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(74) Agent: **BRAINARD, Charles, R.**; Kenyon & Kenyon,
One Broadway, New York, NY 10004-1050 (US).

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(71) Applicant (*for all designated States except BB, US*): **TEVA
PHARMACEUTICAL INDUSTRIES LTD.** [IL/IL]; 5
Basel Street, P.O. Box 3190, 49131 Petah Tiqva (IL).

(71) Applicant (*for BB only*): **TEVA PHARMACEUTICALS
USA, INC.** [US/US]; 1090 Horsham Road, P.O. Box 1090,
North Wales, PA 19454-1090 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **DOLITZKY, Ben,
Zion** [IL/IL]; Lohame HaGhetto 32, 49651 Petach Tiqva
(IL). **ARONHIME, Judith** [IL/IL]; Rehov Harav Maor
Iosef 5a, 76217 Rehovot (IL). **DILLER, Dov** [IL/IL]; Re-
hov Chida 20, Bayit Vegan, 96464 Jerusalem (IL).

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(54) Title: NOVEL CRYSTAL FORMS OF OLANZAPINE, METHODS FOR THEIR PREPARATION AND METHOD FOR THE PREPARATION OF KNOWN OLANZAPINE CRYSTAL FORMS

(57) Abstract: The invention is directed to a series of novel crystalline olanzapine forms, in particular hydrated and solvated crystalline forms of olanzapine, methods of use in pharmaceutical compositions, and method of treating psychiatric disorders using the crystalline forms. One series of the crystalline forms are hydrates, i. e. water containing crystals, wherein water may be present in a ratio of about 2:1.5 to a ratio of about 1:3 olanzapine:water, while another includes solvates such as an isobutanol solvate. The olanzapine crystalline forms include Forms H, G, Y, X, K, S, Q, Z, and J.



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NOVEL CRYSTAL FORMS OF OLANZAPINE, METHODS FOR THEIR PREPARATION,
AND METHODS FOR THE PREPARATION OF KNOWN OLANZAPINE CRYSTAL FORMS

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CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit under 35 U.S.C. § 1.119(e) of Provisional Application Serial No. 60/435,913 filed December 24, 2002, the disclosure of which is incorporated by reference in its entirety herein.

10

FIELD OF THE INVENTION

The present invention is directed to crystal structures of olanzapine, methods of preparing the crystal structures, and use of the crystal structures. In particular, the invention is directed to polymorphic forms of olanzapine, pharmaceutical formulations thereof, and methods of treating psychiatric disorders.

15

BACKGROUND OF THE INVENTION

Olanzapine is an antagonist of dopamine at D-1 and D-2 receptors and has antimuscarinic anti-cholinergic properties and antagonist activity at 5HT-2 receptor sites.

Olanzapine also has antagonist activity at noradrenergic alpha-receptors. The above-identified properties indicate that olanzapine is a potential neuroleptic with relaxant, anxiolytic, or anti-emetic properties, and is useful in treating psychotic conditions such as schizophrenia, schizophreni-form diseases, and acute mania. At lower doses olanzapine can be used in the treatment of mild anxiety states. Olanzapine has also been reported as having a high level of activity in the clinical evaluation of psychiatric patients suffering from schizophrenia and it exhibits this high activity at surprisingly low dosage levels.

25

Olanzapine has shown great promise in the treatment of psychotic patients. Unfortunately, olanzapine typically exhibits a color which is undesirable for commercial pharmaceutical use, especially since the color was found to change over time on exposure to air. Carbon treatment of olanzapine did not removed the undesired color. A pharmaceutical that changes color over time could be particularly troublesome for psychotic patients if a dosage form, such as a tablet, was chosen where color changes were apparent. Consequently, there have been many attempts to provide novel olanzapine polymorphs.

30

Polymorphic forms and hydrate/solvate forms of olanzapine have been disclosed in various patents and publications. For example, U.S. Patent No. 5,736,541 ("the '541 patent") and EP Patent No. 733 635 disclose olanzapine Form II, an anhydrate, however, as disclosed Form II may be difficult to prepare in the absence of technical grade
5 olanzapine or alternative methods for preparing olanzapine. The '541 patent discloses that the prior known Form I of olanzapine, as prepared by the procedures described in US Patent No. 5,229,382, is metastable and unsuitable for commercial use due to discoloration of the compound over time. U.S. Patent No. 5,637,584 discloses a monosolvate of dichloromethane identified as Form I, however as discussed above, Form
10 I may be unsuitable for commercial use. U.S. Patent No. 5,703,232 and EP Patent No. 733,634 disclose olanzapine, which while free of water and acetonitrile, contains solvates of methanol, ethanol, and isopropanol. U.S. Patent No. 6,020,487 and EP Patent No. 831,098 disclose dihydrate forms of olanzapine, selected from dihydrate B, dihydrate D, and dihydrate E, which may be used for the preparation of anhydrate olanzapine. Each of
15 the above-identified patents identifies a different crystalline form of olanzapine as identified by X-ray diffraction peaks and their relative intensities.

U.S. Patent No. 6,348,458 discloses Form III, Form IV, and Form V olanzapine, which are anhydrates produced under aqueous conditions. Form III, Form IV, and Form V olanzapine are synthesized by dissolving olanzapine in mineral acid, followed by
20 reaction with base, and precipitation of the crystalline form. PCT publication WO 02/18390 discloses olanzapine as monohydrate-I and dihydrate-I and WO 02/060906 discloses olanzapine as Form X. In addition to X-ray powder diffractions, FTIR or DSC were used to identify the crystalline olanzapine.

Despite the many attempts by the prior art, there is a need to obtain desirable
25 olanzapine crystals with fewer purification steps, that lacks the harshness of mineral acids, or additional synthetic steps. The present invention provides novel crystalline forms of olanzapine that avoid the synthetic and purification pitfalls of the prior art.

SUMMARY OF THE INVENTION

30 One embodiment of the invention encompasses crystalline olanzapine isobutanol solvate. Another embodiment encompasses a crystalline form of olanzapine characterized by a powder X-ray diffraction pattern having peaks at about 8.7, 18.4, 19.2, 20.0, 21.1, 21.6, 22.4, 23.1, 23.6 and 24.0, ± 0.2 degrees two-theta, which may have additional peaks at about 10.4, 12.5, 14.1, 14.7, 17.2, 17.9, 24.9 and 25.4 ± 0.2 degrees

two-theta. The crystalline form may be an isobutanol solvate. Yet another embodiment of the invention encompasses a crystalline form of olanzapine having a powder X-ray diffraction pattern substantially as depicted in Figure 1. A process for preparing the crystalline form of olanzapine may comprise the steps of dissolving olanzapine in isobutanol, cooling the mixture, and isolating the crystals.

Another embodiment of the invention encompasses a crystalline form of olanzapine characterized by a powder X-ray diffraction pattern having peaks at about 6.6, 9.0, 16.4, 17.9, 18.6, 18.8, 19.6, 22.8 and 25.2, ± 0.2 degrees two-theta, which may have additional peaks at about 14.3, 14.8, 20.5, 23.2, 23.8, 24.2 ± 0.2 degrees two-theta. The crystalline form may be a dihydrate. Yet another embodiment encompasses a crystalline form of olanzapine having a powder X-ray diffraction pattern substantially as depicted in Figure 2. A process for preparing the crystalline form of olanzapine comprises the steps of creating a slurry of olanzapine dihydrate in methyl tertiary-butyl ether, stirring the mixture, and isolating the crystals.

Another embodiment of the invention encompasses a crystalline form of olanzapine characterized by a powder X-ray diffraction pattern having peaks at about 8.4, 8.8, 9.3, 16.9, 18.4, 19.4, 20.1, 22.2, 23.1, 23.8 and 25.2, ± 0.2 degrees two-theta, which may have additional peaks at about 14.2, 14.5 and 18.9 ± 0.2 degrees two-theta. The crystalline form may be a hydrate. Yet another embodiment of the invention encompasses a crystalline form of olanzapine having a powder X-ray diffraction pattern substantially as depicted in Figure 3. A process for preparing the crystalline form comprises the steps of dissolving olanzapine in methylene chloride to form a solution; adding cyclohexane to the solution; cooling the solution; and isolating the crystals. Optionally, the solution is formed by heating.

Another embodiment of the invention encompasses a crystalline olanzapine sesquihydrate. One embodiment of the invention encompasses a crystalline form of olanzapine characterized by a powder X-ray diffraction pattern having peaks at about 9.1, 16.4, 18.5, 22.8, 23.8 and 24.3 ± 0.2 degrees two-theta, which may have additional peaks in the powder X-ray diffraction pattern at about 9.1, 16.4, 18.5, 22.8, 23.8 and 24.3 ± 0.2 degrees two-theta. The crystalline form may be a sesquihydrate. Yet another embodiment of the invention encompasses a crystalline form of olanzapine having a powder X-ray diffraction pattern substantially as depicted in Figure 4. A process for preparing the crystalline form comprises the steps of dissolving olanzapine in an aqueous solution of HCl; precipitating the crystalline form by adding base; and isolating the

crystals. Optionally, the olanzapine is dissolved by heating or the pH prior to isolating the crystals is about 8.5. The process may further comprise cooling the solution prior to isolating the crystals.

Another embodiment of the invention encompasses a crystalline olanzapine trihydrate. One embodiment of the invention encompasses a crystalline form of olanzapine characterized by a powder X-ray diffraction pattern having peaks at about 8.8, 13.7, 16.3, 18.4, 19.6, 20.2 and 22.4 ± 0.2 degrees two-theta, which may have additional peaks in the powder X-ray diffraction pattern at about 15.1, 15.3, 23.0, 24.0, 24.4, 25.1 and 29.7 ± 0.2 degrees two-theta. The crystalline form may be a trihydrate. Yet another embodiment of the invention encompasses a crystalline form of olanzapine having a powder X-ray diffraction pattern substantially as depicted in Figure 5. A process for preparing the crystalline form comprises the steps of dissolving olanzapine in a solution of acetic acid and water; filtering the solution; stirring the solution; precipitating the crystalline form by adding a base; and isolating the crystals. Optionally, the solution is stirred at about 20°C; the base is ammonium hydroxide; or the pH prior to step isolating the crystals is about 9.8.

