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(54) Title: A SOLID STATE FORM OF PERAMPANEL

(57) Abstract: The present disclosure relates to solid state forms of Perampanel, processes for preparation thereof and pharmaceutical compositions thereof.



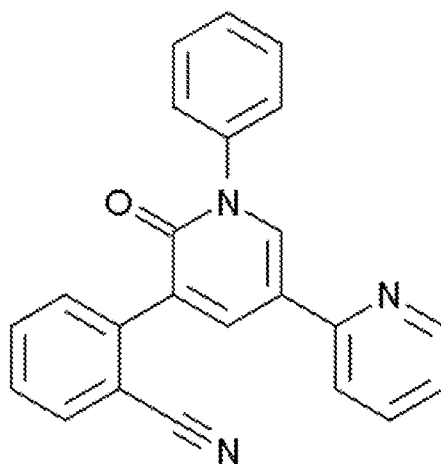
A SOLID STATE FORM OF PERAMPANEL

Field of the Invention

The present disclosure relates to solid state form of Perampanel, processes for preparation thereof and pharmaceutical compositions thereof.

Background of the Invention

Perampanel, (3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one, has the following chemical structure:



Perampanel, also referred herein as "Compound Ia", or "Ia", is a selective antagonist for the AMPA subtype of ionotropic glutamate receptors. It is developed by Eisai Co. under the trade name Fycompa®, for the treatment of epilepsy and diabetic neuropathy.

Perampanel is disclosed in US 6,949,571.

WO 2006/004107, WO 2007/072868, WO 2007/072869, WO 2013/102897 and CN 103664756 disclose solid state forms of Perampanel, including crystalline forms and amorphous form.

Polymorphism, the occurrence of different crystal forms, is a property of some molecules and molecular complexes. A single compound, like Perampanel, may give rise to a variety of polymorphs having distinct crystal structures and physical properties like melting point, thermal behaviors (e.g. measured by thermogravimetric analysis - "TGA", or differential scanning calorimetry - "DSC"), powder X-ray diffraction (PXRD) pattern, infrared absorption fingerprint, Raman absorption fingerprint, and solid state (^{13}C -) NMR spectrum. One or more of these techniques may be used to distinguish different polymorphic forms of a compound.

Different salts and solid state forms (including solvated forms) of an active pharmaceutical ingredient may possess different properties. Such variations in the properties of different salts and solid state forms and solvates may provide a basis for improving formulation, for example, by facilitating better processing or handling characteristics, improving the dissolution profile, or improving stability (polymorph as well as chemical stability) and shelf-life. These variations in the properties of different salts and solid state forms may also provide improvements to the final dosage form, for instance, if they serve to improve bioavailability.

Different salts and solid state forms and solvates of an active pharmaceutical ingredient may also give rise to a variety of polymorphs or crystalline forms, which may in turn provide additional opportunities to use variations in the properties and characteristics of a solid active pharmaceutical ingredient for providing an improved product.

Discovering new salts, solid state forms and solvates of a pharmaceutical product can provide materials having desirable processing properties, such as ease of handling, ease of processing, storage stability, and ease of purification or as desirable intermediate crystal forms that facilitate conversion to other salts or polymorphic forms. New salts, polymorphic forms and solvates of a pharmaceutically useful compound can also provide an opportunity to improve the performance characteristics of a pharmaceutical product (dissolution profile, bioavailability, etc.).

It enlarges the repertoire of materials that a formulation scientist has available for formulation optimization, for example by providing a product with different properties, e.g., a different crystal habit, higher crystallinity or polymorphic stability which may offer better processing or handling characteristics, improved dissolution profile, or improved shelf-life. For at least these reasons, there is a need for additional salts and solid state forms (including solvated forms) of Perampanel.

Summary of the Invention

The present disclosure relates to solid state form of Perampanel, to processes for preparation thereof, and to pharmaceutical compositions comprising this solid state form.

5 The present disclosure also provides the use of the solid state forms of Perampanel for preparing other solid state forms of Perampanel or other Perampanel salts and their solid state forms.

In another embodiment, the present disclosure encompasses the below described solid state form of Perampanel and /or combinations thereof for use in the preparation of pharmaceutical compositions, preferably for the treatment of epilepsy and diabetic neuropathy.

10 In another embodiment, the present disclosure encompasses the use of the below described solid state form of Perampanel and /or combinations thereof for the preparation of pharmaceutical compositions and/or formulations.

The present disclosure further provides pharmaceutical compositions comprising the solid state form of Perampanel according to the present disclosure.

15 In yet another embodiment, the present disclosure encompasses pharmaceutical formulations comprising the below described solid state form of Perampanel and at least one pharmaceutically acceptable excipient.

