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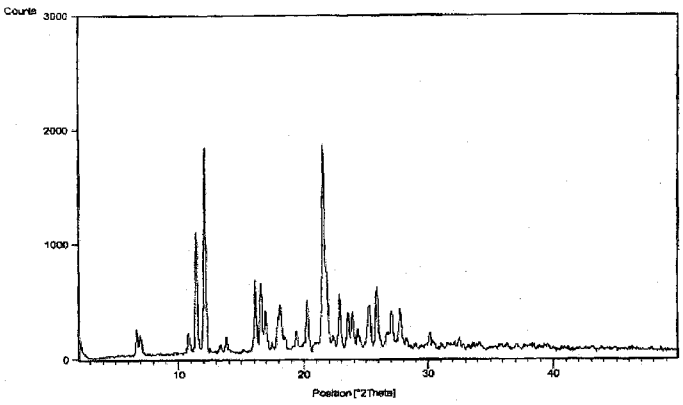
(54) Title: NOVEL POLYMORPHIC FORMS OF TEMAZEPAM AND PROCESSES FOR PREPARING THE SAME

Fig. 1



(57) Abstract: Disclosed herein are novel crystalline polymorphic forms Form I, Form II, Form III, Form IV, Form V, Form VI, Form VII, Form VIII, Form IX, Form X and amorphous form of temazepam characterized by X-ray powder diffraction patterns, DSC, TGA and IR. In addition, the invention describes processes for the preparation of the various polymorphic forms.

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NOVEL POLYMORPHIC FORMS OF TEMAZEPAM AND PROCESSES FOR PREPARING THE SAME

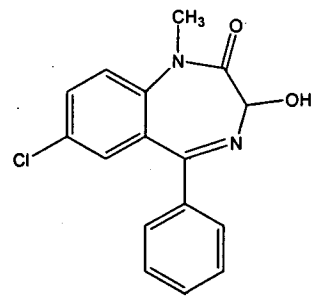
Field of the Invention

This invention, in general relates to novel polymorphic forms of temazepam. More particularly, the present invention is directed to crystalline Form I, Form II, Form III, Form IV, Form V, Form VI, Form VII, Form VIII, Form IX, Form X and amorphous form of temazepam and processes for the preparing the same.

Background of the Invention

The benzodiazepines are well-known central nervous system agents, which are therapeutically used in the treatment of anxiety, neuroses, and tension associated with organic conditions and irritability. In addition, benzodiazepines are used for the treatment of alcoholics, especially for the alleviation of symptoms of alcohol withdrawal or the excited and combative episodes that occur during alcoholic intoxication, and to relieve the anxiety and tension associated with alcoholic post-withdrawal.

U.S. Patent No. 3,296,249 first discloses the benzodiazepine derivative thereof known as temazepam, chemically identified as 7-chloro-1, 3-dihydro-3-hydroxy-1-methyl-5-phenyl-2H-1, 4-benzodiazepin-2-one (Formula I), which is an active sleep-inducing agent. Temazepam is presently prescribed as a sleep-inducing agent for humans in doses of 15-30 mg before retiring to bed.



I

US Patent No. 4,412,952 discloses the preparation of temazepam with high yield and purity. The patent discloses that the product is characterized by melting point interval of 158°C-160°C with 99.8% purity and having less than 0.2% of dione impurity. Further, US'952 discloses that the melting point of the product obtained from US'249 is 119°C-122°C with 68.2% purity and having 20.7% of dione impurity.

The prior arts provide no teaching with respect to the crystal forms of temazepam and Infrared or X-ray powder diffraction data characteristics of the product.

Therefore, temazepam having uniform crystal and polymorphic forms have not been described in prior art. It is known that various polymorphic forms differ from each other significantly in their physicochemical properties (e.g. dissolution speed, bioavailability, chemical stability). In addition, there exists a strong need for morphologically uniform pharmaceutical active form of temazepam that can be produced in a reproducible manner on an industrial scale, as the work up and processing properties of various polymorphs (e.g. filterability, drying, solubility, readiness to be compressed into tablets) differ from each other significantly.

In light of the foregoing discussion, there is a need to develop polymorphic forms of temazepam with uniform morphology and capable of being manufactured in a reproducible manner on an industrial scale.

Summary of the Invention

It is an object of the present invention to provide novel polymorphic forms of temazepam, referred to herein as Form I, Form II, Form III, Form IV, Form V, Form VI, Form VII, Form VIII, Form IX, Form X and amorphous form characterized by X-ray powder diffraction pattern, infrared absorption spectrum, Thermo Gravimetric Analysis (TGA), Differential Scanning Calorimetry (DSC) and/or moisture content.

It is another object of the present invention to provide processes for the preparation of novel polymorphic forms of temazepam by using different solvent systems and conditions.

The above and other objects of the present invention are further attained and supported by the following embodiments described herein. However, the scope of the invention is not restricted to the described embodiments herein after.

In accordance with an embodiment of the present invention, there is provided a crystalline Form I of temazepam as a hydrate characterized by 1.61 % of water and having an X-ray powder diffraction pattern characterized by peaks at 11.40, 12.10, 16.11, 16.57, 21.55, 22.88, and 25.82 ± 0.2 2θ values.

In accordance with another embodiment of the present invention there is provided a process for preparing the crystalline Form I of temazepam, the process comprising hydrolyzing of O–acetyl derivative of temazepam in presence of a base

and an organic solvent, adjusting pH to neutral followed by cooling the resultant to 15-20°C, adding water as an anti solvent and isolating said Form I of temazepam.

In accordance with yet another embodiment of the present invention there is provided a crystalline Form II of temazepam having an X-ray powder diffraction pattern characterized by peaks at 6.34, 12.41, 13.11, 14.04, 20.18, 21.95, and 22.70 ± 0.2 2 θ values.

In accordance with still another embodiment of the present invention, a process for preparing the crystalline Form II of temazepam, the process comprising of contacting a solution of temazepam in a solvent by slow/fast crystallization, slurry or by anti-solvent method.

In accordance with yet another embodiment of the present invention there is provided a crystalline Form III of temazepam having an X-ray powder diffraction pattern characterized by peaks at 7.05, 15.08, 16.95, 18.80, 20.09 and 23.27 ± 0.2 2θ values.

In accordance with still another embodiment of the invention, there is provided a process for preparing the crystalline Form III of temazepam by heating crystalline Form II of temazepam.

In accordance with yet another embodiment of the present invention, there is provided a crystalline Form IV of temazepam as a methanol solvate having 8-12 % of methanol and characterized by an X-ray powder diffraction pattern having peaks at 7.41, 11.87, 12.98, 14.94, 22.30, 23.42, 23.72, and 24.05 ± 0.2 2θ values.

In accordance with still another embodiment of the invention, there is provided a process for producing crystalline Form IV of temazepam by hydrolyzing O–acetyl derivative of temazepam in presence of a base and an organic solvent, cooling the resultant to 15-20°C and isolating Form IV of temazepam.

In accordance with yet another embodiment of the invention, there is provided a crystalline Form V of temazepam having an X-ray powder diffraction pattern characterized by peaks at 5.42, 8.22, 8.47, 10.81, 21.69 and 22.69 ± 0.2 2θvalues.

In accordance with still another embodiment of the invention, there is provided a process for preparing the crystalline Form V of temazepam the process comprising hydrolyzing the O–acetyl derivative of temazepam in presence of a base and an organic solvent, adjusting pH to acidic, subsequently cooling the resultant to

15-20°C followed by addition of water as an anti solvent and isolating Form V of temazepam.

In accordance with yet another embodiment of the invention, there is provided the crystalline Form VI of temazepam having an X-ray powder diffraction pattern characterized by peaks at 6.90, 9.51, 11.40, 17.09, 17.86, 19.02, 19.57, 20.20, 21.91 24.88, and 26.98 ± 0.2 2θ values.

In accordance with still another embodiment of the invention, there is provided a process for preparing the crystalline Form VI of temazepam, the process comprises of hydrolyzing the O–acetyl derivative of temazepam in presence of a base and an organic solvent, adjusting pH to neutral, followed by cooling the resultant to 15-20°C, adding water as an anti solvent and isolating Form VI of temazepam by drying at 80°C.

In accordance with yet another embodiment of the invention, there is provided a crystalline Form VII of temazepam as a dimethyl sulfoxide solvate having 18-22 % of dimethyl sulfoxide and characterized by an X-ray powder diffraction pattern having peaks at 8.08, 12.13, 15.78, 19.88, 20.09, 20.38, 20.72, 24.65, 25.46 and 27.36 ± 0.2 2θ values.

In accordance with still another embodiment of the invention, there is provided a process for preparing crystalline Form VII by fast evaporation of a saturated solution of temazepam in dimethylsulfoxide.

In accordance with yet another embodiment of the invention, there is provided a crystalline Form VIII of temazepam as an ethanediol solvate having 16-18 % of ethanediol and having an X-ray powder diffraction pattern characterized by peaks at 6.53, 10.70, 11.46, 12.54, 16.48, 18.28, 18.85, 19.31, 21.80, 22.56 and 25.51 ± 0.2 2θ values.

In accordance with still another embodiment of the invention, there is provided a process for preparing the crystalline Form VIII of temazepam by slow evaporation of a saturated solution of temazepam in ethanediol.

In accordance with yet another embodiment of the invention, there is provided a crystalline Form IX of temazepam as a dimethylcarbonate solvate having 10-12 % of dimethylcarbonate and having an X-ray powder diffraction pattern characterized by peaks at 12.57, 13.93, 16.22, 17.16, 17.62, 21.60, 23.05 and 26.25 ± 0.2 2θ values.

In accordance with still another embodiment of the invention, there is provided a process for preparing the crystalline Form IX of temazepam by slow evaporation of a saturated solution of temazepam in dimethyl carbonate.

In accordance with yet another embodiment of the invention, there is provided a crystalline Form X of temazepam having an X-ray powder diffraction pattern characterized by peaks at 13.04, 18.55, 21.42, 23.86 and 26.95 ± 0.2 2θ values.

In accordance with still another embodiment of the invention, there is provided a process for preparing the crystalline Form X of temazepam, the process comprising the steps of dissolving temazepam either crystalline or amorphous in a solvent medium at reflux temperature, subsequently adding of an anti solvent and isolating temazepam Form X.

In accordance with yet another embodiment of the invention, there is provided a process for preparing the crystalline Form X of temazepam, the process comprising the steps of hydrolyzing of O–acetyl derivative of temazepam in presence of a base and an organic solvent, adjusting pH to neutral, seeding with Form X of temazepam, subsequently cooling the resultant and isolating temazepam Form X.

In accordance with yet another embodiment of the invention, there is provided an amorphous Form of temazepam characterized by X-ray powder diffraction pattern as depicted in Figure 31 and substantially similar Infra Red (IR) absorption spectrum as depicted in Figure 32.

In accordance with yet another embodiment of the invention, there is provided a process for preparing the amorphous Form of temazepam, the process comprising the steps of hydrolyzing the O–acetyl derivative of temazepam in presence of an acid and a an organic solvent followed by extracting the product in dichloromethane and water, distilling dichloromethane solvent from the resultant and isolating amorphous form of temazepam.

In accordance with an alternate embodiment of the invention, there is provided a process for preparing an amorphous Form of temazepam by heating crystalline Form IV or Form VII or by contacting Form IV in 90 % relative humidity for several days.

In accordance with yet another alternate embodiment of the invention, there is provided a process for preparing crystalline Form V of temazepam comprising of

slurring Form I or amorphous Form of temazepam or amorphous Form in diethyl ether or heptanes or by heating amorphous temazepam.

In accordance with still another alternate embodiment of the invention, there is provided a process for preparing crystalline Form VI of temazepam comprising of slurring Form I temazepam or amorphous Form in diethyl ether or heptanes or by heating temazepam Form I.

Brief Description of the Drawings

Further objects of the present invention together with additional features contributing thereto and advantages accruing there from will be apparent from the following description of preferred embodiments of the invention which are shown in the accompanying drawing figures, wherein:

Figure 1 shows the X-ray powder diffraction pattern of Form I of temazepam.

Figure 2 shows the DSC of Form I of temazepam.

Figure 3 shows the TGA of Form I of temazepam.

Figure 4 shows the X-ray powder diffraction pattern of Form II of temazepam.

Figure 5 shows the DSC of Form II of temazepam.

Figure 6 shows the TGA of Form II of temazepam.

Figure 7 shows the X-ray powder diffraction pattern of Form III of temazepam.

Figure 8 shows the DSC of Form III of temazepam.

Figure 9 shows the TGA of Form III of temazepam.

Figure 10 shows the X-ray powder diffraction pattern of Form IV of temazepam.

Figure 11 shows the DSC of Form IV of temazepam.

Figure 12 shows the TGA of Form IV of temazepam.

Figure 13 shows the X-ray powder diffraction pattern of Form V of temazepam.

Figure 14 shows the DSC of Form V of temazepam.

Figure 15 shows the TGA of Form V of temazepam.

Figure 16 shows the X-ray powder diffraction pattern of Form VI of temazepam.

Figure 17 shows the DSC of Form VI of temazepam.

Figure 18 shows the TGA of Form VI of temazepam.

Figure 19 shows the X-ray powder diffraction pattern of Form VII of temazepam.

Figure 20 shows the DSC of Form VII of temazepam.

Figure 21 shows the TGA of Form VII of temazepam.

Figure 22 shows the X-ray powder diffraction pattern of Form VIII of temazepam.

Figure 23 shows the DSC of Form VIII of temazepam.

Figure 24 shows the TGA of Form VIII of temazepam.

Figure 25 shows the X-ray powder diffraction pattern of Form IX of temazepam.

Figure 26 shows the DSC of Form IX of temazepam.

Figure 27 shows the TGA of Form IX of temazepam.

Figure 28 shows the X-ray powder diffraction pattern of Form X of temazepam.

Figure 29 shows the DSC of Form X of temazepam.

Figure 30 shows the TGA of Form X of temazepam.

Figure 31 shows the X-ray powder diffraction pattern of amorphous Form of temazepam.

Figure 32 shows the Fourier transform infrared (FTIR) of amorphous Form of temazepam.

Detailed Description of the Invention

While this specification concludes with claims particularly pointing out and distinctly claiming that, which is regarded as the invention, it is anticipated that the invention can be more readily understood through reading the following detailed description of the invention and study of the included examples.

The present invention discloses crystalline polymorphic forms of temazepam Form I, Form II, Form III, Form IV, Form V, Form VI, Form VII, Form VIII, Form IX and Form X which may exist as solvate or hydrate forms. In addition, the present invention discloses an amorphous Form of temazepam. The said polymorphic forms differ from each other in their physical properties, spectral data and method of preparation. Furthermore, the polymorphic forms of temazepam are characterized by their X-ray powder diffraction patterns, Thermo Gravimetric Analysis (TGA) and/or by infrared absorption spectrum (IR).

Powder X-ray Diffraction (PXRD)

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

Differential Scanning Calorimetry (DSC)

The DSC measurements were carried out on Mettler Toledo 822 Star^e and *TA Q1000* of TA instruments. The experiments were performed at a heating rate of 10.0°C/min over a temperature range of 30°C-300°C purging with nitrogen at a flow rate of 50ml/min. Standard aluminum crucibles covered by lids with three pin holes were used.

Thermo gravimetric Analysis (TGA)

TGA was recorded using the instrument Mettler Toledo TGA/SDTA 851^e and *TA Q5000* of TA instruments. The experiments were performed at a heating rate of 10.0 °C/min over a temperature range of 30°C-300°C purging with nitrogen at a flow rate of 20ml/min and 25ml/min.

Infrared spectroscopy

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

Karl-Fisher

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

The crystalline Form I of temazepam is characterized by powder X-ray diffraction pattern as shown in Figure 1 with peaks at 6.67, 6.94, 10.77, 11.40, 12.10, 12.59, 13.34, 13.79, 16.11, 16.57, 16.94, 17.39, 18.13, 19.40, 20.27, 21.55, 22.30, 22.88, 23.53, 23.89, 24.34, 25.25, 25.82, 26.64, 27.01, 27.69, 28.20, 29.01, 30.11, 30.40, 30.97, 32.49 and 34.15 ± 0.2 2θ values.

The crystalline Form I of temazepam is further characterized by DSC with two endothermic peaks; first at an extrapolated onset temperature ranging from 70 to 110°C attributed to desolvation, which is identified with peak at 106°C (maxima), and a second at 139°C corresponding to complete melting of the product as shown in Figure 2. The crystalline temazepam Form I is a hydrate with water content of typically ranging approx. 1-4% by weight, preferably 1.5-2.5%, which is analyzed by

TGA as shown in Figure 3 and moisture content of 1-3% by weight determined by KF method.

The present invention provides a process for the preparation of crystalline Form I of temazepam, the process comprising the steps of:

(a) hydrolyzing of *O*–acetyl derivative temazepam in presence of a base and a suitable solvent,

(b) adjusting pH to neutral;

(c) cooling to 15-20°C followed by addition of water as an anti solvent; and

(d) isolating said temazepam Form I

According to an exemplary process of the invention, the *O*–acetyl derivative of temazepam is hydrolyzed in a solvent such as methanol at basic pH *i.e.* pH 11-11.5 using KOH or NaOH followed by neutralization with acetic acid or hydrochloric acid at reflux temperature. The resulting solution is slowly cooled to 15-20°C and water is added resulting in formation of crystalline Form I of temazepam.

According to an alternate embodiment of the invention, crystalline Form I of temazepam is prepared by storing the crystalline Form IV of temazepam in 90% relative humidity for several days.

The crystalline Form II of temazepam is characterized by powder X-ray diffraction pattern as shown in Figure 4 with peaks at 6.34, 11.74, 12.41, 13.11, 13.55, 13.82, 14.04, 16.05, 16.72, 16.94, 17.09, 17.42, 17.90, 20.18, 20.75, 21.49, 21.95, 22.70, 23.54, 24.16, 24.73, 24.89, 25.40, 25.61, 25.99, 27.02, 27.25, 28.25, 28.55, 28.85, 29.77, 30.56, 31.84, 32.98, 33.77, 34.12, 34.57, 35.58, 35.95, 37.37, 37.75, 39.20, 40.03, 41.61 and 46.70 ± 0.2 2θ values.

According to the invention, the crystalline Form II of temazepam is further characterized by DSC with two melting endothermic peaks; first at an extrapolated onset temperature ranging from 75 to 105°C attributed to desolvation, which is identified with a peak at 97°C (maxima), and a second at 124°C corresponding to complete melting of the product. According to an exemplary embodiment, the crystalline Form II of temazepam is a dioxane solvate with dioxane content of 7-13%, preferably 8-11% which is analyzed by TGA as shown in Figure 6 and moisture content typically ranging from approx. 0.1 - 0.4% by weight supported by Karl-Fisher (KF) method. Preferably, the Form II of temazepam is a hemi-dioxane solvate.

In addition, the present invention provides a process for preparing crystalline Form II of temazepam comprising the steps of contacting a solution of temazepam in a solvent by slow/fast crystallization, slurry or by anti-solvent method. The solvents used for crystallization are preferably 1,4-dioxane, isopropyl ether (IPE) or mixtures thereof.

The crystalline Form III of temazepam is characterized by powder X-ray diffraction pattern as shown in Figure 7 with peaks at 7.05, 12.06, 15.08, 16.64, 16.95, 17.98, 18.80, 20.09, 21.24, 22.21, 22.36, 23.27, 24.01, 24.86, 25.85, 26.44, 27.86, 28.92, 29.56, 30.32 and 36.43 ± 0.2 2θ values.

The crystalline Form III of temazepam is further characterized by DSC as shown in Figure 8 with a melting endothermic peak at 124.93°C and TGA shows no significant weight loss as depicted in Figure 9. The water content determined by the KF method is 0.5 %. Preferably, the Form III of temazepam is an anhydrate form.

The present invention further provides a process for the preparation of crystalline Form III of temazepam comprising the steps of heating crystalline Form II of temazepam and recovering the crystalline Form III of temazepam.

The crystalline Form IV of temazepam is characterized by powder X-ray diffraction pattern as shown in Figure 10 with peaks at 5.55, 7.41, 8.48, 9.95, 11.06, 11.87, 12.25, 12.98, 14.94, 16.05, 16.79, 17.35, 18.91, 19.30, 20.04, 20.55, 21.71, 22.30, 22.73, 23.42, 23.72, 24.05, 25.01, 25.86, 26.23, 26.53, 27.54, 28.79, 29.52, 29.85, 30.22, 31.89, 33.28, 33.63, 33.93, 34.39 and 35.68 ± 0.2 2θ values.

The crystalline Form IV of temazepam, is further characterized by DSC as shown in Figure 11, two melting endothermic peaks at about 78.27°C and 122.45°C. The crystalline Form II of temazepam is a methanol solvate with methanol content of 6-12%, preferably 7-10% which is analyzed by TGA as shown in Figure 12 and moisture content typically ranging from approx. 0.1 - 0.4% by weight supported by KF method. Preferably, the Form IV of temazepam is a mono-methanolate solvate. (The water content determined by the KF method is 0.1 %).

The present invention additionally provides a process for the preparation of the crystalline Form IV of temazepam comprising the steps of:

(a) hydrolyzing the O–acetyl derivative of temazepam in presence of base and a suitable solvent;

(b) adjusting pH to acidic;

(c) cooling to 15-20°C; and

(d) isolating Temazepam Form IV

In accordance with an exemplary process, the *O*–acetyl derivative of temazepam is hydrolyzed in a solvent such as methanol using KOH or NaOH followed by neutralization with acetic acid or hydrochloric acid at reflux temperature. The resulting solution is cooled rapidly to 15-20°C in 10-15 min and recovering the crystalline Form IV of temazepam.

According to the invention, the crystalline Form V of temazepam is characterized by powder X-ray diffraction pattern as shown in Figure 13 with peaks at 5.42, 7.50, 8.22, 8.47, 10.18, 10.81, 11.27, 11.67, 13.13, 13.86, 14.27, 15.01, 15.54, 16.25, 16.93, 17.79, 18.00, 18.75, 19.70, 20.36, 21.16, 21.69, 22.07, 22.30, 22.69, 23.78, 24.21, 24.74, 24.98, 25.36, 26.07, 26.40, 26.69, 27.95, 28.43, 30.82, 32.46 and 33.11 ± 0.2 2θ values.

The crystalline Form V of temazepam is further characterized by DSC as shown in Figure 14, which shows an endothermic peak at 124.55°C and TGA shows no significant weight loss as depicted in Figure 15. The water content determined by the KF method is less than 1%. Preferably, the Form V of temazepam is an anhydrate form.

The present invention also provides a process for the preparation of crystalline Form V of temazepam comprising the steps of:

(a) hydrolyzing the *O*–acetyl derivative temazepam in presence of a base and a suitable solvent;

(b) adjusting pH to acidic;

(c) cooling to 15-20°C followed by addition of water as an anti solvent; and

(d) isolating Form V of temazepam.