Another embodiment of the invention encompasses a crystalline form of olanzapine characterized by a powder X-ray diffraction pattern having peaks at about 8.6, 10.3, 11.4, 14.6, 19.8, 21.0, 21.5, 22.3, 23.9 and $29.7, \pm 0.2$ degrees two-theta, which may have additional peaks in the powder X-ray diffraction pattern at about 12.5, 17.0, 17.8, 19.0 and 25.2 ± 0.2 degrees two-theta. The crystalline form may be a dihydrate. Yet another embodiment of the invention encompasses a crystalline form of olanzapine having a powder X-ray diffraction pattern substantially as depicted in Figure 9. A process for preparing the crystalline form comprises the steps of heating Form X olanzapine at a temperature of at least about 100°C. Optionally, the heating temperature is about 160°C.

Another embodiment of the invention encompasses a crystalline olanzapine $\frac{3}{4}$ hydrate. Yet another embodiment of the invention encompasses a crystalline form of olanzapine characterized by a powder X-ray diffraction pattern having peaks at about 8.7, 14.7, 17.1, 17.8, 19.9, 21.0, 21.6, 22.3, 23.9, 25.3 and 26.5 ± 0.2 degrees two-theta, which may have additional peaks in the powder X-ray diffraction pattern at about 9.2, 9.4, 10.4, 11.5, 11.9, 12.5 and 29.7 ± 0.2 degrees two-theta. The crystalline form of olanzapine may be a $\frac{3}{4}$ hydrate. Another embodiment of the invention encompasses a crystalline

form of olanzapine having a powder X-ray diffraction pattern substantially as depicted in Figure 8. A process for preparing the crystalline form comprises the steps of heating Form J at a temperatures of at least about 100°C. Optionally, the heating temperature is about 130°C. Another process for preparing the crystalline form comprises exposing
5 Form II at 100% relative humidity for a period of time ranging between 2 weeks and 2 months. Optionally, the period of time is about 1 month.

Another embodiment of the invention encompasses a crystalline form of olanzapine characterized by a powder X-ray diffraction pattern having peaks at about 8.8, 18.1, 18.8, 19.3, 22.9, 23.3 and 24.8 ± 0.2 degrees two-theta, which may have additional
10 peaks in the powder X-ray diffraction pattern at about 8.2, 12.8, 13.8, 14.3, 14.9, 24.3 and 25.7 ± 0.2 degrees two-theta. The crystalline form of olanzapine may be a dihydrate. Yet another embodiment of the invention encompasses a crystalline form of olanzapine having a powder X-ray diffraction pattern substantially as depicted in Figure 6. A process for preparing the crystalline form comprises the steps of dissolving olanzapine in
15 an organic solvent; adding water; cooling the solution; and isolating the crystals. The organic solvent may be selected from the group consisting of DMSO, dioxane and acetone. The organic solvent may be heated to about 80°C.

Another embodiment of the invention encompasses a crystalline form of olanzapine characterized by a powder X-ray diffraction pattern having peaks at about 9.0, 16.3, 18.5, 19.6, 20.0, 20.4, 22.8, 24.2, and 25.6 ± 0.2 degrees two-theta, which may have
20 additional peaks in the powder X-ray diffraction pattern at about 17.1, 17.5, 21.2, 23.4, 23.7 and 27.6 ± 0.2 degrees two-theta. The crystalline olanzapine may be a dihydrate. Yet another embodiment of the invention encompasses a crystalline form of olanzapine having a powder X-ray diffraction pattern substantially as depicted in Figure 7. A process for preparing the crystalline form comprises the steps of dissolving olanzapine in
25 a mixture of ethyl acetate and toluene; heating the mixture; cooling the mixture; adding water to the mixture; cooling the mixture; and isolating the crystals. Optionally, the mixture is heated to about 80°C; the mixture is cooled during the first time to about 60°C; the mixture is cooled during the second time to room temperature. A process for
30 preparing olanzapine crystalline Form II comprising drying the Form Z, Form H, or Form Q crystalline olanzapine.

One embodiment of the invention encompasses a process for preparing olanzapine crystalline Form V comprising drying the Form G crystalline olanzapine.

Yet another embodiment of the invention encompasses a pharmaceutical composition comprising the crystalline forms of olanzapine selected from the group consisting of Forms H, G, Y, X, K, S, Q and J.

5 BRIEF DESCRIPTION OF THE DRAWINGS

The invention will be further described with reference to the following non-limiting figures.

Figure 1 illustrates the X-ray powder diffraction pattern of olanzapine Form Z;
Figure 2 illustrates the X-ray powder diffraction pattern of olanzapine Form H;
10 Figure 3 illustrates the X-ray powder diffraction pattern of olanzapine Form G;
Figure 4 illustrates the X-ray powder diffraction pattern of olanzapine Form Y;
Figure 5 illustrates the X-ray powder diffraction pattern of olanzapine Form X;
Figure 6 illustrates the X-ray powder diffraction pattern of olanzapine Form Q;
Figure 7 illustrates the X-ray powder diffraction pattern of olanzapine Form J;
15 Figure 8 illustrates the X-ray powder diffraction pattern of olanzapine Form S;
and
Figure 9 illustrates the X-ray powder diffraction pattern of olanzapine Form K.

DETAILED DESCRIPTION OF THE INVENTION

20 The present invention encompasses a series of novel crystalline olanzapine forms, in particular solvated crystalline forms, methods of use in pharmaceutical compositions, and method of treating psychiatric disorders using the crystalline forms. In particular, one series of the crystalline forms are hydrates, *i.e.* water containing crystals, wherein water may be present in a ratio of about 2:1.5 to a ratio of about 1:3 olanzapine:water.
25 Another crystalline form is a crystalline olanzapine isobutanol solvate.

One embodiment of the invention encompasses a crystalline form of olanzapine, herein denominated as Form Z. Form Z is an isobutanol solvate form, in particular a hemisolvate of isobutanol. Form Z is characterized in part by X-ray peaks at about 8.7, 10.4, 12.5, 14.1, 14.7, 17.2, 17.9, 18.4, 19.2, 17.2, 17.9, 18.4, 19.2, 20.0, 21.1, 21.6, 22.4,
30 23.1, 23.6, 24.0, 24.9, and 25.4 degrees two-theta. The data reported herein is within experimental error, such as within ± 0.2 degrees two-theta. The main characterizing peaks are at 8.7, 18.4, 19.2, 20.0, 21.1, 21.6, 22.4, 23.1, 23.6, 24.0 degrees two-theta. Form Z is prepared by crystallizing olanzapine in isobutanol, one of ordinary skill in the art with little or no experimentation can easily determine the necessary crystallization

parameters. Typically, the crystallization process comprises dissolving olanzapine in isobutanol at about 80°C, cooling the dissolved olanzapine – isobutanol solution in an ice bath, and collecting the crystals. If necessary, as understood by the skilled artisan, the crystallization process may include seeding, chilling, scratching the glass of the reaction vessel, and other such common crystallization techniques. If Form Z is dried, such as under vacuum, then the crystalline structure is converted into Form II.

Another embodiment of the invention, encompasses a crystalline olanzapine form herein denominated as Form H. Form H is a crystalline dihydrate of olanzapine. Form H is characterized in part by X-ray peaks at about 6.6, 9.0, 14.3, 14.8, 16.4, 17.9, 18.6, 18.8, 19.6, 20.5, 22.8, 23.2, 23.8, 24.2, 25.2 degrees two-theta. The main peaks are at 6.6, 9.0, 16.4, 17.9, 18.6, 18.8, 19.6, 22.8, 25.2 degrees two-theta. Form H is formed by creating a slurry of olanzapine dihydrate in methyl tertiary-butyl ether (“MTBE”), stirring the mixture, and collecting the crystals. If Form H is dried, then the crystalline structure is converted to Form II.

One embodiment of the invention, encompasses a crystalline olanzapine form herein denominated Form G. Form G is a hydrate form of olanzapine. If Form G is dried, then the crystalline structure is converted into Form V. Form G is characterized in part by X-ray peaks at 8.4, 8.8, 9.3, 14.2, 14.5, 16.9, 18.4, 18.9, 19.4, 20.1, 22.2, 23.1, 23.8, 25.2 degrees two-theta. The main peaks are at 8.4, 8.8, 9.3, 16.9, 18.4, 19.4, 20.1, 22.2, 23.1, 23.8, 25.2 degrees two-theta. Form G is obtained by dissolving olanzapine in methylene chloride while heating, adding cyclohexane, cooling the solution in an ice bath, and collecting the crystalline olanzapine.

Another embodiment of the invention encompasses a crystalline olanzapine sesquihydrate.

Another embodiment of the invention, encompasses a crystalline olanzapine form herein denominated Form Y. Form Y contains water in about 8.5% by weight, as a sesquihydrate. Form Y is characterized in part by X-ray peaks at 9.1, 16.4, 17.2, 17.5, 18.5, 19.7, 20.6, 21.3, 22.8, 23.8, 24.3, 25.6, 27.7 degrees two-theta. The main peaks are at 9.1, 16.4, 18.5, 22.8, 23.8, 24.3 degrees two-theta. Form Y is obtained by dissolving olanzapine in an aqueous solution of HCl (1.6%) while heating the solution, while hot precipitating the crystalline form by adding 10% NaOH to obtain a pH of about 8.5, cooling the solution in an ice bath, and collecting the crystals. Before drying, in the wet form, Form Y may contain up to 43% water. Bases include, but are not limited to, NaOH, NaHCO₃, Na₂CO₃, KOH, KHCO₃, K₂CO₃.

