(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 April 2006 (20.04.2006)

PCT

(10) International Publication Number
WO 2006/040643 A2

(51) International Patent Classification:
C07D 265/18 (2006.01) *A61P 31/18* (2006.01)
A61K 31/535 (2006.01)

(21) International Application Number:
PCT/IB2005/003013

(22) International Filing Date: 10 October 2005 (10.10.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

1959/DEL/2004	11 October 2004 (11.10.2004)	IN
2167/DEL/2004	29 October 2004 (29.10.2004)	IN
2166/DEL/2004	29 October 2004 (29.10.2004)	IN
2164/DEL/2004	29 October 2004 (29.10.2004)	IN
2165/DEL/2004	29 October 2004 (29.10.2004)	IN
2169/DEL/2004	29 October 2004 (29.10.2004)	IN
433/DEL/2005	28 February 2005 (28.02.2005)	IN
716/DEL/2005	31 March 2005 (31.03.2005)	IN
2680/DEL/2005	6 October 2005 (06.10.2005)	IN

(71) Applicant *(for all designated States except US)*: **RANBAXY LABORATORIES LIMITED** [IN/IN]; Plot No. 90, Sector - 32, Gurgaon, Haryana 122 001 (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **SHARMA, Ramnik** [IN/IN]; c/o Sushil Kumar Sharma, H. No. 1406-B/4, Shukul Kund Road, Ambala City, Haryana 133004 (IN). **BHUSHAN, Kumar, Hari** [IN/IN]; B-2/73, Second Floor, Janak Puri, New Delhi 110058 (IN). **ARYAN, Ram, Chander** [IN/IN]; 1066, Sector - A, Pocket A, Vasant Kunj, New Delhi 110070 (IN). **SINGH, Nitu** [IN/IN]; B-34/154, Amravati Nagar Colony, Sunderpur, Varanasi U.P. 221005 (IN). **PANDYA, Bhargav** [IN/IN]; 7, Vallabh Apartment, Maniyasha, Maninagar (East), Ahmedabad, Gujarat 380008 (IN). **KUMAR, Yatendra** [IN/IN]; U-26/5, Phase-III, DLF Qutab Enclave, Gurgaon, Haryana 122001 (IN).

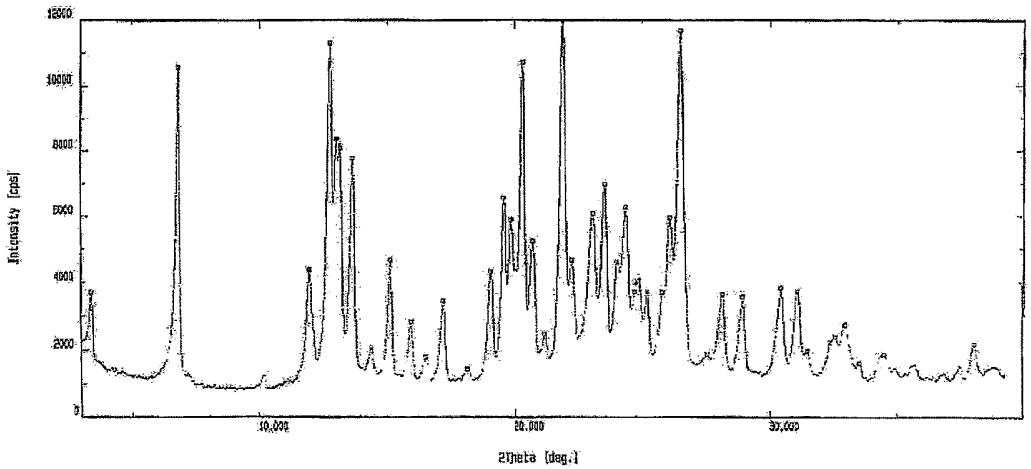
(74) Common Representative: **RANBAXY LABORATORIES LIMITED**; c/o DESHMUKH, Jay R., 600 College Road East, Suite 2100, Princeton, NJ 08540 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: POLYMORPHIC FORMS OF EFAVIRENZ AND PROCESSES FOR THEIR PREPARATION



(57) Abstract: The present invention relates to novel polymorphic forms of efavirenz. The novel polymorphic forms are designated as Forms α, β, γ, γ1, γ2, ω,δ, N, O and P of efavirenz. The present invention further relates to amorphous form of efavirenz. The invention also relates to the processes for their preparation and use in pharmaceutical compositions useful in the treatmentof HIV-1 infection.

WO 2006/040643 A2

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

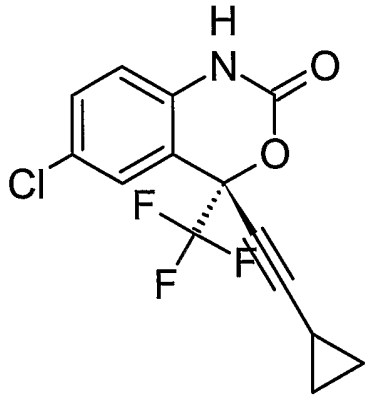
POLYMORPHIC FORMS OF EFAVIRENZ AND PROCESSES FOR THEIR PREPARATION

Field of the Invention

The present invention relates to novel polymorphic forms of efavirenz. The novel polymorphic forms are designated as Forms α, β, γ, γ1, γ2, ω, δ, N, O, and P of efavirenz. The present invention further relates to an amorphous form of efavirenz. The invention also relates to processes for the preparation and pharmaceutical compositions useful in the treatment of HIV-1 infection with the novel polymorphic forms of efavirenz.

Background of the Invention

(4*S*)-6-chloro-4-(cyclopropylethynyl)-4-(trifluoromethyl)-1,4-dihydro-2*H*-3,1-benzoxazin-2-one; commonly known as efavirenz of Formula I is an HIV-1 specific, non-nucleoside, reverse transcriptase inhibitor. Efavirenz in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection.



FORMULA I

US Patent No. 5,519,021, WO 94/03440, and WO 95/20389 disclose the synthesis of efavirenz. In addition, Tetrahedron Letters 36, 937-940 (1995); US Patent No. 5,698,741 and WO 96/37457 also provide various processes for the preparation of efavirenz. US Patent No. 5,663,467 and WO 96/22955 discloses additional processes for preparation of efavirenz.

US Patent No. 6,639,071 and US Patent No. 5,965,729 describe crystalline polymorphic forms of efavirenz designated as Forms I, II and III. The specification of the '071 Patent discloses that efavirenz previously crystallized from a heptane-tetrahydrofuran

(THF) solvent system by a crystallization procedure requires the use of high temperatures (about 90°C) to dissolve the final product. This process produces crystals by nucleation during the cooling process. The crystals produced were Form II and converted to Form I while drying under vacuum at 90°C. This crystallization provides minimal purification and produced material with inconsistent physical properties. The final product slurry is extremely difficult to mix and handle due to its high viscosity and heterogeneous nature.

US Patent No. 6,673,372 discloses polymorphic forms of efavirenz designated as Form 2 and Form 5.

Summary of the Invention

In one general aspect there is provided a polymorphic Form α of efavirenz having an X-ray powder diffraction (XRPD) pattern wherein characteristic 2θ values are obtained at 6.80, 12.76, 21.88 and 26.48. Embodiments of the polymorph may have one or more of the following features. For example, Form α may further include characteristic 2θ values at 3.4, 11.96, 13.0, 13.16, 13.64, 14.36, 15.12, 15.92, 16.5, 17.2, 18.14, 19.06, 19.56, 19.84, 20.32, 20.70, 21.16, 22.22, 23.04, 23.50, 23.98, 24.34, 24.70, 24.86, 25.18, 25.76, 26.06, 27.52, 28.10, 28.88, 30.40, 31.04, 31.44, 32.32, 32.52, 32.90, 33.48, 34.46 and 38.02.

In another general aspect there is provided a polymorphic Form β of efavirenz having an XRPD pattern wherein characteristic 2θ values are obtained at 11.18, 11.68, 20.98, and 27.38. Embodiments of the polymorph may have one or more of the following features. For example, Form β may further include the characteristic 2θ values at 10.24, 12.30, 15.20, 16.40, 17.60, 18.56, 19.08, 19.82, 20.34, 20.62, 21.36, 22.86, 23.52, 24.52, 24.78, 25.62, 26.10, 26.78, 28.24, 28.64, 29.12, 31.04, 31.60, 33.10, 33.52, 34.54, 34.76, 35.56, 36.14, 36.58, 37.50, 38.30, 38.66, 39.54 and 39.68.

In another general aspect there is provided a polymorphic Form γ of efavirenz having an XRPD pattern wherein characteristic 2θ values are obtained at 6.10, 18.44, 21.30, and 22.20. Embodiments of the polymorph may have one or more of the following features. For example, Form γ may further include the characteristic 2θ values at 9.82, 10.98, 12.24, 12.68, 13.10, 14.16, 15.72, 16.20, 16.90, 18.0, 18.76, 19.22, 19.40, 19.78, 20.12, 20.70, 21.92, 23.20, 23.38, 24.12, 24.70, 25.04, 26.22, 26.58, 27.30, 27.96, 28.10,

28.44, 28.54, 29.02, 29.48, 30.82, 31.02, 31.58, 32.02, 32.46, 32.78, 32.94, 37.78 and 37.96.

In another general aspect there is provided a polymorphic Form γ1 of efavirenz having an XRPD pattern wherein characteristic 2θ values are obtained at 6.14, 6.26, 21.24, and 24.94. Embodiments of the polymorph may have one or more of the following features. For example, Form γ1 may further include characteristic 2θ values at 10.50, 11.00, 12.28, 13.08, 13.26, 14.24, 15.30, 15.64, 16.68, 16.94, 17.90, 18.32, 18.54, 19.26, 19.70, 20.16, 21.98, 22.10, 22.32, 23.16, 24.56, 25.62, 26.06, 26.42, 27.26, 27.50, 28.18, 28.74, 29.26, 29.62, 30.84, 31.64, 32.38, and 37.40.

In yet another general aspect there is provided a polymorphic Form γ2 of efavirenz having an XRPD pattern wherein characteristic 2θ values are obtained at 21.18, 21.74, 22.04, and 31.64. Embodiments of the polymorph may have one or more of the following features. For example, Form γ2 may further include characteristic 2θ values at 12.12, 12.38, 12.98, 13.16, 15.64, 16.90, 17.22, 18.14, 18.42, 18.76, 19.34, 19.48, 19.90, 20.06, 20.32, 23.08, 23.30, 23.98, 24.42, 24.60, 24.94, 25.34, 26.14, 26.36, 27.06, 27.30, 28.04, 28.38, 28.98, and 29.24.

In another general aspect there is provided a polymorphic Form ω of efavirenz having an XRPD pattern wherein characteristic 2θ values are obtained at 9.98, 20.40, 22.66, and 28.12. Embodiments of the polymorph may have one or more of the following features. For example, Form ω may further include characteristic 2θ values at 4.98, 11.26, 11.64, 12.06, 14.88, 15.02, 16.64, 17.18, 17.54, 18.06, 18.66, 19.02, 19.72, 20.78, 21.18, 21.58, 21.72, 22.10, 23.40, 23.86, 24.32, 24.74, 25.30, 25.82, 26.04, 26.42, 26.76, 27.60, 28.44, 29.04, 29.82, 37.66, and 37.78.

In another general aspect there is provided a polymorphic Form δ of efavirenz having an XRPD pattern wherein characteristic 2θ values are obtained at 7.18, 13.44, 22.94, and 26.02. Embodiments of the polymorph may have one or more of the following features. For example, Form δ may further include characteristic 2θ values at 11.32, 12.12, 12.64, 13.04, 13.86, 14.44, 15.12, 15.44, 16.38, 17.00, 18.92, 19.56, 20.08, 20.58, 21.80, 22.14, 23.92, 24.66, 25.42, 26.72, 27.32, 27.86, 28.02, 29.22, 29.96, 30.72, 31.74, 32.40, 32.74, and 39.06.

In another general aspect there is provided an amorphous form of efavirenz. The amorphous form of efavirenz may be used in a pharmaceutical composition with one or more pharmaceutical agents and one or more additional therapeutic agents, and may be administered for the treatment of an HIV-1 infection.

In yet another aspect there is provided a polymorphic Form O of efavirenz having an XRPD pattern wherein characteristic 2θ values are obtained at 13.16, 19.58, 20.86, and 25.38. Embodiments of the polymorph may have one or more of the following features. For example, Form O may further include characteristic 2θ values at 3.92, 7.88, 10.70, 11.20, 11.40, 12.04, 12.86, 13.80, 14.38, 15.08, 15.78, 16.46, 17.26, 17.46, 18.44, 20.20, 21.26, 21.50, 21.92, 22.14, 22.34, 22.96, 23.74, 24.58, 26.02, 26.48, 26.90, 27.24, 27.62, 27.86, 28.00, 28.64, and 28.96.

In another general aspect there is provided a polymorphic Form N of efavirenz having an XRPD pattern wherein characteristic 2θ values are obtained at 13.12, 18.40, 20.82, and 25.30. Embodiments of the polymorph may have one or more of the following features. For example, Form N may further include characteristic 2θ values at 3.9, 7.84, 10.66, 12.00, 12.80, 15.04, 15.74, 17.40, 19.54, 22.88, 23.68, 24.96, 25.96, 26.86, 27.16, 27.92 and 28.90.

In another general aspect there is provided a polymorphic Form P of efavirenz having an XRPD pattern wherein characteristic 2θ values are obtained at 13.12, 18.38, 20.80, and 25.28. Embodiments of the polymorph may have one or more of the following features. For example, Form δ may further include characteristic 2θ values at 3.90, 7.84, 8.68, 10.66, 10.82, 11.22, 11.42, 12.00, 12.42, 12.78, 13.66, 14.30, 14.42, 15.04, 15.22, 15.74, 16.34, 16.58, 16.84, 17.40, 17.90, 18.56, 19.52, 21.46, 21.74, 22.18, 22.88, 23.82, 24.34, 24.66, 25.94, 26.20, 26.86, 27.14, 27.92, 28.44 and 28.88.

In another general aspect there is provided a pharmaceutical composition comprising Forms α, β, γ, γ1, γ2, ω, δ, N, O, or P of efavirenz. The pharmaceutical composition may further include one or more pharmaceutically acceptable excipients. The pharmaceutical composition may further include one or more additional therapeutic agents.

In another general aspect there is provided a method of treating HIV-1 infections. The method includes administering to a mammal in need thereof a pharmaceutical

composition comprising the one or more polymorphic Forms α, β, γ, γ1, γ2, ω, δ, N, O or P of efavirenz and one or more pharmaceutically acceptable excipients. The pharmaceutical composition administered may further include one or more additional therapeutic agents.

In another general aspect there is provided a process for preparation of polymorphic Form α of efavirenz. The process includes dissolving efavirenz in a mixture of one or more halogenated hydrocarbons and one or more hydrocarbon organic solvents to form a solution; partially concentrating the solution; and isolating Form α of efavirenz from the reaction mass thereof.

Embodiments of the process may include one or more of the following features. For example, the one or more halogenated hydrocarbons may be dichloromethane, 1,1,1-trichloroethane, tetrachloroethylene and trichloroethylene. The one or more hydrocarbon organic solvents may be C_{5-7} alkane, petroleum ether and cycloalkane.

In another general aspect there is provided a process for the preparation of polymorphic Form ω of efavirenz. The process includes dissolving efavirenz in one or more water miscible alkanols to form a solution; adding the solution to a mixture of one or more water miscible alkanols and water to form a mixture; stirring the reaction mixture at a temperature between 2°C and 10°C; and isolating Form ω of efavirenz from the reaction mass thereof.

Embodiments of the process may include one or more of the following features. For example, the one or more water miscible alkanols may be methanol, ethanol, n-propanol, isopropanol or mixtures thereof.

In another general aspect there is provided a process for the preparation of polymorphic Form ω of efavirenz. The process includes dissolving efavirenz in one or more water miscible organic solvents to form a solution; treating the solution with a mixture of water, one or more water miscible organic solvents and one or more agents for lowering the freezing point of water to cause precipitation of a solid; treating the solid with water; and isolating Form ω of efavirenz from the reaction mass thereof.

Embodiments of the process may include one or more of the following features. For example, the one or more water miscible organic solvents may be methanol, ethanol,

n-propanol and isopropanol. The one or more agents for lowering the freezing point of water may be alkali metal salts or alkaline earth metal salts. For example, the alkali metal salt may sodium chloride.

In another general aspect there is provided a process for the preparation of polymorphic Form δ of efavirenz. The process includes dissolving efavirenz in one or more halogenated hydrocarbons to form a solution; adding the solution to a second organic solvent including C_{5-7} alkane, cycloalkane, petroleum ether; and isolating Form δ of efavirenz from the reaction mass thereof.

In another general aspect there is provided a process for preparation of amorphous efavirenz. The process includes dissolving efavirenz in one or more organic solvents to form a solution; recovering the solvent from the solution; and isolating amorphous efavirenz from the reaction mass thereof.

In yet another general aspect there is provided a process for the preparation of amorphous efavirenz. The process includes dissolving efavirenz in one or more water miscible organic solvents to form a solution; adding the solution to a second solution of one or more inorganic salts; and isolating amorphous efavirenz from the reaction mass thereof.

In another general aspect there is provided a process for the preparation of Form O of efavirenz. The process includes dissolving efavirenz in one or more water miscible organic solvents to form a solution; removing the solvent from the solution to leave a product; grinding the product between two surfaces; and isolating Form O of efavirenz from the reaction mass thereof.

Embodiments of the process may include one or more of the following features. For example, the one or more water miscible organic solvents may be methanol, ethanol, isopropanol, acetonitrile, acetone, tetrahydrofuran and 1,4-dioxane.

