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(71) Applicant (for all designated States except US): **RANBAXY LABORATORIES LIMITED** [IN/IN]; Head Office: 12th Floor, Devika Tower, 06 Nehru Place, New Delhi, Delhi 110019 (IN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **JAYACHANDRA, Suresh, Babu** [IN/IN]; C-237, Sushant Lok - 1, Gurgaon, Haryana 122002 (IN). **SINGH, Tarun, Kumar** [IN/IN]; 485, Eldeco II, Abhishek, SGPGI Road, Lucknow, Uttar Pradesh 226015 (IN). **GAHLOT, Udaibhan, Singh** [IN/IN]; Sukhadia Colony, Moya Bus Stand, TB, Hospital, Bari, Udaipur, Rajasthan 313025 (IN).

(74) Common Representative: **RANBAXY LABORATORIES LIMITED**; c/o Dr. B. Vijayaraghavan, Intellectual

Property Dept., 600 College Road East, Suite 2100, Princeton, NJ 08540 (US).

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(54) Title: CRYSTALLINE FORMS OF LURASIDONE HYDROCHLORIDE

(57) Abstract: The present invention provides crystalline forms of lurasidone hydrochloride, processes for their preparation, pharmaceutical compositions comprising them and their use for the treatment of schizophrenia.



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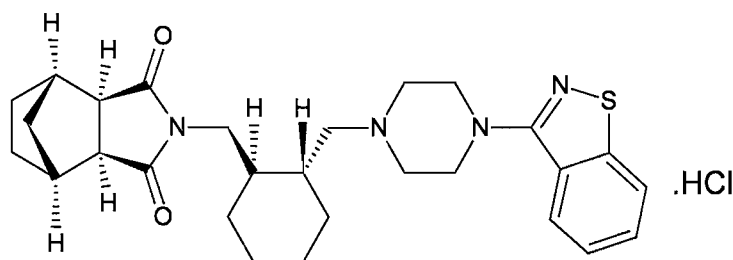
CRYSTALLINE FORMS OF LURASIDONE HYDROCHLORIDE

Field of the Invention

The present invention provides crystalline forms of lurasidone hydrochloride, processes for their preparation, pharmaceutical compositions comprising them and their use for the treatment of schizophrenia.

Background of the Invention

Lurasidone hydrochloride is chemically (3aR,4S,7R,7aS)-2-[(1R,2R)-2-[4-(1,2-benzisothiazol-3-yl)piperazin-1-ylmethyl]cyclohexylmethyl]hexahydro-4,7-methano-2H-isoindole-1,3-dione hydrochloride, having the structure as represented by Formula I and is known from U.S. Patent No. 5,532,372.



Formula I

U.S. Patent No. 5,532,372 describes the preparation of lurasidone hydrochloride using mixture of acetone and iso-propanol solution of hydrogen chloride.

U.S. Patent No. 7,605,260 describes the preparation of lurasidone hydrochloride using aqueous hydrogen chloride.

Summary of the Invention

The present invention provides crystalline forms of lurasidone hydrochloride, processes for their preparation, pharmaceutical compositions comprising them and their use for the treatment of schizophrenia. The crystalline forms of lurasidone hydrochloride of the present invention are highly pure, easy to filter, free-flowing solids having small average particle size. The crystalline forms of the present invention are stable towards polymorphic conversion and show little or no variation in dissolution profile.

A first aspect of the present invention provides crystalline Form 1 of lurasidone hydrochloride characterized by X-ray diffraction peaks at d-spacing of about 5.81, 5.72, 5.55, 5.26 and 4.93 Å.

A second aspect of the present invention provides crystalline Form 2 of lurasidone hydrochloride characterized by X-ray diffraction peaks at d-spacing of about 5.83, 5.56, 5.28, 4.94 and 4.29 Å.

A third aspect of the present invention provides crystalline Form 3 of lurasidone hydrochloride characterized by X-ray diffraction peaks at d-spacing of about 6.50, 5.16, 5.09, 3.61 and 3.43 Å.

A fourth aspect of the present invention provides crystalline Form 4 of lurasidone hydrochloride characterized by X-ray diffraction peaks at d-spacing of about 9.65, 5.82, 5.74, 4.83 and 3.94 Å.

A fifth aspect of the present invention provides a process for the preparation of crystalline Form 1 of lurasidone hydrochloride comprising the steps of:

- i) contacting lurasidone base with dry hydrogen chloride in iso-propanol; and
- ii) isolating crystalline Form 1 of lurasidone hydrochloride.

A sixth aspect of the present invention provides a process for the preparation of crystalline Form 1 of lurasidone hydrochloride comprising the steps of:

- i) contacting lurasidone base with acetone;
- ii) adding dry hydrogen chloride in iso-propanol; and
- iii) isolating crystalline Form 1 of lurasidone hydrochloride.

A seventh aspect of the present invention provides a process for the preparation of crystalline Form 2 of lurasidone hydrochloride comprising the steps of:

- i) contacting lurasidone base with ethyl acetate;
- ii) adding dry hydrogen chloride in iso-propanol; and
- iii) isolating crystalline Form 2 of lurasidone hydrochloride.

An eighth aspect of the present invention provides a process for the preparation of crystalline Form 2 of lurasidone hydrochloride comprising the steps of:

- i) contacting lurasidone base with toluene;
- ii) adding aqueous hydrogen chloride; and
- iii) isolating crystalline Form 2 of lurasidone hydrochloride.

A ninth aspect of the present invention provides a process for the preparation of crystalline Form 3 of lurasidone hydrochloride comprising the steps of:

- i) contacting lurasidone base with acetone;
- ii) adding aqueous hydrogen chloride solution;
- iii) adding an anti-solvent; and
- iv) isolating crystalline Form 3 of lurasidone hydrochloride.

A tenth aspect of the present invention provides a process for the preparation of crystalline Form 4 of lurasidone hydrochloride comprising the steps of:

- i) contacting lurasidone base with ethyl acetate;
- ii) adding aqueous hydrogen chloride solution; and
- iii) isolating crystalline Form 4 of lurasidone hydrochloride.

An eleventh aspect of the present invention provides a process for the purification of lurasidone base comprising contacting crude lurasidone base with a solvent.

A twelfth aspect of the present invention provides lurasidone base having purity greater than 97% as determined by High Performance Liquid Chromatography (HPLC).

A thirteenth aspect of the present invention provides pharmaceutical compositions comprising crystalline Form 1, 2, 3 or 4 of lurasidone hydrochloride and one or more pharmaceutically acceptable carriers, diluents or excipients.

A fourteenth aspect of the present invention provides use of crystalline Form 1, 2, 3 or 4 of lurasidone hydrochloride for the treatment of schizophrenia.

Brief Description of the Figures

Figure 1: X-ray diffraction (XRPD) spectrum of crystalline Form 1 of lurasidone hydrochloride.

Figure 2: Infra-red (IR) spectrum of crystalline Form 1 of lurasidone hydrochloride.

Figure 3: Differential Scanning Thermogram (DSC) of crystalline Form 1 of lurasidone hydrochloride.

Figure 4: Thermogravimetric Analysis (TGA) of crystalline Form 1 of lurasidone hydrochloride.

Figure 5: X-ray diffraction (XRPD) spectrum of crystalline Form 2 of lurasidone hydrochloride.

Figure 6: Infra-red (IR) spectrum of crystalline Form 2 of lurasidone hydrochloride.

Figure 7: Differential Scanning Thermogram (DSC) of crystalline Form 2 of lurasidone hydrochloride.

Figure 8: Thermogravimetric Analysis (TGA) of crystalline Form 2 of lurasidone hydrochloride.

Figure 9: X-ray diffraction (XRPD) spectrum of crystalline Form 3 of lurasidone hydrochloride.

Figure 10: Infra-red (IR) spectrum of crystalline Form 3 of lurasidone hydrochloride.

Figure 11: X-ray diffraction (XRPD) spectrum of crystalline Form 4 of lurasidone hydrochloride.

Figure 12: Infra-red (IR) spectrum of crystalline Form 4 of lurasidone hydrochloride.

Figure 13: HPLC chromatogram of crude lurasidone base.

Figure 14: HPLC chromatogram of pure lurasidone base.

Detailed Description of the Invention

Various embodiments and variants of the present invention are described hereinafter.

The term “contacting” may include dissolving, slurrying, stirring, or a combination thereof.

The term “ambient temperature”, as used herein, refers to a temperature in the range of about 20°C to about 30°C.

The term “about”, as used herein with respect to XRPD peaks, refers to a d-spacing range of $\pm 0.1 \text{ \AA}$ and a 2θ range of $\pm 0.2^\circ$.

Crystalline Form 1 of lurasidone hydrochloride may be characterized by XRPD peaks at about 15.26 (d-spacing at about 5.81 Å), 15.49 (5.72 Å), 15.98 (5.55 Å), 16.85 (5.26 Å) and 18.00 (4.93 Å) $\pm 0.2^\circ 2\theta$. It may be further characterized by XRPD peaks at about 9.01 (9.82 Å), 14.16 (6.25 Å), 18.46 (4.81 Å), 20.77 (4.28 Å) and 21.44 (4.14 Å) $\pm 0.2^\circ 2\theta$. Crystalline Form 1 of lurasidone hydrochloride may also be characterized by XRPD pattern as depicted in Figure 1. Table 1 summarizes the d-spacing in Å and the corresponding 2θ values. Crystalline Form 1 may also be characterized by DSC having endotherms at about 72.50°C and 214.67°C. It may also be characterized by a melting point in the range of about 204°C to 216°C with decomposition. Figures 2, 3 and 4 provide IR, DSC and TGA for crystalline Form 1 of lurasidone hydrochloride, respectively. Crystalline Form 1 of lurasidone hydrochloride of the present invention has purity greater than 97% as determined by High Performance Liquid Chromatography (HPLC).

Table 1: XRPD peaks of crystalline Form 1 of lurasidone hydrochloride

Position (2θ)	d-spacing (Å)	Relative Intensity (%)
4.81	18.38	5.72
5.19	17.02	4.56
8.00	11.05	34.89
9.01	9.82	44.78
9.23	9.58	31.64
9.55	9.27	3.04
10.39	8.51	1.72
12.81	6.91	2.13
13.22	6.65	2.20

Position (°2θ)	d-spacing (Å)	Relative Intensity (%)
14.16	6.25	45.17
14.99	5.91	28.70
15.26	5.81	69.25
15.49	5.72	99.25
15.98	5.55	100.00
16.85	5.26	63.75
17.15	5.17	19.69
18.00	4.93	66.22
18.46	4.81	60.23
19.40	4.58	10.85
19.87	4.47	14.96
20.25	4.39	32.33
20.77	4.28	55.03
21.44	4.14	48.89
21.79	4.08	23.23
22.37	3.98	23.76
22.63	3.93	29.84
23.11	3.85	19.32
23.50	3.79	11.79
23.93	3.72	7.15
24.51	3.63	10.34
24.85	3.58	10.86
25.44	3.50	29.14
25.78	3.46	19.29
26.45	3.37	43.96
26.98	3.31	16.73
27.45	3.25	13.96
27.81	3.21	12.55
28.24	3.16	13.31
29.17	3.06	11.02
29.57	3.02	10.79
29.96	2.98	10.49
30.78	2.91	24.42
31.10	2.88	13.27
31.48	2.84	10.45
32.20	2.78	11.77
32.98	2.72	9.03
33.44	2.68	14.11
35.13	2.55	14.90
35.49	2.53	9.89
36.56	2.46	6.27
37.10	2.42	10.26
39.98	2.31	8.11

Crystalline Form 2 of lurasidone hydrochloride may be characterized by XRPD peaks at about 15.20 (d-spacing at about 5.83 Å), 15.93 (5.56 Å), 16.80 (5.28 Å), 17.95 (4.94 Å) and 20.72 (4.29 Å) $\pm 0.2^\circ 2\theta$. It may be further characterized by XRPD peaks at about 8.96 (9.87 Å), 14.11 (6.28 Å), 15.41 (5.75 Å), 21.41 (4.15 Å) and 26.41 (3.38 Å) $\pm 0.2^\circ 2\theta$. Crystalline Form 2 of lurasidone hydrochloride may also be characterized by XRPD pattern as depicted in Figure 5. Table 2 summarizes the d-spacing in Å and the corresponding 2θ values. Crystalline Form 2 may also be characterized by DSC having endotherms at about 75.01°C and 214.99°C. It may also be characterized by a melting point in the range of about 211°C to 213°C with decomposition. Figures 6, 7 and 8 provide IR, DSC and TGA for crystalline Form 2 of lurasidone hydrochloride, respectively. Crystalline Form 2 of lurasidone hydrochloride of the present invention has purity greater than 98% as determined by HPLC.