According to an exemplary process, the *O*–acetyl derivative of temazepam is hydrolyzed in a solvent such as methanol at pH 11-11.5 using KOH or NaOH followed by adjusting the pH 2-3 with acetic acid or hydrochloric acid at reflux temperature, cooling slowly the resulting solution to 15-20°C, subsequently adding water and recovering the crystalline Form V of temazepam.

According to the present invention, the crystalline Form V of temazepam can also be prepared by slurring amorphous form or Form I in diethyl ether or heptane.

According to an alternate process, Form V is prepared by heating the amorphous form of temazepam.

The crystalline Form VI of temazepam is characterized by powder X-ray diffraction pattern as shown in Figure 16 with peaks at 6.90, 7.50, 9.51, 10.03, 10.79, 11.40, 12.77, 13.32, 13.86, 14.41, 15.08, 15.62, 16.04, 17.09, 17.45, 17.86, 18.38, 19.02, 19.57, 20.20, 20.63, 20.90, 21.32, 21.91, 22.84, 23.39, 23.96, 24.40, 24.88, 25.26, 25.77, 26.98, 27.42, 28.13, 28.80, 29.66, 29.96, 30.27, 30.69, 31.54, 32.98, 33.56, 33.81, 34.12, 34.77, 35.16, 37.78, 38.36, 40.49, 41.51, 44.19, 48.04 and 48.97 ± 0.2 2θ values.

The crystalline Form VI of temazepam is further characterized by DSC as shown in Figure 17, which shows endothermic peak at 136.92°C and TGA shows no significant weight loss as depicted in Figure 18. The water content determined by the KF method is 0.2 %. Preferably, the Form VI of temazepam is an anhydrate form.

In addition, the present invention provides a process for the preparation of crystalline Form VI of temazepam comprising the steps of:

(a) hydrolyzing the *O*–acetyl derivative temazepam in presence of base and a suitable solvent;

(b) adjusting pH to neutral;

(c) cooling to 15-20°C followed by addition of water as an anti solvent; and

(d) isolating Form VI of temazepam by drying at 80°C.

According to an exemplary process, the *O*–acetyl derivative of temazepam is hydrolyzed in a solvent such as methanol at pH 11-11.5 using KOH or NaOH followed by neutralization with acetic acid or hydrochloric acid at reflux temperature. The resulting solution is slowly cooled to 15-20°C and water was added. The obtained solid is dried at 80°C under vacuum for 48 hr and recovering crystalline Form VI of temazepam.

According to an alternate embodiment of the invention, the crystalline Form VI of temazepam can also be prepared by slurring the amorphous form or Form I in isopropyl ether. Another alternate method of preparing Form VI is by heating crystalline Form I.

The crystalline Form VII of temazepam is characterized by powder X-ray diffraction pattern as shown in Figure 19 with peaks at 8.08, 10.03, 10.28, 11.85, 12.13, 14.11, 14.46, 15.78, 16.57, 16.82, 17.18, 17.71, 19.88, 20.09, 20.38, 20.72,

21.21, 22.14, 23.10, 23.46, 23.76, 24.21, 24.65, 25.46, 26.24, 27.04, 27.36, 27.96, 28.64, 28.87, 29.11, 29.29, 30.57, 31.00, 31.27, 31.79, 31.97, 32.26, 32.90, 33.22, 34.42, 35.82, 36.33, 36.61, 37.29, 37.83, 38.37, 40.21, 40.85, 41.12, 41.69, 42.46 and 44.06 ± 0.2 2θ values.

The crystalline Form VII of temazepam is further characterized by DSC as shown in Figure 20, which shows no desolvation peak but a sharp endothermic peak at 101.69°C due to melting of the product. However, TGA of crystalline Form VII of temazepam shows a two step weight loss ranging 18-22%, preferably 18-20%, attributed to desolvation as shown in Figure 21 Preferably, the Form VII of temazepam is a mono-DMSO solvate. (The water content determined by the KF method is 0.3 %). and moisture content typically ranging from approx. 0.1 - 0.3% by weight supported by KF method.

The present invention further provides a method for the preparation of crystalline Form VII of temazepam comprising the steps of fast evaporation of a saturated solution of temazepam in dimethylsulfoxide.

The crystalline Form VIII of temazepam is characterized by powder X-ray diffraction pattern as shown in Figure 22 with peaks at 6.53, 6.85, 10.70, 11.15, 11.46, 12.54, 13.64, 14.61, 15.96, 16.48, 16.98, 17.36, 17.58, 17.93, 18.28, 18.85, 19.31, 20.07, 20.49, 20.83, 21.80, 22.08, 22.56, 23.21, 23.74, 21.14, 24.56, 25.51, 26.30, 26.72, 27.75, 28.54, 29.01, 29.62, 30.32, 30.74, 31.45, 32.43, 32.78, 33.66, 34.08, 39.33 and 41.48 ± 0.2 2θ values.

The crystalline Form VIII of temazepam is further characterized by DSC as shown in Figure 23, which shows three broad endothermic peaks; first at an extrapolated onset temperature ranging from 35 to 80°C attributed to desolvation of surfacial water, which is identified with a peak at 60°C (maxima), and a second at an extrapolated onset temperature ranging from 90 to 130°C attributed to desolvation followed by complete melting of the product, which is identified with a peak at 116.16°C (maxima).

The crystalline Form VIII of temazepam is an ethanediol solvate with ethanediol content of 16-20%, preferably 16-18% which is analyzed by TGA as shown in Figure 24 and moisture content typically ranging from approx. 3- 4% by

weight supported by KF method. Preferably, the Form VIII of temazepam is a mono-ethanediol solvate.

The present invention further provides a process for the preparation of crystalline Form VIII of temazepam comprising the steps of slow evaporation of a saturated solution of temazepam in ethanediol.

The crystalline Form IX of temazepam is characterized by powder X-ray diffraction pattern as shown in Figure 25 with peaks at 4.38, 5.42, 6.34, 7.04, 7.68, 9.76, 11.8, 12.13, 12.57, 12.76, 13.17, 13.93, 14.24, 15.03, 15.59, 16.22, 16.82, 17.16, 17.62, 17.91, 18.14, 18.83, 19.40, 19.81, 20.18, 21.09, 21.60, 21.83, 22.07, 22.59, 23.05, 23.99, 24.61, 25.46, 26.25, 26.69, 27.37, 27.73, 28.17, 28.54, 29.18, 29.67, 30.22, 30.97, 31.89, 32.30, 33.05, 33.97, 34.78, 35.59, 36.40, 43.17 and 47.27 ± 0.2 2θ values.

The crystalline Form IX of temazepam is further characterized by DSC as shown in Figure 26, which shows a broad endothermic peak at 121.35°C; peaks at an extrapolated onset temperature ranging from 55 to 130°C attributed to desolvation followed by complete melting of the product, which is identified with a peak at 121.35°C (maxima). The crystalline Form IX of temazepam is a dimethyl carbonate (DMC) solvate with DMC content of 8-12%, preferably 9-12%, which is analyzed by TGA as shown in Figure 27. Preferably, the Form IX of temazepam is a hemi-DMC solvate.

The present invention also provides a process for the preparation of crystalline Form IX of temazepam comprising the steps of slow evaporation of a saturated solution of temazepam in dimethyl carbonate.

The crystalline Form X of temazepam is characterized by powder X-ray diffraction pattern as shown in Figure 7 with peaks at 13.04, 13.33, 14.50, 14.79, 16.87, 18.55, 18.88, 20.48, 21.42, 21.78, 22.41, 22.93, 23.36, 23.86, 25.40, 26.17, 26.46, 26.95, 27.31, 27.79, 28.15, 29.06, 29.45, 30.40, 33.07 and 43.68 ± 0.2 2θ values.

The crystalline Form X of temazepam is further characterized by DSC as shown in Figure 29 with a melting endothermic peak at 158.97°C and TGA shows no significant weight loss as depicted in Figure 30. Further, the water content determined

by the KF method is less than 0.5 %. Preferably, the Form X of temazepam is an anhydrate form.

The present invention also provides a method for the preparation of crystalline Form X of temazepam comprising the steps of:

(a) dissolving temazepam either crystalline or amorphous in a solvent medium at reflux temperature,

(b) addition of an anti solvent and

(c) isolating Form X of temazepam.

According to the invention, the crystalline or amorphous temazepam is dissolved in a solvent system selected from the group comprising alcohols, esters, chlorinated solvents, lower aliphatic ketones, nitriles, amides at reflux temperature followed by addition of a second solvent as an antisolvent such as hydrocarbons, ethers, water or mixtures there of at same temperature. After stirring the solution for 15-30 min at same temperature, solid is precipitated out. The resulting slurry is slowly cooled to 5-10°C. The solid obtained is filtered, dried at 80°C under vacuum for 24 hr and recovered to obtain the crystalline Form X of temazepam.

The crystalline Form X of temazepam can also be prepared by adding the seeds of Form X during hydrolysis of *O*–acetyl derivative of temazepam comprising the steps of:

(a) hydrolyzing of the *O*–acetyl derivative of temazepam in presence of a base and an organic solvent and adjusting pH to neutral;

(b) seeding with Form X of temazepam;

(c) cooling the resultant and isolating Form X of temazepam.

The amorphous form of temazepam is characterized by powder X-ray diffraction pattern as shown in Figure 31 and FTIR as shown in Figure 32. The amorphous form contains the water up to approximately 1.3 % by weight determined by the KF method.

The present invention also provides the preparation of amorphous form of temazepam comprising the steps of:

(a) hydrolyzing the *O*–acetyl derivative of temazepam in presence of an acid and a suitable solvent,

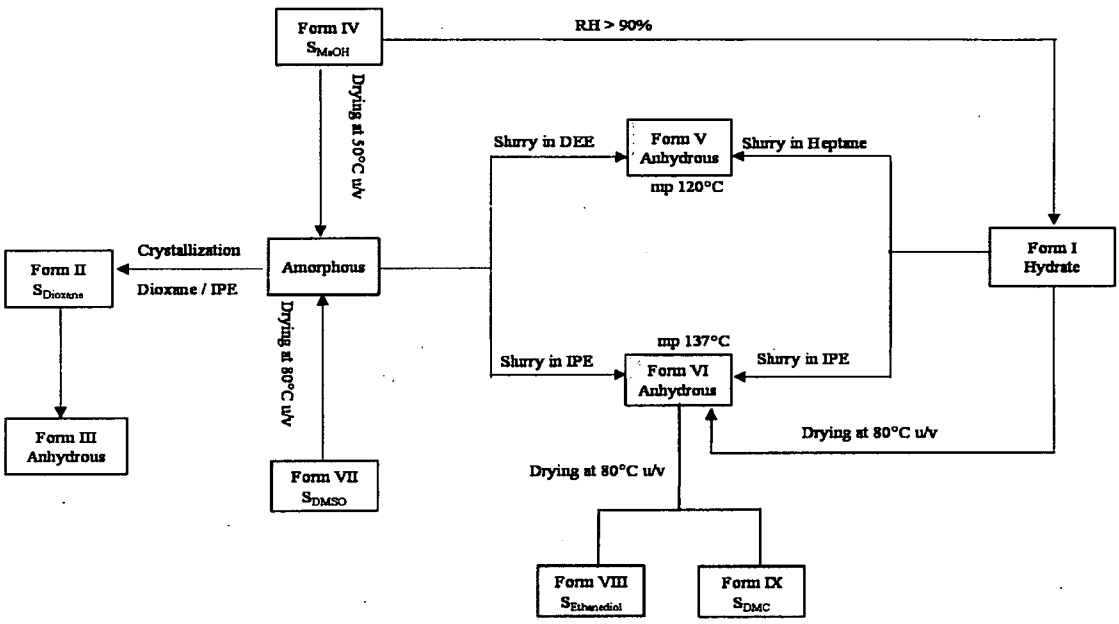
(b) extracting the product in dichloromethane and water,

(c) isolating amorphous form of temazepam by complete distillation of dichloromethane

The *O*–acetyl derivative of temazepam is hydrolyzed in a solvent such as 1,4-dioxane in acidic condition using hydrochloric acid or acetic acid etc. The solid isolated after hydrolysis is extracted in dichloromethane (DCM)/water followed by removal of the solvent and recovering the amorphous form of temazepam.

According to an alternate process, the amorphous form of temazepam is prepared by heating the crystalline Form IV or Form VII of temazepam.

According to an embodiment of the present invention, each form is isolated in pure form as depicted in Scheme 1. Further the transformation kinetics of various forms are described hereafter:



Scheme – 1

The Form I (Hydrate) can be prepared from Form IV (MeOH solvate) by exposing the sample to humidity (RH> 90%) for several days. According to an alternate process, the Form I when kept under drying at 80°C gets converted to stable anhydrous Form VI. Form I is also converted to the anhydrous Form VI by slurring in

IPE for two days at room temperature. Similarly, Form I is converted to the anhydrous Form V by slurring in heptane for two days at room temperature.

The anhydrous Form VI can be prepared by drying the Form VIII (ethanediol solvate) or Form IX (DMC solvate) under vacuum at around 80°C for two days. Alternatively, the anhydrous Form III is prepared by drying the Form II (dioxane solvate) under vacuum at around 80°C for two days. Form X is also prepared by recrystallizing any crystalline or amorphous form of temazepam in MeOH/water or in EtOH/water mixture.

The amorphous form can be prepared by drying the Form IV (MeOH solvate) or Form VII (DMSO solvate) under vacuum at around 50-80°C for two days. Amorphous form is also converted to anhydrous Form V or Form VI by slurring in DEE or IPE for two days at room temperature respectively. The amorphous form is converted to Form II (dioxane solvate) by crystallization from dioxane/IPE mixture at 0-5°C.

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

Example 1

Preparation of amorphous form of temazepam

10g of the *O*-acetyl temazepam is suspended in 1, 4-dioxane (220 ml) at 25-30°C and stir for 10 minutes. To this slurry hydrochloric acid (2.9 ml) added at 25-30°C. The light yellow colored suspension is further stirred for 17 hrs at 25-30°C. The solid obtained was filtered and suspended in dichloromethane (50 ml) at 25-30°C. To this suspension chilled water (20 ml) was added and stirred for 10 min to get a clear solution. The organic layer is separated and concentrated under vacuum at 35-40°C to dryness. The solid obtained was filtered and identified as amorphous form of temazepam.

Example 2

Preparation of Form I of temazepam by basic hydrolysis

15g of *O*-acetyl temazepam was suspended in methanol (30 ml) at 25-30°C and stirred for 10 minutes. The slurry was heated to reflux at 65-70°C for 15 min. In another flask potassium hydroxide (0.04 g) was dissolved in methanol (20 ml) and added to the reaction mass at 65-70°C. After the complete addition when the solution

becomes clear yellow colored, hydrochloric acid (0.4 ml) was added and stirred for 10 min at 65-70°C. Distilled Mineral Water (DMW) (2.5 ml) was added to it at 65-70°C and then the solution was cooled to 15-20°C followed by stirring for 2 hrs at the same temperature. 8 ml of DMW was added to the clear solution following which the solid was immediately precipitated out. Slurry was further cooled to 0-5°C and stirred for 1 hr. The solid obtained was filtered and identified as crystalline pure Form I of temazepam.

Example 3

Preparation of Form II of Temazepam

1g of temazepam (Amorphous) was dissolved in 1,4-dioxane (4 ml) at 25-30°C and stirred for 10 minutes. In another flask IPE (30 ml) was taken and cooled to 0-5°C. To this the temazepam solution was added slowly and stirred for 1 hr at 0-5°C. The solid obtained was filtered and identified as crystalline Form II of temazepam.

Example 4

Preparation of Form II of temazepam

1g of temazepam (Form VI) was suspended in 1,4-dioxane (5 ml) at 25-30°C and stirred for 10 minutes. This slurry was heated to 70-80°C and stirred for 10 min at same temperature. The hot solution was filtered through cotton to remove any undissolved solid particulate. The clear solution obtained was then transferred to a conical flask and the solvent was evaporated slowly at ambient temperature. The resultant solid obtained was filtered and identified as crystalline Form II of temazepam.

Example 5

Preparation of Form II of temazepam

1g of temazepam (Form VI) was suspended in 1, 4-dioxane (5 ml) at 25-30°C and stirred for 10 minutes. This slurry was heated to 70-80°C and stirred for 10 min at same temperature. The hot solution was filtered through cotton to remove any undissolved solid particulate. The clear solution obtained was then transferred to a Petri dish and the solvent evaporated rapidly at ambient temperature. The resultant solid obtained was filtered and identified as crystalline Form II of temazepam.

Example 6

Preparation of Form III of temazepam by heating Form II of temazepam

1g of temazepam (Form II) was heated to 70-80°C under vacuum in a static dryer for 48 hrs. The solid obtained was identified as crystalline Form III of temazepam.

Example 7

Preparation of Form IV of temazepam by basic hydrolysis

5g of O-acetyl temazepam was suspended in methanol (10 ml) at 25-30°C and stirred for 10 minutes. The slurry was heated to reflux at 65-70°C for 15 min. In another flask potassium hydroxide (0.04 g) was dissolved in methanol 10 ml) and added to the reaction mass at 65-70°C. After the complete addition the solution becomes clear and yellow colored. To this clear solution acetic acid (0.1 ml) was added and stirred for 10 min at 65-70°C. Subsequently, DMW r (1.2 ml) was added to the mixture at 65-70°C and the resulting solution was cooled to 15-20°C. The solid precipitated was stirred for 30 min at 0-5°C, filtered and identified as crystalline Form IV of temazepam.

Example 8

Preparation of Form V of temazepam by basic hydrolysis

15g of *O*-acetyl temazepam was suspended in methanol (30 ml) at 25-30°C and stirred for 10 minutes. The slurry was heated to reflux at 65-70°C for 15 min. In another flask potassium hydroxide (0.04 g) was dissolved in methanol (20 ml) and added to the reaction mass at 65-70°C. After the complete addition, the solution becomes clear yellow colored. To the clear solution hydrochloric acid (0.4 ml) was added to adjust the pH between 2-3 and stirred for 10 min at 65-70°C. DM water (2.5 ml) was added to it at 65-70°C and the solution cooled to 15-20°C and, stirred for 2 hrs at same temperature. 8 ml of DMW was added to the clear solution resulting in immediate precipitation of the solid. Slurry was further cooled to 0-5°C and stirred for 1 hr. The solid obtained was filtered and identified as crystalline pure Form V of temazepam.

Example 9

Preparation of Form VI of temazepam by basic hydrolysis

15g of *O*-acetyl temazepam was suspended in methanol (30 ml) at 25-30°C and stirred for 10 minutes. The slurry was heated to reflux at 65-70°C for 15 min. In another flask potassium hydroxide (0.04 g) was dissolved in methanol (20 ml) and added to the reaction mass at 65-70°C. After the complete addition, the solution

becomes clear and yellow colored. To the clear solution hydrochloric acid (0.4 ml) was added and stirred for 10 min at 65-70°C. Subsequently, DM water (2.5 ml) was added to the solution at 65-70°C and the solution was cooled to 15-20°C. The cooled solution was then stirred for 2 hrs at same temperature, 8 ml of DMW was added resulting in immediate precipitation of the solid. Slurry was further cooled to 0-5°C, stirred for 1 hr, filtered and dried at 80°C under vacuum for 48 hr. The product obtained was identified as crystalline pure Form VI of temazepam.

Example 10

Preparation of Form VII of temazepam

1g of temazepam (Form V) was suspended in DMSO (5 ml) at 25-30°C and stirred for 10 minutes. This slurry was heated to 70-80°C and stirred for 10 min at same temperature. The hot solution was filtered through cotton to remove any undissolved solid particulate. The clear solution obtained was then transferred to Petri dish to evaporate the solvent rapidly at ambient temperature. The resultant solid obtained was filtered and identified as crystalline Form VII of temazepam.

Example 11

Preparation of Form VIII of temazepam

1g of temazepam (Form V) was suspended in ethanediol (5 ml) at 25-30°C and stirred for 10 minutes. The slurry so obtained was heated to 70-80°C and stirred for 10 min at same temperature. The hot solution was filtered through cotton to remove any undissolved solid particulate. The clear solution so obtained was then transferred to conical flask and the solvent evaporated slowly at ambient temperature. The solid obtained was filtered and identified as crystalline Form VIII of temazepam.

Example 12

Preparation of Form IX of temazepam

1g of temazepam (amorphous) was suspended in DMC (5 ml) at 25-30°C and stirred for 10 minutes. The slurry was heated to 70-80°C and stirred for 10 min at same temperature. The hot solution was filtered through cotton to remove any undissolved solid particulate. The clear solution obtained was then transferred to Petri dish and the solvent was evaporated rapidly at ambient temperature. The resultant solid obtained was filtered and identified as crystalline Form IX of temazepam.

Example 13

Preparation of Form X of temazepam

1g of temazepam was suspended in indicated solvents at the indicated volumes at 25-30°C and stirred for 10 minutes. The slurry was heated for complete dissolution between 50-80°C followed by addition of an antisolvent and allowed for crystallization. The results obtained are displayed in the next table.

Process	Input	Solvents	Volume ratio	Temperature	Result
Anti solvent	Forms I, II, IV, V, VI, VII, VIII or amorphous	MeOH/Water	2:1	70-80°C	Form X
	Form VI	MeOH/IPE			
	Form VI	MeOH/hexane			
	Form VI	Acetone /Water		50-60°C	
	Form VI	EtOAc/ IPE		70-80°C	
	Form VI	CAN /Water		70-80°C	
	Form VI	DMF/Water		70-80°C	

Example 14

Preparation of Form X of temazepam

15g of *O*-acetyl temazepam was suspended in methanol (30 ml) at 25-30°C and stirred for 10 minutes. The slurry was heated to reflux at 65-70°C for 15 min. In another flask potassium hydroxide (0.12 g) was dissolved in methanol (30 ml) and added to the reaction mass to adjust the pH = 11.1-11.4 and stirred for 10 min at 65-70°C. After the complete addition, the solution becomes clear and slight yellow colored. To this clear solution acetic acid (0.4 ml) was added to adjust the pH = 7-7.1 at 65-70°C. To this neutralized solution DMW (3.6 ml) was added which is then seeded with Form X of temazepam and stirred for 30-40 min at 65-70°C. The slurry was further cooled to 15-20°C and stirred for 1 hr at same temperature. 8 ml of DMW was added to the solution at 15-20°C. The slurry was further cooled to 0-5°C and stirred for 1 hr. The solid obtained was filtered and dried at 80°C under vacuum for 24 hr. The product obtained was identified as crystalline pure Form X of temazepam.

