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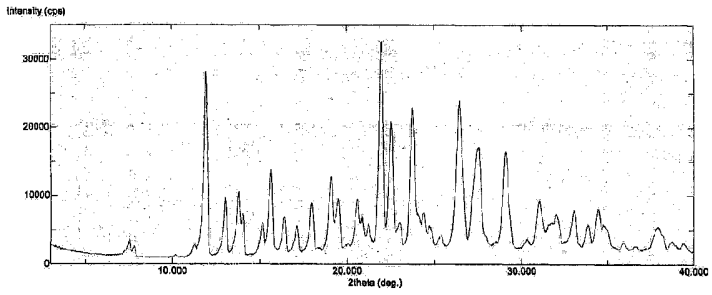

Fig.1

(57) Abstract: The present invention provides polymorph of 3-(4-amino-1-oxo-1,3- dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione, and also the preparing methods and pharmaceutical compositions thereof.

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POLYMORPH OF 3-(SUBSTITUTEDDIHYDROISOINDOLINONE-2-YL)-2,6-DIOXOPIPERIDINE, AND PHARMACEUTICAL COMPOSITIONS THEREOF

FIELD OF THE INVENTION

The present invention is in the field of polymorph of pharmaceutical compounds, and more specifically it relates to polymorph of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione, and as well the preparing methods and pharmaceutical compositions thereof.

BACKGROUND OF THE INVENTION

One kind of 3-(substituted dihydroisoindolinone-2-yl)-2,6-dioxopiperidine, in particular 3-(4-amino-1-oxo-1,3-dihydro-2*H*-isoindole-2-yl)-piperidine- 2,6-dione was disclosed in the article "Amino-substituted thalidomide analogs: Potent inhibitors of TNF-α production" (Muller etc., Bioorganic & Medicinal Chemistry Letters, Vol. 9, Issue 11, 7th June, 1999: pp1625-1630) and Chinese Patent ZL97180299.8. In December 2005 , 3-(4-amino-1-oxo-1,3-dihydro-2H- isoindole-2-yl)-piperidine-2,6-dione was approved as a kind of immunomodulator with anti-tumor activities, indicated for the treatment of myelodysplastic syndromes and multiple myeloma.

The diseases and syndromes which can be treated by 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione include, but are not limited to: myeloproliferative disorder, myelodysplasia syndrome, vasculogenesis, cancer, pain, macular degeneration, asbestosis, anaemia, nervous system disease, dyssomnia, dermatosis, pulmonary hypertension, immune deficiency disorder, parasitic diseases, central lesion etc., namely that were described in the following Chinese Patents with the application numbers, which are incorporated herein in their entirety by reference: 97180299.8, 98805614.3, 03825761.0, 03825567.7, 03813733.X, 03816899.5, 200610150484.3, 200380107531.0, 200710103924.4, 200380108093.X, 200380108398.0, 200480043341.1, 200480038171.8, 200480035556.9, 200480020445.0, 200480043535.1, 200480040004.7, 200480041252.3, 200480042208.4, 200580017546.7, 200580016344.0, 200580020628.7, 200580037220.0, 200580047364.4, 200580046371.2, 200580047031.1 etc.

Eight polymorphs of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)- piperidine-2,6-dione and the preparation methods thereof were described by the US Celgene Corporation in the Chinese Patent CN 1871003A (publication number). By the methods, 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)- piperidine-2,6-dione was added into water or organic solvent (e.g. hexane, toluene, acetone, acetonitrile, methanol, ethyl acetate) where it is practically insoluble, and then was dissolved by heating. It will crystallize when being cooled or crystal transform when being stirred for long time in slurrying system of solid-liquid diphase.

Because 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6- dione is practically insoluble in water or organic solvent (e.g. hexane, toluene, acetone, acetonitrile, methanol, ethyl acetate etc.), even in the condition of heating, a large amount (over 100 times) of solvent is needed, which is disadvantageous in industrial production; in addition, with the method described in the Patent CN 1871003A, the appearance, color and luster of the products can not be improved from light yellow to white or off-white; also, it was not taken into consideration that harmful organic solvent sorted in or above class II (e.g. toluene and acetonitrile etc.) should be tried not to use in synthesis of final products to minimize the negative effects of the residual organic solvent in products on human body.

In terms of polymorphs of drug, each polymorph has different chemical and physical characteristics, including melting point, chemical stability, apparent solubility, rate of dissolution, optical and mechanical properties, vapor pressure as well as density. Such characteristics can directly influence the work-up or manufacture of bulk drug and formulation, and also affect the stability, solubility and bioavailability of formulation. Consequently, polymorph of drug is of great importance to quality, safety and efficacy of pharmaceutical preparation. When it comes to 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione, there are still needs in the art for new polymorphs suitable for industrial production and with excellent physical and chemical properties as well.

SUMMARY OF THE INVENTION

The inventors of this invention have experienced a large amount of researches and unexpectedly found new polymorphs of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione to overcome the deficiencies of the prior art, and the new polymorphic forms have excellent physical and chemical properties and good

stabilities, which are suitable for industrial production.

A purpose of this invention is to provide new polymorphs of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione.

Another purpose of this invention is to provide the synthetic methods of these new polymorphs mentioned above.

The third purpose of this invention is to provide pharmaceutical compositions comprising the mentioned new polymorphs.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig.1 is an XRPD pattern of the Polymorph I of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione of this invention.

Fig.2 is an IR diagram of the Polymorph I of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione of this invention.

Fig.3-1 and Fig.3-2 are respectively DSC diagram and TGA diagram of the Polymorph I of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine- 2,6-dione of this invention.

Fig.4 is a 13C MAS NMR spectrum of the Polymorph I of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione of this invention.

Fig.5 is an XRPD pattern of the Polymorph I of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione of this invention after strong illumination for 10 days.

Fig.6 is a DSC diagram of the Polymorph I of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione of this invention after strong illumination for 10 days.

Fig.7 is an XRPD pattern of the Polymorph I of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione of this invention after high

temperature test of 60°C for 10 days.

Fig.8 is a DSC diagram of the Polymorph I of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione of this invention after high temperature test of 60°C for 10 days.

Fig.9 is an XRPD pattern of the Polymorph I of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione of this invention after high humidity for 10 days.

Fig.10-1 and Fig.10-2 are respectively DSC diagram and TGA diagram of the Polymorph I of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)- piperidine-2,6-dione of this invention after high humidity for 10 days.

Fig.11 is an XRPD pattern of the Polymorph I of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione of this invention after accelerated test at 40°C for six months.

Fig.12-1 and Fig.12-2 are respectively DSC diagram and TGA diagram of the Polymorph I of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)- piperidine-2,6-dione of this invention after accelerated test at 40°C for six months.

Fig.13 is an XRPD pattern of the Polymorph II of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione of this invention.

Fig.14 is an IR diagram of the Polymorph II of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione of this invention.

Fig.15-1 and Fig.15-2 are respectively DSC diagram and TGA diagram of the Polymorph II of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)- piperidine-2,6-dione of this invention.

Fig.16 is an XRPD pattern of the Polymorph II of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione of this invention after strong illumination for 10 days.

Fig.17 is a DSC diagram of the Polymorph II of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione of this invention after strong illumination for 10 days.

Fig.18 is an XRPD pattern of the Polymorph II of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione of this invention after high temperature test of 60°C for 10 days.

Fig.19 is a DSC diagram of the Polymorph II of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione of this invention after high temperature test of 60°C for 10 days.

Fig.20 is an XRPD pattern of the Polymorph II of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione of this invention after high humidity for 10 days.

Fig.21-1 and Fig.21-2 are respectively DSC diagram and TGA diagram of the Polymorph II of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)- piperidine-2,6-dione of this invention after high humidity for 10 days.

Fig.22 is an XRPD pattern of the Polymorph II of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione of this invention after accelerated test at 40°C for six months.

Fig.23-1 and Fig.23-2 are respectively DSC diagram and TGA diagram of the Polymorph II of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)- piperidine-2,6-dione of this invention after accelerated test at 40°C for six months.

Fig.24 is an XRPD pattern of the Polymorph III of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione of this invention.

Fig.25 is an IR diagram of the Polymorph III of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione of this invention.

Fig.26-1 and Fig.26-2 are respectively DSC diagram and TGA diagram of the Polymorph III of

3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)- piperidine-2,6-dione of this invention.

Fig.27 is XRPD pattern of the Polymorph III of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione of this invention after strong illumination for 10 days.

Fig.28 is DSC diagram of the Polymorph III of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione of this invention after strong illumination for 10 days.

Fig.29 is an XRPD pattern of the Polymorph III of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione of this invention after high temperature test of 60°C for 10 days.

Fig.30 is a DSC diagram of the Polymorph III of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione of this invention after high temperature test of 60°C for 10 days.

Fig.31 is an XRPD pattern of the Polymorph III of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione of this invention after high humidity for 10 days.

Fig.32-1 and Fig.32-2 are respectively DSC diagram and TGA diagram of the Polymorph III of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)- piperidine-2,6-dione of this invention after high humidity for 10 days.

Fig.33 is an XRPD pattern of the Polymorph III of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione of this invention after accelerated test at 40°C for six months.

Fig.34-1 and Fig.34-2 are respectively DSC diagram and TGA diagram of the Polymorph III of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)- piperidine-2,6-dione of this invention after accelerated test at 40°C for six months.

Fig.35 is a comparative IR spectrum of the Polymorph I, II and III of

3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione of this invention.

DETAILED DESCRIPTION OF THE INVENTION

More specifically, this invention provides a Polymorph I of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione with a half-molecule water and substantially without other solvents.

The invention provides a Polymorph I of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione hemihydrate having the X-ray powder diffraction pattern by using Cu-Ka radiation, characterized by diffraction peaks at 11.9±0.2 and 22.0±0.2 of 2θ indicated with degree, further, one or multiple (in optional combination, including two or more peaks, or all peaks) of diffraction peaks at 15.6±0.2, 22.5±0.2, 23.8±0.2, 26.4±0.2, 27.5±0.2 and 29.1±0.2; as is shown in Fig. 1.

The Polymorph I of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)- piperidine-2,6-dione hemihydrate:

Peak Number	2θ	Flex Width	d-Value	Intensity	L/LO
1	11.940	0.212	7.4060	17891	84
2	13.020	0.235	6.7940	5996	28
3	13.780	0.188	6.4210	6550	31
6	15.620	0.235	5.6685	9017	42
9	17.960	0.259	4.9349	5895	28
10	19.080	0.235	4.6476	8374	39
11	19.480	0.235	4.5531	6273	30
12	20.580	0.235	4.3121	6162	29
15	21.980	0.235	4.0405	21530	100
16	22.520	0.259	3.9449	13747	64
18	23.760	0.259	3.7417	15053	70
19	24.400	0.212	3.6450	5016	24
21	26.440	0.282	3.3682	15819	74
22	27.520	0.353	3.2384	11455	54
23	29.060	0.306	3.0702	11190	52

24	30.980	0.306	2.8842	6238	29
25	32.000	0.376	2.7945	4934	23
26	33.040	0.306	2.7089	5313	25
28	34.440	0.259	2.6019	5469	26

The Polymorph I of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)- piperidine-2,6-dione hemihydrate provided by this invention is characterized in that its DSC (differential scanning calorimetry) has the first endothermic peak between 140°C and 180°C, more specifically, at about 164.87°C, and the second endothermic peak, namely the maximal endothermic transformation, at about 268.86°C. DSC diagram of the Polymorph I of 3-(4-amino-1-oxo-1,3- dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione hemihydrate of this invention is as in Fig. 3-1, and TGA (Thermal Gravimetric Analysis) diagram is as in Fig. 3-2.

In addition, the Polymorph I of 3-(4-amino-1-oxo-1,3-dihydro-2H -isoindole-2-yl)-piperidine-2,6-dione hemihydrate in this invention has IR (Infrared Spectrum) in KBr disc, which is characterized by absorption peaks at about 3561.4 cm^{-1}, 3507.4 cm^{-1}, 3424.2cm^{-1}, 3345.8cm^{-1}, 3091.0cm^{-1}, 2912.5 cm^{-1}, 1697.8 cm^{-1}, 1658.8 cm^{-1}, 1610.0cm^{-1}, 1494.3 cm^{-1}, 1349.5 cm^{-1}, 1201.4 cm^{-1}; as in Fig. 2.

The Polymorph I of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)- piperidine-2,6-dione hemihydrate in this invention has characteristic chemical shifts δ(ppm) in ^{13}C solid-state NMR spectrum: 22.25 ppm, 30.18ppm, 43.63ppm, 45.98ppm, 50.45ppm, 110.19ppm, 111.24ppm, 114.25ppm, 115.06ppm, 117.25ppm, 118.18ppm, 124.22ppm, 125.20ppm, 125.91 ppm, 126.88ppm, 128.87ppm, 129.93ppm, 132.96ppm, 133.88ppm, 140.62ppm, 143.27ppm, 168.67ppm, 170.13ppm, 171.38ppm, 173.44ppm, 174.67ppm; as is shown in Fig. 4.

In one embodiment of the invention, this invention provides a preparing method of the Polymorph I of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole -2-yl)-piperidine-2,6-dione hemihydrates, including the following steps:

(1). 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione is added into dimethylformamide (DMF) or dimethylsulfoxide (DMSO), in which: the volume to weight ratio of DMF to 3-(4-amino-1-oxo-1,3- dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione is generally over 1:1; preferably, the volume to weight ratio is over 2:1; more preferably, the volume to weight ratio is from 3.5:1 to 4:1, whereas the volume to weight ratio of DMSO to

3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione is generally over 1:1; preferably, the volume to weight ratio is over 1.5:1; more preferably, the volume to weight ratio is from 2.5:1 to 3:1; and dissolved by stirring and heating.

(2). purified water or a mixed solvent system of purified water and an organic solvent is added; wherein: the volume ratio of purified water or the mixed solvent system to DMF or DMSO is generally over 1:1; preferably, the volume ratio is over 2:1; more preferably, the volume ratio is over 3:1; wherein, the mentioned organic solvent is one kind of solvent or a mixed solvent of several kinds, to which 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6- dione is insoluble or slightly soluble; preferably, is selected from the group consisting of acetonitrile, trichloromethane, cyclohexane, 1,2- dichloroethene, dichloromethane, 1,2-dimethoxyethane, dioxane, 2-ethoxyethanol, ethylene glycol, n-hexane, methanol, 2-methoxyethanol, methylbutyl ketone, methylcyclohexane, N-methylpyrrolidone, pyridine, tetralin, tetrahydrofuran, toluene, 1,1,2-trichloroethylene, dimethylbenzene, acetone, methoxybenzene, n-butanol, 2-butanol, butyl acetate, methyl tertiary-butyl ether, isopropylbenzene, ethanol, ethyl acetate, ethyl ether, ethyl formate, n-heptane, isobutyl acetate, isopropyl acetate, methyl acetate, 3-methyl-1-butanol, butanone, methyl isobutyl ketone, isobutanol, n-pentane, n-pentanol, n-propanol, isopropanol, propyl acetate, 1,1-diethoxypropane, 1,1-dimethoxymethane, 2,2-dimethoxypropane, isooctane, isopropyl ether, methyl isopropyl ketone, methyltetrahydrofuran and petroleum ether; more preferably, is selected from one or more mixtures of acetone, methoxybenzene, n-butanol, 2-butanol, butyl acetate, methyl tertiary-butyl ether, isopropylbenzene, ethanol, ethyl acetate, ethyl ether, ethyl formate, n-heptane, isobutyl acetate, isopropyl acetate, methyl acetate, 3-methyl-1-butanol, butanone, methyl isobutyl ketone, isobutanol, n-pentane, n-pentanol, n-propanol, isopropanol, propyl acetate, 1,1-diethoxypropane, 1,1-dimethoxymethane, 2,2-dimethoxypropane, isooctane, isopropyl ether, methyl isopropyl ketone, methyltetrahydrofuran and petroleum ether etc., wherein the mixed solvent system is a dual or multiple mixture system consisting of water and organic solvent, and the weight ratio of water to organic solvent mentioned above is generally over 10%; preferably, this ratio was over 20%; more preferably this ratio was over 30%;

(3). Crystalline solid is precipitated by stirring and cooling down slowly;

(4). recover the solid and dry it under vacuum.

In another embodiment, this invention provides a solvated Polymorph II of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione having the X-ray powder diffraction pattern by using Cu-Ka radiation, characterized by diffraction peaks at 15.7±0.2 and 25.2±0.2 of 2θ indicated with degree, further, one or multiple (in optional combination, including two or more peaks, or all peaks) of diffraction peaks at 7.8±0.2, 8.6±0.2, 14.2±0.2, 17.1±0.2, 17.9±0.2, 18.8±0.2, 21.4±0.2, 21.9±0.2, 22.6±0.2, 23.4±0.2, 24.2±0.2, 27.1±0.2 and 29.3±0.2; as is shown in Fig. 13

The solvated Polymorph II of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole -2-yl)-piperidine-2,6-dione:

Peak number	2θ	Flex Width	d-Value	Intensity	L/LO
1	7.780	0.212	11.3542	3887	35
2	8.580	0.259	10.2972	3889	35
4	14.180	0.259	6.2407	10819	95
5	14.600	0.188	6.0621	2759	25
6	15.040	0.235	5.8857	3457	31
7	15.680	0.212	5.6469	11410	100
8	16.360	0.212	5.4137	3413	30
9	17.060	0.212	5.1931	9678	85
10	17.920	0.259	4.9458	4770	42
11	18.760	0.235	4.7262	4035	36
12	19.520	0.212	4.5439	3733	33
13	19.920	0.235	4.4535	3350	30
14	21.400	0.212	4.1487	5096	45
15	21.940	0.259	4.0478	5065	45
16	22.580	0.235	3.9345	6307	56
17	23.380	0.376	3.8017	5613	50
18	24.160	0.235	3.6807	6624	59
19	24.540	0.235	3.6245	3649	32
20	25.160	0.235	3.5366	10617	94
21	26.800	0.188	3.3238	3634	32
22	27.060	0.188	3.2924	4818	43
24	29.300	0.259	3.0456	4521	40

26	30.480	0.212	2.9304	2319	21
27	30.860	0.235	2.8951	3105	28

The (acetonitrile) solvated Polymorph II of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione provided by this invention is characterized in that its DSC has the first endothermic peak between 140°C and 170°C., more specifically, at about 152.73°C, and the second endothermic peak, namely the maximal endothermic transformation, at about 269.12°C. DSC diagram of the (acetonitrile) solvated Polymorph II of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)- piperidine-2,6-dione of this invention is as in Fig. 15-1, and TGA diagram is as in Fig. 15-2.

The (acetonitrile) solvated Polymorph II of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione provided by this invention has IR in KBr disc, which is characterized by absorption peaks at about 3466.9cm^{-1}, 3366.5cm^{-1}, 3223.8 cm^{-1}, 3078.0 cm^{-1}, 2957.2cm^{-1}, 2871.0cm^{-1}, 1687.2 cm^{-1}, 1666.7 cm^{-1}, 1346.5cm^{-1} and 1199.1cm^{-1}; as in Fig.14.

In an embodiment, this invention provides preparing method of the (acetonitrile) solvated Polymorph II of 3-(4-amino-1-oxo-1,3-dihydro- 2H-isoindole-2-yl)-piperidine-2,6-dione, including the following steps:

(1). 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione is added into anhydrous dimethylformamide (DMF), in which: the volume to weight ratio of anhydrous DMF to 3-(4-amino-1-oxo-1,3- dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione is generally over 1:1; preferably, the volume to weight ratio is over 2:1; more preferably, the volume to weight ratio is from 3.5:1 to 4:1; and dissolved by stirring and heating;

(2). several times of the volume of an anhydrous organic solvent to DMF is added, wherein, 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)- piperidine-2,6-dione is insoluble or slightly soluble to the anhydrous organic solvent, and the volume ratio of the organic solvent to DMF is generally over 1:1; preferably, the volume ratio is over 2:1; more preferably, the volume ratio is over 3:1. Here, the mentioned organic solvent is one kind of solvent or a mixed solvent of several kinds; preferably, is selected from the group consisting of acetonitrile, trichloromethane, cyclohexane, 1,2-dichloroethene, dichloromethane, 1,2-dimethoxyethane, dioxane, 2-ethoxyethanol, ethylene glycol, n-hexane, methanol, 2-methoxyethanol, methylbutyl

ketone, methylcyclohexane, N-methylpyrrolidone, pyridine, tetralin, tetrahydrofuran, toluene, 1,1,2-trichloroethylene, dimethylbenzene, acetone, methoxybenzene, n-butanol, 2-butanol, butyl acetate, methyl tertiary-butyl ether, isopropylbenzene, ethanol, ethyl acetate, ethyl ether, ethyl formate, n-heptane, isobutyl acetate, isopropyl acetate, methyl acetate, 3-methyl-1-butanol, butanone, methyl isobutyl ketone, isobutanol, n-pentane, n-pentanol, n-propanol, isopropanol, propyl acetate, 1,1-diethoxypropane, 1,1-dimethoxymethane, 2,2-dimethoxypropane, isooctane, isopropyl ether, methyl isopropyl ketone, methyltetrahydrofuran and petroleum ether; more preferably, is selected from one or more mixtures of acetone, methoxybenzene, n-butanol, 2-butanol, butyl acetate, methyl tertiary-butyl ether, isopropylbenzene, ethanol, ethyl acetate, ethyl ether, ethyl formate, n-heptane, isobutyl acetate, isopropyl acetate, methyl acetate, 3-methyl-1- butanol, butanone, methyl isobutyl ketone, isobutanol, n-pentane, n-pentanol, n-propanol, isopropanol, propyl acetate, 1,1-diethoxypropane, 1,1-dimethoxymethane, 2,2-dimethoxypropane, isooctane, isopropyl ether, methyl isopropyl ketone, methyltetrahydrofuran and petroleum ether etc..

(3). crystalline solid is precipitated by stirring and cooling down slowly;

(4). recover the solid and dry it under vacuum.

In another embodiment, this invention provides a solvated polymorph III of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione having X-ray powder diffraction pattern by using Cu-Ka radiation, characterized by diffraction peaks at 17.4±0.2 and 24.5±0.2 of 2θ indicated with degree, further, one or multiple (in optional combination, including two or more peaks, or all peaks) of diffraction peaks at 14.5±0.2, 15.5±0.2, 18.7±0.2, 21.0±0.2, 21.9±0.2, 22.1±0.2, 24.0±0.2, 25.3±0.2 and 27.8±0.2; as is shown in Fig. 24.

The solvated Polymorph III of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole -2-yl)-piperidine-2,6-dione:

Peak number	2θ	Flex Width	d- Value	Intensity	L/LO
1	7.660	0.165	11.5318	911	12
2	8.700	0.212	10.1555	970	13
3	13.980	0.212	6.3295	1777	24
4	14.480	0.212	6.1121	3334	44

6	15.440	0.212	5.7342	3384	45
7	15.720	0.165	5.6326	2108	28
8	16.300	0.212	5.4335	1679	23
9	17.340	0.235	5.1099	4285	57
10	17.780	0.235	4.9844	1551	21
11	18.140	0.212	4.8863	1585	21
12	18.640	0.212	4.7563	3080	41
13	19.380	0.188	4.5764	2319	31
14	20.200	0.329	4.3924	2199	29
15	20.920	0.235	4.2428	4001	53
16	21.820	0.188	4.0698	2919	39
17	22.120	0.188	4.0153	4094	54
18	22.740	0.235	3.9072	1962	26
19	23.540	0.235	3.7762	2590	35
20	24.020	0.282	3.7018	4122	55
21	24.520	0.282	3.6274	7608	100
22	25.240	0.235	3.5256	4272	57
23	27.760	0.235	3.2110	4234	56
24	29.540	0.212	3.0214	1965	26
25	30.040	0.235	2.9723	2254	30
26	30.300	0.212	2.9474	2162	29
30	35.700	0.306	2.5129	2036	27

The (acetone) solvated Polymorph III of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione provided by this invention is characterized in that its DSC has the first endothermic peak between 150°C and 200°C, more specifically, at about 188.96°C, and the second endothermic peak, namely the maximal endothermic transform, at about 268.19°C. DSC diagram of the (acetone) solvated Polymorph III of 3-(4-amino-1-oxo-1,3- dihydro-2H-isoindole-2-yl)- piperidine-2,6-dione of this invention is as in Fig. 26-1, and TGA diagram is as in Fig. 26-2.

The (acetone) solvated polymorph III of 3-(4-amino-1-oxo-1,3-

dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione provided by this invention has IR in KBr disc, which is characterized by absorption peaks at about 3466.7cm^{-1}, 3363.3cm^{-1}, 3228.2cm^{-1}, 3081.7cm^{-1}, 2958.5cm^{-1}, 2877.2cm^{-1}, 1688.5cm^{-1}, 1666.2 cm^{-1}, 1609.1 cm^{-1} , 1491.7cm^{-1}, 1347.3cm^{-1} and 1199.5cm^{-1}; as in Fig. 25.

In one embodiment, this invention provided a preparing method of the (acetone) solvated Polymorph III of 3-(4-amino-1-oxo-1,3-dihydro- 2H-isoindole-2-yl)-piperidine-2,6-dione, which including the following steps:

(1). 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione is added into anhydrous dimethylsulfoxide (DMSO), wherein: the volume to weight ratio of anhydrous DMSO to 3-(4-amino-1-oxo-1,3-dihydro-2H- isoindole-2-yl)-piperidine-2,6-dione is generally over 1:1; preferably, the volume to weight ratio is over 2:1; more preferably, the volume to weight ratio is over 3:1; and dissolved by stirring and heating;

(2). several times of the volume of an anhydrous organic solvent to DMSO is added, wherein, 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)- piperidine-2,6-dione is insoluble or slightly soluble to the anhydrous organic solvent, and the volume ratio of organic solvent to DMSO is generally over 1:1; preferably, the volume ratio is over 2:1; more preferably, the volume ratio is over 3:1. Here, the mentioned organic solvent is one kind of solvent or a mixed solvent of several kinds; preferably, is selected from the group consisting of acetonitrile, trichloromethane, cyclohexane, 1,2-dichloroethene, dichloromethane, 1,2-dimethoxyethane, dioxane, 2-ethoxyethanol, ethylene glycol, n-hexane, methanol, 2-methoxyethanol, methylbutyl ketone, methylcyclohexane, N-methylpyrrolidone, pyridine, tetralin, tetrahydrofuran, toluene, 1,1,2-trichloroethylene, dimethylbenzene, acetone, methoxybenzene, n-butanol, 2-butanol, butyl acetate, methyl tertiary-butyl ether, isopropylbenzene, ethanol, ethyl acetate, ethyl ether, ethyl formate, n-heptane, isobutyl acetate, isopropyl acetate, methyl acetate, 3-methyl-1-butanol, butanone, methyl isobutyl ketone, isobutanol, n-pentane, n-pentanol, n-propanol, isopropanol, propyl acetate, 1,1-diethoxypropane, 1,1-dimethoxymethane, 2,2-dimethoxypropane, isooctane, isopropyl ether, methyl isopropyl ketone, methyltetrahydrofuran and petroleum ether; more preferably, is selected from one or more mixtures of acetone, methoxybenzene, n-butanol, 2-butanol, butyl acetate, methyl tertiary-butyl ether, isopropylbenzene, ethanol, ethyl acetate, ethyl ether, ethyl formate, n-heptane, isobutyl acetate, isopropyl acetate, methyl acetate, 3-methyl-1-butanol, butanone, methyl isobutyl ketone, isobutanol, n-pentane, n-pentanol, n-propanol, isopropanol, propyl acetate, 1,1-diethoxypropane,

1,1-dimethoxymethane, 2,2-dimethoxypropane, isooctane, isopropyl ether, methyl isopropyl ketone, methyltetrahydrofuran and petroleum ether etc..

(3). crystalline solid is precipitated by stirring and cooling down slowly;

(4). recover the solid and dry it under vacuum.

In this invention, the scientific instruments and the test conditions involved in X-ray powder diffraction were: anode target-rotating X-ray diffractometer D/max-2500/PC-type (Japan Rigaku); Cu-target, graphite monochromator, tube voltage of 40kV, tube current of 100mA, both divergence slit and antidivergence slit of 1°, receiving slit of 0.3mm, scanning speed of 5°/min and scanning range of from 3 to 40°.

The scientific instruments and the test conditions involved in DSC in this invention were: US Perkin Elmer Diamond DSC; heating from 25°C to 300°C at the rate of 10°C /min.

The scientific instruments and the test conditions involved in TGA in this invention were: US Perkin Elmer Thermal Analysis Pyris 1 TGA; heating from 25°C to 300°C at the rate of 10°C /min.

The scientific instruments and the test conditions involved in solid-state NMR in this invention were: instruments: wide-bore solid-state NMR spectrometer AVANCE III 400MH-type (BRUKER); test conditions: CP-MAS; methods: rotating speed of 14000Hz, scanning times of 1404, relaxation delay of 40s, contact time of 2ms, 13C frequency of 100.6234936MHz and 1H frequency of 400.1413530MHz.

The conditions and methods of related substance test involved in this invention were in accordance with HPLC (Appendix VD of Chinese Pharmacopoeia Edition 2005).

Chromatographic conditions and system applicability: octadecylsilane bonded silica as the filler; 0.01mol/L of potassium dihydrogen phosphate (adjusted to pH 3.5 by phosphoric acid)-methanol-acetonitrile (80:15:5) as the mobile phase; detection wavelength was 240nm; the number of theoretical plates should be not less than 2000, calculated according to the peak of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione. The resolution of the peak of 3-(4-amino-1-oxo-1,3-dihydro-2H- isoindole-2-yl)-piperidine-2,6-dione from the peaks

of adjacent impurities should meet requirements.