Table 2: XRPD peaks of crystalline Form 2 of lurasidone hydrochloride

Position ($^\circ 2\theta$)	d-spacing (Å)	Relative Intensity (%)
4.77	18.53	7.98
7.96	11.11	34.52
8.96	9.87	50.12
9.5	9.30	2.79
10.41	8.50	1.91
13.39	6.61	2.59
14.11	6.28	53.60
14.30	6.20	12.50
15.20	5.83	58.77
15.41	5.75	38.36
15.93	5.56	100.00
16.26	5.45	7.90
16.80	5.28	62.30
17.95	4.94	78.15
19.34	4.59	11.88
20.31	4.37	21.06
20.72	4.29	62.37
21.41	4.15	49.06
22.32	3.98	24.81
22.74	3.91	10.12
23.40	3.80	9.35
24.79	3.59	13.43
25.27	3.52	12.11
26.41	3.38	48.11
26.88	3.32	12.56

Position (°2 θ)	d-spacing (Å)	Relative Intensity (%)
27.42	3.25	14.90
28.18	3.17	15.43
29.12	3.07	10.38
29.55	3.02	10.68
29.91	2.99	9.83
30.53	2.93	12.07
31.43	2.85	10.55
32.17	2.78	8.65
32.94	2.72	8.51
33.54	2.67	11.73
34.86	2.57	14.53
37.01	2.43	9.74
38.56	2.33	4.72
39.38	2.29	5.55

Crystalline Form 3 of lurasidone hydrochloride may be characterized by XRPD peaks at about 13.62 (d-spacing at about 6.50 Å), 17.17 (5.16 Å), 17.41 (5.09 Å), 24.68 (3.61 Å) and 25.99 (3.43 Å) $\pm$ 0.2° 2 θ . It may be further characterized by XRPD peaks at about 4.13 (21.41 Å), 12.40 (7.14 Å), 13.87 (6.39 Å), 15.64 (5.66 Å), and 26.32 (3.39 Å) $\pm$ 0.2° 2 θ . Crystalline Form 3 of lurasidone hydrochloride may also be characterized by XRPD pattern as depicted in Figure 9. Table 3 summarizes the d-spacing in Å and the corresponding 2 θ values. Crystalline Form 3 may also be characterized by IR spectrum as depicted in Figure 10. Crystalline Form 3 of lurasidone hydrochloride of the present invention has purity greater than 98% as determined by HPLC.

Table 3: XRPD peaks of crystalline Form 3 of lurasidone hydrochloride

Position (°2 θ)	d-spacing (Å)	Relative Intensity (%)
4.13	21.41	61.99
8.25	10.72	8.53
9.13	9.68	25.72
10.84	8.16	35.79
12.40	7.14	56.82
13.62	6.50	65.30
13.87	6.39	63.43
15.64	5.66	56.77
15.85	5.59	46.71
17.17	5.16	99.15
17.41	5.09	100.00
17.82	4.98	13.78

Position (°2 θ)	d-spacing (Å)	Relative Intensity (%)
18.32	4.84	19.17
19.20	4.62	27.28
19.67	4.51	50.60
20.68	4.29	31.84
21.79	4.08	35.02
22.56	3.94	16.50
23.96	3.71	26.99
24.68	3.61	86.84
24.94	3.57	39.1
25.99	3.43	70.04
26.32	3.39	30.08
26.90	3.31	61.10
27.48	3.25	13.41
28.11	3.17	26.18
28.47	3.13	29.16
28.89	3.09	11.23
29.90	2.99	23.50
30.77	2.91	15.60
32.69	2.74	26.76
34.42	2.60	14.41
36.76	2.44	6.69
38.26	2.35	5.98

Crystalline Form 4 of lurasidone hydrochloride may be characterized by XRPD peaks at about 9.16 (d-spacing at about 9.65 Å), 15.22 (5.82 Å), 15.44 (5.74 Å), 18.39 (4.83 Å) and 22.54 (3.94 Å) $\pm$ 0.2° 2 θ . It may be further characterized by XRPD peaks at about 15.88 (5.58 Å), 20.18 (4.40 Å), 21.46 (4.14 Å), 25.38 (3.51 Å), and 30.72 (2.91 Å) $\pm$ 0.2° 2 θ . Crystalline Form 4 of lurasidone hydrochloride may also be characterized by XRPD pattern as depicted in Figure 11. Table 4 summarizes the d-spacing in Å and the corresponding 2 θ values. Crystalline Form 4 may also be characterized by IR spectrum as depicted in Figure 12. Crystalline Form 4 of the present invention may also be characterized by a melting point in the range of about 214°C to 216°C with decomposition. Crystalline Form 4 of lurasidone hydrochloride of the present invention has purity greater than 98% as determined by HPLC.

Table 4: XRPD peaks of crystalline Form 4 of lurasidone hydrochloride

Position (°2θ)	d-spacing (Å)	Relative Intensity (%)
4.44	19.88	2.32
5.12	17.25	3.43
8.01	11.04	9.33
9.16	9.65	31.35
13.18	6.72	4.57
14.94	5.93	19.71
15.22	5.82	31.63
15.44	5.74	100.00
15.88	5.58	23.75
16.56	5.35	7.97
17.07	5.20	20.64
18.39	4.83	61.98
19.80	4.48	14.68
20.18	4.40	29.99
20.61	4.31	14.72
21.46	4.14	22.40
21.73	4.09	19.73
22.54	3.94	31.15
23.04	3.86	19.19
23.50	3.79	7.13
23.86	3.73	6.96
24.45	3.64	6.56
25.38	3.51	26.72
25.71	3.46	12.07
26.44	3.37	9.56
26.91	3.31	9.67
27.75	3.22	7.07
29.13	3.07	5.62
29.46	3.03	5.92
30.72	2.91	21.85
32.37	2.77	5.60
33.40	2.68	8.09
33.41	2.53	5.61
35.85	2.51	3.35
37.28	2.41	3.40
38.27	2.35	2.89
39.00	2.31	5.02

Crystalline Forms 3 and 4 of the present invention may also be characterized by their Differential Scanning Thermogram (DSC) and Thermogravimetric Analysis (TGA).

Lurasidone base used for the preparation of crystalline forms of lurasidone hydrochloride of the present invention may be obtained by the method known in U.S. Patent No. 5,532,372, which is incorporated herein by reference. It may be obtained as a solution directly from a reaction in which it is formed and used as such without isolation.

In general, lurasidone base may be obtained by refluxing a reaction mixture containing *trans*-3a,7a-octahydroisindolium-2-spiro-1'-[4'-(1,2-benzisothiazol-3-yl)]piperazine methane sulfonate, bicyclo[2.2.1]heptane-2-exo-3-exo-dicarboximide, dibenzo-18-crown-6 and potassium carbonate in xylene or toluene for about 16 to 36 hours to obtain crude lurasidone base.

Purification of lurasidone base may be carried out by contacting with a solvent selected from the group consisting of alcohols, ketones, alkyl acetates, chlorinated hydrocarbons, ethers and hydrocarbons. Examples of alcohols are methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, sec-butanol and n-pentanol. Examples of ketones are acetone, methyl ethyl ketone and methyl isobutyl ketone. Examples of alkyl acetates are ethyl acetate and isopropyl acetate. Examples of chlorinated hydrocarbons are dichloromethane and chloroform. Examples of ethers are diethyl ether, diisopropyl ether and methyl butyl ether. Examples of hydrocarbons are xylene, toluene, hexane, heptanes and pentane. An anti-solvent may also be added in the purification step. The anti-solvent may be selected from water or hydrocarbons. Examples of hydrocarbons are xylene, toluene, hexane, heptanes and pentane. The examples cited herein are for illustrative purposes only and are not meant to limit the choice to only those solvents identified so.

In a preferred embodiment of the present invention, crude lurasidone base may be purified using iso-propanol.

The purification process of the present invention provides lurasidone base having HPLC purity greater than 97%.

Both crude and purified lurasidone base may be used for the preparation of crystalline forms of the present invention.

Crystalline Forms 1, 2, 3 and 4 of lurasidone hydrochloride may be prepared by contacting lurasidone base with hydrogen chloride at a temperature in the range from about 0°C to about 120°C or by contacting a solution of lurasidone base in a solvent with

hydrogen chloride at a temperature in the range from about 0°C to about 120°C. The reaction mixture may be cooled to about -5°C to ambient temperature and stirred for about 1 hour to 2 days. An anti-solvent may be added to the reaction mixture followed by drying. Drying may be carried out using any suitable method, such as drying under reduced pressure, drying under atmospheric pressure, air drying or drying under an inert gas atmosphere, such as under nitrogen. Preferably, drying may be carried out at ambient temperature to about 80°C.

Crystalline Form 1 of lurasidone hydrochloride of the present invention may be obtained by contacting lurasidone base with dry hydrogen chloride in iso-propanol. It may also be obtained by contacting a solution of lurasidone base in acetone with dry hydrogen chloride in iso-propanol.

Crystalline Form 2 of lurasidone hydrochloride of the present invention may be obtained by contacting lurasidone base with an alkyl acetate solvent and adding dry hydrogen chloride in iso-propanol. It may also be prepared by contacting lurasidone base with toluene and adding aqueous hydrogen chloride solution.

Crystalline Form 3 of lurasidone hydrochloride of the present invention may be obtained by contacting lurasidone base with acetone, adding aqueous hydrogen chloride followed by an addition of an anti-solvent selected from ethers and hydrocarbons. Both acyclic and cyclic ethers may be used as anti-solvents. Examples of acyclic ethers may include dimethyl ether, diethyl ether or di-isopropyl ether. Examples of cyclic ethers may include tetrahydrofuran or 1, 4-dioxane. Examples of hydrocarbons may include xylene, toluene, hexane, heptanes or pentane. Preferably, di-isopropyl ether may be used.

Crystalline Form 4 of lurasidone hydrochloride of the present invention may be obtained by contacting lurasidone base with ethyl acetate and adding aqueous hydrogen chloride.