The present disclosure encompasses processes to prepare said pharmaceutical formulations of Perampanel comprising combining the below solid state form and at least one
20 pharmaceutically acceptable excipient.

The solid state form as defined herein as well as the pharmaceutical compositions or formulations of the solid state form of Perampanel can be used as medicaments, particularly for the treatment of epilepsy and diabetic neuropathy.

The present disclosure also provides a method of treating epilepsy and diabetic
25 neuropathy; comprising administering a therapeutically effective amount of the solid state form of Perampanel of the present disclosure and /or combinations thereof, or at least one of the above

pharmaceutical compositions or formulations, to a subject suffering from epilepsy and diabetic neuropathy, or otherwise in need of the treatment.

The present disclosure also provides the use of the solid state form of Perampanel of the present disclosure, or at least one of the above pharmaceutical compositions or formulations for the manufacture of a medicament for treating epilepsy and diabetic neuropathy.

Brief Description of the Figures

Figure 1 shows a powder X-ray diffraction pattern ("powder XRD" or "PXRD") of Perampanel form VI.

Figure 2 shows a differential scanning calorimetry (DSC) of Perampanel form VI.

Figure 3 shows solid state ^{13}C NMR spectrum of Perampanel Form VI.

Figure 4a shows a Raman spectrum of Perampanel Form VI, range: 4000 to 150 cm^{-1} .

Figure 4b shows a Raman spectrum of Perampanel Form VI, range 1800 to 160 cm^{-1} .

Figure 5a shows an FT-IR spectrum of Perampanel form VI, range: 4000 to 400 cm^{-1} .

Figure 5b shows an FT-IR spectrum of Perampanel form VI, range: 1800 to 400 cm^{-1} .

Detailed Description of the Invention

The present disclosure relates to Perampanel, to solid state forms thereof, such as crystalline form VI, to processes for preparation thereof and to pharmaceutical compositions comprising at least one of, or a combination of, these solid state forms. The disclosure also relates to the conversion of the Perampanel form to other solid state forms of Perampanel or to other Perampanel salts and their solid state forms.

The solid state form of Perampanel of the present disclosure may have advantageous properties selected from at least one of: chemical or polymorphic purity, flowability, solubility, dissolution rate, bioavailability, morphology or crystal habit, stability - such as chemical stability as well as thermal and mechanical stability with respect to polymorphic conversion,

stability towards dehydration and/or storage stability, a lower degree of hygroscopicity, low content of residual solvents and advantageous processing and handling characteristics such as compressibility, or bulk density.

A crystal form may be referred to herein as being characterized by graphical data "as depicted in" a Figure. Such data include, for example, powder X-ray diffractograms and solid state NMR spectra. As is well-known in the art, the graphical data potentially provides additional technical information to further define the respective solid state form (a so-called "fingerprint") which can not necessarily be described by reference to numerical values or peak positions alone. In any event, the skilled person will understand that such graphical representations of data may be subject to small variations, *e.g.*, in peak relative intensities and peak positions due to factors such as variations in instrument response and variations in sample concentration and purity, which are well known to the skilled person. Nonetheless, the skilled person would readily be capable of comparing the graphical data in the Figures herein with graphical data generated for an unknown crystal form and confirm whether the two sets of graphical data are characterizing the same crystal form or two different crystal forms. A crystal form of Perampanel, *e.g.* Perampanel Form VI, referred to herein as being characterized by graphical data "as depicted in" a Figure will thus be understood to include any crystal forms of the Perampanel, *e.g.*, Perampanel Form VI, characterized with the graphical data having such small variations, as are well known to the skilled person, in comparison with the Figure.

A solid state form (or polymorph) may be referred to herein as polymorphically pure or as substantially free of any other solid state (or polymorphic) forms. As used herein in this context, the expression "substantially free of any other forms" will be understood to mean that the solid state form contains 20% or less, 10% or less, 5% or less, 2% or less, or 1% or less of any other forms of the subject compound as measured, for example, by PXRD. Thus, solid state of Perampanel described herein as substantially free of any other solid state forms would be understood to contain greater than 80% (w/w), greater than 90% (w/w), greater than 95% (w/w), greater than 98% (w/w), or greater than 99% (w/w) of the subject solid state form of Perampanel. Accordingly, in some embodiments of the disclosure, the described solid state forms of Perampanel may contain from 1% to 20% (w/w), from 5% to 20% (w/w), or from 5% to 10% (w/w) of one or more other solid state forms of Perampanel

As used herein, unless stated otherwise, PXRD peaks reported herein are preferably measured using CuK α radiation, $\lambda = 1.5419$ Å. Preferably, PXRD peaks reported herein are measured using CuK α radiation, $\lambda = 1.5419$ Å, at a temperature of $25 \pm 3^\circ\text{C}$. Alternatively, if an instrument with a different wavelength is used, for example, when using high resolution XRD method, such as synchrotron, the data may be corrected to wavelength of 1.5419 respectively.