The test conditions and method of dissolution test were referred to Method 1 in Appendix XC of Chinese Pharmacopoeia Edition 2005.

According to the method of dissolution test, the sample was added into 500ml (for 5mg strength) or 1000ml (for 10mg or 25mg of strength) of water as medium, and stirred at 100 rounds per minute, then preceded the procedure in the Method 1. After 45 minutes, a quantity of the solution was filtered, and the first filtrate was discarded and the following filtrate was taken as test solution for study (for 5mg or 10mg of strength); 10ml of the following filtrate was measured accurately to be sample solution for study (for 25mg of strength). Then a proper quantity of standard 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione was measured accurately and mixed with water to be the standard solution containing 10μg 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione per ml. According to UV-vis spectrophotometry (Appendix IVA of Chinese Pharmacopoeia Edition 2005), absorbency of sample solution and standard solution were determined at 240nm wavelength and the dissolving-out amount of per pill (or tablet) was calculated by absorbency on the basis of ESTD.

The characteristics of the Polymorph I of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione (hemihydrate)

1. Solubility

Test was performed according to the Examples of Chinese Pharmacopoeia Edition 2005. Method: a definite quantity of the Polymorph I of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione (hemihydrate) measured accurately was added into a certain quantity of solvent slowly, while the mixture was shaken strongly for 30 seconds every 5 minutes and the dissolving status within 30 minutes was observed. Results were listed in Tab.1.

Table 1: solubility test of the Polymorph I of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione (hemihydrate)

Solvent	Sample quantity (g)	Solvent quantity (ml)	Solute: Solvent	Dissolving status	Conclusion
water	0.0113	100	1 : 8849.6	fully dissolved	very slightly soluble
0.1mol/L NaOH solution	0.0516	5	1 : 97.5	fully dissolved	sparingly soluble
0.1mol/L HCl solution	0.1019	100	1 : 981.4	fully dissolved	slightly soluble
ethanol	0.0109	70	1 : 6422.0	fully dissolved	very slightly soluble
acetonitrile	0.0520	50	1 : 961.5	fully dissolved	slightly soluble
ethyl acetate	0.0111	70	1 : 6306.3	fully dissolved	very slightly soluble
methanol	0.0115	10	1 : 869.6	fully dissolved	slightly soluble
acetic acid	0.1008	3	1 : 29.8	fully dissolved	soluble
acetone	0.0521	25	1 : 479.8	fully dissolved	slightly soluble
DMSO	0.1003	1	1: 9.97	fully dissolved	freely soluble
DMF	0.1011	3	1: 29.7	fully dissolved	soluble

The Polymorph I of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)- piperidine-2,6-dione (hemihydrate) was: freely soluble in dimethylsulfoxide; soluble in N,N-dimethylformamide and acetic acid; sparingly soluble in 0.1mol/L NaOH solution; slightly soluble in 0.1mol/L HCL solution, acetonitrile, methanol and acetone; very slightly soluble in water, ethanol and ethyl acetate.

2. Stability

2.1 Photostability test

The Polymorph I of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)- piperidine-2,6-dione (hemihydrate) was distributed homogeneously in open petri dish with the thickness of the raw material not more than 5mm, and the distance was adjusted to make illumination intensity at 4500±500Lx. Sample was tested at the 5th and 10th day respectively and the results were contrasted with that of the Day 0. Results were listed in Tab.2. After strong illumination for 10 days, the X-ray powder diffraction pattern was shown in Fig.5; DSC diagram of the Polymorph I of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine- 2,6-dione (hemihydrate) was in Fig.6.

Table 2: Photostability Test (4500±500lx)

Time (days)	Items			
	Appearance	Related substance	Content	Melting point (Decomposition point)
0	off-white powder	0.05%	99.87%	268.66°C
5	off-white powder	0.05%	99.85%	/
10	off-white powder	0.05%	99.86%	267.08°C

Note: the fluctuation of temperature was between 23°C and 26°C; relative humidity was between 56% and 63%.

2.2 High Temperature Test

The raw material of Polymorph I of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione (hemihydrate) was put into a clean sealed glass bottle and then put in thermostatic drying chamber at 60°C. Sample was tested at the 5th and 10th day respectively and the results were contrasted with that of the Day 0. Results were listed in Tab.3. After high temperature test of 60°C for 10 days, the X-ray powder diffraction pattern was shown in Fig.7; DSC diagram was in Fig.8.

Table 3: High Temperature Test (60°C)

Time (days)	Items			
	Appearance	Related substance	Content	Melting point (°C)

0	off-white powder	0.05%	99.87%	268.66
5	off-white powder	0.05%	99.86%	/
10	off-white powder	0.06%	99.84%	267.32

Note: the variation of relative humidity was between 54% and 62%.

2.3 High Humidity Test

The raw material of Polymorph I of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione (hemihydrate) was distributed homogeneously in open petri dish with thickness of the raw material not more than 5mm and put into thermostatic and humidostatic incubator at room temperature (about 25°C) and 75±5% relative humidity. Sample was tested at the 5th and 10th day respectively and the results were contrasted with that of the Day 0. Results were listed in Tab.4. After high humidity test of 75±5% relative humidity for 10 days, the X-ray powder diffraction pattern was shown in Fig.9; DSC diagram was in Fig.10-1; TGA diagram was in Fig.10-2.

Table 4: High Humidity Test (room temperature and 75±5% relative humidity)

Time (days)	Items			
	Appearance	Weight gain of moisture absorption (%)	Content (%)	Melting point (°C)
0	off-white powder	/	99.87	268.66
5	off-white powder	0.65	99.85	/
10	off-white powder	0.66	99.85	267. 16

Note: the fluctuation of temperature was between 23°C and 26°C.

2.4 Accelerated Test

The raw material of Polymorph I of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione (hemihydrate) was hermetically packed in plastic bags of polyethylene film and put in thermostatic and humidostatic incubator at 40±2°C and 75±5% relative humidity for six months. Sample was tested at the end of the 1st, 2nd, 3rd and 6th month respectively and the results were contrasted with that of the zeroth month. Results

were listed in Tab.5. After accelerated test at 40°C for six months, the X-ray powder diffraction pattern was shown in Fig.11; DSC diagram was in Fig.12-1; TGA diagram was in Fig.12-2

Table 5: Accelerated Test (40°C and 75% relative humidity)

Time(months)	Items			
	Appearance	Related substance (%)	Content (%)	Melting point (°C)
0	Off-white powder	0.05	99.87	268.66
1	Off-white powder	0.05	99.85	/
2	Off-white powder	0.05	99.81	/
3	Off-white powder	0.06	99.78	/
6	Off-white powder	0.07	99.75	267.50

As is known from above results that in photostability test and high temperature test both appearance and content of Polymorph I of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione (hemihydrate) obtained by this invention had few significant variation, which demonstrated the characteristic of stability; in high humidity test, both appearance and content of this product had few obvious change, which verified the characteristic of very slight moisture absorption.

In the observation test of long-term sample storage, crystal transformation was not found, which means that the crystal morphology of this polymorph is relatively stable.

In addition, weight-loss process of the polymorph I happened during a period from 100°C to 180°C, which could identify the existence of Van Der Waals forces between molecules, calculate weight loss: 100.2825%-96.8165% =3.466% according to TGA scan diagram of the Polymorph I of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)- piperidine-2,6-dione (Fig.3-2), which verified that the Polymorph I of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione is hemihydrate.

The characteristics of the Polymorph II of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione

1. Solubility

Test was performed according to the Examples of Chinese Pharmacopoeia Edition 2005. Method: a definite quantity of the (acetonitrile) solvated Polymorph II of 3-(4-amino-1-oxo-1,3-dihydro-2H- isoindole-2-yl)-piperidine-2,6-dione measured accurately was added into a certain quantity of solvent slowly, while the mixture was shaken strongly for 30 seconds every 5 minutes and the dissolving status within 30 minutes was observed. Results were listed in Tab.61.

Table 6: solubility test of the Polymorph II of 3-(4-amino-1-oxo-1,3-dihydro-2h-isoindole-2-yl)-piperidine-2,6-dione

Solvent	Sample quantity (g)	Solvent quantity (ml)	Solute Solvent	Dissolving status	Conclusion
water	0.0102	105	1 : 10294	cannot fully dissolved	practically insoluble
0.1mol/L NaOH solution	0.0515	50	1 : 970.9	fully dissolved	slightly soluble
0.1mol/L HCl solution	0.0510	5	1 : 98.0	fully dissolved	sparingly soluble
ethanol	0.0108	50	1 : 4629.6	fully dissolved	very slightly soluble
acetonitrile	0.0114	10	1 : 877.2	fully dissolved	slightly soluble
ethyl acetate	0.0109	105	1 : 9633.0	fully dissolved	very slightly soluble
methanol	0.0107	50	1 : 4672.9	fully dissolved	very slightly soluble
Acetic acid	0.0508	5	1 : 98.4	fully dissolved	sparingly soluble
Acetone	0.0512	50	1 : 976.6	fully dissolved	slightly soluble
DMSO	0.1012	1	1 : 9.88	fully dissolved	freely soluble

DMF	0.1023	1	1 : 9.78	fully dissolved	freely soluble

The Polymorph II of 3-(4-amino-1-oxo-1,3-dihydro-2h-isoindole-2-yl)- piperidine-2,6-dione was: freely soluble in dimethylsulfoxide and N,N-dimethylformamide; sparingly soluble in acetic acid and 0.1mol/L HCL solution; slightly soluble in acetonitrile, acetone and 0.1mol/L NaOH solution; very slightly soluble in methanol, ethanol and ethyl acetate; nearly insoluble in water.

2. Stability

2.1 Photostability test

The Polymorph II of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole- 2-yl)-piperidine-2,6-dione was distributed homogeneously in open petri dish with the thickness of the raw material not more than 5mm and the distance was adjusted to make illumination intensity at 4500±500Lx. Sample was tested at the 5^{th} and 10^{th} day respectively and the results were contrasted with that of the Day 0. Results were listed in Tab.7. After strong illumination for 10 days, the X-ray powder diffraction pattern was shown in Fig.16; DSC diagram was in Fig.17

Table 7: Photostability Test （4500±500lx）

Time (days)	Items			
	Appearance	Related substance (%)	Content (%)	Melting point (°C)
0	off-white powder	0.09	99.89	269.12
5	off-white powder	0.09	99.89	/
10	off-white powder	0.09	99.88	268.69

Note: the fluctuation of temperature was between 23°C and 26°C; relative humidity was between 56% and 63%.

2.2 High Temperature Test

The raw material of Polymorph II of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione was put into a clean

sealed glass bottle and then put in thermostatic drying chamber at 60°C. Sample was tested at the 5th and 10th day respectively and the results were contrasted with that of the Day 0. Results were listed in Tab.8. After high temperature test of 60°C for 10 days, the X-ray powder diffraction pattern was shown in Fig.18; DSC diagram was in Fig.19.

Table 8: High Temperature Test (60°C)

Time (days)	Items			
	Appearance	Related substance (%)	Content (%)	Melting point (°C)
0	Off-white powder	0.09	99.89	269.12
5	Off-white powder	0.09	99.86	/
10	Off-white powder	0.10	99.87	269.11

Note: the variation of relative humidity was between 54% and 62%.

2.3 High Humidity Test

The raw material of Polymorph II of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione was distributed homogeneously in open petri dish with thickness of the raw material not more than 5mm and put into thermostatic and humidostatic incubator at room temperature (about 25°C) and 75±5% relative humidity. Sample was tested at the 5th and 10th day respectively and the results were contrasted with that of the Day 0. Results were listed in Tab.9. After high humidity test of 75±5% relative humidity for 10 days, the X-ray powder diffraction pattern was shown in Fig.20; DSC diagram was in Fig.21-1; TGA diagram was in Fig.21-2.

Table 9: High Humidity Test (room temperature and 75±5% relative humidity)

Time (days)	Items			
	Appearance	Weight gain of moisture absorption (%)	Content (%)	Melting point (°C)
0	off-white powder	/	99.89	269.12
5	off-white powder	1.33	99.87	/

10	off-white powder	2.15	99.87	268.68

Note: the fluctuation of temperature was between 23°C and 26°C.

2.4 Accelerated Test

The raw material of Polymorph II of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione was hermetically packed in plastic bags of polyethylene film and put in thermostatic and humidostatic incubator at 40±2°C and 75±5% relative humidity for six months. Sample was tested at the end of the 1st, 2nd, 3rd and 6th month respectively and the results were contrasted with that of the zeroth month. Results were listed in Tab.10. After accelerated test at 40°C for six months, the X-ray powder diffraction pattern was shown in Fig.22; DSC diagram was in Fig.23-1; TGA diagram was in Fig.23-2

Table 10: Accelerated Test (40°C and 75% relative humidity)

Time (months)	Items			
	Appearance	Related substance (%)	Content (%)	Melting point (°C)
0	off-white powder	0.09	99.89	269.12
1	off-white powder	0.09	99.85	/
2	off-white powder	0.10	99.77	/
3	off-white powder	0.10	99.72	/
6	off-white powder	0.12	99.68	268.82

As is known from above results that in photostability test and high temperature (60°C) test both appearance and content of Polymorph II of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione obtained by this invention had few significant variation, which verified the characteristic of stability; in high humidity test, both appearance and content of this product had few obvious change, but there is lower moisture absorption. In the observation test of long-term sample storage in high humidity, it was revealed by DSC scanning that a small amount of Polymorph II had transformed to Polymorph I.

The characteristics of the polymorph III of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione

1. Solubility

Test was performed according to the Examples of Chinese Pharmacopoeia Edition 2005. Method: a definite quantity of the (acetone) solvated polymorph III of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)- piperidine-2,6-dione measured accurately was added into a certain quantity of solvent slowly while the mixture was shaken strongly for 30 seconds every 5 minutes and the dissolving status within 30 minutes was observed. Results were listed in Tab.11.

Table 11: solubility test of the Polymorph III of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione

Solvent	Sample quantity (g)	Solvent quantity (ml)	Solute: Solvent	Dissolving status	Conclusion
water	0.0106	110	1 : 10377	cannot fully dissolved	practically insoluble
0.1mol/L NaOH solution	0.0512	5	1 : 97.7	fully dissolved	sparingly soluble
0.1mol/L HCl solution	0.1030	100	1 : 970.9	fully dissolved	slightly soluble
ethanol	0.0101	70	1 : 6930.7	fully dissolved	very slightly soluble
acetonitrile	0.0524	50	1 : 954.2	fully dissolved	slightly soluble
ethyl acetate	0.0108	70	1 : 6481.5	fully dissolved	very slightly soluble
methanol	0.0115	10	1 : 869.6	fully dissolved	slightly soluble
acetic acid	0.1010	9	1 : 89.1	fully dissolved	sparingly soluble

acetone	0.0522	25	1：478.9	fully dissolved	slightly soluble
DMSO	0.1017	3	1: 29.5	fully dissolved	soluble
DMF	0.1016	3	1: 29.5	fully dissolved	soluble

The Polymorph III of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)- piperidine-2,6-dione was: soluble in dimethylsulfoxide and N,N- dimethylformamide; sparingly soluble in acetic acid and 0.1mol/L NaOH solution; slightly soluble in 0.1mol/L HCL solution, acetonitrile, methanol and acetone; very slightly soluble in water, ethanol and ethyl acetate.

2. Stability

2.1 Photostability test

The Polymorph III of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)- piperidine-2,6-dione was distributed homogeneously in open petri dish with the thickness of the raw material not more than 5mm and the distance was adjusted to make illumination intensity at 4500±500Lx. Sample was tested at the 5^{th} and 10^{th} day respectively and the results were contrasted with that of the Day 0. Results were listed in Tab.12. After strong illumination for 10 days, the X-ray powder diffraction pattern was shown in Fig.27; DSC diagram was in Fig.28

Table 12: Photostability Test （4500±500lx）

Time (days)	Items			
	Appearance	Related substance (%)	Content (%)	Melting point (°C)
0	off-white powder	0.07	99.86	268.19
5	off-white powder	0.07	99.85	/
10	off-white powder	0.07	99.85	268.15

Note: the fluctuation of temperature was between 23°C and 26°C; relative humidity was between 56% and 63%.

2.2 High Temperature Test

The raw material of Polymorph III of 3-(4-amino-1-oxo-1,3-dihydro -2H-isoindole-2-yl)-piperidine-2,6-dione was put into a clean sealed glass bottle and then put in thermostatic drying chamber at 60°C. Sample was tested at the 5th and 10th day respectively and the results were contrasted with that of the Day 0. Results were listed in Tab.13. After high temperature test of 60°C for 10 days, the X-ray powder diffraction pattern was shown in Fig.29; DSC diagram was in Fig.30.

Table 13: High Temperature Test (60°C)

Time (days)	Items			
	Appearance	Related substance (%)	Content (%)	Melting point (°C)
0	off-white powder	0.07	99.86	268.19
5	off-white powder	0.07	99.84	/
10	off-white powder	0.08	99.83	268.11

Note: the variation of relative humidity was between 54% and 62%.

2.3 High Humidity Test

The raw material of Polymorph III of 3-(4-amino-1-oxo-1,3-dihydro -2H-isoindole-2-yl)-piperidine-2,6-dione was distributed homogeneously in open petri dish with thickness of the raw material not more than 5mm and put into thermostatic and humidostatic incubator at room temperature (about 25°C) and 75±5% relative humidity. Sample was tested at the 5th and 10th day respectively and the results were contrasted with that of the Day 0. Results were listed in Tab.14. After high humidity test of 75±5% relative humidity for 10 days, the X-ray powder diffraction pattern was shown in Fig.31; DSC diagram was in Fig.32-1; TGA diagram was in Fig.32-2.

Table 14: High Humidity Test (room temperature and 75±5% relative humidity)

Time (days)	Items			
	appearance	Weight gain of moisture absorption (%)	Content (%)	Melting point (°C)

0	off-white powder	/	99.86	268.19
5	off-white powder	1.25	99.83	/
10	off-white powder	1.37	99.82	268.10

Note: the fluctuation of temperature was between 23°C and 26°C.

2.4 Accelerated Test

The raw material of Polymorph III of 3-(4-amino-1-oxo-1,3-dihydro -2H-isoindole-2-yl)-piperidine-2,6-dione was hermetically packed in plastic bags of polyethylene film and put in thermostatic and humidostatic incubator at 40±2°C and 75±5% relative humidity for six months. Sample was tested at the end of the 1st, 2nd, 3rd and 6th month respectively and the results were contrasted with that of the zeroth month. Results were listed in Tab.15. After accelerated test at 40°C for six months, the X-ray powder diffraction pattern was shown in Fig.33; DSC diagram was in Fig.34-1; TGA diagram was in Fig.34-2

Table 15: Short-Time Test (40°C and 75% relative humidity)

Time (months)	Items			
	Appearance	Related substance (%)	Content (%)	Melting point (°C)
0	off-white powder	0.07	99.86	268.19
1	off-white powder	0.07	99.81	/
2	off-white powder	0.07	99.76	/
3	off-white powder	0.08	99.71	/
6	off-white powder	0.08	99.62	268.08

As is known from above results that in illumination test and high temperature (60°C) test both appearance and content of Polymorph III of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione obtained by this invention had few significant variation, which demonstrated the characteristic of stability; in high humidity test, both appearance and content of this product had few obvious change, but there is lower moisture absorption. In the observation test of long-term sample storage in high humidity, it was revealed by DSC scanning that a small amount of Polymorph III had transformed to Polymorph I.

In another embodiment of this invention, it provides pharmaceutical compositions comprising one or more of the Polymorph I, II and III of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione and a pharmaceutical excipient; preferably, the pharmaceutical composition contains 500mg of the polymorph of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione; more preferably, it contains 5mg, 10mg, 15mg or 25mg of the polymorph of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione. According to the teaching in the prior art of this field and referring to the patents cited by this invention, the pharmaceutical compositions of this invention could be prepared into all kinds of formulations and the proper pharmaceutical excipient could be selected. For instance, according to the diseases and objects, the pharmaceutical compositions of this invention could be delivered through such administration routes: oral, parenteral (e.g. intramuscular, intraperitoneal, intravenous, intracerebroventricular, intracisternal and subcutaneous injection or infusion), inhalation spray, nasal, vaginal, rectal, sublingual or local delivery; preferably, it is oral solid formulations, such as tablets, granules or capsules.

The pharmaceutical compositions of this invention containing the polymorph of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione, could comprises other therapeutic components depending on the needs.

The pharmaceutical composition of this invention was administrated once or multiple times every day on the basis of daily dose, and the daily dose was about from 0.10mg to 500mg per day, more preferably from 1mg to 250mg per day. Alternatively, the pharmaceutical composition was administrated every two days on the dose of about from 0.10mg to 150mg per day or from 1mg to 250mg per day.

The diseases and syndromes which can be treated by 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione of the invention include, but not limited to: myeloproliferative disorder, osteomyelodysplasia syndrome, vasculogenesis, cancer, pain, macular degeneration, asbestosis, anaemia, nervous system disease, dyssomnia, dermatosis, pulmonary hypertension, immune deficiency disorder, parasitic diseases and central lesion etc., and the specific methods and doses could refer to Chinese Patents with the application numbers: 97180299.8, 98805614.3, 03825761.0, 03825567.7, 03813733.X, 03816899.5, 200610150484.3, 200380107531.0, 200710103924.4, 200380108093.X, 200380108398.0, 200480043341.1, 200480038171.8, 200480035556.9, 200480020445.0,

200480043535.1, 200480040004.7, 200480041252.3, 200480042208.4, 200580017546.7, 200580016344.0, 200580020628.7, 200580037220.0, 200580047364.4, 200580046371.2 and 200580047031.1.

The technical advantages of this invention include: although eight polymorphs of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione and the preparation methods thereof has been reported in the patent documentation of CN 1871003A, the polymorphs of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione prepared by the methods of the Patent CN 1871003A was verified that the polymorph A and the polymorph B had poor chemical stability in 0.1mol/L diluted HCl solution and in the oxidation destroy experiment, and also the crystal transformation method described in the patent was unsuitable for industrial production.

By the existing technique in patent document CN 1871003A, the preparation method was that: 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione was added into water or organic solvent (e.g. hexane, toluene, acetone, acetonitrile, methanol and ethyl acetate) where it is practically insoluble for, after dissolved by heating, crystal was precipitated when being cooled or crystal transformed when being stirred for long time in slurrying system of solid-liquid diphase.

1. In patent document US 5635517 and Chinese Patent CN 101080400A, to prepare the target 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione, in the last step of chemical reaction, nitro was reduced by the method of Pd/C hydrogenation to yield the target compound, while the poor solubility of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione in all kinds of reaction systems easily led to excess heavy metal in the products obtained by this method;

2. Because 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine- 2,6-dione was practically insoluble in water or the organic solvents mentioned above, a large quantity (more than 100 times) of solvent should be used even in the condition of heating. And it was not taken into consideration that harmful organic solvent sorted in or above Class II (e.g. toluene and acetonitrile etc.) should not be tried to use in synthesis of final products to minimize the negative effects of the residual organic solvent in products on human body;

3. By the method of crystal transformation described in the Patents of CN 1871003A and

CN 101080400A, the appearance, color and luster of the products can not be improved, for example, from original light yellow to white or off-white;

4. The polymorph A and the polymorph B by the preparation methods of polymorph instructed in patent documents of CN1871003A and CN 101080400A were easily destroyed to be decomposed within shorter time in 0.1mol/L diluted HCl solution and in the oxidation destroy, which indicated their poor chemical stability.

5. Crystal transformation technique to prepare polymorphs in patents CN1871003A and CN 101080400A, which was time-consuming with poor controllability, was unsuitable to industrial production.

In a word, the methods of polymorph preparation in patents CN1871003A and CN 101080400A were unsuitable to industrial production.

However, this invention provided the methods suitable to industrially manufacturing polymorphs of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-. piperidine-2,6-dione, which overcame the problems in existing technique.

In terms of the three new polymorphs of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione in this invention, the crystallization conditions were in views of the insolubility of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione in most solvents and difficult purification, and easy and feasible preparation methods were adopted:

1. the preparation technique of this invention was simple, quite easy for operation and convenient for industrial production, and the quality of the products was controllable and the polymorphs had good stability suitable to long-term storage;

2. by the methods of crystal transformation, strong-polar impurities were removed easily, resulting in dramatically reduction in related substance;

3. excess or over limit of heavy metal residue could be lowed significantly;

4. the appearance, color and luster of the products could be improved evidently from light

yellow to white or off-white;

5. by comparison to the polymorph A described in patent CN1871003A, the Polymorph I of this invention had better stability in water, 0.1mol/L HCl solution and in the oxidation destroy experiment, where it was substantially undecomposed or decomposition degree was obviously less than that of the polymorph A disclosed in patent CN1871003A. So the polymorph of this invention had more advantages for formulation;

6. by the methods of polymorph preparation in this invention, the amount of organic solvent used in crystal transformation could be reduced greatly, which led to reduced cost of products;

7. by the methods of this invention, water or organic solvents in Class III with low toxicity could be used selectively to prepare the polymorphs of this invention, avoiding the toxic effects on human body by the organic solvents such as toluene and methyl ethyl ketone etc. with high potential toxicity used in the patent CN1871003A.

Due to the above-mentioned advantages, this invention was beneficial to dramatic improvement in products quality and suitable to industrial production.

EXAMPLES

Preparation of the polymorphs of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione

Example 1

Preparation of the Polymorph I of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione:

100g of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine- 2,6-dione was added into 400mL DMF (or 300mL DMSO), and dissolved by stirring and heating. Then 1600mL water (or a mixed solvents system of 1000mL water and 600mL organic solvent, namely a dual or multiple mixture system consisting of water and organic solvent such as acetone, acetonitrile, ethyl acetate, dichloromethane, isopropanol, methanol, ethanol and etc. in which

3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione was insoluble) was added and crystal precipitated when the mixture was stirred and cooled slowly. The solid was recovered and dried under vacuum to yield the Polymorph I of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)- piperidine-2,6-dione.

DMF/water system: the product weighted 78g and yield was 78%;

DMSO/water system: the product weighted 90g and yield was 90%.

Contrasts / Items	Index of raw material before transformation	Index of Polymorph I
Appearance	Yellow crystal powder	White to off-white crystal powder
Related substance	< 0.31%	≤0.05%
Heavy metal	≥20ppm、≤50ppm	≤10ppm
Water content	0.097%	3.613%
Melting point	263.97°C	268.86°C

Example 2

Preparation of the Polymorph II of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione:

100g of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine- 2,6-dione was added into 400mL anhydrous DMF and dissolved by stirring and heating; then 1800mL anhydrous ethanol (or 1600 – 2000mL sole or mixed solvents consisting of methanol, acetone, ethyl acetate, acetonitrile, dichloromethane and etc.) was added and crystal precipitated when the mixture was stirred and cooled slowly. The solid was recovered and dried under vacuum to yield the Polymorph II of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)- piperidine-2,6-dione.

The product weighted 72g and yield was 72%.

Contrasts / Items	Index of raw material	Index of polymorph II
Appearance	Yellow crystal powder	White to off-white crystal powder
Related substance	< 0.31%	≤0.09%
Heavy metal	≥20ppm、≤50ppm	≤10ppm
Weight loss before 180°C by TGA	0.097%	11.31%
Melting by DSC	263.97°C	269.12°C

Example 3

Preparation of the Polymorph III of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione:

100g of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6 -dione was added into 300mL anhydrous DMSO and dissolved by stirring and heating. Then 2000mL anhydrous ethanol (alternative organic solvent such as methanol, acetone, ethyl acetate, acetonitrile, dichloromethane and etc. in which 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione was insoluble) was added and crystal precipitated when the mixture was stirred and cooled slowly. The solid was recovered and dried under vacuum to yield the polymorph III of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)- piperidine-2,6-dione.

The product weighted 86g and yield was 86%.

Contrasts / Items	Index of raw material	Index of polymorph III
Appearance	Yellow crystal powder	White to off-white crystal powder
Related substance	< 0.31%	≤0.09%
Heavy metal	≥20ppm、≤50ppm	≤10ppm

Weight loss before 200℃by TGA	0.097%	12.663%
melting point by DSC	263.97℃	268.19℃

Example 4

Prescription and preparation method of tablets:

According to the below-mentioned methods, several excipients and the above-mentioned Polymorph I or II or III of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione or a mixture of the Polymorph I, II and III in any ratio were formulated into tablets containing 10mg per tablet.

Raw material and adjunct	Amount (g/1000 tablets)	
	Recipe 1	Recipe 2
3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl) -piperidine-2,6-dione (I, II, III)	10g	10g
anhydrous lactose	30g	15g
starch	30g	50g
microcrystal cellulose	20g	15g
croscarmellose sodium	9g	/
sodium carboxylmethyl starch	/	7g
10%PVP solution	50ml	40ml
magnesium stearate	0.25g	0.15g

The manufacturing method of tablets containing the polymorph I or II or III of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione or a mixture of the above-mentioned Polymorph I, II and III in any ratio was: the above-mentioned excipients were mixed homogeneously with the Polymorph I or II or III of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)- piperidine-2,6-dione or a mixture of the above-mentioned Polymorph I, II and III in any ratio, and a proper amount of 10% PVP solution was added to form the damp mass, which was then granulated by screening. The moist granules were dried and size stabilized by screening, and then magnesium stearate and talcum powder were added to be homogeneous mixture, which was tableted at last.