In one embodiment, the present invention provides crystalline Form 1 of lurasidone hydrochloride prepared by contacting lurasidone base with dry hydrogen chloride in iso-propanol at a temperature of about 35°C to 55°C, cooling to ambient temperature, optionally diluting with iso-propanol, stirring for about 2 hours to 2 days

followed by isolation and drying. Drying may be carried out under reduced pressure at a temperature of about 30°C to 60°C, preferably at about 40°C to 45°C.

In another embodiment, the present invention provides crystalline Form 1 of lurasidone hydrochloride prepared by contacting a solution of lurasidone base in acetone with dry hydrogen chloride in iso-propanol at ambient temperature, stirring the reaction mixture for about 2 hours to about 20 hours, cooling to about -15°C to -20°C, diluting with iso-propanol, stirring at ambient temperature for about 1 hour to about 5 hours followed by isolation and drying under reduced pressure at a temperature of about 30°C to about 60°C, preferably at about 40°C to about 45°C.

In another embodiment, the present invention provides crystalline Form 2 of lurasidone hydrochloride prepared by contacting a solution of lurasidone base in ethyl acetate with dry hydrogen chloride in iso-propanol at about 0°C to 5°C, raising the temperature to ambient temperature, stirring for about 1 to 5 hours, followed by isolation and drying. Drying may be carried out under reduced pressure at a temperature of about 30°C to 60°C, preferably at about 40°C to 45°C.

In another embodiment, the present invention provides crystalline Form 2 of lurasidone hydrochloride prepared by contacting a solution of lurasidone base in toluene with 4% to 5% aqueous hydrochloric acid at ambient temperature, overnight stirring followed by isolation and drying. Drying may be carried out under reduced pressure at a temperature of about 30°C to 60°C.

In another embodiment, the present invention provides crystalline Form 3 of lurasidone hydrochloride prepared by contacting a solution of lurasidone base in acetone with about 4% aqueous hydrogen chloride solution, stirring for about 30 minutes to 2 hours, cooling to about -5°C to 10°C, adding an anti-solvent such as ether, cooling to about -5°C to 10°C, filtering and drying under reduced pressure at ambient temperature to about 80°C, preferably at about 50°C. In a preferred embodiment, di-isopropyl ether may be added as an anti-solvent.

In another embodiment, the present invention provides crystalline Form 4 of lurasidone hydrochloride prepared by contacting a solution of lurasidone base in ethyl acetate with 7% aqueous hydrogen chloride solution at about 40°C, cooling to ambient

temperature, diluting with ethyl acetate, filtering and drying under reduced pressure at ambient temperature to about 80°C, preferably at about 50°C.

The crystalline forms of the present invention may be administered as part of a pharmaceutical composition for the treatment of schizophrenia. Accordingly, in a further aspect, there are provided pharmaceutical composition(s) that comprise crystalline forms of lurasidone hydrochloride of the present invention, and one or more pharmaceutically acceptable carrier(s), diluents(s) or excipients(s) and optionally other therapeutic ingredients. The crystalline forms of lurasidone hydrochloride of the present invention may conventionally be formulated into tablets, capsules, suspensions, dispersions, injectables and other pharmaceutical forms. Any suitable route of administration may be employed, for example, peroral or parental.

In the foregoing section, embodiments are described by way of examples to illustrate the processes of invention. However, these are not intended in any way to limit the scope of the present invention. Several variants of the examples would be evident to persons ordinarily skilled in the art which are within the scope of the present invention.

Methods

X-ray diffraction patterns were recorded using Panalytical Expert PRO with copper radiation, Xcelerator as detector, 3-40 as scan range, 0.02 as step size and 3-40° 2 θ as range.

IR spectrum was recorded using Perkin Elmer Spectrum one FT-IR spectrometer.

Melting points were recorded using Buchi melting point B-545.

HPLC purity was determined using a YMC Pack ODS-AM(250x4.6)mm, 5 μ m column with a flow rate: 1.5 mL/minute; column oven temperature: 45°C; Detector: UV at 230nm; Injection volume: 10 μ L; Run time: 37 minutes using buffer and acetonitrile as diluent and 1mL o-phosphoric acid + 100 mL water as buffer.

EXAMPLES

Example 1: Preparation of Lurasidone base

Step A: Preparation of crude lurasidone base

A reaction mixture containing *trans*-3a,7a-octahydroisoindolium-2-spiro-1'-[4'-(1,2-benzisothiazol-3-yl)]piperazine methane sulfonate (3.0 g), bicyclo[2.2.1]heptane-2-exo-3-exo-dicarboximide (1.7 g), dibenzo-18-crown-6 (0.03 g) and potassium carbonate (1.4 g) in xylene (40 mL) was refluxed for about 24 hours. The contents were filtered at about 50°C and concentrated under reduced pressure at a temperature of about 70°C to obtain crude lurasidone base as a sticky solid (4.0 g).

HPLC Purity: 95.35%

Step B: Purification of lurasidone base

2.8 g of the crude lurasidone base was treated with iso-propanol (20 mL) to isolate pure lurasidone base as a free-flowing white solid (1.9 g).

Yield: 70%

HPLC Purity: 97.42%

Melting point: 126.3°C

Example 2: Preparation of Crystalline Form 1 of Lurasidone Hydrochloride from Crude Lurasidone base

A reaction mixture containing 2.2 g of crude lurasidone base and dry hydrogen chloride in iso-propanol (10 mL) was heated to a temperature of about 45°C. The reaction mixture was cooled to ambient temperature and stirred for about 20 hours. The solid material was filtered, washed with iso-propanol (5 mL) and dried under reduced pressure at about 45°C to obtain crystalline Form 1 of lurasidone hydrochloride as a white solid (1.2 g).

Yield: 50.5%

HPLC purity: 97.05%

Melting point: 204°C -211°C with decomposition

Example 3: Preparation of Crystalline Form 1 of Lurasidone Hydrochloride from Pure Lurasidone base

A reaction mixture containing 4.0 g of pure lurasidone base and dry hydrogen chloride in iso-propanol (20 mL) was heated to a temperature of about 40°C. The reaction mixture was cooled to ambient temperature, diluted with iso-propanol (40 mL) and further stirred for about 5 hours. The solid material was filtered, washed with iso-propanol (15 mL) and dried under reduced pressure at about 45°C to obtain crystalline Form 1 of lurasidone hydrochloride as a white solid (3.3 g).

Yield: 77%

HPLC purity: 98.84%

Melting point: 214°C -216°C with decomposition

Example 4: Preparation of Crystalline Form 1 of Lurasidone Hydrochloride from Pure Lurasidone base

Dry hydrogen chloride in iso-propanol (5 mL) was added to a solution of pure lurasidone base (1 g) in acetone (5 mL) at ambient temperature. The reaction mixture was stirred for about 8 hours and cooled to about -15°C to -20°C. The reaction mass was diluted with iso-propanol (5 mL), stirred for about 3 hours at ambient temperature, filtered, washed with acetone (3 mL) and dried under reduced pressure at about 45°C to obtain crystalline Form 1 of lurasidone hydrochloride as a white solid (0.35 g).

Yield: 32.6%

Example 5: Preparation of Crystalline Form 2 of Lurasidone Hydrochloride from Crude Lurasidone base

0.5 g of crude lurasidone base was dissolved in ethyl acetate (5 mL) by heating at a temperature of about 40°C. The solution was cooled to about 0°C to 5°C. Dry hydrogen chloride in iso-propanol (2 mL) was added drop-wise. The temperature was raised to ambient temperature and the contents were stirred for about 2.5 hours. The solid material

was filtered, washed with ethyl acetate (3 mL) and dried under reduced pressure at about 45°C to obtain crystalline Form 2 of lurasidone hydrochloride as a white solid.

Yield: 47%

HPLC purity: 99.03%

Example 6: Preparation of Crystalline Form 2 of Lurasidone Hydrochloride from Pure Lurasidone base

4.0 g of pure lurasidone base was dissolved in ethyl acetate (40 mL) by heating at a temperature of about 40°C. The solution was cooled to about 0°C to 5°C. Dry hydrogen chloride in iso-propanol (20 mL) was added drop-wise. The temperature was raised to ambient temperature and the contents were stirred for about 3.5 hours. The solid material was filtered, washed with ethyl acetate (10 mL) and dried under reduced pressure at about 45°C to obtain crystalline Form 2 of lurasidone hydrochloride as a white solid (4.0 g).

Yield: 93%

HPLC purity: 98.65%

Melting point: 211°C -213°C with decomposition

Example 7: Preparation of Crystalline Form 2 of Lurasidone Hydrochloride from Pure Lurasidone base

4%-5% aqueous hydrochloric acid (2.5 mL) was added to a solution of pure lurasidone base (0.25 g) in toluene (4 mL) at ambient temperature. The reaction mixture was stirred overnight, diluted with toluene (4 mL), filtered, washed with toluene (3 mL) and dried under reduced pressure at about 50°C to obtain crystalline Form 2 of lurasidone base (0.17 g).

Yield: 63%

Example 8: Preparation of Crystalline Form 3 of Lurasidone Hydrochloride from Crude Lurasidone base

3.0 g of crude lurasidone base was dissolved in acetone (30 mL) by heating the reaction mixture at a temperature of about 55°C followed by drop-wise addition of 4% aqueous hydrochloric acid solution (6 mL). The reaction mixture was stirred for about 1 hour and then cooled to about 0°C. Solvent was recovered completely from the reaction mixture. Fresh acetone (50 mL) was added and the reaction mixture was dried over anhydrous sodium sulphate (1.0 g). Di-isopropyl ether (5mL) was added drop-wise to the reaction mixture. Turbidity was observed. The reaction mixture was cooled to about 0°C to -5°C and filtered. Solid material was dried under reduced pressure at about 50°C to obtain crystalline Form 3 of lurasidone hydrochloride as a white solid (1.2 g).

Yield: 37%

HPLC purity: 98.09%

Example 9: Preparation of Crystalline Form 4 of Lurasidone Hydrochloride from Pure Lurasidone base

1.0 g of pure lurasidone base was dissolved in ethyl acetate (10 mL) by heating the reaction mixture at a temperature of about 40°C followed by drop-wise addition of about 7% aqueous hydrogen chloride solution (5 mL). The reaction mixture was cooled to ambient temperature, diluted with ethyl acetate (15 mL) and stirred for about 2 hours. The solid material was filtered, washed with ethyl acetate (10 mL) and dried under reduced pressure at about 45°C to obtain crystalline Form 4 of lurasidone hydrochloride as a white solid (1.0 g).