XRD of the sample showed it to be Form X

Example 15

Preparation of Form V of temazepam by Crystallization

1g of temazepam was suspended in indicated solvents at the indicated volumes at 25-30°C and stir for 10 minutes. This slurry is heated for complete dissolution and

allowed for crystallization at room temperature. The results obtained are displayed in the next table.

Process	Input	Solvents	Volume ratio	Temperature	Result
Fast Crystallization	Form V	DMF	1:10	70-80°C	Form V
		DMA	1:10	70-80°C	Form V
Slow Crystallization	Amorphous	Nitromethane	1:10	70-80°C	Form V
Antisolvent method	Form VI	DCM/Pet.Ether	2:3	25-30°C	Form V

Example 16

Slurry, Relative Humidity (RH) and Thermal Stability of temazepam

2g of temazepam was subjected to different crystallization conditions for understanding chemical stability and transformation kinetics of different polymorphs. The results obtained are shown in next table.

Process	Input	Solvents	Volume ratio	Time	Temperature	Result
Slurry conversion	Amorphous or Form I	IPE	1:5	2-3 hr	25-30°C	Form VI
	Amorphous	DEE				Form V
	Form I	Heptane				
Relative Humidity (RH >90%)	Form IV	-	-	2 days	25-30°C	Form I
Heating	Form IV	-	-	1 day	45-50°C	Amorphous
	Form VII	-	-	2 days	75-80°C	Amorphous
	Form II	-	-	3-4 hr	100°C	Form III
	Form I	-	-	2 days	75-80°C	Form VI

Certain modifications and improvements of the disclosed invention will occur to those skilled in the art without departing from the scope of invention, which is limited only by the appended claims.

We Claim:

1. A crystalline Form I of temazepam.

2. The crystalline form according to claim 1, wherein said crystalline Form I is having an X-ray powder diffraction pattern characterized by peaks at 11.40, 12.10, 16.11, 16.57, 21.55, 22.88, and 25.82 ± 0.2 2θ values.

3. The crystalline form according to claim 1, wherein said crystalline Form I is characterized by DSC as depicted in Figure 2 and TGA as depicted in Figure 3.

4. The crystalline form according to claim 1, wherein said crystalline Form I is a hydrate containing 1.61 % of water.

5. A process for preparing the crystalline Form I of temazepam as claimed in claim 1, the process comprising:

(a) hydrolyzing of *O*–acetyl derivative of temazepam in presence of a base and an organic solvent;

(b) adjusting pH to neutral;

(c) cooling the resultant to 15-20°C followed by addition of water as an anti solvent; and

(d) isolating said Form I of temazepam.

6. The process according to claim 5, wherein the base used is sodium hydroxide or potassium hydroxide.

7. A crystalline Form II of temazepam.

8. The crystalline form according to claim 7, wherein said crystalline Form II is having an X-ray powder diffraction pattern characterized by peaks at 6.34, 12.41, 13.11, 14.04, 20.18, 21.95, and 22.70 ± 0.2 2θ values.

9. A process for preparing the crystalline Form II of temazepam according to claim 7, the process comprising contacting a solution of temazepam in a solvent by slow/fast crystallization, slurry or by anti-solvent method.

10. The process according to claim 9, wherein the solvent used is selected from 1,4-dioxane, isopropyl ether or mixture thereof.

11. A crystalline Form III of temazepam.

12. The crystalline form according to claim 11, wherein said crystalline Form III is having an X-ray powder diffraction pattern characterized by peaks at 7.05, 15.08, 16.95, 18.80, 20.09 and 23.27 ± 0.2 2θ values.

13. The crystalline form according to claim 11, wherein said crystalline Form III is characterized by DSC as depicted in Figure 8 and TGA as depicted in Figure 9.

14. A process for preparing the crystalline Form III of temazepam as claimed in claim 11, wherein said crystalline form is obtained by heating crystalline Form II of temazepam.

15. A crystalline Form IV of temazepam.

16. The crystalline form according to claim 15, wherein said crystalline Form IV is having an X-ray powder diffraction pattern characterized by peaks at 7.41, 11.87, 12.98, 14.94, 22.30, 23.42, 23.72, and 24.05 ± 0.2 2θ values.

17. The crystalline form according to claim 15, wherein said crystalline Form IV is characterized by DSC as depicted in Figure 11 and TGA as depicted in Figure 12.

18. The crystalline form according to claim 15, wherein said crystalline Form IV is a methanol solvate having 6-12 % of methanol.

19. A process for preparing the crystalline Form IV of temazepam according to claim 15, the process comprising:

(a) hydrolyzing *O*–acetyl derivative of temazepam in presence of a base and an organic solvent;

(b) cooling the resultant to 15-20°C; and

(c) isolating Form IV of temazepam.

20. A crystalline Form V of temazepam.

21. The crystalline form according to claim 20, wherein said crystalline Form V is having an X-ray powder diffraction pattern characterized by peaks at 5.42, 8.22, 8.47, 10.81, 21.69 and 22.69 ± 0.2 2θ values.

22. The crystalline form according to claim 20, wherein said crystalline Form V is characterized by DSC as depicted in Figure 14 and TGA as depicted in Figure 15.

23. A process for preparing the crystalline Form V of temazepam according to claim 20, the process comprising:

(a) hydrolyzing *O*–acetyl derivative of temazepam in presence of a base and an organic solvent;

(b) adjusting pH to acidic;

(c) cooling the resultant to 15-20°C followed by addition of water as an anti solvent; and

(c) isolating Form V of temazepam.

24. The process according to claim 23, wherein the base used is sodium hydroxide or potassium hydroxide.

25. A crystalline Form VI of temazepam.

26. The crystalline form according to claim 25, wherein said crystalline Form VI is having an X-ray powder diffraction pattern characterized by peaks at 6.90, 9.51, 11.40, 17.09, 17.86, 19.02, 19.57, 20.20, 21.91 24.88, and 26.98 ± 0.2 2θ values.

27. The crystalline form according to claim 25, wherein said crystalline Form VI is characterized by DSC as depicted in Figure 17 and TGA as depicted in Figure 18.

28. A process for preparing the crystalline Form VI of temazepam according to claim 25, the process comprising:

(a) hydrolyzing *O*–acetyl derivative of temazepam in presence of a base and an organic solvent;

(b) adjusting pH to neutral;

(c) cooling the resultant to 15-20°C followed by addition of water as an anti solvent; and

(d) isolating Form VI of temazepam by drying at 80°C.

29. A crystalline Form VII of temazepam.

30. The crystalline form according to claim 29, wherein said crystalline Form VII is having an X-ray powder diffraction pattern characterized by peaks at 8.08, 12.13, 15.78, 19.88, 20.09, 20.38, 20.72, 24.65, 25.46 and 27.36 ± 0.2 2θ values.

31. The crystalline form according to claim 29, wherein said crystalline Form VII is characterized by DSC as depicted in Figure 20 and TGA as depicted in Figure 21.

32. The crystalline form according to claim 29, wherein said crystalline Form VII is a dimethyl sulfoxide solvate having 18-22 % of dimethyl sulfoxide.

33. A process for preparing crystalline Form VII of temazepam according to claim 29, wherein said crystalline form is obtained by fast evaporation of a saturated solution of temazepam in dimethylsulfoxide.

34. A crystalline Form VIII of temazepam.

35. The crystalline form according to claim 34, wherein said crystalline Form VIII is having an X-ray powder diffraction pattern characterized by peaks at 6.53, 10.70, 11.46, 12.54, 16.48, 18.28, 18.85, 19.31, 21.80, 22.56 and 25.51 ± 0.2 2θ values.

36. The crystalline form according to claim 34, wherein said crystalline Form VIII is characterized by DSC as depicted in Figure 23 and TGA as depicted in Figure 24.

37. The crystalline form according to claim 34, wherein said crystalline Form VIII is ethanediol solvate having 16-18 % of ethanediol.

38. A process for preparing the crystalline Form VIII of temazepam according to claim 34, wherein said crystalline form is obtained by slow evaporation of a saturated solution of temazepam in ethanediol.

39. A crystalline Form IX of temazepam.

40. The crystalline form according to claim 39, wherein said crystalline Form IX is having an X-ray powder diffraction pattern characterized by peaks at 12.57, 13.93, 16.22, 17.16, 17.62, 21.60, 23.05, and 26.25 ± 0.2 2θ values.

41. The crystalline form according to claim 39, wherein said crystalline Form IX is characterized by DSC as depicted in Figure 26 and TGA as depicted in Figure 27.

42. The crystalline form according to claim 39, wherein said crystalline Form IX is dimethyl carbonate solvate having 9-12 % of dimethylcarbonate.

43. A process for preparing the crystalline Form IX of temazepam according to claim 39, wherein said crystalline form is obtained by slow evaporation of a saturated solution of temazepam in dimethyl carbonate.

44. A crystalline Form X of temazepam.

45. The crystalline form according to claim 44, wherein said crystalline Form X is having an X-ray powder diffraction pattern characterized by peaks at 13.04, 18.55, 21.42, 23.86 and 26.95 ± 0.2 2θ values.

46. The crystalline form according to claim 44, wherein said crystalline Form X is characterized by DSC as depicted in Figure 29 and TGA as depicted in Figure 30.

47. A process for preparing the crystalline Form X of temazepam according to claim 44, wherein the process comprising the steps of:

(a) dissolving Temazepam either crystalline or amorphous in a solvent medium at reflux temperature;

(b) adding of an anti solvent; and

(c) isolating Temazepam Form X.

48. The process according to claim 47, wherein the solvent used in the process selected from the group consisting of alcohols, esters, chlorinated solvents, lower aliphatic ketones, nitriles and amides. Preferably the solvents used are methanol, ethanol, dichloromethane, acetone, ethylacetate, acetonitrile, DMF and water or mixtures thereof.

49. A process for preparing the crystalline Form X of temazepam according to claim 44, wherein the process comprising the steps of:

(a) hydrolyzing of *O*–acetyl derivative of temazepam in presence of a base and an organic solvent;

(b) adjusting pH to neutral;

(b) seeding with Form X of temazepam; and

(c) cooling the resultant and isolating temazepam Form X.

50. An amorphous Form of temazepam.

51. The amorphous form according to claim 50, wherein said amorphous form is having a substantially similar X-ray powder diffraction pattern as depicted in Figure 31.

52. The amorphous form according to claim 50, wherein said amorphous form is having a substantially similar IR as depicted in Figure 32.

53. A process for preparing the amorphous Form of temazepam as claimed in claim 50, the process comprising:

(a) hydrolyzing of *O*–acetyl derivative of temazepam in presence of an acid and a an organic solvent;

(b) extracting the product in dichloromethane and water;

(c) distilling dichloromethane solvent from the resultant and isolating amorphous form of temazepam.

54. The process according to claim 53, wherein the acid used is hydrochloric acid or acetic acid.

55. A process for preparing an amorphous Form of temazepam comprising heating crystalline Form IV or Form VII obtained according to claim 19 and 28.

56. A process for preparing a crystalline Form I of temazepam comprising, contacting said temazepam Form IV in 90 % relative humidity for several days obtained according to claim 19.

57. A process for preparing a crystalline Form V of temazepam comprising slurring said Form I or amorphous Form of temazepam in diethyl ether or heptanes obtained according to claim 5 and 53 or heating said amorphous temazepam obtained according to claim 53.

58. A process for preparing a crystalline Form VI of temazepam comprising slurring Form I temazepam or amorphous Form in diethyl ether or heptanes obtained according to claim 5 and 53 or heating said temazepam Form I obtained according to claim 5.

Fig. 1

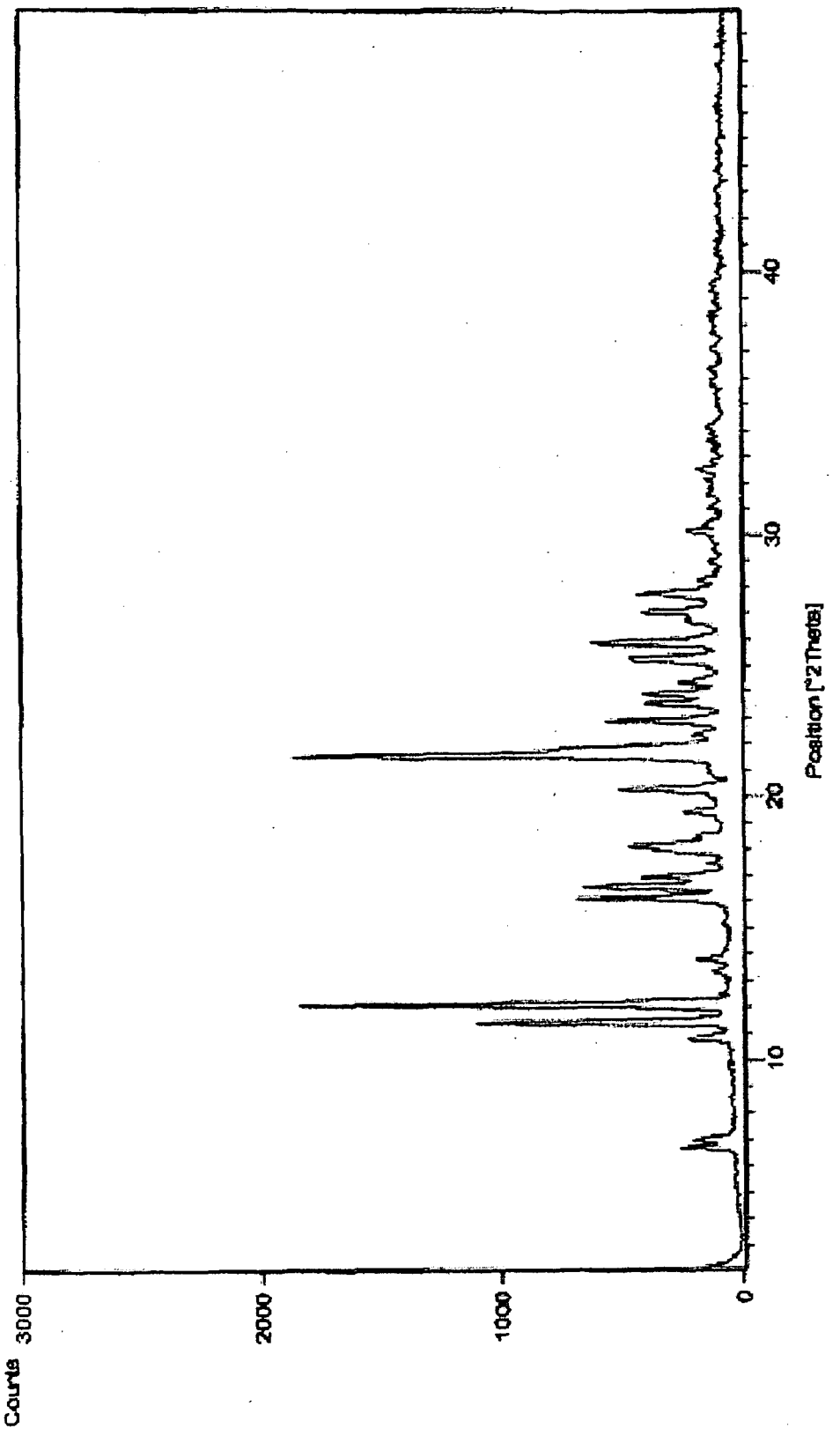


Fig. 2

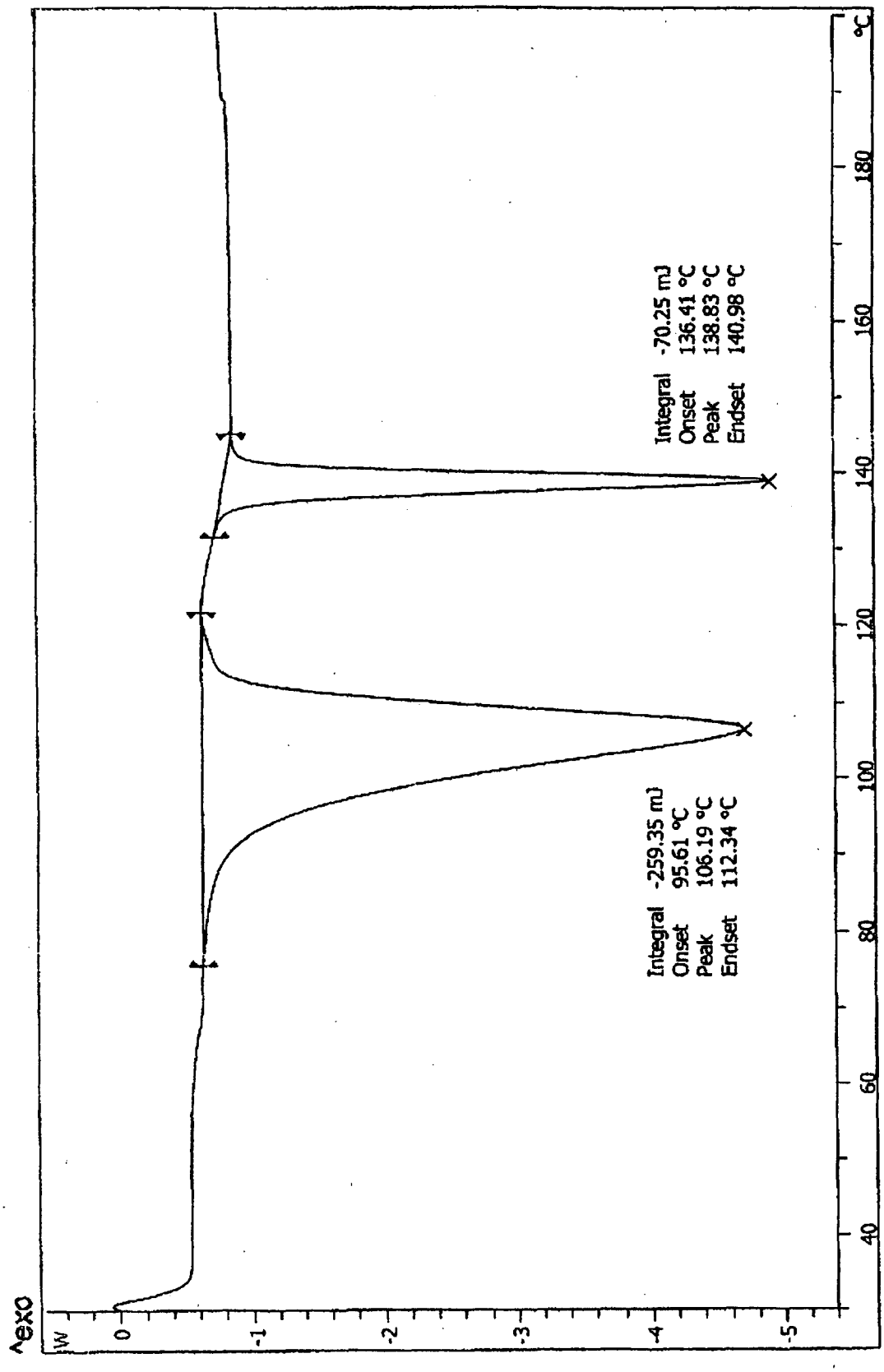

Integral -70.25 mJ
Onset 136.41 °C
Peak 138.83 °C
Endset 140.98 °C
Integral -259.35 mJ
Onset 95.61 °C
Peak 106.19 °C
Endset 112.34 °C
exo
W
°C