Polymorph I tablet---accumulated dissolution%

Time	1 #	2 #	3 #	4 #	5 #	average %	SD%	RSD%
0	0	0	0	0	0	0	0	0
5	64.40	65.14	69.30	60.78	70.55	66.0	3.94	5.97
10	97.72	96.74	99.01	97.49	99.00	98.0	0.99	1.01
20	98.85	96.49	98.54	97.94	87.07	95.8	4.95	5.17
30	97.98	96.99	100.27	98.03	97.55	98.2	1.25	1.27
45	96.76	95.27	97.51	96.59	96.83	96.6	0.82	0.84
60	97.08	94.62	96.16	96.59	96.73	96.2	0.96	1.00

Example 5

Prescription and preparation method of capsules:

According to the below-mentioned methods, several excipients and the Polymorph I or II or III of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione or a mixture of the above-mentioned polymorphs in any ratio were formulated into capsules containing 10mg per capsule.

Raw material and adjunct	Amount (g/1000capsules)		
	Recipe1	Recipe2	Recipe3
3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl) -piperidine-2,6-dione (I, II, III)	10g	10g	10g
anhydrous lactose	30g	50g	/
starch	30g	/	60g
microcrystal cellulose	30g	40g	25g
croscarmellose sodium	/	6.5g	7.5
sodium carboxylmethyl starch	8g	/	/
10%PVP solution	45ml	55ml	35ml
magnesium stearate	0.3g	0.2g	0.25g

The manufacturing method of capsules containing the Polymorph I or II or III of

3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione or a mixture of the above-mentioned Polymorph I, II and III in any ratio was: the above-mentioned excipients were mixed homogeneously with the Polymorph I or II or III of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione or a mixture of the above-mentioned three polymorphs in any ratio and a proper amount of 10% PVP solution was added to form the moist granules, which were dried and size stabilized by screening. Then magnesium stearate was added to be homogeneous mixture, which was capsuled. Alternatively, without granulation the homogeneous mixture of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione and above-mentioned excipients was screened and capsuled directly.

Polymorph I capsule---accumulated dissolution%

Time	1 #	2 #	3 #	4 #	5 #	average %	SD%	RSD%
0	0	0	0	0	0	0	0	0
5	60.86	59.90	35.00	50.84	22.77	45.9	16.57	36.12
10	91.04	93.30	85.66	91.23	83.92	89.0	4.02	4.51
20	94.08	96.78	92.84	95.18	93.02	94.4	1.64	1.73
30	95.38	96.14	93.62	95.42	93.56	94.8	1.17	1.23
45	93.02	95.66	93.91	94.11	93.00	93.9	1.09	1.16
60	94.63	94.10	93.38	93.83	92.08	93.6	0.97	1.03

Comparative test

The methods of destruction experiment of the Polymorph I of this invention (hereinafter referred to as "Polymorph I") contrasting with the Polymorph A and B of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione prepared by the method in CN 1871003A (hereinafter referred to as "Polymorph A " and "polymorph B") and results of stability are followed:

Table 16: results of stability of Polymorph A, Polymorph B and Polymorph I in destruction test

Polymorph kind / Conditions Results	Polymorph A	Polymorph B	Polymorph I
Major impurities in raw materials before destruction	**Total impurities:0.06%** tR5.948 0.01% tR6.855 0.01% tR11.165 0.04%	**Total impurities:0.07%** tR5.921 0.01% tR6.847 0.01% tR11.165 0.05%	**Total impurities:0.04%** tR5.872 0.01% tR10.961 0.03%
Major impurities generated by oxidation destruction	**Total impurities:0.82%** tR5.655 0.39% tR10.401 0.08% tR32.318 0.08% tR35.098 0.14%	**Total impurities:0.89%** tR5.649 0.36% tR10.397 0.11% tR32.302 0.10% tR35.063 0.13%	**Total impurities:0.16%** tR5.660 0.09% tR10.372 0.03% tR32.279 0.01% tR35.082 0.02%
Major impurities generated by 0.1mol/L acid destruction for 1 hour	**Total impurities:1.13%** tR4.722 0.33% tR7.378 0.72% tR11.100 0.04%	**Total impurities:1.22%** tR4.717 0.33% tR7.367 0.72% tR11.096 0.04%	**Total impurities:0.62%** tR4.737 0.20% tR7.381 0.41% tR11.067 0.01%

Procedure:

Acid destruction: 50mg of sample weighted accurately was added into measuring flask of 100mL, and 10mL 0.1mol/L HCl solution was added. After standing at room temperature for 1 hour, an equal amount of 0.1mol/L NaOH solution was added for neutralization. Then the mixture was diluted with mobile phase to scale and shook to be homogeneous, and determined by HPLC.

Oxidation destruction: 50mg of sample weighted accurately was added into measuring flask of 100mL, and 10mL 30% H_2O_2 was added. After standing at room temperature for 2 hour, the mixture was diluted with mobile phase to scale and shook to be homogeneous, and determined by HPLC.

Related substances determination

HPLC conditions and system applicability: octadecylsilane bonded silica as the filler; 0.01mol/L of potassium dihydrogen phosphate (adjusted to pH 3.5 by phosphoric acid)-methanol-acetonitrile (80:15:5) as the mobile phase; detection wavelength was 240nm; the number of theoretical plates should be not less than 2000, calculated according to the peak of lenalidomide. The resolution of the peak of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione from the peaks of adjacent impurities should meet requirements.

Determination method: sample was dissolved in mobile phase to be the solution containing 0.5mg per 1mL. 20μL of such solution was injected into liquid chromatograph and chromatogram was recorded until fourfold the retention time of major component peak. If there were impurities peaks in the chromatogram of sample solution, total impurities and sole impurity were calculated by normalization method on the basis of peak area.

As is revealed in the experimental results, by comparison with Polymorph A and Polymorph B, Polymorph I of this invention had better stability whether in the acid condition or in the oxidating condition, indicating that Polymorph I was more suitable to be made into pharmaceuticals.

CLAIMS

1. A Polymorph I of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)- piperidine-2,6-dione hemihydrate, characterized by diffraction peaks at 11.9±0.2 and 22.0±0.2 of 2θ indicated with degree in its X-ray powder diffraction pattern using Cu-Ka radiation.

2. The Polymorph I according to Claim 1, further having one or multiple diffraction peaks at 15.6±0.2, 22.5±0.2, 23.8±0.2, 26.4±0.2, 27.5±0.2 and 29.1±0.2 in its X-ray powder diffraction pattern.

3. The Polymorph I according to Claim 1 or Claim 2, having an endothermic peak at about 164.87℃, and the maximal endothermic transform at about 268.86℃ in its DSC diagram.

4. The polymorph I according to Claim 1 or Claim 2, characterized by absorption peaks at about 3561.4 cm^{-1}, 3507.4 cm^{-1}, 3424.2cm^{-1}, 3345.8cm^{-1}, 3091.0cm^{-1}, 2912.5 cm^{-1}, 1697.8 cm^{-1}, 1658.8 cm^{-1}, 1610.0cm^{-1}, 1494.3 cm^{-1}, 1349.5 cm^{-1}, 1201.4 cm^{-1} in its infrared spectrum in KBr disc.

5. A solvated Polymorph II of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione, characterized by diffraction peaks at 15.7±0.2 and 25.2±0.2 of 2θ indicated with degree in its X-ray powder diffraction pattern using Cu-Ka radiation,.

6. The Polymorph II according to Claim 5, further having one or multiple diffraction peaks at 7.8±0.2, 8.6±0.2, 14.2±0.2, 17.1±0.2, 17.9±0.2, 18.8±0.2, 21.4±0.2, 21.9±0.2, 22.6±0.2, 23.4±0.2, 24.2±0.2, 27.1±0.2 and 29.3±0.2 of 2θ indicated with degree in its X-ray powder diffraction pattern using Cu-Ka radiation.

7. The Polymorph II according to Claim 5 or Claim 6, having an endothermic peak at about 152.73°C, and the maximal endothermic transform at about 269.12°C in its DSC diagram.

8. The Polymorph II according to Claim 5 or Claim 6, characterized by absorption peaks at about 3466.9cm^{-1}, 3366.5cm^{-1}, 3223.8 cm^{-1}, 3078.0 cm^{-1}, 2957.2cm^{-1}, 2871.0cm^{-1}, 1687.2 cm^{-1}, 1666.7 cm^{-1}, 1346.5cm^{-1} and 1199.1cm^{-1} in its infrared spectrum in KBr disc.

9. A solvated Polymorph III of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione, characterized by diffraction peaks at 17.4±0.2 and 24.5±0.2 of 2θ indicated with degree in its X-ray powder diffraction pattern using Cu-Ka radiation.

10. The solvated polymorph III according to Claim 9, further having one or multiple diffraction peaks at 14.5±0.2, 15.5±0.2, 18.7±0.2, 21.0±0.2, 21.9±0.2, 22.1±0.2, 24.0±0.2, 25.3±0.2 and 27.8±0.2 of 2θ indicated with degree in its X-ray powder diffraction pattern using Cu-Ka radiation.

11. The solvated Polymorph III according to Claim 9 or Claim 10, having an endothermic peak at about 188.96°C, and the maximal endothermic transform at about 268.19°C in its DSC diagram.

12. The solvated Polymorph III according to Claim 9 or Claim 10, characterized by absorption peaks at about 3466.7cm^{-1}, 3363.3cm^{-1}, 3228.2cm^{-1}, 3081.7cm^{-1}, 2958.5cm^{-1}, 2877.2cm^{-1}, 1688.5cm^{-1}, 1666.2 cm^{-1}, 1609.1 cm^{-1} , 1491.7cm^{-1}, 1347.3cm^{-1} and 1199.5cm^{-1} in its infrared spectrum in KBr disc.

13. A preparation method of the Polymorph I according to any one of Claim 1 to 4 includes the

following steps:

(1) 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione is added into dimethylformamide or dimethylsulfoxide, and dissolved by stirring and heating;

(2) purified water or a mixed solvent system of purified water and an organic solvent is added; wherein, the mentioned organic solvent is one kind of solvent or a mixed solvent of several kinds, to which 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione is insoluble or slightly soluble;

(3) solid is precipitates by stirring and cooling down slowly;

(4) recover the solid and dry it under vacuum.

14. A preparation method of the Polymorph II according to any one of Claim 5 to 8 includes the following steps:

(1) 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione is added into anhydrous dimethylformamide, and dissolved by stirring and heating;

(2) an anhydrous organic solvent is added; wherein, the mentioned organic solvent is one kind of solvent or a mixed solvent of two or more kinds, to which 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione is insoluble or slightly soluble;

(3) solid is precipitates by stirring and cooling down slowly;

(4) recover the solid and dry it under vacuum.

15. A preparation method of the Polymorph III according to any one of Claim 9 to 12 includes the following steps:

(1) 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione is added into anhydrous dimethylsulfoxide, and dissolved by stirring and heating;

(2) an anhydrous organic solvent is added; wherein, the mentioned organic solvent is one kind of solvent or a mixed solvent of two or more kinds, to which 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione is insoluble or slightly soluble;

(3) solid is precipitates by stirring and cooling down slowly;

(4) recover the solid and dry it under vacuum.

16. A pharmaceutical compositions comprising one or more of the polymorphs of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindole-2-yl)-piperidine-2,6-dione according to any one of Claim 1 to 4, Claim 5 to 8 and Claim 9 to 12.

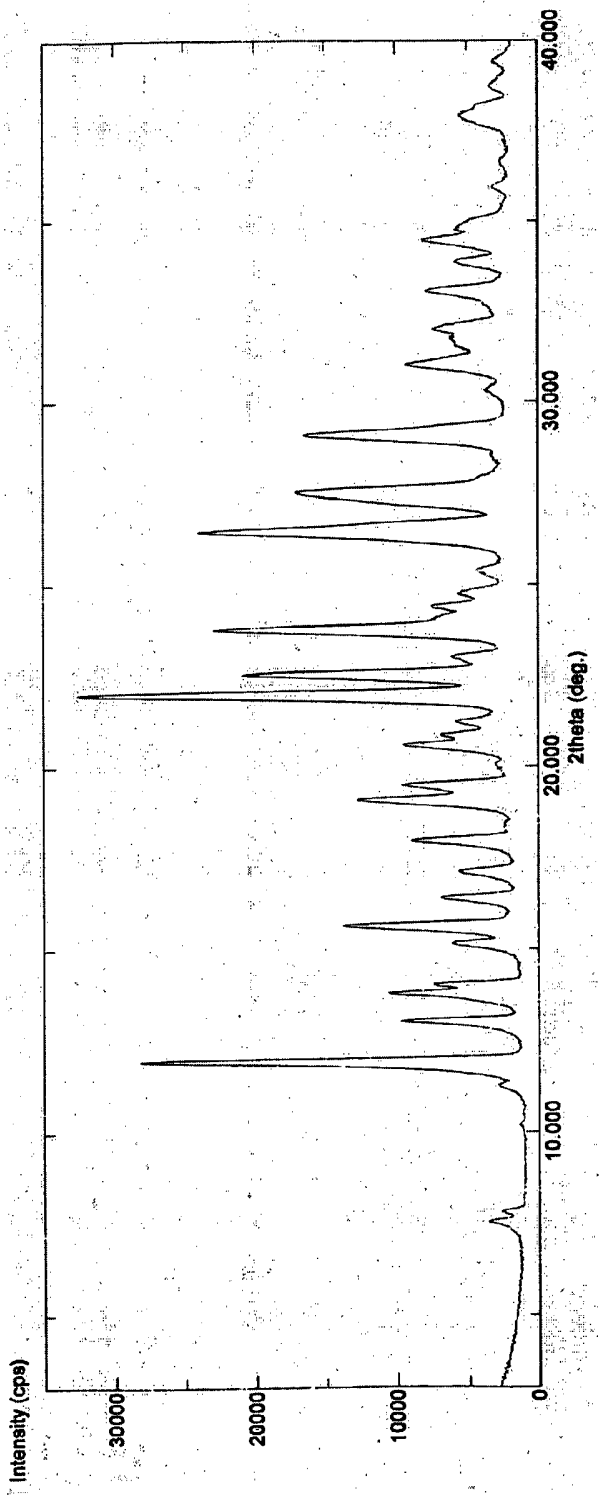

Intensity (cps)
30000
20000
10000
0
10.000
20.000
30.000
40.000
2theta (deg.)

Fig.1

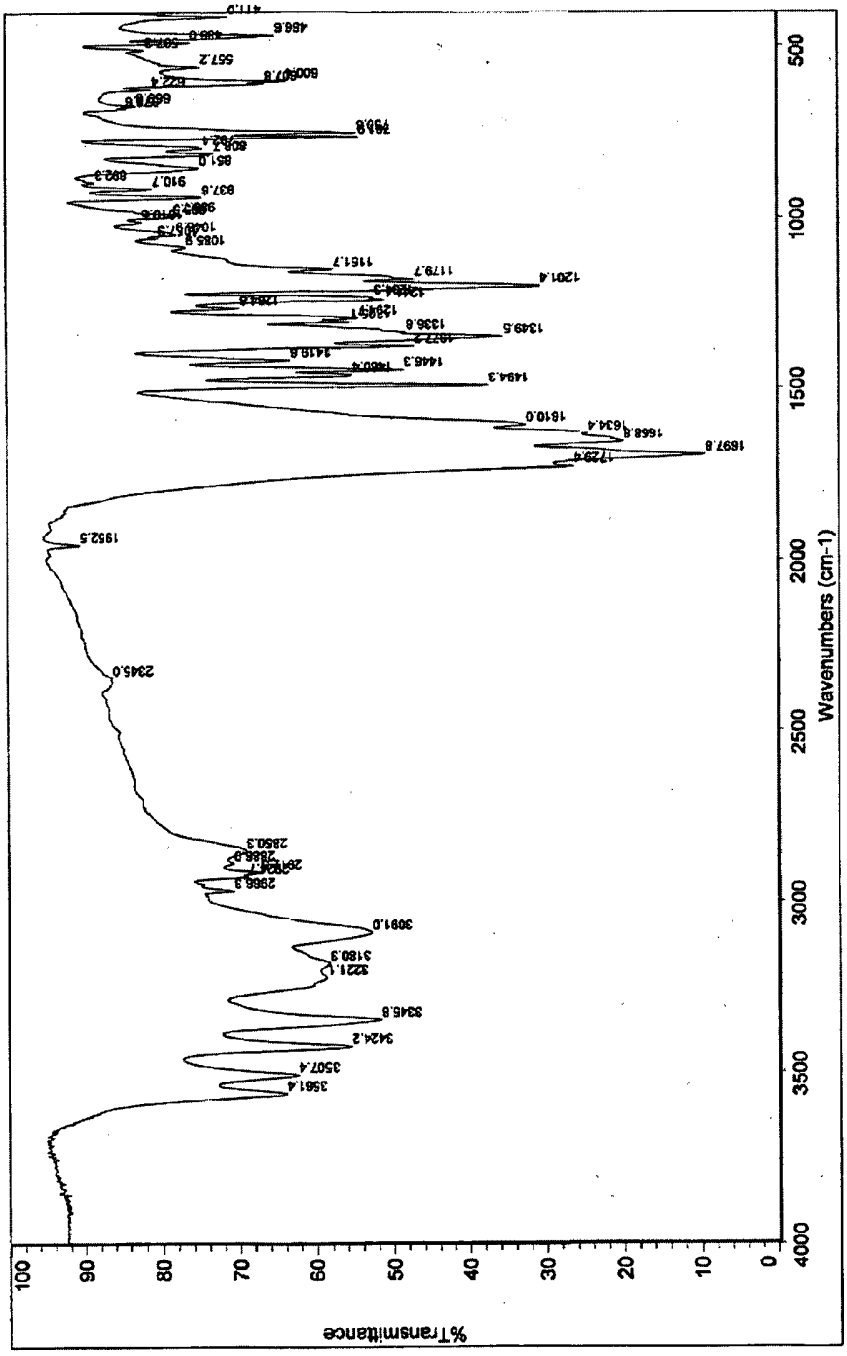

%Transmittance
Wavenumbers (cm-1)
100
90
80
70
60
50
40
30
20
10
0
4000
3500
3000
2500
2000
1500
1000
500
3561.4
3507.4
3424.2
3345.8
3221.1
3180.3
3081.0
2850.3
2345.0
1952.5
1897.8
1729.4
1668.8
1634.4
1610.0
1494.3
1446.3
1439.5
1356.8
1289.7
1201.4
1179.7
1161.7
1085.8
910.7
837.8
785.8
685.8
622.4
557.2
466.6
411.0

Fig.2

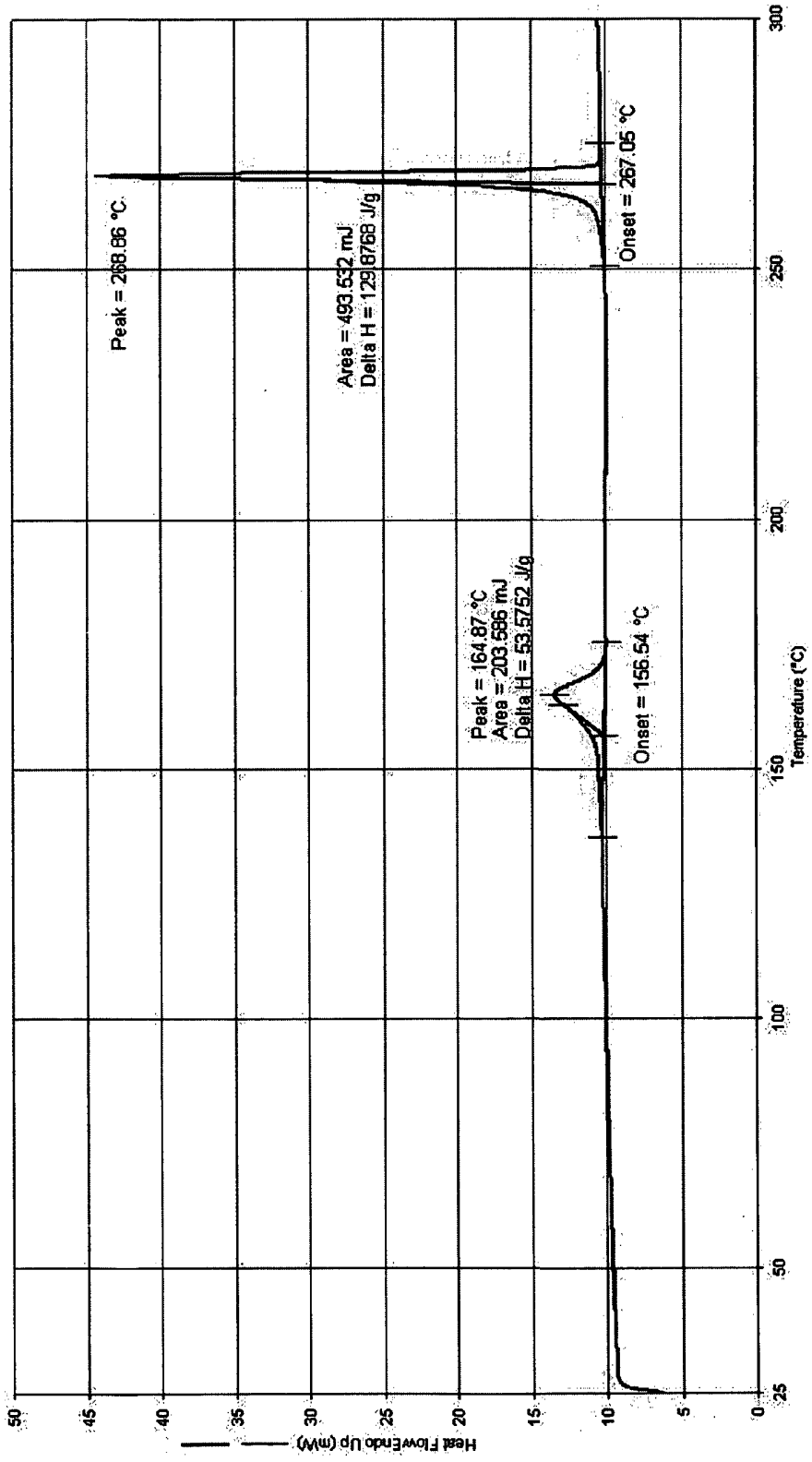

Peak = 268.86 °C
Area = 493.532 mJ
Delta H = 129.8768 J/g
Onset = 267.05 °C
Peak = 164.87 °C
Area = 203.686 mJ
Delta H = 53.5752 J/g
Onset = 156.54 °C
Heat Flow Endo Up (mW)
Temperature (°C)
50
45
40
35
30
25
20
15
10
5
0
25
50
100
150
200
250
300

Fig.3-1

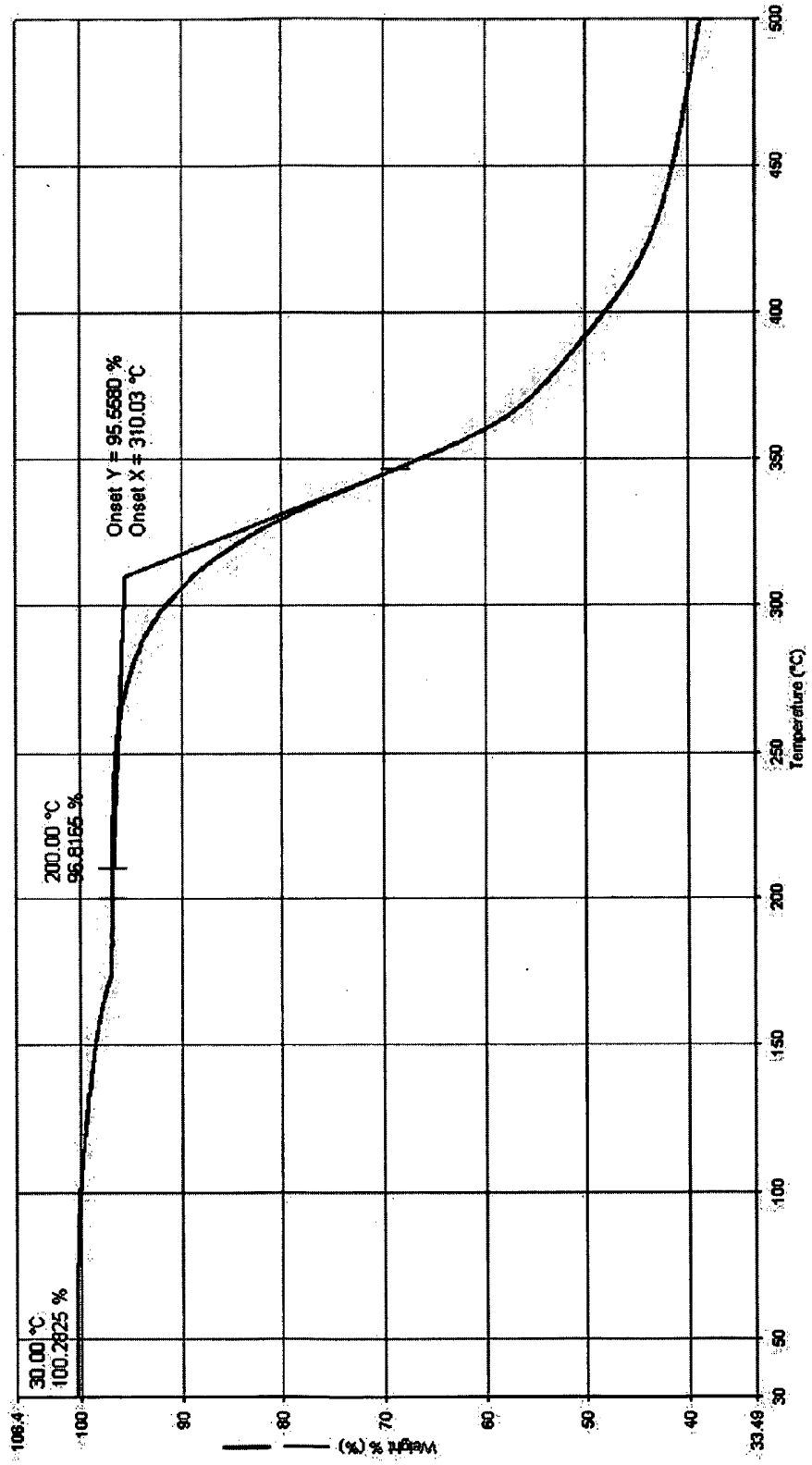

Onset Y = 95.5580 %
Onset X = 310.03 °C
200.00 °C
96.8165 %
30.00 °C
100.2825 %
106.4
33.49
Weight (%)
Temperature (°C)
100
90
80
70
60
50
40
30
50
100
150
200
250
300
350
400
450
500

Fig.3-2

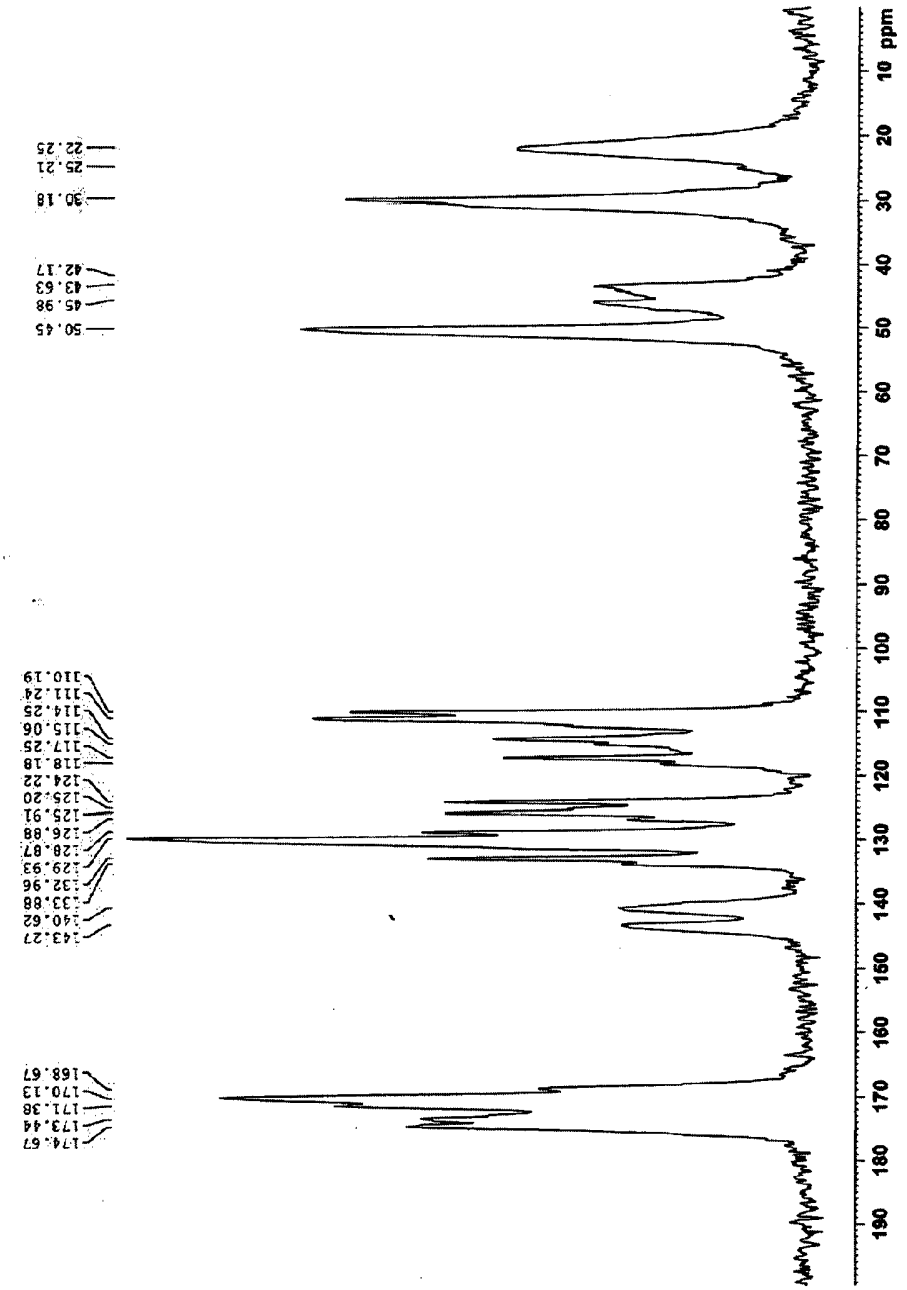
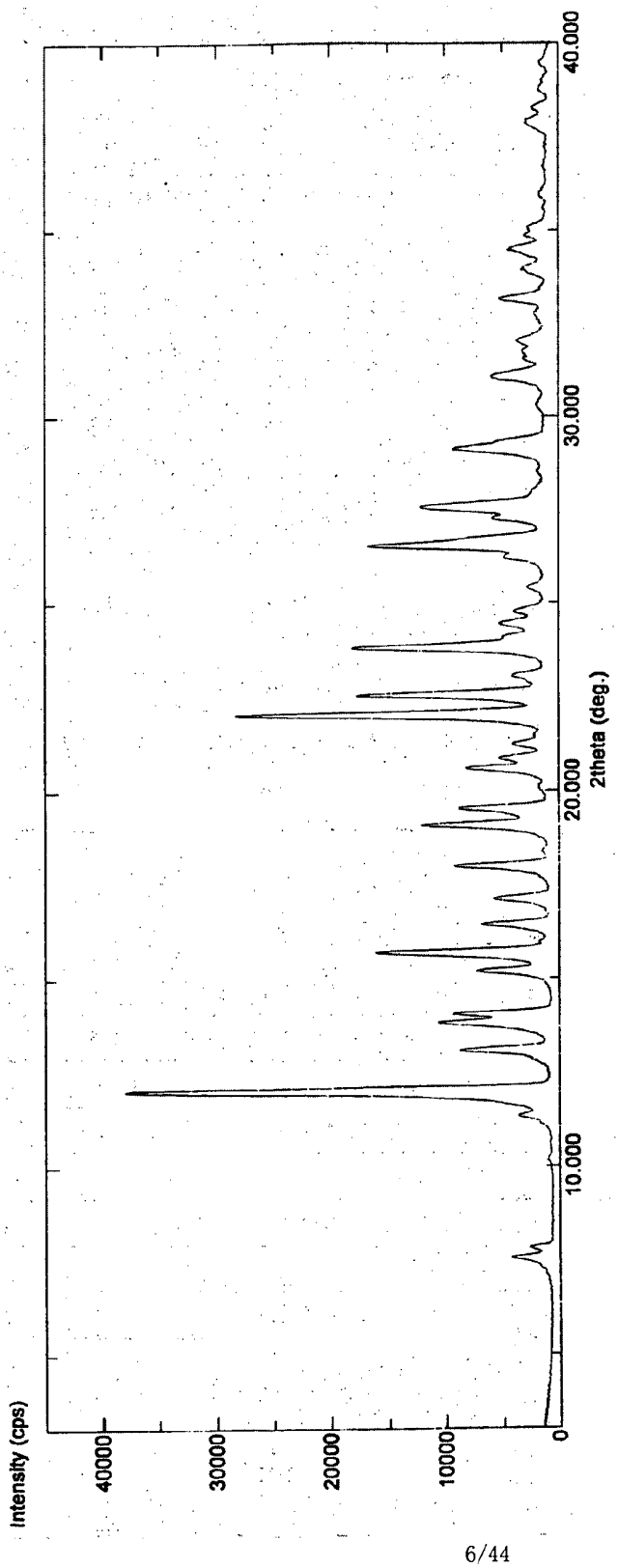

10 ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
22.25
25.21
30.18
42.17
43.63
45.98
50.45
110.19
111.24
114.25
115.06
117.25
118.18
124.22
125.20
125.91
126.88
128.87
129.93
132.96
133.88
140.62
143.27
168.67
170.13
171.38
173.44
174.67

Fig.4


Intensity (cps)
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30000
20000
10000
0
10.000
20.000
30.000
40.000
2theta (deg.)