Yield: 93%

HPLC purity: 98.98%

Melting point: 214°C -216°C with decomposition

We claim:

1. A crystalline form of lurasidone hydrochloride characterized by having at least one X-ray diffraction peak with a relative intensity of not less than 2% at d-spacing in the range 17.0-22.0.
2. Crystalline Form 1 of lurasidone hydrochloride characterized by X-ray diffraction peaks at d-spacing of about 5.81, 5.72, 5.55, 5.26 and 4.93 Å.
3. Crystalline Form 1 of lurasidone hydrochloride of claim 2 further characterized by XRPD peaks at about 9.82, 6.25, 4.81, 4.28 and 4.14 Å.
4. Crystalline Form 1 of lurasidone hydrochloride of claim 2 characterized by XRPD pattern as depicted in Figure 1.
5. Crystalline Form 1 of lurasidone hydrochloride of claim 2 characterized by IR spectrum as depicted in Figure 2.
6. Crystalline Form 1 of lurasidone hydrochloride of claim 2 characterized by DSC having endotherms at about 72.50°C and 214.67°C.
7. Crystalline Form 1 of lurasidone hydrochloride of claim 2 characterized by DSC as depicted in Figure 3.
8. Crystalline Form 1 of lurasidone hydrochloride of claim 2 characterized by TGA as depicted in Figure 4.
9. A process for the preparation of crystalline Form 2 of lurasidone hydrochloride comprising the steps of:
 - i) contacting lurasidone base with dry hydrogen chloride in iso-propanol; and
 - ii) isolating crystalline Form 1 of lurasidone hydrochloride.
10. The process according to claim 9, wherein lurasidone base is contacted with dry hydrogen chloride in iso-propanol at about 35°C to 55°C.
11. The process according to claim 9, wherein the reaction mixture is stirred for about 2 hours to 20 hours.
12. Crystalline Form 2 of lurasidone hydrochloride characterized by X-ray diffraction peaks at d-spacing of about 5.83, 5.56, 5.28, 4.94 and 4.29 Å.

13. Crystalline Form 2 of lurasidone hydrochloride of claim 12 further characterized by XRPD peaks at about 9.87, 6.28 Å, 5.75, 4.15 and 3.38 Å.
14. Crystalline Form 2 of lurasidone hydrochloride of claim 12 characterized by XRPD pattern as depicted in Figure 5.
15. Crystalline Form 2 of lurasidone hydrochloride of claim 12 characterized by IR spectrum as depicted in Figure 6.
16. Crystalline Form 2 of lurasidone hydrochloride of claim 12 characterized by DSC having endotherms at about 75.01°C and 214.99°C.
17. Crystalline Form 2 of lurasidone hydrochloride of claim 12 characterized by DSC as depicted in Figure 7.
18. Crystalline Form 2 of lurasidone hydrochloride of claim 12 characterized by TGA as depicted in Figure 8.
19. A process for the preparation of crystalline Form 2 of lurasidone hydrochloride comprising the steps of:
 - i) contacting lurasidone base with ethyl acetate;
 - ii) adding dry hydrogen chloride in iso-propanol; and
 - iii) isolating crystalline Form 2 of lurasidone hydrochloride.
20. The process according to claim 19, wherein a solution of lurasidone base in ethyl acetate is contacted with dry hydrogen chloride in iso-propanol at about 0°C to about 5°C.
21. The process according to claim 19, wherein the reaction mixture is stirred for about 1 hour to 5 hours.
22. A process for the preparation of crystalline Form 2 of lurasidone hydrochloride comprising the steps of:
 - i) contacting lurasidone base with toluene;
 - ii) adding aqueous hydrogen chloride; and
 - iii) isolating crystalline Form 2 of lurasidone hydrochloride.

23. The process according to claim 22, wherein a solution of lurasidone base in toluene is contacted with 4% to 5% aqueous hydrogen chloride.
24. The process according to claim 22, wherein a solution of lurasidone base in toluene is contacted with 4% to 5% aqueous hydrogen chloride at ambient temperature.
25. Crystalline Form 3 of lurasidone hydrochloride characterized by X-ray diffraction peaks at d-spacing of about 6.50, 5.16, 5.09, 3.61 and 3.43 Å.
26. Crystalline Form 3 of lurasidone hydrochloride of claim 25 further characterized by XRPD peaks at about 21.41, 7.14, 6.39, 5.66 and 3.39 Å.
27. Crystalline Form 3 of lurasidone hydrochloride of claim 25 characterized by XRPD pattern as depicted in Figure 9.
28. Crystalline Form 3 of lurasidone hydrochloride of claim 25 characterized by IR spectrum as depicted in Figure 10.
29. A process for the preparation of crystalline Form 3 of lurasidone hydrochloride comprising the steps of:
- i) contacting lurasidone base with acetone;
 - ii) adding aqueous hydrogen chloride solution;
 - iii) adding an anti-solvent; and
 - iv) isolating crystalline Form 3 of lurasidone hydrochloride.
30. The process according to claim 29, wherein a solution of lurasidone base in acetone is contacted with about 4% aqueous hydrogen chloride solution.
31. The process according to claim 29, wherein the reaction mixture is stirred for about 30 minutes to 2 hours.
32. The process according to claim 29, wherein ether is added as anti-solvent.
33. The process according to claim 29, wherein di-isopropyl ether is added as anti-solvent.
34. Crystalline Form 4 of lurasidone hydrochloride characterized by X-ray diffraction peaks at d-spacing of about 9.65, 5.82, 5.74, 4.83 and 3.94 Å.

35. Crystalline Form 4 of lurasidone hydrochloride of claim 34 further characterized by XRPD peaks at about 5.58, 4.40, 4.14, 3.51 and 2.91 Å.
36. Crystalline Form 4 of lurasidone hydrochloride of claim 34 characterized by XRPD pattern as depicted in Figure 11.
37. Crystalline Form 4 of lurasidone hydrochloride of claim 34 characterized by IR spectrum as depicted in Figure 12.
38. A process for the preparation of crystalline Form 4 of lurasidone hydrochloride comprising the steps of:
- i) contacting lurasidone base with ethyl acetate;
 - ii) adding aqueous hydrogen chloride solution; and
 - iii) isolating crystalline Form 4 of lurasidone hydrochloride.
39. The process according to claim 38, wherein a solution of lurasidone base in ethyl acetate is contacted with about 7% aqueous hydrogen chloride solution.
40. The process according to claim 38, wherein a solution of lurasidone base in ethyl acetate is contacted with about 7% aqueous hydrogen chloride solution at about 40°C.
41. A process for the purification of lurasidone base comprising contacting crude lurasidone base with a solvent selected from alcohols, ketones, alkyl acetates, chlorinated hydrocarbons, ethers and hydrocarbons.
42. The process according to claim 41, wherein an alcohol is used as solvent.
43. The process according to claim 41, wherein iso-propanol is used as solvent.
44. Lurasidone base having purity greater than 97% as determined by High Performance Liquid Chromatography (HPLC).
45. Pharmaceutical composition(s) comprising crystalline Form 1, 2, 3 or 4 of lurasidone hydrochloride and one or more pharmaceutically acceptable carrier(s), diluents(s) or excipient(s).
46. Use of crystalline Form 1, 2, 3 or 4 of lurasidone hydrochloride for the treatment of schizophrenia.