In another general aspect there is provided a process for preparation of polymorphic Form N of efavirenz. The process includes treating Form O of efavirenz with water, and isolating Form N of efavirenz from the reaction mass thereof.

In yet another general aspect there is provided a process for the preparation of polymorphic Form N of efavirenz. The process includes mixing Form ω of efavirenz with

a catalytic quantity of Form N of efavirenz to form a mixture; drying the mixture under vacuum for a sufficient time; and isolating Form N of efavirenz from the reaction mass thereof.

Embodiments of the process may include one or more of the following features. For example, the drying may be carried out at a temperature of 10°C or less. The drying may be carried out in a rotary evaporator and may be rotated at a speed of 10 to 100 revolutions per minute.

In another general aspect there is provided a process for the preparation of Form P of efavirenz. The process includes dissolving efavirenz in one or more water miscible organic solvents to form a solution; adding the solution to a mixture of Form N in water; and isolating Form P of efavirenz from the reaction mass thereof.

Brief Description of the Drawings

Figure 1 is an XRPD of Form α of efavirenz.

Figure 2 is an DSC of Form α of efavirenz.

Figure 3 is an XRPD of Form β of efavirenz.

Figure 4 is a DSC of Form β of efavirenz.

Figure 5 is an XRPD of Form γ of efavirenz.

Figure 6 is a DSC of Form γ of efavirenz.

Figure 7 is an XRPD of Form γ1 of efavirenz.

Figure 8 is a DSC of Form γ1 of efavirenz.

Figure 9 is an XRPD of Form γ2 of efavirenz.

Figure 10 is a DSC of Form γ2 of efavirenz.

Figure 11 is an XRPD of Form ω of efavirenz.

Figure 12 is an XRPD of Form ω of efavirenz.

Figure 13 is a DSC of Form ω of efavirenz.

Figure 14 is an XRPD of Form δ of efavirenz.

Figure 15 is a DSC of Form δ of efavirenz.

Figure 16 is an XRPD of amorphous form of efavirenz.

Figure 17 is an XRPD of Form O of efavirenz.

Figure 18 is an XRPD of Form N of efavirenz.

Figure 19 is an XRPD of Form N of efavirenz.

Figure 20 is a DSC of Form N of efavirenz.

Figure 21 is a FTIR of Form N of efavirenz.

Figure 22 is an XRPD of Form P of efavirenz.

Detailed Description of the Invention

The present invention relates to novel polymorphic forms of efavirenz. The novel polymorphic forms are designated as Forms α, β, γ, γ1, γ2, ω, δ, N, O, and P of efavirenz. The present invention further relates to an amorphous form of efavirenz. The invention also relates to processes for their preparation and their use in pharmaceutical compositions useful in the treatment of HIV-1 infection.

The present invention provides the novel polymorphic Form α of efavirenz having a typical XRPD pattern as depicted in Figure 1 of the accompanying drawing. The XRPD of Form α shows characteristic 2θ values at 3.4, 6.8, 11.96, 12.76, 13.0, 13.16, 13.64, 14.36, 15.12, 15.92, 16.5, 17.2, 18.14, 19.06, 19.56, 19.84, 20.32, 20.70, 21.16, 21.88, 22.22, 23.04, 23.50, 23.98, 24.34, 24.70, 24.86, 25.18, 25.76, 26.06, 26.48, 27.52, 28.10, 28.88, 30.40, 31.04, 31.44, 32.32, 32.52, 32.90, 33.48, 34.46 and 38.02. The novel polymorphic Form α has a characteristic differential scanning calorimetry (DSC) thermogram as depicted in Figure 2 of the accompanying drawings. The DSC thermogram shows three characteristic endothermic peaks at 70°C - 85°C, 85°C - 95°C and 130°C - 145°C.

Also provided herein is a process for the preparation of the novel polymorphic Form α of efavirenz. The process includes:

a) dissolving efavirenz in a mixture of one or more halogenated hydrocarbons and one or more hydrocarbon organic solvents to form a solution;

b) partially concentrating the solution; and

c) isolating Form α of efavirenz from the reaction mass thereof.

The efavirenz starting material may be prepared by any method known in the art. Efavirenz is first dissolved in a mixture of one or more halogenated hydrocarbons and one or more hydrocarbon organic solvents. The one or more halogenated hydrocarbon solvents may include dichloromethane, 1,1,1-trichloroethane, tetrachloroethylene and trichloroethylene. The one or more hydrocarbon organic solvents may include C_{5-7} alkane, petroleum ether and cycloalkane. The solution is partially concentrated under a vacuum. The reaction mixture is stirred and the precipitated compound is filtered off to get Form α of efavirenz having the characteristic XRPD (Figure 1) and DSC (Figure 2) patterns.

Also provided herein is a process for the preparation of novel polymorphic Form α of efavirenz. The process includes:

a) treating efavirenz with one or more C_{5-7} alkanes, petroleum ethers or C_{5-7} cycloalkane solvents; and

b) isolating Form α of efavirenz from the reaction mass thereof.

The efavirenz starting material may be prepared by any method known in the art. The efavirenz is treated with one or more C_{5-7} alkanes, petroleum ethers or C_{5-7} cycloalkane solvents. The reaction mixture is stirred at a lower temperature and the precipitated compound is filtered off to get Form α of efavirenz having the characteristic XRD (Figure 1) and DSC (Figure 2) patterns.

Also provided in the present invention is a novel polymorphic Form β of efavirenz having typical XRPD pattern as depicted in Figure 3 of the accompanying drawing. The XRPD of Form β shows characteristic 2θ values at 10.24, 11.18, 11.68, 12.30, 15.20, 16.40, 17.60, 18.56, 19.08, 19.82, 20.34, 20.62, 20.98, 21.36, 22.86, 23.52, 24.52, 24.78, 25.62, 26.10, 26.78, 27.38, 28.24, 28.64, 29.12, 31.04, 31.60, 33.10, 33.52, 34.54, 34.76, 35.56, 36.14, 36.58, 37.50, 38.30, 38.66, 39.54 and 39.68. The novel polymorphic form β has a characteristic DSC thermogram as depicted in Figure 4 of the accompanying drawing. The DSC thermogram shows two characteristic endothermic peaks at 105°C - 110°C and at 135°C - 140°C.

Also provided herein is a process for the preparation of novel polymorphic Form β of efavirenz. The process includes:

a) dissolving efavirenz in one or more water miscible organic solvents to form a solution;

b) adding the solution to a mixture of one or more water miscible organic solvents and water to form a mixture;

c) stirring the reaction mixture at a temperature of about 0°C or less; and

d) isolating Form β of efavirenz from the reaction mass thereof.

The efavirenz starting material may be prepared by any method known in the art. The efavirenz is first dissolved in one or more water miscible organic solvents to form a solution. The solution is added to a mixture of one or more water miscible organic solvents and water to form a mixture. The resultant mixture is stirred at a temperature of about 0°C or less. The one or more water miscible organic solvents may include methanol, ethanol, acetone, acetonitrile, dimethylsulfoxide, dimethylformamide and dioxane. After complete precipitation of solids, the mass is filtered and the product obtained is dried under vacuum at about 30°C - 35°C to get Form β of efavirenz having the characteristic XRPD (Figure 3) and DSC (Figure 4) patterns.

Also provided in the present invention is the novel polymorphic Form γ of efavirenz having typical XRPD pattern as depicted in Figure 5 of the accompanying drawing. The XRPD of Form γ shows characteristic 2θ values at 6.10, 9.82, 10.98, 12.24, 12.68, 13.10, 14.16, 15.72, 16.20, 16.90, 18.0, 18.44, 18.76, 19.22, 19.40, 19.78, 20.12, 20.70, 21.30, 21.92, 22.20, 23.20, 23.38, 24.12, 24.70, 25.04, 26.22, 26.58, 27.30, 27.96, 28.10, 28.44, 28.54, 29.02, 29.48, 30.82, 31.02, 31.58, 32.02, 32.46, 32.78, 32.94, 37.78 and 37.96. The novel polymorphic Form γ has characteristic DSC thermogram as depicted in Figure 6 of the accompanying drawing. The DSC thermogram shows two characteristic endothermic peaks at 75°C - 95°C and at 120°C - 140°C.

Also provided is a process for the preparation of the novel polymorphic Form γ of efavirenz. The process includes:

a) dissolving efavirenz in one or more polar aprotic solvents to form a solution;

b) adding the solution to a salt solution; and

c) isolating Form γ of efavirenz from the reaction mass thereof.

The efavirenz starting material may be prepared by any method known in the art. The efavirenz is first dissolved in one or more polar aprotic solvents to form a solution. The solution is added to a salt solution. The resultant mass is stirred and filtered off. The product obtained is dried under vacuum at about 35°C - 40°C to get Form γ of efavirenz having the characteristic XRPD (Figure 5) and DSC (Figure 6) patterns.

Also provided in the present invention is the novel polymorphic Form γ1 of efavirenz having typical XRPD pattern as depicted in Figure 7 of the accompanying drawings. The XRPD of Form γ1 shows characteristic 2θ values at 6.14, 6.26, 10.50, 11.00, 12.28, 13.08, 13.26, 14.24, 15.30, 15.64, 16.68, 16.94, 17.90, 18.32, 18.54, 19.26, 19.70, 20.16, 21.24, 21.98, 22.10, 22.32, 23.16, 24.56, 24.94, 25.62, 26.06, 26.42, 27.26, 27.50, 28.18, 28.74, 29.26, 29.62, 30.84, 31.64, 32.38 and 37.40. The novel polymorphic Form γ1 has characteristic DSC thermogram as depicted in Figure 8 of the accompanying drawings. The DSC thermogram shows one characteristic endothermic peak at 130°C - 142°C.

Also provided herein is a process for the preparation of novel polymorphic Form γ1 of efavirenz. The process includes:

a) dissolving efavirenz in one or more lower alkanols to form a solution;

b) adding the solution to a mixture of one or more lower alkanols and salt solution;

c) stirring the resultant reaction mass for a period not exceeding 1 hour; and

d) isolating Form γ1 of efavirenz from the reaction mass thereof.

The efavirenz starting material may be prepared by any method known in the art. The efavirenz is first dissolved in one or more lower alkanols to form a solution. The solution is added to a mixture of one or more lower alkanols and water. The resultant mass is stirred for a period not exceeding 1 hour followed by filtration. The sticky product obtained gradually solidifies which is then dried under vacuum at about 30°C to get Form γ1 of efavirenz having the characteristic XRPD (Figure 7) and DSC (Figure 8) patterns.

Also provided in the present invention is the novel polymorphic Form γ2 of efavirenz having typical XRPD pattern as depicted in Figure 9 of the accompanying drawings. The XRPD of Form γ2 shows characteristic 2θ values at 12.12, 12.38, 12.98, 13.16, 15.64, 16.90, 17.22, 18.14, 18.42, 18.76, 19.34, 19.48, 19.90, 20.06, 20.32, 21.18,

21.74, 22.04, 23.08, 23.30, 23.98, 24.42, 24.60, 24.94, 25.34, 26.14, 26.36, 27.06, 27.30, 28.04, 28.38, 28.98, 29.24 and 31.64. The novel polymorphic Form α2 has characteristic DSC thermogram as depicted in Figure 10 of the accompanying drawings. The DSC thermogram shows one characteristic endothermic peak at 130°C - 140°C.

Also provided herein is a process for the preparation of novel polymorphic Form γ2 of efavirenz. The process includes:

a) dissolving efavirenz in one or more lower alkanols to form a solution;

b) adding the solution to a mixture of one or more lower alkanols and salt solution;

c) stirring the resultant mass for a period over about 1.5 hours; and

d) isolating Form γ2 of efavirenz from the reaction mass thereof.

The efavirenz starting material may be prepared by any method known in the art. The efavirenz is first dissolved in one or more lower alkanols. The solution is added to a mixture of one or more lower alkanols and water. The resultant mass is stirred for a period over about 1.5 hours and then filtered. The product obtained is dried under vacuum at about 30°C - 35°C to get Form γ2 of efavirenz having the characteristic XRPD (Figure 9) and DSC (Figure 10) patterns.

Also provided in the present invention is the novel polymorphic Form ω of efavirenz having typical XRPD pattern as depicted in Figure 11 of the accompanying drawings. The XRPD of Form ω shows characteristic 2θ values at 4.98, 9.98, 11.26, 11.64, 12.06, 14.88, 15.02, 16.64, 17.18, 17.54, 18.06, 18.66, 19.02, 19.72, 20.40, 20.78, 21.18, 21.58, 21.72, 22.10, 22.66, 23.40, 23.86, 24.32, 24.74, 25.30, 25.82, 26.04, 26.42, 26.76, 27.60, 28.12, 28.44, 29.04, 29.82, 37.66 and 37.78. The novel polymorphic Form ω has characteristic DSC thermogram as depicted in Figure 13 of the accompanying drawings The DSC thermogram shows two characteristic endothermic peaks at 92°C - 105°C and 135°C - 142°C.

Also provided herein is a process for the preparation of the novel polymorphic Form ω of efavirenz. The process includes:

a) dissolving efavirenz in one or more water miscible organic solvents to form a solution;

b) adding the solution to a mixture of one or more water miscible alkanols and water to form a mixture;

c) stirring the reaction mixture at a temperature between about 2°C and about 10°C; and

d) isolating Form ω of efavirenz from the reaction mass thereof.

The efavirenz starting material may be prepared by any method known in the art. The efavirenz is first dissolved in one or more water miscible alkanols to form a solution. The solution is added to a mixture of one or more water miscible alkanols and water to form a mixture. The resultant mixture is stirred at a temperature about 2°C and about 10°C. After complete precipitation of the solids, the mass is filtered and the product obtained is dried under vacuum at about 30°C -35°C to get Form ω of efavirenz having the characteristic XRPD (Figure 11) and DSC (Figure 13) patterns.

Also provided in the present invention is a process for the preparation of polymorphic Form ω of efavirenz. The process includes:

a) dissolving efavirenz in one or more water miscible organic solvents to form a solution;

b) treating the solution a mixture of water, one or more water miscible organic solvents and one or more agents for lowering the freezing point of water to precipitate out a solid;

c) treating the solid with water; and

d) isolating Form ω of efavirenz from the reaction mass thereof.

The efavirenz starting material may be prepared by any method known in the art. The efavirenz is dissolved in one or more water miscible alkanols to form a solution. The solution is added to a mixture of water, one or more water miscible organic solvents and one or more agents for lowering the freezing point of water. The water miscible organic solvents may include methanol, ethanol, n-propanol and isopropanol. The agent for lowering the freezing point of water may be an alkali metal salt or an alkaline earth metal salt. The resultant mixture is stirred at a temperature of about –10°C or less. After complete precipitation of solids, the solid is filtered and treated with water at a temperature between about 0°Cand about 10°C accompanied by stirring. The solid

obtained is dried under vacuum to get Form ω of efavirenz having the characteristic XRPD (Figure 12).

Also provided in the present invention is the novel polymorphic Form δ of efavirenz having typical XRPD pattern as depicted in Figure 14 of the accompanying drawing. The XRPD of Form δ shows characteristic 2θ values at 7.18, 11.32, 12.12, 12.64, 13.04, 13.44, 13.86, 14.44, 15.12, 15.44, 16.38, 17.00, 18.92, 19.56, 20.08, 20.58, 21.80, 22.14, 22.94, 23.92, 24.66, 25.42, 26.02, 26.72, 27.32, 27.86, 28.02, 29.22, 29.96, 30.72, 31.74, 32.40, 32.74 and 39.06. The novel polymorphic Form δ has the characteristic DSC thermogram as depicted in Figure 15 of the accompanying drawings. The DSC thermogram shows two characteristic endothermic peaks at 85°C - 95°C and 135°C - 142°C.

Also provided herein is a process for the preparation of novel polymorphic Form δ of efavirenz. The process includes:

a) dissolving efavirenz in one or more halogenated hydrocarbons to form a solution;

b) adding the solution to a second organic solvent including one or more of C_{5-7} alkane, cycloalkane, and petroleum ether; and

c) isolating Form δ of efavirenz from the reaction mass thereof.

The efavirenz starting material may be prepared by any method known in the art. The efavirenz is first dissolved in one or more halogenated hydrocarbons including dichloromethane, chloroform, ethylene dichloride, ethylene dibromide and mixtures thereof. The solution is added to a second organic solvent including one or more of C_{5-7} alkane, C_{5-7} cycloalkane, and petroleum ether. The resultant mixture is stirred at a low temperature of about -50°C to 15°C. The reaction mass can be partially concentrated to about half of its volume to effect precipitation. Addition of seed of Form δ of efavirenz can also be effectively employed to improve the crystallization. After complete precipitation of solids, the mass is filtered and the product obtained is dried under vacuum to get Form δ of efavirenz having the characteristic XRPD (Figure 14) and DSC (Figure 15) patterns.

Also provided in the present invention is amorphous efavirenz having an XRPD pattern as shown in Figure 16 of the accompanying drawings. The amorphous efavirenz may be prepared by the following process:

a) dissolving efavirenz in one or more water miscible organic solvents to form a solution;

b) adding the solution to a second solution of one or more inorganic salts; and

c) isolating amorphous efavirenz from the reaction mass thereof.

The efavirenz starting material may be prepared by any method known in the art. The efavirenz is first dissolved in one or more organic solvents. The solution is added to a second solution of one or more inorganic salts to form a mixture. The resultant mixture is stirred at a temperature of about –50°C to 15°C. Optionally, the reaction mass may be partially concentrated to about half of its volume under cooling to effect precipitation. After complete precipitation of solids, the mass is filtered, washed and the product obtained is dried to get amorphous efavirenz having the characteristic XRPD (Figure 16) pattern.