Fig.5

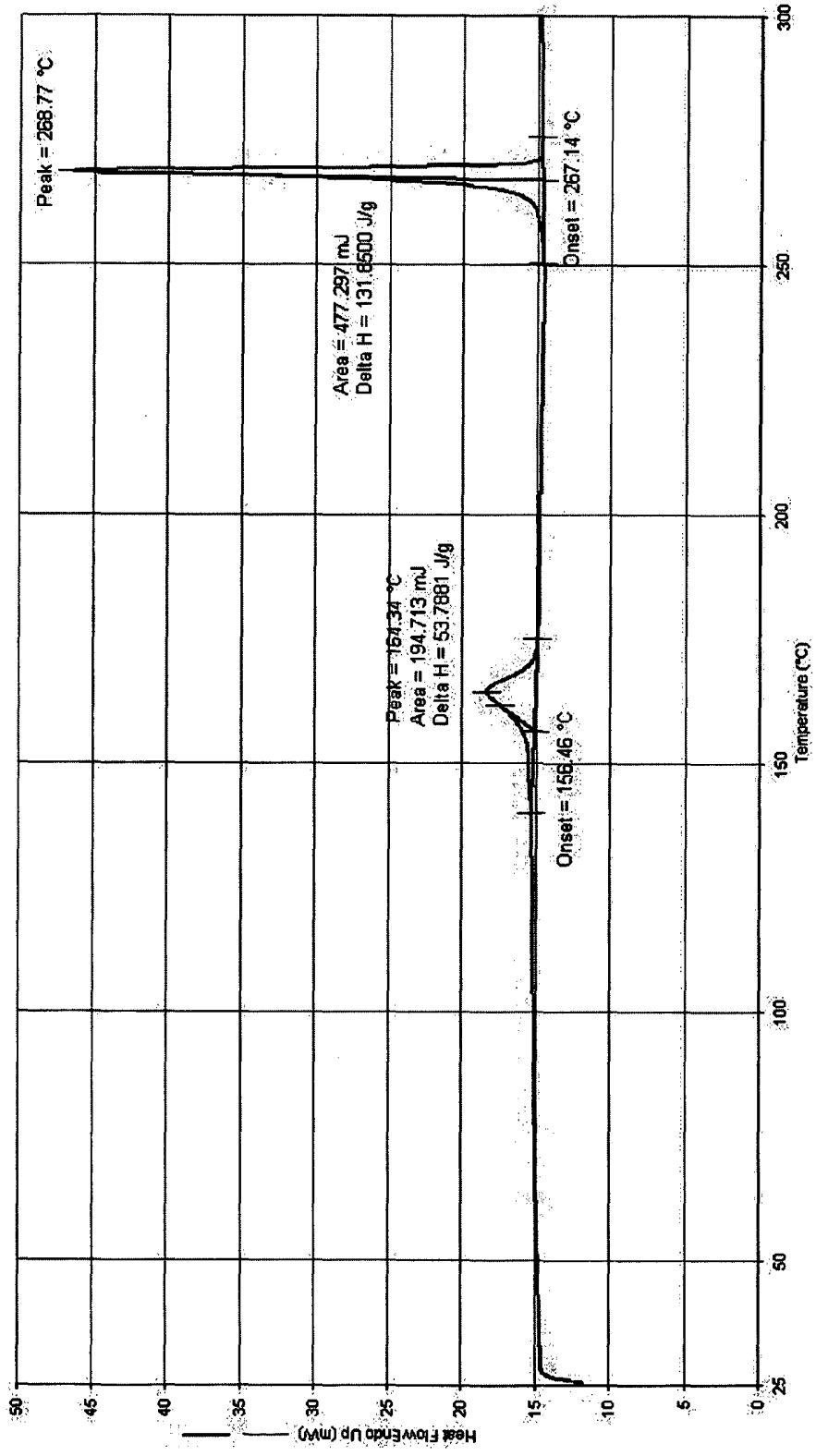

Peak = 268.77 °C
Area = 477.297 mJ
Delta H = 131.8500 J/g
Onset = 267.14 °C
Peak = 164.34 °C
Area = 194.713 mJ
Delta H = 53.7881 J/g
Onset = 156.46 °C
Heat flow Endo Up (mW)
Temperature (°C)
50
45
40
35
30
25
20
15
10
5
0
25
50
100
150
200
250
300

Fig.6

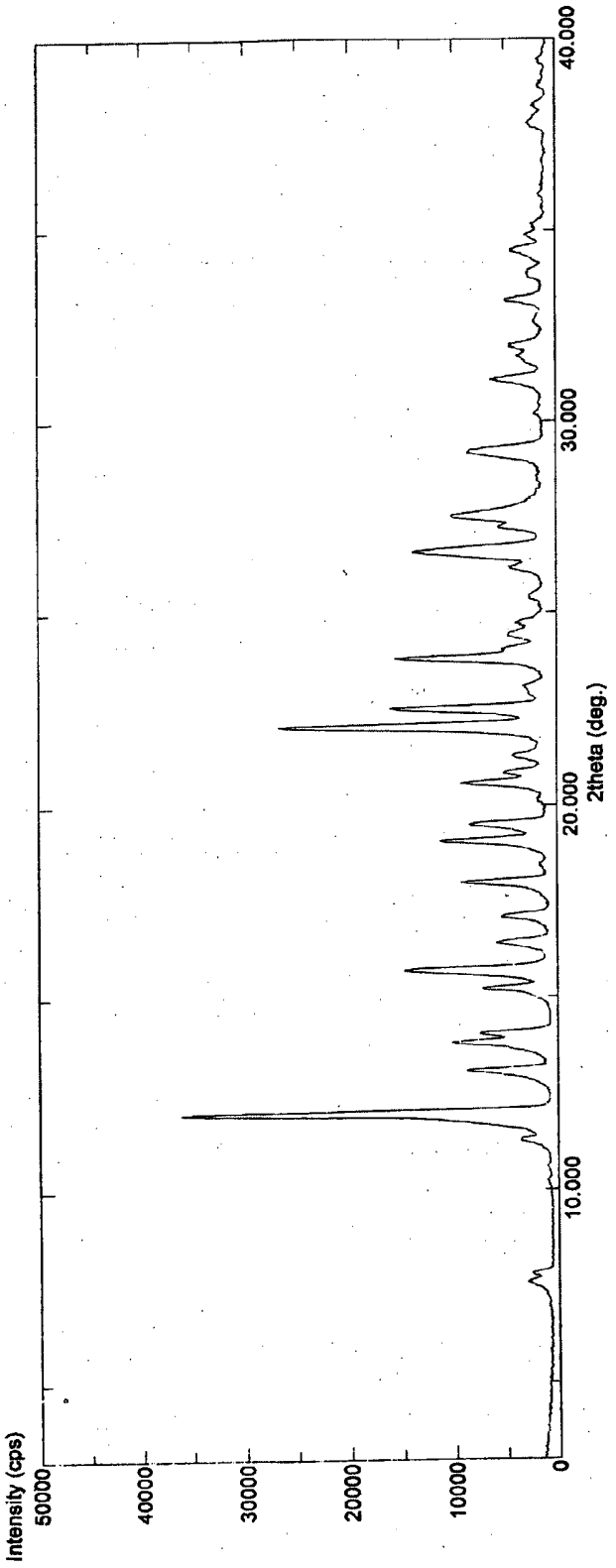

Intensity (cps)
50000
40000
30000
20000
10000
0
10.000
20.000
30.000
40.000
2theta (deg.)

Fig.7

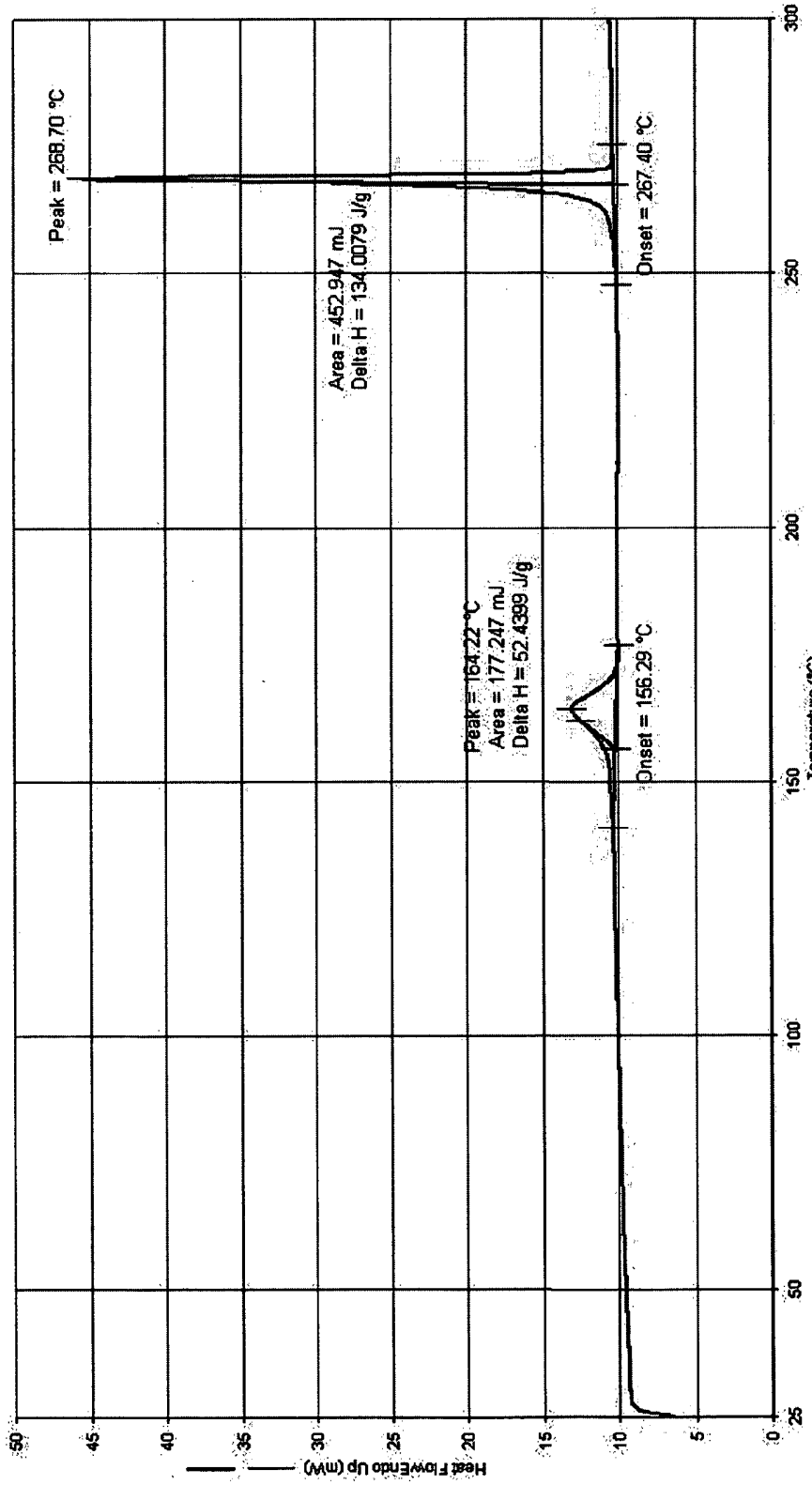

Peak = 268.70 °C
Area = 452.947 mJ
Delta H = 134.0079 J/g
Onset = 267.40 °C
Peak = 164.22 °C
Area = 177.247 mJ
Delta H = 52.4399 J/g
Onset = 156.29 °C
Heat FlowEndo Up (mW)
Temperature (°C)
50
45
40
35
30
25
20
15
10
5
0
25
50
100
150
200
250
300

Fig.8

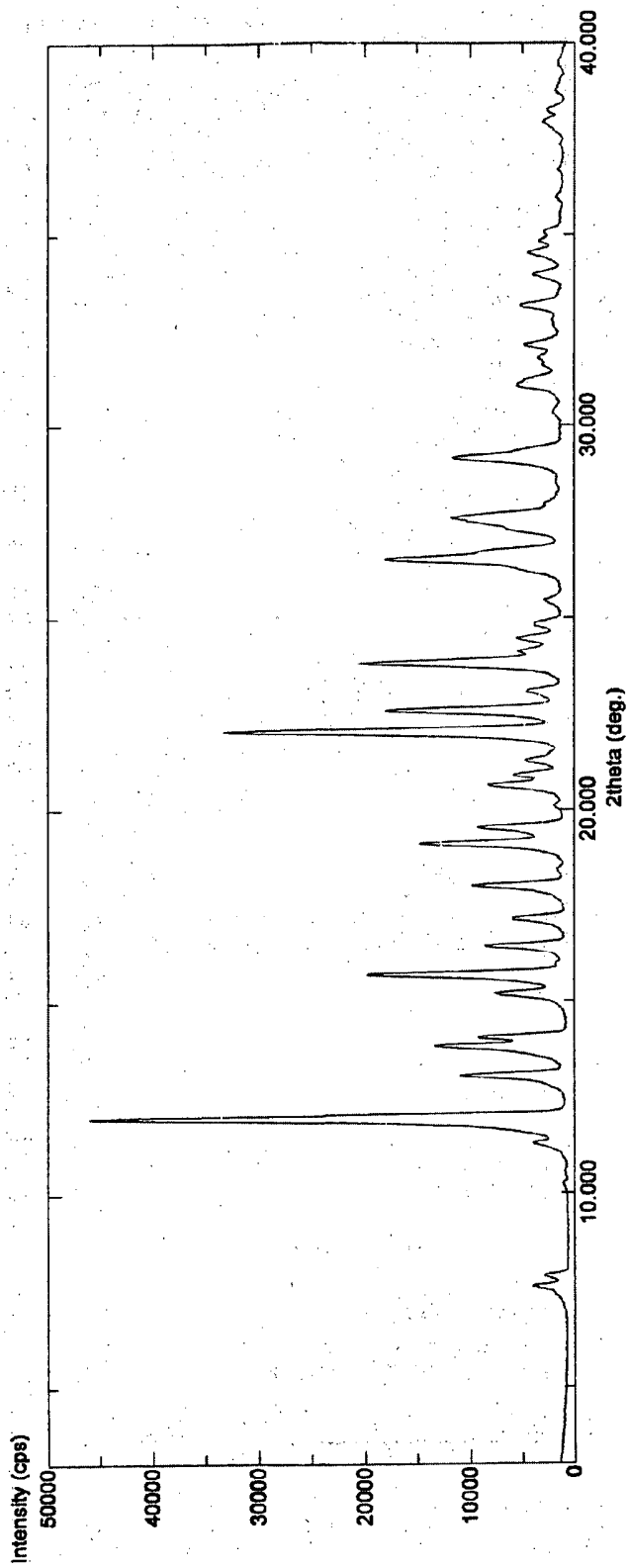

Intensity (cps)
50000
40000
30000
20000
10000
0
10.000
20.000
30.000
40.000
2theta (deg.)

Fig.9

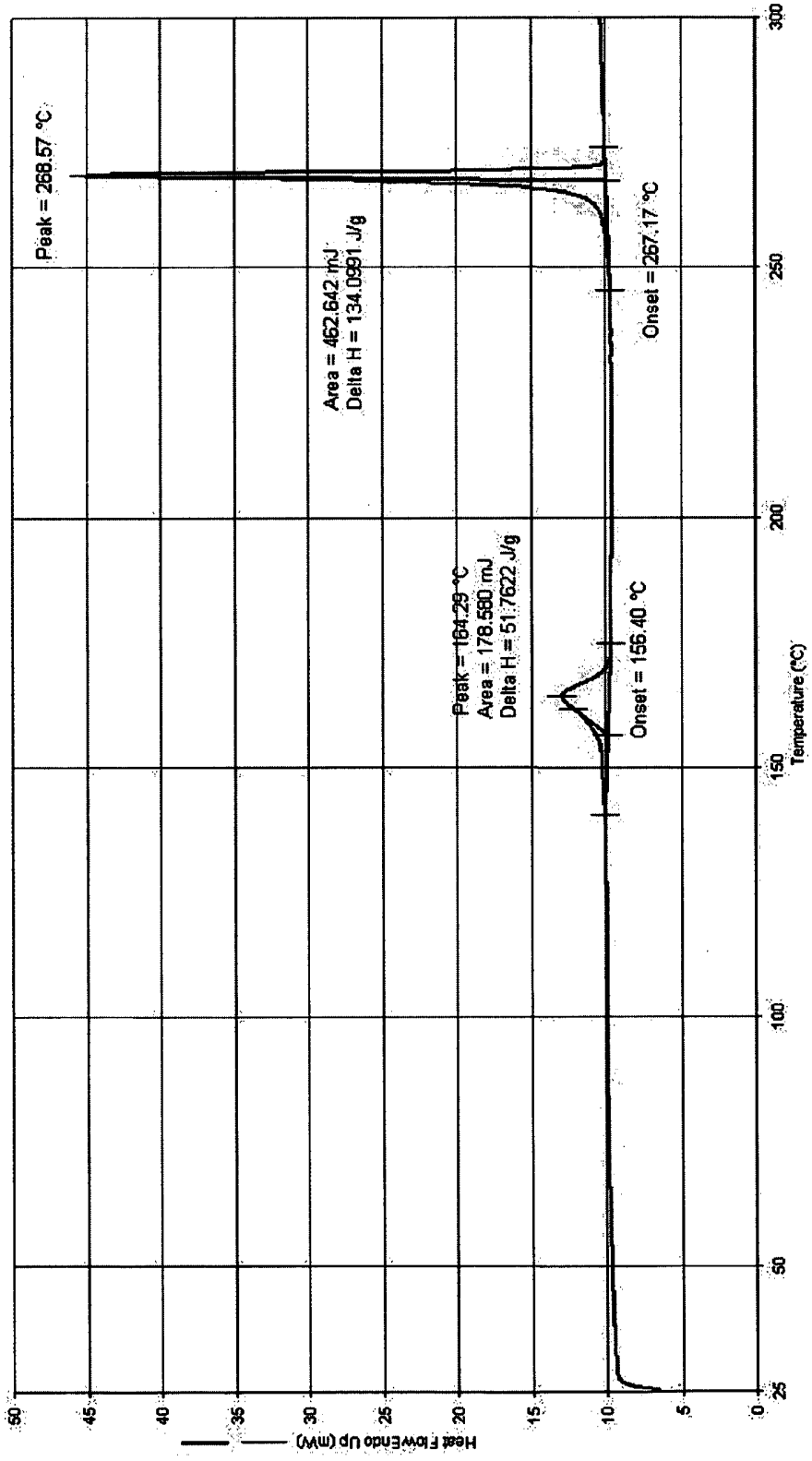

Peak = 268.57 °C
Area = 462.642 mJ
Delta H = 134.0991 J/g
Onset = 267.17 °C
Peak = 164.29 °C
Area = 178.580 mJ
Delta H = 51.7622 J/g
Onset = 156.40 °C
Heat FlowEndo Up (mW)
Temperature (°C)
60
45
40
35
30
25
20
15
10
5
0
25
50
100
150
200
250
300

Fig.10-1

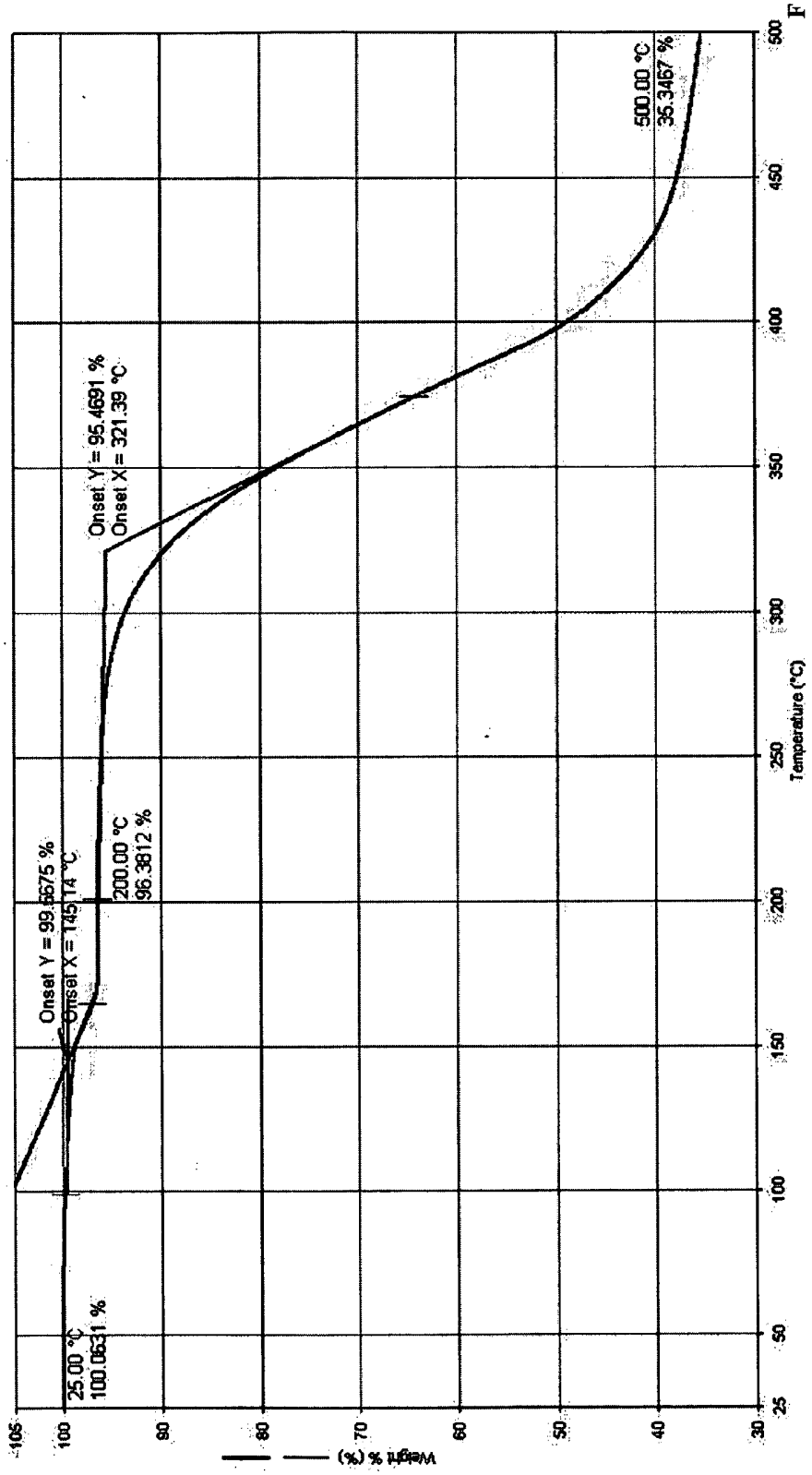

F
500.00 °C
35.3467 %
Onset Y = 95.4691 %
Onset X = 321.39 °C
200.00 °C
96.3812 %
Onset Y = 99.8675 %
Onset X = 145.14 °C
25.00 °C
100.0631 %
Temperature (°C)
Weight % (%)

Fig.10-2

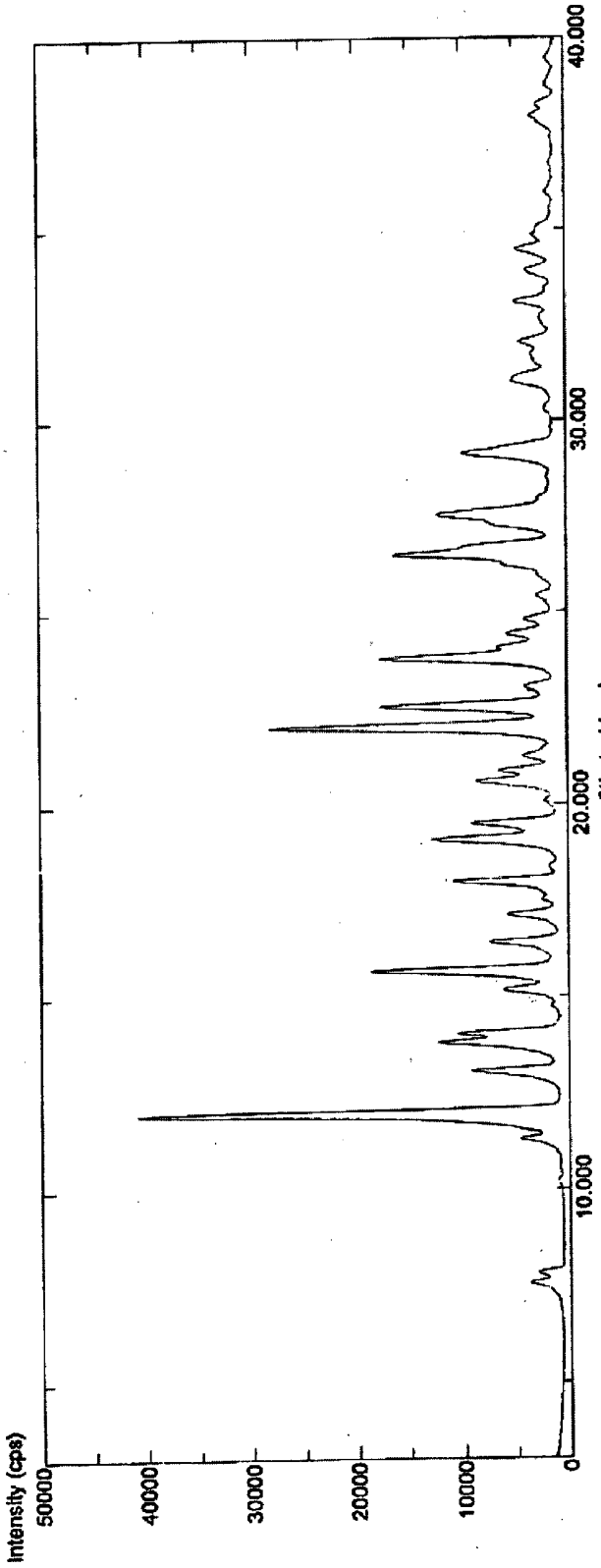

Intensity (cps)
50000
40000
30000
20000
10000
0
10.000
20.000
30.000
40.000
2theta (deg.)