Fig. 3

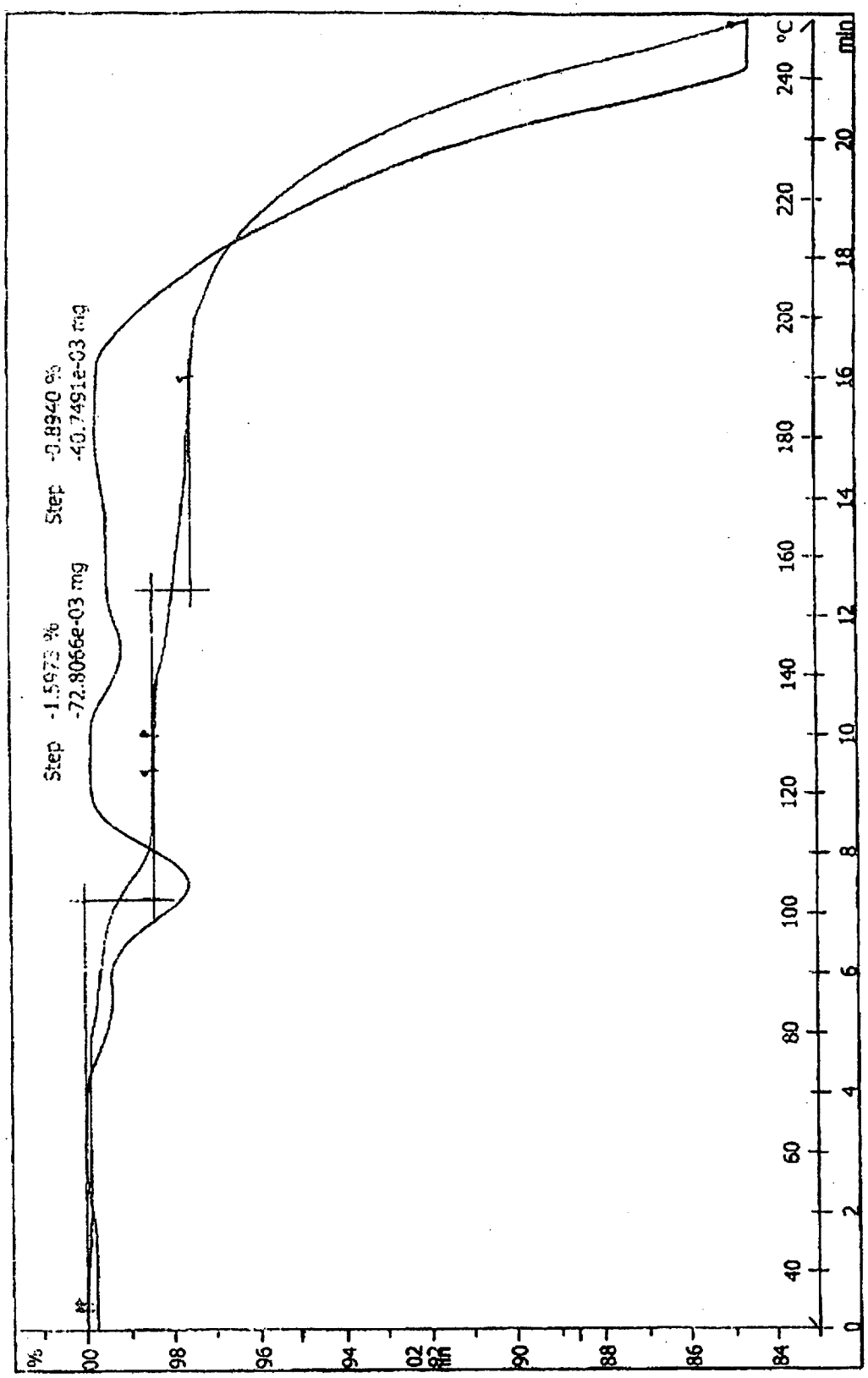


Fig. 4

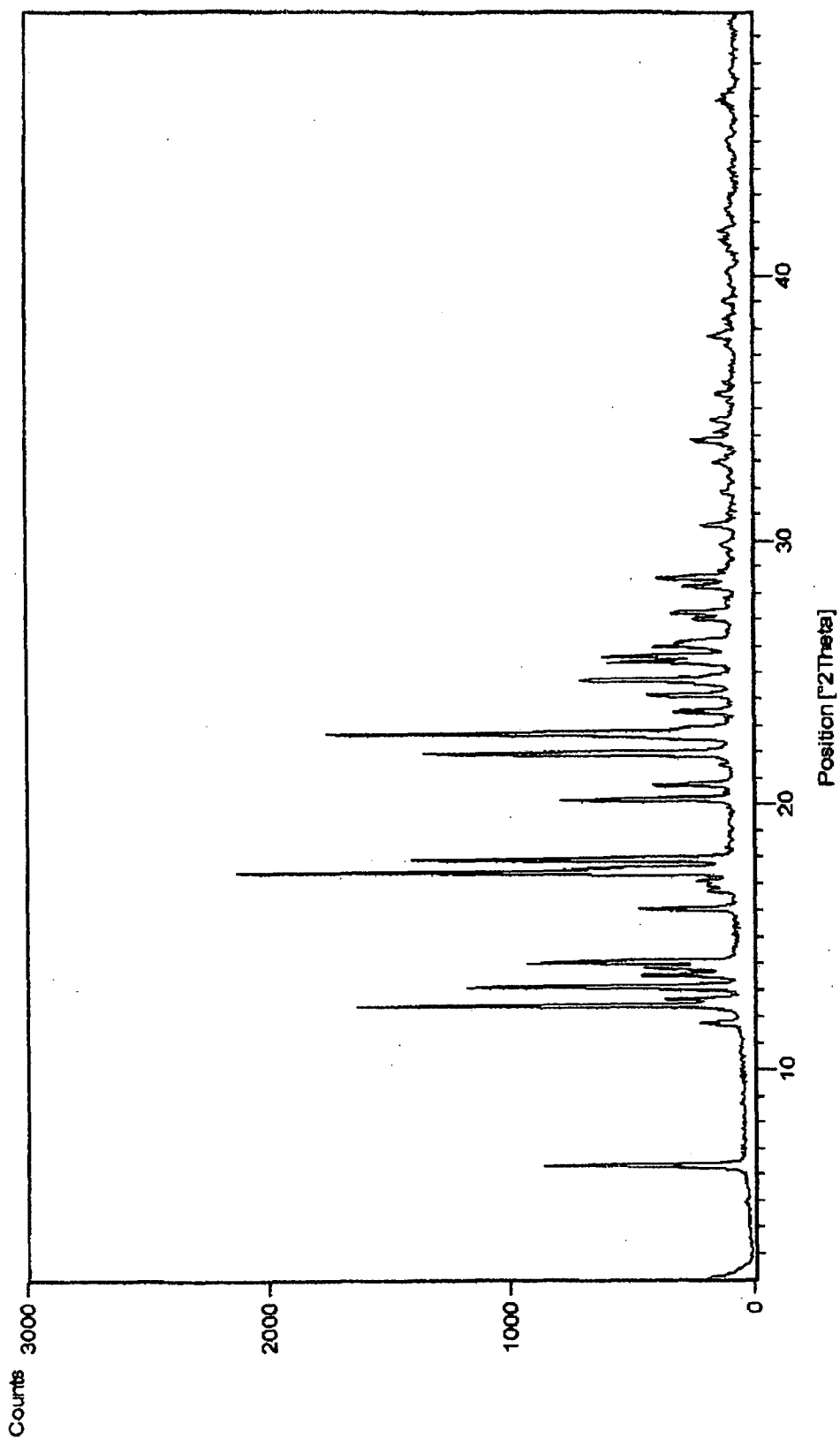


Fig. 5

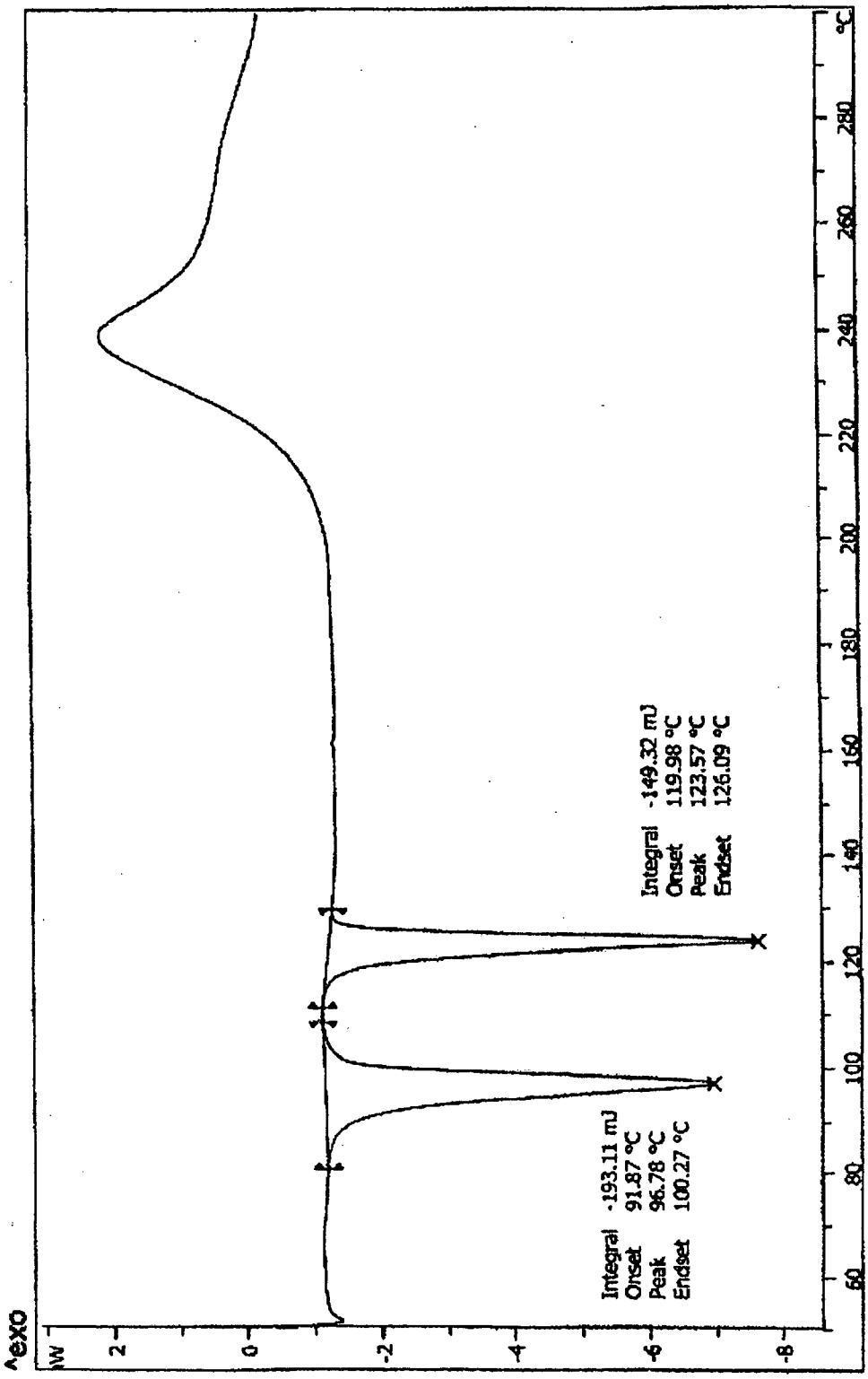

^exo
mW
2
0
-2
-4
-6
-8
60
80
100
120
140
160
180
200
220
240
260
280
°C
Integral -193.11 mJ
Onset 91.87 °C
Peak 96.78 °C
Endset 100.27 °C
Integral -149.32 mJ
Onset 119.98 °C
Peak 123.57 °C
Endset 126.09 °C

Fig. 6

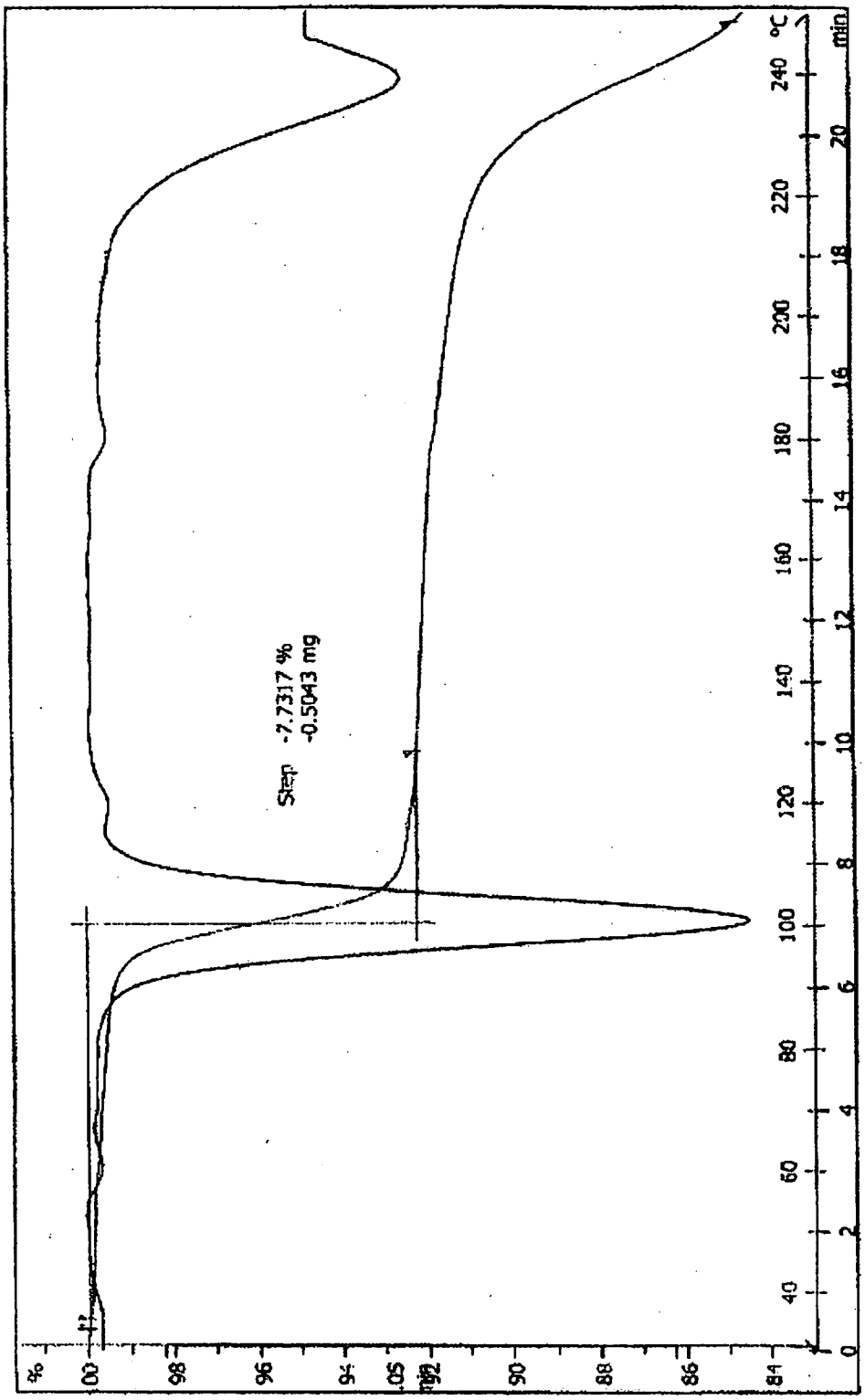


Fig. 7

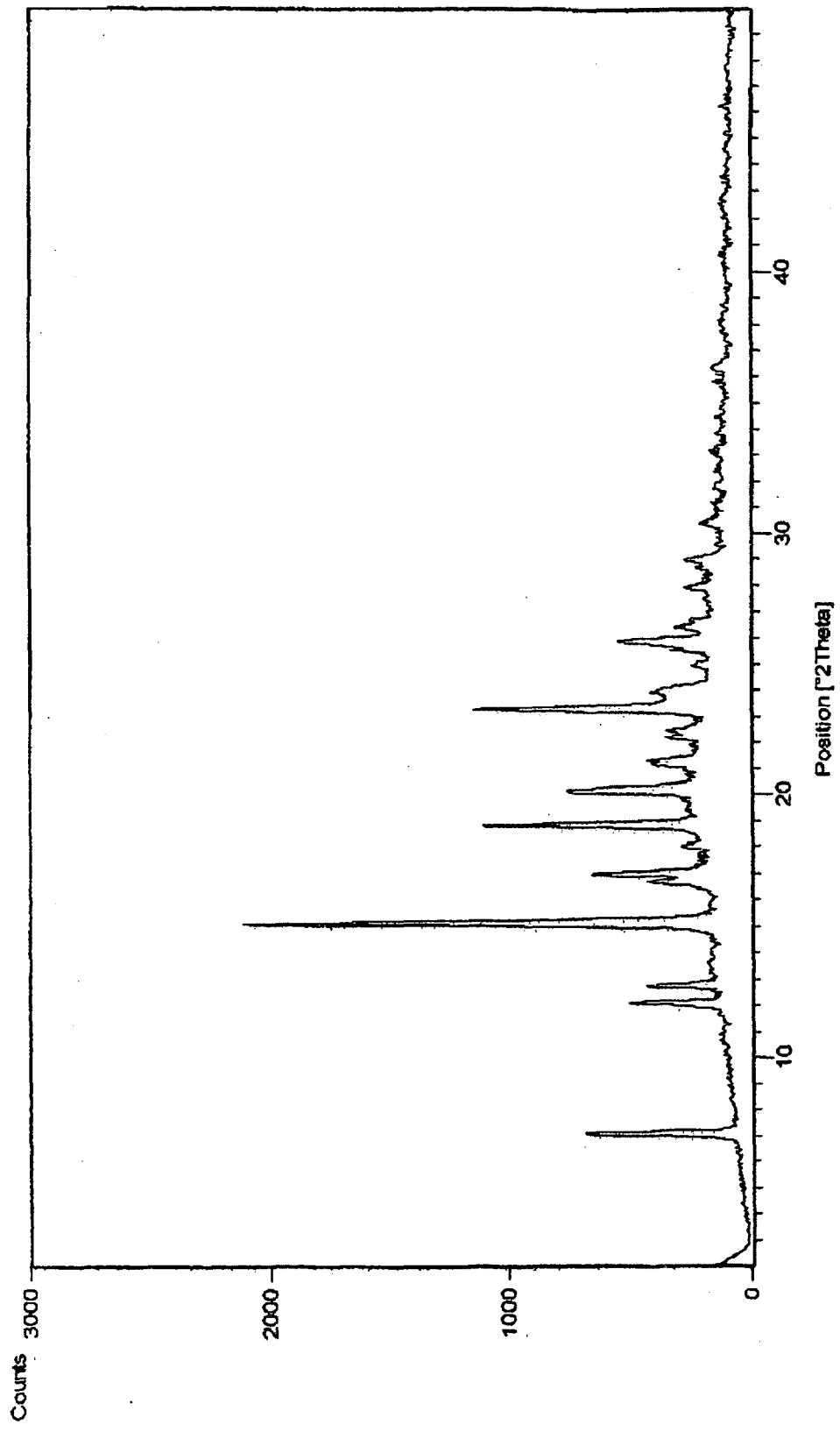
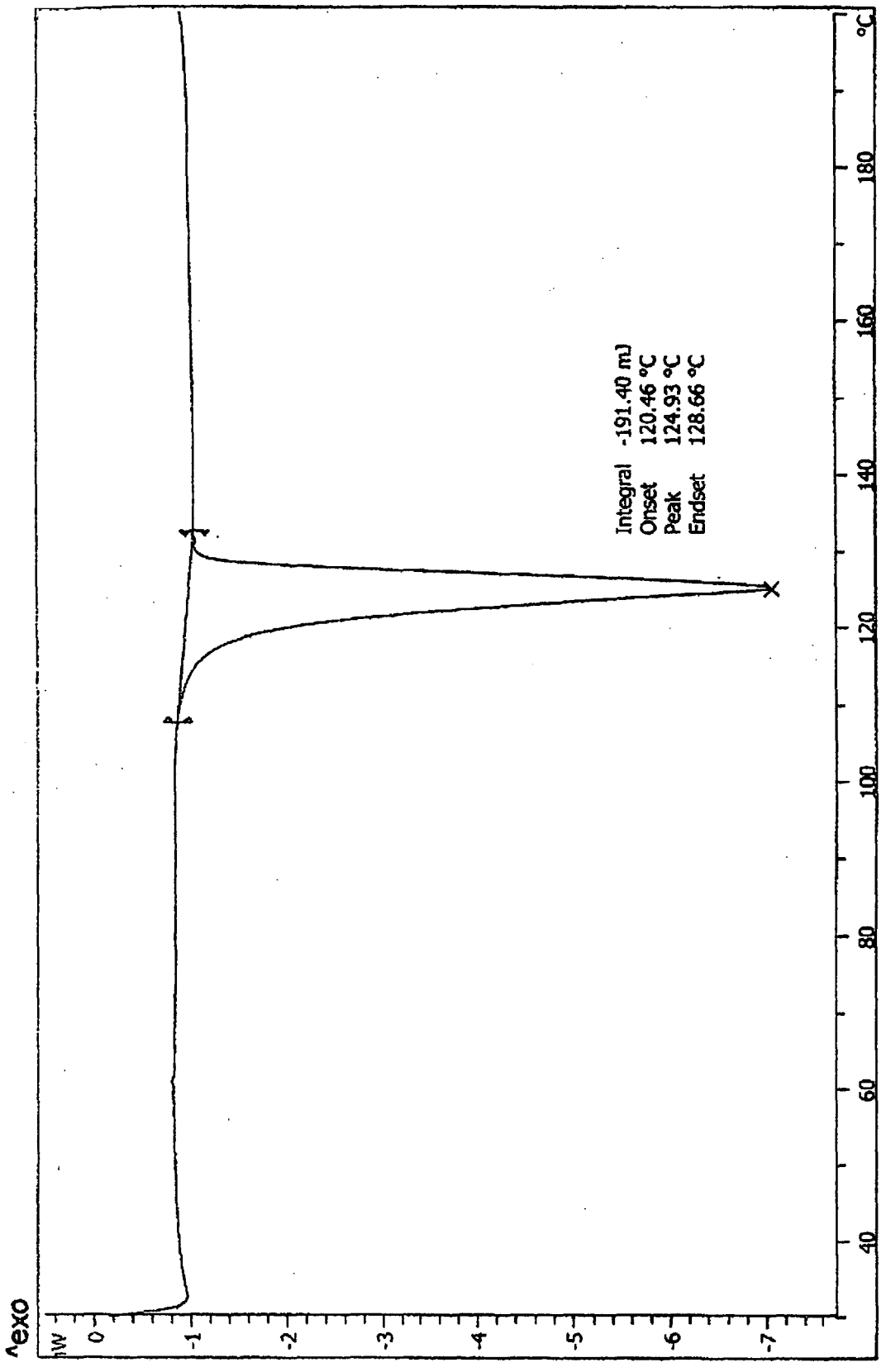


Fig. 8


Integral -191.40 mJ
Onset 120.46 °C
Peak 124.93 °C
Endset 128.66 °C
exo
mW
°C

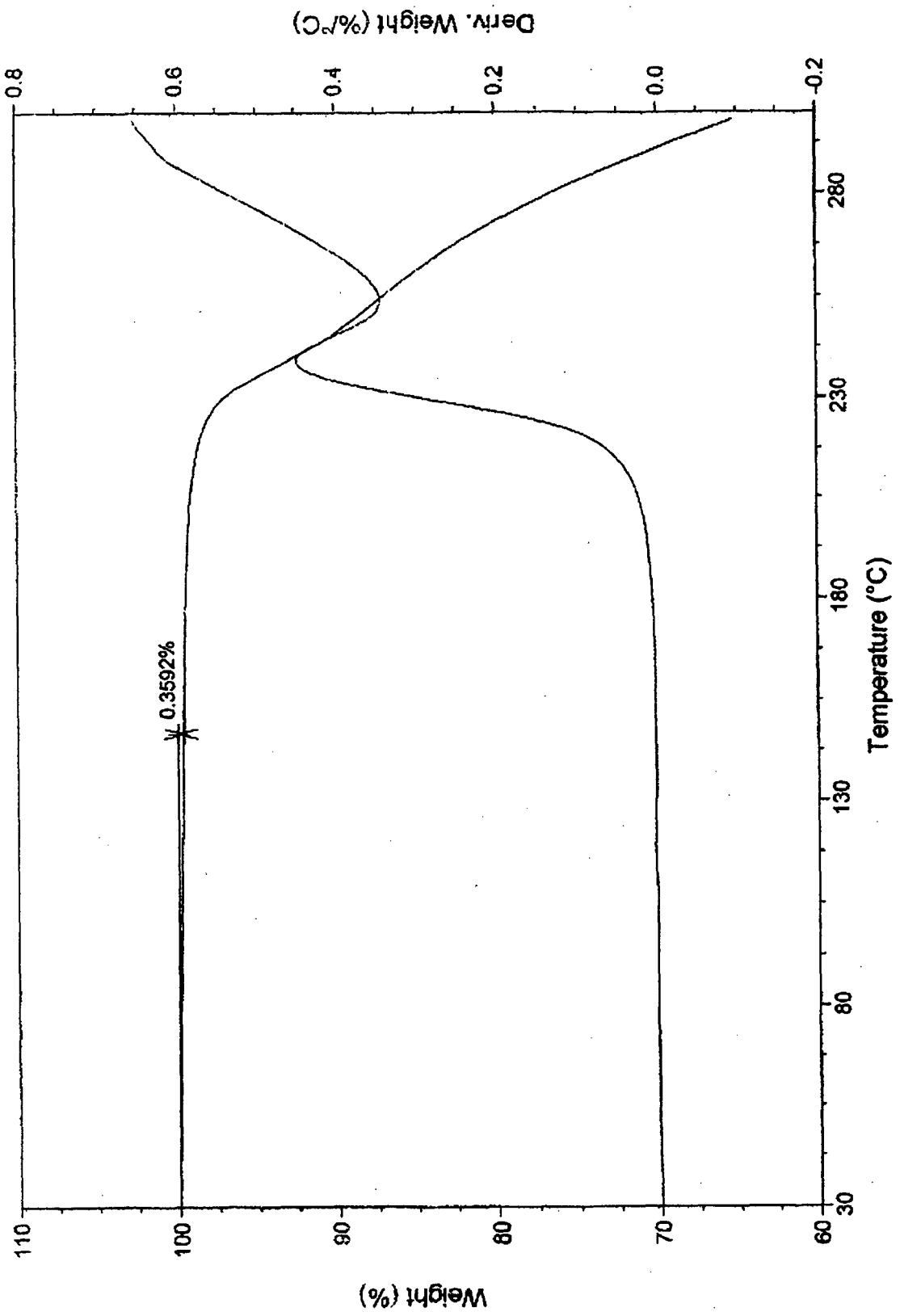

Deriv. Weight (%/°C)
0.8
0.6
0.4
0.2
0.0
-0.2
0.3592%
Weight (%)
110
100
90
80
70
60
Temperature (°C)
30
80
130
180
230
280