The inorganic salt may include one or more of water soluble salts of magnesium, potassium, calcium or sodium. Chloride salts of calcium, potassium and sodium may also be used.

Also provided in the present invention is a process for the preparation of amorphous efavirenz. The process includes:

a) dissolving efavirenz in one or more organic solvents to form a solution;

b) recovering the solvent from the solution; and

c) isolating amorphous efavirenz from the mass thereof.

The efavirenz starting material is dissolved in one or more organic solvents and the solution is concentrated optionally under a vacuum. The organic solvent may be dichloromethane or methanol. The residue obtained is further dried and recovered to get amorphous efavirenz.

Also provided in the present invention is the polymorphic Form O of efavirenz, which exhibits a typical XRPD pattern as depicted in Figure 17 of the accompanying

drawings. The XRPD of Form O of efavirenz shows characteristic 2θ values at 3.92, 7.88, 10.70, 11.20, 11.40, 12.04, 12.86, 13.16, 13.80, 14.38, 15.08, 15.78, 16.46, 17.26, 17.46, 18.44, 19.58, 20.20, 20.86, 21.26, 21.50, 21.92, 22.14, 22.34, 22.96, 23.74, 24.58, 25.38, 26.02, 26.48, 26.90, 27.24, 27.62, 27.86, 28.00, 28.64 and 28.96.

Also provided herein is a process for the preparation of Form O of efavirenz. The process includes:

a) dissolving efavirenz in one or more water miscible organic solvents to form a solution;

b) removing the solvent from the solution;

c) grinding the product obtained in step b) between two surfaces; and

d) isolating Form O of efavirenz from the reaction mass thereof.

The efavirenz starting material may be prepared by any method known in the art. The efavirenz is dissolved in one or more water miscible organic solvents including methanol, ethanol, isopropanol, acetonitrile, acetone, tetrahydrofuran and 1,4-dioxane or mixtures thereof. The solvent may be removed from the resultant solution optionally under vacuum and the product obtained is then subjected to grinding between two surfaces, which can be further dried under vacuum to get Form O of efavirenz.

Also provided in the present invention is the polymorphic Form N of efavirenz. The Form N of efavirenz exhibits a typical X-Ray Powder diffraction (XRPD) pattern as depicted in Figure 18 of the accompanying drawing. The XRPD of Form N exhibits characteristic 2θ values at 7.84, 13.12, 15.04, 18.40, 19.54, 20.82, 25.30 and 25.96. Form N of efavirenz is further characterized by a XRPD pattern comprising 2θ values at 3.9, 7.84, 10.66, 12.00, 12.80, 13.12, 15.04, 15.74, 17.40, 18.40, 19.54, 20.82, 22.88, 23.68, 24.96, 25.30, 25.96, 26.86, 27.16, 27.92 and 28.90. The Fourier Transform Infrared (FTIR) spectrum of Form N of efavirenz in potassium bromide is depicted in Figure 21 of the accompanying drawings. The novel polymorphic Form N has characteristic DSC thermogram as depicted in Figure 20 of the accompanying drawings. The DSC thermogram shows two characteristic endothermic peaks at 85°C - 100°C and 132°C - 144°C.

Also provided herein is a process for the preparation of Form N of efavirenz. The process includes:

a) treating Form O of efavirenz with water; and

b) isolating Form N of efavirenz from the reaction mass thereof.

Form O of Efavirenz is stirred in water at a low temperature for sufficient time to produce Form N. The resultant mixture is filtered and dried optionally under vacuum to get Form N of efavirenz having the characteristic XRPD (Figure 18) pattern.

Also provided in the present invention is a process for the preparation of polymorphic Form N of efavirenz. The process includes:

a) mixing Form ω of efavirenz with a catalytic quantity of Form N of efavirenz to form a mixture;

b) drying the mixture under a vacuum for sufficient time; and

c) isolating Form N of efavirenz from the reaction mass thereof.

The starting compounds such as Form ω and Form N of efavirenz can be prepared by the methods provided in the present invention. Form ω of efavirenz is mixed with catalytic quantity of Form N of efavirenz. The mixture is placed in a flask and a vacuum is applied to the mixture for sufficient time to effect the formation of Form N. The vacuum can be applied so as to obtain a pressure of 5 mmHg or less. The process can also be accompanied by the rotation of the flask. The flask can be rotated at a speed of 10 to 100 revolutions per minute. The process is carried out at a temperature of about 10°C or less. Further drying is optionally carried out under vacuum at 30°C to 45°C. Form N of efavirenz having characteristic XRPD (Figure 19) pattern is isolated from the reaction mass.

Also provided in the present invention is polymorphic Form P of efavirenz having the typical XRPD pattern as depicted in Figure 22 of the accompanying drawing. The XRPD of Form P of efavirenz shows characteristic 2θ values at 8.6 and 24.66. The polymorphic Form P is further characterized by an XRPD pattern comprising 2θ values at 3.90, 7.84, 8.68, 10.66, 10.82, 11.22, 11.42, 12.00, 12.42, 12.78, 13.12, 13.66, 14.30, 14.42, 15.04, 15.22, 15.74, 16.34, 16.58, 16.84, 17.40, 17.90, 18.38, 18.56, 19.52, 20.80,

21.46, 21.74, 22.18, 22.88, 23.82, 24.34, 24.66, 25.28, 25.94, 26.20, 26.86, 27.14, 27.92, 28.44 and 28.88.

Also provided herein is a process for the preparation of Form P of efavirenz. The process includes:

a) dissolving efavirenz in one or more water miscible organic solvents to form a solution;

b) adding the solution to a mixture of Form N in water; and

c) isolating Form P of efavirenz from the reaction mass thereof.

The efavirenz starting material may be prepared by any method known in the art. A solution of efavirenz may be prepared in one or more water miscible organic solvents including methanol, ethanol, isopropanol, acetonitrile, acetone, tetrahydrofuran, 1,4-dioxane, and mixtures thereof. The solution is then added to a mixture of Form N in water. The precipitated solids are filtered and dried suitably to get Form P of efavirenz.

Also provided in the present invention are pharmaceutical compositions of Forms α, β, γ, γ1, γ2, ω, δ, N, O and P of efavirenz. The pharmaceutical compositions may include one or more pharmaceutically acceptable excipients.

Also provided in the present invention are methods of treating HIV-1 infections. The method includes administering to a mammal in need thereof a therapeutically effective amount of one or more of polymorphic Forms α, β, γ, γ1, γ2, ω, δ, N, O and P of efavirenz.

Powder XRPD of the samples were determined by using X-Ray Diffractometer, Rigaku Corporation, RU-H3R, Goniometer CN2155A3, X-Ray tube with Cu target anode, Divergence slits 1 0, Receiving slit 0.15mm, Scatter slit 1°, Power: 40 KV, 100 mA, Scanning speed: 2 deg/min step: 0.02 deg, Wavelength: 1.5406 A.

FT-IR of the samples were determined by using as the instrument a Perkin Elmer,16 PC, SCAN: 16scans, 4.0 cm^{-1}, according to the USP 25, general test methods page 1920, infrared absorption spectrum by potassium bromide pellet method.

DSC thermograms were recorded using DSC821 e, Mettler Toledo, Sample weight: 3-5 mg, Temperature range: 50-350°C, Heating rate: 20°C/min, Nitrogen 80.0 mL/min, Number of holes in the crucible: 1.

EXAMPLE 1

PREPARATION OF FORM α OF EFAVIRENZ

Efavirenz (1.0 gm) was dissolved in dichloromethane (4 ml) and hexane (50 ml) was added to the solution obtained. 25 ml of the reaction mixture was evaporated under vacuum at 40°C and 5 ml under vacuum at 25°C. The reaction mixture was stirred for 10 minutes and the precipitated compound was filtered off to get the title compound.

Yield: 0.53 gm

EXAMPLE 2

PREPARATION OF FORM α OF EFAVIRENZ

Efavirenz (5.0 gm) was dissolved in cyclohexane by heating to 55°C. The solution was cooled to 45°C and was seeded with Form α. The solution was further cooled to 25°C and again seeded with Form α. The resultant mass was stirred at 7°C for 20 minutes and filtered to get the title compound.

Yield: 3.5 gm

EXAMPLE 3

PREPARATION OF FORM β OF EFAVIRENZ

Efavirenz (5 gm) was dissolved in methanol (5 ml) under stirring. This solution was added drop-wise into a pre-cooled mixture of water (150 ml) and methanol (15 ml) while maintaining the temperature below -6°C. The resultant mass was stirred at -5°C for about 3 hours and the separated solids were filtered. The solids were dried in a vacuum oven at a temperature of 30° to 35°C for 6 hours to get the title compound.

Yield: 4.2 gm

EXAMPLE 4

PREPARATION OF FORM γ OF EFAVIRENZ

Efavirenz (1.0 gm) was dissolved in N,N-dimethylformamide (1.0 ml) under stirring. This solution was added drop-wise into a sodium chloride solution (15%) at 25°C. The resultant mass was stirred at the same temperature for about 5 hours and the

separated solid was filtered and washed with water. The solid was dried in a vacuum oven at a temperature of 35°Cto 40°C for 2 hours to get the title compound.

Yield: 0.7 gm

EXAMPLE 5

PREPARATION OF FORM γ_1 OF EFAVIRENZ

Efavirenz (1.0 gm) was dissolved in methanol (1.0 ml) under stirring. This solution was added drop-wise into a pre-cooled mixture of 15% sodium chloride in water (30 ml) and methanol (3 ml) while maintaining the temperature below -8°C. The resultant mass was stirred at -5°C for about 10 minutes followed by filtration and washing with water. The sticky compound solidified after 2 hours was dried in vacuum oven at 30°C for 6 hrs to get the title compound.

Yield: 0.8 gm

EXAMPLE 6

PREPARATION OF FORM γ_2 OF EFAVIRENZ

Efavirenz (1.0 gm) was dissolved in methanol (1.0 ml) under stirring. This solution was added drop-wise into a pre-cooled mixture of 15% sodium chloride in water (30 ml) and methanol (3 ml) while maintaining the temperature below -8°C. The resultant mass was stirred at -8°C to 5°C for about 3 hours followed by filtration and washing with water. The solid was dried in a vacuum oven at a temperature of 30°Cto 35°C for 6 hours to get the title compound.

Yield: 0.82 gm

EXAMPLE 7

PREPARATION OF FORM ω OF EFAVIRENZ

Efavirenz (10.0 gm) was dissolved in methanol (10.0 ml) under stirring. This solution was added drop-wise into a pre-cooled mixture of water (150 ml) and methanol (15 ml) while maintaining the temperature below -6°C. The resultant mass was stirred at 2°C to 3°C for about 3 hours and the separated solid was filtered. The solid was dried in a vacuum oven at a temperature of 30°Cto 35°C for 6 hours to get the title compound.

Yield: 9.10 gm

EXAMPLE 8

PREPARATION OF FORM ω OF EFAVIRENZ

A solution of efavirenz (49.17 gm) in methanol (300 ml) was prepared and a mixture of sodium chloride (150 gm), methanol (150 ml) and water (1250 ml) at a temperature of –14°C was added over a period of 10 minutes. The resulting solution was stirred at –16°C to –20°C for 2 hours, filtered and washed with cold water (1000 ml, 3°C to 5°C). The solid obtained was made into slurry with cold water (1250 ml, 3°C to 5°C) and stirred for 15 minutes. The solid was filtered and washed again with cold water (50 ml, 3°C to 5°C) to obtain the title compound.

Yield: 48.5 gm

EXAMPLE 9

PREPARATION OF FORM δ OF EFAVIRENZ

To a solution of efavirenz (3.0 gm) in dichloromethane (12 ml) n-hexane (150 ml) was added. The resulting mass was cooled to 4°C in ice water bath for 5 minutes. Without heating the mixture, 75 ml of solvent was recovered from the reaction mixture under vacuum (45 mm), during which period the compound precipitated was filtered to get the title compound.

Yield: 2.5 gm

EXAMPLE 10

PREPARATION OF FORM δ OF EFAVIRENZ

A solution of efavirenz (1.0 gm) in dichloromethane (1.0 ml) was added drop-wise to a pre-cooled (-10°C) mixture of n-pentane (10 ml) and n-hexane (17 ml). The mixture was stirred for 1 hour at -10°C and filtered to get the title compound.

Yield: 0.85 gm

EXAMPLE 11

PREPARATION OF FORM δ OF EFAVIRENZ

Form δ seed (0.1 gm) was added to a pre-cooled n-pentane (60 ml) at -15°C followed by the addition of a solution of efavirenz (3 gm) in dichloromethane (3 ml). The

mass was cooled further to -40°C, stirred for 45 minutes at -40°C to -35°C and filtered to get the title compound.

Yield: 2.8 gm

EXAMPLE 12

PREPARATION OF AMORPHOUS EFAVIRENZ

A mixture of efavirenz (4.0 gm) in methanol (12 ml) was added to a solution of calcium chloride (18.0 gm), water (120 ml) and methanol (24 ml) cooled to about –18°C. The resultant mixture was stirred at -23°C to -20°C for 2 hours and filtered. The product was washed with water and dried at room temperature to get the title compound.

Yield: 3.6 gm

EXAMPLE 13

PREPARATION OF AMORPHOUS EFAVIRENZ

A mixture of efavirenz (4.0 gm) in methanol (16 ml) was added to a solution of sodium chloride (15% in water) at about -5°C. The resultant mixture was cooled to about -20°C and stirred for 2.5 hours. The separated product was filtered, washed with water and dried in vacuum desiccator at room temperature for 24 hours and further dried at 40°C for 24 hours to get the title compound.

Yield: 3.75 gm

EXAMPLE 14

PREPARATION OF AMORPHOUS EFAVIRENZ

Efavirenz (5 gm) was dissolved in methanol (50 ml), the solvent was recovered under vacuum, and the resultant residue was kept under vacuum for further 1 to 2 hours at 40°C. The product was removed and dried at 25°C under vacuum to get the title compound.

Yield: 3 gm

EXAMPLE 15

PREPARATION OF AMORPHOUS EFAVIRENZ

Efavirenz (5 gm) was dissolved in dichloromethane (50 ml) and the solvent was recovered under vacuum. The resultant residue was kept under vacuum for a further 1 to 2 hours at 40°C. The product was removed and dried at 25°C under vacuum to get the title compound.

Yield: 4.3 gm

EXAMPLE 16

PREPARATION OF FORM O OF EFAVIRENZ

Efavirenz (20 gm) was dissolved in methanol (200 ml) at 25°C. Methanol was recovered completely from the resulting solution under vacuum at 38°C. The product obtained was further dried under vacuum at 25°C for 15 hours. The resulting material was ground further to obtain the title compound.

Yield: 8 gm

EXAMPLE 17

PREPARATION OF FORM N OF EFAVIRENZ

Form O of efavirenz (1.0 gm) as prepared by Example 1 was stirred in water (20 ml) at 10°C for 1.5 hours. The resultant mixture was filtered and dried at 40°C under vacuum for 15 hours to obtain the title compound.

Yield: 0.2 gm

EXAMPLE 18

PREPARATION OF FORM N OF EFAVIRENZ

A mixture of Form ω (48 gm) and Form N (10.1 gm) of efavirenz was loaded in a 2 L rotary evaporator flask and 4 Teflon coated magnetic beads were added. A high vacuum (0 to 2 mmHg) was applied to the rotary evaporator and the evaporator flask was dipped into ice water bath at 0°C to 2°C. The rotary evaporator flask was rotated at 20 rpm for 5 minutes and the speed was increased to 60 to 80 rpm. The rotation at 60 to 80 rpm under vacuum was continued for 5 hours at 0°C to 2°C. The solid was isolated from

the walls of the flask and kept in vacuum oven at 38°C for 15 hours to get the title compound.

Yield: 52.5 gm

PREPARATION OF FORM P OF EFAVIRENZ

Form N of efavirenz (0.2 gm) was added to water (40 ml) at 1°C and stirred for 2 minutes. Efavirenz (1.0 gm) in methanol (5.0 ml) was added to the above mixture over a period of 25 minutes. The mixture obtained was further stirred for 30 minutes at 0° to 10 C, filtered and dried at 25°C under vacuum for 15 hours to get the title compound.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention. For example, the various novel polymorphic Forms α, β, γ, γ1, γ2, ω, δ, N, O, and P of efavirenz, and the amorphous form of efavirenz may be combined with one or more pharmaceutical excipients and carriers to form a dosage form suitable for administration to a patient in need thereof, such as a patient in need of treatment of an HIV-1 infection. The dosage form may be any conventionally used dosage form, such as a tablet, capsule, injection, intravenous, inhalation, powder, dispersible tablet, etc. As efavirenz is commonly administered with addition therapeutic agents, the dosage forms of these novel polymorphic forms of efavirenz may further include one or more additional therapeutic agents suitable for the treatment of an HIV-1 infection.

We Claim:

1. A polymorphic Form α of efavirenz having a XRPD pattern wherein characteristic 2θ values are obtained at 6.80, 12.76, 21.88 and 26.48.

2. The polymorphic form of claim 1, further comprising the characteristic 2θ values at 3.4, 11.96, 13.0, 13.16, 13.64, 14.36, 15.12, 15.92, 16.5, 17.2, 18.14, 19.06, 19.56, 19.84, 20.32, 20.70, 21.16, 22.22, 23.04, 23.50, 23.98, 24.34, 24.70, 24.86, 25.18, 25.76, 26.06, 27.52, 28.10, 28.88, 30.40, 31.04, 31.44, 32.32, 32.52, 32.90, 33.48, 34.46 and 38.02.

3. A polymorphic Form β of efavirenz having a XRPD pattern wherein characteristic 2θ values are obtained at 11.18, 11.68, 20.98, and 27.38.