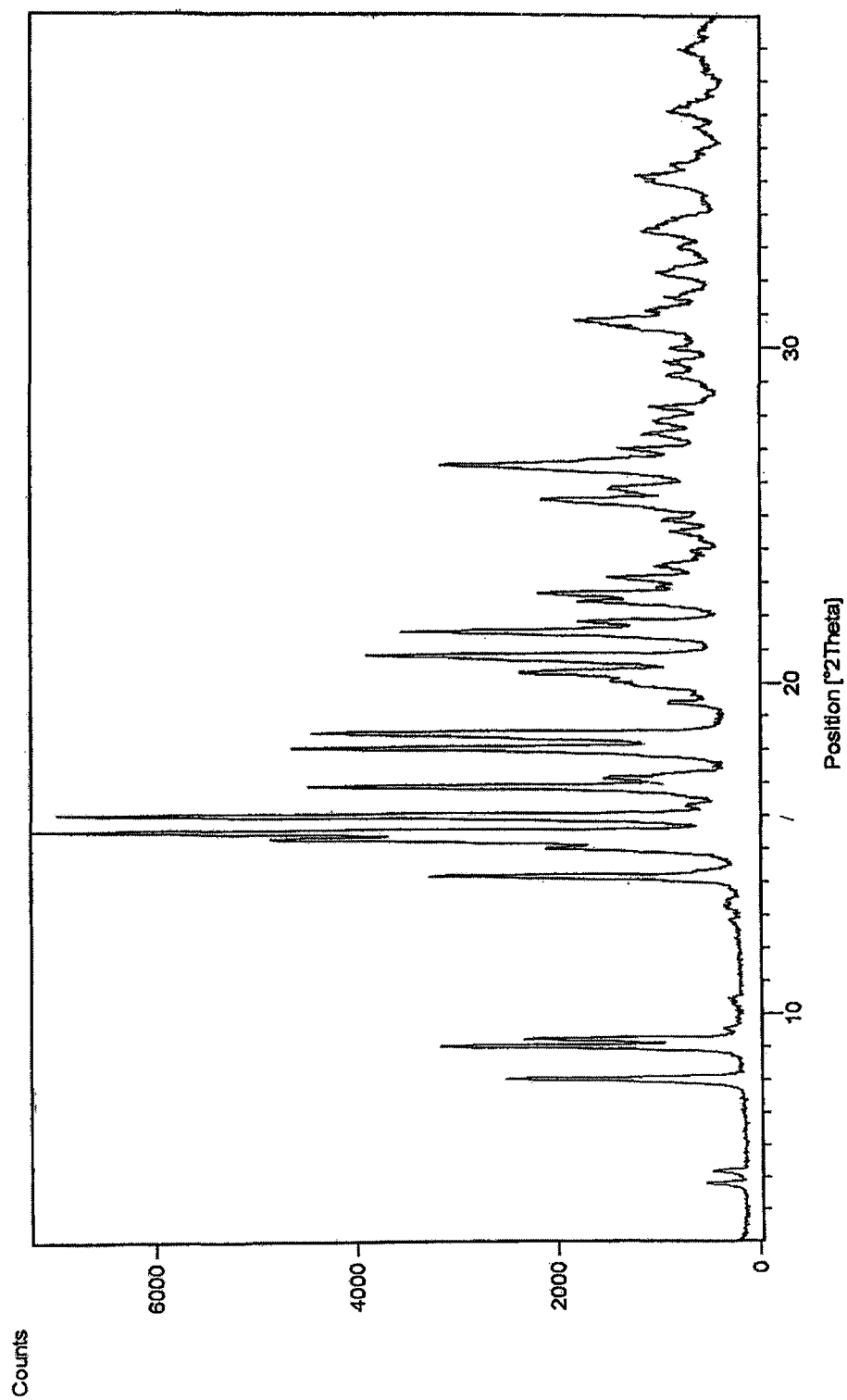
FIGURE 1

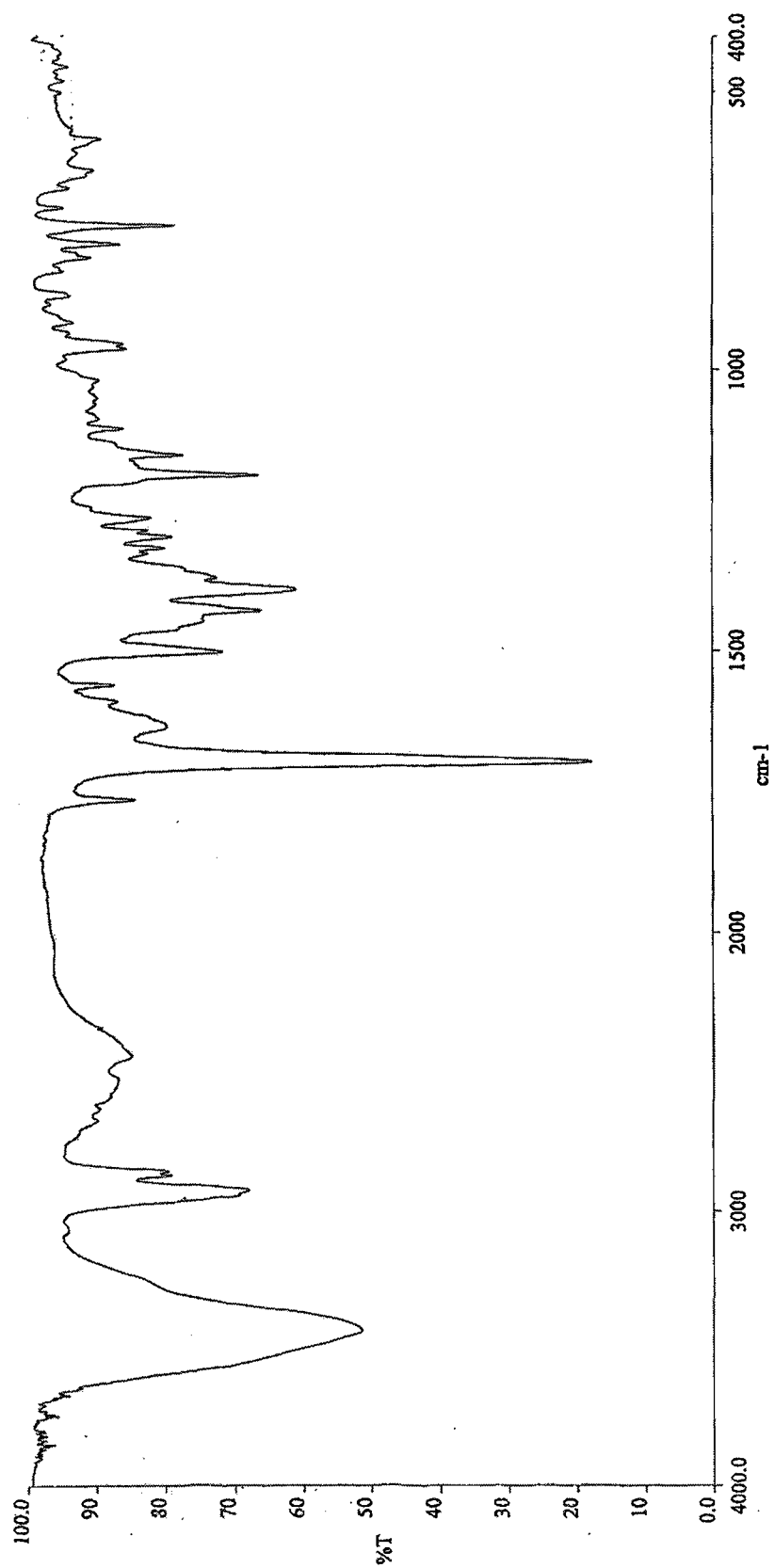
FIGURE 2

FIGURE 3

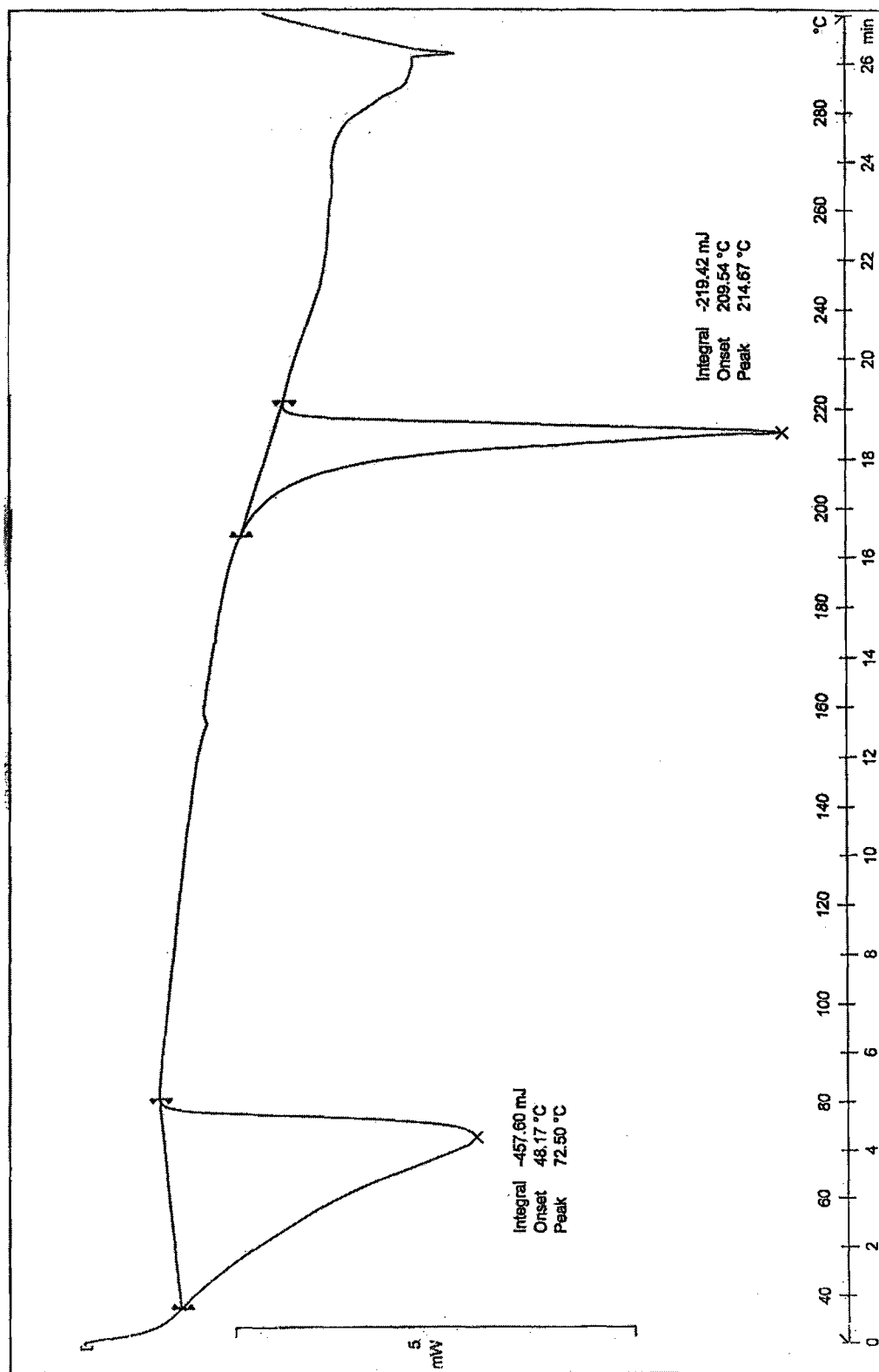


FIGURE 4

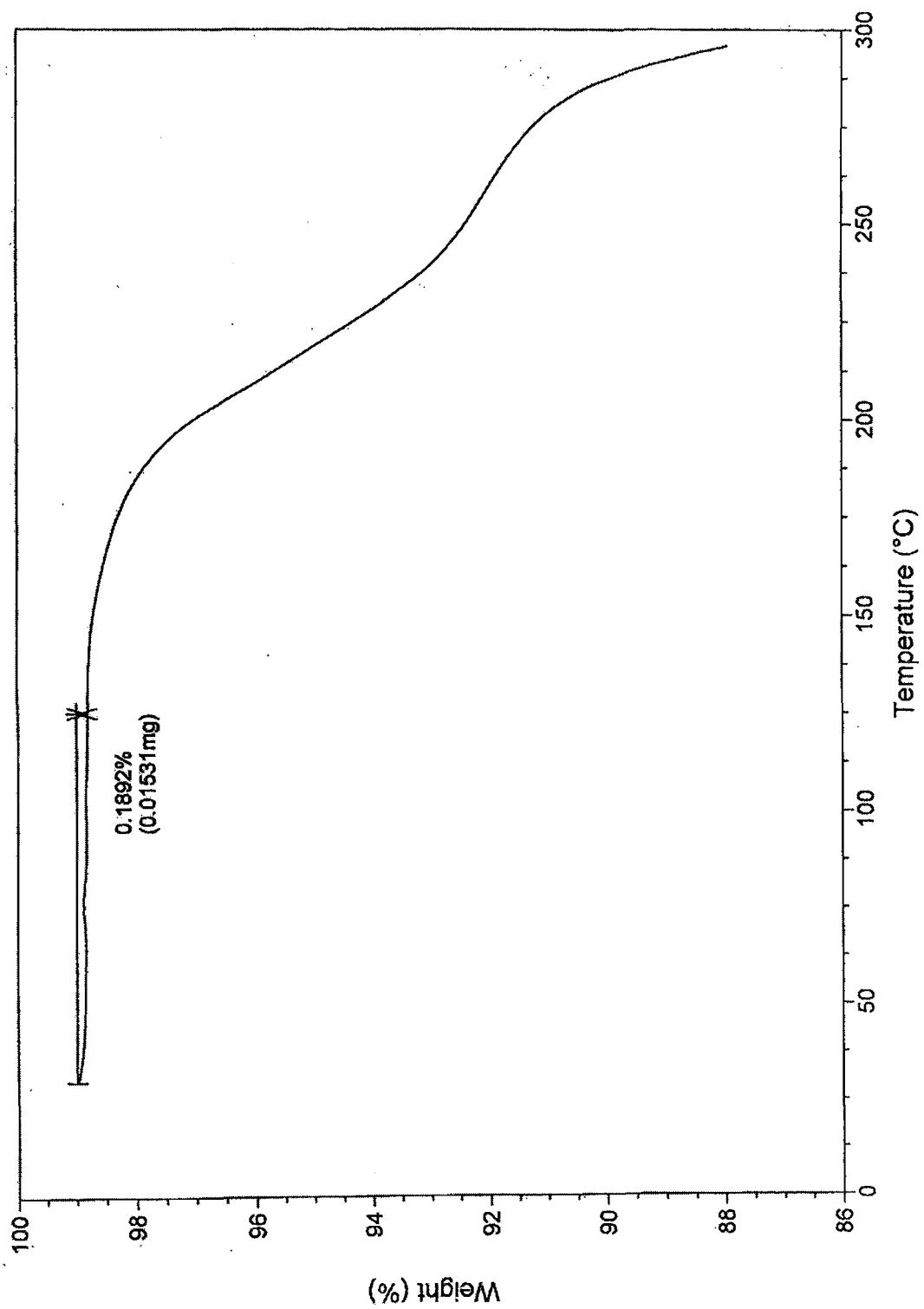


FIGURE 5

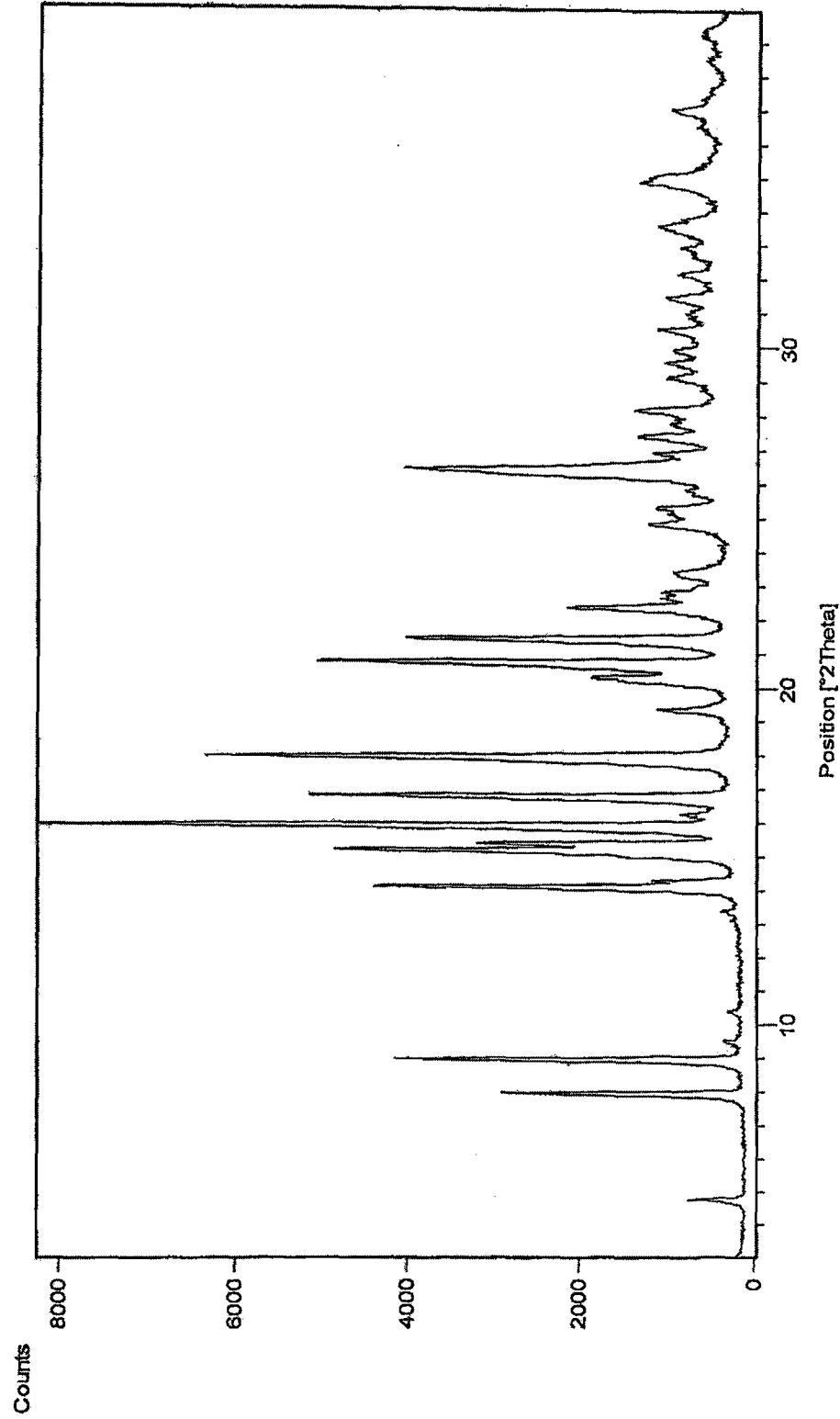


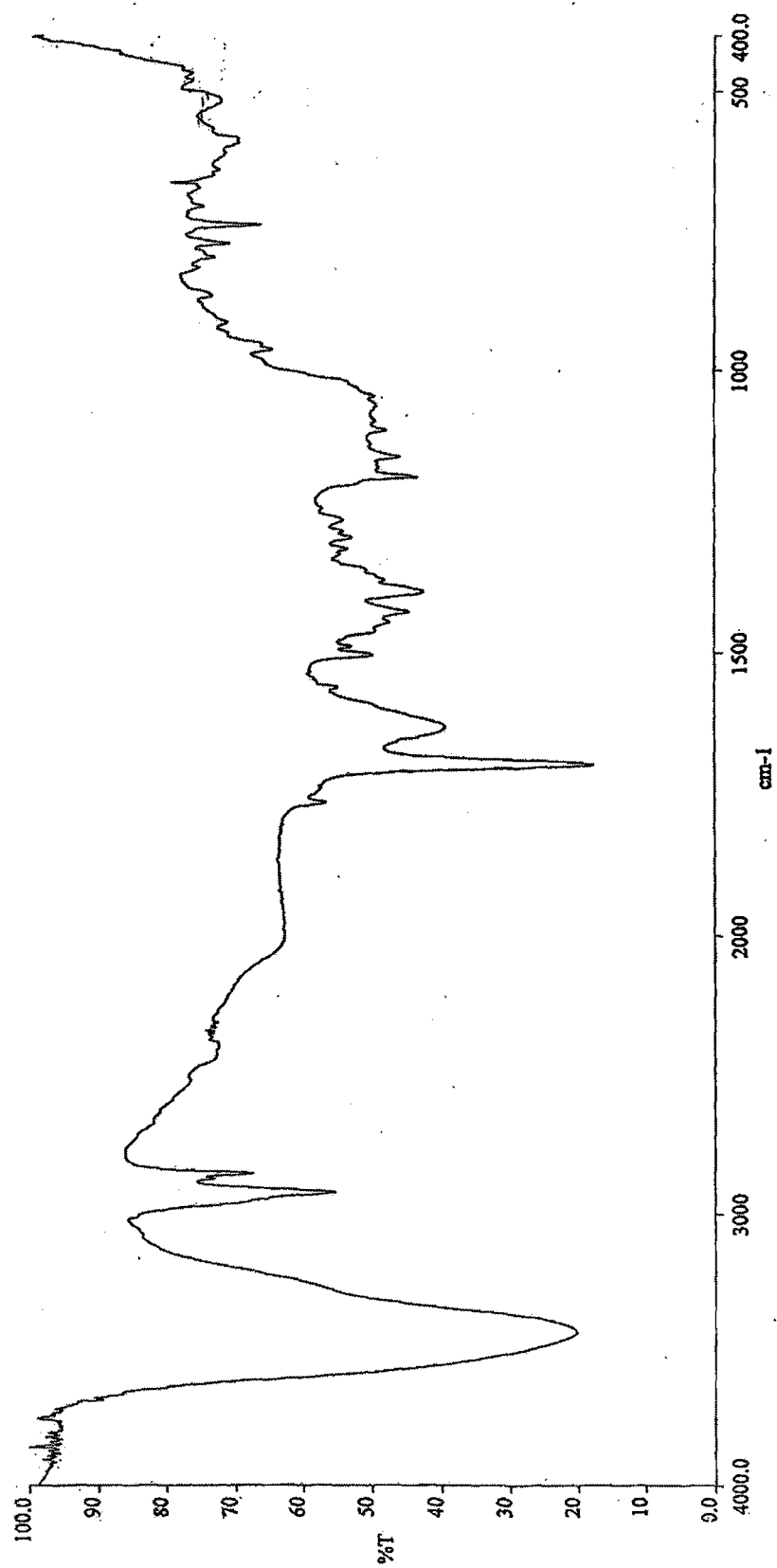
FIGURE 6

FIGURE 7