Fig. 9

Fig. 10

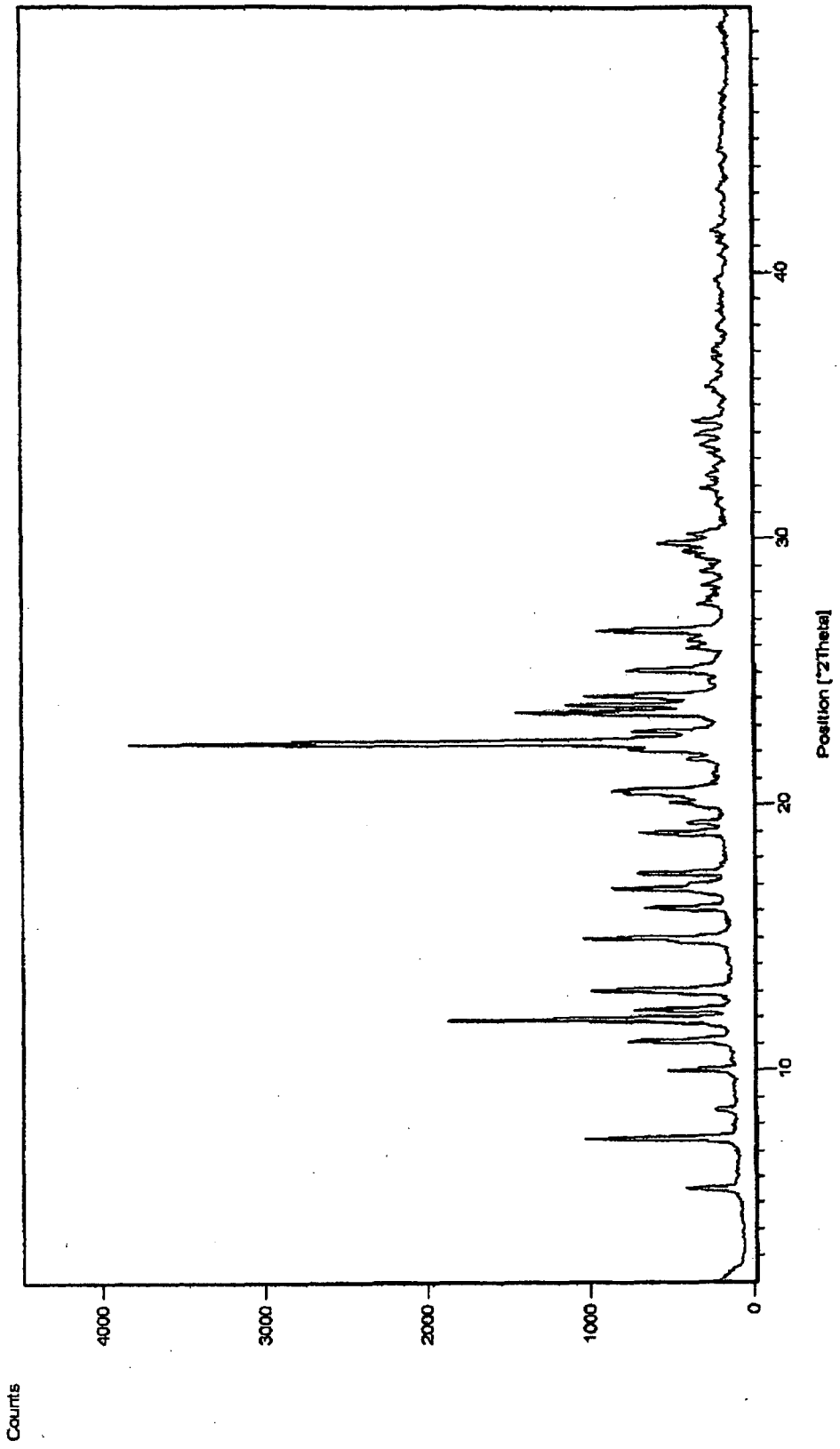


Fig. 11

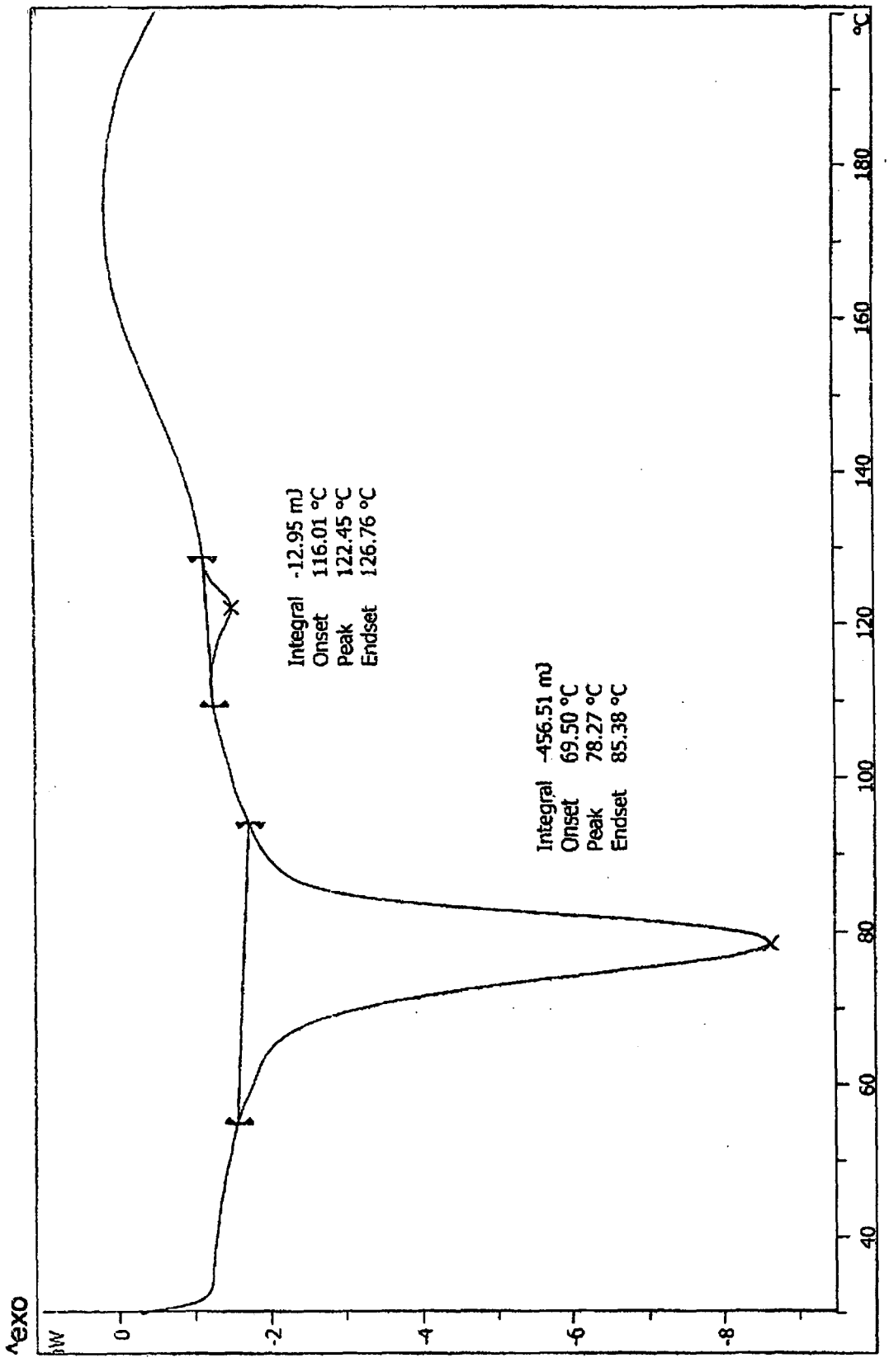

Integral -12.95 mJ
Onset 116.01 °C
Peak 122.45 °C
Endset 126.76 °C
Integral -456.51 mJ
Onset 69.50 °C
Peak 78.27 °C
Endset 85.38 °C
exo
mW
0
-2
-4
-6
-8
40
60
80
100
120
140
160
180
°C

Fig. 12

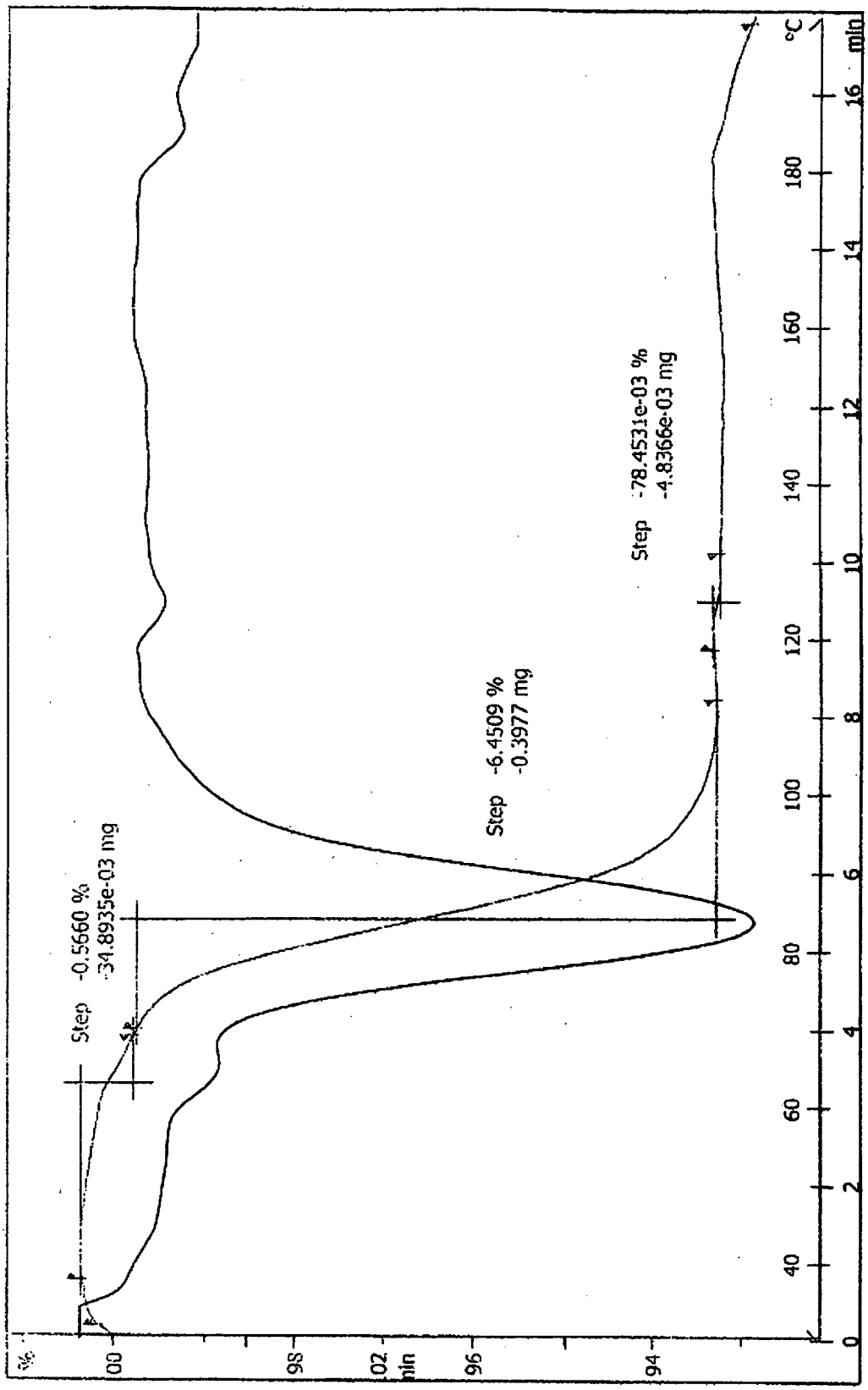

Step -0.5660 %
-34.8935e-03 mg
Step -6.4509 %
-0.3977 mg
Step -78.4531e-03 %
-4.8366e-03 mg
°C
min
%
100
98
96
94
0
40
60
80
100
120
140
160
180
2
4
6
8
10
12
14
16

Fig. 13

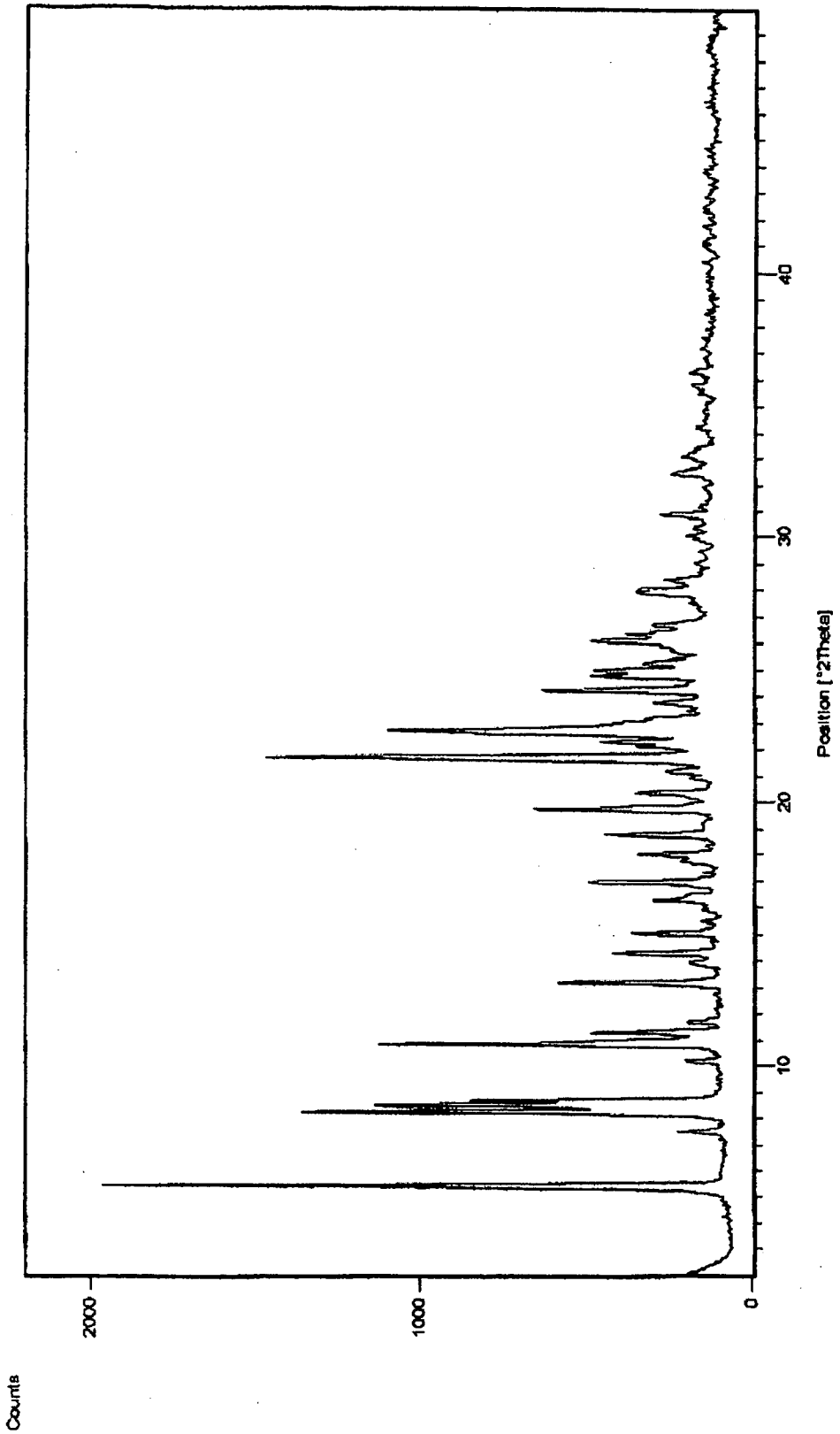
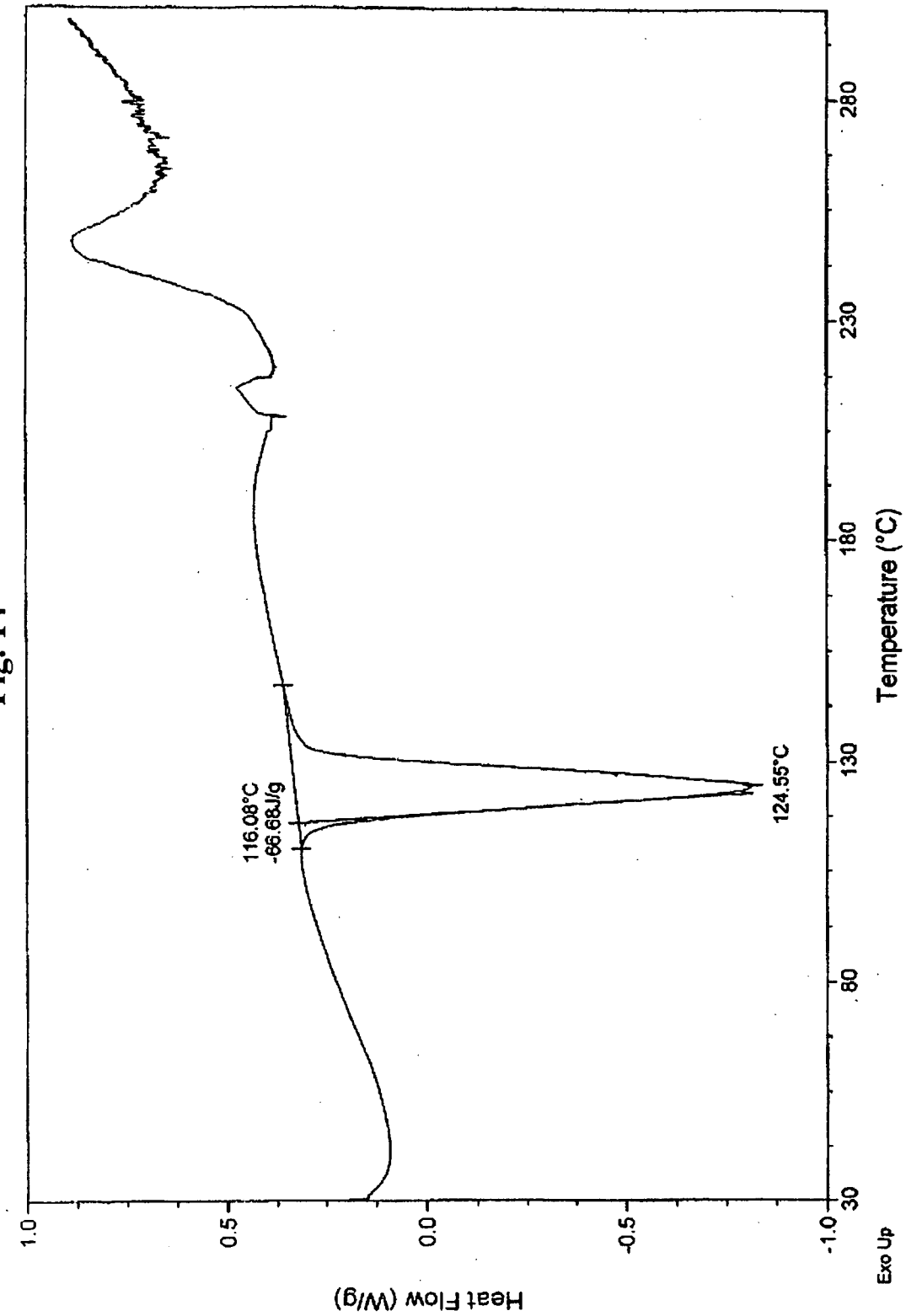


Fig. 14


116.08°C
-66.68J/g
124.55°C
Heat Flow (W/g)
Exo Up
Temperature (°C)
1.0
0.5
0.0
-0.5
-1.0
30
80
130
180
230
280

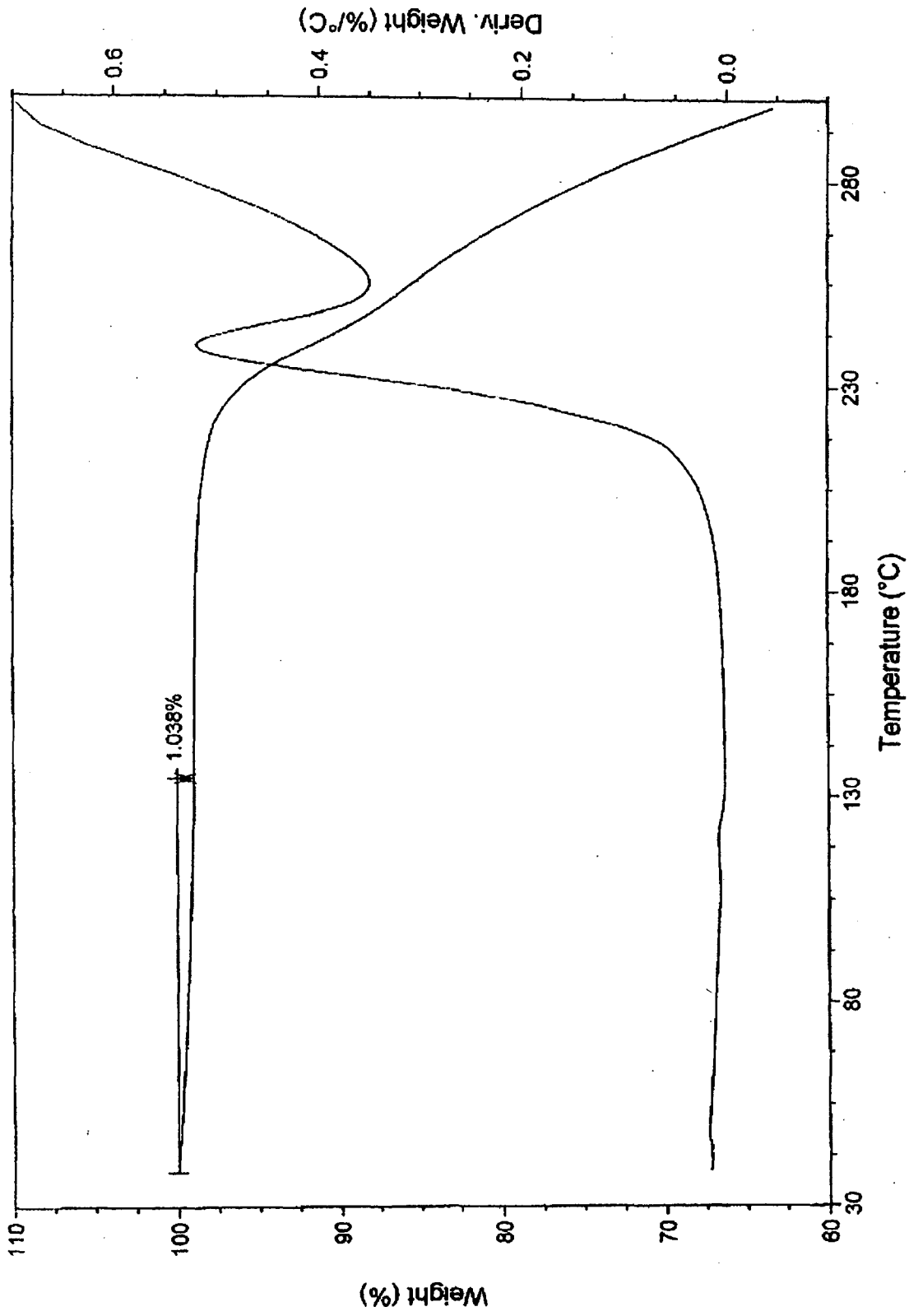

Deriv. Weight (%/°C)
0.6
0.4
0.2
0.0
1.038%
110
100
90
80
70
60
Weight (%)
30
80
130
180
230
280
Temperature (°C)