4. The polymorphic form of claim 3, further comprising the characteristic 2θ values at 10.24, 12.30, 15.20, 16.40, 17.60, 18.56, 19.08, 19.82, 20.34, 20.62, 21.36, 22.86, 23.52, 24.52, 24.78, 25.62, 26.10, 26.78, 28.24, 28.64, 29.12, 31.04, 31.60, 33.10, 33.52, 34.54, 34.76, 35.56, 36.14, 36.58, 37.50, 38.30, 38.66, 39.54 and 39.68.

5. A polymorphic Form γ of efavirenz having a XRPD pattern wherein characteristic 2θ values are obtained at 6.10, 18.44, 21.30, and 22.20.

6. The polymorphic form of claim 5, further comprising the characteristic 2θ values at 9.82, 10.98, 12.24, 12.68, 13.10, 14.16, 15.72, 16.20, 16.90, 18.0, 18.76, 19.22, 19.40, 19.78, 20.12, 20.70, 21.92, 23.20, 23.38, 24.12, 24.70, 25.04, 26.22, 26.58, 27.30, 27.96, 28.10, 28.44, 28.54, 29.02, 29.48, 30.82, 31.02, 31.58, 32.02, 32.46, 32.78, 32.94, 37.78 and 37.96.

7. A polymorphic Form γ1 of efavirenz having a XRPD pattern wherein characteristic 2θ values are obtained at 6.14, 6.26, 21.24, and 24.94.

8. The polymorphic form of claim 7, further comprising the characteristic 2θ values at 10.50, 11.00, 12.28, 13.08, 13.26, 14.24, 15.30, 15.64, 16.68, 16.94, 17.90, 18.32, 18.54, 19.26, 19.70, 20.16, 21.98, 22.10, 22.32, 23.16, 24.56, 25.62, 26.06, 26.42, 27.26, 27.50, 28.18, 28.74, 29.26, 29.62, 30.84, 31.64, 32.38 and 37.40.

9. A polymorphic Form γ2 of efavirenz having a XRPD pattern wherein characteristic 2θ values are obtained at 21.18, 21.74, 22.04, and 31.64.

10. The polymorphic form of claim 9, further comprising the characteristic 2θ values at 12.12, 12.38, 12.98, 13.16, 15.64, 16.90, 17.22, 18.14, 18.42, 18.76, 19.34, 19.48, 19.90, 20.06, 20.32, 23.08, 23.30, 23.98, 24.42, 24.60, 24.94, 25.34, 26.14, 26.36, 27.06, 27.30, 28.04, 28.38, 28.98, and 29.24.

11. A polymorphic Form ω of efavirenz having a XRPD pattern wherein characteristic 2θ values are obtained at 9.98, 20.40, 22.66, and 28.12.

12. The polymorphic form of claim 11, further comprising the characteristic 2θ values at 4.98, 11.26, 11.64, 12.06, 14.88, 15.02, 16.64, 17.18, 17.54, 18.06, 18.66, 19.02, 19.72, 20.78, 21.18, 21.58, 21.72, 22.10, 23.40, 23.86, 24.32, 24.74, 25.30, 25.82, 26.04, 26.42, 26.76, 27.60, 28.44, 29.04, 29.82, 37.66 and 37.78.

13. A polymorphic Form δ of efavirenz having a XRPD pattern wherein characteristic 2θ values are obtained at 7.18, 13.44, 22.94, and 26.02.

14. The polymorphic form of claim 13, further comprising the characteristic 2θ values at 11.32, 12.12, 12.64, 13.04, 13.86, 14.44, 15.12, 15.44, 16.38, 17.00, 18.92, 19.56, 20.08, 20.58, 21.80, 22.14, 23.92, 24.66, 25.42, 26.72, 27.32, 27.86, 28.02, 29.22, 29.96, 30.72, 31.74, 32.40, 32.74 and 39.06.

15. Amorphous efavirenz.

16. A polymorphic Form O of efavirenz having a XRPD pattern wherein characteristic 2θ values are obtained at 13.16, 19.58, 20.86, and 25.38.

17. The polymorphic form of claim 16, further comprising the characteristic 2θ values at 3.92, 7.88, 10.70, 11.20, 11.40, 12.04, 12.86, 13.80, 14.38, 15.08, 15.78, 16.46, 17.26, 17.46, 18.44, 20.20, 21.26, 21.50, 21.92, 22.14, 22.34, 22.96, 23.74, 24.58, 26.02, 26.48, 26.90, 27.24, 27.62, 27.86, 28.00, 28.64 and 28.96.

18. A polymorphic Form N of efavirenz having a XRPD pattern wherein characteristic 2θ values are obtained at 13.12, 18.40, 20.82, and 25.30.

19. The polymorphic form of claim 18, further comprising the characteristic 2θ values at 3.9, 7.84, 10.66, 12.00, 12.80, 15.04, 15.74, 17.40, 19.54, 22.88, 23.68, 24.96, 25.96, 26.86, 27.16, 27.92 and 28.90.

20. A polymorphic Form P of efavirenz having a XRPD pattern wherein characteristic 2θ values are obtained at 13.12, 18.38, 20.80, and 25.28.

21. The polymorphic form of claim 20, further comprising the characteristic 2θ values at 3.90, 7.84, 8.68, 10.66, 10.82, 11.22, 11.42, 12.00, 12.42, 12.78, 13.66, 14.30, 14.42, 15.04, 15.22, 15.74, 16.34, 16.58, 16.84, 17.40, 17.90, 18.56, 19.52, 21.46, 21.74, 22.18, 22.88, 23.82, 24.34, 24.66, 25.94, 26.20, 26.86, 27.14, 27.92, 28.44 and 28.88.

22. A pharmaceutical composition comprising one or more of Forms α, β, γ, γ1, γ2, ω, δ, N, O or P of efavirenz, and one or more pharmaceutically acceptable excipients.

23. The pharmaceutical composition of claim 22, wherein the pharmaceutical agent further comprises one or more additional therapeutic agents.

24. A method of treating HIV-1 infections, the method comprising administering to a mammal in need thereof a pharmaceutical composition comprising one or more polymorphic Forms α, β, γ, γ1, γ2, ω, δ, N, O or P of efavirenz and one or more pharmaceutically acceptable excipients.

25. The method of claim 24, wherein the method further comprises administering one or more additional therapeutic agents with the efavirenz.

FIGURE 1

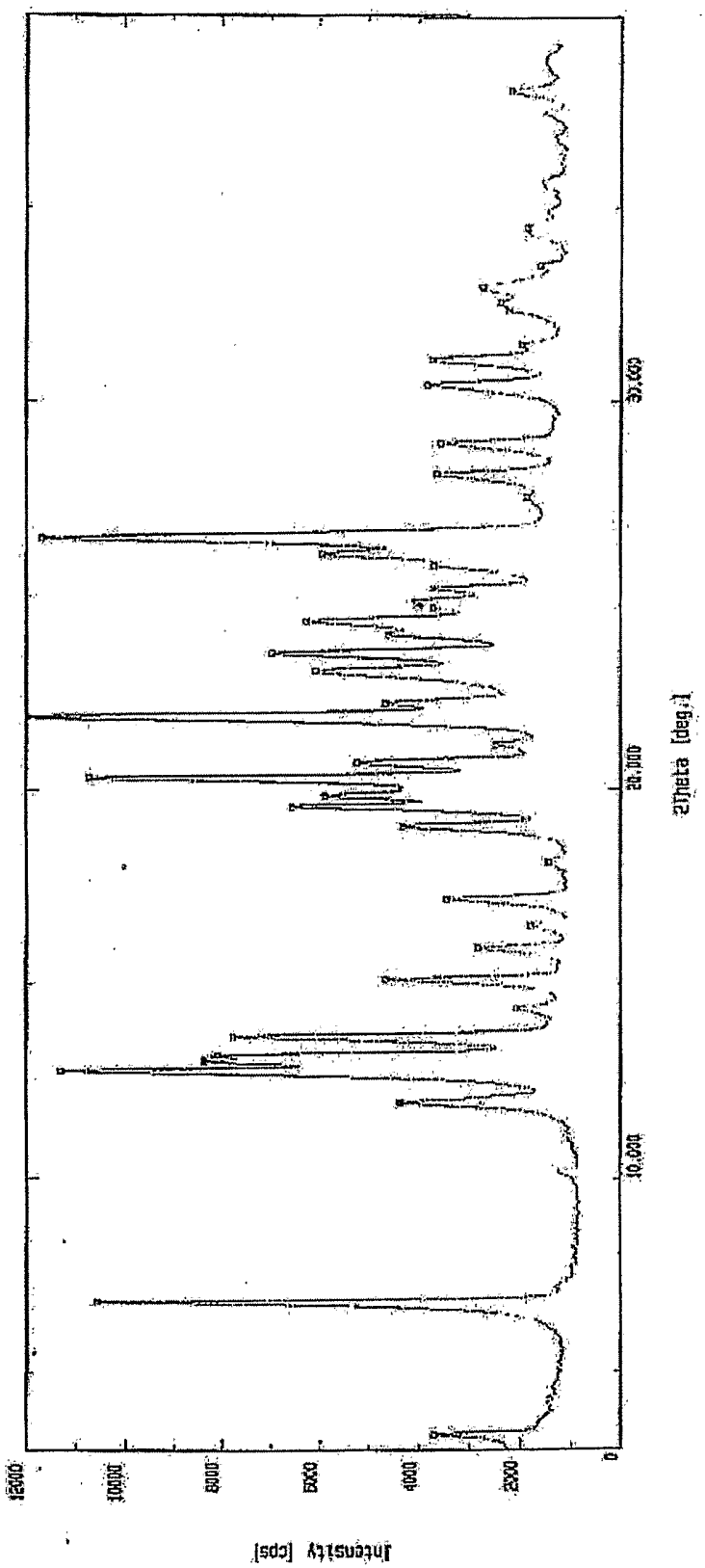

Intensity [cps]
12000
10000
8000
6000
4000
2000
0
10.000
20.000
30.000
2Theta [deg.]

FIGURE 2

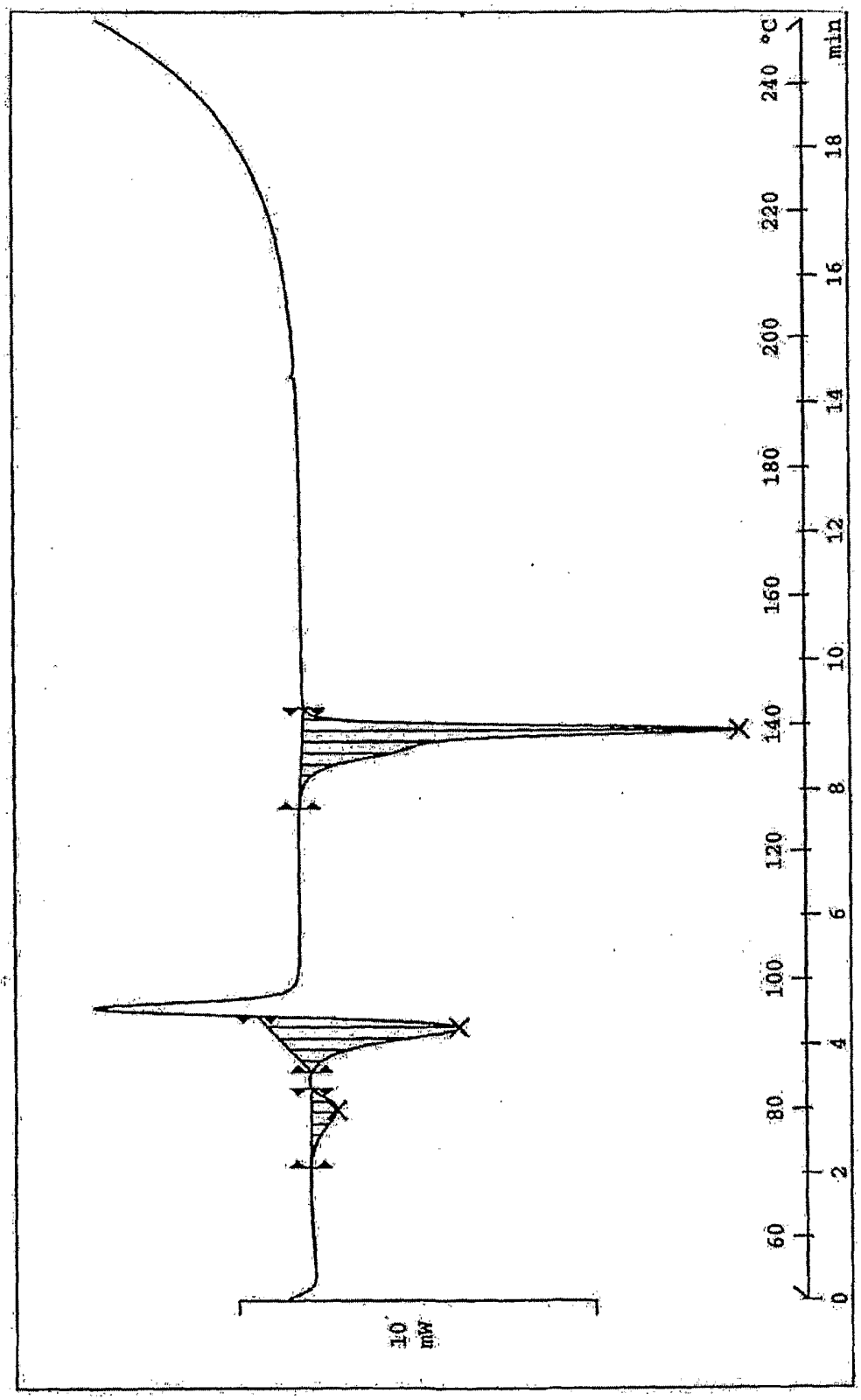
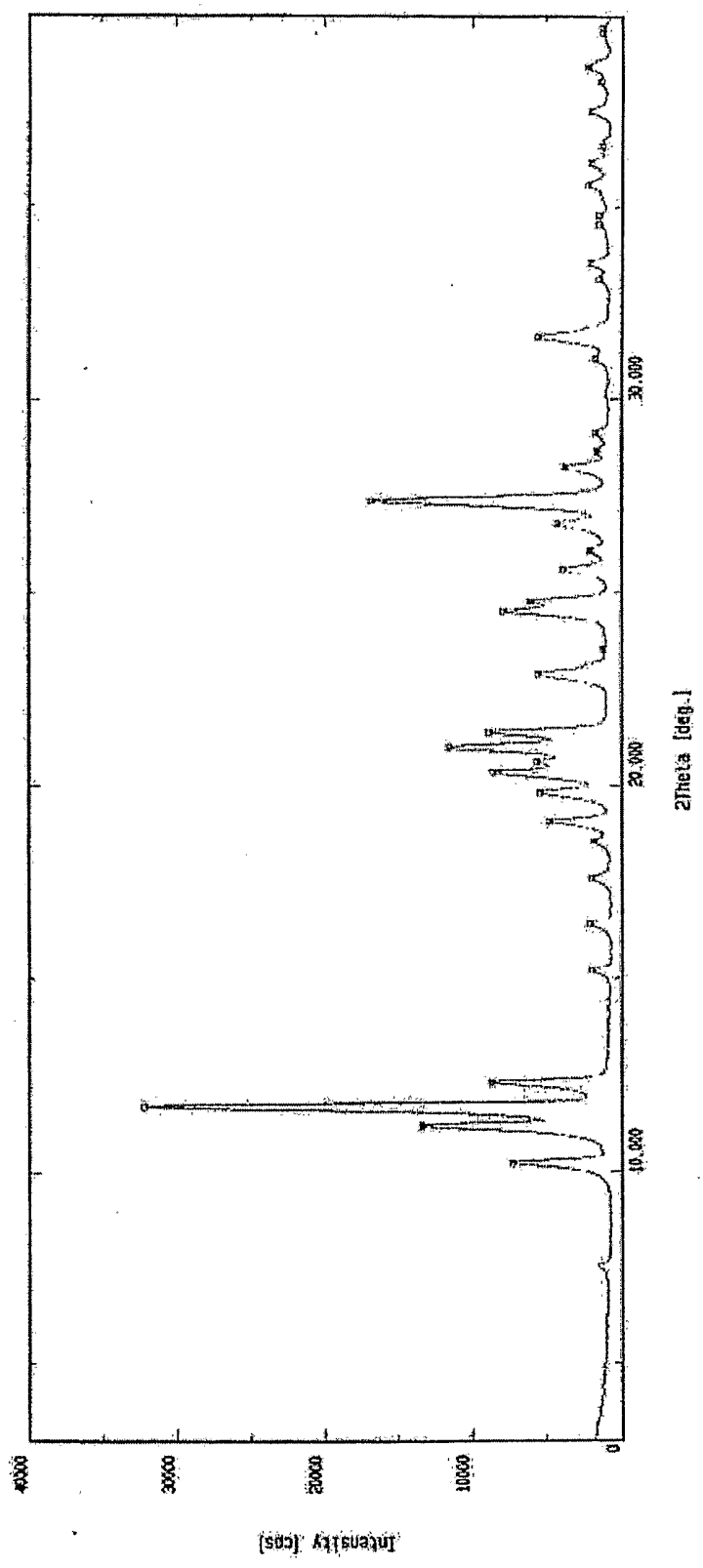

°C
min
240
220
200
180
160
140
120
100
80
60
18
16
14
12
10
8
6
4
2
0
10
mW

FIGURE 3


Intensity [cps]
40000
30000
20000
10000
0
10.000
20.000
30.000
2Theta [deg.]