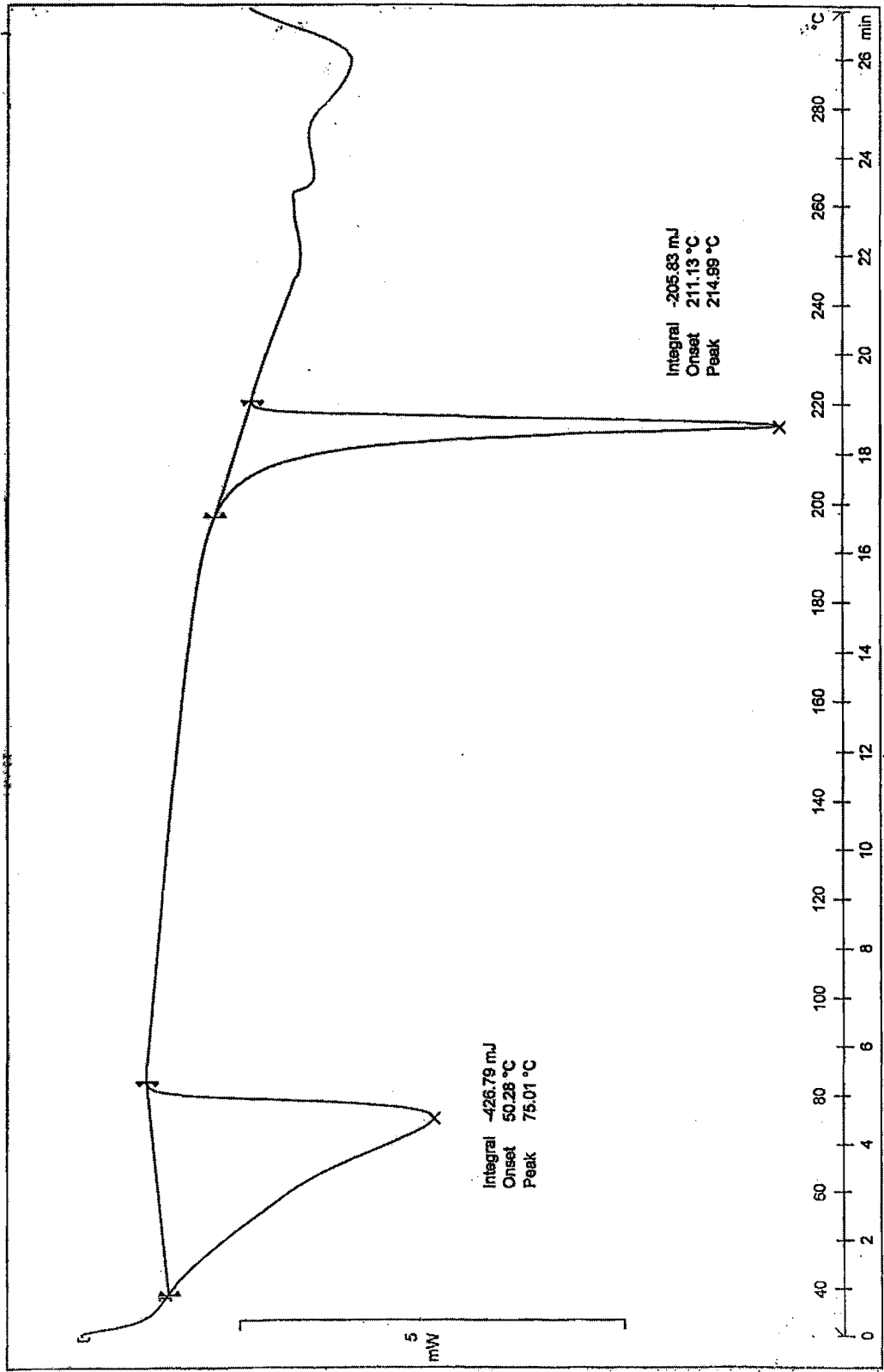


FIGURE 8

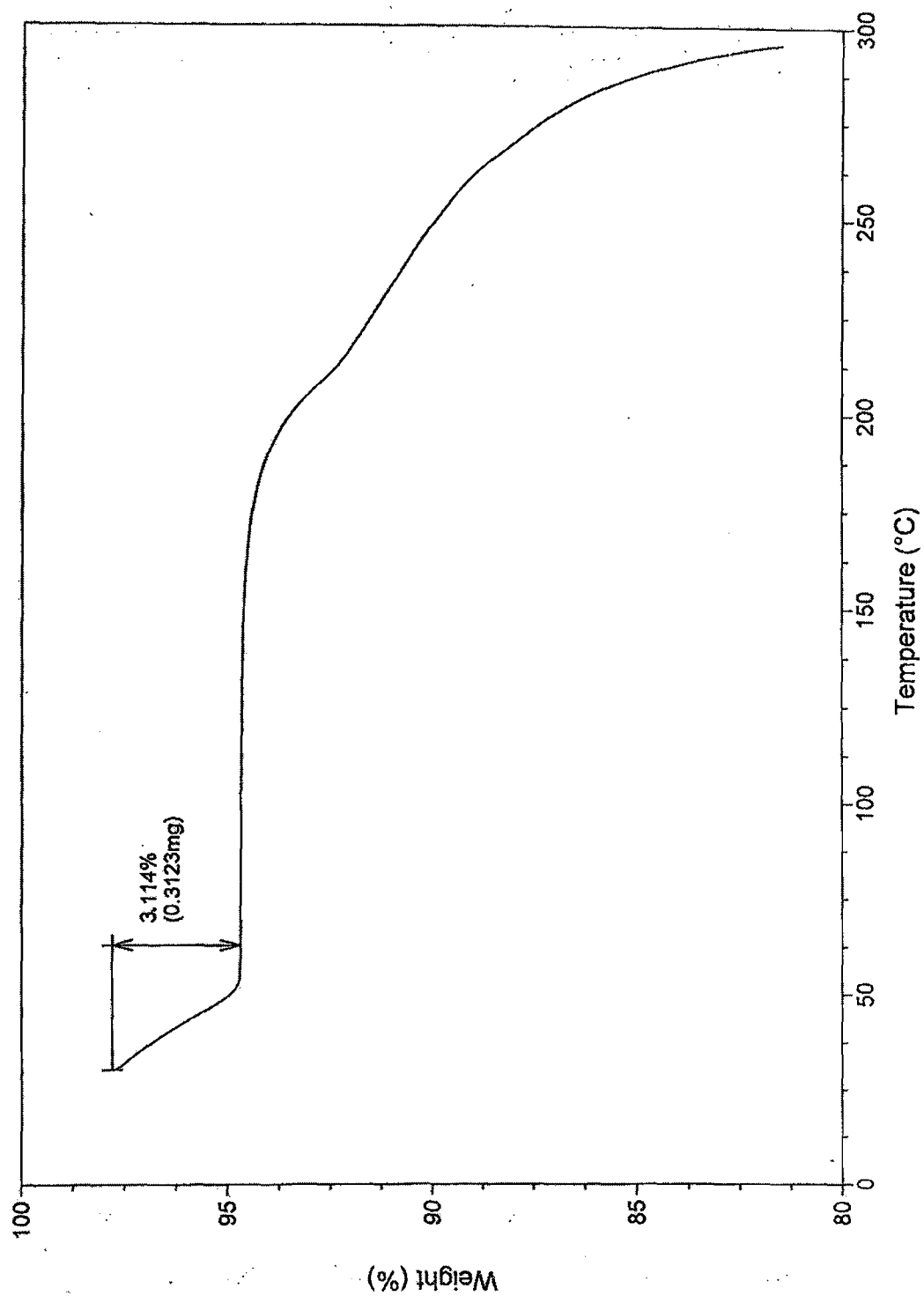


FIGURE 9

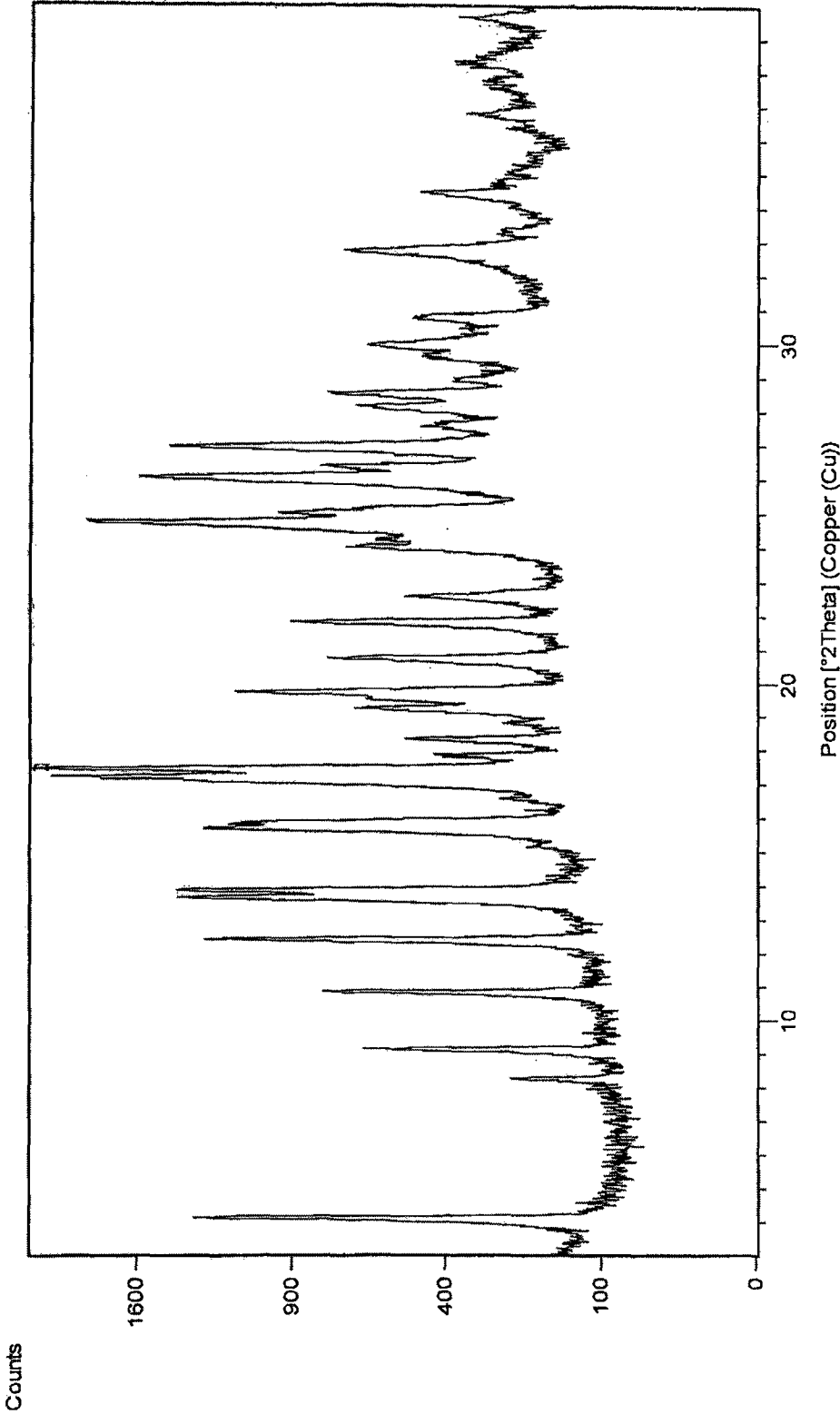


FIGURE 10

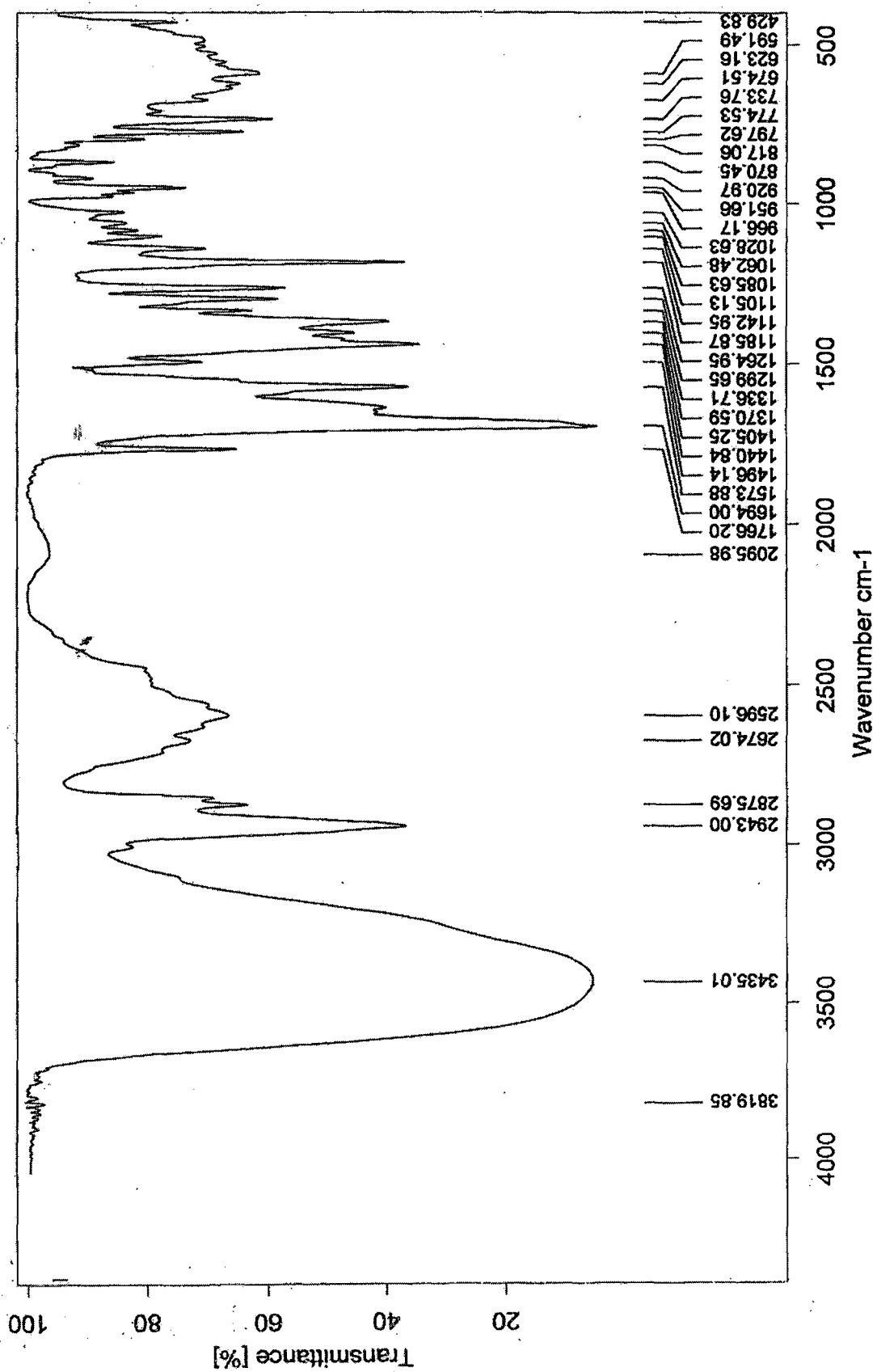


FIGURE 11

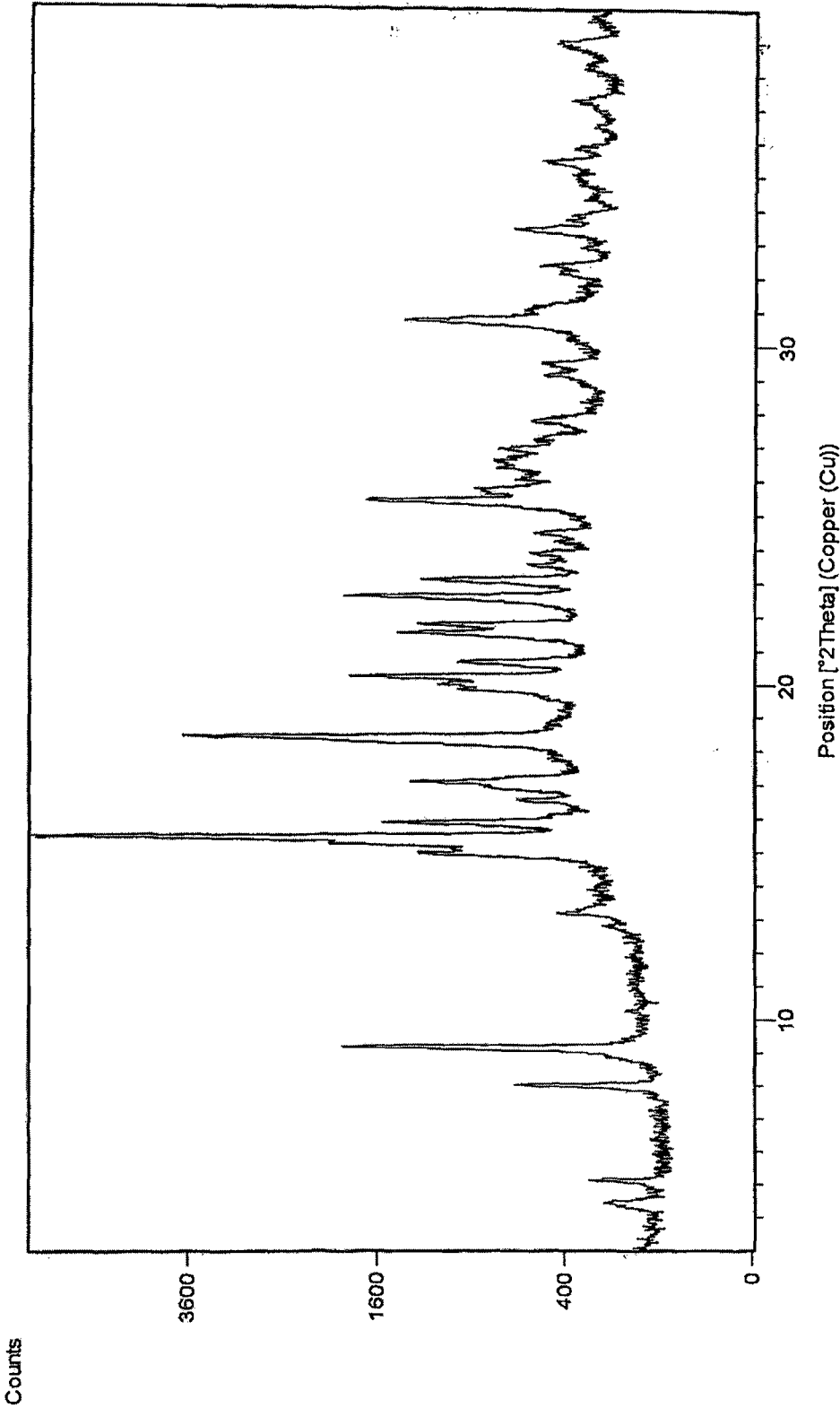


FIGURE 12

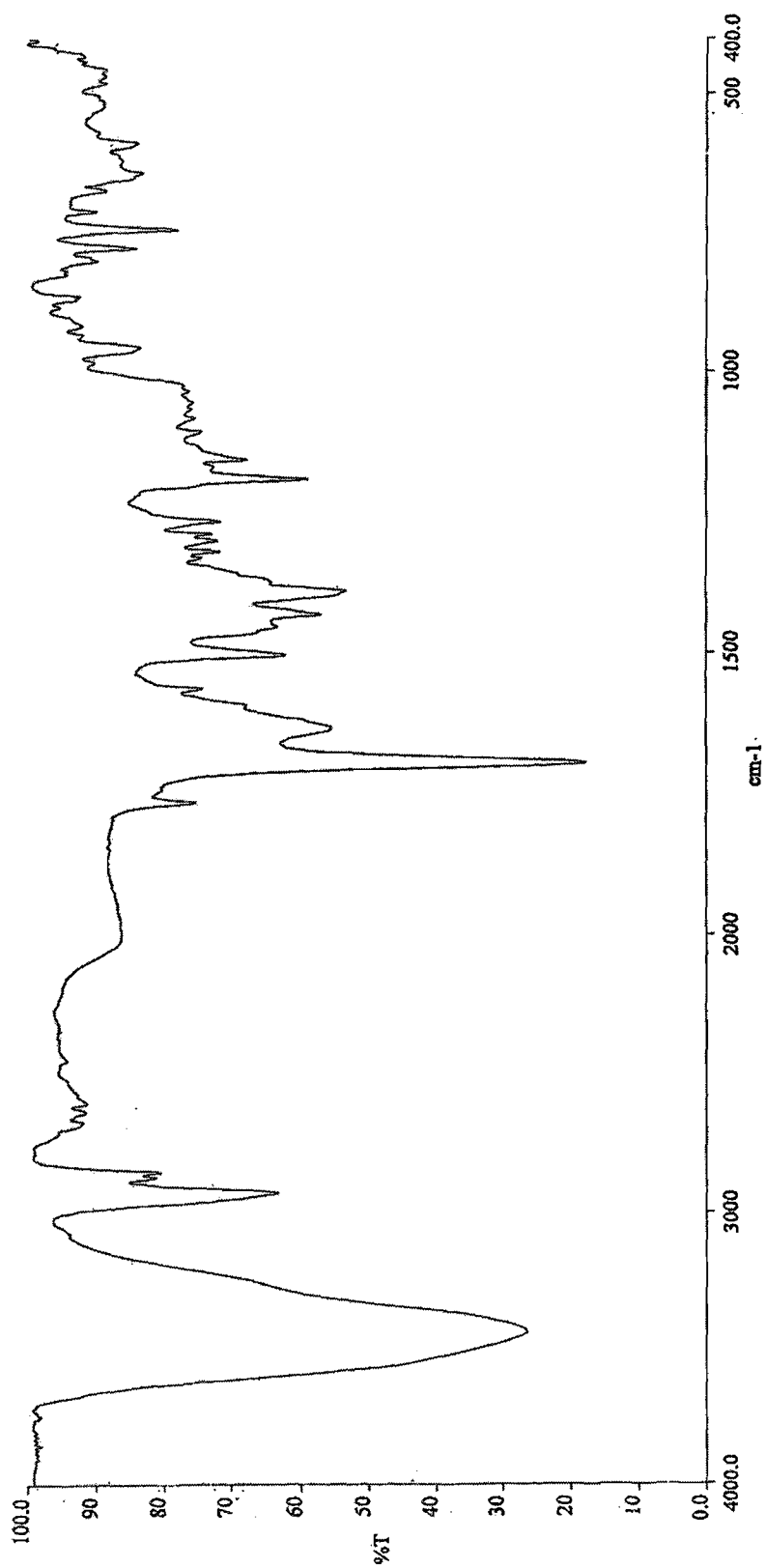
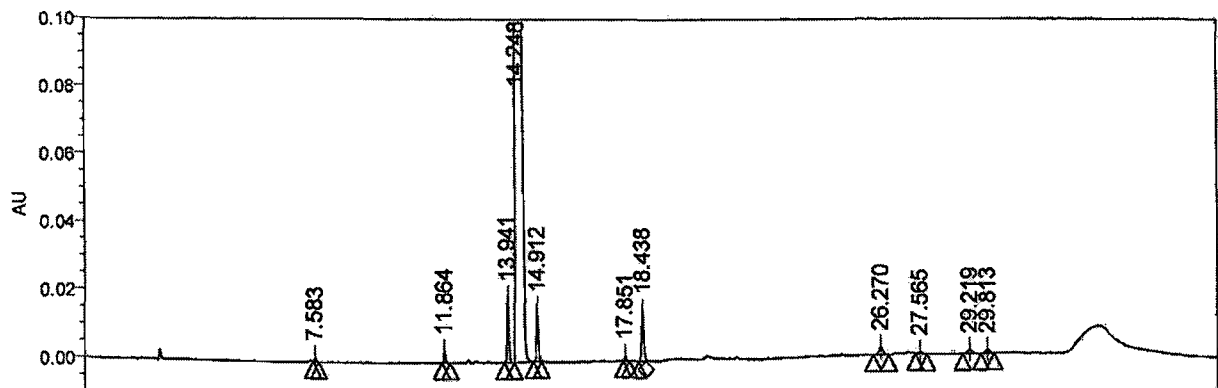