Fig. 15

Fig. 16

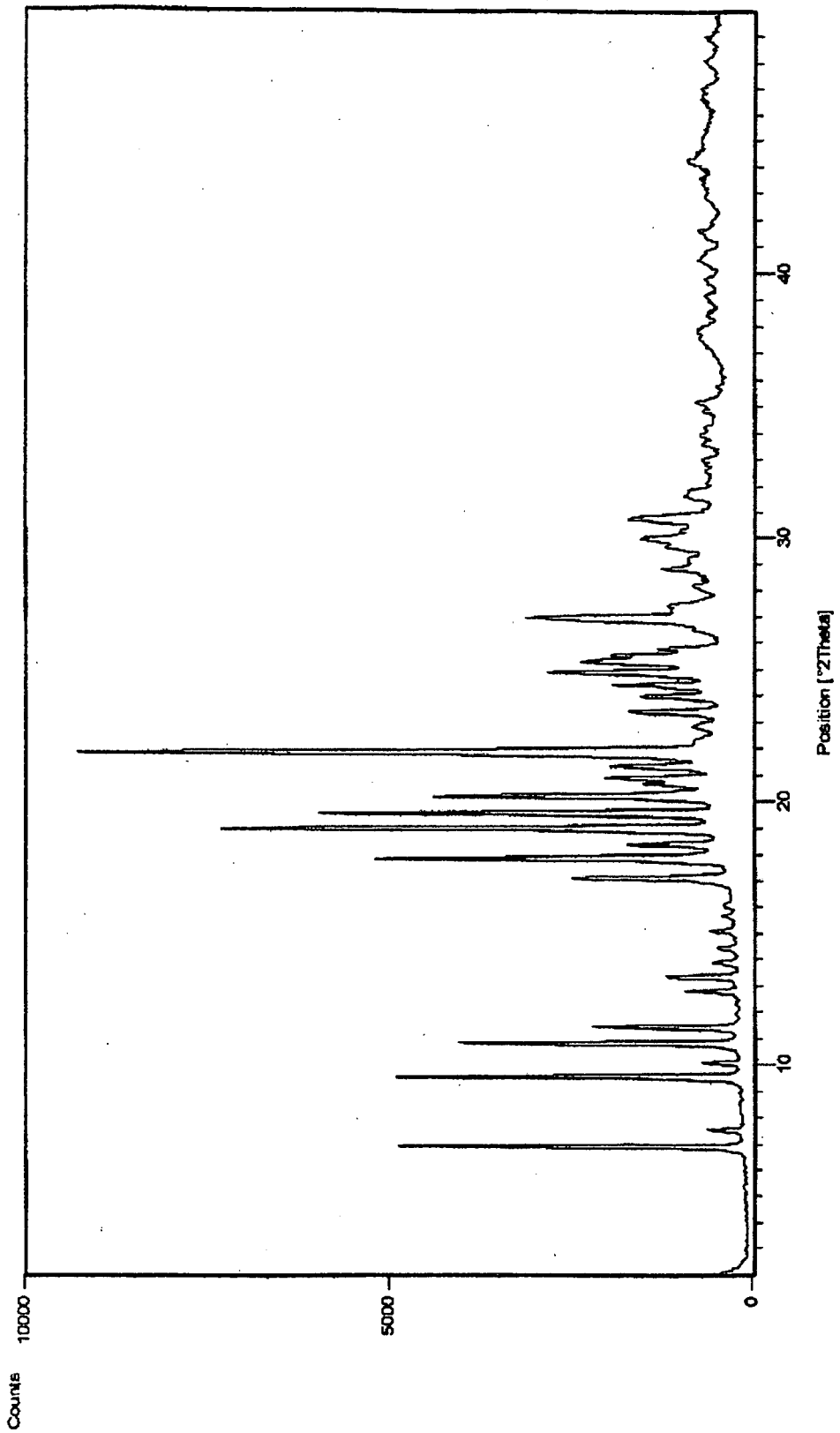


Fig. 17

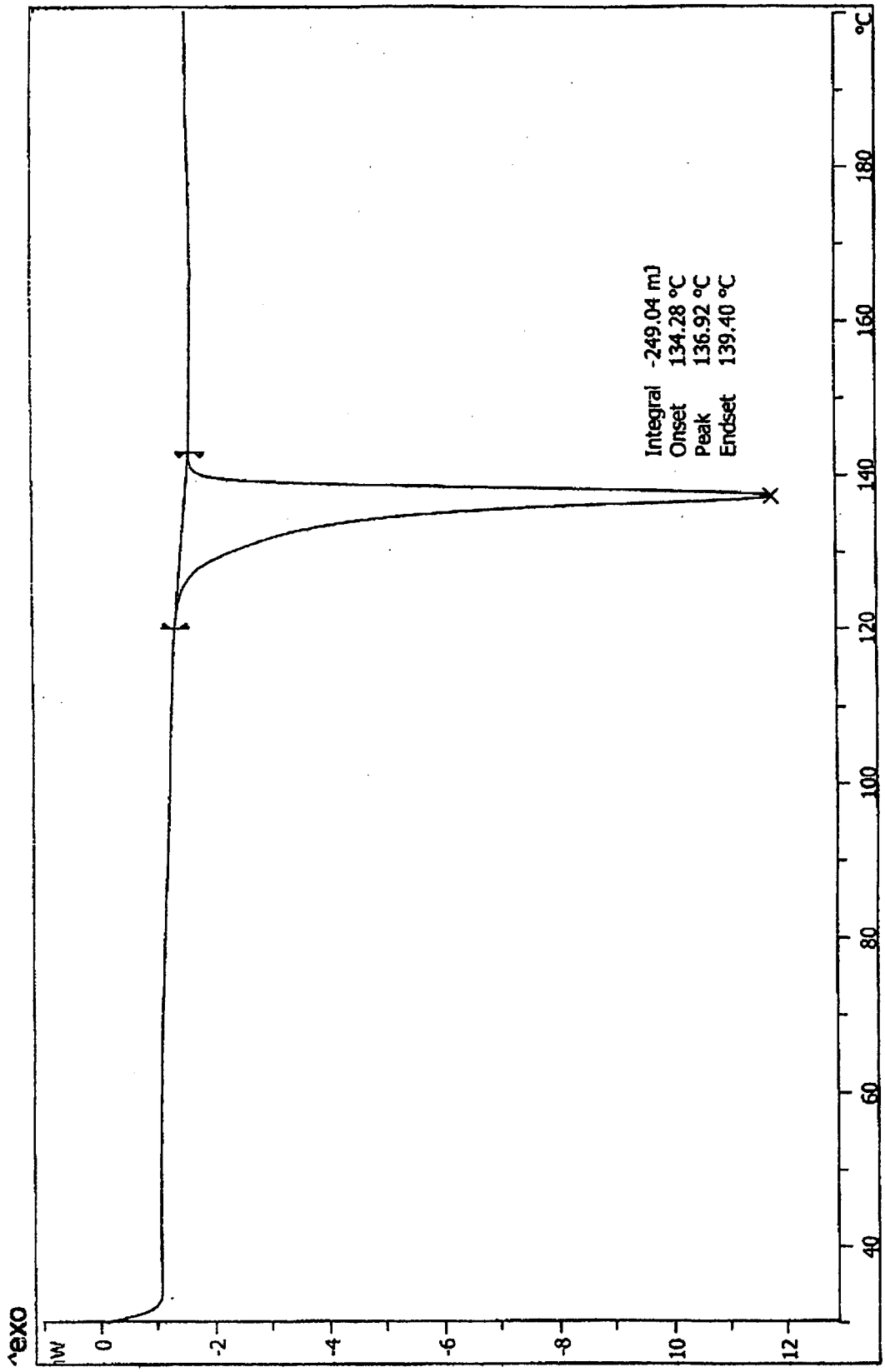

exo
mW
0
-2
-4
-6
-8
-10
-12
40
60
80
100
120
140
160
180
°C
Integral -249.04 mJ
Onset 134.28 °C
Peak 136.92 °C
Endset 139.40 °C

Fig. 18

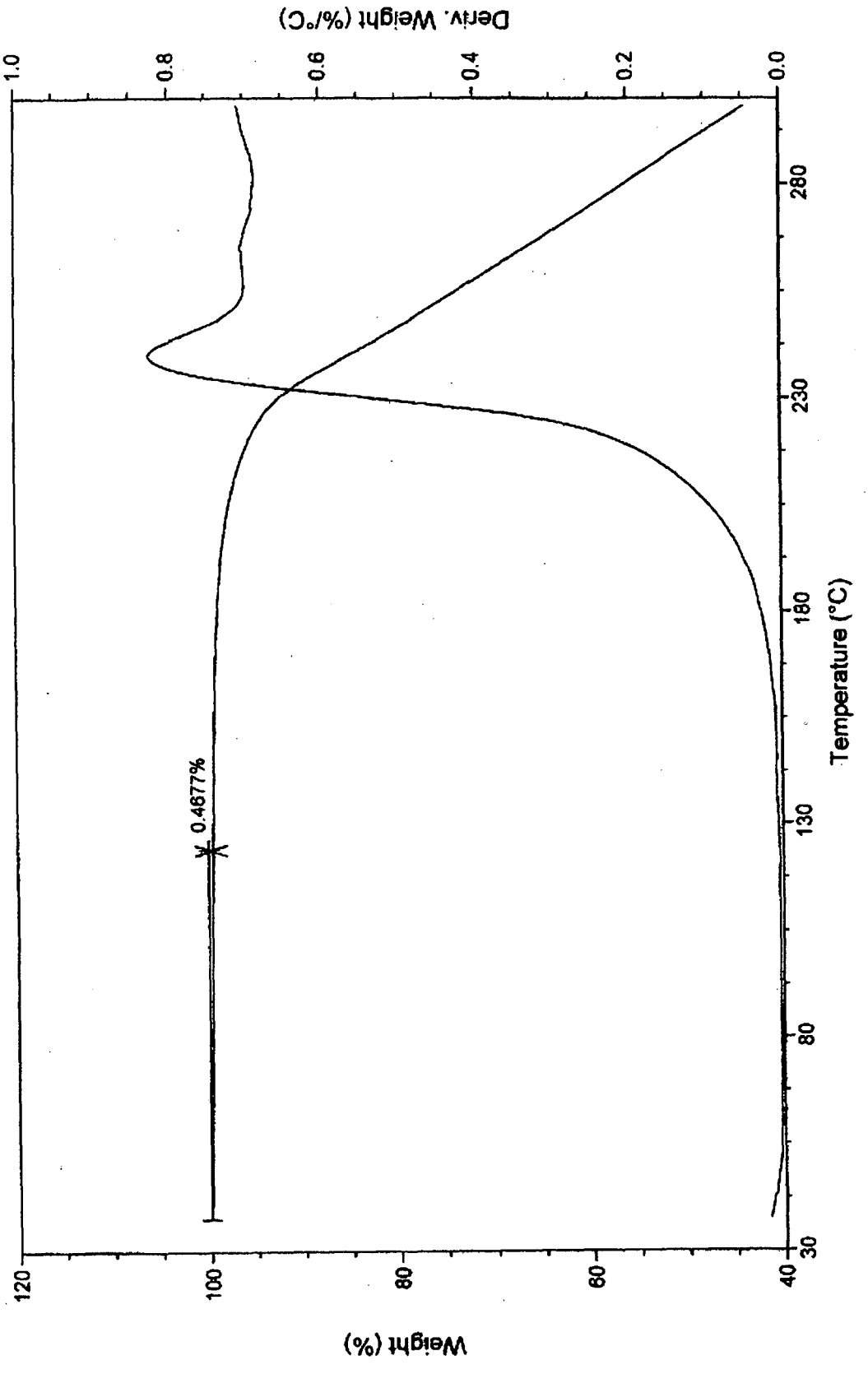

Deriv. Weight (%/°C)
1.0
0.8
0.6
0.4
0.2
0.0
0.4677%
120
100
80
60
40
Weight (%)
30
80
130
180
230
280
Temperature (°C)

Fig. 19

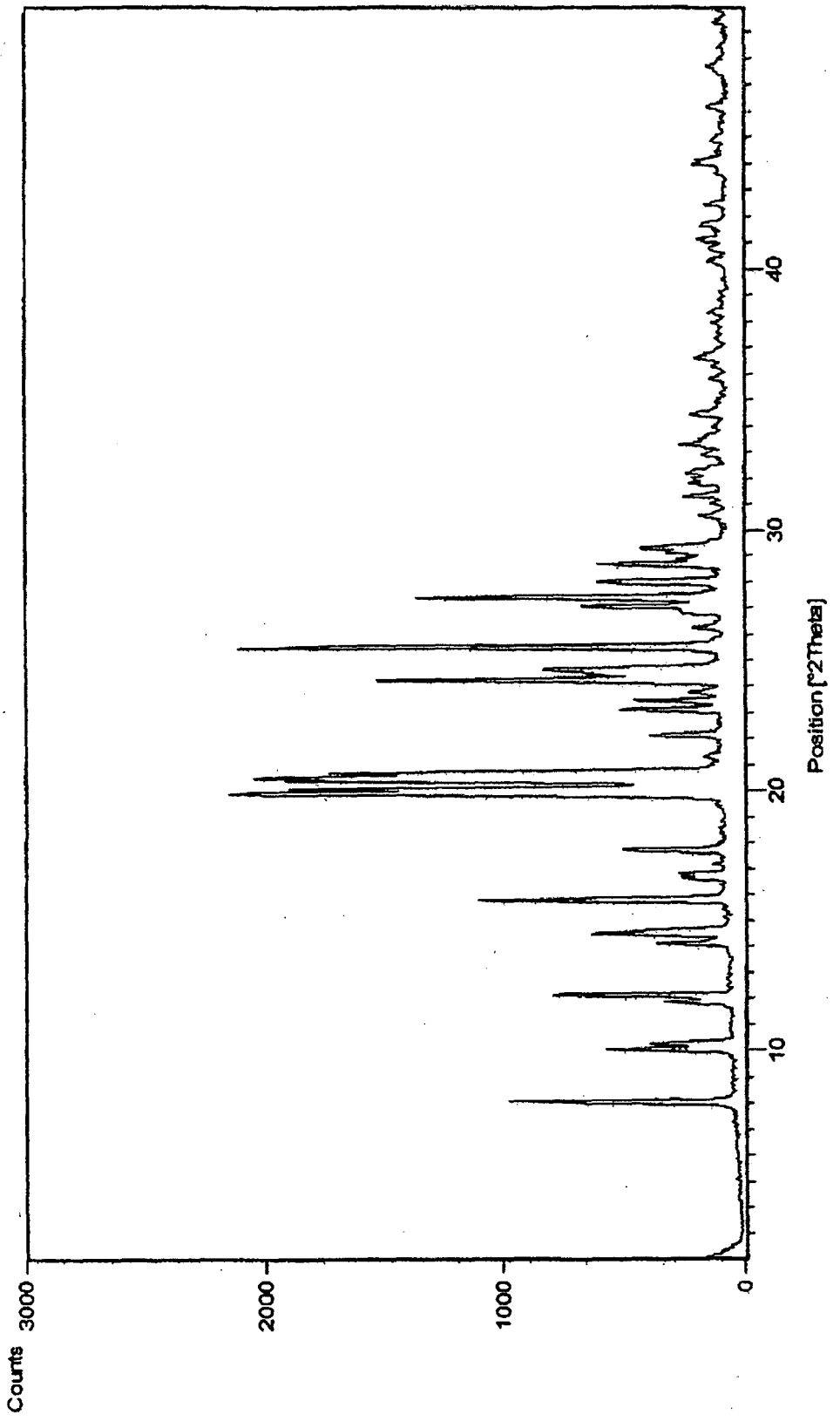


Fig. 20

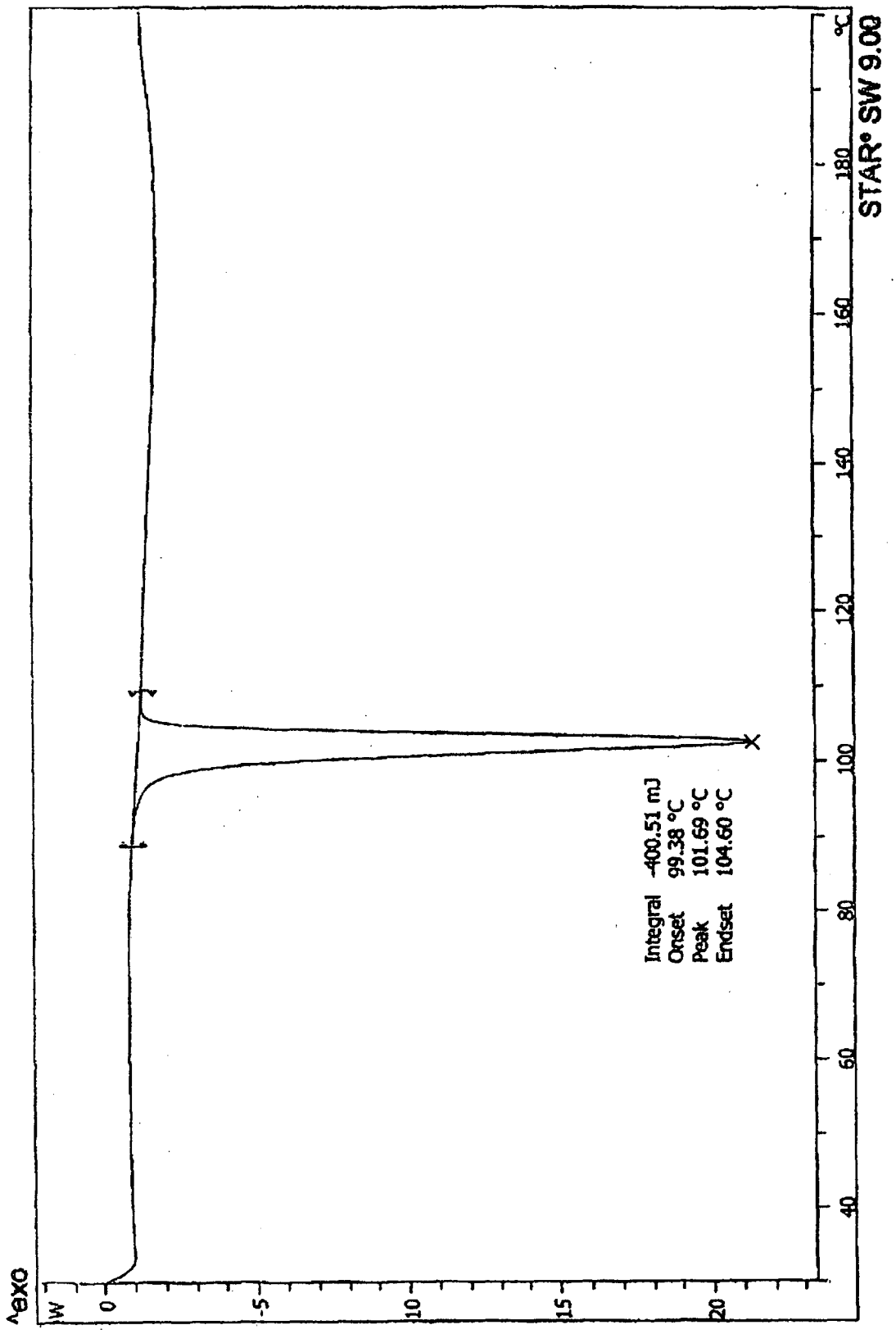

^exo
W
0
-5
10
15
20
40
60
80
100
120
140
160
180
°C
STAR° SW 9.00
Integral -400.51 mJ
Onset 99.38 °C
Peak 101.69 °C
Endset 104.60 °C

