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(54) Title: NOVEL SALTS OF SIBUTRAMINE AND THEIR CRYSTAL FORMS

(57) Abstract: The present invention relates to novel acid addition salt of Sibutramine, [1-(4- chlorophenyl)-N,N-dimethyl-a-(2-methylpropyl)-cyclobutane-ethanamine] Sibutramine Maleate and the processes for their preparation.The present invention further relates to novel polymorphic forms of Sibutramine Fumarate, which include an anhydrate (Form-I), dihydrate (Form-II) and an amorphousform.

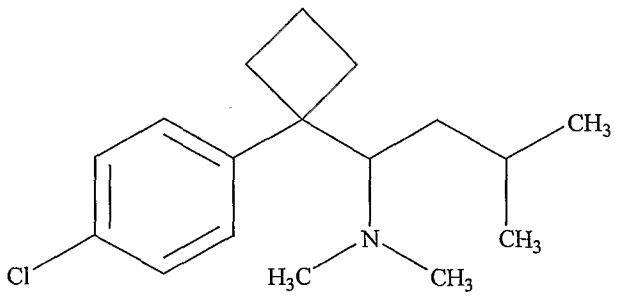
"NOVEL SALTS OF SIBUTRAMINE AND THEIR CRYSTAL FORMS"

Filed of Invention

The present invention relates to novel acid addition salt of Sibutramine namely, Sibutramine Maleate and process for the preparation of the same. The present invention also relates to novel polymorphic forms of Sibutramine Fumarate such as amorphous, anhydrate and dihydrate forms.

Background of the invention

Sibutramine, 1-(4-chlorophenyl)-N,N-dimethyl-α-(2-methylpropyl)cyclobutane-methanamine has the structure represented by formula (I), is a inhibitor of 5-hydroxytryptamine and noradrenaline reuptake in vivo (neuropharmacology,28,p129-134), is useful in the treatment of depression, Parkinson's disease, obesity, insulin-independent diabetes mellitus, epilepsy, and the like. In addition, Sibutramine reduces body weight gain by dual action to reduce food intake by enhancing satiety and to increase energy expenditure by stimulating heat generation.



(I)

Korean Patent Publication No. 1900-0000274 discloses that Sibutramine is utilized in as salts formed with acids providing non-toxic acid addition salts containing pharmaceutically acceptable anions, for example in the form of hydrochloride, malate,

citrate, fumarate, tartarate, succinate, aspartate or glutamate salt. Brazilian patent application 0105486 discloses Sibutramine sulfate. Also methanesulfonate hemihydrate salt of Sibutramine is disclosed in KR 10-03-53752.

WO 2006/073290 A1 discloses oxalate and malonate salts. WO 2006/073291 A1 [eq. US 7,429,679] discloses sulfonic acid salts like besylate, camsylate, tosylate, edisylate, esylate hemihydrate salts of Sibutramine. Hydrogen sulfate, bromate and phosphate monohydrate salts of Sibutramine have been disclosed in US 7,432,398.

During the development of novel salts of Sibutramine, two dicarboxylic acid addition salts of Sibutramine, Sibutramine Maleate and Sibutramine Fumarate in anhydrous forms have been found to possess remarkably high solubility in water and also at several pH. These salt forms exhibit non-hygroscopicity and stability.

During the polymorphic screening studies on Sibutramine Maleate and Sibutramine Fumarate, three novel polymorphic forms of Sibutramine Fumarate have been found to exist as anhydrate, hydrate and an amorphous form.

Object of the Invention

The main object of the present invention is to provide novel salt Sibutramine Maleate and process for preparing the same.

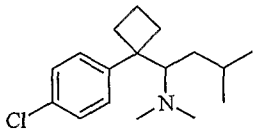
Another object of the present invention relates to novel polymorphic forms of Sibutramine Fumarate such as amorphous, Form I and Form II.

Yet another object of the present invention relates to process for the preparation of polymorphic forms of Sibutramine Fumarate such as amorphous, Form I and Form II.

Summary of the Invention

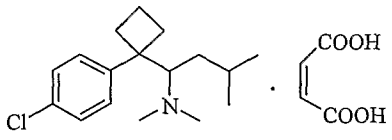
This invention encompasses acid addition salt of Sibutramine namely Sibutramine Maleate and process for preparation of the same.

The present invention also encompasses Sibutramine Fumarate polymorphic forms amorphous, Form-I (anhydrous) and Form-II (dihydrate) and processes for preparing the same.

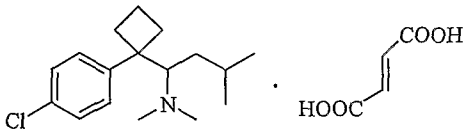


Sibutramine

(I)



Sibutramine Maleate



Sibutramine Fumarate

In accordance with one preferred aspect of the present invention, there is provided anhydrous crystalline Sibutramine Maleate with a moisture content of 0-1% characterized by Thermo gravimetric analysis (TGA) and KF method.

In accordance with another aspect of present invention, there is provided a crystalline Sibutramine Fumarate Form I as an anhydrate form with a moisture content of 0-0.3% characterized by Thermo gravimetric analysis (TGA) and KF method.

In accordance with the other aspect of present invention, there is provided a crystalline Sibutramine Fumarate Form II as a dihydrate with a moisture content of 9-11 % characterized by thermo gravimetric analysis (TGA) and KF method.

Furthermore, according to another aspect of present invention, there is provided an amorphous form of Sibutramine Fumarate characterized by powder X-ray diffraction pattern as shown in Figure 10.

Brief Description of the Drawings

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

Figure 1 is the X-ray powder diffraction pattern of Sibutramine Maleate
Figure 2 is the DSC of crystalline Sibutramine Maleate.
Figure 3 is the TGA/DTA of crystalline Sibutramine Maleate.
Figure 4 is the X-ray powder diffraction pattern of Sibutramine Fumarate Form I
Figure 5 is the DSC of crystalline Sibutramine Fumarate Form I.
Figure 6 is the TGA/DTA of crystalline Sibutramine Fumarate Form I.
Figure 7 is the X-ray powder diffraction pattern of Sibutramine Fumarate Form II.
Figure 8 is the DSC of crystalline Sibutramine Fumarate Form II.
Figure 9 is the TGA of crystalline Sibutramine Fumarate Form II.
Figure 10 is the X-ray powder diffraction pattern of amorphous Sibutramine Fumarate

Detailed Description of the Invention

The present invention relates to novel crystalline Maleate salt of Sibutramine. The present invention also relates to novel polymorphic forms of Sibutramine Fumarate; Form-I, Form-II and amorphous. The said salts differ from the other prior art salts in its physical properties and method of preparation. These salts and their polymorphs are further characterized by its X-ray powder diffraction pattern, Differential scanning calorimetry (DSC), Thermo gravimetric analysis and/or moisture content (MC).

One aspect of the present invention is to provide Sibutramine Maleate.

One embodiment of the present invention is to provide Sibutramine Maleate characterized by PXRD pattern as shown in Figure I having peaks at about 12.84, 14.22, 15.37, 17.19, 17.54, 19.26, 22.63, 24.16, 24.73, 25.26, 25.57, 25.87, 28.70, (± 0.2°θ).

Sibutramine Maleate is further characterized by PXRD peaks at about 12.48, 12.84, 14.22, 15.37, 16.01, 16.47, 17.19, 17.54, 19.26, 21.42, 22.63, 24.16, 24.73, 25.26, 25.57, 25.87, 26.45, 28.70, 32.38 (± 0.2°θ).

One more embodiment of the present invention is to prepare Sibutramine Maleate further characterized by DSC (Figure 2) with sharp endothermic peak at 140°C corresponding to melting of the product and TGA shows no significant weight loss (<1%) as depicted in Figure 3. The water content determined by Karl-Fisher method ranges from approx. 0.1-0.5 %. Preferably, the Sibutramine Maleate is crystalline anhydrous form.

One more embodiment of the present invention is to provide novel process for the preparation of crystalline Sibutramine Maleate comprising the steps of:

a) reacting Sibutramine base with maleic acid in a suitable solvent,
b) cooling the reaction mass and
c) isolating Sibutramine Maleate salt.