Fig.11

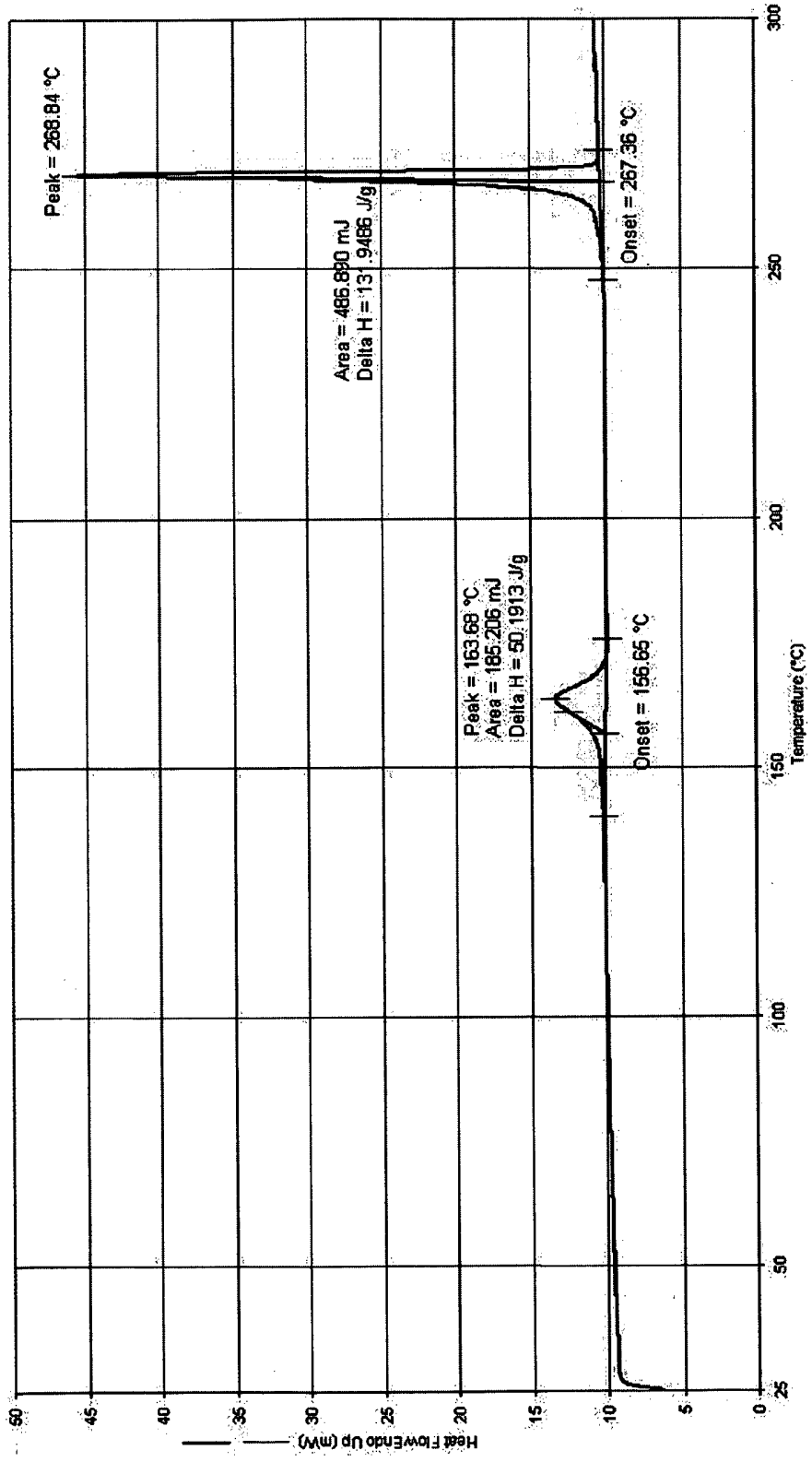

Peak = 268.84 °C
Area = 486.890 mJ
Delta H = 131.9486 J/g
Onset = 267.36 °C
Peak = 163.68 °C
Area = 185.206 mJ
Delta H = 50.1913 J/g
Onset = 156.65 °C
Temperature (°C)
Heat FlowEndo Up (mW)

Fig.12-1

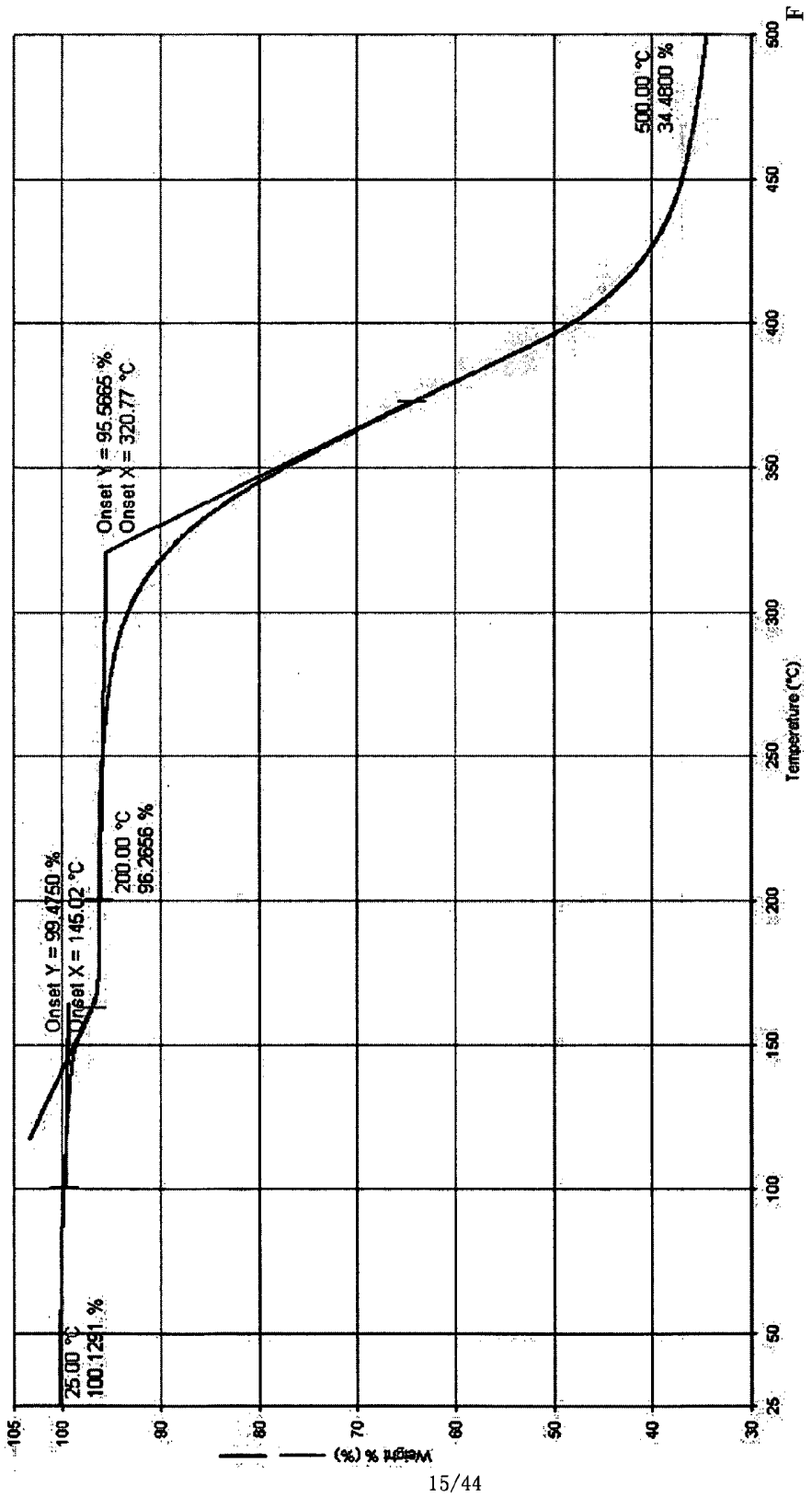
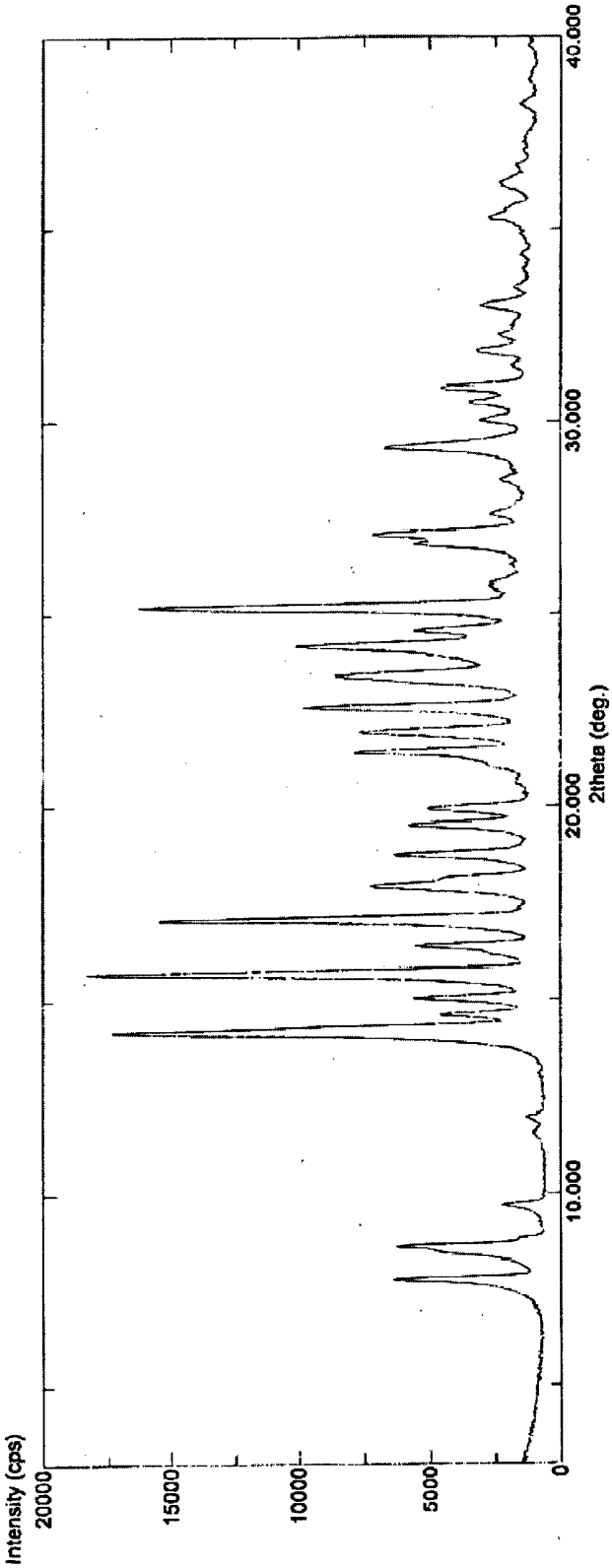

Onset Y = 99.4750 %
Onset X = 145.02 °C
200.00 °C
96.2656 %
Onset Y = 95.5665 %
Onset X = 320.77 °C
500.00 °C
34.4600 %
25.00 °C
100.1291 %
Temperature (°C)
Weight % (%)

Fig.12-2


Intensity (cps)
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15000
10000
5000
0
10.000
20.000
30.000
40.000
2theta (deg.)

Fig.13

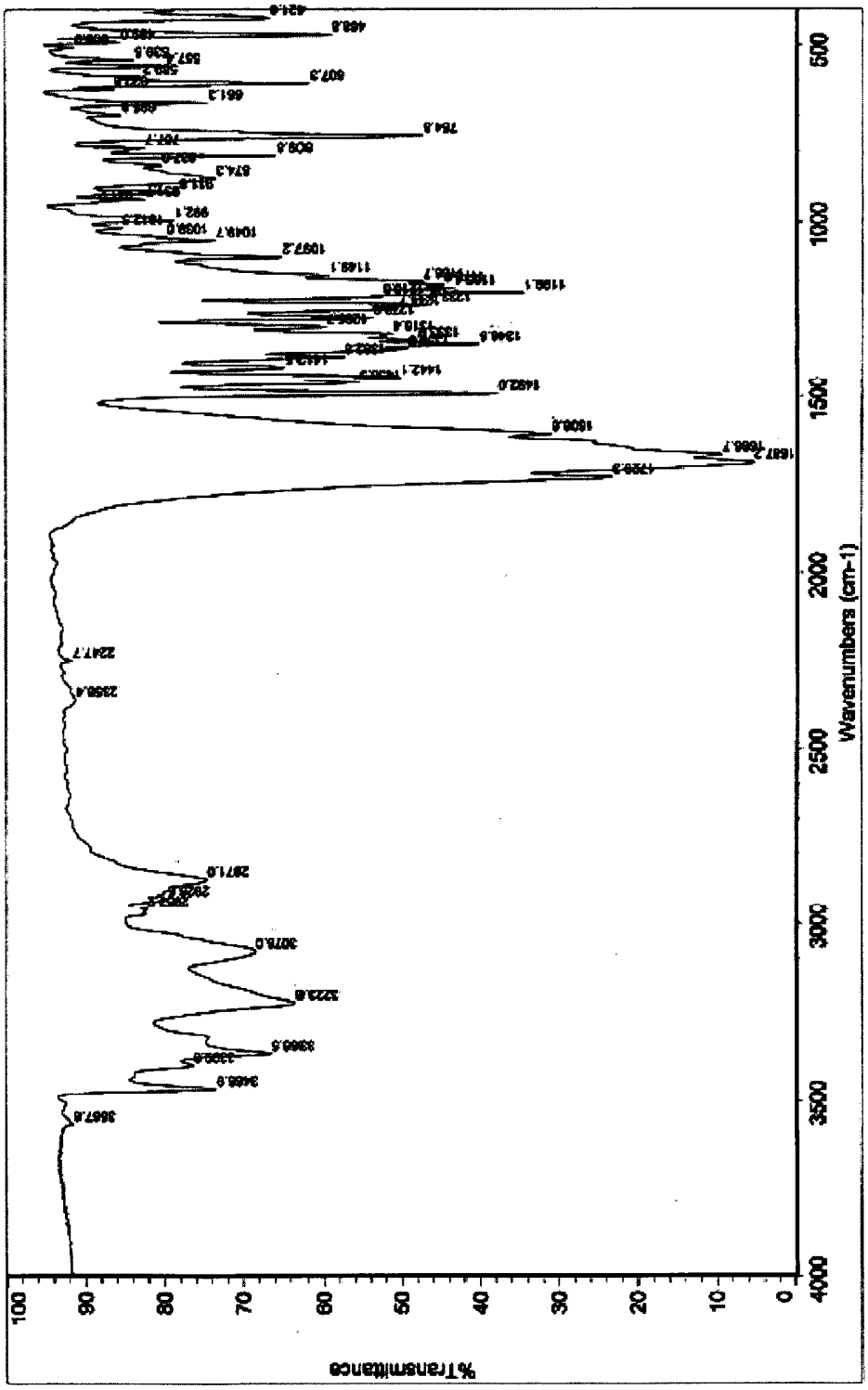

%Transmittance
Wavenumbers (cm-1)
100
90
80
70
60
50
40
30
20
10
0
4000
3500
3000
2500
2000
1500
1000
500
3667.8
3466.9
3360.5
3223.8
3078.0
2871.0
2247.7
2358.4
1687.2
1600.7
1508.6
1482.0
1442.1
1396.8
1257.4
1168.1
1098.1
1057.2
1049.7
992.1
874.3
764.8
607.3
661.3
468.8
421.6

Fig.14

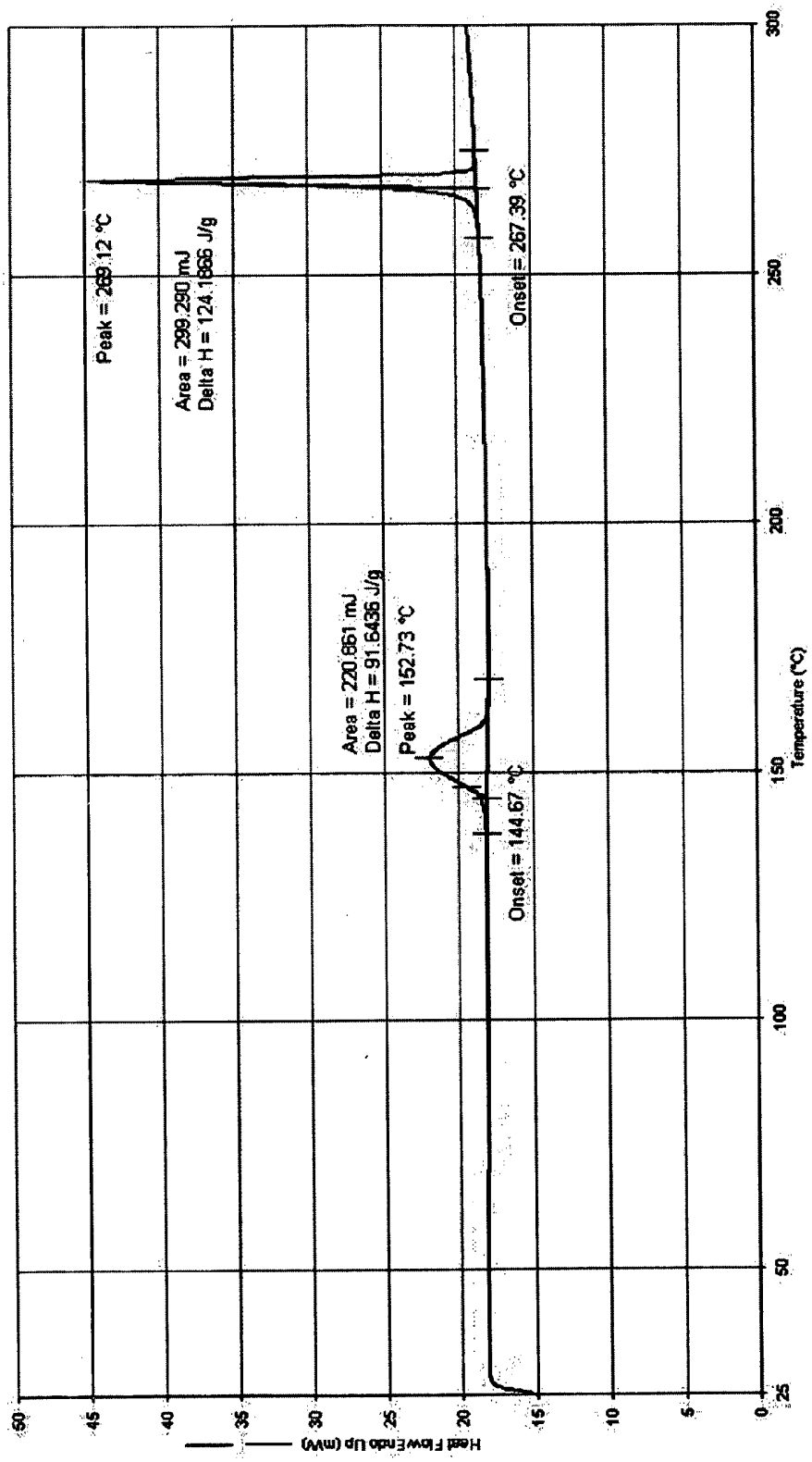

Peak = 269.12 °C
Area = 299.290 mJ
Delta H = 124.1866 J/g
Onset = 267.39 °C
Area = 220.861 mJ
Delta H = 91.6436 J/g
Peak = 152.73 °C
Onset = 144.67 °C
Heat Flow Endo Up (mW)
Temperature (°C)

Fig.15-1

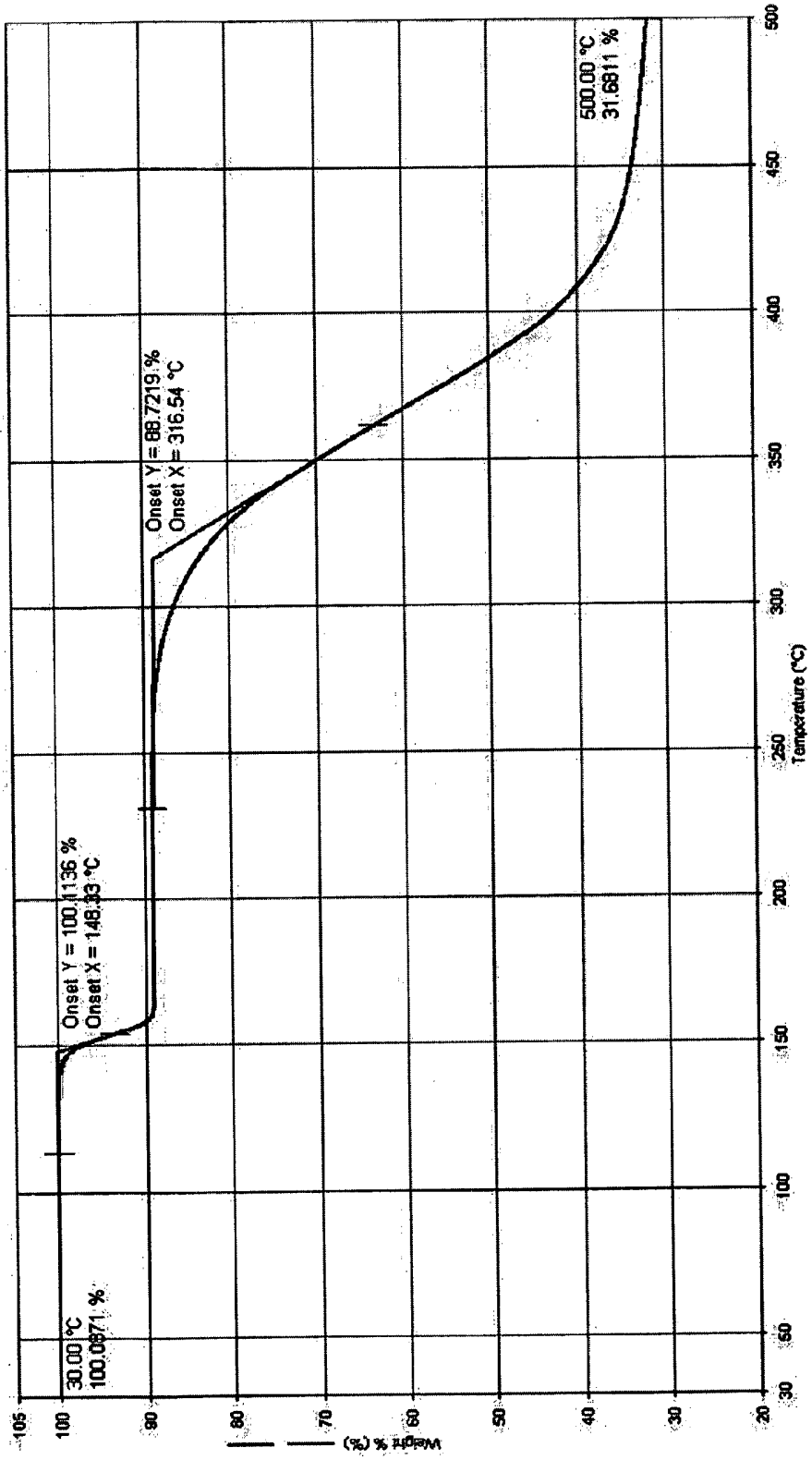

30.00 °C
100.0871 %
Onset Y = 100.1136 %
Onset X = 148.33 °C
Onset Y = 88.7219 %
Onset X = 316.54 °C
500.00 °C
31.6811 %
Weight % (%)
Temperature (°C)

Fig.15-2

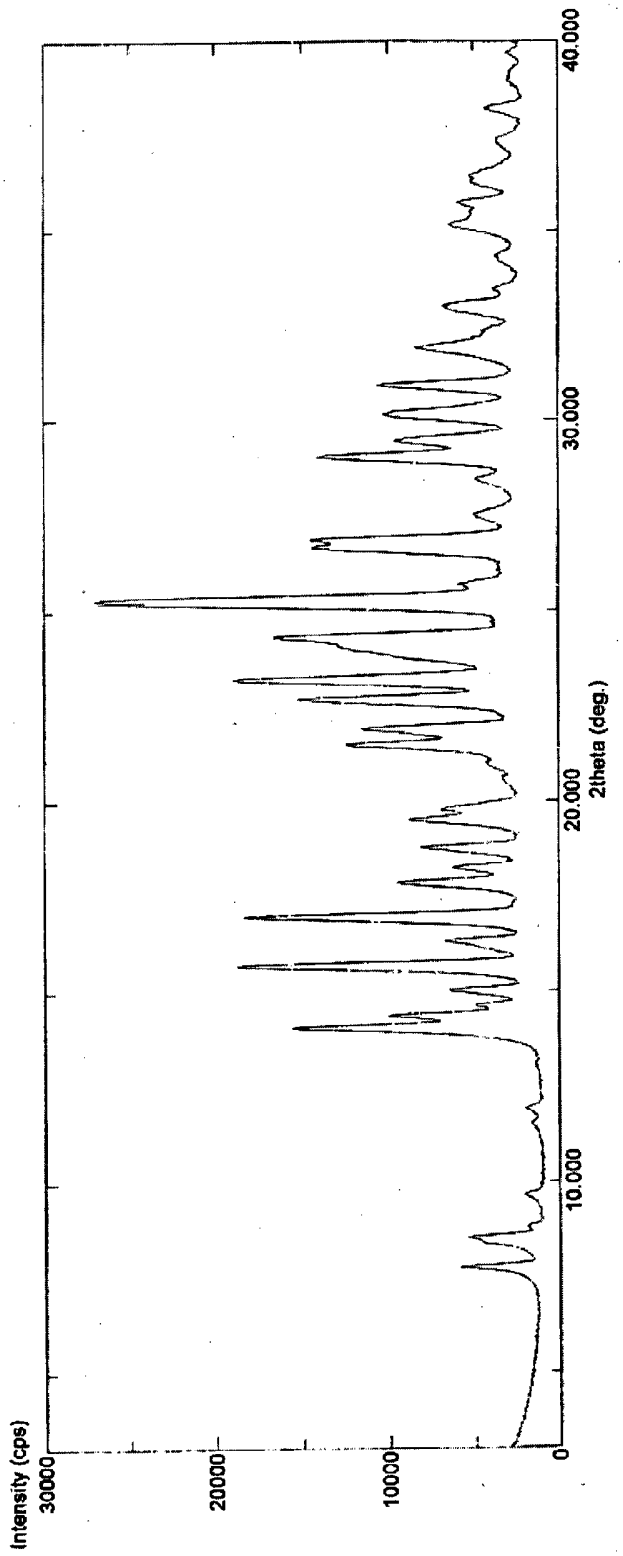

Intensity (cps)
30000
20000
10000
0
10.000
20.000
30.000
40.000
2theta (deg.)