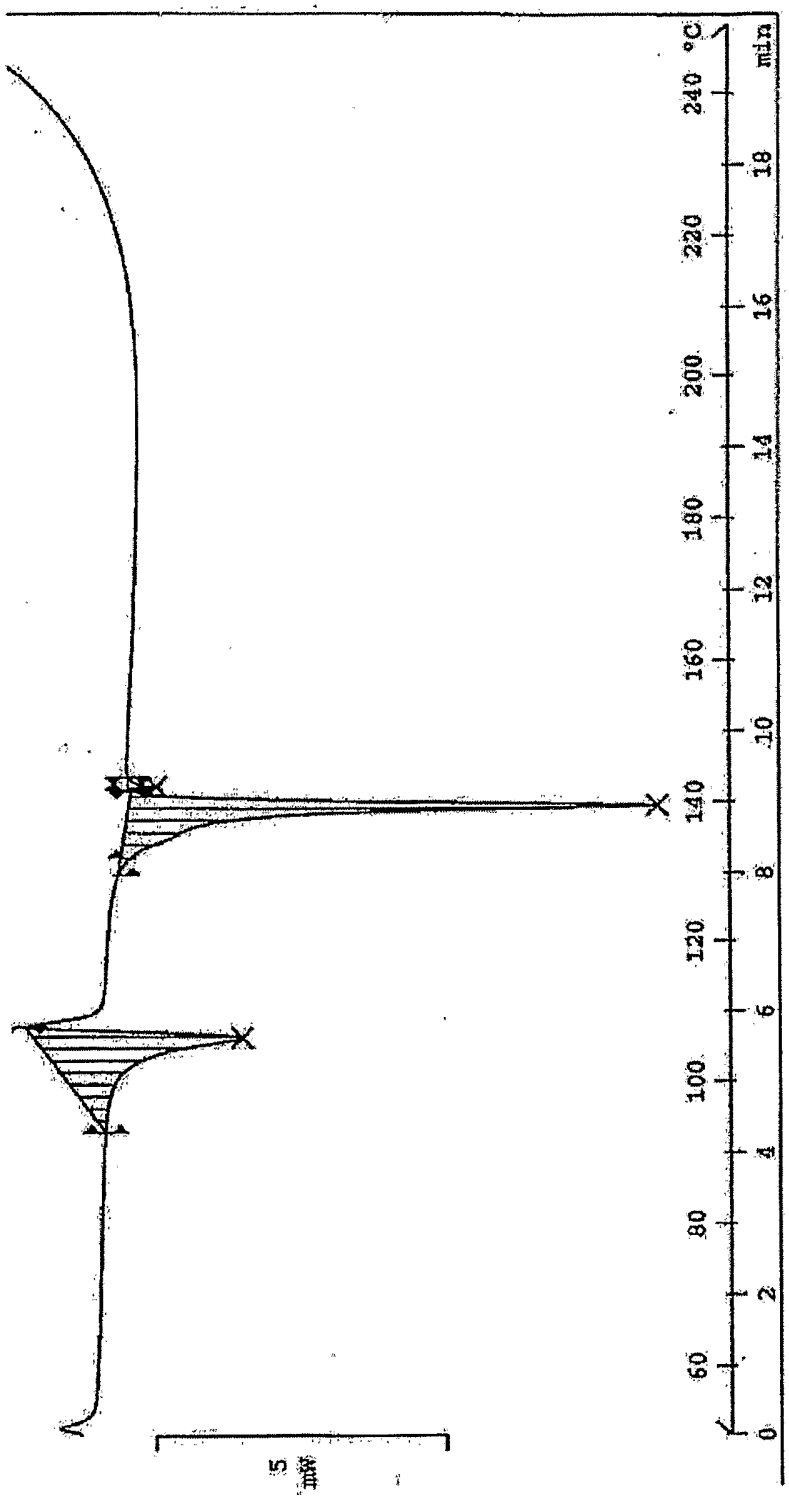
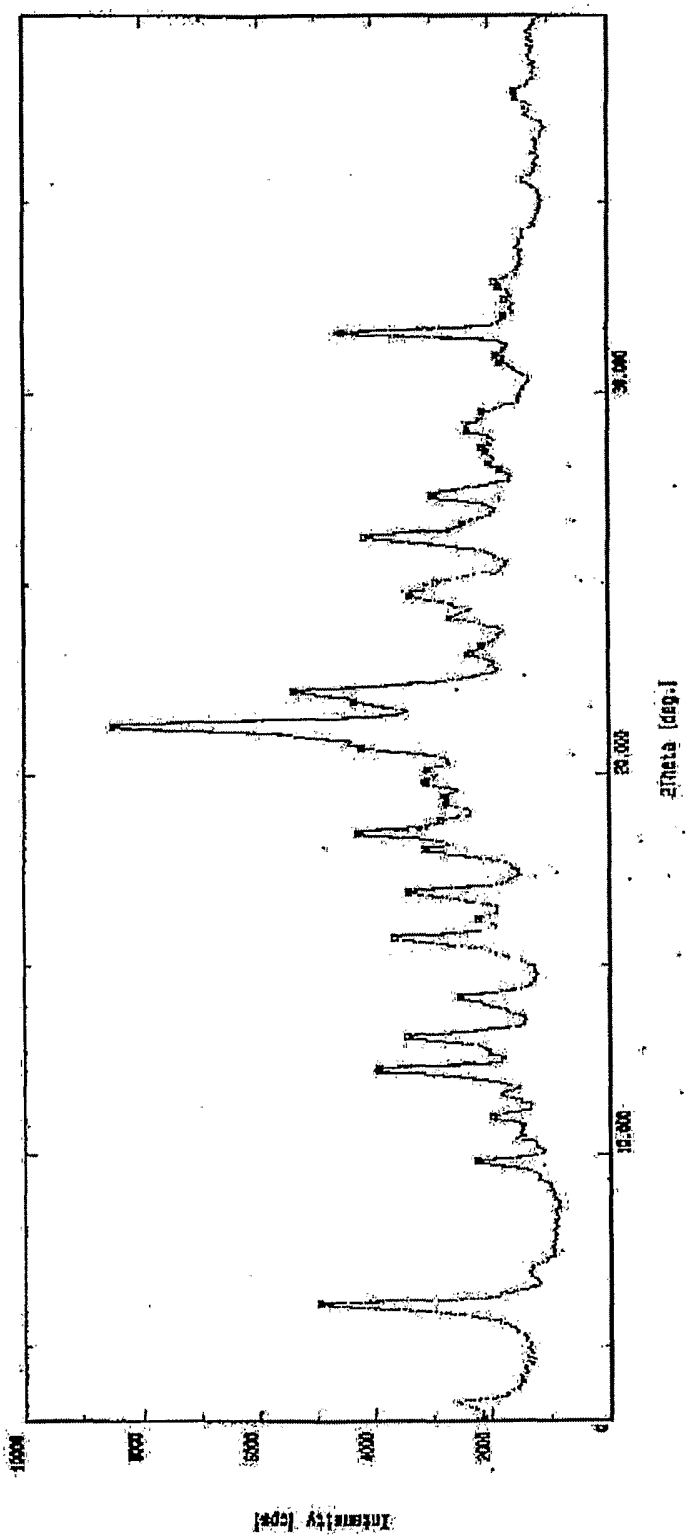

240 °C
min
220
200
180
160
140
120
100
80
60
18
16
14
12
10
8
6
4
2
0
5
mW

FIGURE 4

FIGURE 5



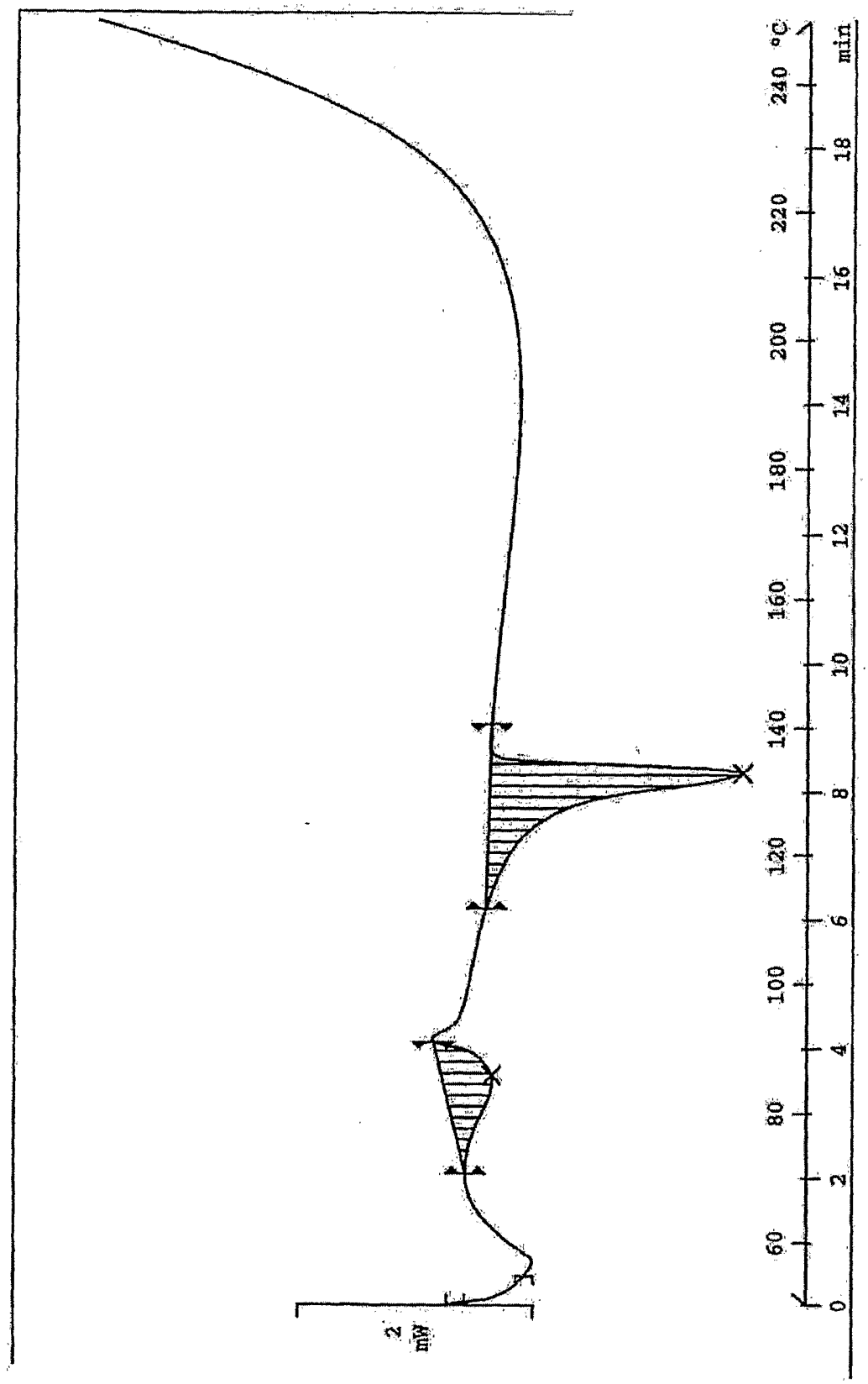

2 mW
0
60
2
80
4
100
6
120
8
140
10
160
12
180
14
200
16
220
18
240 °C
min

FIGURE 7

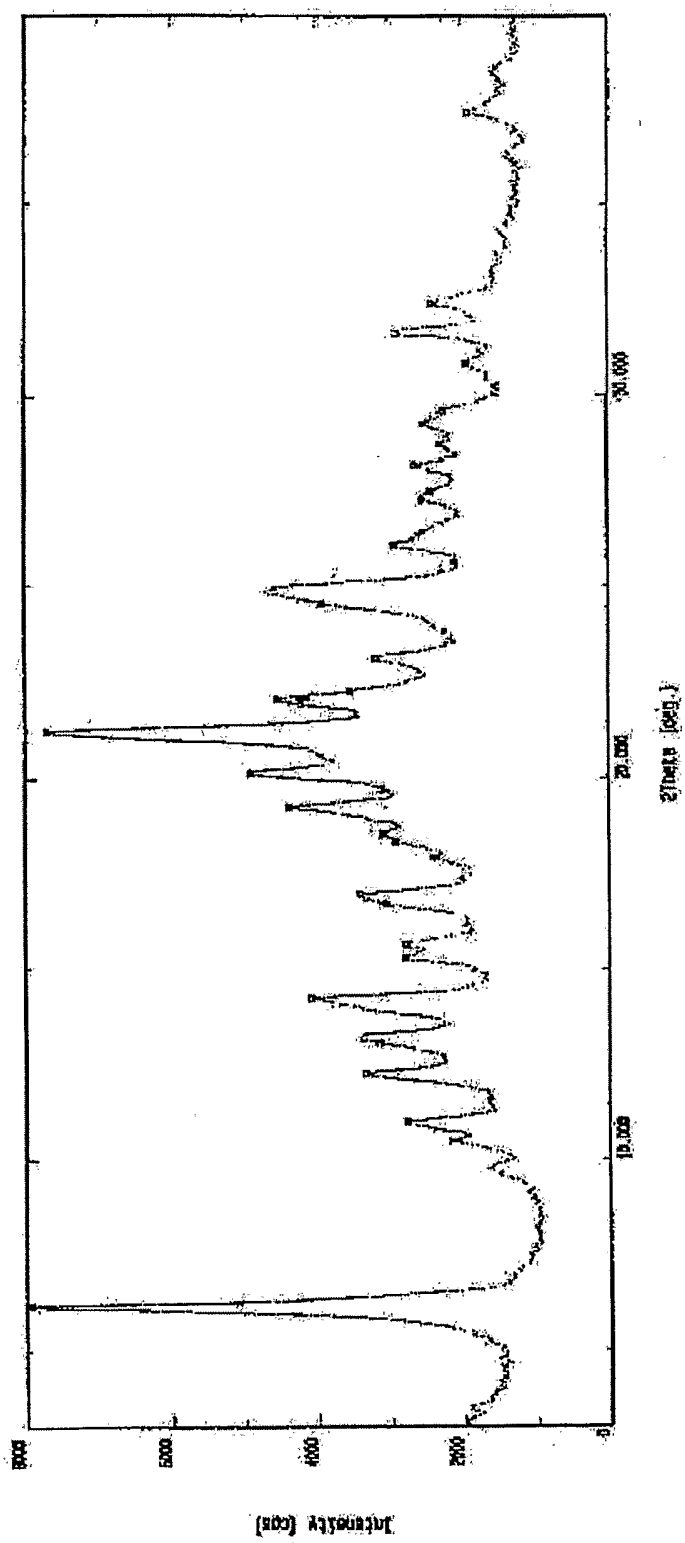

Intensity (cps)
8000
6000
4000
2000
0
10.000
20.000
30.000
2Theta (deg.)