According to the present invention, Sibutramine base is reacted with maleic acid in a solvent, which is selected from ketone, ester solvents such as acetone and ethylacetate. The reaction can be carried out at about 20-50°C preferably at 25-30°C. The obtained mass is then cooled to 0-10°C preferably 0-5°C. Precipitated solid is filtered to isolate Sibutramine Maleate.

Another embodiment of the present invention is to provide process for the preparation of Sibutramine Maleate comprising the steps of:

(a) reacting Sibutramine base with maleic acid in a solvent,
(b) adding anti solvent and
(c) isolating the anhydrous Sibutramine Maleate salt.

According to the present invention, Sibutramine base is reacted with maleic acid in a solvent which is selected from alcohol such as methanol, ethanol, isopropyl alcohol

preferably methanol. To the resulting mass anti solvent is added. Anti solvent can be selected from ether solvent such as isopropyl ether, diethyl ether preferably isopropyl ether. Precipitated solid is filtered to isolate Sibutramine Maleate.

Yet another embodiment of the present invention is to provide Sibutramine Fumarate Form I, characterized by PXRD pattern as shown in Figure 4 having peaks at 10.84, 11.88, 16.38, 17.77, 19.66, 20.57, 22.96, 23.54, 24.03, 24.43, 25.14 (± 0.2θ).

Sibutramine Fumarate Form I is further characterized by PXRD peaks at about 10.84, 11.88, 14.24, 16.38, 17.77, 18.10, 18.93, 19.66, 20.57, 21.75, 22.96, 23.54, 24.03, 24.43, 25.14, 25.87, 26.16, 28.93, 30.43, 30.91, 31.16, 34.88, 36.73 (± 0.2θ).

Form I further characterized by DSC (Figure 5) with sharp endothermic peak at 155 °C corresponding to melting of the product and TGA shows no significant weight loss (less than 0.5%) as depicted in Figure 6. The moisture content determined by the Karl-Fisher method is in the range of 0.2 to 1.0 %. Preferably, the Sibutramine Fumarate Form I is crystalline anhydrous form

Another embodiment of the present invention provides novel process for the preparation of Sibutramine Fumarate Form-I comprising the steps of:

(a) reacting Sibutramine base with fumaric acid in a solvent;
(b) cooling the reaction mass; and
(c) isolating the Sibutramine Fumarate Form I.

According to the present invention, Sibutramine is reacted with fumaric acid in a solvent selected from alcohol solvent such as methanol, ethanol, isopropyl alcohol preferably methanol. The reaction can be carried out at temperatures 20-75°C preferably 50-60°C. The obtained reaction mass is cooled to 0-10°C preferably 0-5°C. Precipitated solid is filtered to isolate Sibutramine Fumarate Form I.

Another embodiment of the present invention provides novel Sibutramine Fumarate Form-II characterized by PXRD pattern as depicted in Figure 7 having peaks at about 11.57, 14.82, 15.43, 15.98, 16.84, 18.97, 19.99, 23.74, 24.74, 26.76, 27.63, (± 0.2°θ).

Sibutramine Fumarate Form-II is further characterized by PXRD peaks at about 11.57, 13.44, 14.09, 14.82, 15.43, 15.98, 16.84, 18.97, 19.99, 21.23, 23.74, 24.74, 25.22, 25.48, 25.95, 26.76, 27.63, 28.89 (± 0.2°θ).

Form II is further characterized by the DSC (Figure 8), which shows two melting endothermic peaks; first broad endotherm at an onset temperature ranging from 30 to 110°C with peak maxima at 96°C attributed to loss of water and a second sharp endotherm at 152°C corresponding to complete melting of the product. Crystalline Sibutramine Fumarate Form II is a dihydrate with water content approx. 9.25 % which is analyzed by TGA as shown in Figure 9 and moisture content of 9-11% determined by KF method. Preferably, Sibutramine Fumarate Form II is dihydrate.

Another embodiment of the present invention provides novel process for the preparation of Sibutramine Fumarate Form-II comprising the steps of:

(a) Dissolving Sibutramine Fumarate Form I in a suitable solvent;
(b) adding water; and
(c) isolating the crystalline Sibutramine Fumarate Form II.

According to the present invention, Sibutramine Fumarate Form I is dissolved in a solvent selected from aprotic solvents, polar protic solvents or mixtures thereof. Aprotic solvent is selected from the dimethyl sulfoxide (DMSO), dimethyl formamide (DMF) and dimethyl acetamide (DMA). Polar solvent is selected from methanol, ethanol, propanol or mixtures thereof. To the reaction mass water is added to isolate crystalline Sibutramine Fumarate Form II.

Another embodiment of the present invention relates to amorphous Sibutramine Fumarate as depicted in Figure 10.

Still another embodiment of the present invention provides process for the preparation of amorphous Sibutramine Fumarate which comprises the steps of:

(a) suspending crystalline Sibutramine Fumarate in a suitable solvent,
(b) removing the solvent; and
(c) isolating amorphous Sibutramine Fumarate.

According to the present invention, Sibutramine Fumarate is suspended in a solvent selected from methanol, ethanol, isopropyl alcohol, preferably methanol at a temperature selected from 25-75°C preferably 50-60°C. Solvent is removed by distillation under reduced pressure to obtain Sibutramine Fumarate amorphous.

Another embodiment of the present invention provides a process for preparation of crystalline Sibutramine Fumarate Form I by slurring Sibutramine Fumarate Form II in a suitable solvent followed by filtration and drying under vacuum at 40-80°C preferably at 50-60°C for several hours. The solvents used are selected from the group consisting of ethyl acetate, isopropyl ether (IPE), n-heptane, acetonitrile (ACN) and mixtures thereof.

Another embodiment of the present invention provides a process for the preparation of crystalline Sibutramine Fumarate Form I by drying crystalline Sibutramine Fumarate Form II above 50°C for several hours.

Still another embodiment of the present invention provides process for the preparation of crystalline Sibutramine Fumarate Form I by contacting Sibutramine Fumarate amorphous to atmosphere.

Still another embodiment of the present invention provides process for the preparation of crystalline Sibutramine Form I by suspending Sibutramine base, Fumaric acid in suitable

solvent and further heating the suspension to get clear solution. The clear solution is cooled to low temperatures and seeded with Form I. Precipitated solid is filtered and vacuum dried to get Sibutramine Form I. Solvent employed for the dissolution of Sibutramine base in Fumaric acid can be selected from ethanol, methanol, isopropyl alcohol preferably methanol. Dissolution of Sibutramine can be carried out at 50-60°C.

The basic characteristics of these salts, i.e. Sibutramine Maleate and Sibutramine Fumarate (Form I and Form II), shows great stability to heat and to humidity (Table 3). The present invention further provides the above salts possess high solubility in 0.1N HCl solution (Table 5)

Powder X-ray Diffraction (PXRD)

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

Differential Scanning Calorimetry (DSC)

The DSC measurements were carried out on 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 on out using the instrument Mettler Toledo TGA/SDTA 851^e and ***TGA 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 25ml/min.