Fig.16

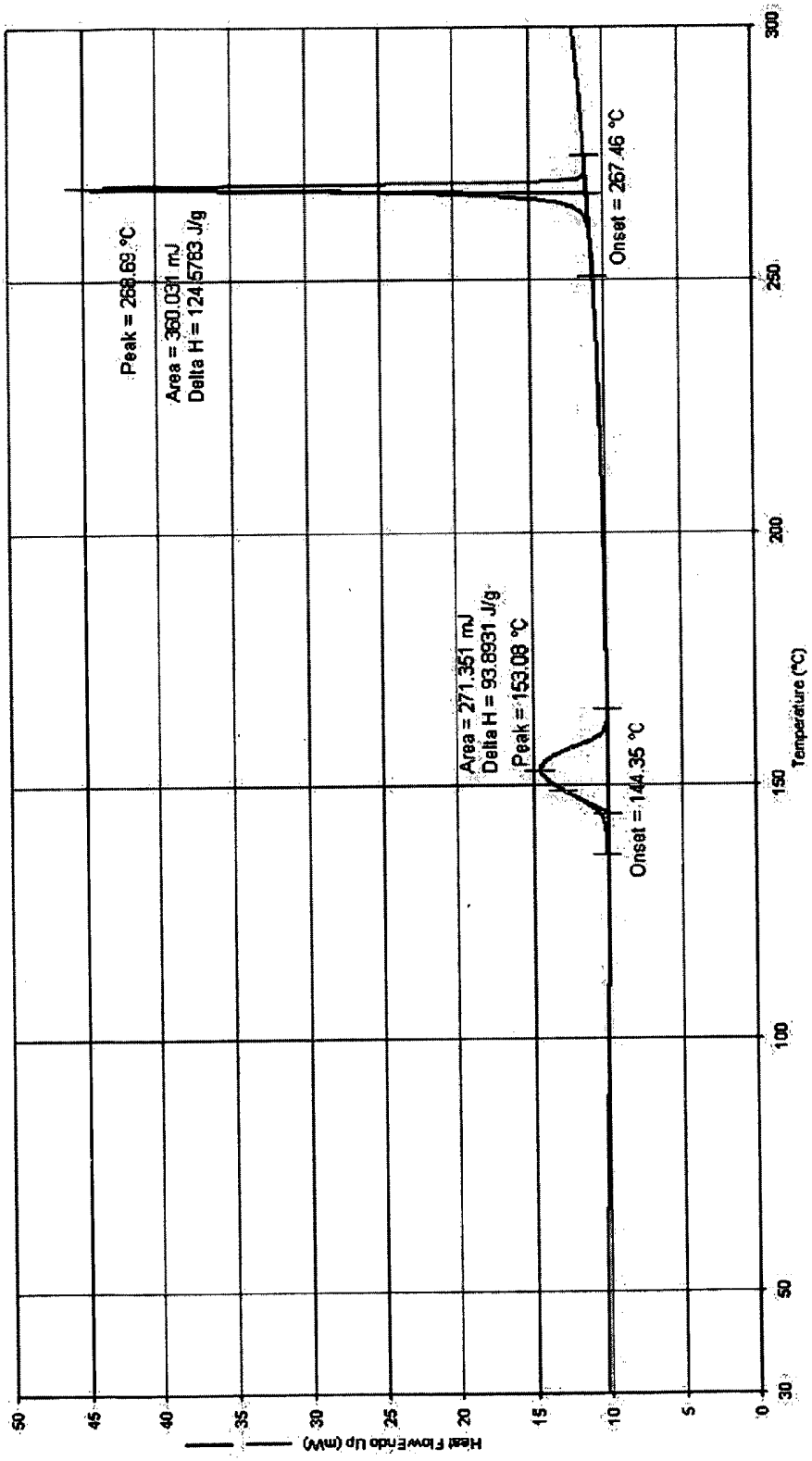

Peak = 268.69 °C
Area = 360.031 mJ
Delta H = 124.5783 J/g
Onset = 267.46 °C
Area = 271.351 mJ
Delta H = 93.8931 J/g
Peak = 153.08 °C
Onset = 144.35 °C
Heat FlowEndo Up (mW)
Temperature (°C)
50
45
40
35
30
25
20
15
10
5
0
300
250
200
150
100
50
30

Fig.17

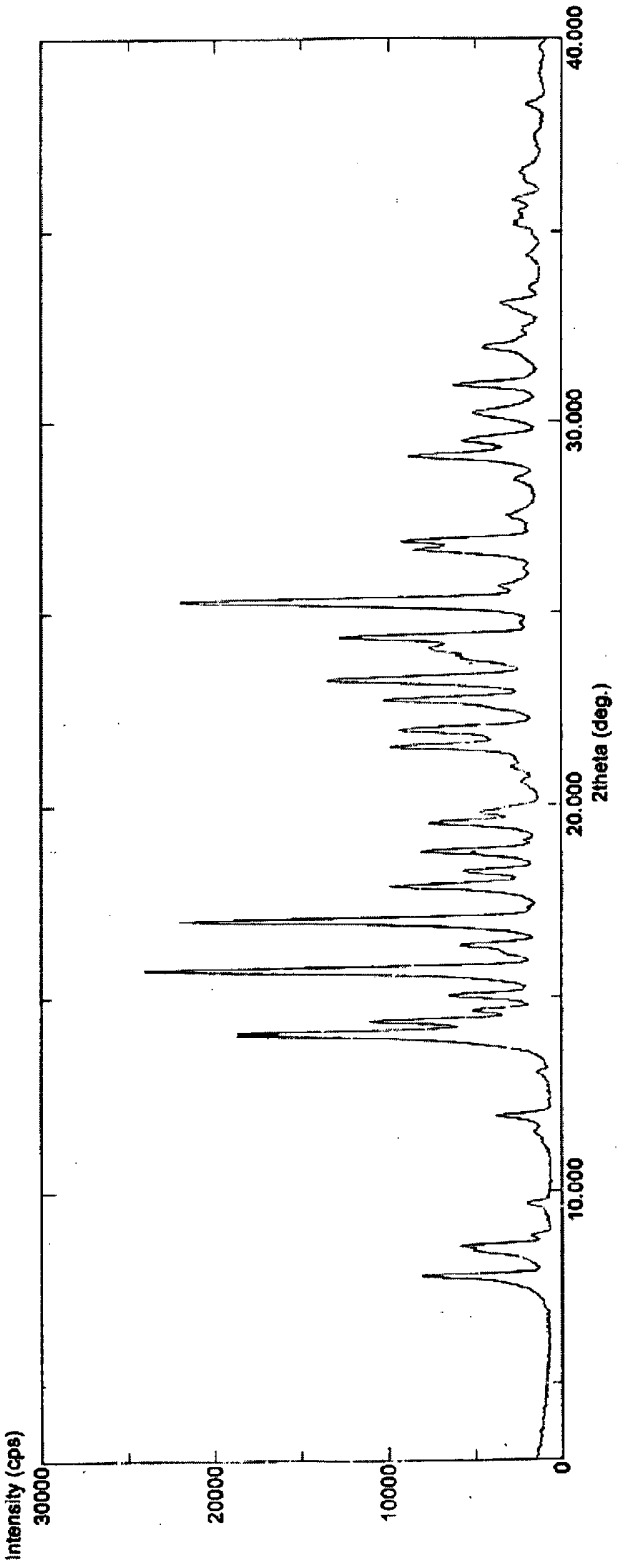

Intensity (cps)
30000
20000
10000
0
10.000
20.000
30.000
40.000
2theta (deg.)

Fig.18

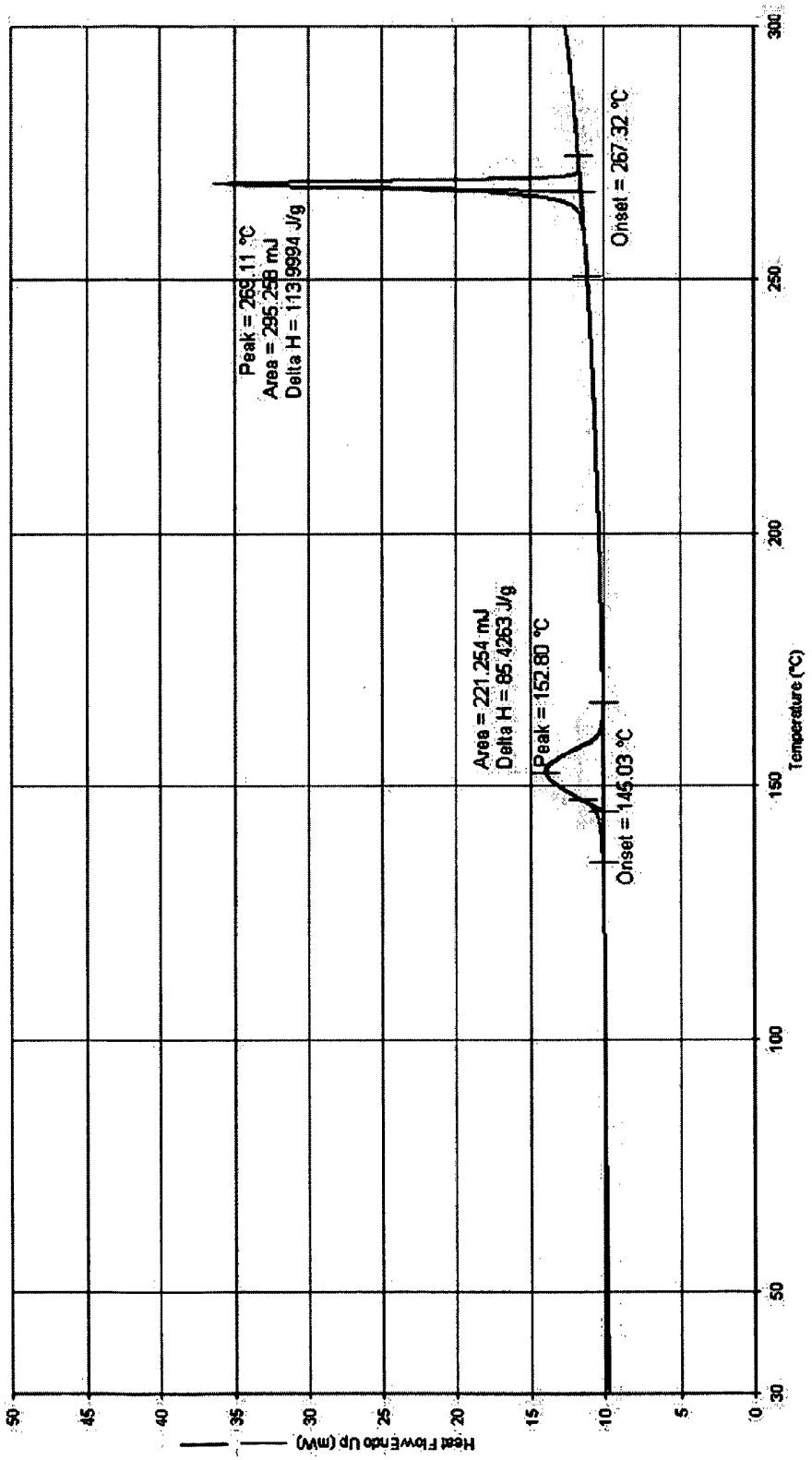
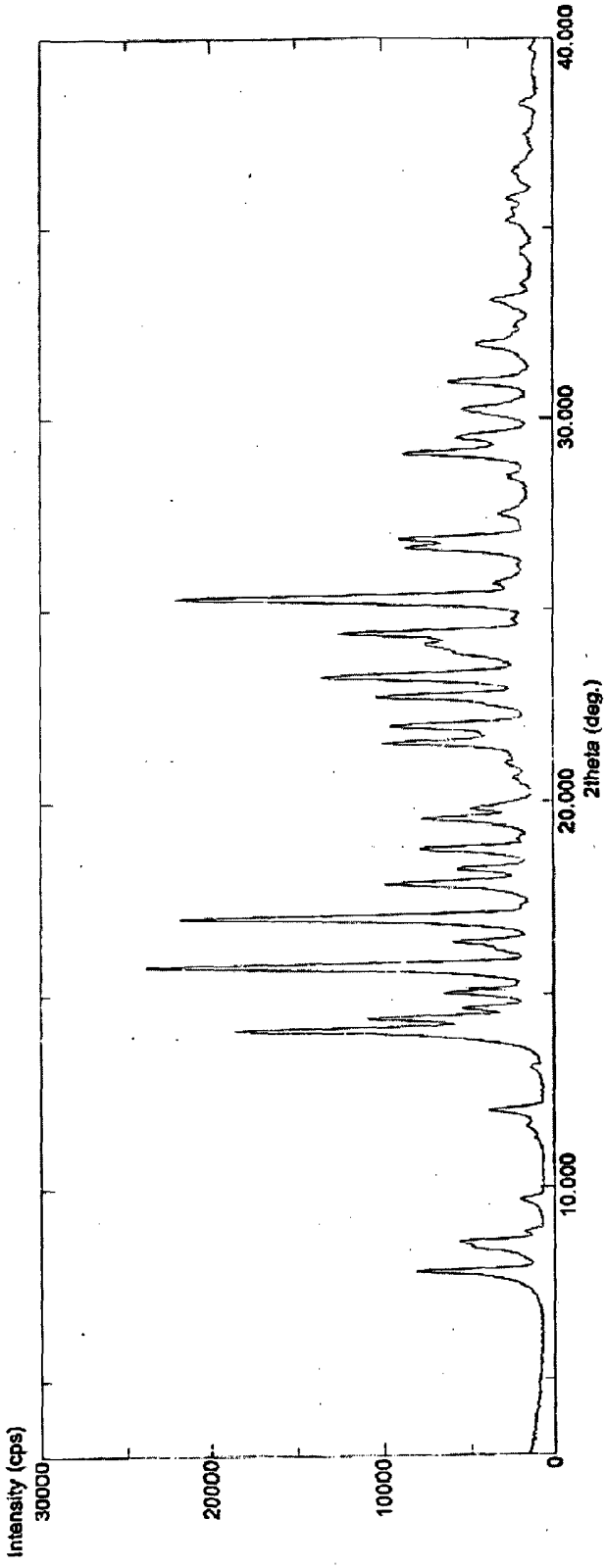

Peak = 269.11 °C
Area = 295.258 mJ
Delta H = 1139994 J/g
Onset = 267.32 °C
Area = 221.254 mJ
Delta H = 85.4263 J/g
Peak = 152.80 °C
Onset = 145.03 °C
Heat Flow Endo Up (mW)
Temperature (°C)

Fig.19


Intensity (cps)
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20000
10000
0
10.000
20.000
30.000
40.000
2theta (deg.)

Fig.20

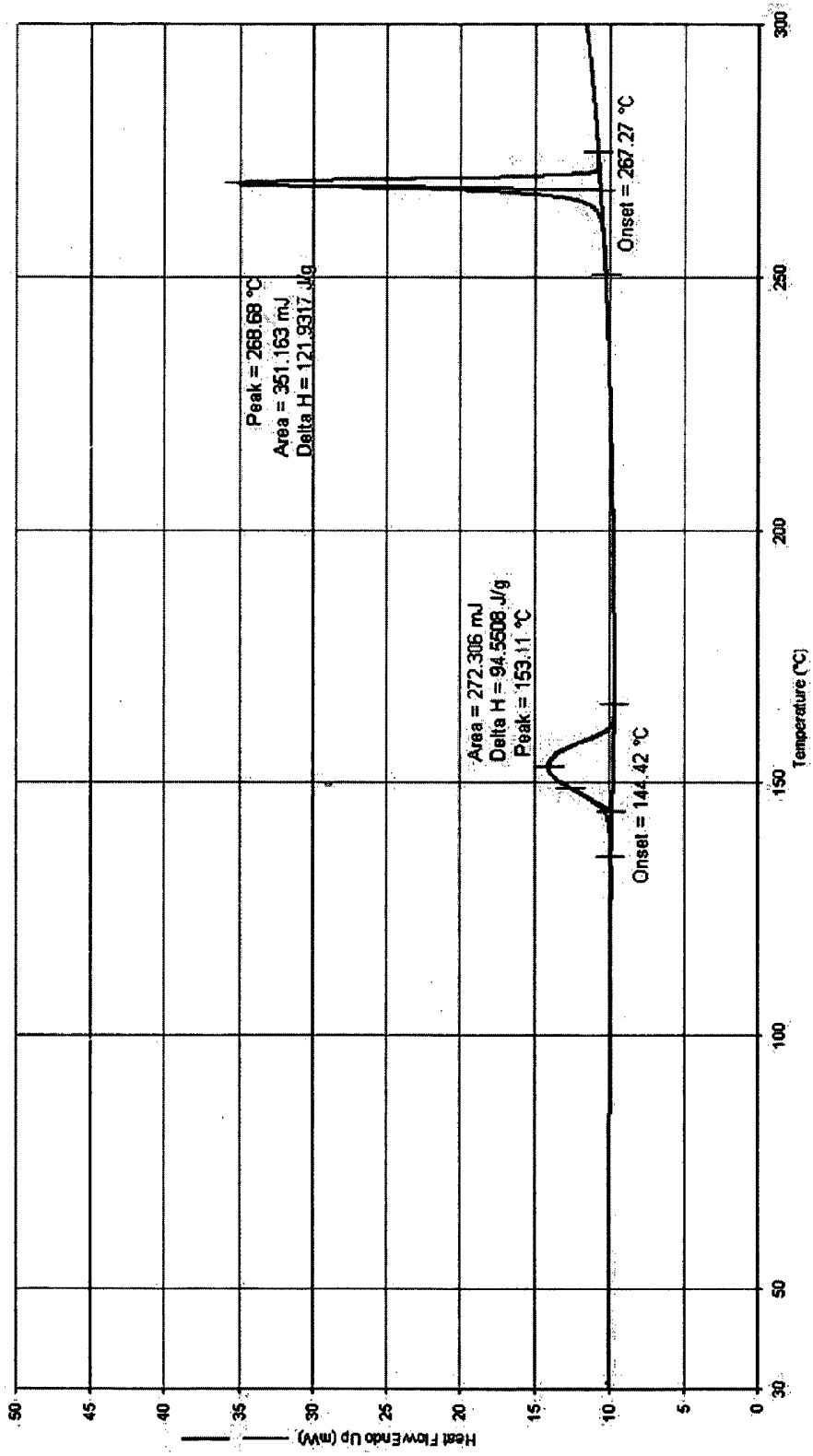
Peak = 268.68 °C
Area = 351.163 mJ
Delta H = 121.9317 J/g
Onset = 267.27 °C
Area = 272.386 mJ
Delta H = 94.5508 J/g
Peak = 153.11 °C
Onset = 144.42 °C
Heat FlowEndo Up (mW)
Temperature (°C)
50
45
40
35
30
25
20
15
10
5
0
300
250
200
150
100
50
30

Fig.21-1

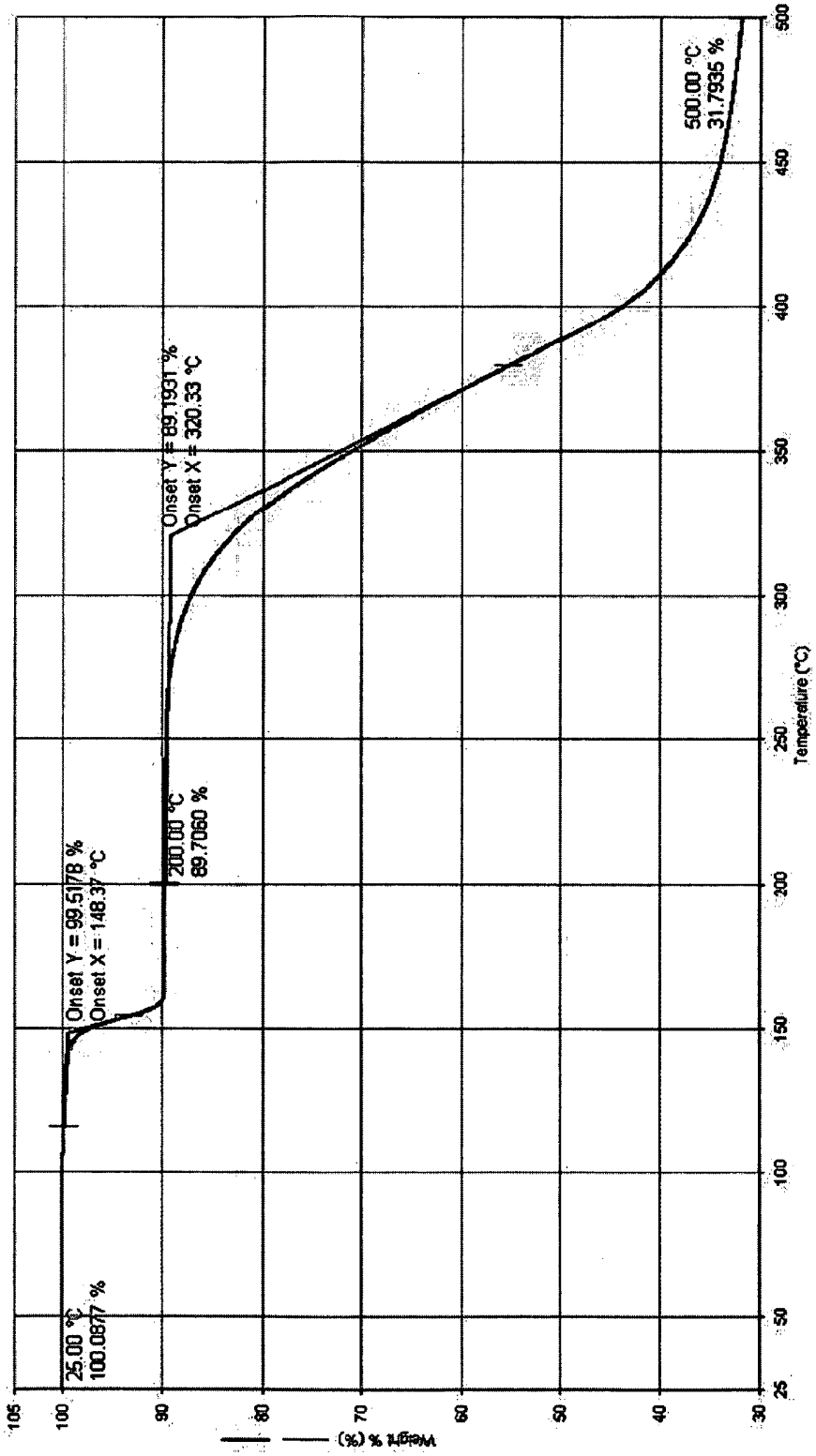
25.00 °C
100.0877 %
Onset Y = 99.5178 %
Onset X = 148.37 °C
200.00 °C
89.7060 %
Onset Y = 89.1931 %
Onset X = 320.33 °C
500.00 °C
31.7935 %
Temperature (°C)
Weight % (%)

Fig.21-2

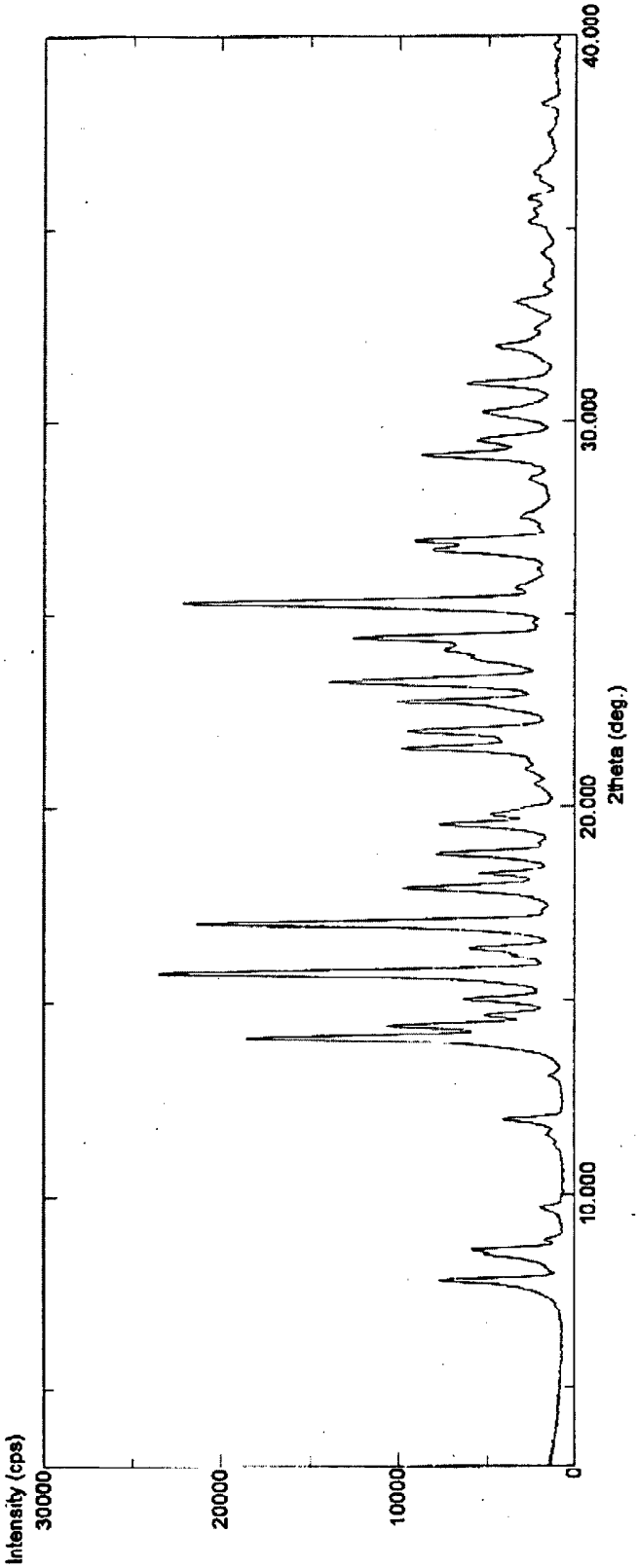
Intensity (cps)
30000
20000
10000
0
10.000
20.000
30.000
40.000
2theta (deg.)

Fig.22

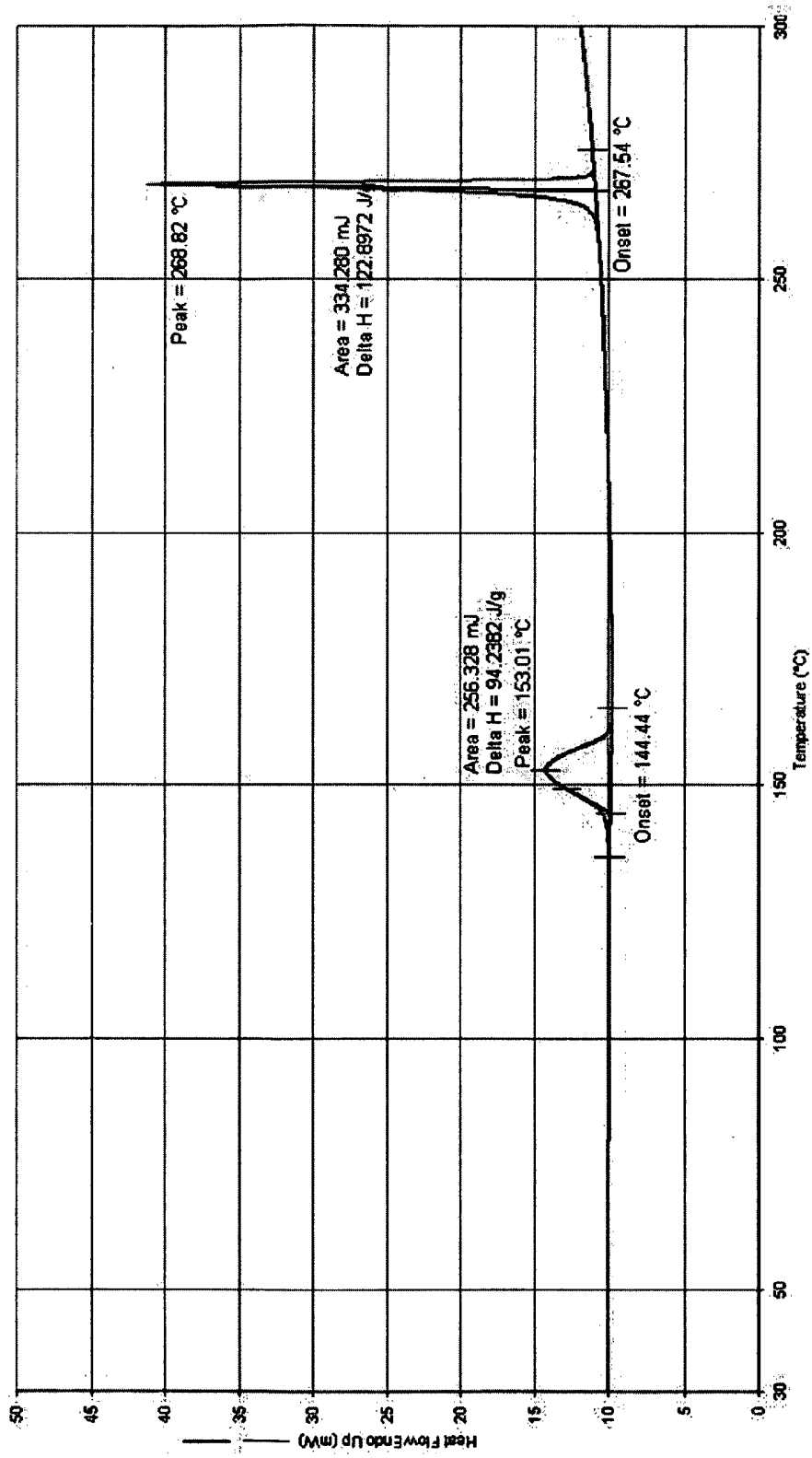
Peak = 268.82 °C
Area = 334.280 mJ
Delta H = 122.8972 J/g
Onset = 267.54 °C
Area = 256.328 mJ
Delta H = 94.2382 J/g
Peak = 153.01 °C
Onset = 144.44 °C
Heat FlowEndo Up (mW)
Temperature (°C)