As used herein, unless stated otherwise, ^{13}C solid state NMR was measured at 125 MHz at 0°C at a spin rate of 11 kHz.

As used herein, unless stated otherwise, Raman spectroscopy was measured using 1064 nm excitation laser, a CaF $_2$ beam splitter and Ge detector.

As used herein, unless stated otherwise, FT-IR was measured using a KBr pellet.

As used herein, unless stated otherwise, TGA was carried out at a heating rate of $10^\circ\text{C}/\text{min}$.

As used herein, unless stated otherwise, unit cell information was obtained by indexation and LeBail fitting/refinement. The analysis can be carried out on any LeBail analysis software. Preferably LeBail refinement may be carried out on any one of GSAS (General Structure Analysis System), TOPAS (Total Pattern Analysis Solutions - Bruker) or more preferably using HighScore Plus software, version 4.1 (PanAlytical BV, Netherlands).

As used herein, the term "isolated" in reference to solid state forms of Perampanel of the present disclosure corresponds to a solid state form of Perampanel that is physically separated from the reaction mixture in which it is formed.

A thing, *e.g.*, a reaction mixture, may be characterized herein as being at, or allowed to come to "room temperature", often abbreviated "RT." This means that the temperature of the thing is close to, or the same as, that of the space, *e.g.*, the room or fume hood, in which the thing is located. Typically, room temperature is from about 20°C to about 30°C , or about 22°C to about 27°C , or about 25°C .

A process or step may be referred to herein as being carried out "overnight." This refers to a time interval, *e.g.*, for the process or step, that spans the time during the night, when that

process or step may not be actively observed. This time interval is from about 8 to about 20 hours, or about 10-18 hours, typically about 16 hours.

As used herein, the expression "wet crystalline form" refers to a polymorph that was not dried using any conventional techniques to remove residual solvent. Examples for such conventional techniques can be, but are not limited to, evaporation, vacuum drying, oven drying, drying under nitrogen flow, etc.

As used herein, the expression "dry crystalline form" refers to a polymorph that was dried using any conventional techniques to remove residual solvent. Examples of such conventional techniques can be, but are not limited to, evaporation, vacuum drying, oven drying, drying under nitrogen flow, etc.

As used herein, and unless stated otherwise, the term "anhydrous" in relation to crystalline Perampanel relates to crystalline Perampanel which does not include any crystalline water (or other solvents) in a defined, stoichiometric amount within the crystal. Moreover, an "anhydrous" form does not contain more than 1% (w/w) of either water or organic solvents as measured for example by TGA.

The term "solvate", as used herein and unless indicated otherwise, refers to a crystal form that incorporates a solvent in the crystal structure. When the solvent is water, the solvate is often referred to as a "hydrate." The solvent in a solvate may be present in either a stoichiometric or in a non-stoichiometric amount.

The amount of solvent employed in a chemical process, e.g., a reaction or a crystallization may be referred to herein as a number of "volumes" or "vol" or "V." For example, a material may be referred to as being suspended in 10 volumes (or 10 vol or 10V) of a solvent. In this context, this expression would be understood to mean milliliters of the solvent per gram of the material being suspended, such that suspending 5 grams of a material in 10 volumes of a solvent means that the solvent is used in an amount of 10 milliliters of the solvent per gram of the material that is being suspended or, in this example, 50 mL of the solvent. In another context, the term "v/v" may be used to indicate the number of volumes of a solvent that are added to a

liquid mixture based on the volume of that mixture. For example, adding MTBE (1.5 v/v) to a 100 mL reaction mixture would indicate that 150 mL of MTBE was added.

As used herein, the term "reduced pressure" refers to a pressure of about 10 mbar to about 50 mbar.

5 As used herein, and unless indicated otherwise, the term "thermo-dynamical stability" in relation to solid state forms of Perampanel refers to resistance of the solid state form to polymorphic conversion under certain conditions, for example, heating, melting or dissolving. In some embodiments, the term refers to less than 20%, 10%, 5%, 1%, or 0.5% (w/w) conversion of crystalline Perampanel to any other solid state form of Perampanel as measured by PXRD. In
10 some embodiments, the conversion is 1%-20%, 1%-10% or 1%-5% (w/w).

The present disclosure encompasses solid state form of Perampanel, in particular crystalline Form VI.