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 Sibutramine Maleate

50g Sibutramine base and maleic acid (20.7g) are dissolved in acetone (175 ml) at room temperature and stirred for 1-2 hrs. The resulting solution was then slowly cooled to 0-5°C and stirred for 2hrs. The solid obtained was filtered and dried under vacuum at 50-55°C for 12hrs. The product (60g) obtained was identified to be crystalline Sibutramine Maleate.
XRD showed it to be crystalline Sibutramine Maleate

Example 2: Preparation of Sibutramine Maleate

5g of Sibutramine base and maleic acid (2g) are dissolved in ethyl acetate (30 ml) at 40°C and stirred for 15-30 min. The clear solution is then cooled to 25-30°C and stirred for 1hr. The solid obtained was filtered and dried under vacuum at 50-55°C for 12hrs. The product obtained is identified as crystalline Sibutramine Maleate.
XRD showed it to be crystalline Sibutramine Maleate

Example 3: Preparation of Sibutramine Maleate

5g Sibutramine base and maleic acid (2g) are dissolved in methanol (20 ml) at 50- 60°C and stirred for 15-30 min. The clear solution is then cooled to 25-30°C and anti solvent IPE (80 ml) was added slowly. The solution was stirred for 1 hr at 25-30°C. The solid obtained was filtered, washed with IPE (50 ml) and dried at 50-55°C under vacuum for 12hrs. The product obtained is identified as crystalline Sibutramine Maleate.
XRD showed it to be crystalline Sibutramine Maleate

Example 4: Preparation of Sibutramine Fumarate Form I

5g of Sibutramine base and Fumaric acid (2g) are dissolved in methanol (20 ml) at 50-60°C and stirred for 15-30 min. The resulting clear solution was slowly cooled to 25-30 °C and then further to 0-5°C and stirred for 1hr. The solid obtained was filtered, washed with methanol (5 ml) and dried at 50-55°C under vacuum for 12 hrs. The product obtained is identified as crystalline Sibutramine Fumarate Form I.
XRD showed it to be Form I.

Example 5: Preparation of Sibutramine Fumarate Form I by seeding

60g of Sibutramine base and Fumaric acid (24.8g) are suspended in methanol (240 ml) and heated to 50-60°C to get clear solution. The resulting clear solution was slowly cooled to 25-30 °C and then further to 0-5°C and stirred for 1hr at same temperature. 0.2g seeds of Sibutramine Fumarate are added to the above solution and stirred for 4 hrs at 0-5°C. The solid obtained was filtered, washed with methanol (50 ml) at 25-30°C and dried at 50-55°C under vacuum for 12hrs. The product (67g) obtained is identified as crystalline Sibutramine Fumarate Form I.
XRD showed it to be Form I.

Example 6: Preparation of Sibutramine Fumarate Form I

1g of Sibutramine Fumarate was suspended in appropriate solvents in appropriate volumes at 25-30°C and stirred for 2-3 hrs. The results obtained are displayed in Table 1.

Table 1

Process	Input	Solvents	Volume and/or ratio	Temp. (°C)	Result
Slurry	Form II	ACN	1:25	25-30	Form I
		EtOAc	1:25	25-30	Form I
		IPE	1:25	25-30	Form I
		n-Heptane	1:25	25-30	Form I

Example 7: Preparation of Sibutramine Fumarate Form II

2g of Sibutramine Fumarate Form I was suspended in appropriate solvents in appropriate volumes at 25-30°C and stirred to get the complete dissolution and subjected to different crystallization methods. The results obtained are displayed in Table-2.

Table-2

Process	Input	Solvents	Volume and/or ratio	Temp. (°C)	Result
Antisolvent	Form I	DMF/Water	1:5	25-30	Form II
		DMSO/Water	1:12	25-30	Form II
		DMA/Water	1:12	25-30	Form II
		Methanol/Water	1:10	25-30	Form II
Slow evaporation	Form I	Water	1:10	25-30	Form II

Example 8: Preparation of Amorphous Sibutramine Fumarate

2g of crystalline Sibutramine Fumarate dissolved in methanol (40ml) at 40-50°C. The clear solution is then subjected to distillation to remove the solvent completely under vacuum at 35°C. The isolated solid is identified as amorphous Sibutramine Fumarate.
XRD showed it to be amorphous Sibutramine Fumarate.

Example 9: Preparation of Sibutramine Fumarate Form I from Form II by heating

2g of Sibutramine Fumarate Form II obtained as described above (Example 7) was kept in a static dryer and heated at 40-50°C under vacuum. The resulting solid is identified as Sibutramine Fumarate Form I.
XRD of dried sample showed it to be Form I

Chemical Stability

The solid state stability of the anhydrous Sibutramine Maleate and Sibutramine Fumarate salts prepared in above examples was determined by storing approximately 3.0 g of the sample a) at 50°C, b) at 40°C/75% relative humidity (RH), open exposure, and c) at 40°C/75% relative humidity (RH), close exposure for 10 days. The material was tested by HPLC for final purity and degradation products in both the cases. The results are given in Table 3.

Table 3

Sibutramine Salt	Condition	HPLC Purity (%)
Maleate	Initial	99.97
	50°C/10 Days	99.96
	40°C/75% RH (Open) 10 Days	99.97
	40°C/75% RH (Close) 10 Days	99.93
Fumarate	Initial	99.97
	50°C/10 Days	99.96
	40°C/75% RH (Open) 10 Days	99.96
	40°C/75% RH (Close) 10 Days	99.96

Further Sibutramine Maleate and Fumarate salts show no significant degradation when stored in different relative humid conditions for a period of 10 days which suggests that these salts are chemically stable.

Physical and chemical stability under accelerated condition

The physical and chemical stability of the anhydrous Sibutramine Maleate and Sibutramine Fumarate salts prepared in above examples was determined by storing

approximately 3.0 g of the sample at 40°C/75% relative humidity (RH) for 1 month. The material was tested by HPLC, Karl-Fisher and PXRD for final content. The results are given in Table 4.

Table 4

Sibutramine Salt	Condition	HPLC purity (%)	m/c (%)	PXRD
Maleate	Initial	99.93	0.14	Crystalline
	1 month	99.94	0.21	Same as initial
Fumarate	Initial	99.94	0.15	Crystalline
	1 month	99.94	0.25	Same as initial

Sibutramine Maleate and Fumarate salts shows no significant degradation, no substantial increase in moisture content and no change in PXRD pattern when stored at 40°C/75% relative humidity (RH) for 1 month which suggests that these salts are physically and chemically stable.

Solubility Studies

The solubility of anhydrous Sibutramine Maleate and Sibutramine Fumarate salts prepared in above examples and the commercially available Sibutramine hydrochloride monohydrate are determined in distilled water and at several pH at 25°C. The results are given in Table 5.

Table 5

Medium	Solubility (mg/ml)		
	HCl	Maleate	Fumarate
0.1 N HCl	11.4	20.3	15.0
Purified water	23.6	10.5	8.6
pH 4.5	22.3	11.1	7.3
pH 6.8	19.1	8.7	6.2

Sibutramine Maleate and Sibutramine Fumarate salts look comparable in solubility to Sibutramine hydrochloride monohydrate.

Hygroscopicity Studies

The hygroscopicity of the anhydrous Sibutramine Maleate and Sibutramine Fumarate salts prepared in above examples was determined by storing approximately 3.0 g of the sample a) at 25°C/90% relative humidity (RH), and b) at 40°C/75% relative humidity (RH) for 3, 10 ,15 days and 1 month. The material was tested by Karl-Fisher for final moisture content in both the cases. The results are shown in Table 6.

Table 6

Storage Humidity	Storage Period	Sibutramine Maleate (% m/c)	Sibutramine Fumarate (% m/c)
90% Relative Humidity at 25°C	Initial	0.14	0.14
	3 Days	0.14	0.48
	10 Days	0.11	0.42
	1 Month	0.35	0.48
75% Relative Humidity at 40°C	15 Days	0.33	0.23
	1 Month	0.21	0.25

Sibutramine Maleate and Fumarate salts shows no substantial increase in moisture content when stored in different relative humidity conditions for a period of 1month which suggests that these salts are non-hygroscopic in nature.

We Claim:

1. Sibutramine Maleate

2. Sibutramine Maleate according to claim 1, characterized by a PXRD pattern with peaks at about 12.84, 14.22, 15.37, 17.19, 17.54, 19.26, 22.63, 24.16, 24.73, 25.26, 25.57, 25.87, 28.70, (± 0.2°θ).

3. A method of preparing Sibutramine Maleate comprising:
   a) reacting Sibutramine base with maleic acid in a solvent,
   b) cooling the reaction mass and
   c) isolating Sibutramine Maleate salt.

4. A method of preparing Sibutramine Maleate comprising
   a) reacting Sibutramine base with maleic acid in a solvent,
   b) adding anti solvent and
   c) isolating the anhydrous Sibutramine Maleate salt.