One embodiment of the invention encompasses a crystalline olanzapine trihydrate.

Another embodiment of the invention encompasses a crystalline olanzapine form herein denominated as Form X. Form X contains water in about 13-15 % by weight, and is a trihydrate. Form X is characterized in part by X-ray peaks at 8.8, 13.7, 15.1, 15.3, 16.3, 18.4, 19.6, 20.2, 22.4, 23.0, 24.0, 24.4, 25.1, 29.7 degrees two-theta. The main peaks are at 8.8, 13.7, 16.3, 18.4, 19.6, 20.2, 22.4 degrees two-theta. Form X is prepared by dissolving olanzapine in a solution of acetic acid and water, filtering the solution, and stirring at about 20°C, precipitating the crystal by adjusting the pH to about 9.8 with an ammonium solution, and collecting the crystals by filtration. Preferably, the acetic acid:water ratio is about 1:1.3.

Another embodiment of the invention encompasses a crystalline olanzapine form herein denominated Form K. Form K contains water in about up to 12% by weight, and is a dihydrate. Form K is characterized in part by X-ray peaks at 8.6, 10.3, 11.4, 12.5, 14.6, 17.0, 17.8, 19.0, 19.8, 21.0, 21.5, 22.3, 23.9, 25.2, 29.7 degrees two-theta. The main peaks are at 8.6, 10.3, 11.4, 14.6, 19.8, 21.0, 21.5, 22.3, 23.9, 29.7 degrees two-theta. Form K is obtained by heating olanzapine Form X at temperatures above 100°C for a time dependent upon on the temperature and quantity employed. For small samples and elevated temperatures, such as 50 mg to 100 mg and a temperature of 160°C, a period of 15 minutes is sufficient. For larger quantities or lower temperatures the duration of time has to be adequate in order to bring the transformation to completion, which may be monitored using X-ray diffraction.

One embodiment of the invention encompasses a crystalline olanzapine $\frac{3}{4}$ hydrate.

Another embodiment of the invention encompasses a crystalline olanzapine form herein denominated Form S. Form S contains water in about 4% by weight, as a $\frac{3}{4}$ hydrate. Form S is characterized in part by X-ray peaks at 8.7, 9.2, 9.4, 10.4, 11.5, 11.9, 12.5, 14.7, 17.1, 17.8, 19.9, 21.0, 21.6, 22.3, 23.9, 25.3, 26.5, 29.7 degrees two-theta. The main peaks are at 8.7, 14.7, 17.1, 17.8, 19.9, 21.0, 21.6, 22.3, 23.9, 25.3, 26.5, degrees two-theta. Form S is obtained by heating olanzapine Form J at temperatures above 100°C for a period of time dependent on the temperature and quantity used. For small samples and elevated temperatures, such as 50-100 mg and a temperature of 160°C, a period of 15 minutes is sufficient. For larger quantities or lower temperatures the time duration may be adjusted to complete the transformation. Also Form S may be obtained

by exposing Form II at elevated relative humidity, preferably 100%RH, for a period of time ranging from about 2 weeks to about 2 months, preferably, for about 1 month.

Another embodiment of the invention encompasses a crystalline olanzapine form herein denominated Form Q. Form Q contains water up to 12% by weight and is a dihydrate form. Form Q is characterized in part by X-ray peaks at 8.2, 8.8, 12.8, 13.8, 14.3, 14.9, 18.1, 18.8, 19.3, 22.9, 23.3, 24.3, 24.8, 25.7 degrees two-theta. The main peaks are at 8.8, 18.1, 18.8, 19.3, 22.9, 23.3, 24.8 degrees two-theta. Form Q is obtained by crystallizing olanzapine in mixtures of water with an organic solvent. Examples of organic solvents include, but are not limited to, DMSO, dioxane, or acetone. Typically, Form Q is obtained by heating an organic solvent to about 80°C; dissolving olanzapine in the heated organic solvent; adding water; cooling the solution in an ice bath, and collecting the crystals by filtration. Form Q may be converted into Form II by drying.

One embodiment of the invention encompasses a crystalline olanzapine form herein of denominated as Form J. Form J is a dihydrate crystalline form. Form J is characterized in part by X-ray peaks at 9.0, 16.3, 17.1, 17.5, 18.5, 19.6, 20.0, 20.4, 21.2, 22.8, 23.4, 23.7, 24.2, 25.6, 27.6 degrees two-theta. The main peaks are at 9.0, 16.3, 18.5, 19.6, 20.0, 20.4, 22.8, 24.2, 25.6 degrees two-theta. Form J is obtained by dissolving olanzapine in a mixture of ethylacetate/toluene in a ratio of about 16:1 heated to about 80°C, cooling the mixture to about 60°C, adding water dropwise, cooling the solution to room temperature, and collecting the crystals by filtration. Drying Form J converts the crystalline olanzapine into Form S.

Table 1 summarizes some of the embodiment of the invention.

TABLE 1 - Summary

Experiment	Solvent	Form (wet)	Water content (%)	LOD (%)	Form (dry)
1	isobutanol	Z	3.6	9.5	II
2	Acetone/water	Q	9.0	12.4	II
3	Dioxane/water	Q	5.7	8.9	II
4	DMSO/water	Q	11.7	10.7+ 7.4+	II
5	Methylenechloride/ hexane	G	7.0	12.1	V
6	MTBE	H	10.3	16.8	II
7	Acetic acid/water+ammonia	X	11.3	13-15	K (heat at high temperatures)
8	HCl/water+ammonia	Y	8.5	8.5	Y
9	Ethylacetate/toluene+ water	J	10.7	10.6	S (heat at high temperatures)

Exposing Form II at 100% RH 1 month	S	4.2
Heating form X	K	13%

Olanzapine has been found to have a wide range of therapeutic effects, particularly for the treatment of schizophrenia, schizophreniform disorders, psychosis, mild anxiety states and functional bowel disorders.

Pharmaceutical formulations according to the invention comprise substantially pure Form G, H, J, K, Q, S, X, or Y olanzapine or a pharmaceutically acceptable salt thereof as an active ingredient together with one or more pharmaceutically acceptable carriers, excipients or diluents. Any conventional technique may be used for the preparation of pharmaceutical formulations according to the invention. Examples of suitable carriers include, but are not limited to, sugars, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, syrup, methyl cellulose, methyl- and propyl-hydroxy-benzoate, talc, magnesium stearate or mineral oil. The active ingredient may be contained in a formulation that provides quick release, sustained release, or delayed release after administration to the patient.

As used herein "substantially pure" refers to an olanzapine crystal form associated with less than about 5% of another crystal form, preferably less than about 2%, and more preferably less than about 1% of another crystal form by weight of the total olanzapine.

Pharmaceutical compositions may be formulated for transdermal delivery, oral delivery or as a suppository. Formulations may be in the form of capsules, tablets or gels for oral delivery or as a suspension for transdermal delivery. Pharmaceutical compositions according to the present invention may contain about 0.25 mg to about 100 mg of active ingredient or, preferably, about 1 mg to about 30 mg active ingredient, along with a pharmaceutically acceptable carrier.

Having described the invention with reference to certain preferred embodiments, other embodiments will become apparent to one skilled in the art from consideration of the specification. The invention is further defined by reference to the following examples describing in detail the compositions, preparation of the compositions, and methods of administration of the invention. It will be apparent to those skilled in the art that many

modifications, both to materials and methods, may be practiced without departing from the scope of the invention.

EXAMPLES

5 Water content was measured using the Karl Fisher technique (USP method).
Weight loss was measured using TGA analysis (Mettler Toledo TG50). TGA analysis
was performed with a Mettler TG50, the sample size was about 10 mg and the samples
were scanned at a rate of 10°C/min from 25°C to 200°C. The oven was constantly purged
with nitrogen gas at a flow rate of 40 ml/min. Standard alumina crucibles covered by lids
10 with one hole were used. X-ray powder diffraction data were obtained using methods
known in the art and by using a SCINTAG powder X-ray diffractometer model XTRA
equipped with a solid state detector. Copper radiation of 1.5418 Å was used. A round
aluminum sample holder with round zero background quartz plate, with cavity of
25(diameter)*0.5(depth) mm.

15

Experiment 1: Preparation of Form Z

Four grams of olanzapine (4 g) were dissolved in 45 ml of isobutanol using a 80°C
water bath. Thereafter, the solution was stirred over night at room temperature and
cooled in an ice bath for 1 h. The resulting crystals were collected by filtration and
20 determined to be of Form Z. The Form Z crystals were dried for 2.5 h in a vacuum oven
at 65°C. Upon analysis, the dry crystals were identified as polymorph II. Yield 2.45 g.

Experiment 2: Preparation of Form Q

Four grams of olanzapine (4 g) were dissolved in 90 ml of acetone using an 80°C
25 water bath. Upon addition of 65 ml of water, crystals precipitated from solution. The
material was stirred overnight. The solution and crystals were cooled in ice and the
crystals were collected by filtration in a yield of 87.5%.

Experiment 3: Preparation of Form Q

30 Four grams of olanzapine (4 g) were dissolved in 24 ml dioxane and heated in an
80°C water bath. Upon additional of water (8 ml), crystals precipitated from the solution.
The solution was reheated in the water bath and left overnight at room temperature with

stirring. Subsequently, the solution was cooled in an ice bath and the crystals collected by filtration in a yield of 93.5%.