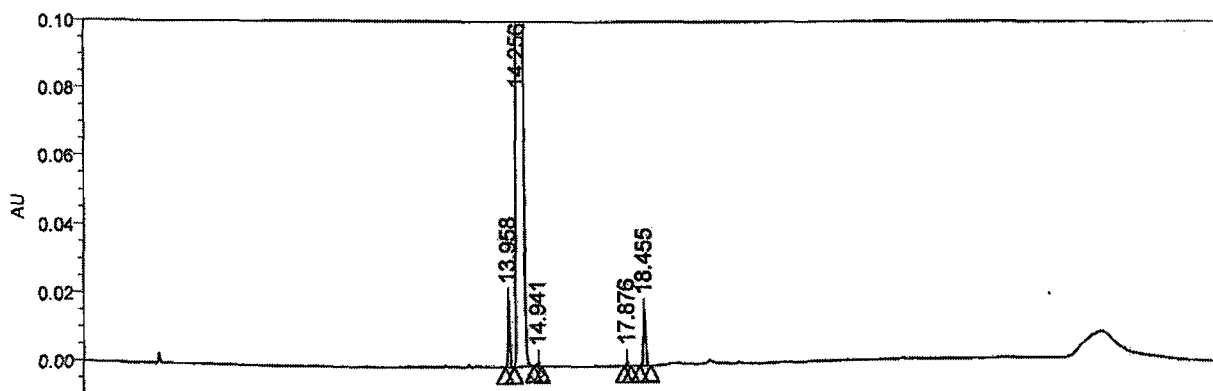
FIGURE 13



Peak Results

	Name	Retention Time (min)	Area	% Area	RT Ratio
1	Peak1	7.583	4536	0.07	0.53
2	Peak2	11.864	14425	0.23	0.83
3	Peak3	13.941	78808	1.23	0.98
4	Peak4	14.248	6089051	95.35	
5	Peak5	14.912	69391	1.09	1.05
6	Peak6	17.851	5525	0.09	1.25
7	Peak7	18.438	77260	1.21	1.29
8	Peak8	26.270	19053	0.30	1.84
9	Peak9	27.565	5695	0.09	1.93
10	Peak10	29.219	12057	0.19	2.05
11	Peak11	29.813	10452	0.16	2.09

FIGURE 14



Peak Results

	Name	Retention Time (min)	Area	% Area	RT Ratio
1	Peak1	13.958	81272	1.19	0.98
2	Peak2	14.256	6640880	97.42	
3	Peak3	14.941	5441	0.08	1.05
4	Peak4	17.876	5968	0.09	1.25
5	Peak5	18.455	83510	1.23	1.29