Fig.23-1

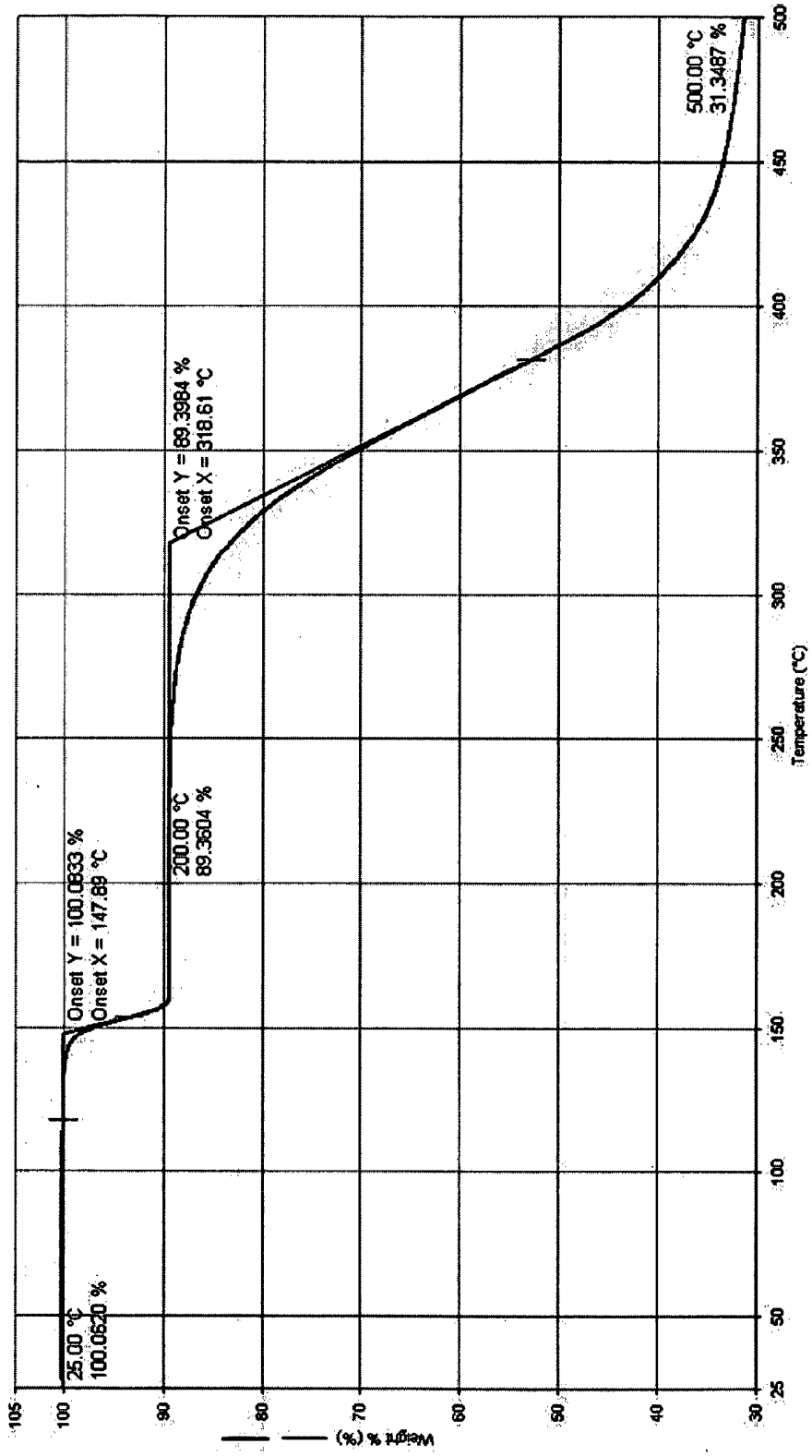
25.00 °C
100.0620 %
Onset Y = 100.0833 %
Onset X = 147.89 °C
200.00 °C
89.3804 %
Onset Y = 89.3984 %
Onset X = 318.61 °C
500.00 °C
31.3487 %
Temperature (°C)
Weight % (%)

Fig.23-2

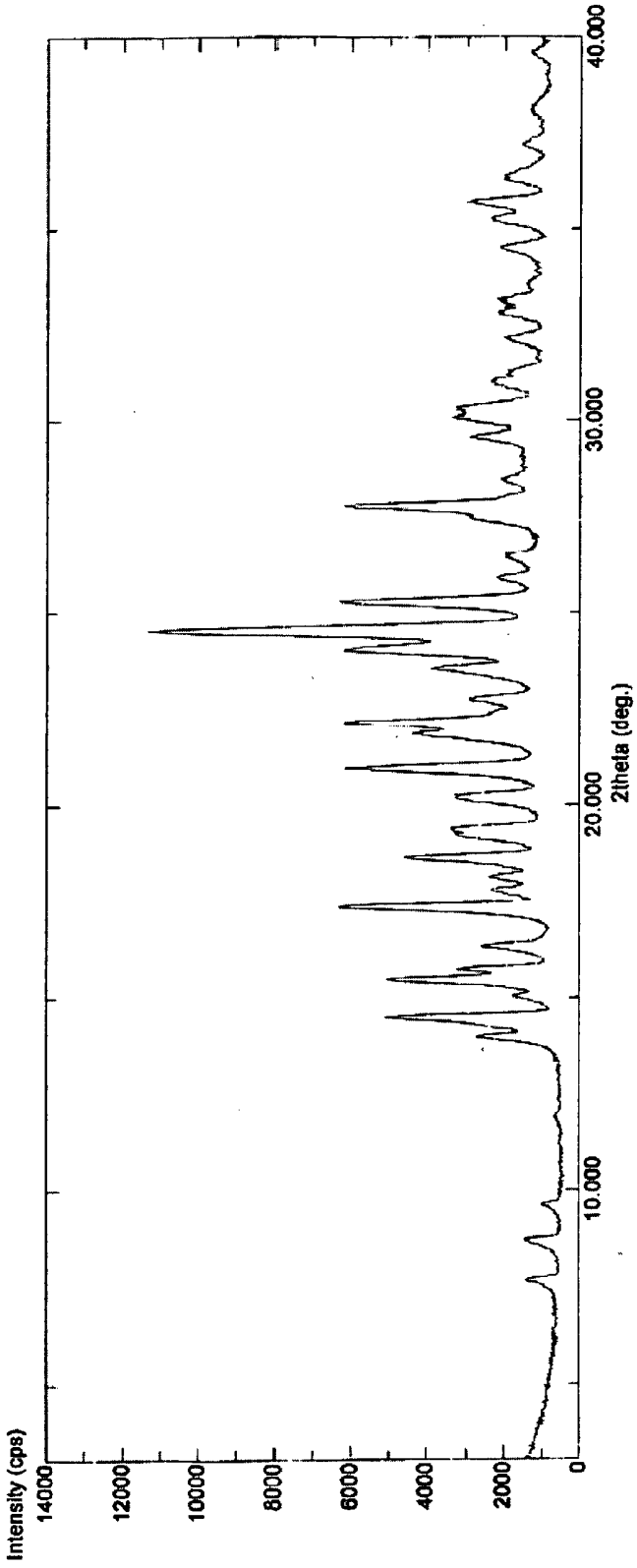
Intensity (cps)
14000
12000
10000
8000
6000
4000
2000
0
10.000
20.000
30.000
40.000
2theta (deg.)

Fig.24

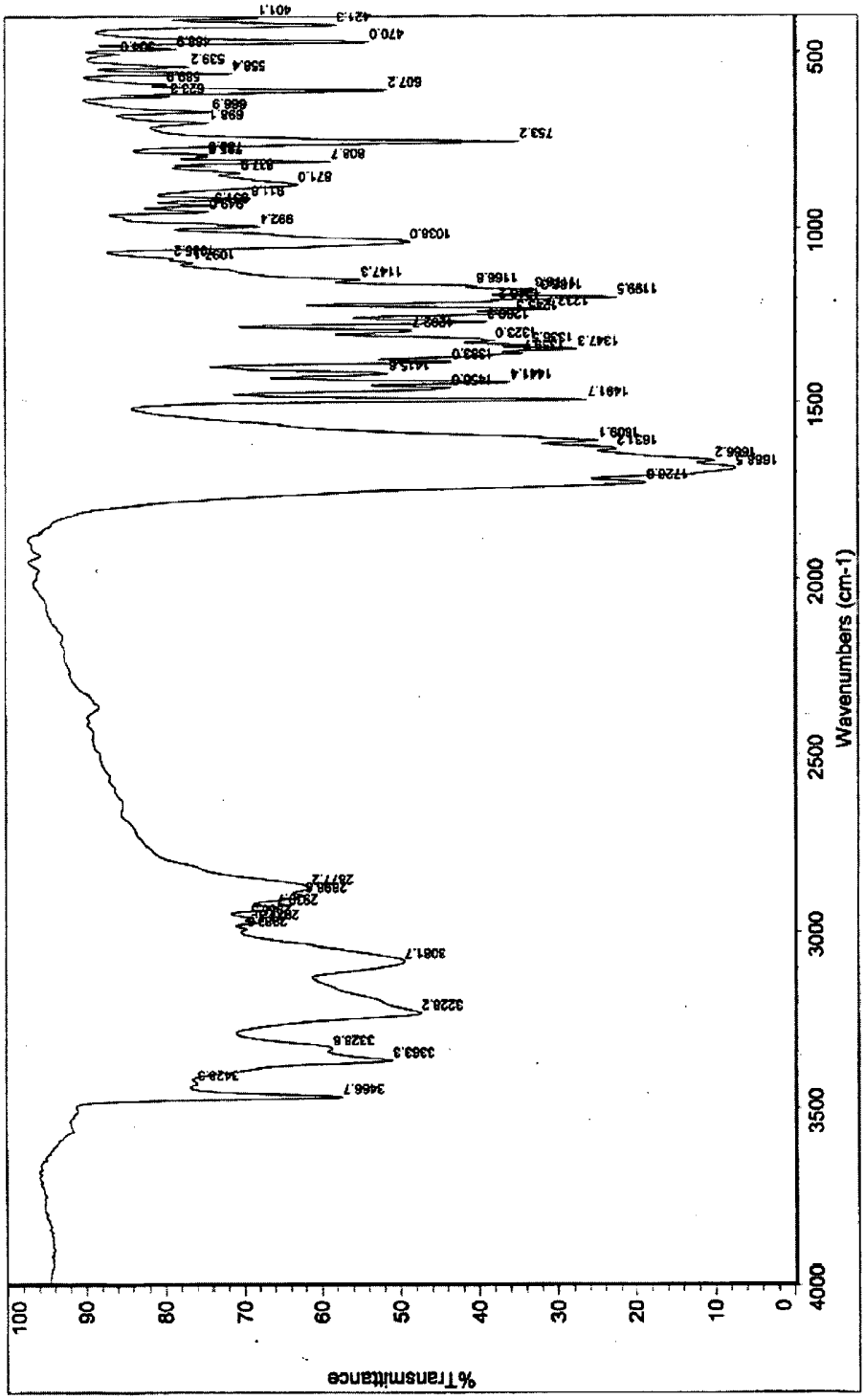
%Transmittance
Wavenumbers (cm-1)
100
90
80
70
60
50
40
30
20
10
0
4000
3500
3000
2500
2000
1500
1000
500
3466.7
3363.3
3328.8
3228.2
3081.7
2871.2
1720.8
1686.2
1631.2
1609.1
1491.7
1441.4
1347.3
1199.5
1147.3
1038.0
892.4
871.0
807.2
753.2
556.4
539.2
470.0
421.3
401.1

Fig.25

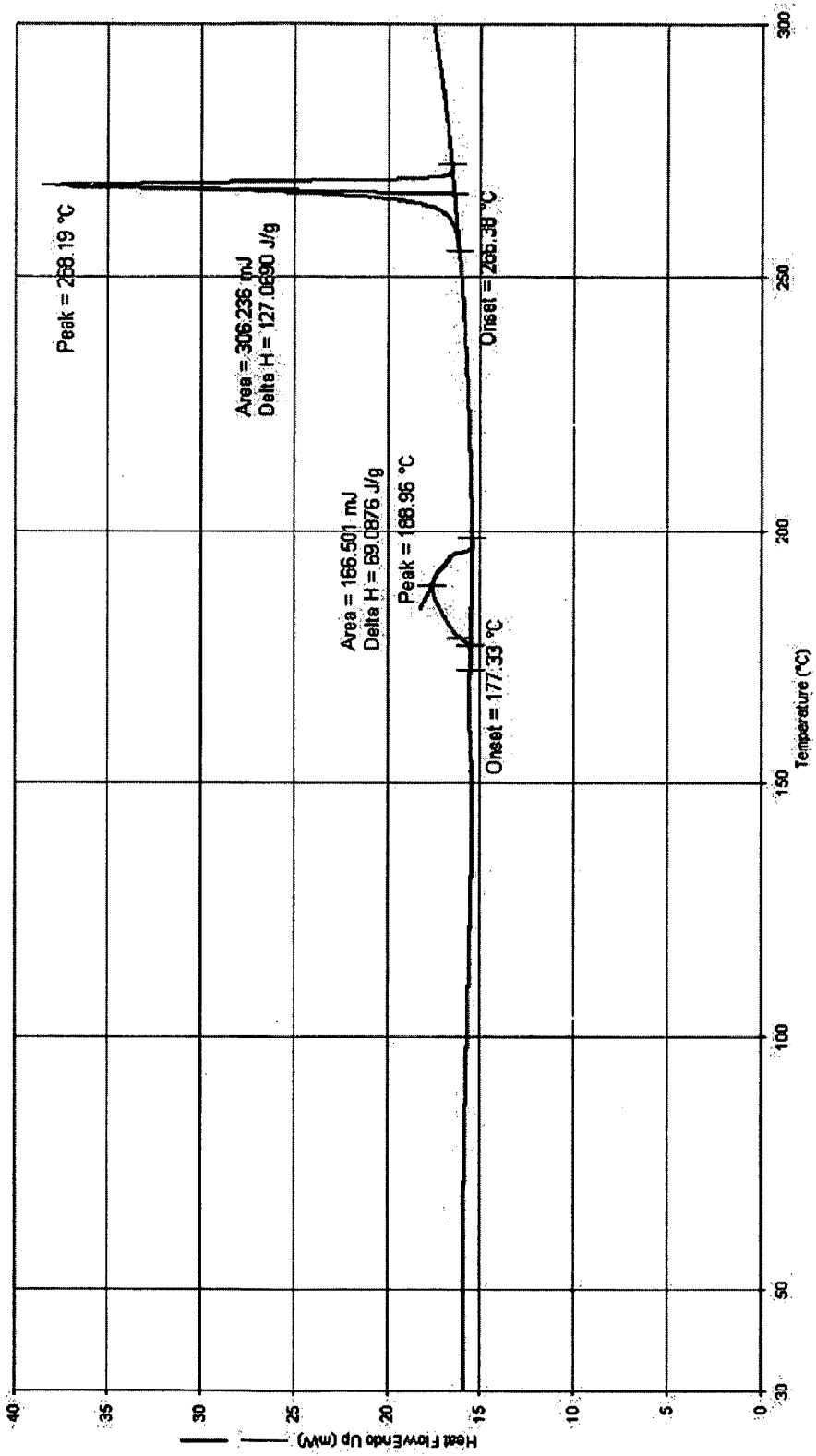
Peak = 268.19 °C
Area = 306.236 mJ
Delta H = 127.0690 J/g
Onset = 265.38 °C
Peak = 188.96 °C
Area = 166.501 mJ
Delta H = 69.0876 J/g
Onset = 177.33 °C
Heat FlowEndo Up (mW)
Temperature (°C)

Fig.26-1

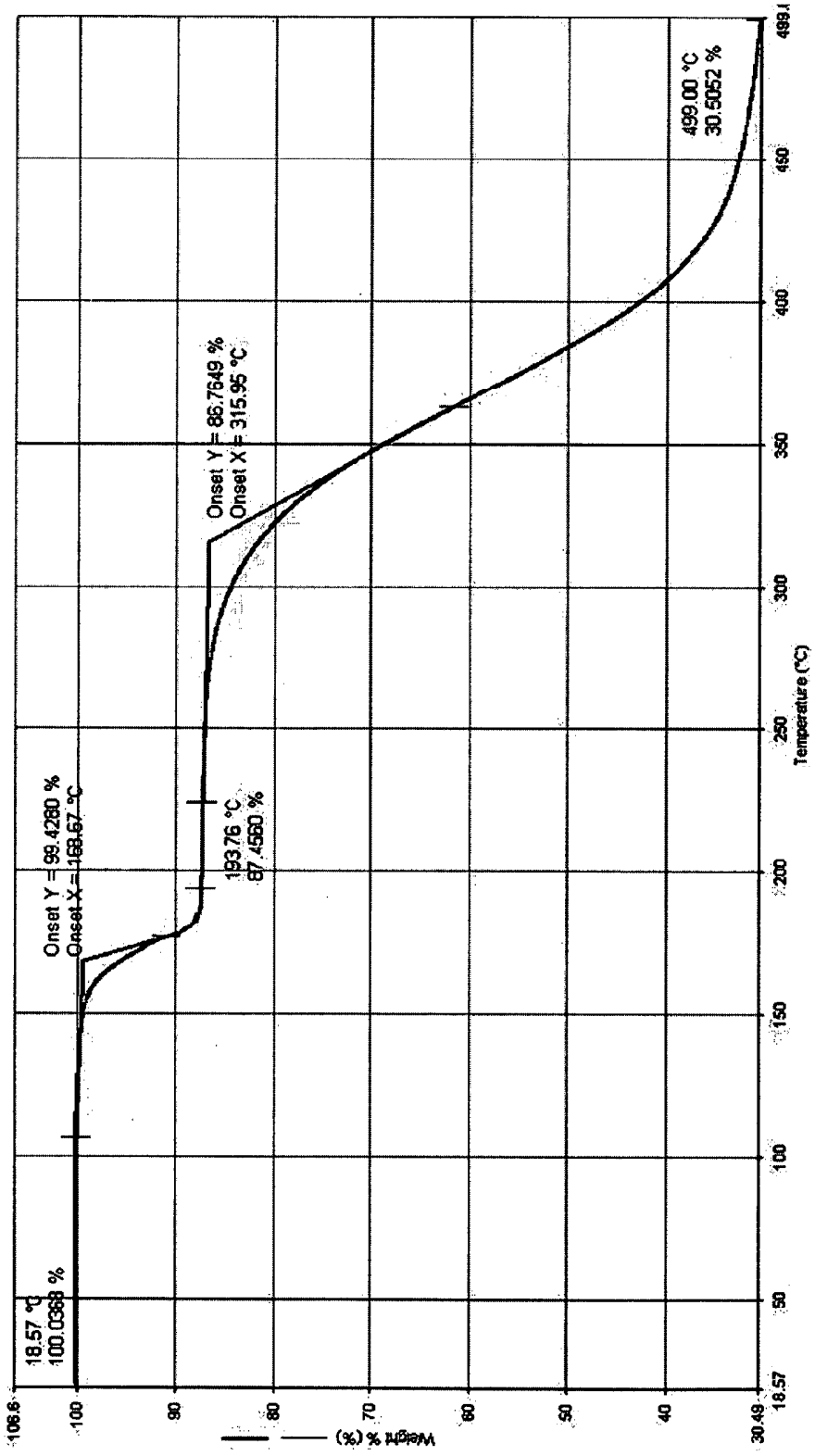
Onset Y = 99.4280 %
Onset X = 168.67 °C
193.76 °C
87.4560 %
Onset Y = 86.7649 %
Onset X = 315.95 °C
499.00 °C
30.5052 %
18.57 °C
100.0368 %
Weight % (%)
Temperature (°C)

Fig.26-2

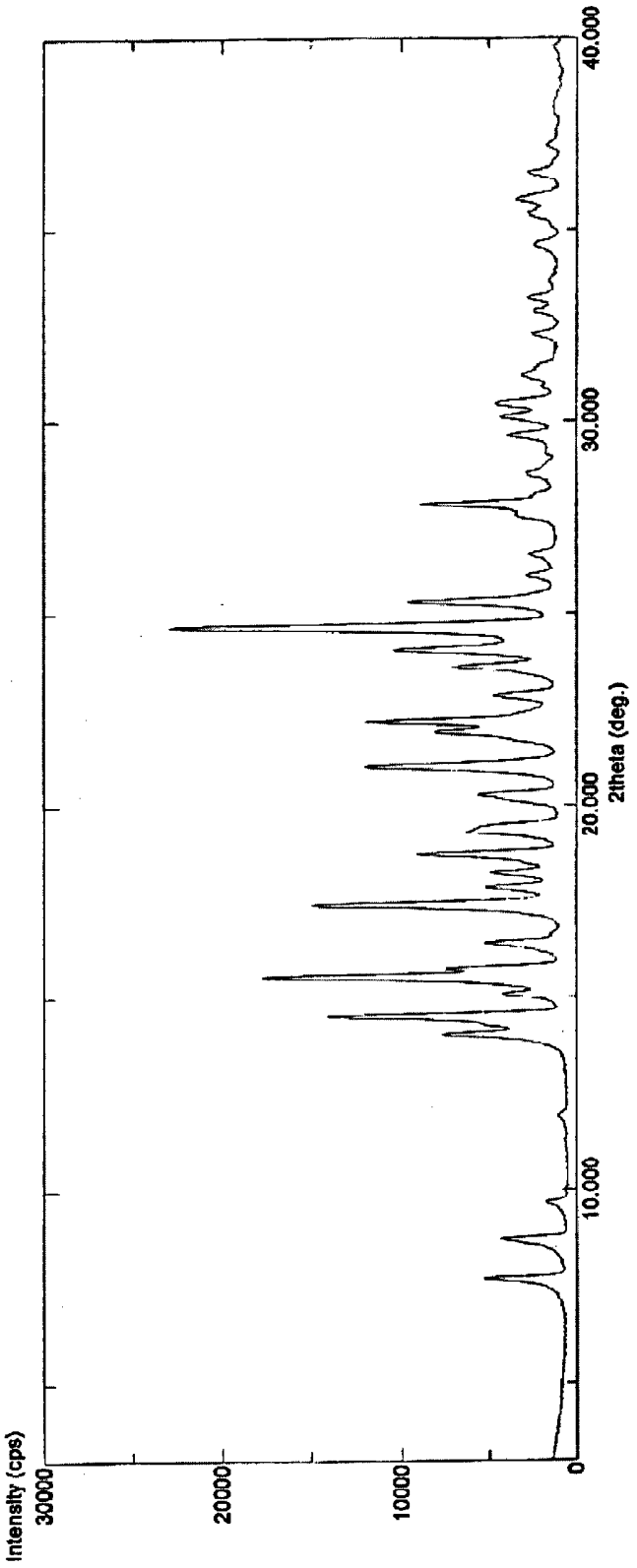
Intensity (cps)
30000
20000
10000
0
10.000
20.000
30.000
40.000
2theta (deg.)

Fig.27

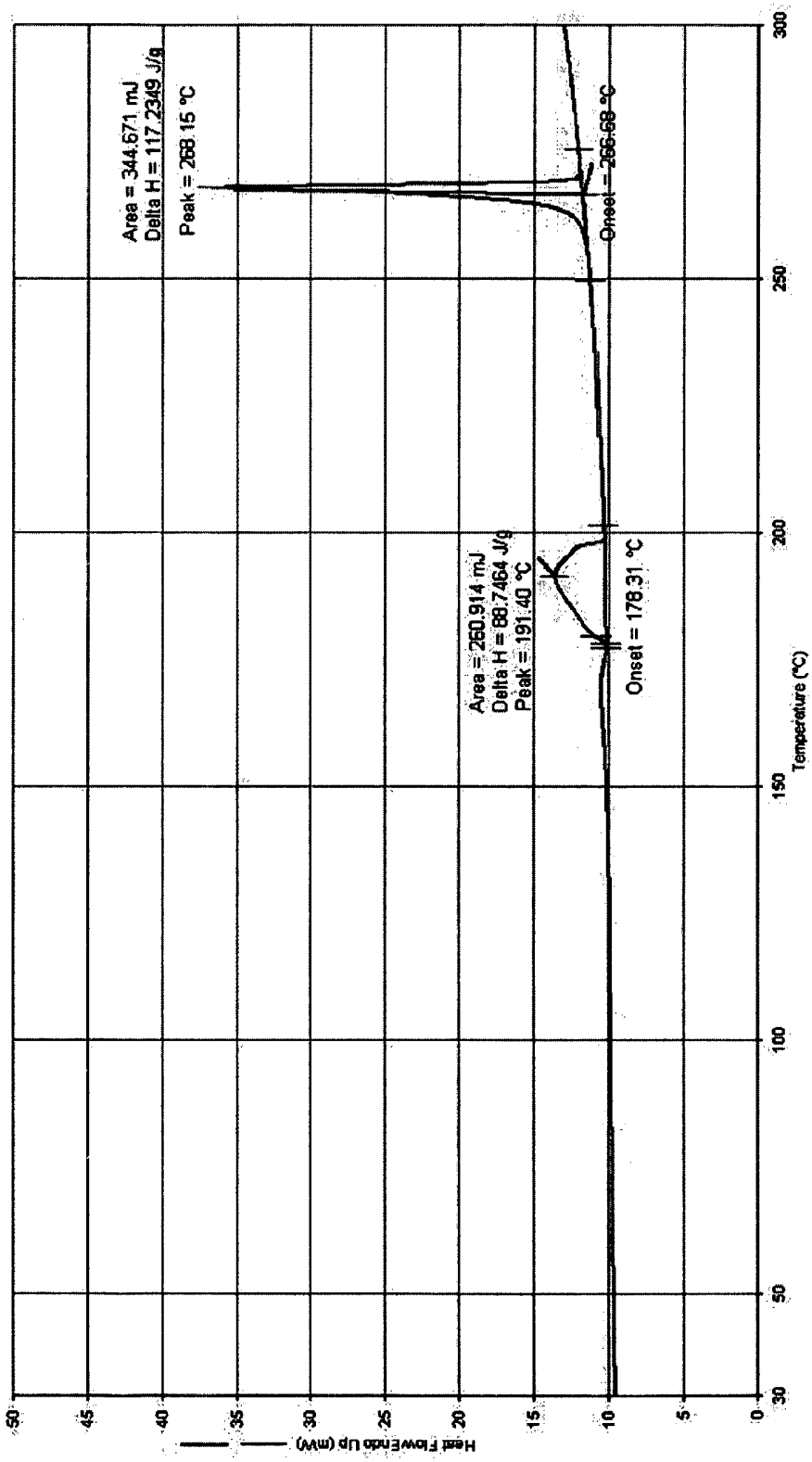
Area = 344.671 mJ
Delta H = 117.2349 J/g
Peak = 268.15 °C
Onset = 266.68 °C
Area = 260.914 mJ
Delta H = 88.7464 J/g
Peak = 191.40 °C
Onset = 178.31 °C
Heat Flow Endo Up (mW)
Temperature (°C)
50
45
40
35
30
25
20
15
10
5
0
30
50
100
150
200
250
300

Fig.28

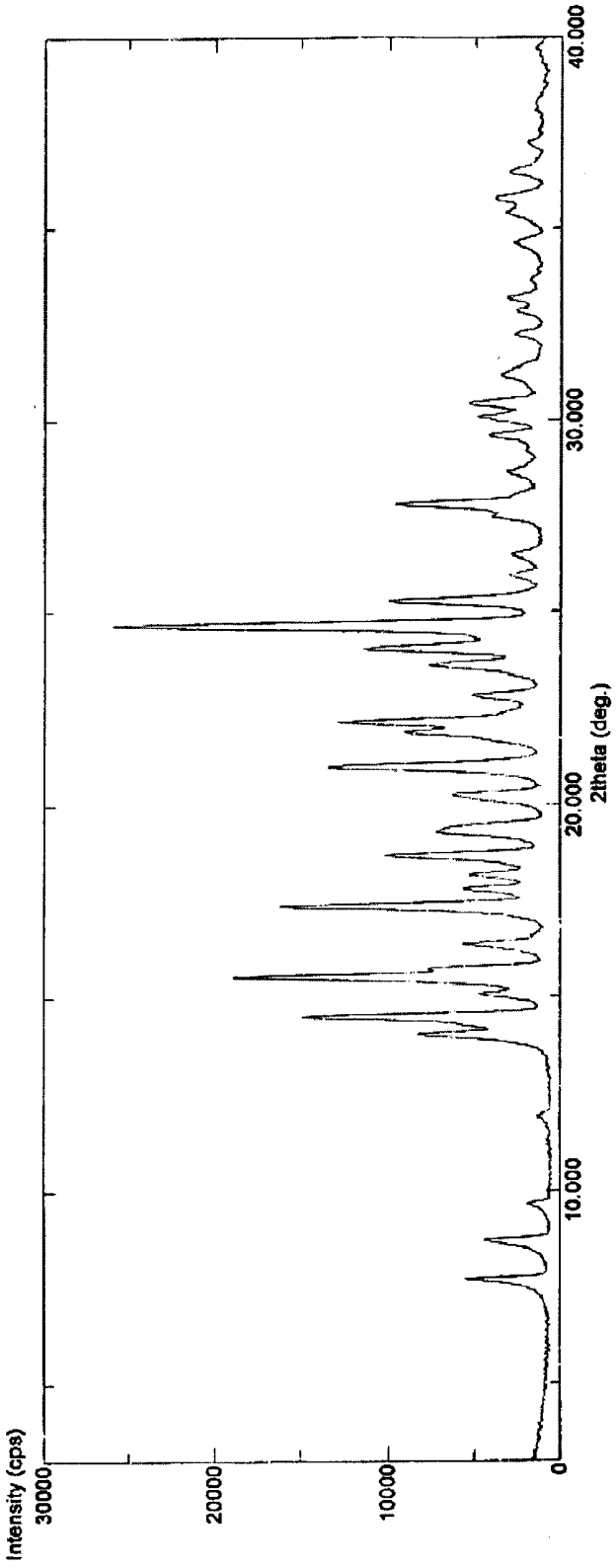
Intensity (cps)
30000
20000
10000
0
10.000
20.000
30.000
40.000
2theta (deg.)