Experiment 4: Preparation of Form Q

- 5 Four grams of olanzapine (4 g) were dissolved in 8 ml DMSO by heating in a water bath at 80 °C. Upon addition of water (1 ml), crystals precipitated from solution. The solution was left to stir at room temperature for 48 hours, and subsequently cooled in ice bath. The crystals were collected by filtration in a yield of 100%.

10 Experiment 5: Preparation of Form G

Olanzapine (4 g) was dissolved in 50 ml methylene chloride while heating. Cyclohexane (100 ml) was added with stirring. Thereafter, the solution was cooled in an ice bath and crystals were collected by filtration in a yield of 53.3%.

15 Experiment 6: Preparation of Form H

Olanzapine dihydrate (2 g) was slurried in MTBE (10 ml). The slurry was stirred overnight. Thereafter, the crystals were collected by filtration in a yield of 98%.

Experiment 7: Preparation of Form X

- 20 Olanzapine (10 g) was dissolved in a solution of acetic acid (30 ml) and water (40 ml). The solution was filtered through Celite and GF/F paper and stirred at 20°C. Thirty (30) ml of 25% ammonium hydroxide were added and the pH of the solution was approximately 5.9. The solution was stirred for 30 min, upon which the solution became cloudy, but nothing precipitated. Thereafter, an additional 34 ml of ammonia solution
- 25 was added and the pH was 9.75. A crystal precipitated and was collected by filtration in a yield of 68.5%.

Experiment 8: Preparation of Form Y

- 30 Olanzapine (10 g) was dissolved in 110 ml HCl 1.6% while heating. The hot solution was filtered through GF/F filter paper. While still hot, the pH was adjusted to 8.5 by slowly adding 10% NaOH with stirring. During base addition, crystals formed. The solution was stirred for 30 min in an ice bath and the crystals were collected by filtration in a yield of 100%.

Experiment 9: Preparation of Form J

Olanzapine (6 g) was slurried in 120 ml ethyl acetate and 7.2 ml toluene. The mixture was heated to 80 °C and the materials dissolved. Thereafter, the mixture was cooled to 60 °C and water (12 ml) was added with stirring by dripping in with a Pasteur
5 pipette. The solution was allowed to cool to room temperature with stirring and crystals appeared. The solution was stirred for approximately 1½ hours at room temperature. Thereafter, the crystals were collected by filtration in a yield of 63.3%.

Experiment 10: Preparation of Form S

10 Form J, made as described above, was kept in an oven at 130°C for 40 minutes. Thereafter, the crystals were collected to obtain Form S crystalline olanzapine.

Experiment 11: Preparation of Form S

A small aliquot of Form II (about 50 mg) was exposed to 100% relative humidity
15 for a period of 1 month. Thereafter, the crystals were collected to obtain Form S crystalline olanzapine.

Experiment 12: Preparation of Form K

Form X, made as described above, was kept at 130 °C for about 40 minutes. Form
20 X was kept at 160 °C for about 15 minutes. Thereafter, the crystals were collected to obtain Form K crystalline olanzapine.

CLAIMS

What is claimed is:

1. Crystalline olanzapine isobutanol solvate.
2. A crystalline form of olanzapine characterized by a powder X-ray diffraction pattern having peaks at about 8.7, 18.4, 19.2, 20.0, 21.1, 21.6, 22.4, 23.1, 23.6 and 24.0, ± 0.2 degrees two-theta.
3. The crystalline form according to claim 2, having additional peaks in the powder X-ray diffraction pattern at about 10.4, 12.5, 14.1, 14.7, 17.2, 17.9, 24.9 and 25.4 ± 0.2 degrees two-theta.
4. The crystalline form of olanzapine according to claim 3, having a powder X-ray diffraction pattern substantially as depicted in Figure 1.
5. The crystalline form of olanzapine according to claim 2, which is an isobutanol solvate.
6. A process for preparing the crystalline form of olanzapine of claim 2 comprising the steps of dissolving olanzapine in isobutanol, cooling the mixture, and isolating the crystals.
7. A crystalline form of olanzapine characterized by a powder X-ray diffraction pattern having peaks at about 6.6, 9.0, 16.4, 17.9, 18.6, 18.8, 19.6, 22.8 and 25.2, ± 0.2 degrees two-theta.
8. The crystalline form according to claim 7, having additional peaks in the powder X-ray diffraction pattern at about 14.3, 14.8, 20.5, 23.2, 23.8, 24.2 ± 0.2 degrees two-theta.
9. The crystalline form of olanzapine according to claim 8, having a powder X-ray diffraction pattern substantially as depicted in Figure 2.

10. The crystalline form of olanzapine according to claim 7, which is a dihydrate.
11. A process for preparing the crystalline form of olanzapine of claim 7 comprising the steps of creating a slurry of olanzapine dihydrate in methyl tertiary-butyl ether, stirring the mixture, and isolating the crystals.
12. A crystalline form of olanzapine characterized by a powder X-ray diffraction pattern having peaks at about 8.4, 8.8, 9.3, 16.9, 18.4, 19.4, 20.1, 22.2, 23.1, 23.8 and 25.2, ± 0.2 degrees two-theta.
13. The crystalline form according to claim 12, having additional peaks in the powder X-ray diffraction pattern at about 14.2, 14.5 and 18.9 ± 0.2 degrees two-theta.
14. The crystalline form of olanzapine according to claim 13, having a powder X-ray diffraction pattern substantially as depicted in Figure 3.
15. The crystalline form of olanzapine according to claim 12, which is a hydrate.
16. A process for preparing the crystalline form according to claim 12 comprising the steps of:
- a) dissolving olanzapine in methylene chloride to form a solution;
 - b) adding cyclohexane to the solution;
 - c) cooling the solution; and
 - d) isolating the crystals.
17. The process of claim 16, wherein the solution is formed by heating.
18. Crystalline olanzapine sesquihydrate.
19. A crystalline form of olanzapine characterized by a powder X-ray diffraction pattern having peaks at about 9.1, 16.4, 18.5, 22.8, 23.8 and 24.3 ± 0.2 degrees two-theta.

20. The crystalline form according to claim 19, having additional peaks in the powder X-ray diffraction pattern at about 9.1, 16.4, 18.5, 22.8, 23.8 and 24.3 ± 0.2 degrees two-theta.
- 5 21. The crystalline form of olanzapine according to claim 20, having a powder X-ray diffraction pattern substantially as depicted in Figure 4.
22. The crystalline form of olanzapine according to claim 19, which is a sesquihydrate.
- 10 23. A process for preparing the crystalline form according to claim 19 comprising the steps of:
- a) dissolving olanzapine in an aqueous solution of HCl;
 - b) precipitating the crystalline form by adding base; and
 - 15 c) isolating the crystals.
24. The process of claim 23, wherein olanzapine is dissolved by heating.
25. The process of claim 23, wherein the pH prior to step (c) is about 8.5.
- 20 26. The process of claim 23, further comprising cooling the solution prior to step (c).
27. Crystalline olanzapine trihydrate.
- 25 28. A crystalline form of olanzapine characterized by a powder X-ray diffraction pattern having peaks at about 8.8, 13.7, 16.3, 18.4, 19.6, 20.2 and 22.4 ± 0.2 degrees two-theta.
29. The crystalline form according to claim 28, having additional peaks in the powder X-ray diffraction pattern at about 15.1, 15.3, 23.0, 24.0, 24.4, 25.1 and 29.7 ± 0.2 degrees two-theta.
- 30 30. The crystalline form of olanzapine according to claim 29, having a powder X-ray diffraction pattern substantially as depicted in Figure 5.

31. The crystalline form of olanzapine according to claim 28, which is a trihydrate.
32. A process for preparing the crystalline form according to claim 28 comprising the
5 steps of:
a) dissolving olanzapine in a solution of acetic acid and water;
b) filtering the solution;
c) stirring the solution;
d) precipitating the crystalline form by adding a base; and
10 e) isolating the crystals.
33. The process of claim 32, wherein step (c) is carried out at a temperature of about 20°C.
- 15 34. The process of claim 32, wherein the base is ammonium hydroxide.
35. The process of claim 32, wherein the base is added to reach a pH prior to step (e) of about 9.8.
- 20 36. A crystalline form of olanzapine characterized by a powder X-ray diffraction pattern having peaks at about 8.6, 10.3, 11.4, 14.6, 19.8, 21.0, 21.5, 22.3, 23.9 and 29.7, ± 0.2 degrees two-theta.
- 25 37. The crystalline form according to claim 36, having additional peaks in the powder X-ray diffraction pattern at about 12.5, 17.0, 17.8, 19.0 and 25.2 ± 0.2 degrees two-theta.
- 30 38. The crystalline form of olanzapine according to claim 37, having a powder X-ray diffraction pattern substantially as depicted in Figure 9.
39. The crystalline form of olanzapine according to claim 36, which is a dihydrate.

40. A process for preparing the crystalline form according to claim 36 comprising the steps of heating Form X olanzapine at a temperature of at least about 100°C.
41. The process of claim 40, wherein the heating temperature is about 160°C.
- 5 42. Crystalline olanzapine $\frac{3}{4}$ hydrate.
43. A crystalline form of olanzapine characterized by a powder X-ray diffraction pattern having peaks at about 8.7, 14.7, 17.1, 17.8, 19.9, 21.0, 21.6, 22.3, 23.9, 10 25.3 and 26.5 ± 0.2 degrees two-theta.
44. The crystalline form according to claim 43, having additional peaks in the powder X-ray diffraction pattern at about 9.2, 9.4, 10.4, 11.5, 11.9, 12.5 and 29.7 ± 0.2 degrees two-theta.
- 15 45. The crystalline form of olanzapine according to claim 44, having a powder X-ray diffraction pattern substantially as depicted in Figure 8.
46. The crystalline form of olanzapine according to claim 43, which is a $\frac{3}{4}$ hydrate.
- 20 47. A process for preparing the crystalline form according to claim 43 comprising the steps of heating Form J at a temperatures of at least about 100°C.
48. The process of claim 47, wherein the heating temperature is about 130°C.
- 25 49. A process for preparing the crystalline form according to claim 43 comprising exposing Form II at 100% relative humidity for a period of time ranging between 2 weeks and 2 months.
- 30 50. The process of claim 49, wherein the period of time is about 1 month.