5. Sibutramine Fumarate Form-I characterized by a PXRD pattern with peaks at about 10.84, 11.88, 16.38, 17.77, 19.66, 20.57, 22.96, 23.54, 24.03, 24.43, 25.14 (± 0.2θ).

6. A method of preparing Sibutramine Fumarate Form I, comprising:
   a) reacting Sibutramine base with fumaric acid in a solvent,
   b) cooling the reaction mass and
   c) isolating the Sibutramine Fumarate Form I.

7. Sibutramine Fumarate Form-II, characterized by a PXRD pattern with peaks at about 11.57, 14.82, 15.43, 15.98, 16.84, 18.97, 19.99, 23.74, 24.74, 26.76, 27.63, (± 0.2°θ).

8. A method of preparing Sibutramine Fumarate Form II comprising
   a) Dissolving Sibutramine Fumarate Form I in a suitable solvent,
   b) adding water and

c) isolating the crystalline Sibutramine Fumarate Form II.

9. Amorphous Sibutramine Fumarate.

10. A method of preparing amorphous Sibutramine comprising:
    a) suspending crystalline Sibutramine Fumarate in a suitable solvent,
    b) removing the solvent and
    c) isolating amorphous Sibutramine Fumarate.

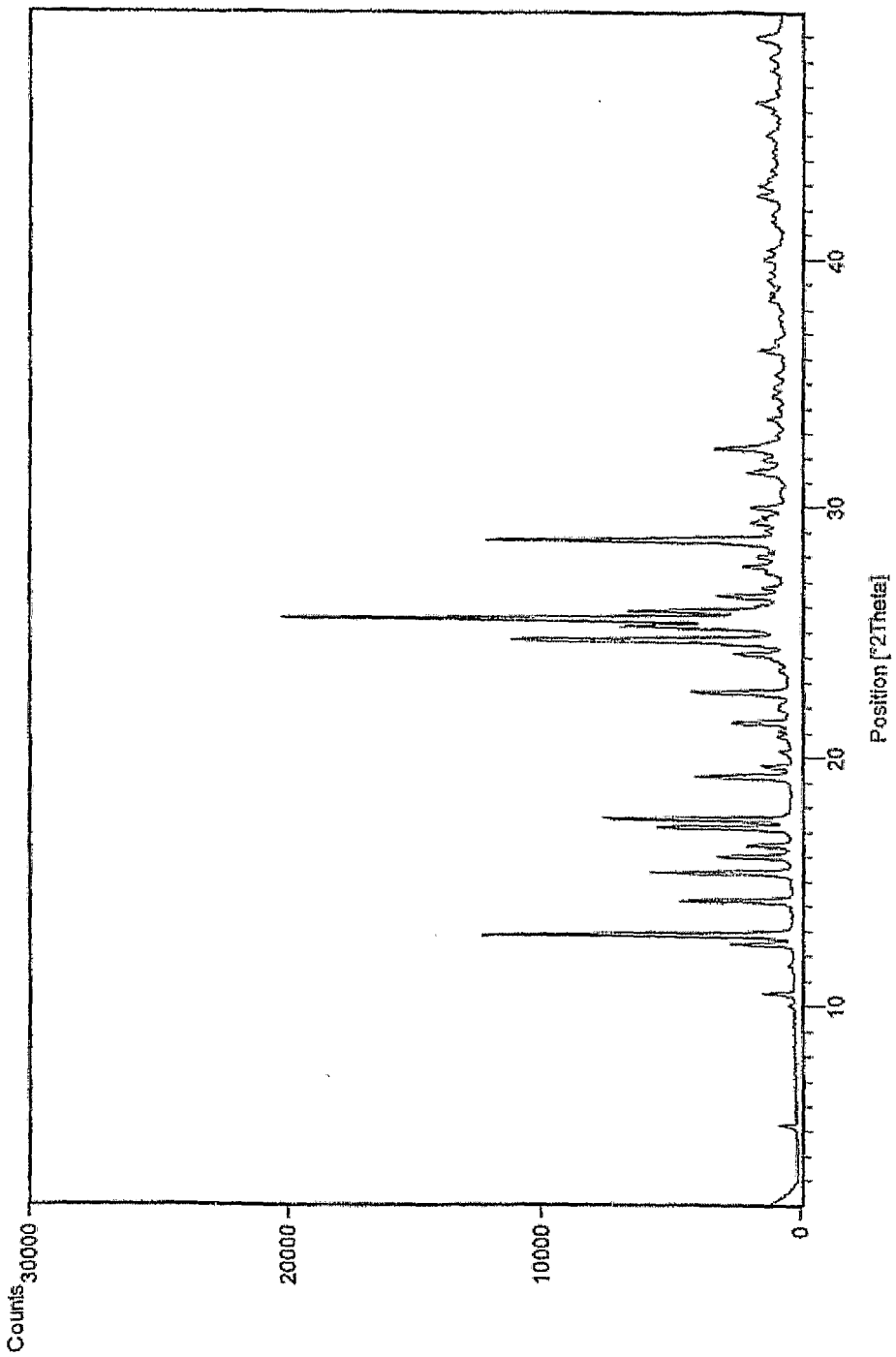


Figure 1

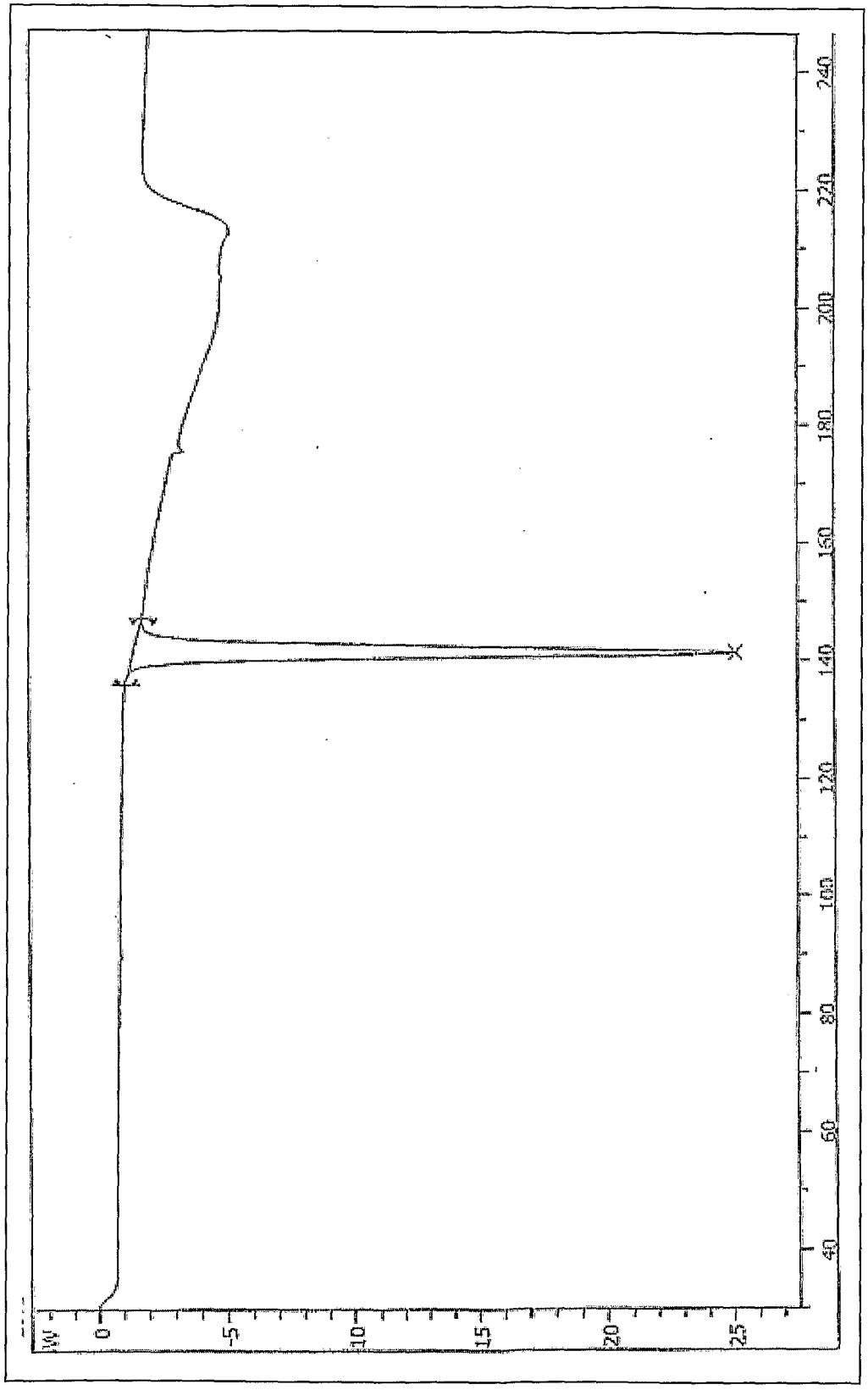


Figure 2

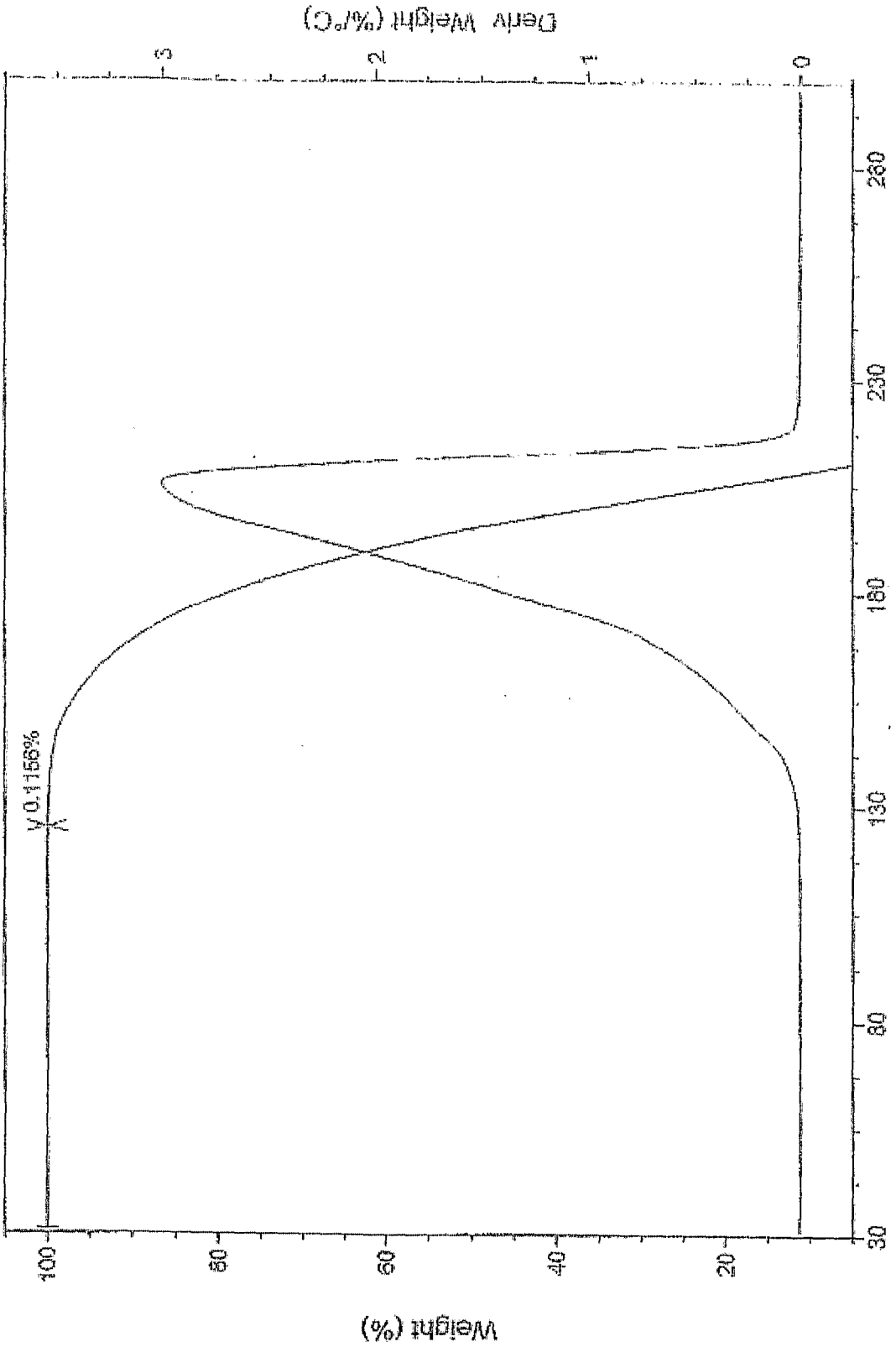

Deriv. Weight (%/°C)
3
2
1
0
Weight (%)
100
80
60
40
20
30
80
130
180
230
280
0.1156%