Fig. 21

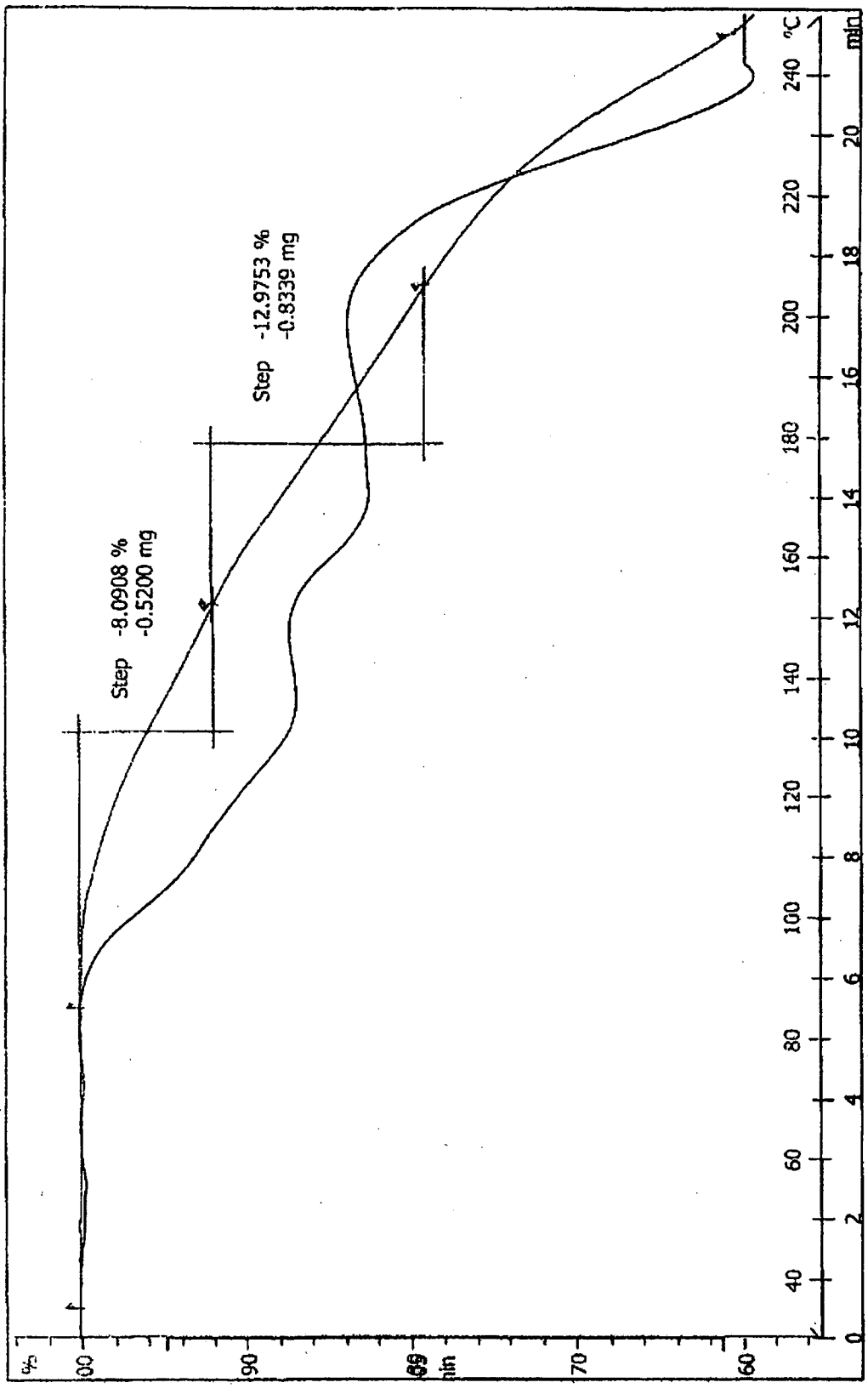


Fig. 22

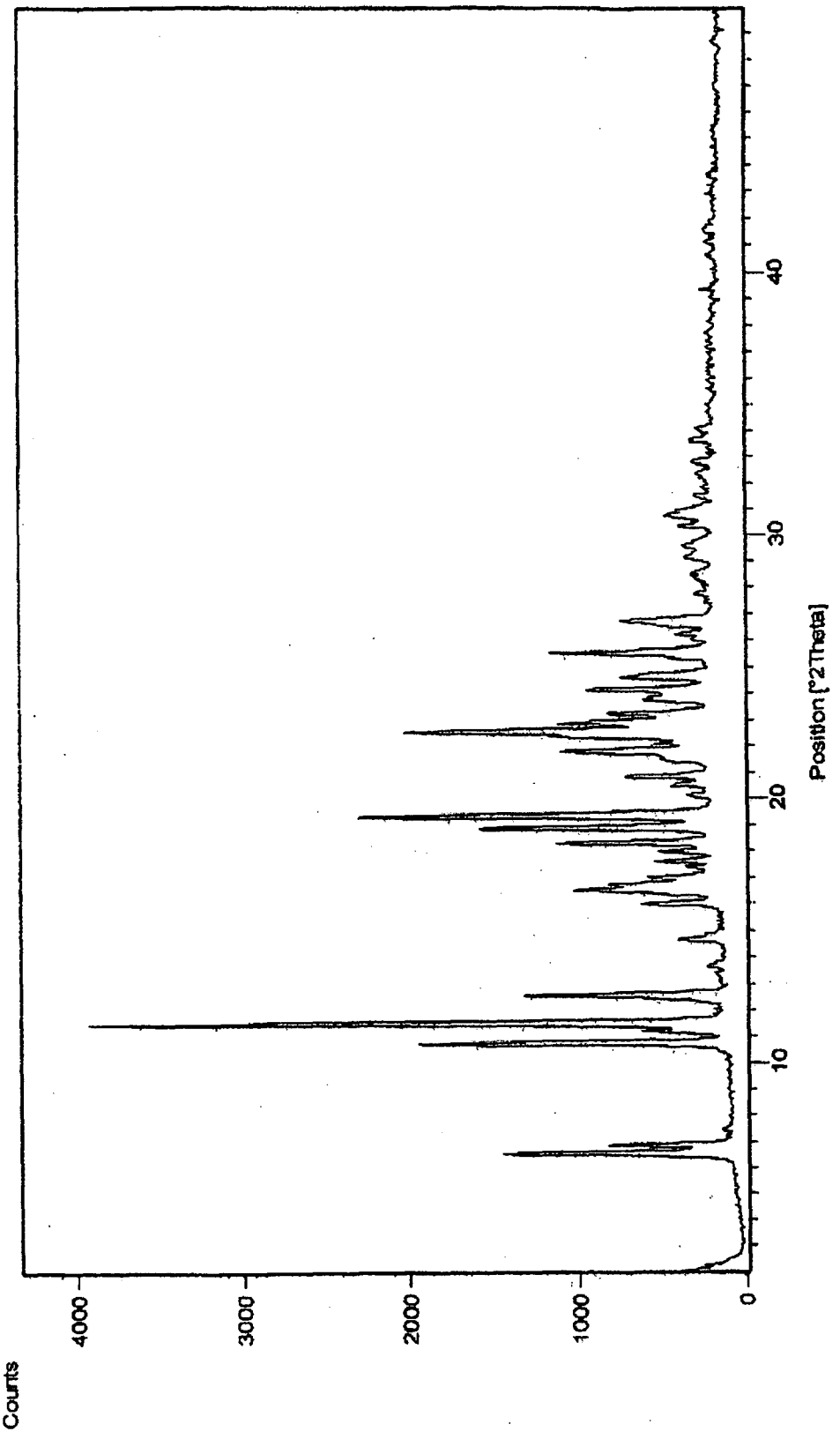


Fig. 23

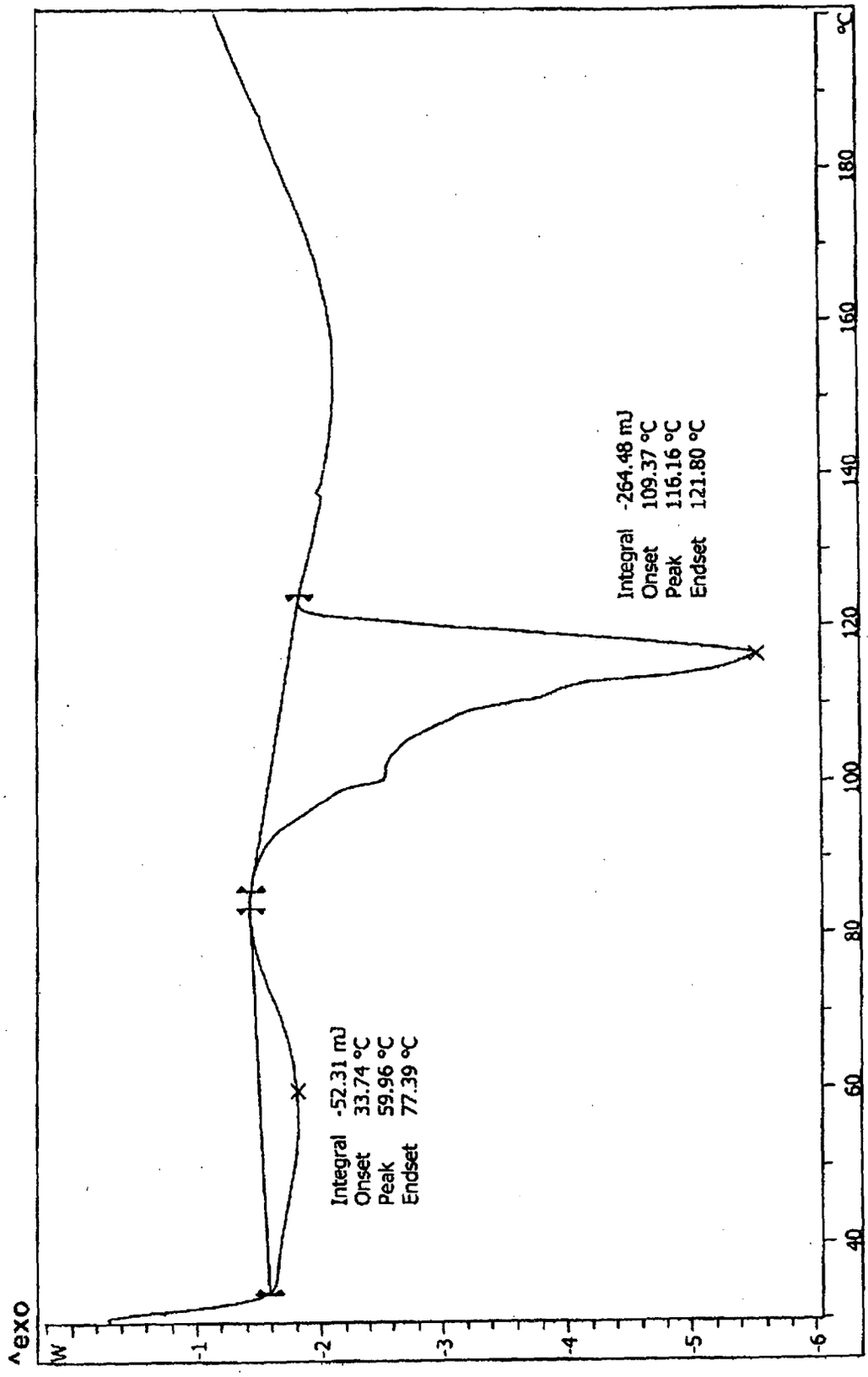

^exo
W
-1
-2
-3
-4
-5
-6
40
60
80
100
120
140
160
180
°C
Integral -52.31 mJ
Onset 33.74 °C
Peak 59.96 °C
Endset 77.39 °C
Integral -264.48 mJ
Onset 109.37 °C
Peak 116.16 °C
Endset 121.80 °C

Fig. 24

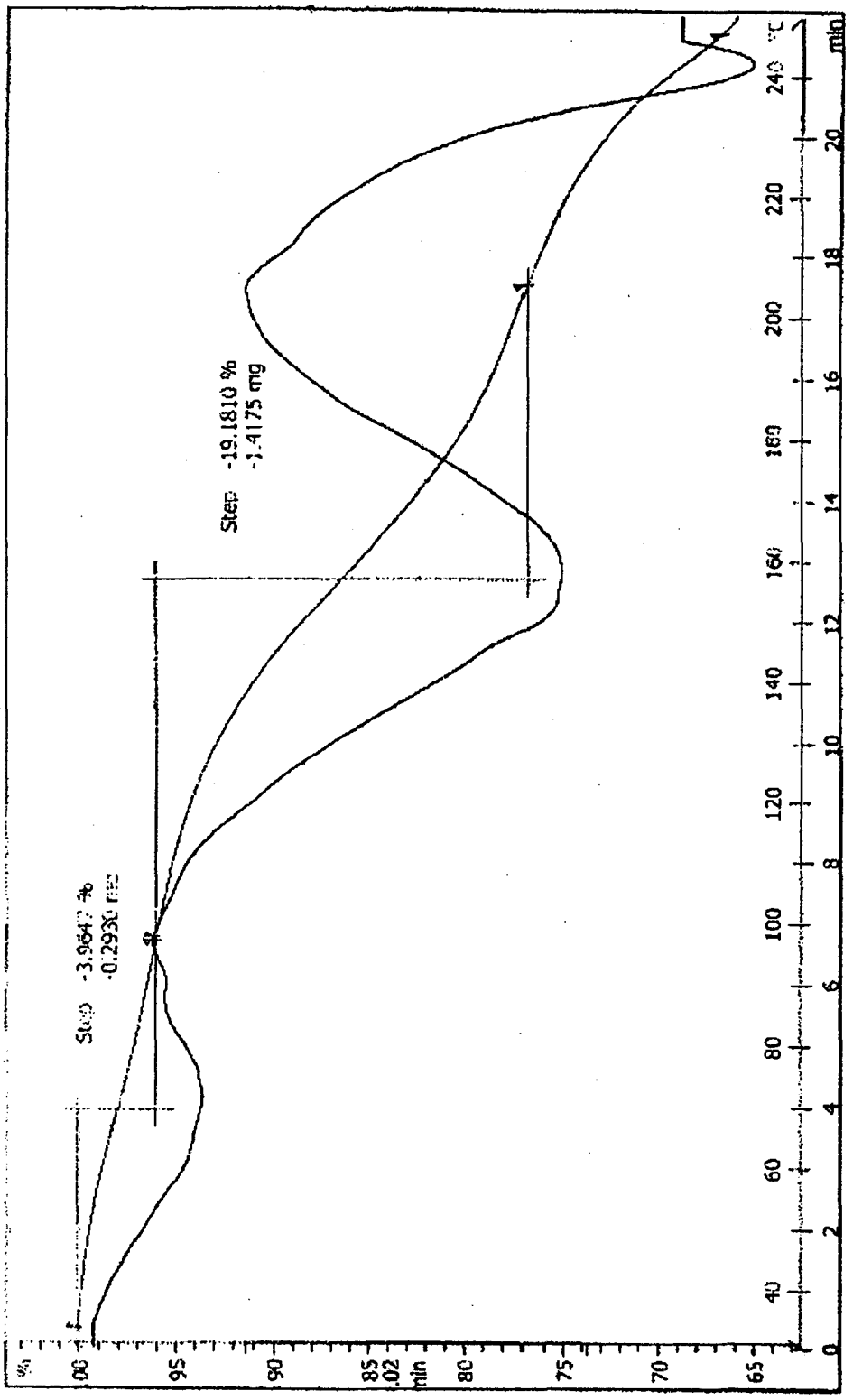


Fig. 25

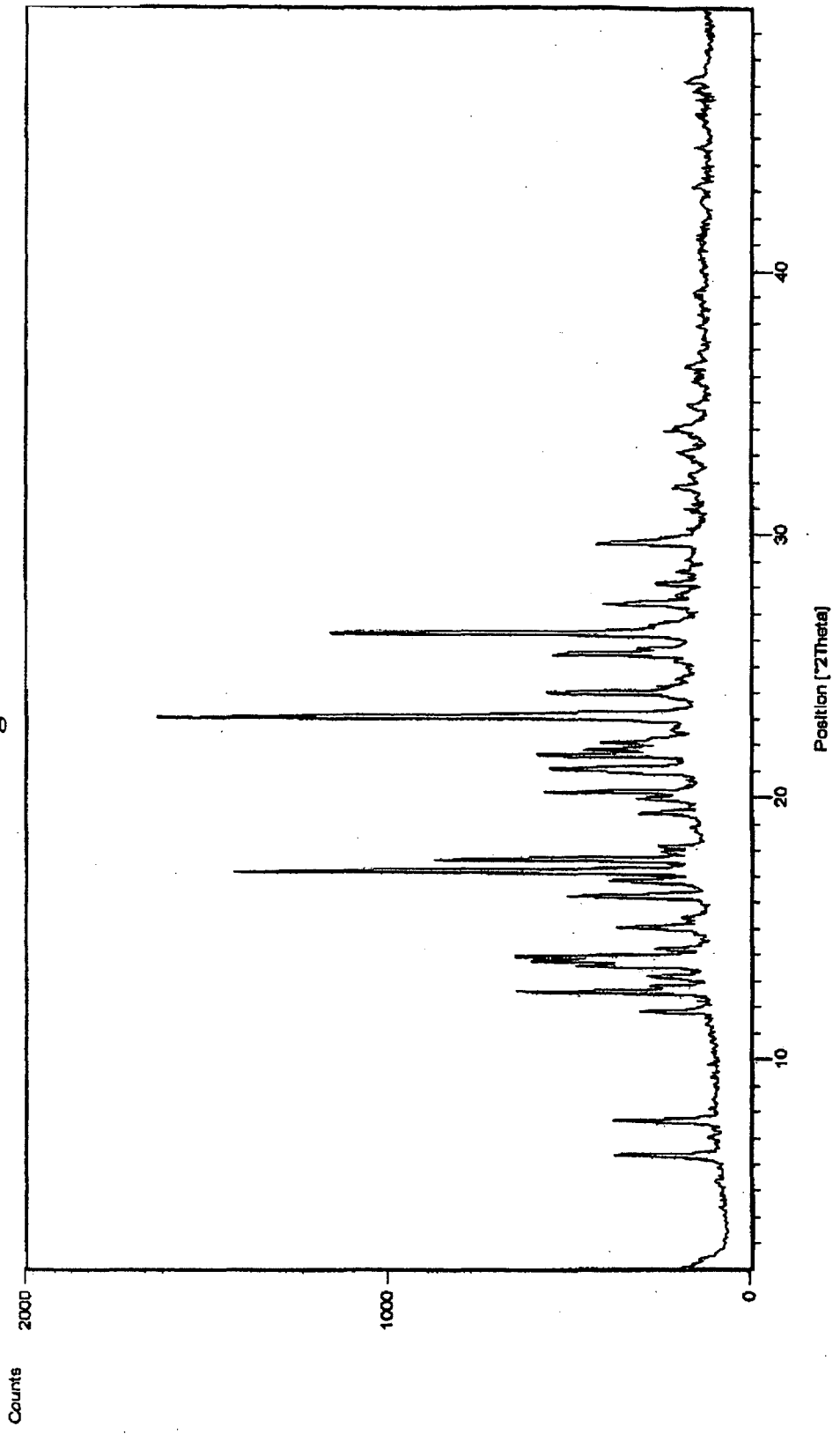


Fig. 26

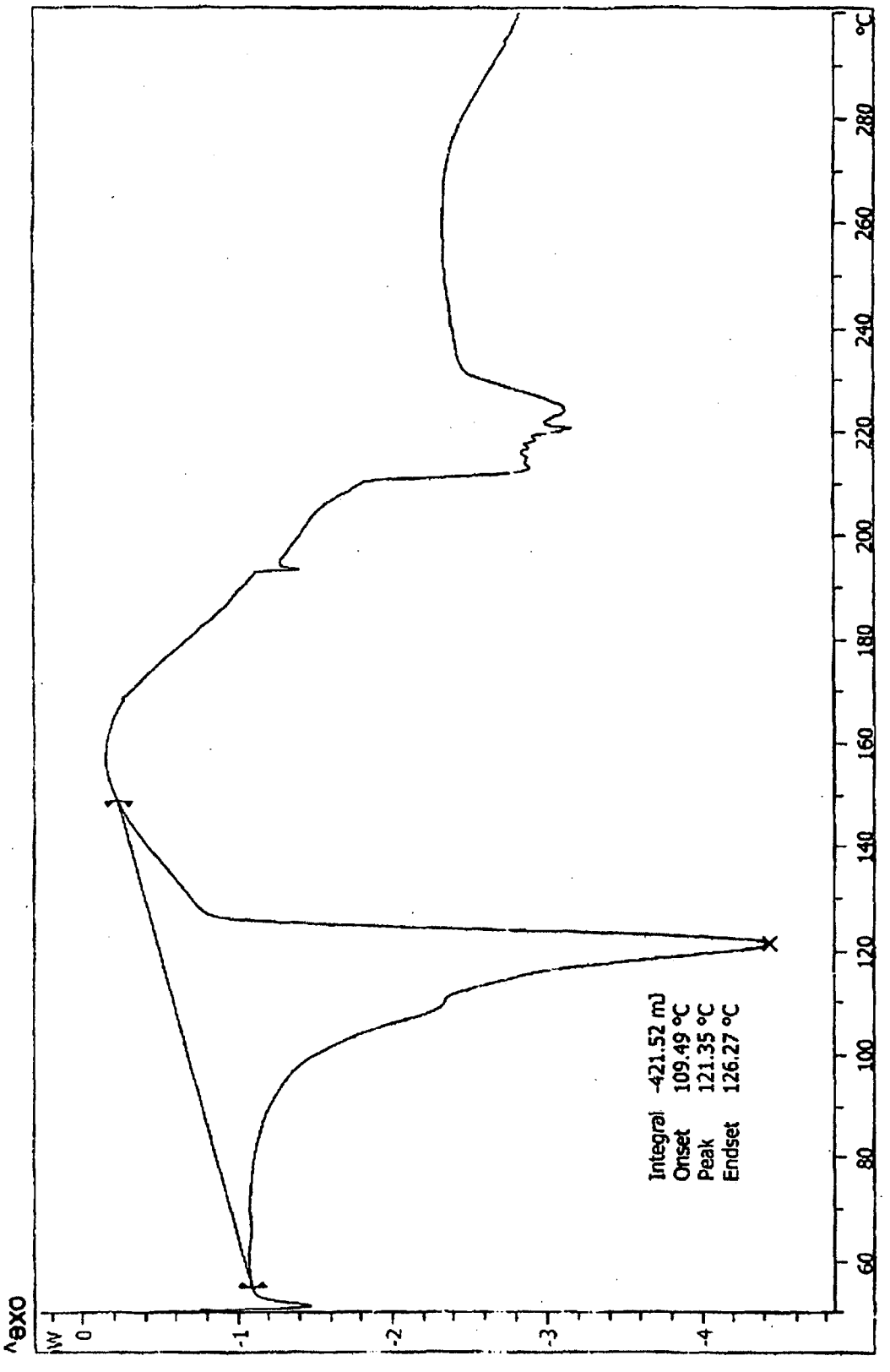

^exo
W
0
-1
-2
-3
-4
60
80
100
120
140
160
180
200
220
240
260
280
°C
Integral -421.52 mJ
Onset 109.49 °C
Peak 121.35 °C
Endset 126.27 °C