Fig.29

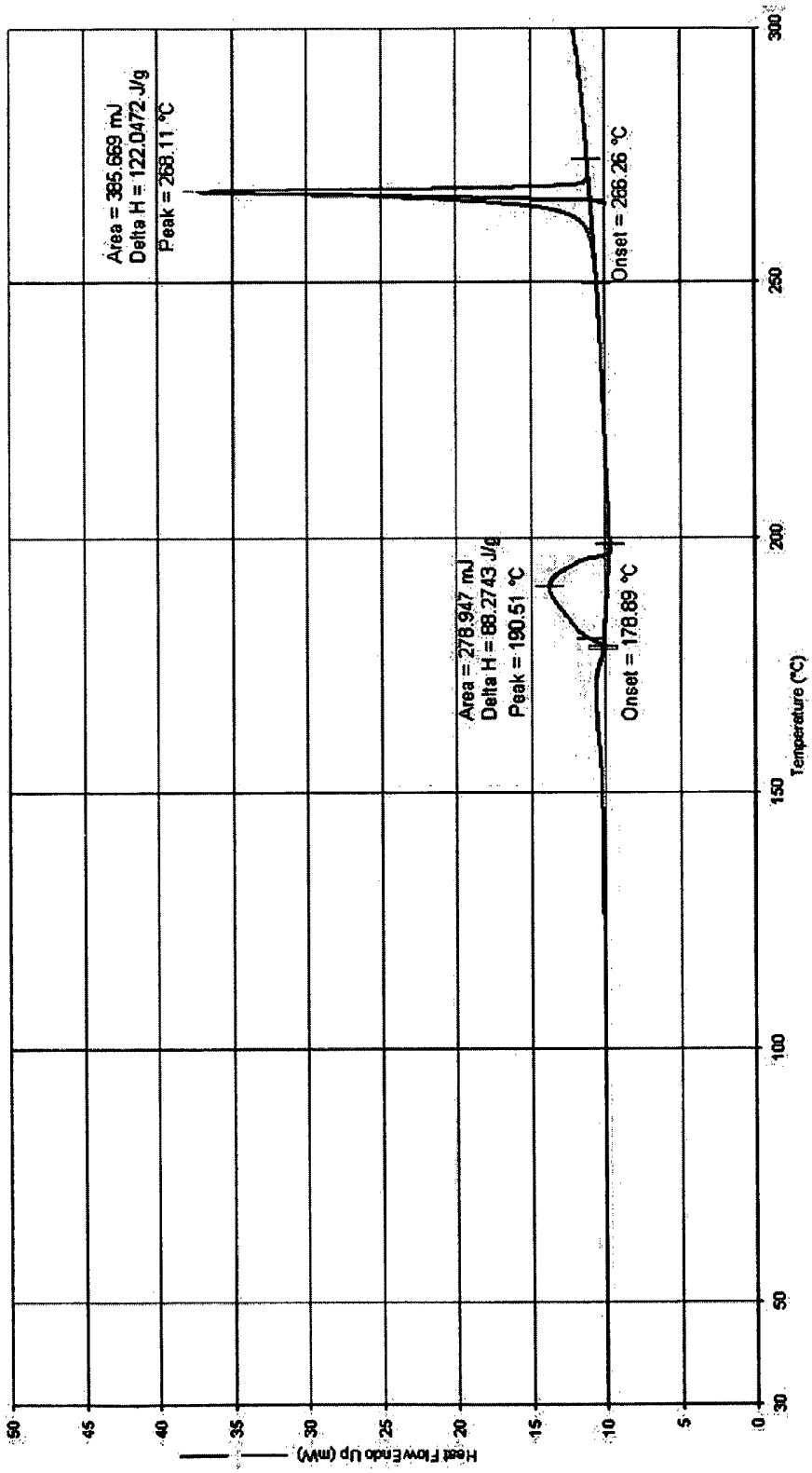
Area = 385.669 mJ
Delta H = 122.0472 J/g
Peak = 268.11 °C
Onset = 266.26 °C
Area = 278.947 mJ
Delta H = 88.2743 J/g
Peak = 190.51 °C
Onset = 178.89 °C
Heat Flow Endo Up (mW)
Temperature (°C)
50
45
40
35
30
25
20
15
10
5
0
30
50
100
150
200
250
300

Fig.30

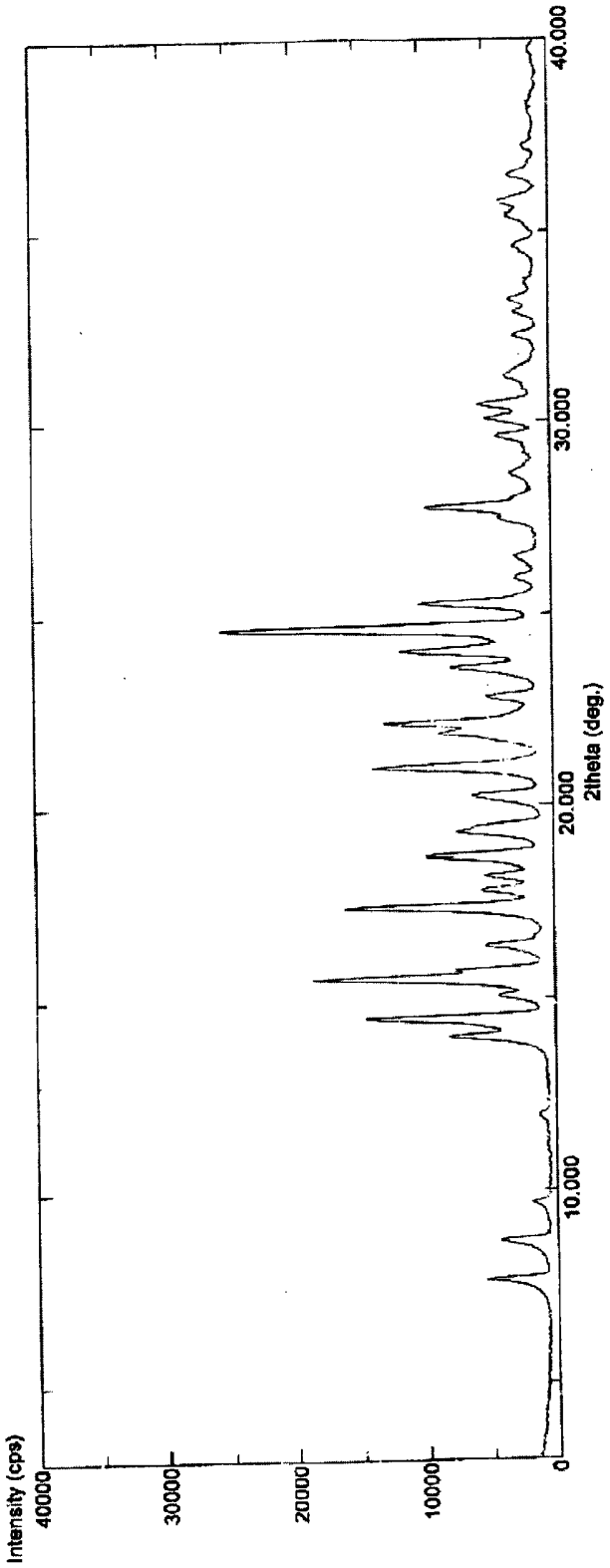
Intensity (cps)
40000
30000
20000
10000
0
10.000
20.000
30.000
40.000
2theta (deg.)

Fig.31

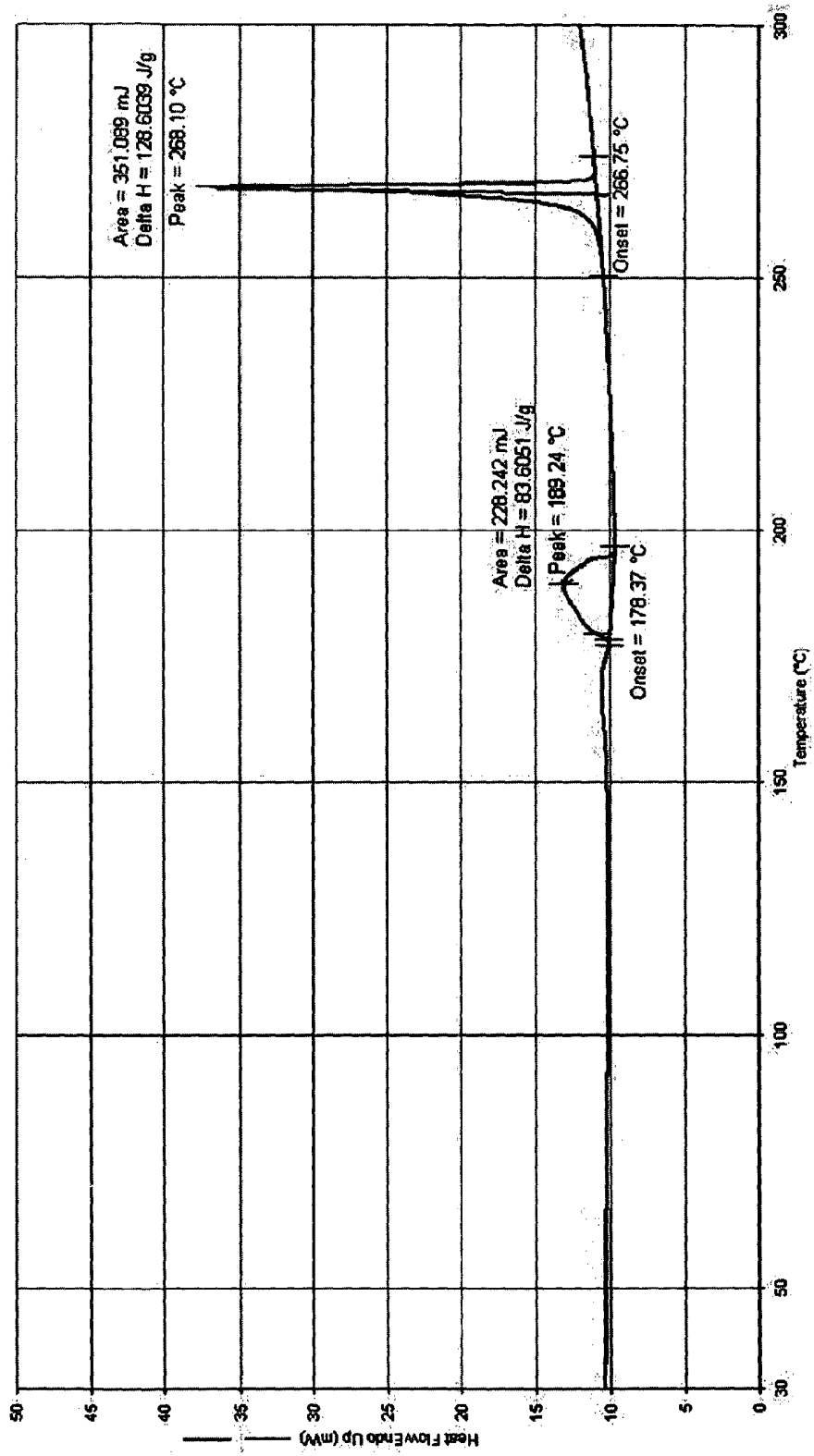
Area = 351.089 mJ
Delta H = 128.6039 J/g
Peak = 268.10 °C
Onset = 266.75 °C
Area = 228.242 mJ
Delta H = 83.6051 J/g
Peak = 189.24 °C
Onset = 178.37 °C
Heat Flow Endo Up (mW)
Temperature (°C)
50
45
40
35
30
25
20
15
10
5
0
30
50
100
150
200
250
300

Fig.32-1

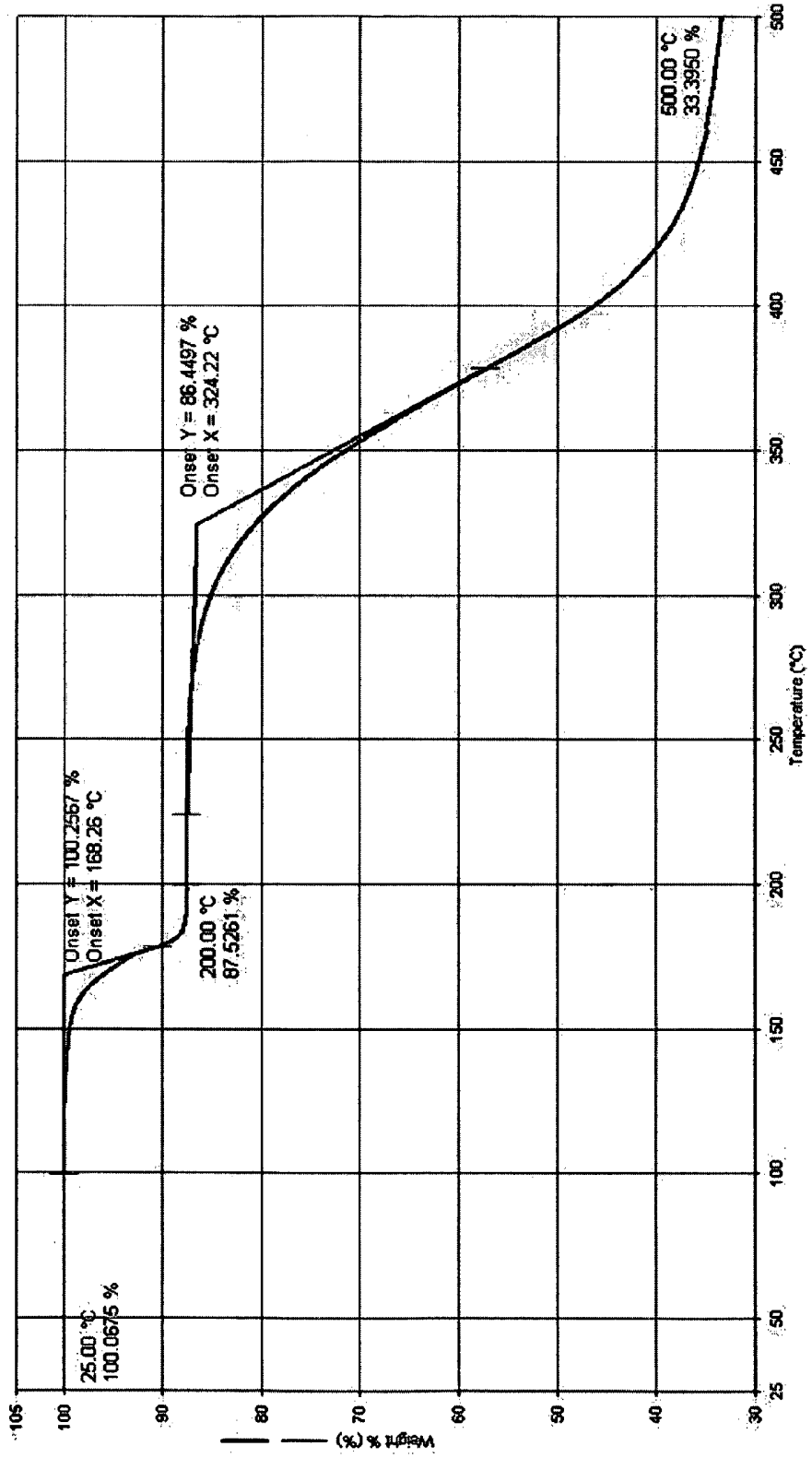
Onset Y = 100.2567 %
Onset X = 168.26 °C
25.00 °C
100.0675 %
Onset Y = 86.4497 %
Onset X = 324.22 °C
200.00 °C
87.5261 %
500.00 °C
33.3950 %
Weight % (%)
Temperature (°C)

Fig.32-2

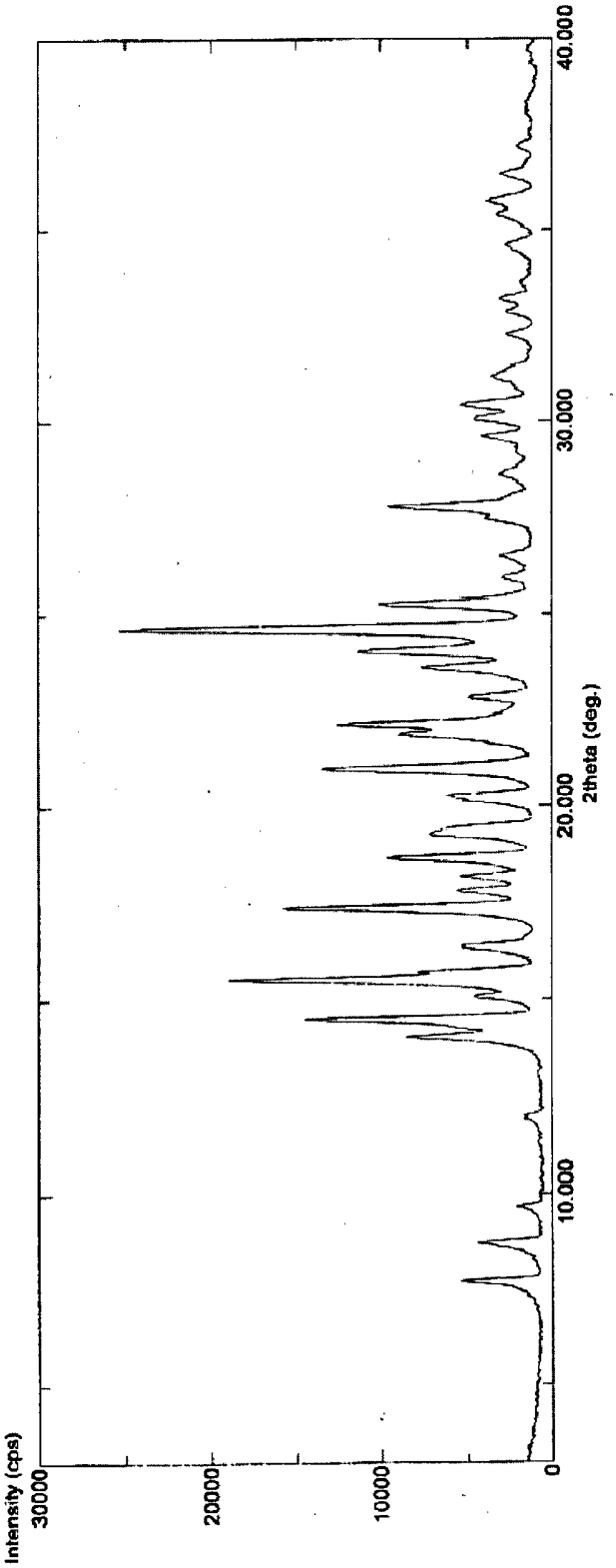
Intensity (cps)
30000
20000
10000
0
10.000
20.000
30.000
40.000
2theta (deg.)

Fig.33

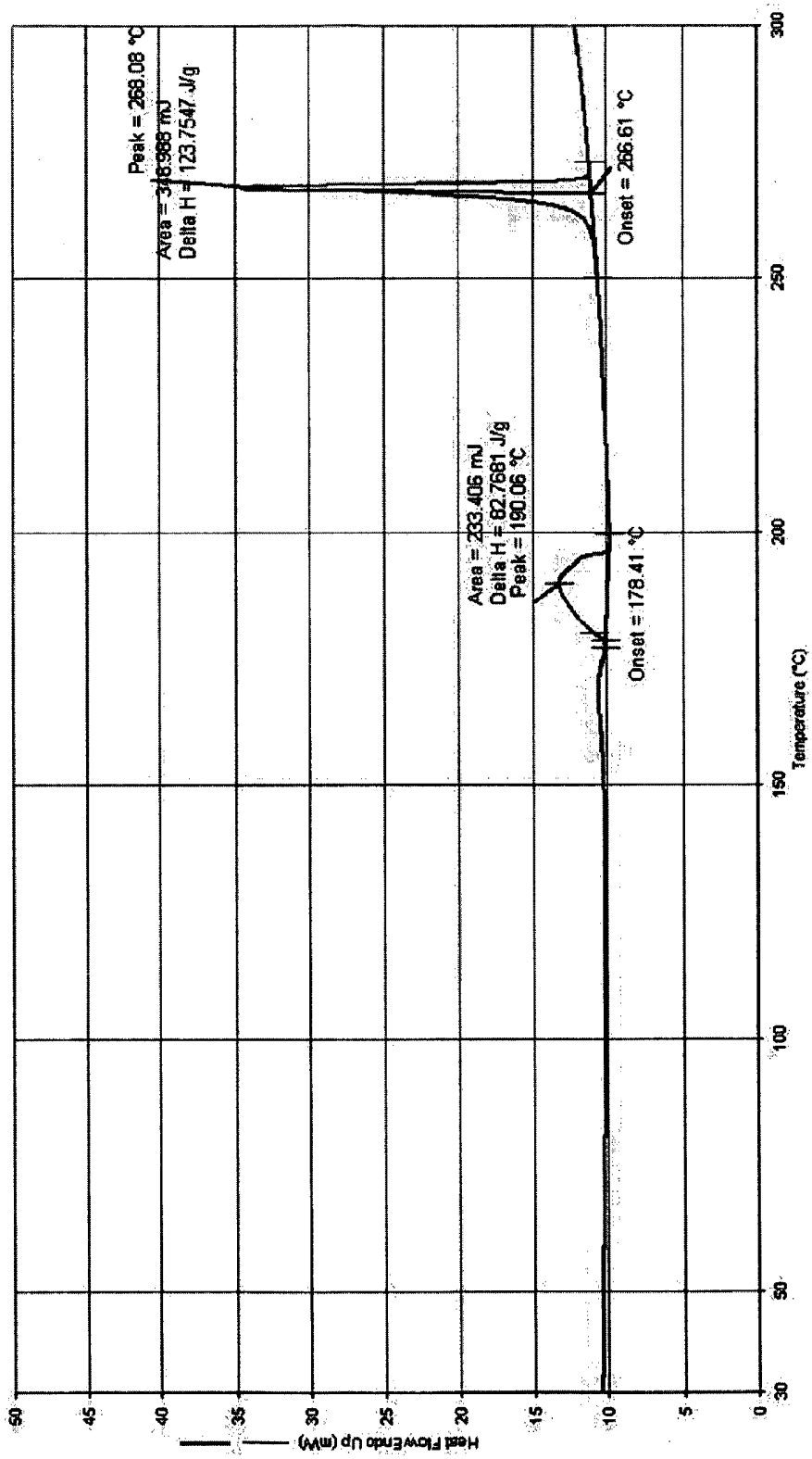
Peak = 268.08 °C
Area = 348.988 mJ
Delta H = 123.7547 J/g
Onset = 266.61 °C
Area = 233.406 mJ
Delta H = 82.7681 J/g
Peak = 190.06 °C
Onset = 178.41 °C
Heat Flow Endo Up (mW)
Temperature (°C)
50
45
40
35
30
25
20
15
10
5
0
30
50
100
150
200
250
300

Fig.34-1

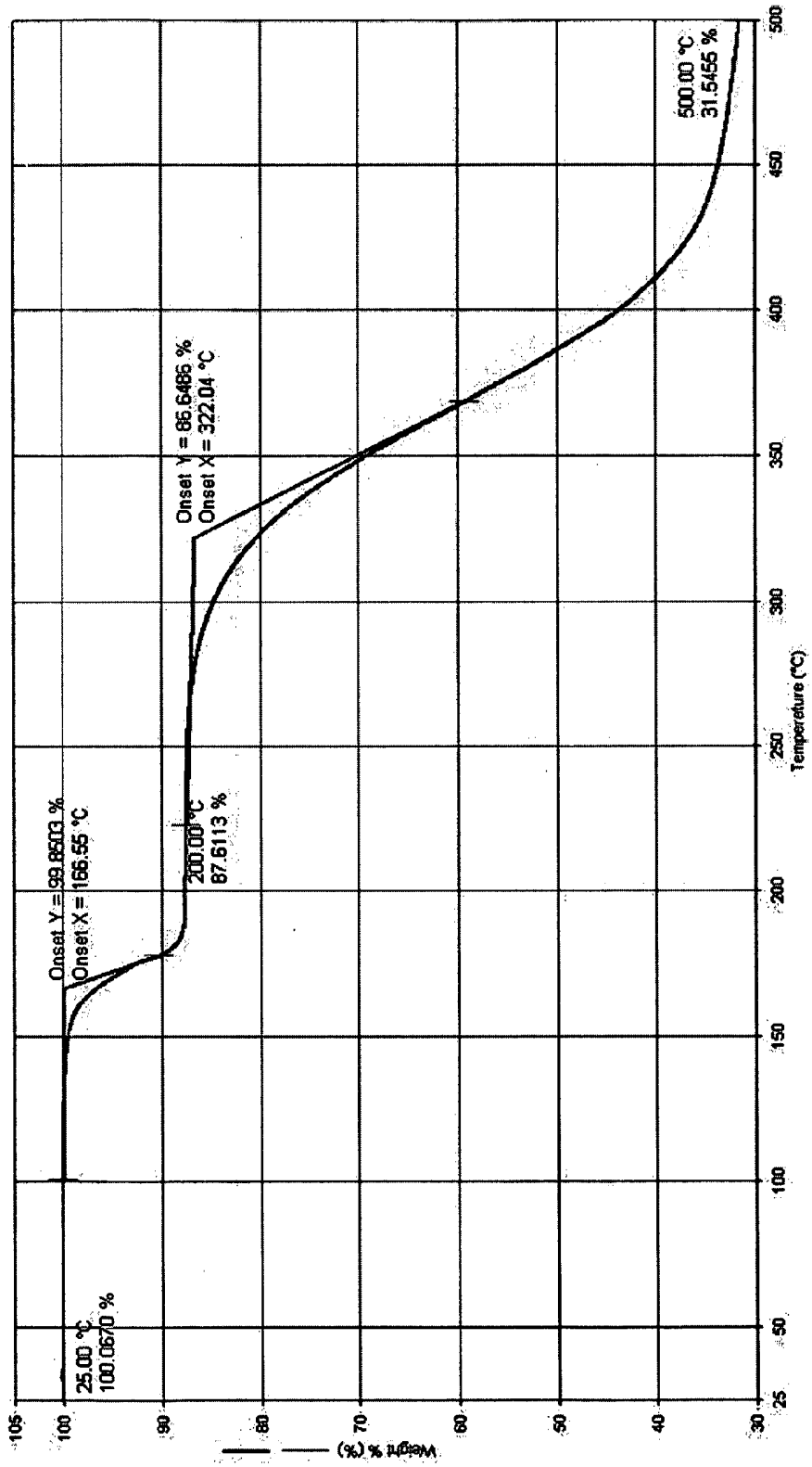
Onset Y = 99.8503 %
Onset X = 166.55 °C
25.00 °C
100.0670 %
Onset Y = 86.6486 %
Onset X = 322.04 °C
200.00 °C
87.6113 %
500.00 °C
31.5455 %
Weight % (%)
Temperature (°C)

Fig.34-2

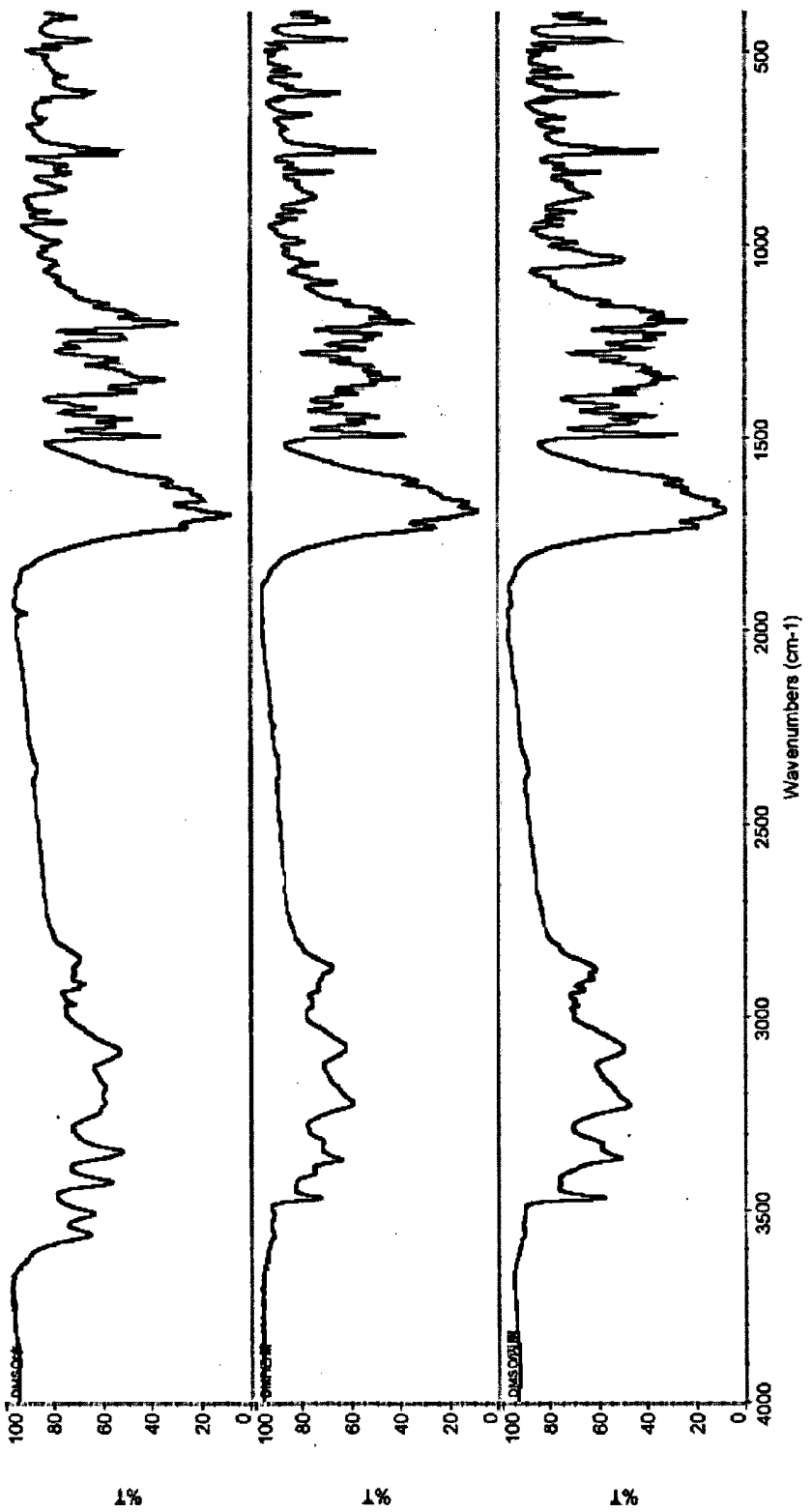
%T
%T
%T
100
80
60
40
20
0
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

Fig.35