Figure 3

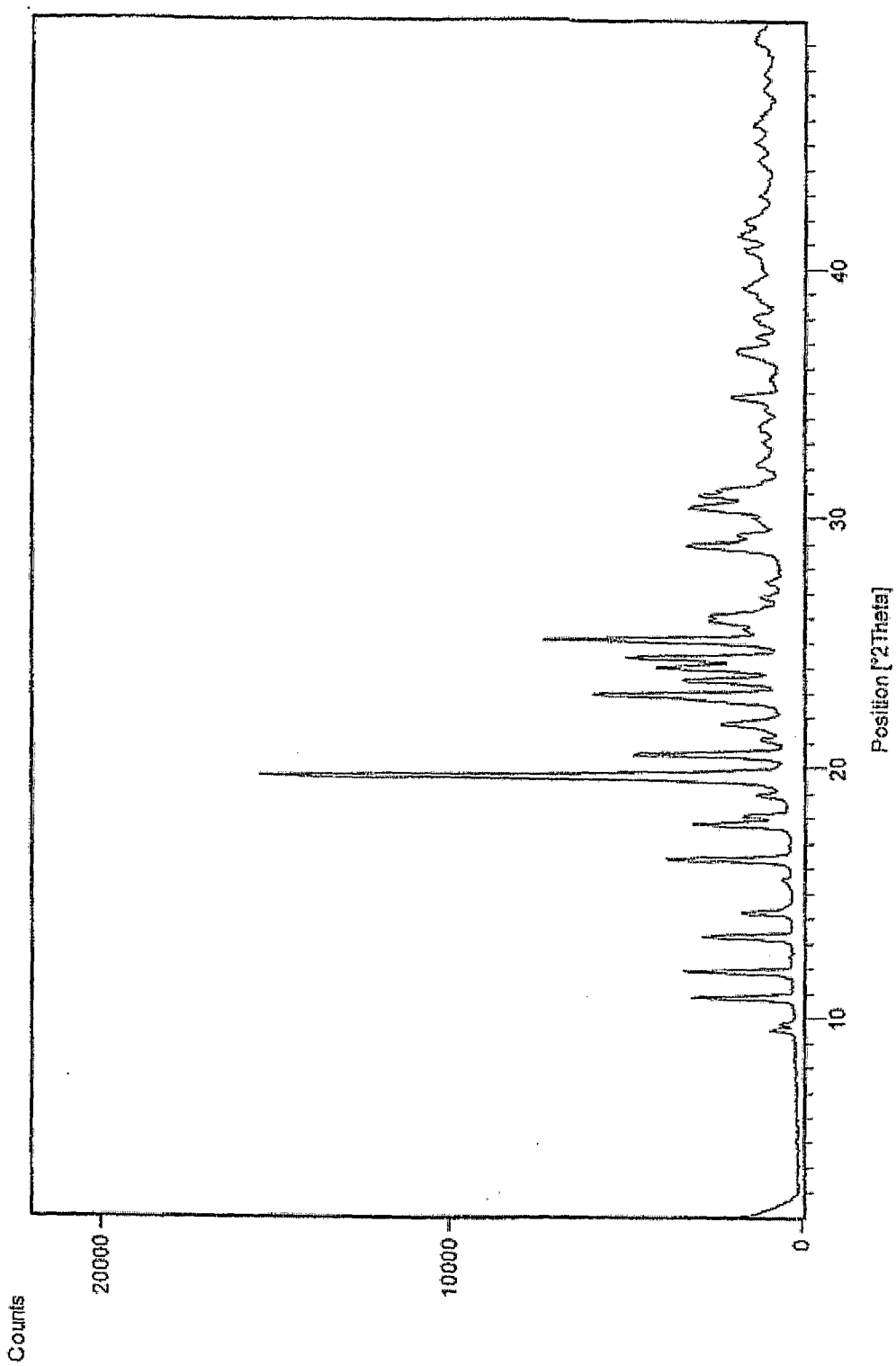


Figure 4

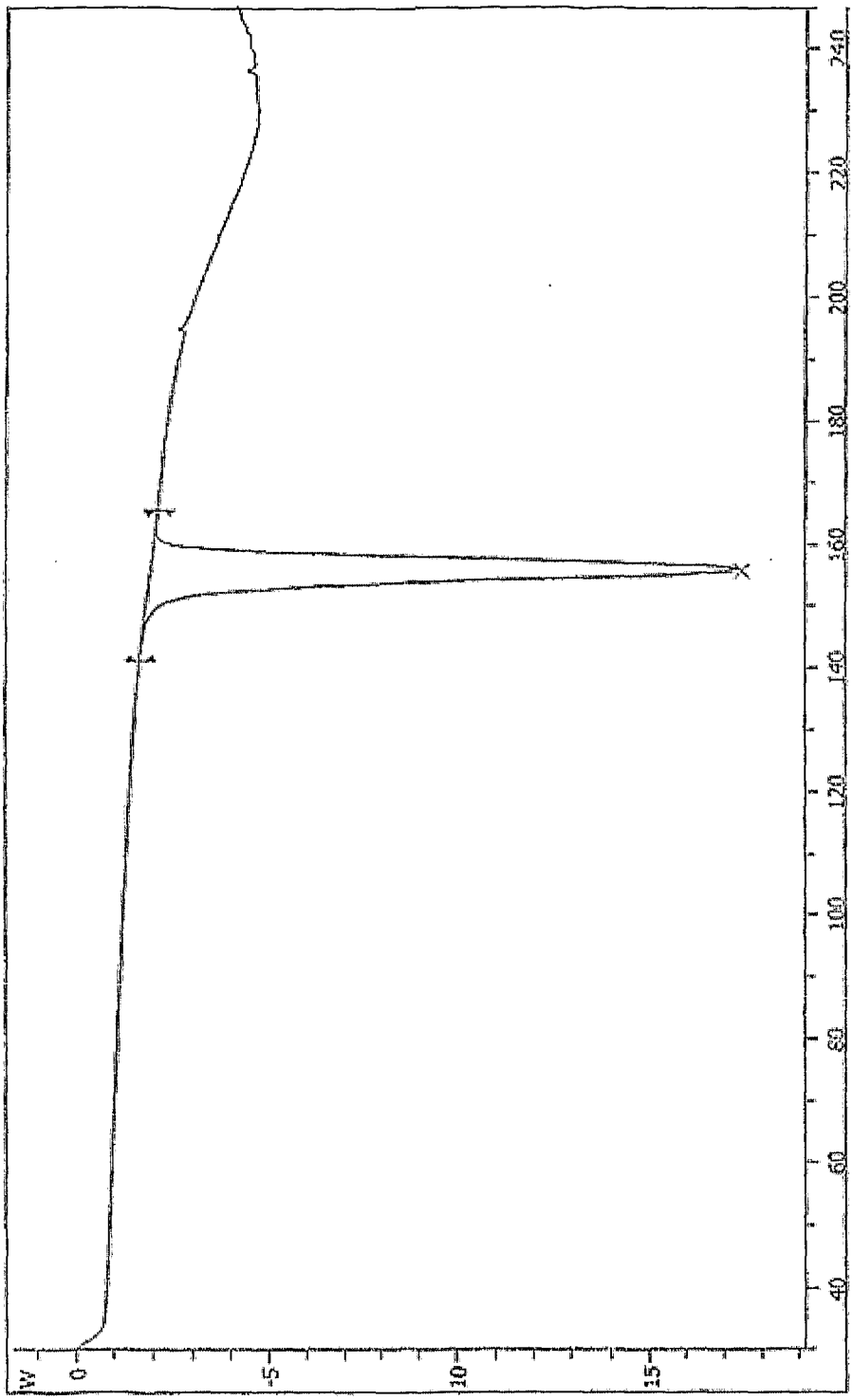


Figure 5

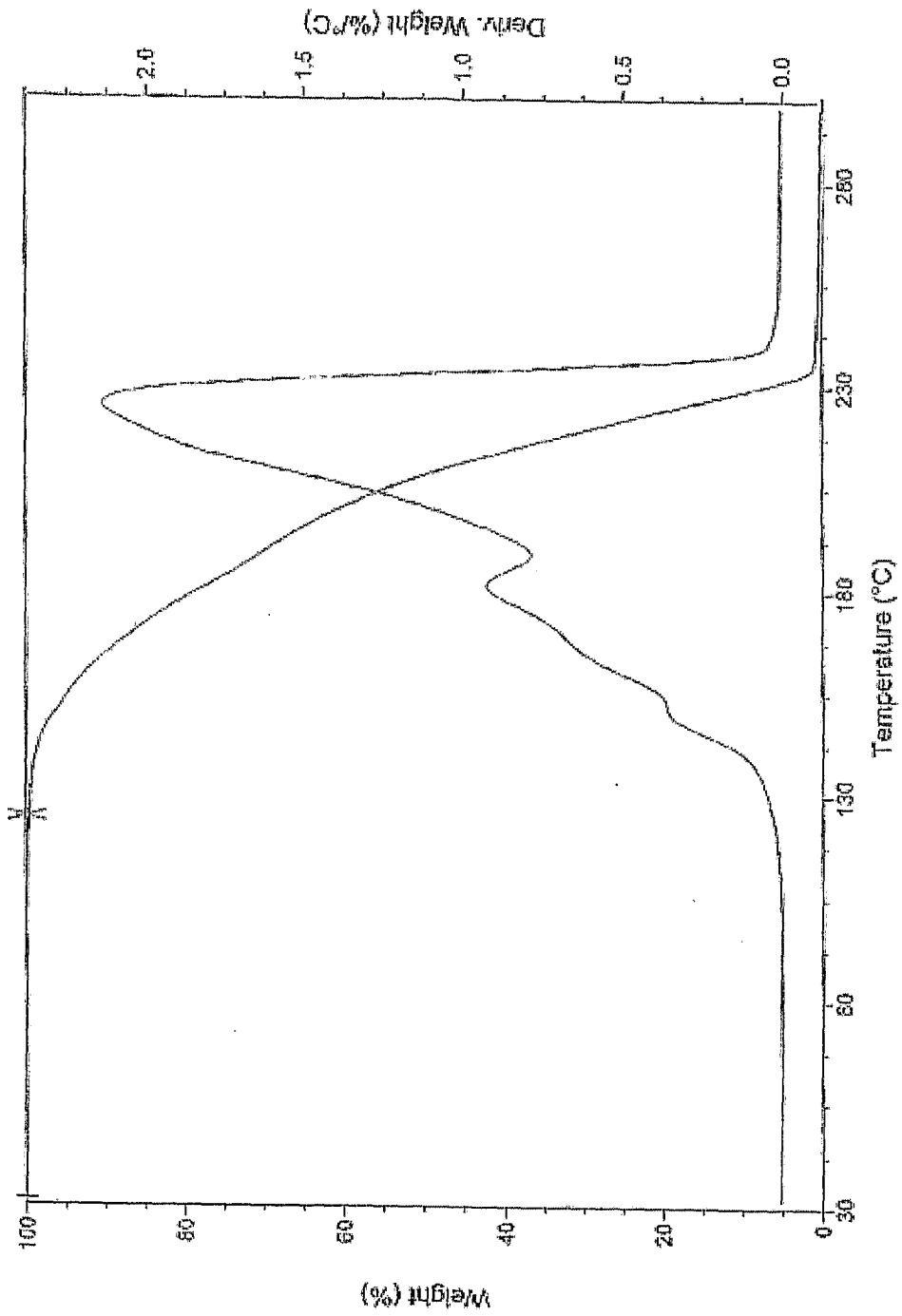

Deriv. Weight (%/°C)
2.0
1.5
1.0
0.5
0.0
Weight (%)
100
80
60
40
20
0
30
60
130
180
230
280
Temperature (°C)

