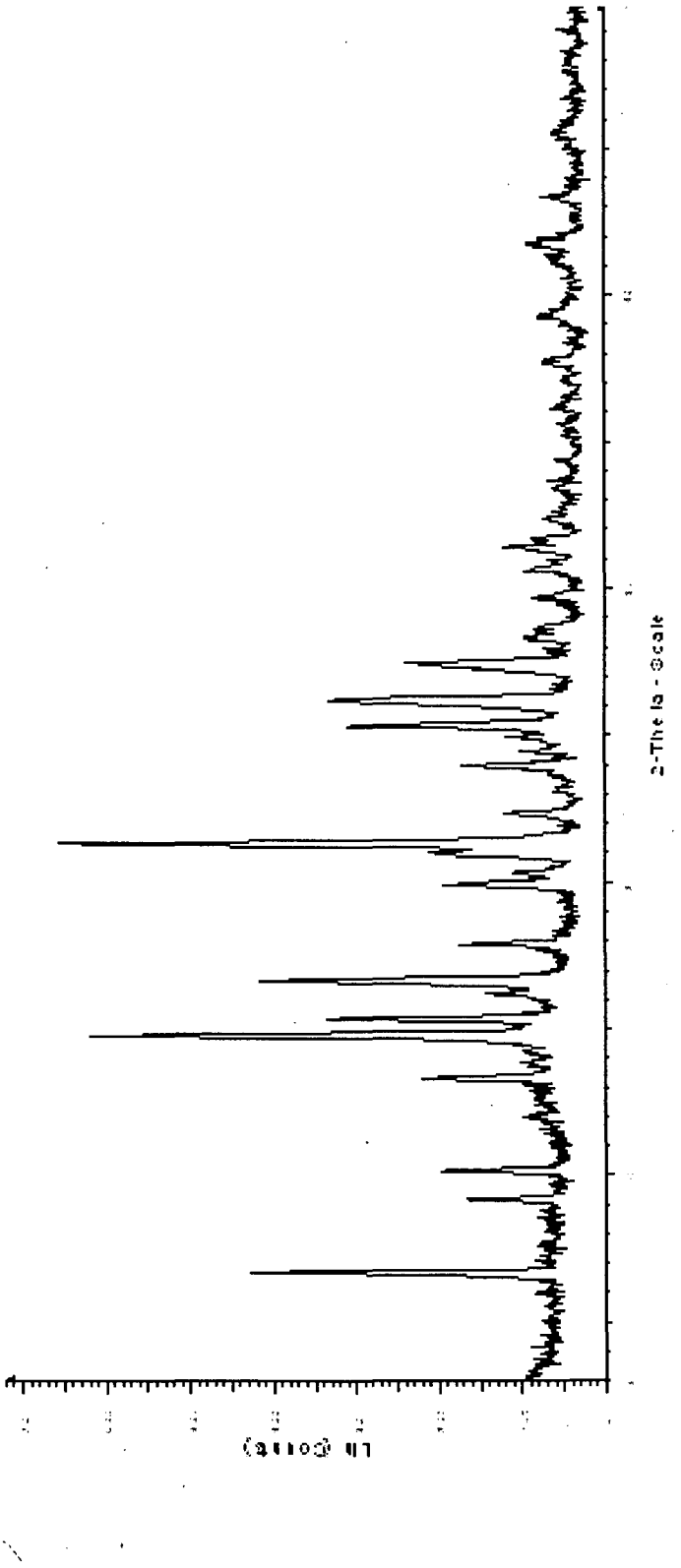

Figure 7

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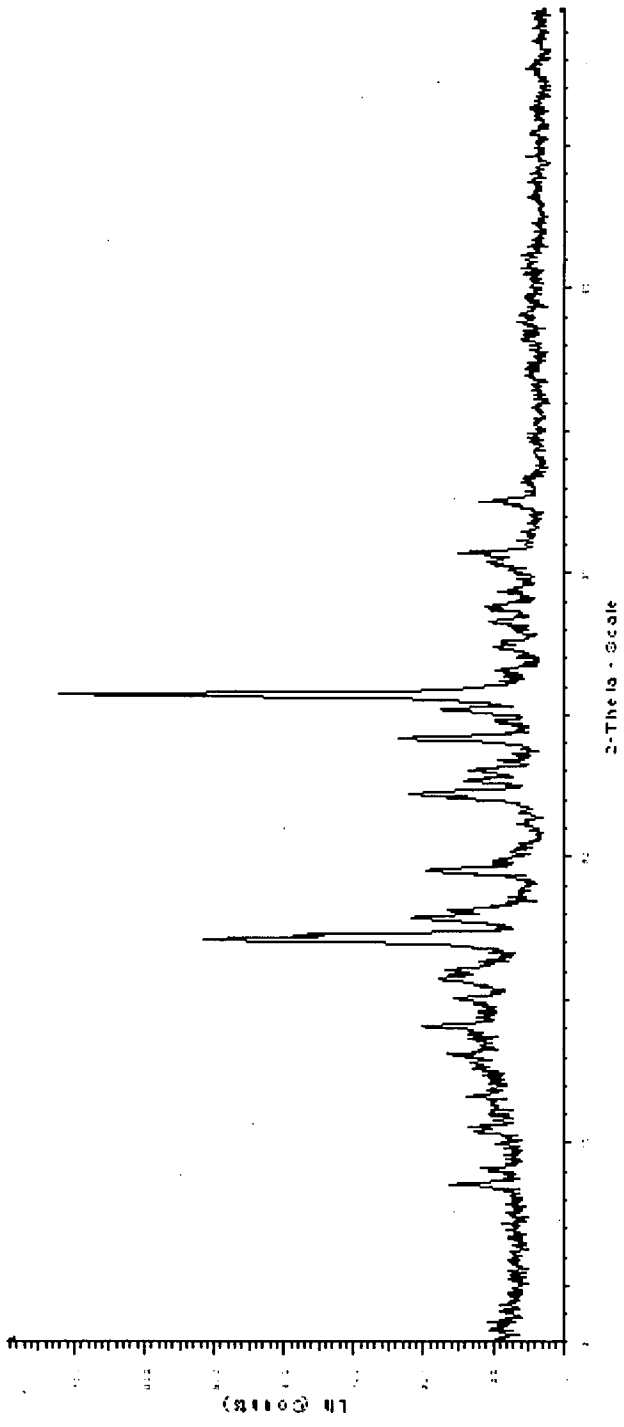

Figure 8