51. A crystalline form of olanzapine characterized by a powder X-ray diffraction pattern having peaks at about 8.8, 18.1, 18.8, 19.3, 22.9, 23.3 and 24.8 ± 0.2 degrees two-theta.
- 5 52. The crystalline form according to claim 51, having additional peaks in the powder X-ray diffraction pattern at about 8.2, 12.8, 13.8, 14.3, 14.9, 24.3 and 25.7 ± 0.2 degrees two-theta.
- 10 53. The crystalline form of olanzapine according to claim 52, having a powder X-ray diffraction pattern substantially as depicted in Figure 6.
54. The crystalline form of olanzapine according to claim 51, which is a dihydrate.
- 15 55. A process for preparing the crystalline form according to claim 51 comprising the steps of:
- a) dissolving olanzapine in an organic solvent;
 - b) adding water;
 - c) cooling the solution; and
 - d) isolating the crystals.
- 20 56. The process of claim 55, wherein the organic solvent is at least one of DMSO, dioxane, or acetone.
- 25 57. The process of claim 55, wherein the organic solvent in step (a) is heated to about 80°C .
- 30 58. A crystalline form of olanzapine characterized by a powder X-ray diffraction pattern having peaks at about 9.0, 16.3, 18.5, 19.6, 20.0, 20.4, 22.8, 24.2, and 25.6 ± 0.2 degrees two-theta.
59. The crystalline form according to claim 58, having additional peaks in the powder X-ray diffraction pattern at about 17.1, 17.5, 21.2, 23.4, 23.7 and 27.6 ± 0.2 degrees two-theta.

60. The crystalline form of olanzapine according to claim 59, having a powder X-ray diffraction pattern substantially as depicted in Figure 7.
61. The crystalline form of olanzapine according to claim 58, which is a dihydrate.
- 5
62. A process for preparing the crystalline form according to claim 58 comprising the steps of:
- a) dissolving olanzapine in a mixture of ethylacetate and toluene;
 - b) heating the mixture;
 - 10 c) cooling the mixture;
 - d) adding water to the mixture;
 - e) cooling the mixture; and
 - f) isolating the crystals.
- 15
63. The process of claim 62, wherein the mixture is heated to about 80°C.
64. The process of claim 62, wherein the mixture in step (c) is cooled to about 60°C.
65. The process of claim 62, wherein the mixture in step (e) is cooled to room
- 20 temperature.
66. A process for preparing olanzapine crystalline Form II comprising drying the form of claim 2, claim 7, or claim 51.
- 25
67. A process for preparing olanzapine crystalline Form V comprising drying the form of claim 12.
68. A pharmaceutical composition comprising the forms selected from the group consisting of Forms H, G, Y, X, K, S, Q and J.
- 30