Figure 6

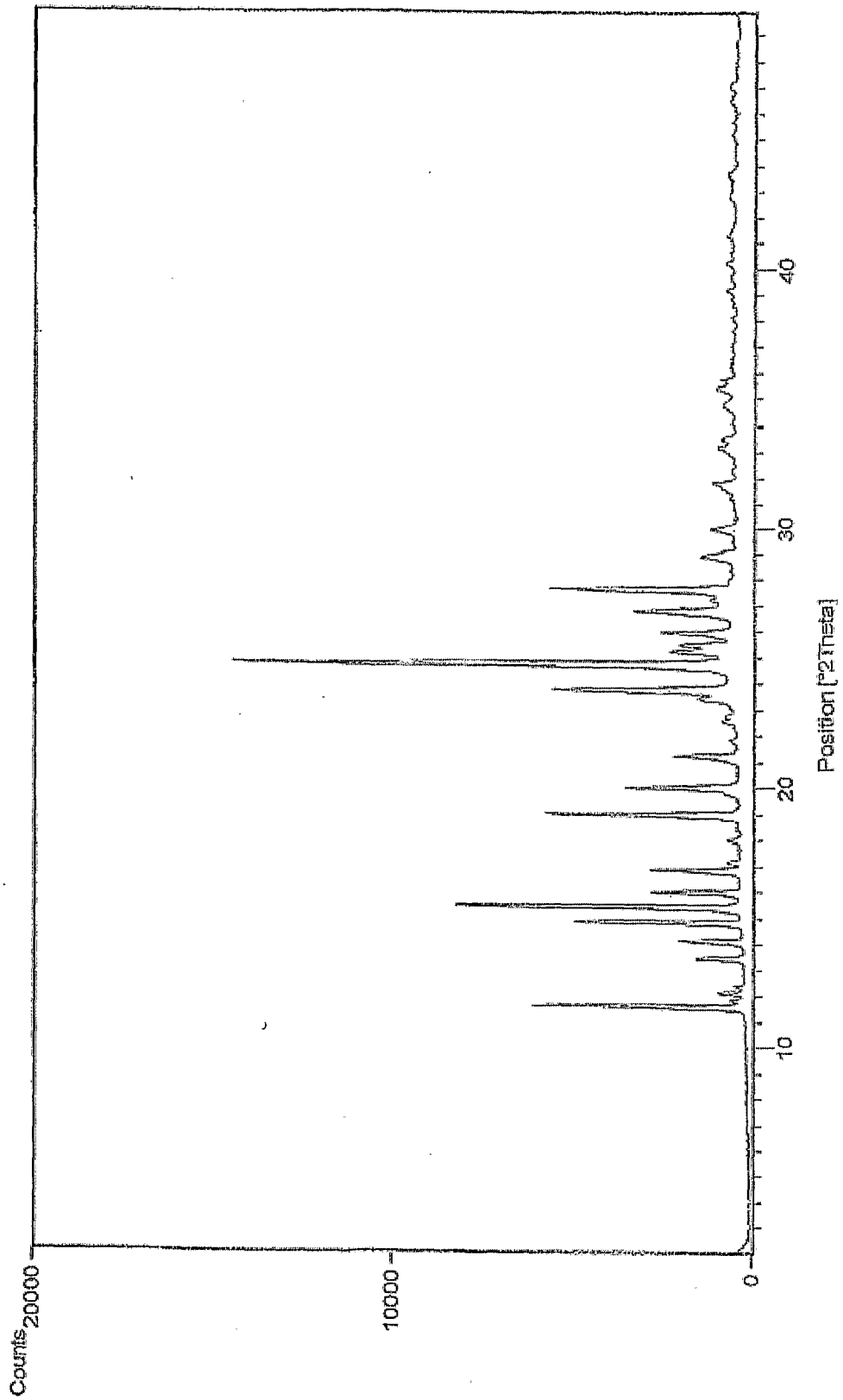


Figure 7

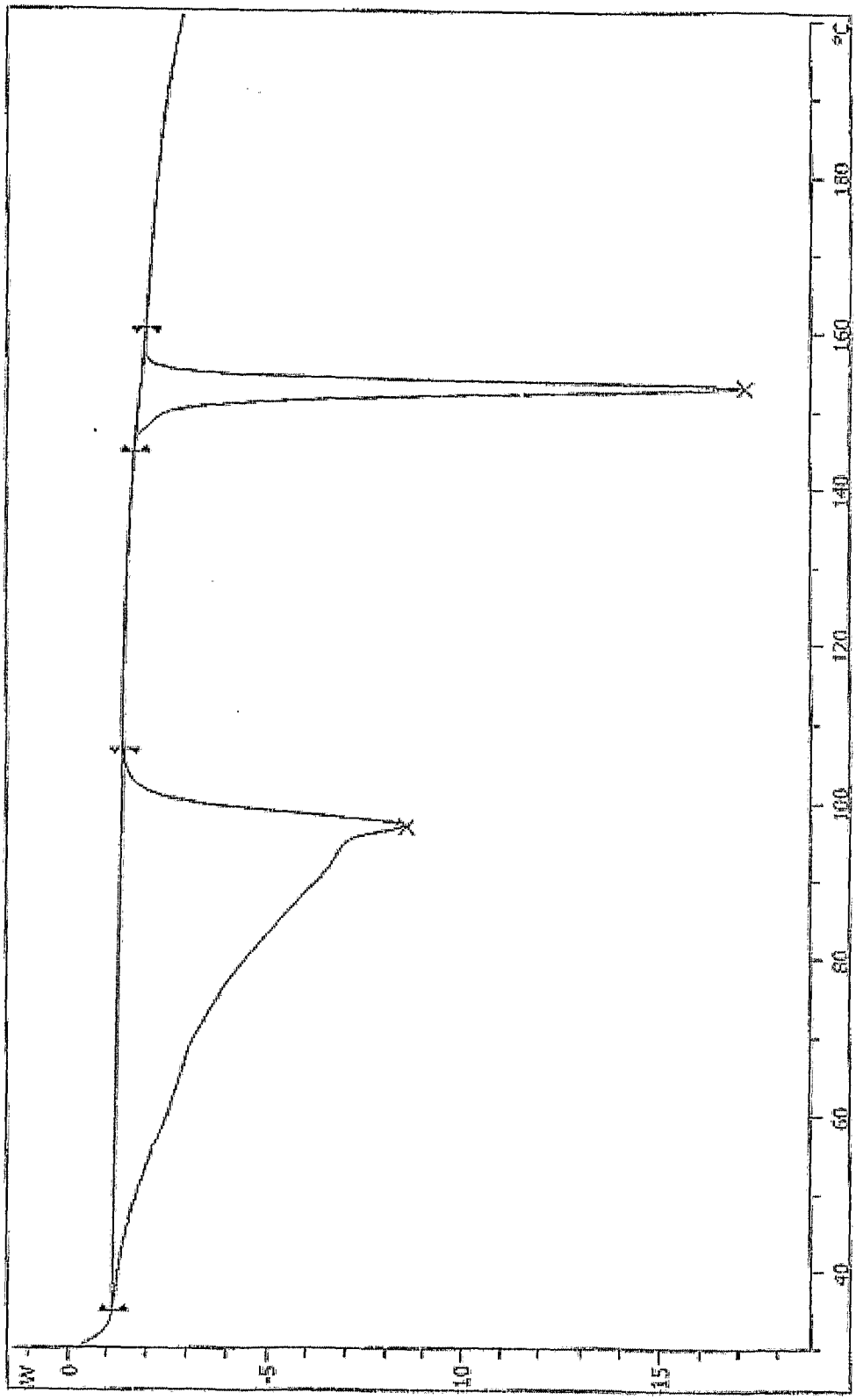


Figure 8

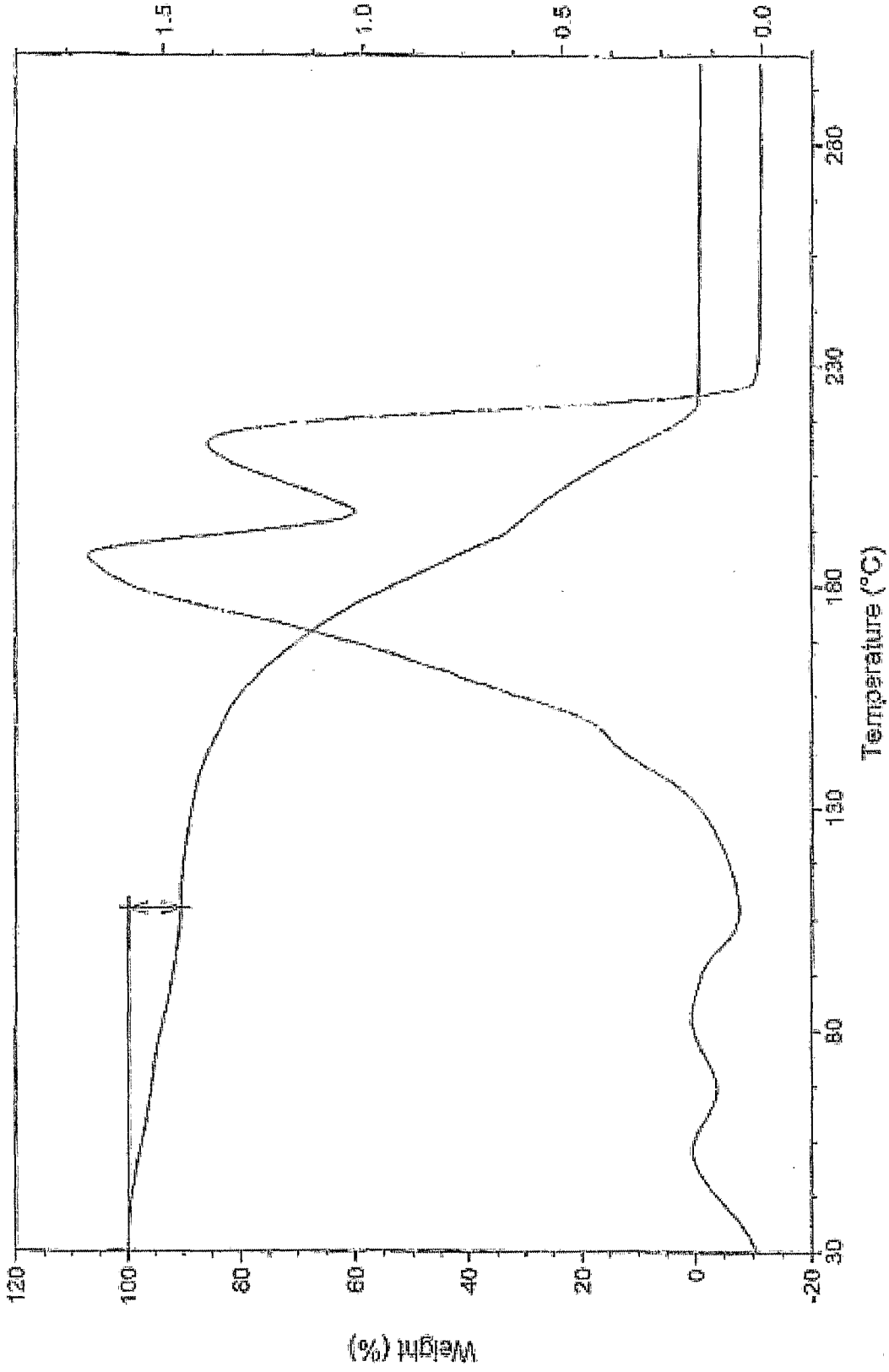