Fig. 27

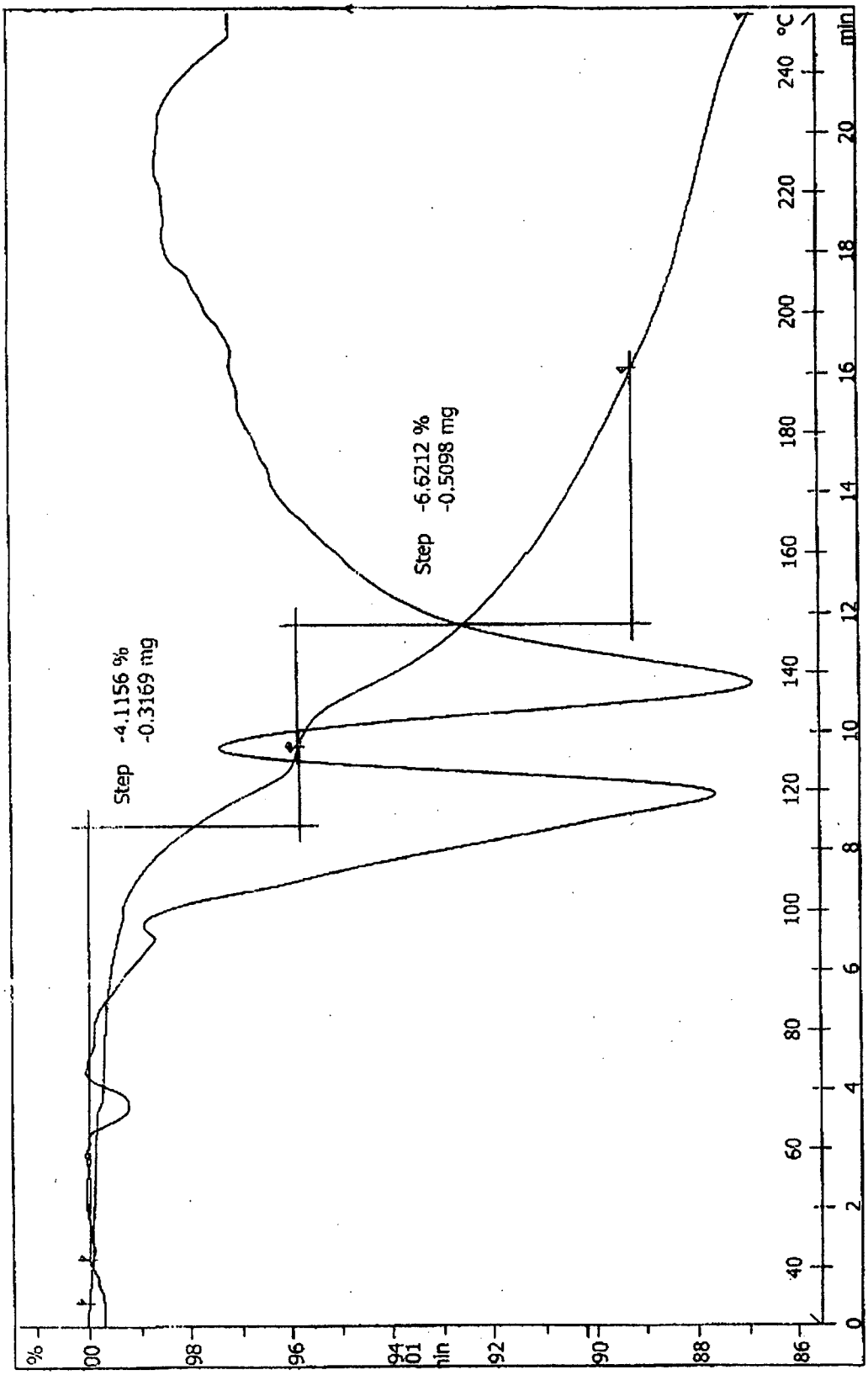

Step -4.1156 %
-0.3169 mg
Step -6.6212 %
-0.5098 mg
%
100
98
96
94
92
90
88
86
mln
°C
240
220
200
180
160
140
120
100
80
60
40
min
0
2
4
6
8
10
12
14
16
18
20

Fig. 28

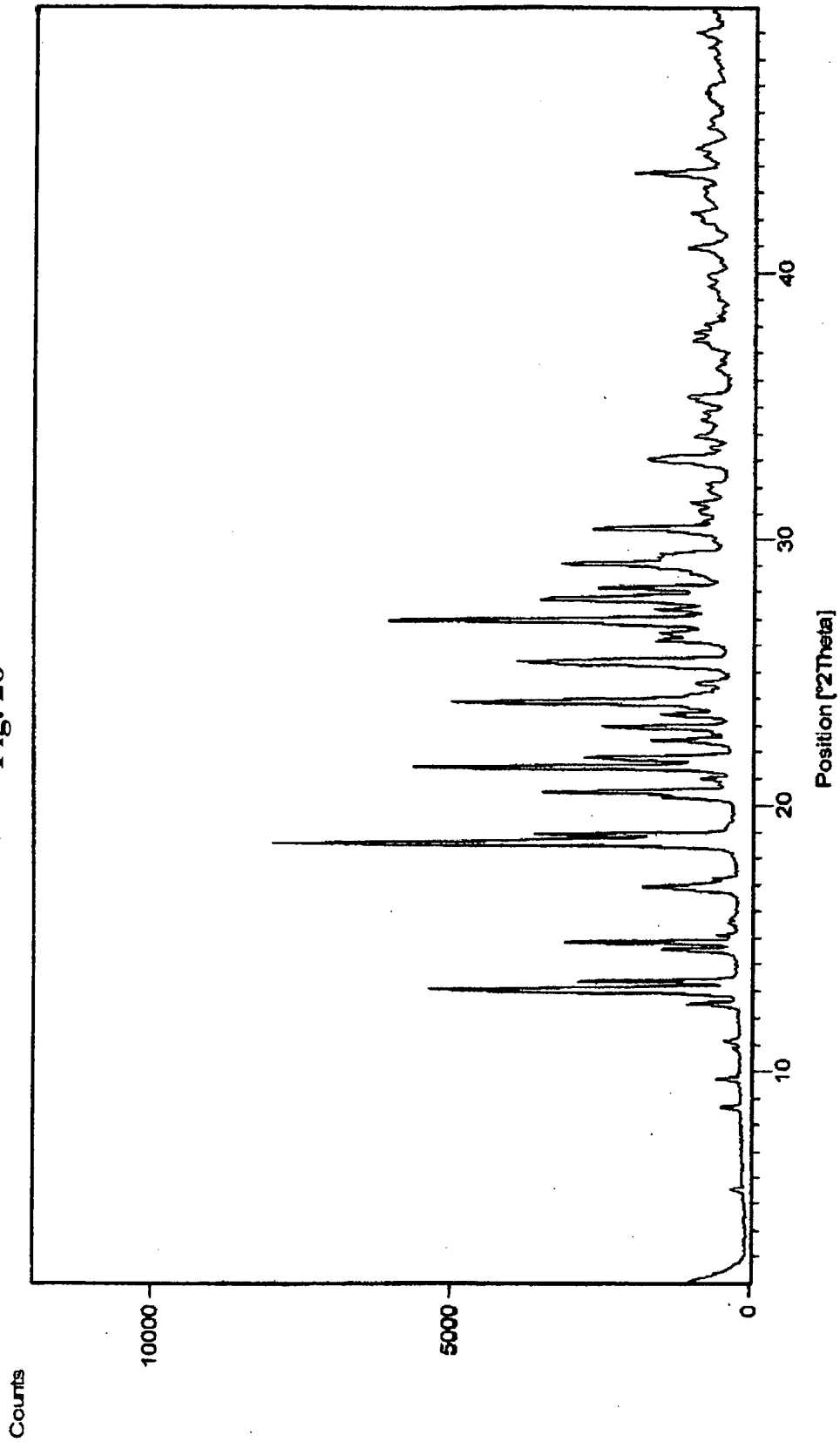
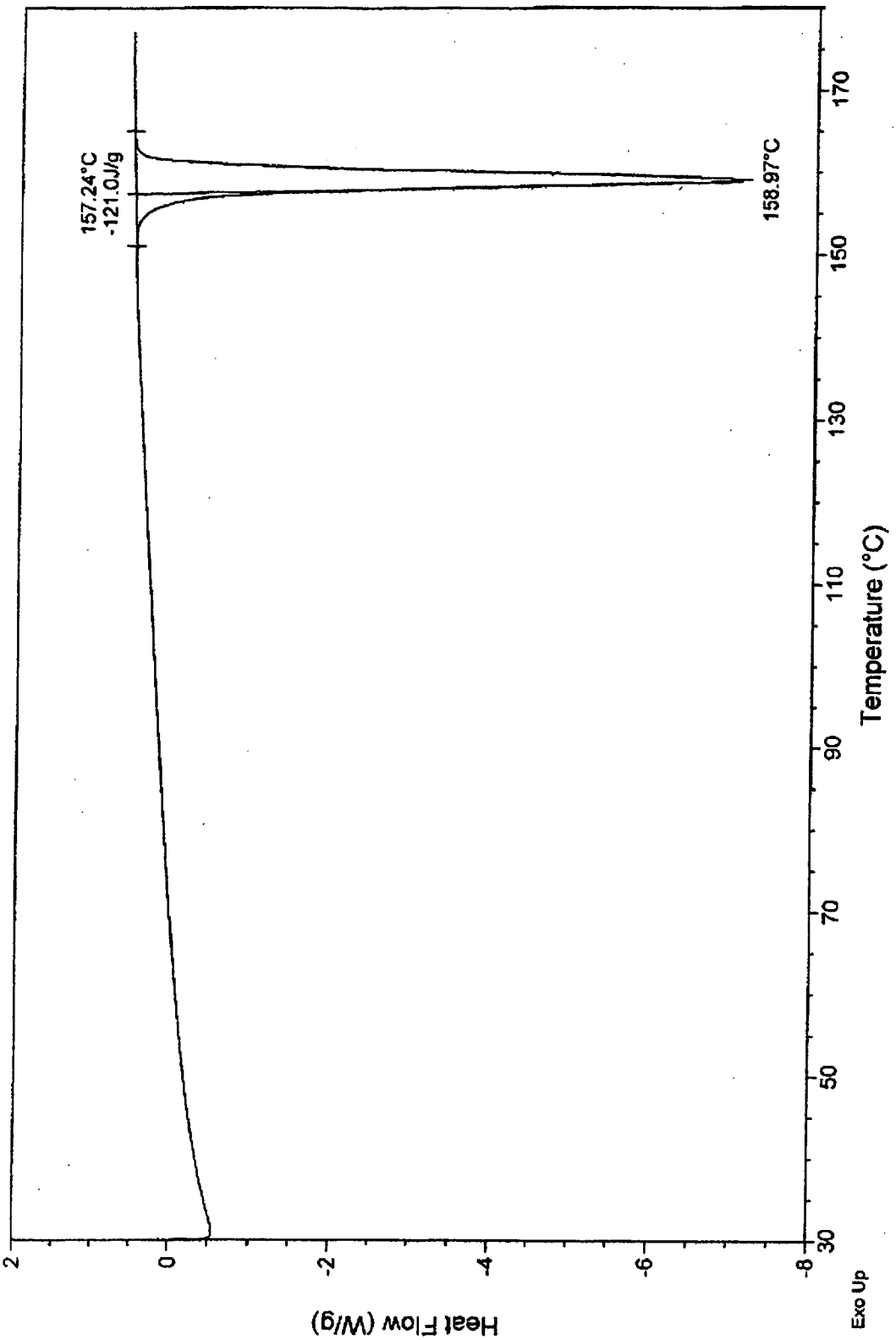


Fig. 29


157.24°C
-121.0J/g
158.97°C
Heat Flow (W/g)
Exo Up
Temperature (°C)
2
0
-2
-4
-6
-8
30
50
70
90
110
130
150
170

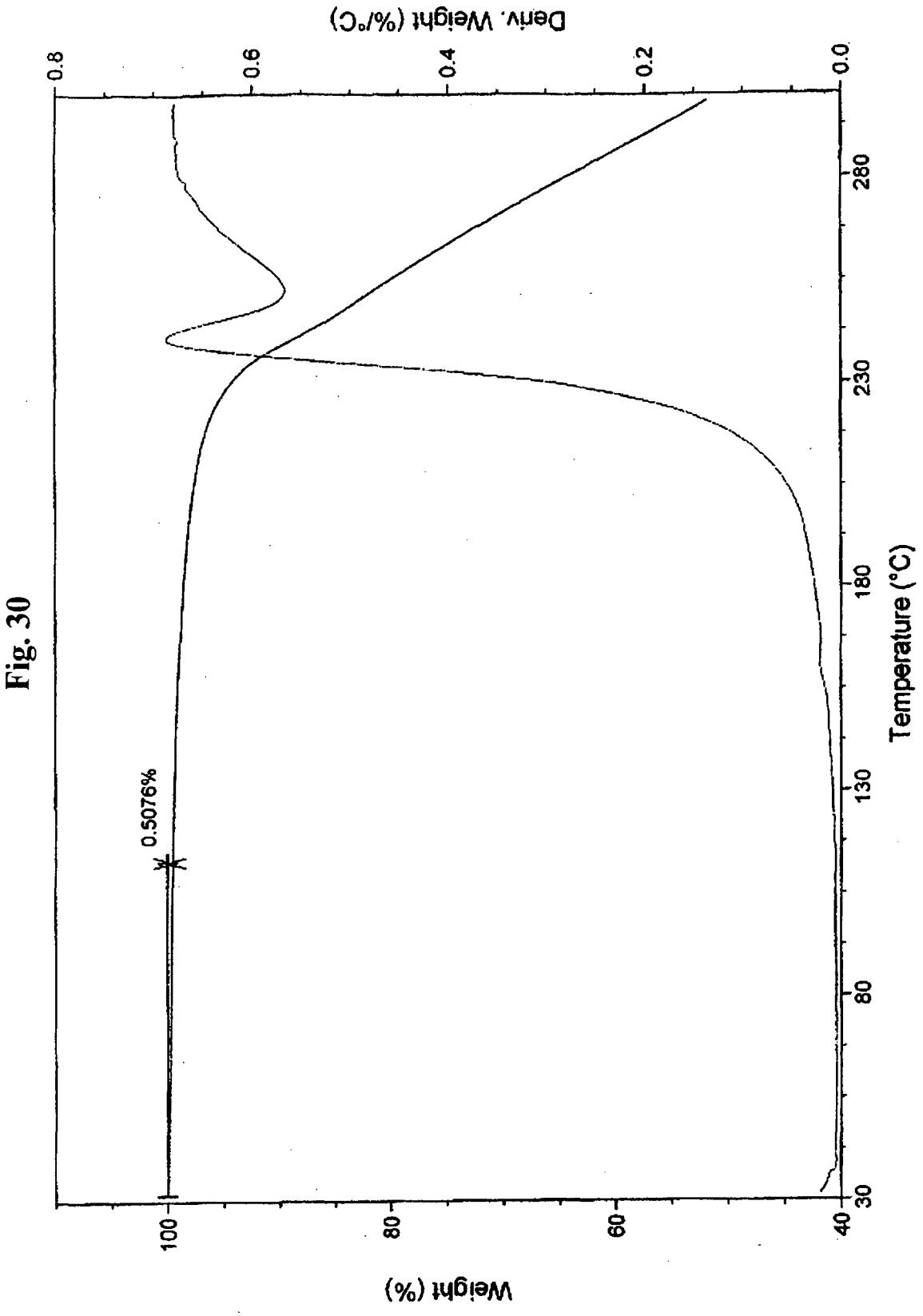

Deriv. Weight (%/°C)
0.8
0.6
0.4
0.2
0.0
280
230
180
130
80
30
Temperature (°C)
0.5076%
100
80
60
40
Weight (%)

Fig. 30

Fig. 31

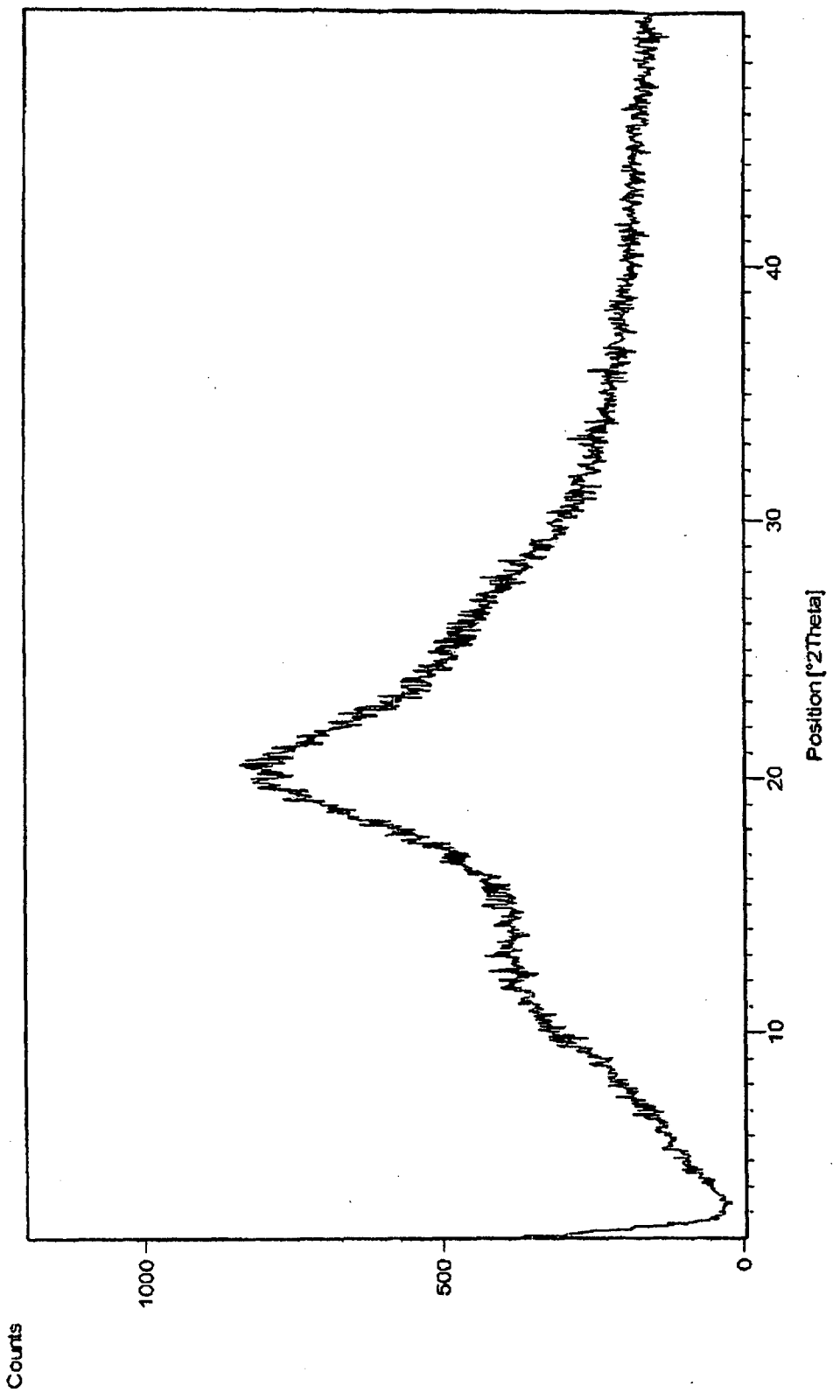
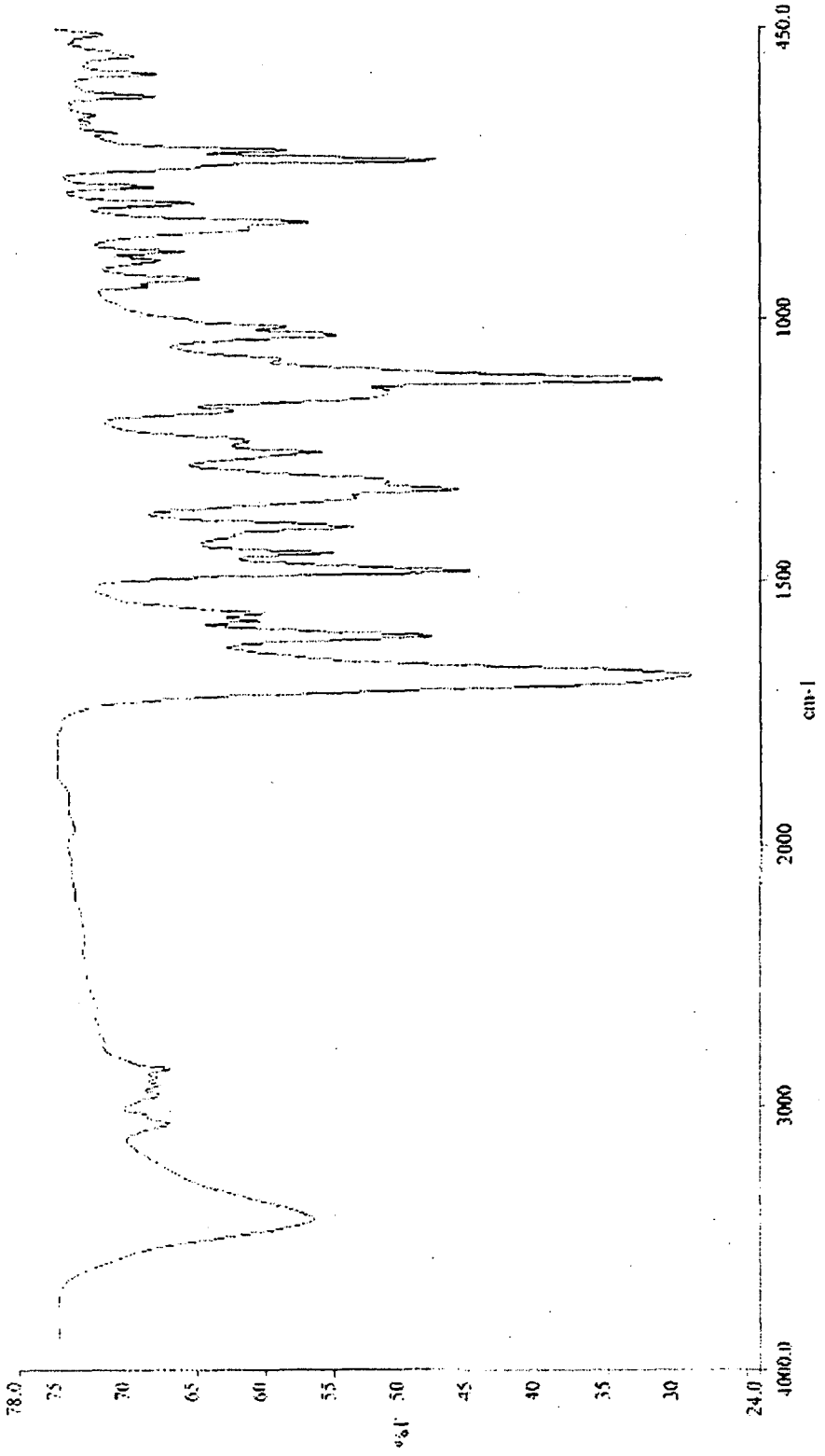


Fig. 32


4000.0
3000
2000
1500
1000
450.0
cm-1
%T
78.0
75
70
65
60
55
50
45
40
35
30
24.0