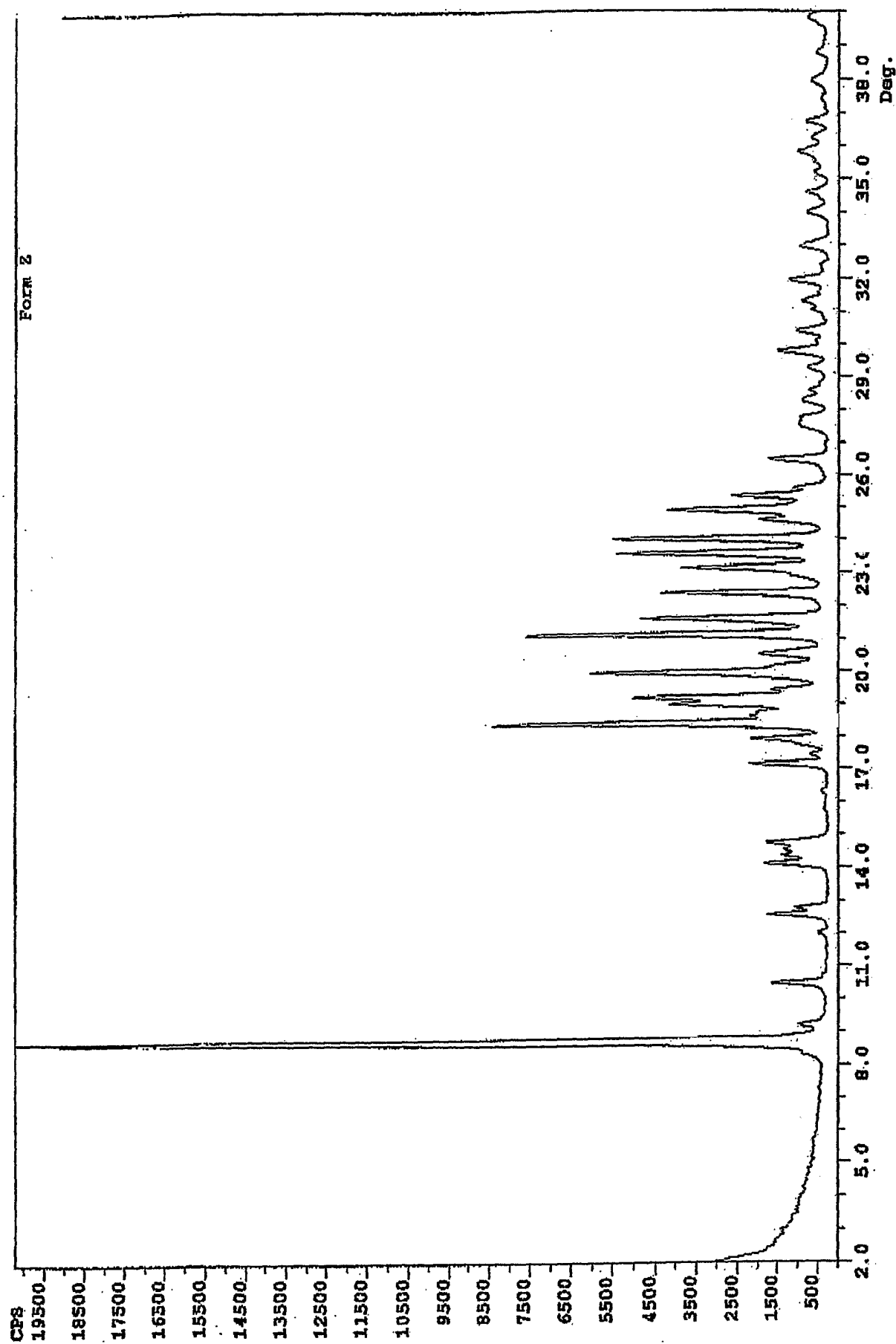


FIG. 1

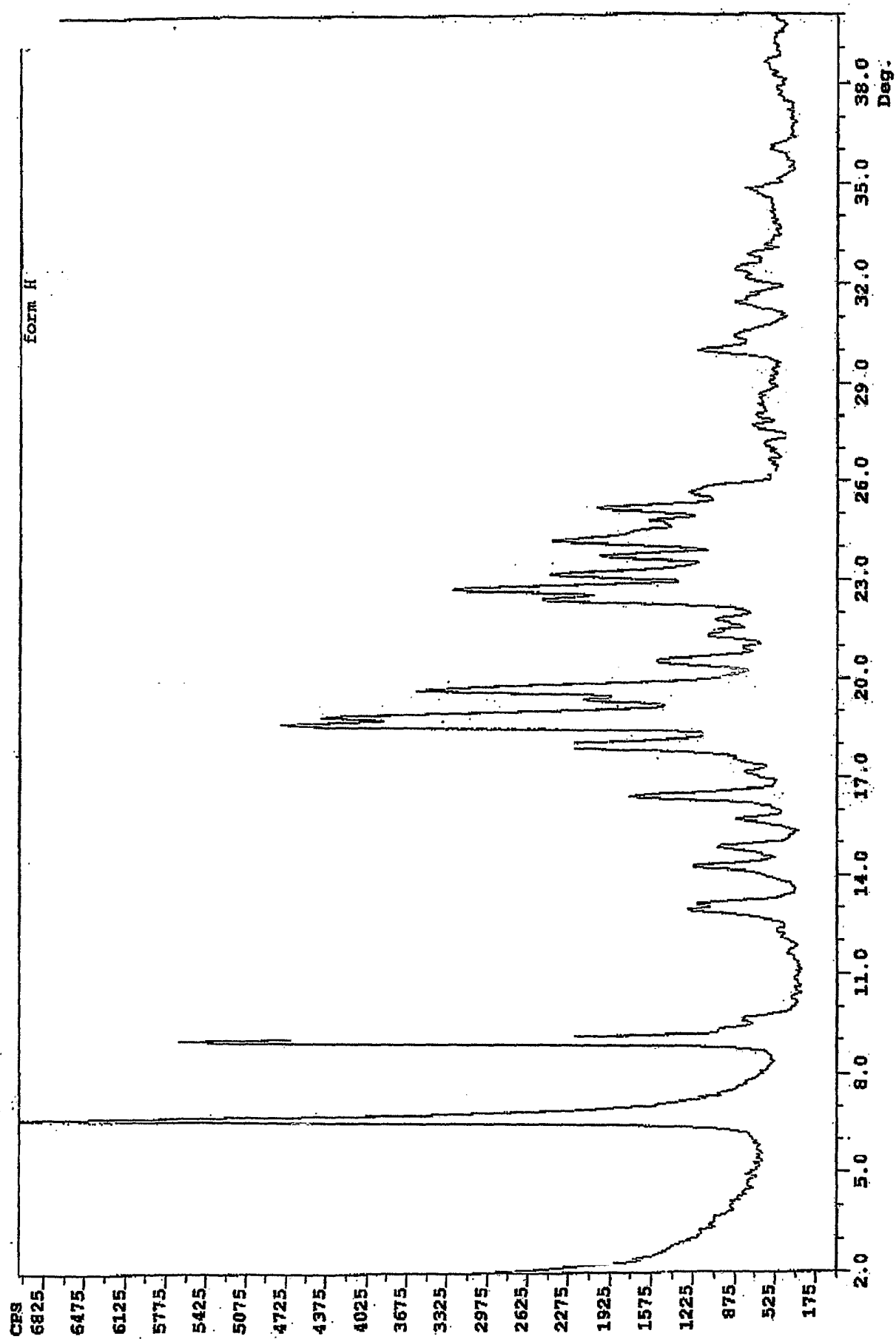


FIG. 2

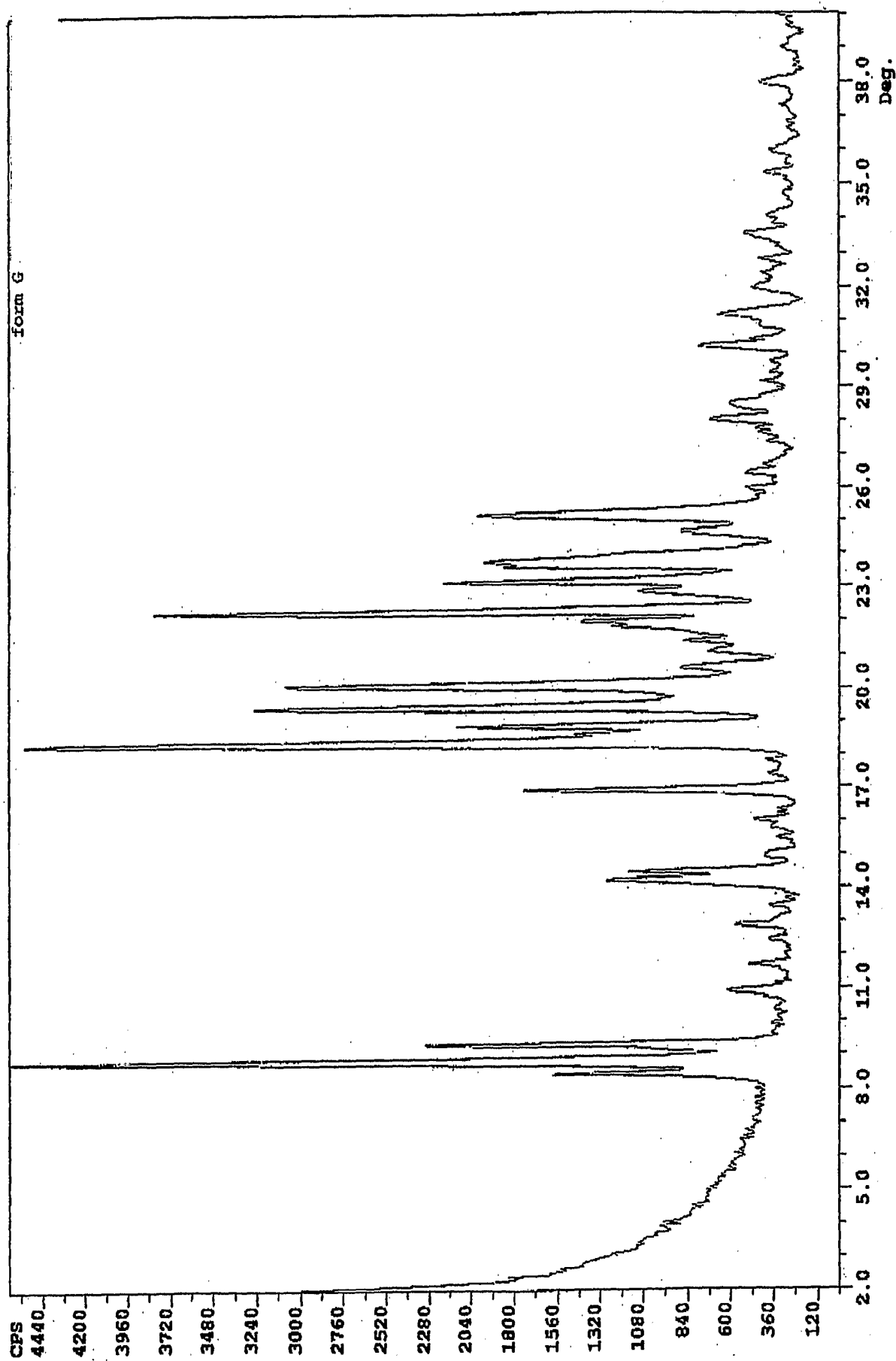


FIG. 3

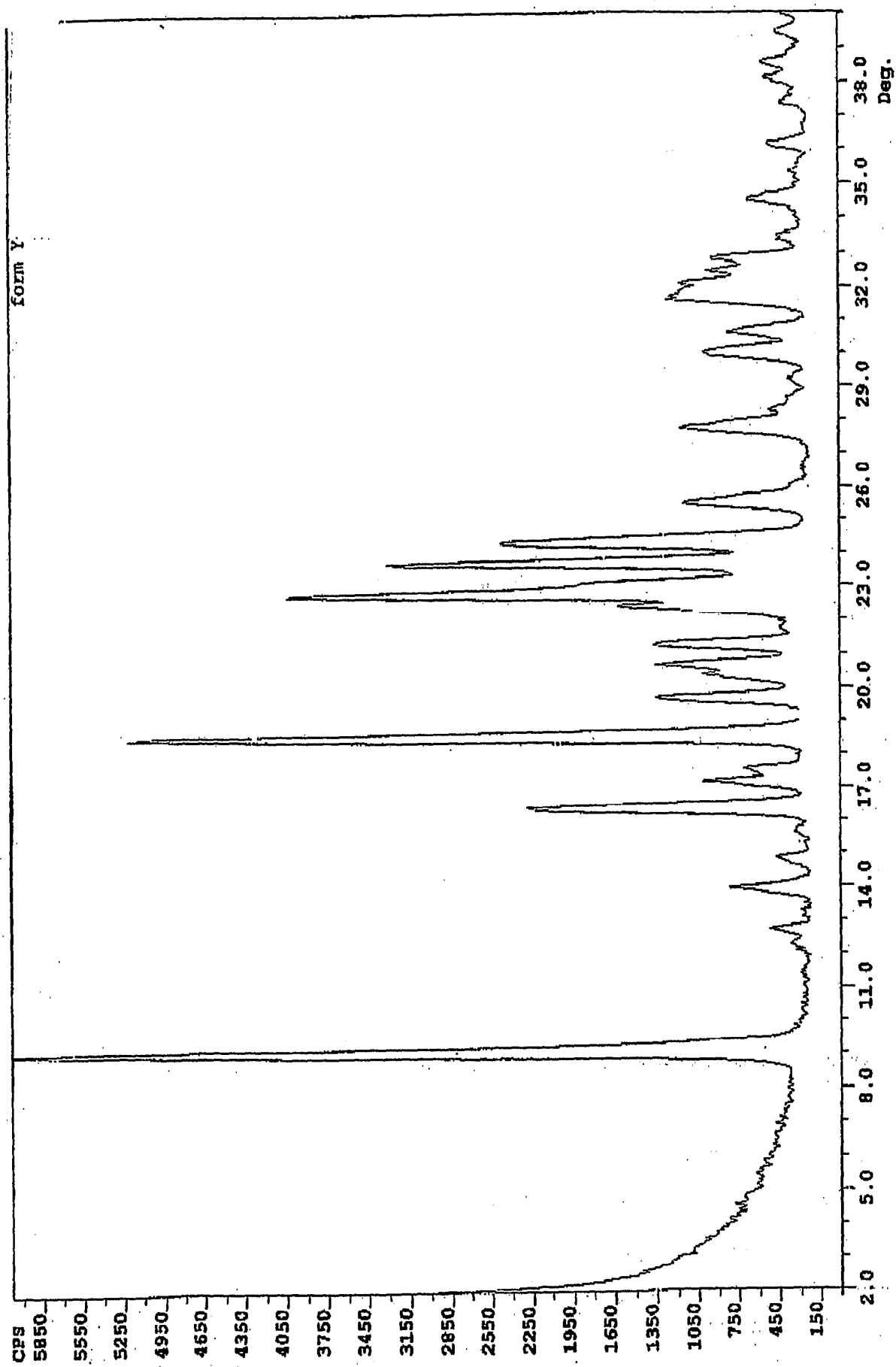


FIG. 4

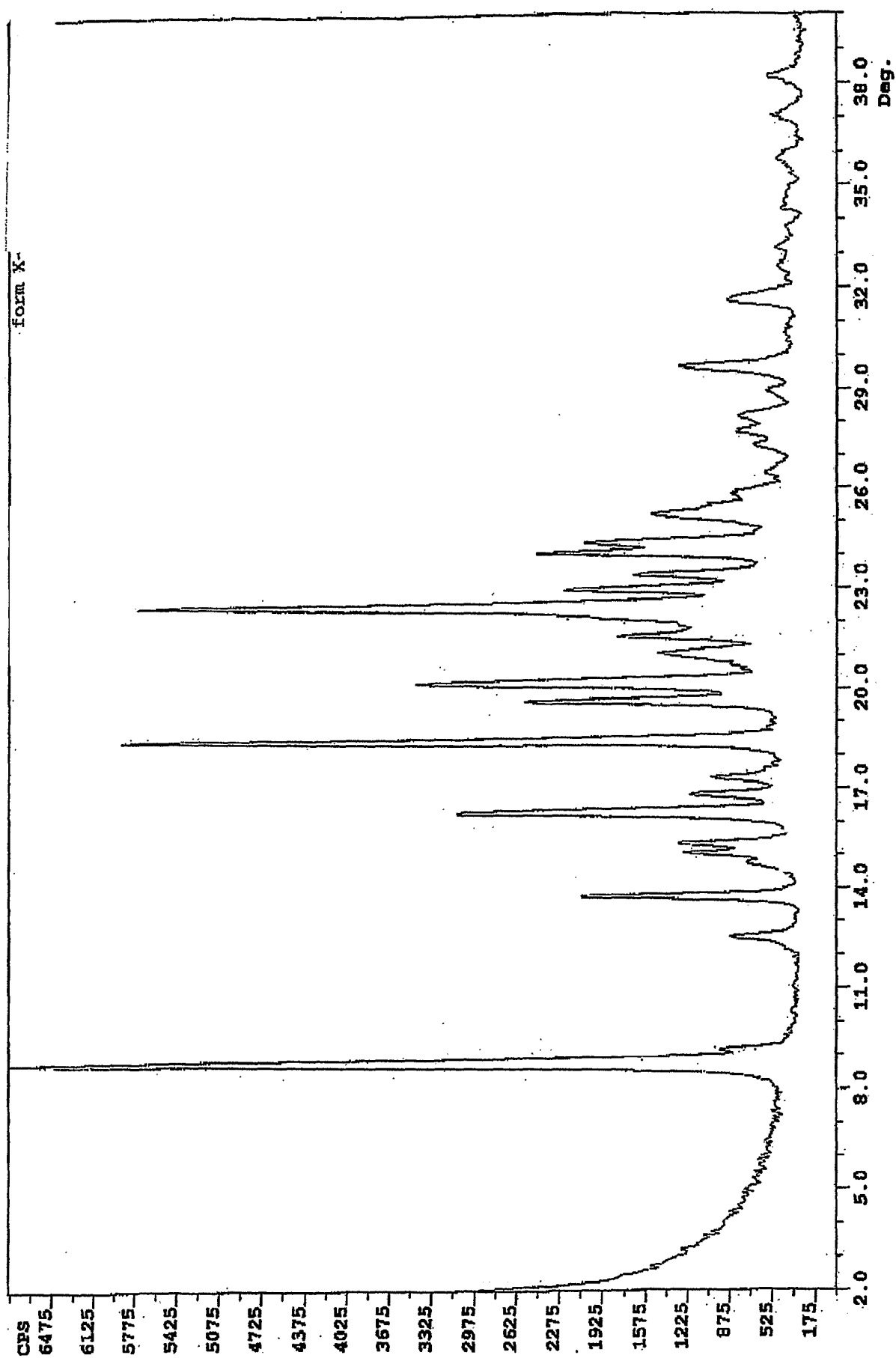


FIG. 5

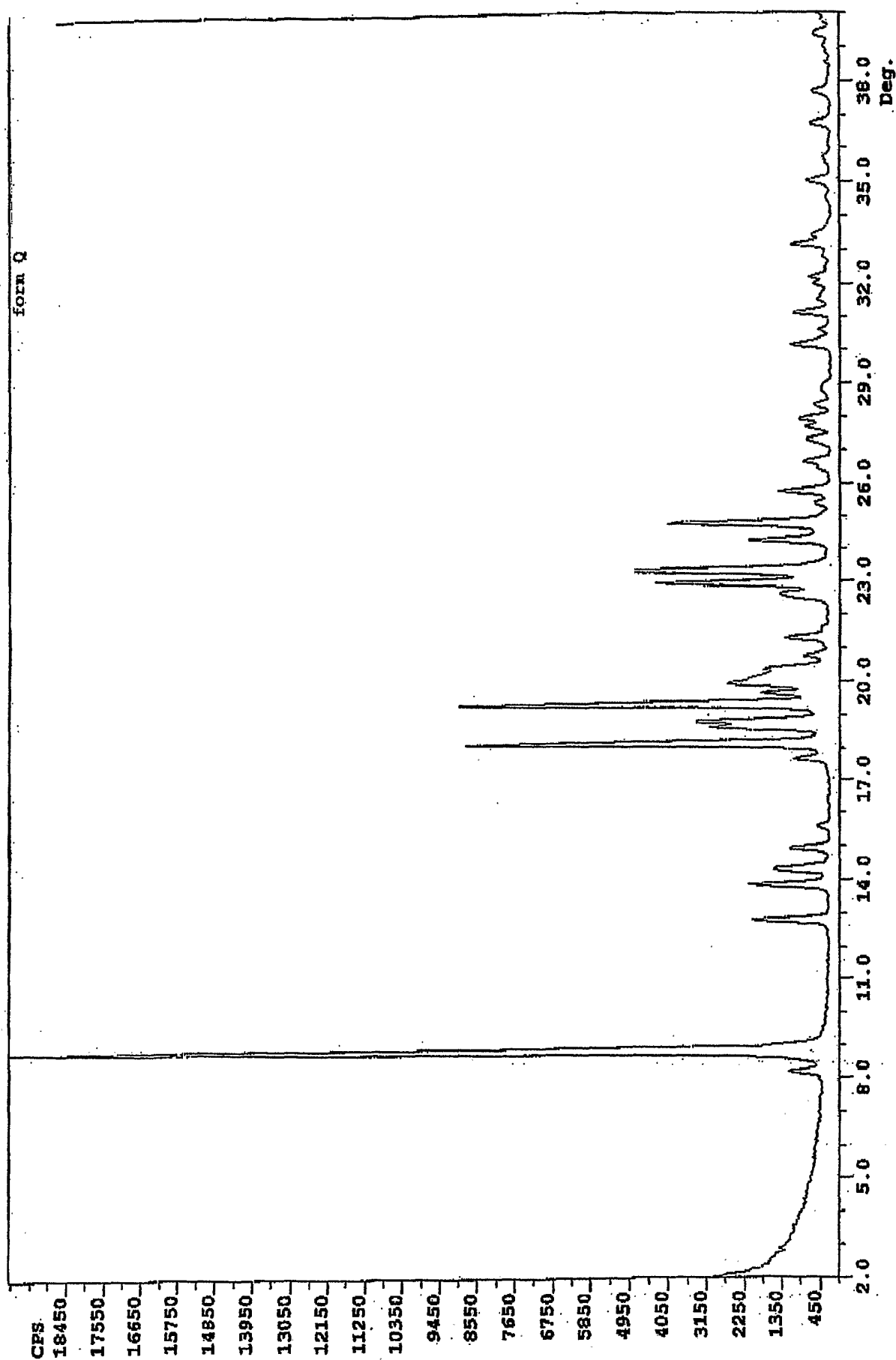


FIG. 6

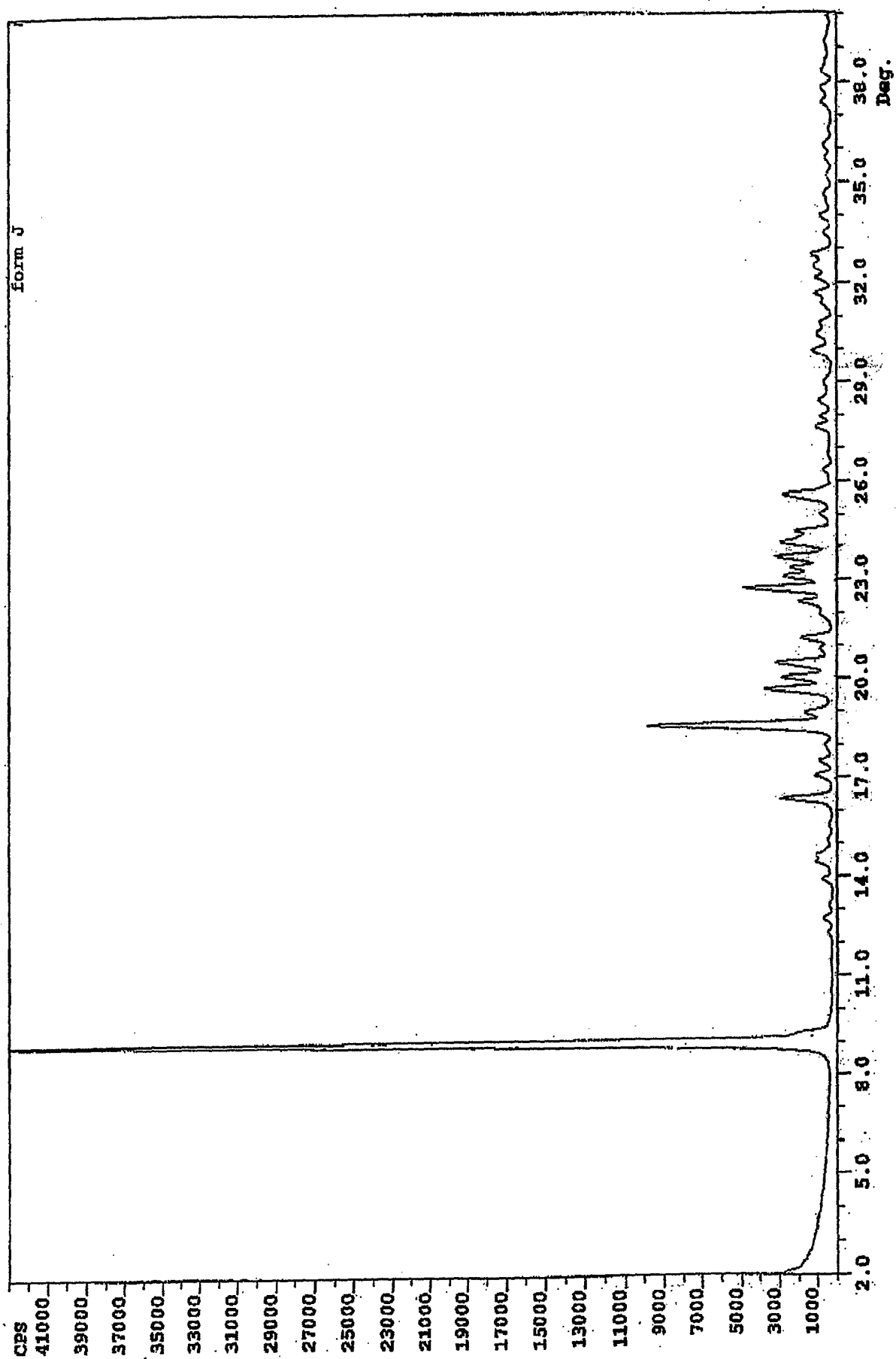


FIG. 7

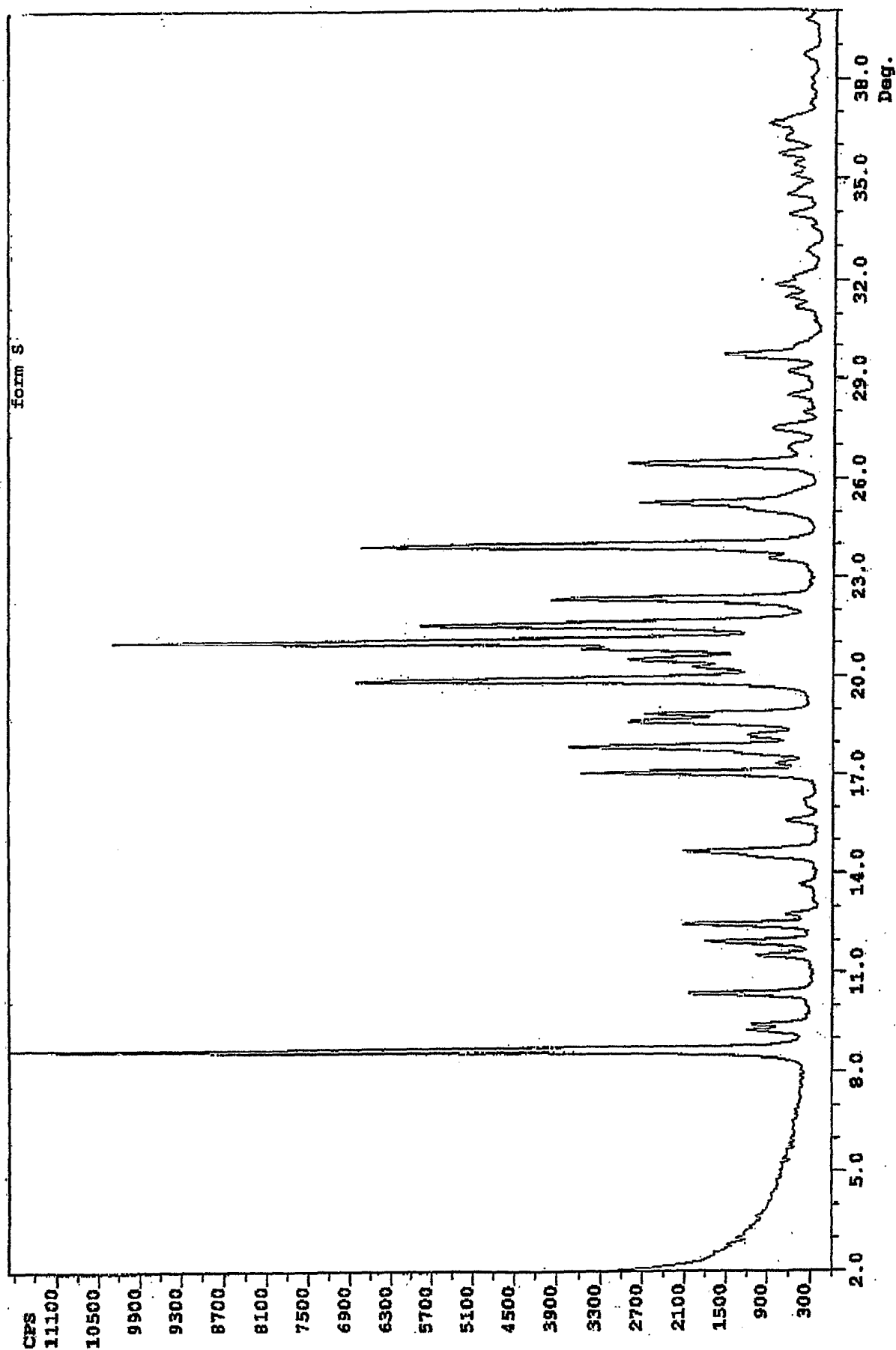


FIG. 8

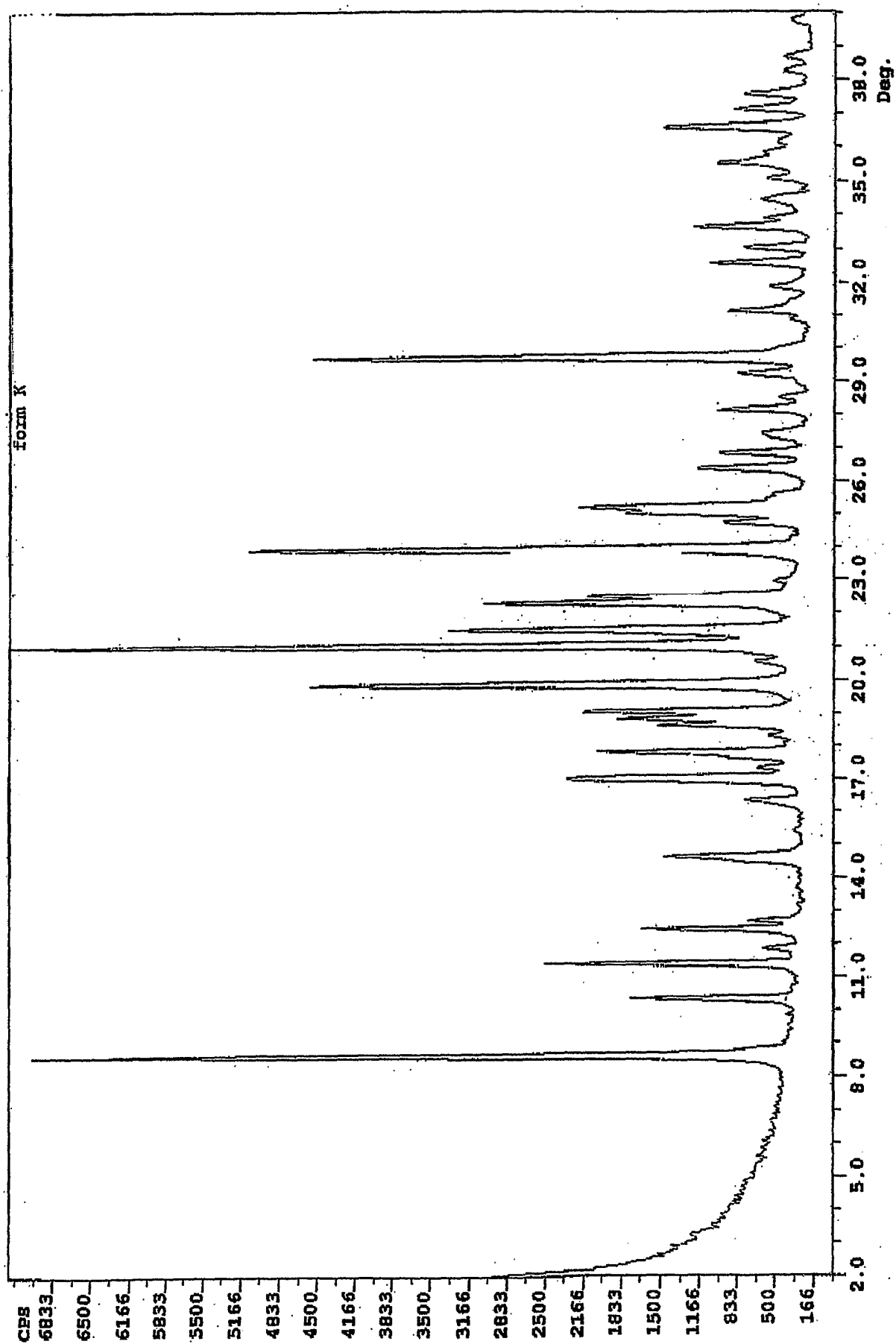


FIG. 9

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/41123

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07D495/04 A61K31/551 A61P25/18		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07D A61K A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	US 5 736 541 A (HENDRIKSEN BARRY ARNOLD ET AL) 7 April 1998 (1998-04-07) cited in the application Claims 1,16 (form II),20; example 2 (form II); example 1, therein two possible cryst. forms i.e. (1) cryst. from DMSO/MeOH/H ₂ O as wet cake, and (2) wet cake dried i. vac./45 °C overnight. ----- -/--	1-68
☒ Further documents are listed in the continuation of box C.		
☒ Patent family members are listed in annex.		
* Special categories of cited documents : *A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *&* document member of the same patent family		
Date of the actual completion of the international search 16 April 2004		Date of mailing of the international search report 03/05/2004
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Weisbrod, T

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X	WO 02/060906 A (GANO JAMES EDWARD ; DAVIES JULIAN (US); GENEVA PHARMACEUTICALS INC (US) 8 August 2002 (2002-08-08) cited in the application Claims 1-13 (olanzapine form X) and 13-18; examples 1,2. -----	1-68
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