FIGURE 8

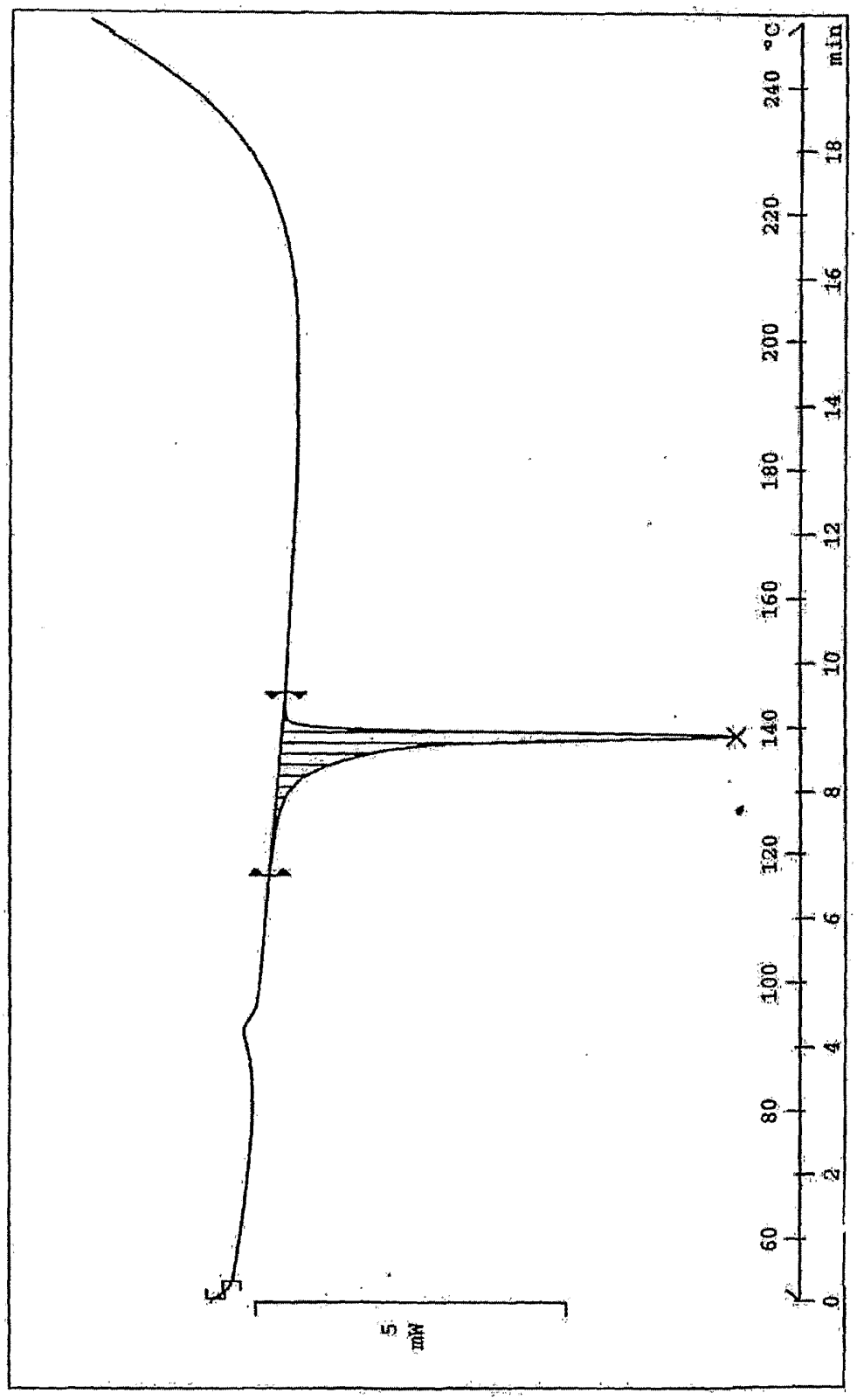

°C
min
240
220
200
180
160
140
120
100
80
60
18
16
14
12
10
8
6
4
2
0
5
mW

FIGURE 9

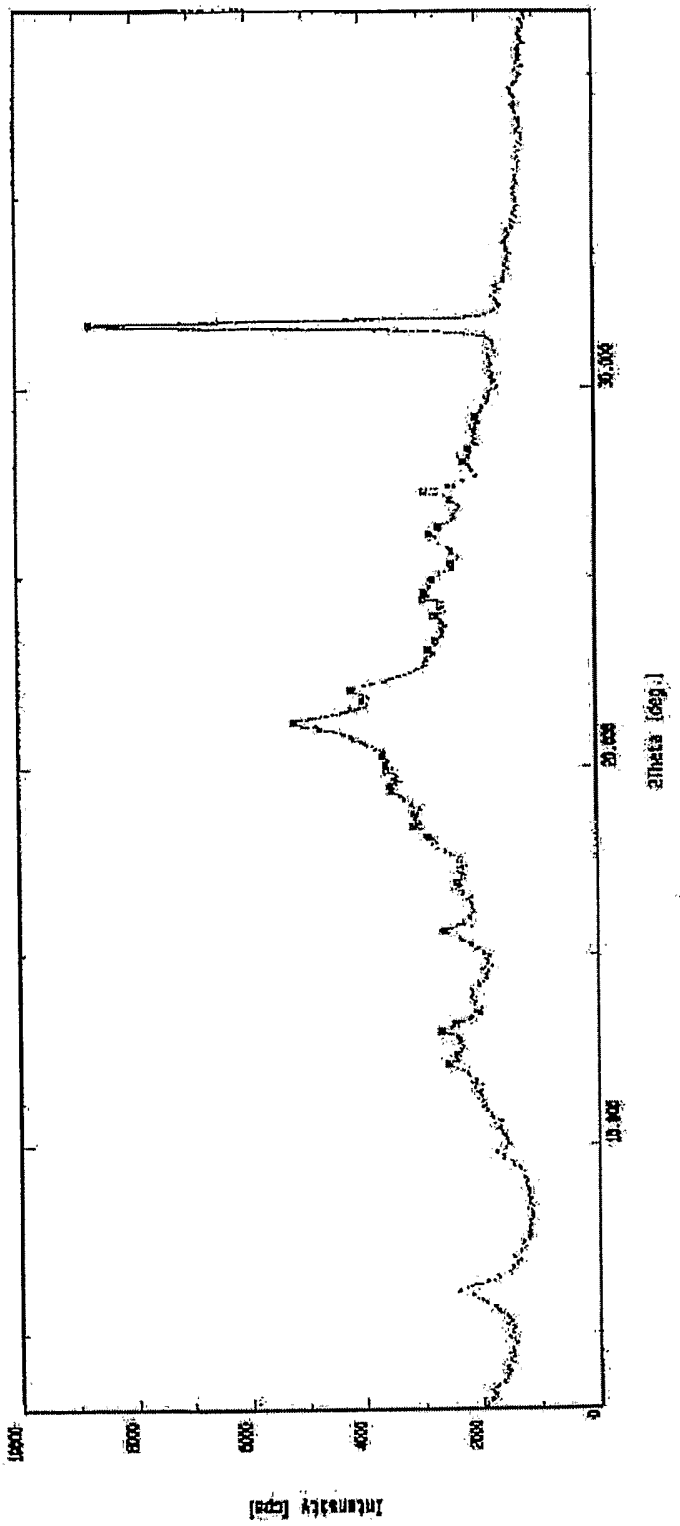


FIGURE 10

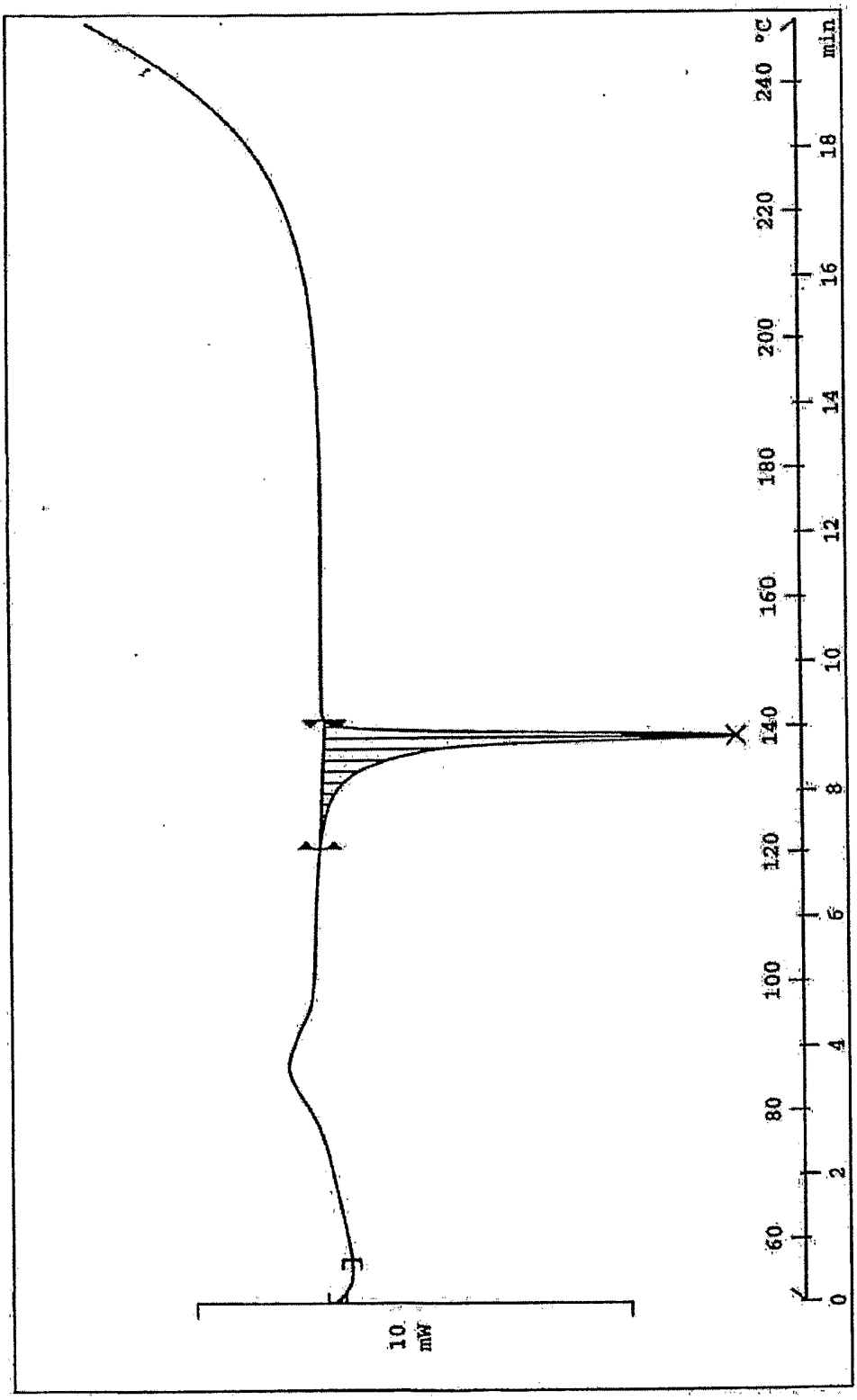

240 °C
min
220
200
180
160
140
120
100
80
60
18
16
14
12
10
8
6
4
2
0
10 mW

FIGURE 11

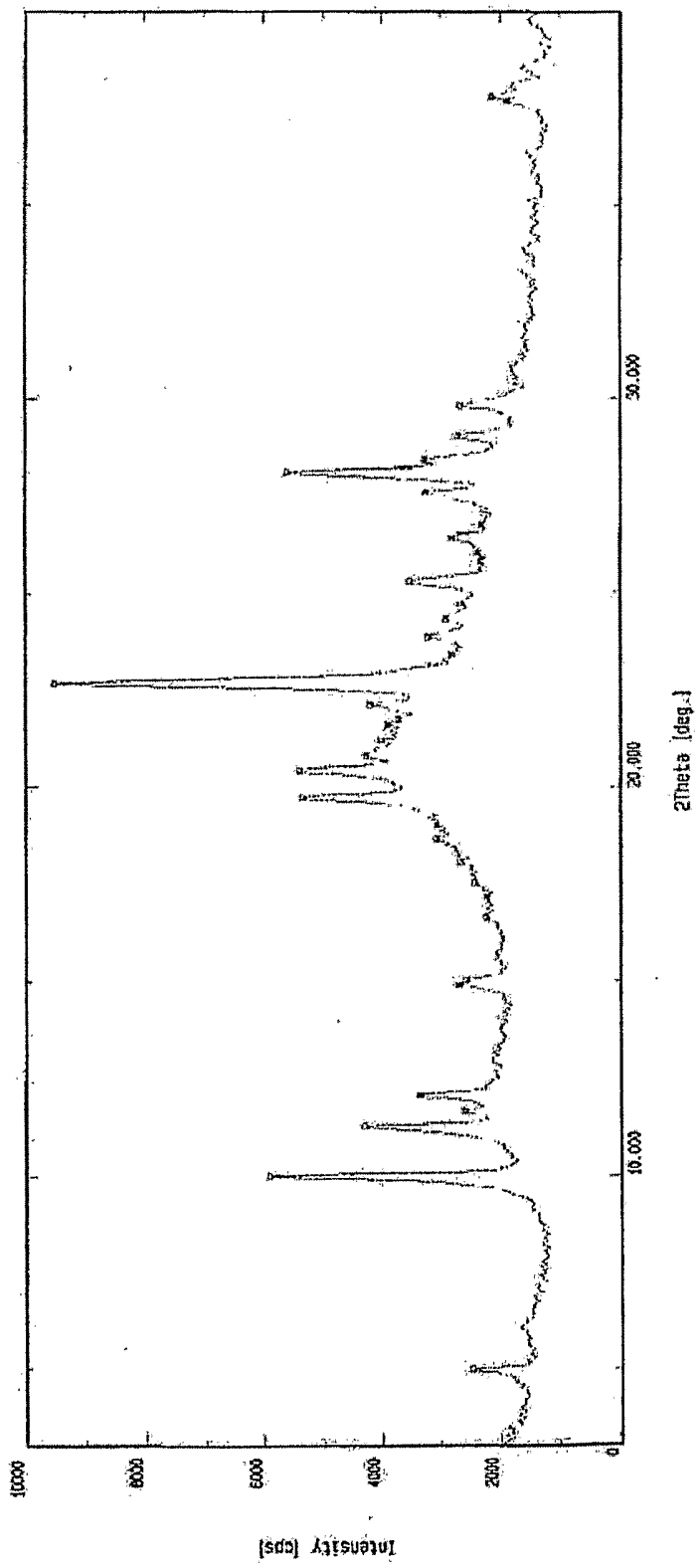
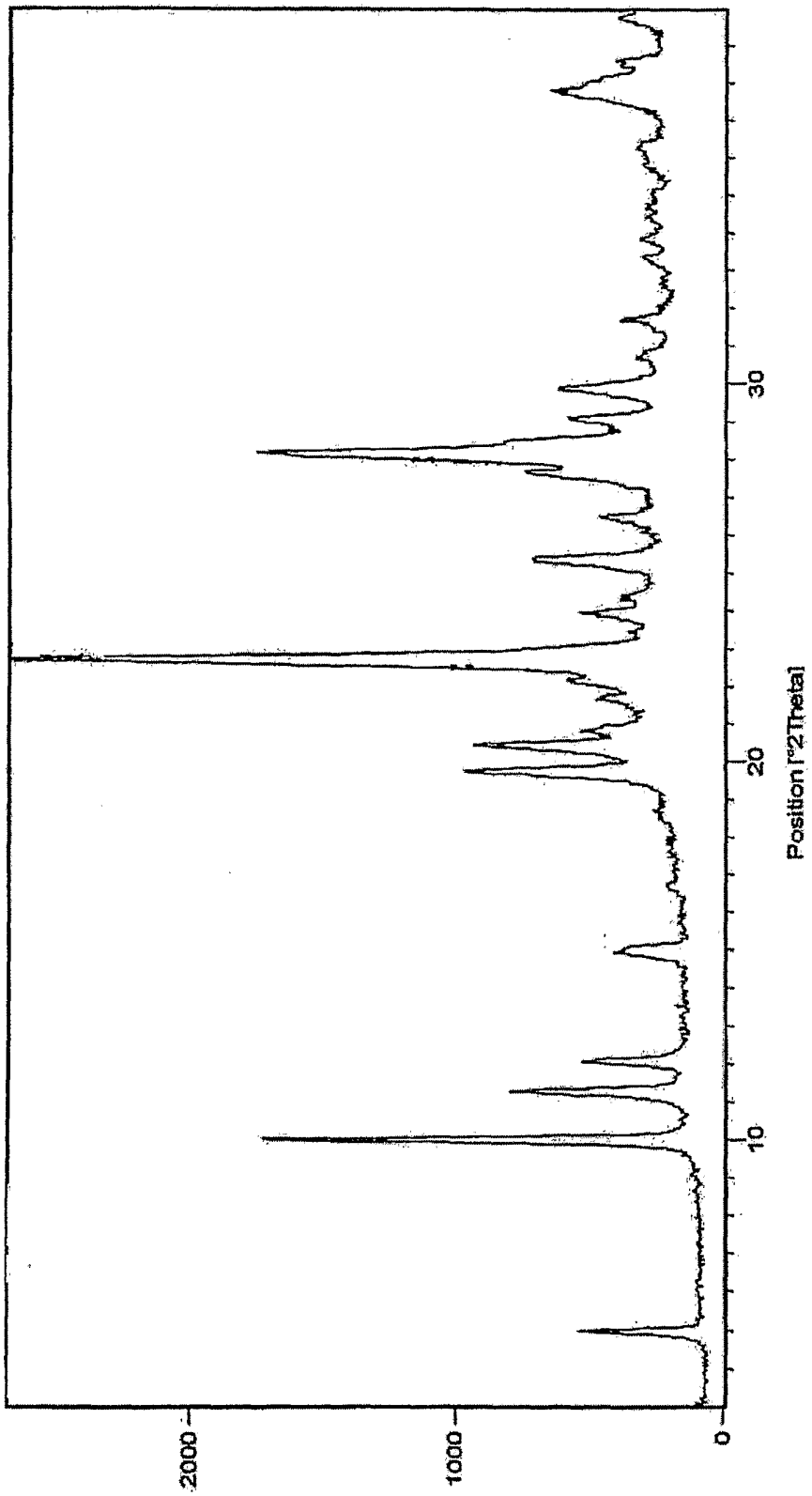

Intensity [cps]
10000
8000
6000
4000
2000
0
10.000
20.000
30.000
2Theta [deg.]