Weight (%)
120
100
80
60
40
20
0
-20
30
80
130
180
230
280
Temperature (°C)
1.5
1.0
0.5
0.0

Figure 9

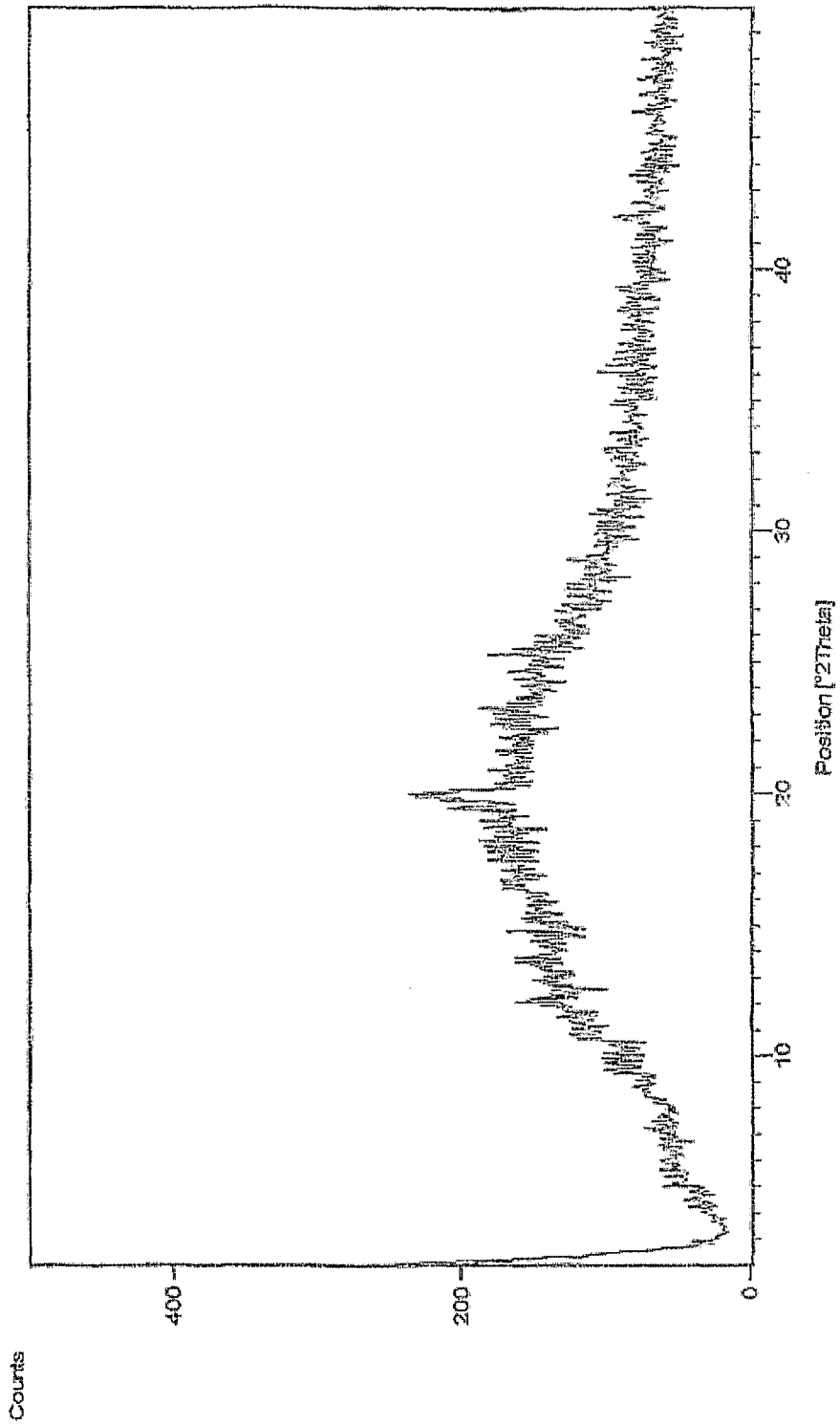


Figure 10