FIGURE 12



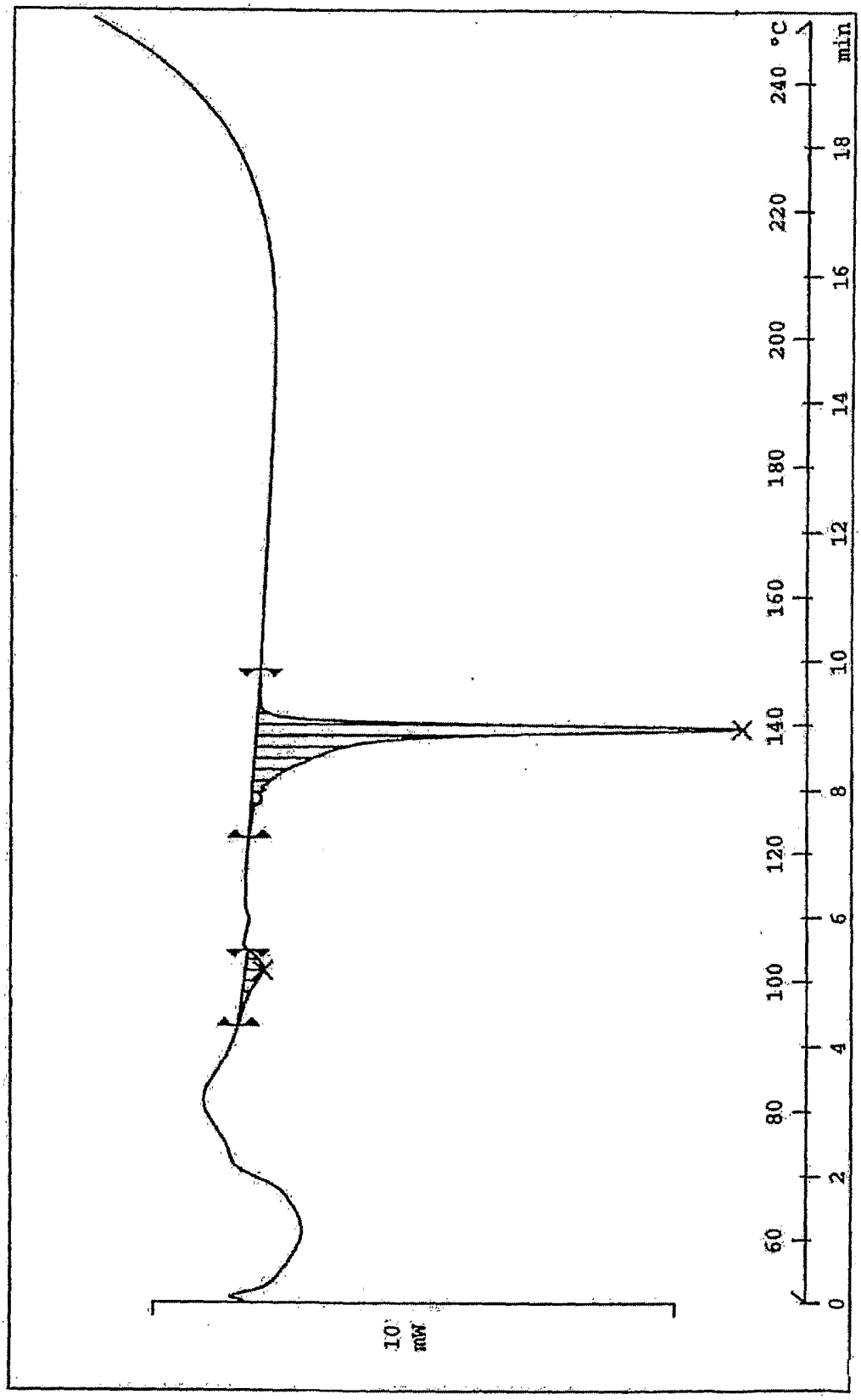

10 mW
0
60
80
100
120
140
160
180
200
220
240 °C
2
4
6
8
10
12
14
16
18
min

FIGURE 13

FIGURE 14

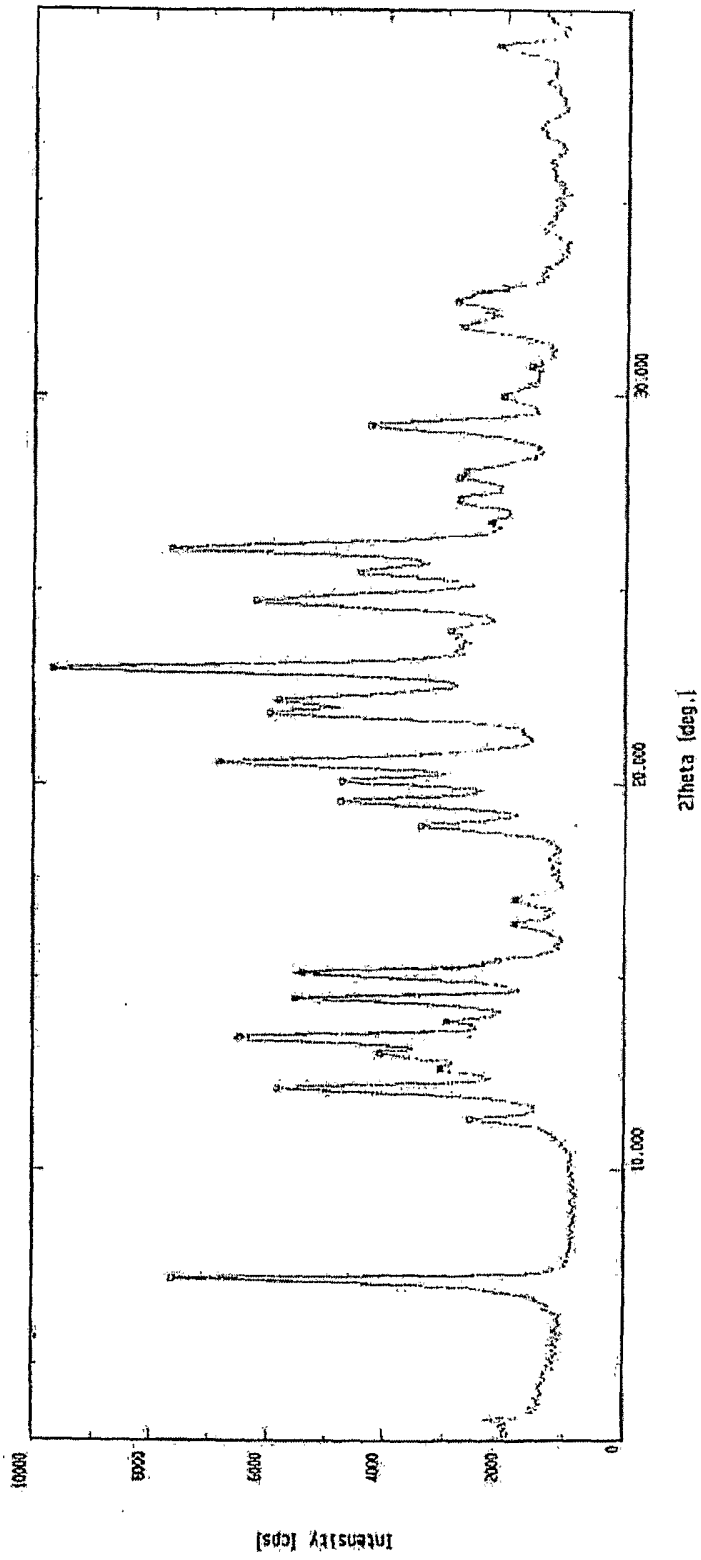

Intensity [cps]
10000
8000
6000
4000
2000
0
10.000
20.000
30.000
2Theta [deg.]

FIGURE 15

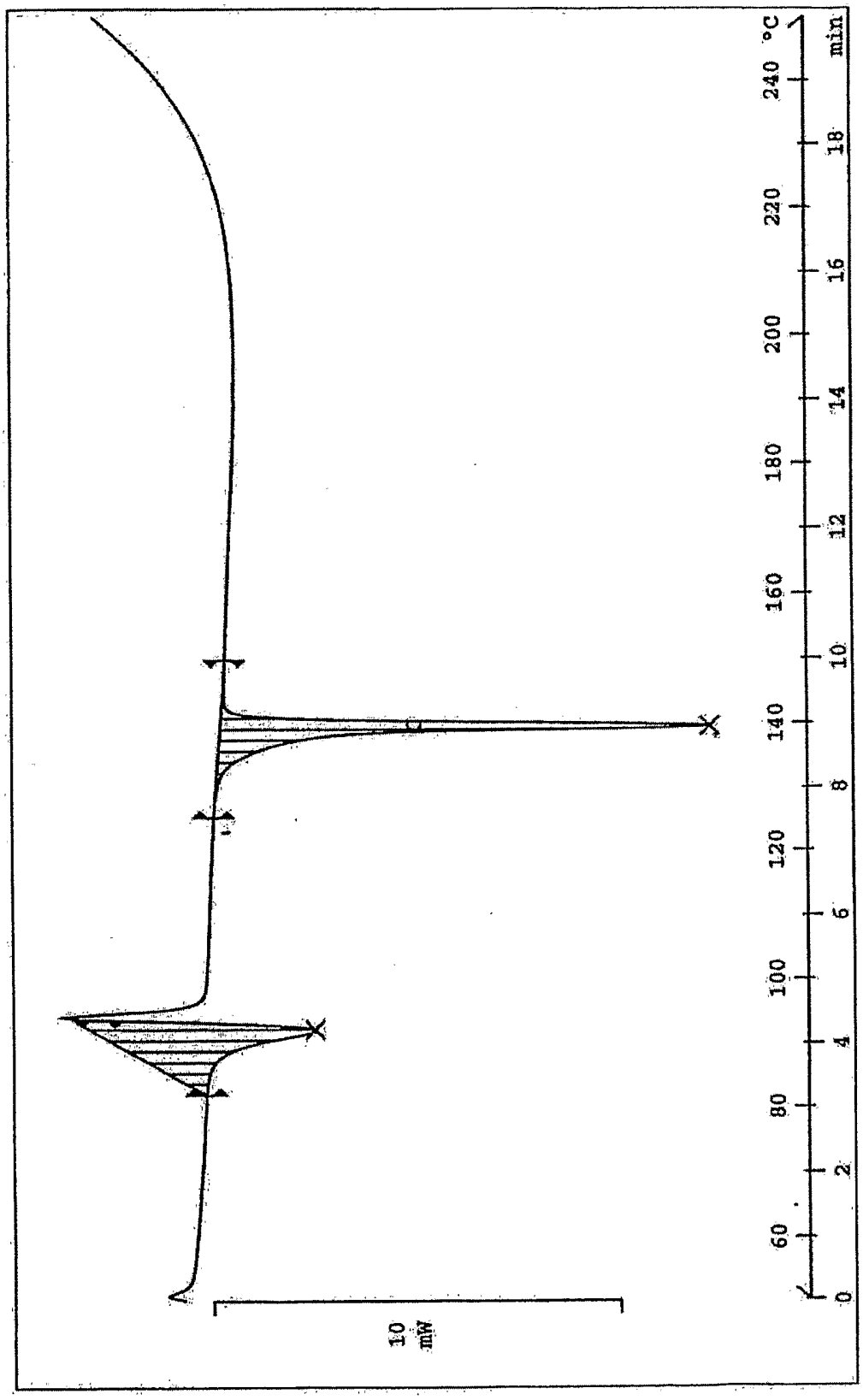

60
80
100
120
140
160
180
200
220
240 °C
0
2
4
6
8
10
12
14
16
18
min
10 mW

FIGURE 16

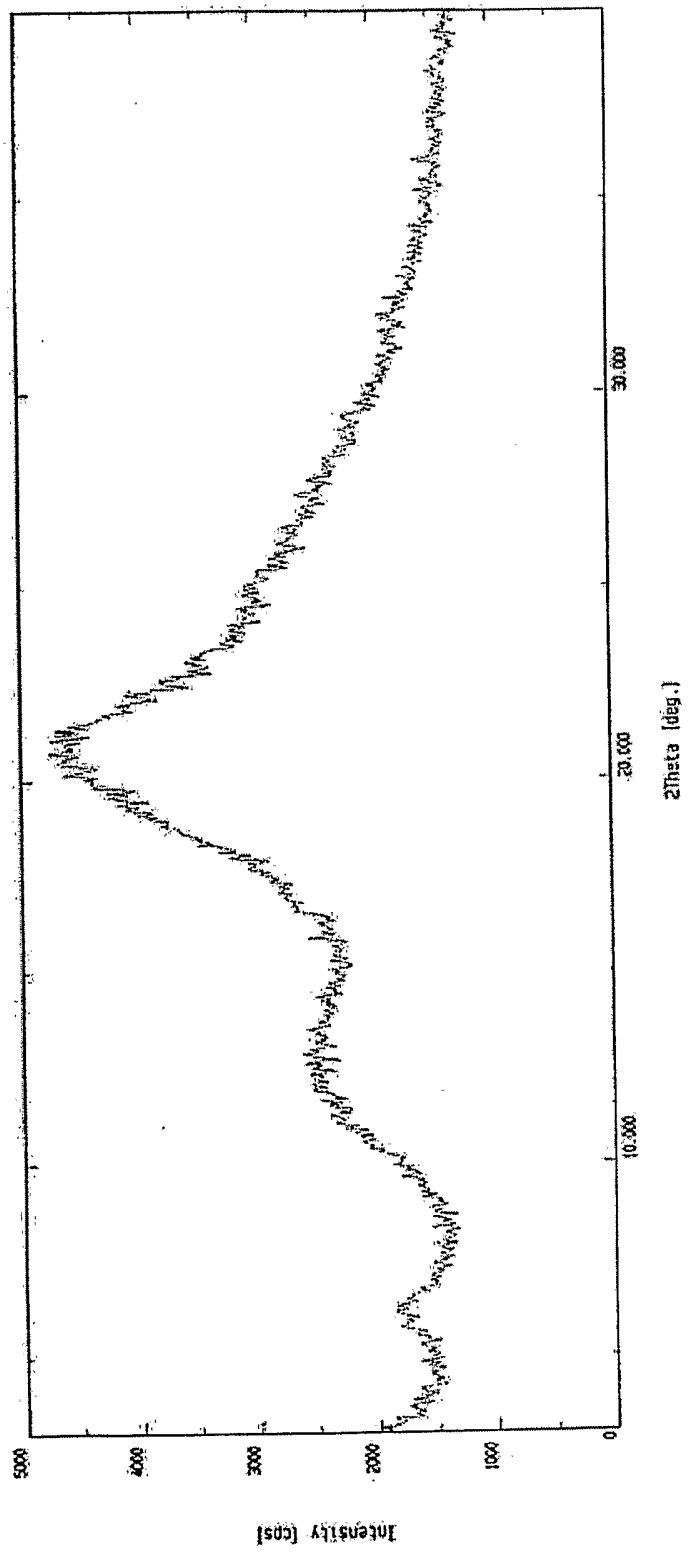

Intensity [cps]
5000
4000
3000
2000
1000
0
10.000
20.000
30.000
2Theta [deg.]

FIGURE 17

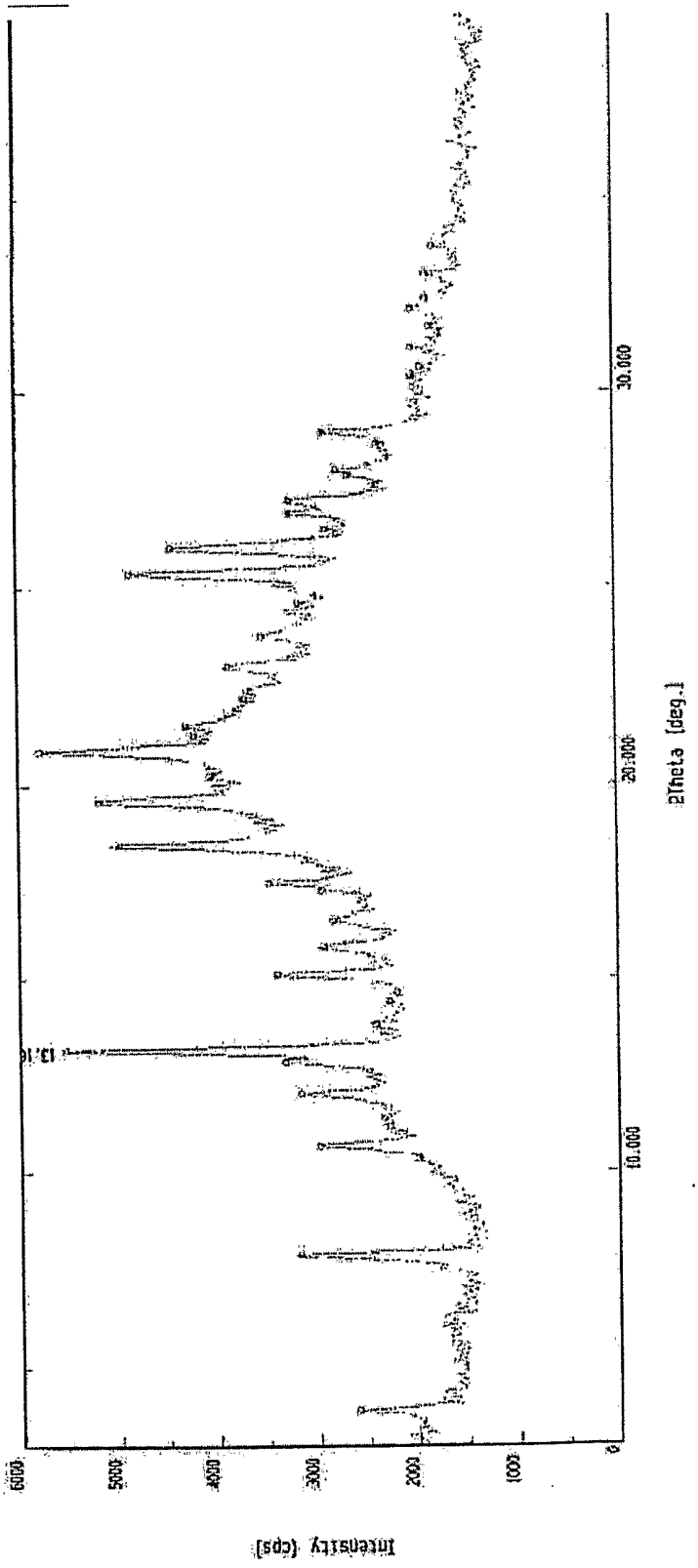

Intensity (cps)
6000
5000
4000
3000
2000
1000
0
10.000
20.000
30.000
2Theta (deg.)

FIGURE 18

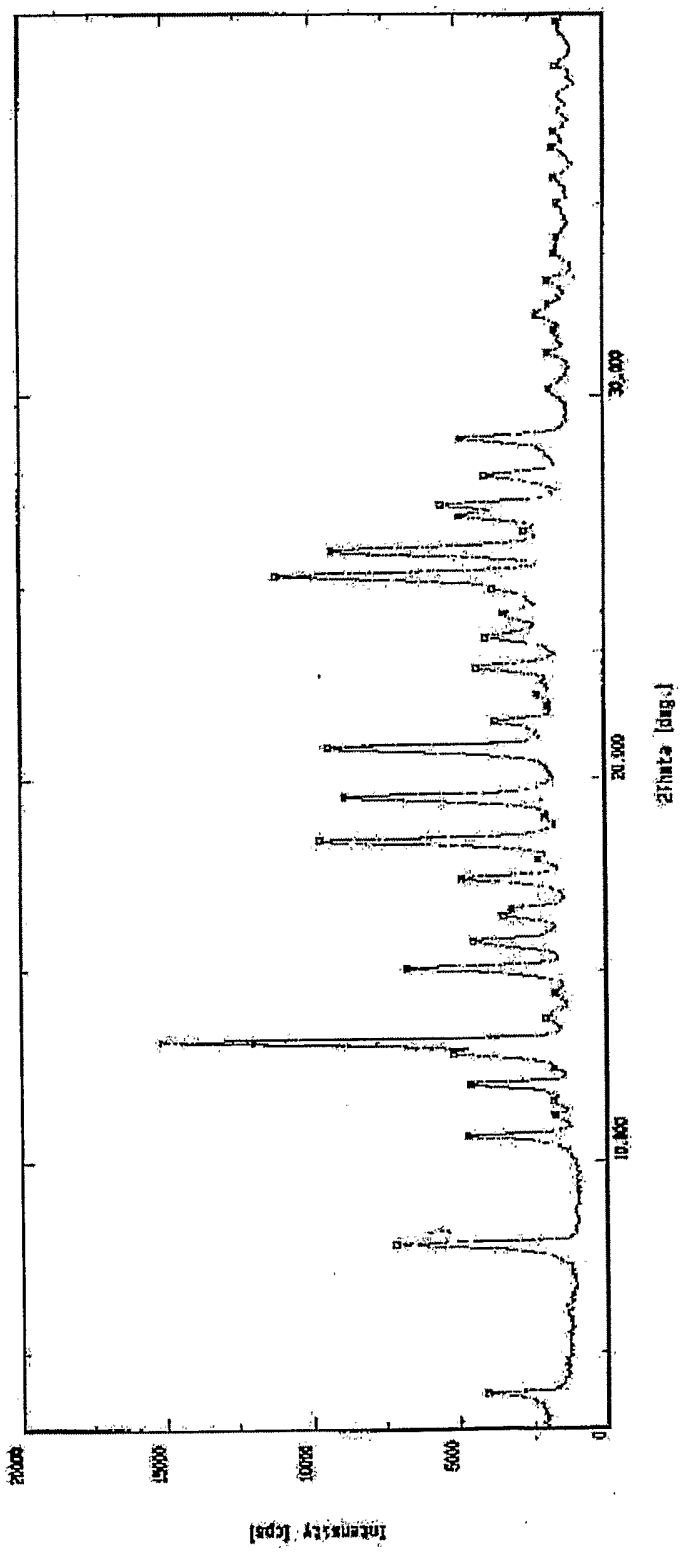
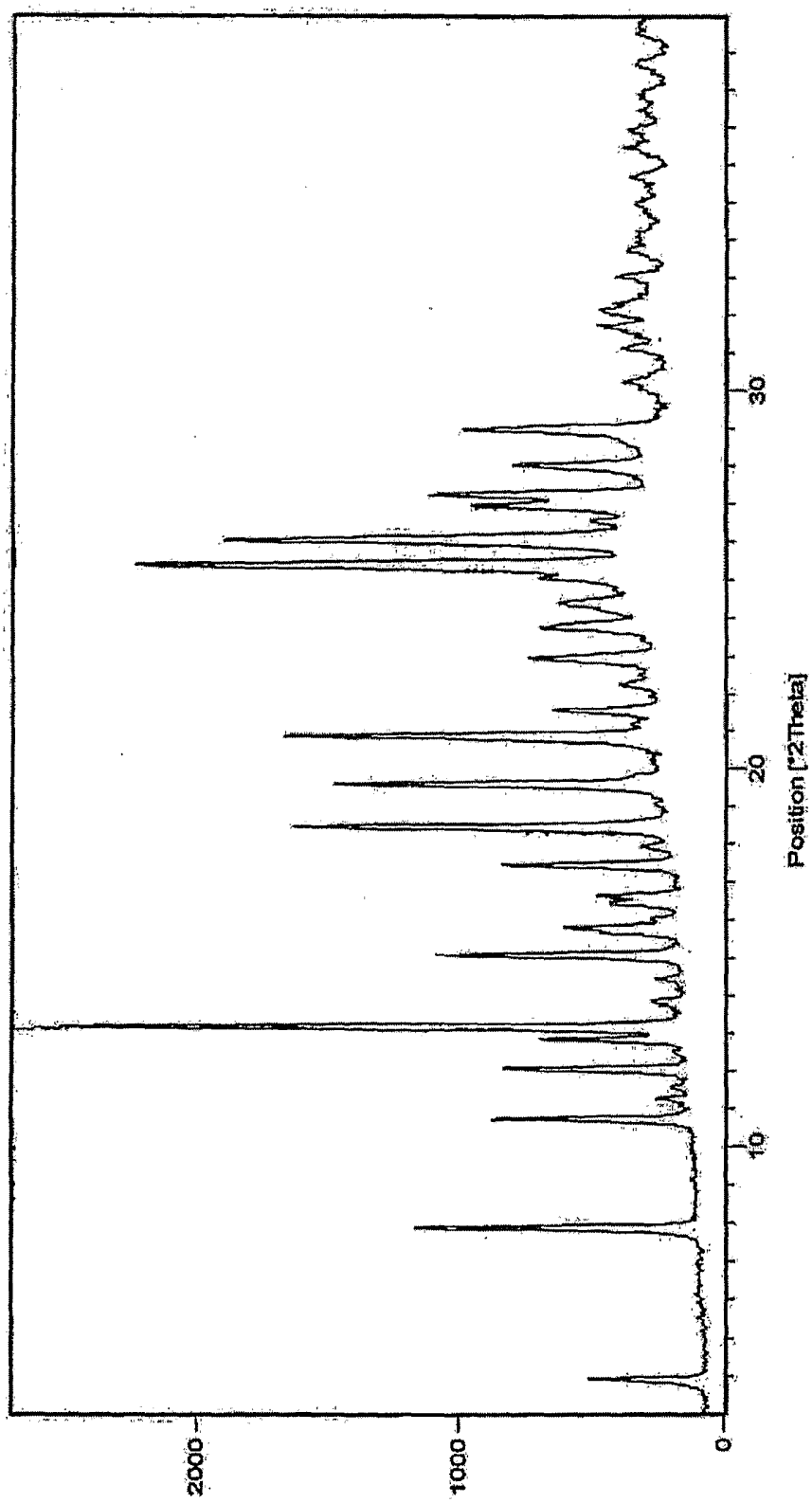

Intensity [cps]
20000
15000
10000
5000
0
10.000
20.000
30.000
2theta [deg.]

FIGURE 19



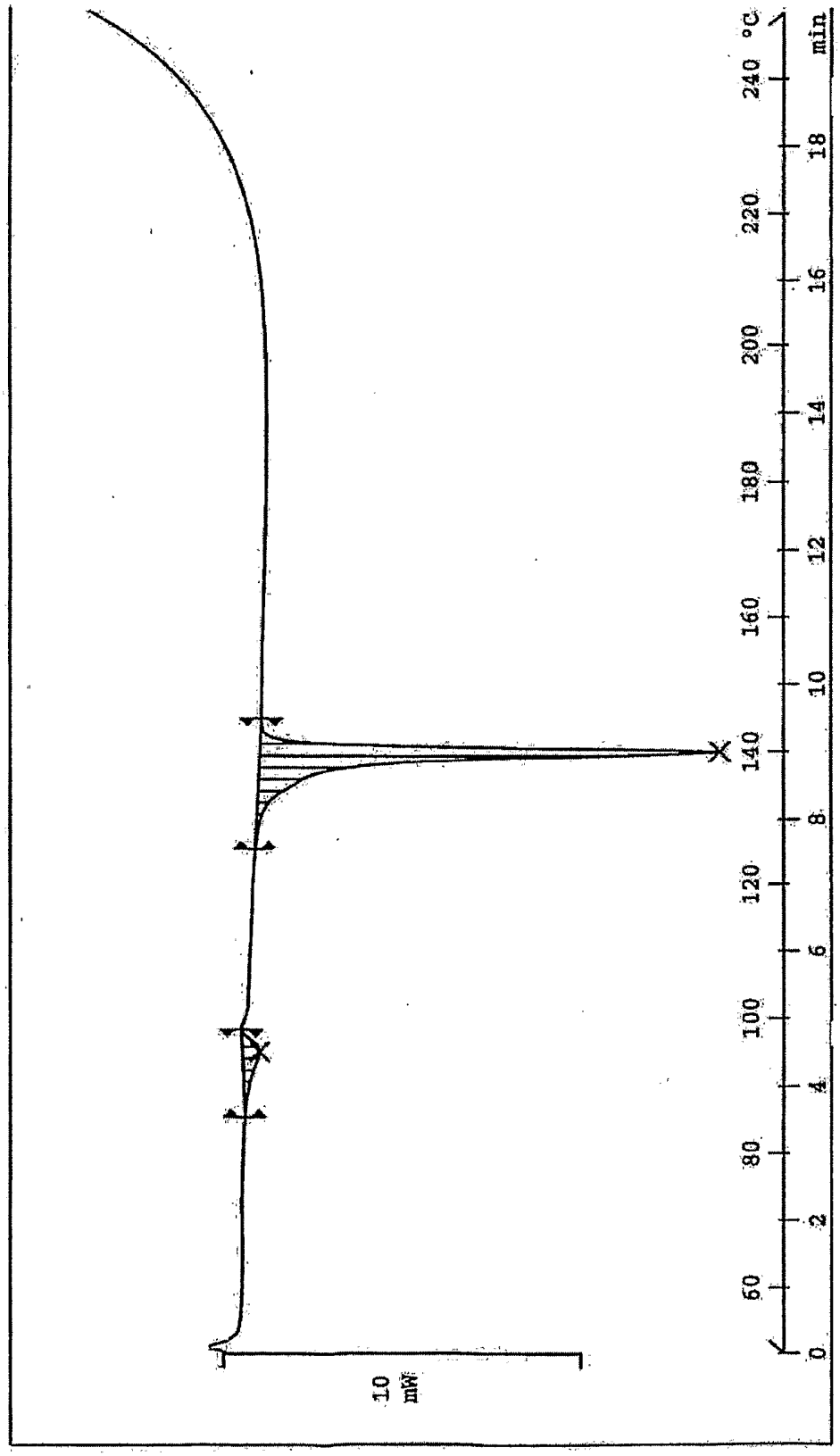

10 mW
0
60
80
100
120
140
160
180
200
220
240 °C
2
4
6
8
10
12
14
16
18
min

FIGURE 20

FIGURE 21

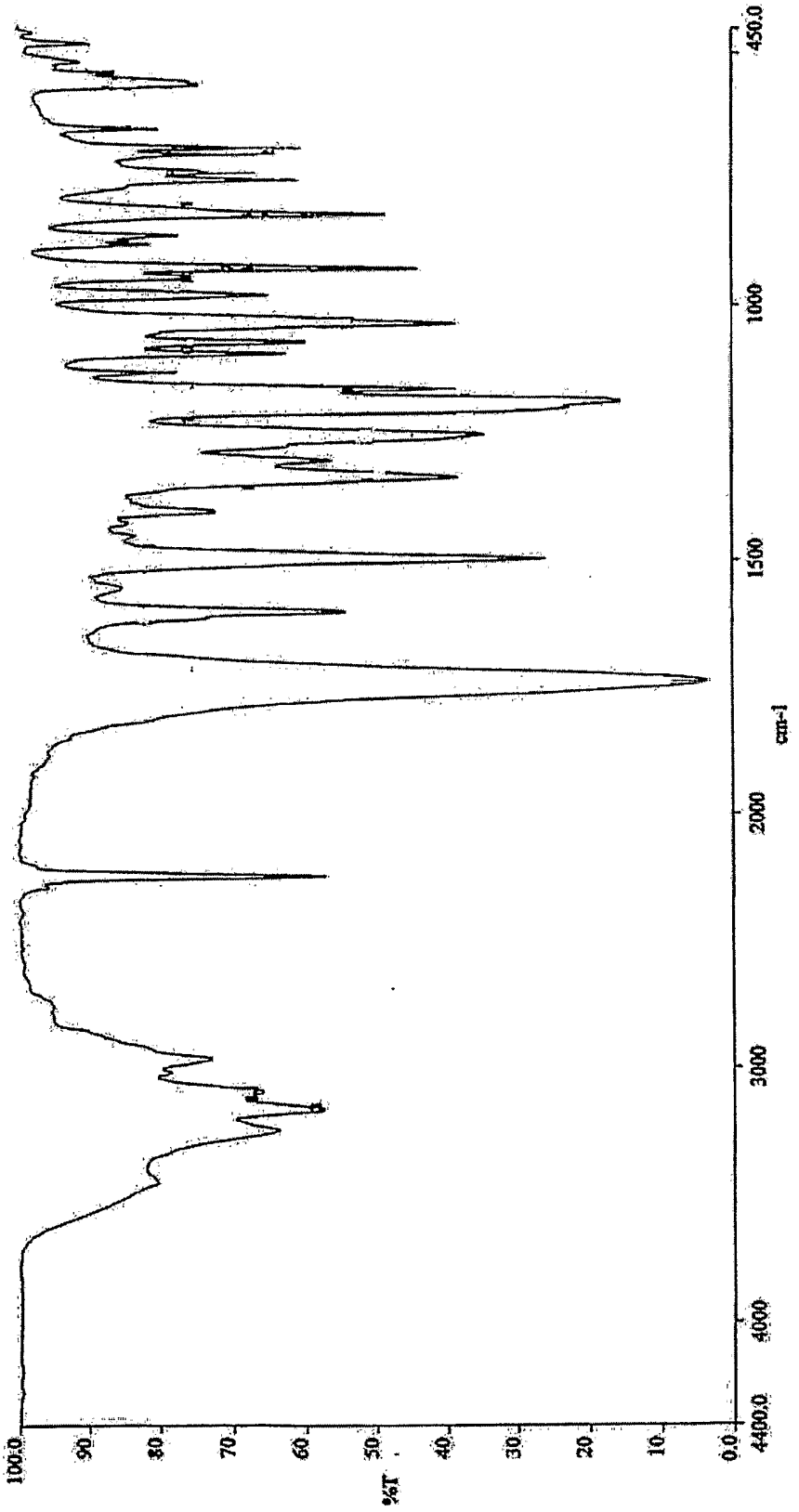
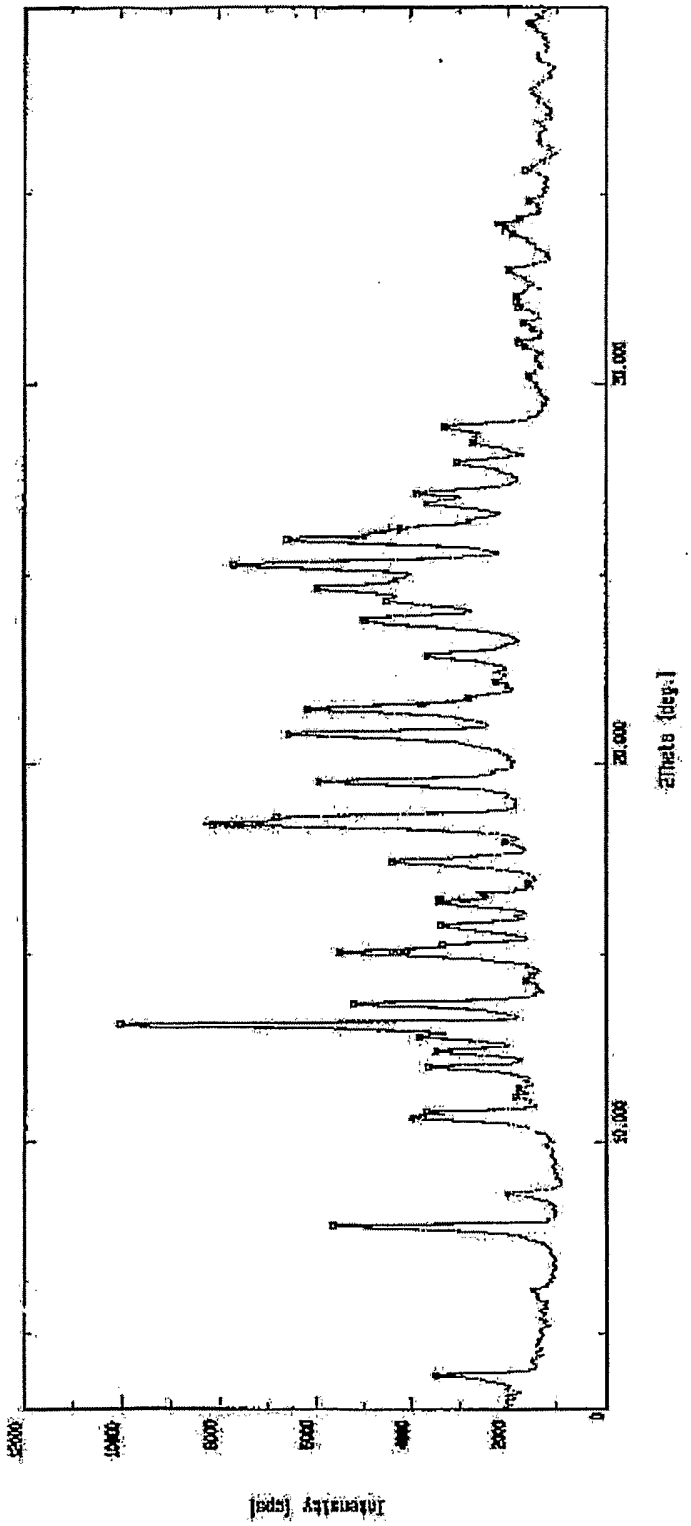

100.0
90
80
70
60
50
40
30
20
10
0.0
%T
4400.0
4000
3000
2000
1500
1000
450.0
cm-1

FIGURE 22


Intensity [cps]
25000
20000
15000
10000
5000
0
10.000
20.000
30.000
2Theta [deg.]