The present disclosure comprises a crystalline form of Perampanel designated as Form VI. The crystalline Form VI of Perampanel can be characterized by data selected from one or
15 more of the following:

- a. orthorhombic structure, with the largest unit cell dimension $a = 37.85 \text{ \AA} \pm 0.1 \text{ \AA}$, obtained by LeBail refinement of the laboratory powder diffraction pattern in combination with a PXRD pattern having peaks at 9.6, 14.4, 15.5, 16.2 and 20.6 degrees 2-theta ± 0.1 degrees 2-theta or a PXRD pattern as depicted in
20 Figure 1;
- b. a solid state ^{13}C NMR spectrum with peaks at 127.4, 125.9, 120.8, 114.2 and 107.2 ppm ± 0.2 ppm;
- c. a solid state ^{13}C NMR spectrum having the following chemical shift absolute differences from a peak at 149.0 ppm ± 1 ppm of 21.6, 23.1, 28.2, 34.8 and
25 41.8 ppm ± 0.1 ppm;
- d. a solid state ^{13}C NMR spectrum having chemical shift difference from a peak at 107.2 ppm ± 1 ppm of 18.7 ppm ± 0.1 ppm;

- e. a solid state ^{13}C NMR spectrum having chemical shift difference from a-peak a peak at $107.2 \text{ ppm} \pm 1 \text{ ppm}$ of $13.6 \text{ ppm} \pm 0.1 \text{ ppm}$;
- f. a solid state ^{13}C NMR spectrum as depicted in Figure 3; and
- g. combinations of these data.

5 Crystalline Form VI of Perampanel may be further characterized by solid state ^{13}C NMR spectrum having peaks at: 159.9, 152.3, 151.9, 149.0, 141.2, 140.7, 137.6, 136.9, 134.8, 133.7, 131.0, 129.4, 128.3, 127.4, 126.6, 125.9, 120.8, 117.9, 114.2 and $107.2 \pm 0.2 \text{ ppm}$.

Crystalline Form VI of Perampanel may be further characterized by orthorhombic structure with the largest unit cell dimension of $a = 37.85 \text{ \AA} \pm 0.1 \text{ \AA}$, obtained by LeBail
 10 refinement of the laboratory powder diffraction pattern and an X-ray powder diffraction pattern having peaks at 9.6, 14.4, 15.5, 16.2 and 20.6 degrees 2-theta ± 0.1 degrees 2-theta and also having one, two, three, four or five additional peaks selected from: 4.8, 7.8, 10.3, 15.0 and 18.4 degrees two theta ± 0.1 degrees two theta.

Crystalline Form VI of Perampanel may be further characterized by data selected from
 15 one or more of the following: a DSC showing a melting peak maximum at about 181 degrees Celsius ± 3 degrees Celsius; a DSC thermogram as depicted in Figure 2; Raman spectrum having peaks at 1622, 1157, 279, 266 and $191 \text{ cm}^{-1} \pm 1 \text{ cm}^{-1}$; Raman spectrum as depicted in any one of Figures 4a or 4b; FT-IR spectrum having peaks at 1156, 934, 895, 779 and $698 \text{ cm}^{-1} \pm 1 \text{ cm}^{-1}$; FT-IR spectrum as depicted in any one of Figures 5a or 5b; and combinations of these data.

20 Crystalline Form VI of Perampanel may be further characterized by one or more of the following: Raman spectrum having maxima of the characteristic bands optionally with the intensities as listed in the following table:

Peak position [cm^{-1}]	Raman Intensity
3133	7
3113	11
3073	65
3056	57

3016	17
2218	72
1664	15
1622	158
1594	191
1569	138
1550	147
1476	72
1458	18
1437	28
1401	53
1372	49
1325	80
1292	34
1276	41
1266	90
1247	93
1223	33
1188	38
1168	19
1157	38
1136	61
1098	31
1069	12
1049	41
1020	78
1002	96
991	153
934	10
878	46
822	16
803	20
786	16
779	16
766	10
754	15
673	40
631	14
618	17
596	8
576	12

558	15
544	12
506	11
491	18
458	11
444	9
405	31
383	18
332	16
318	24
298	18
279	23
266	44
237	55
191	37

FT-IR spectrum having maxima of the characteristic bands, optionally with the intensities as listed in the following table:

Peak position [cm ⁻¹]	Transmittance [%]
3056	72
3015	79
2337	94
2218	37
1954	89
1664	0
1620	15
1585	6
1567	7
1550	15
1477	12
1458	32
1436	12
1371	40
1319	12
1294	31
1276	19
1265	25

1247	23
1222	48
1187	69
1156	56
1133	58
1097	52
1079	75
1033	70
1018	79
1002	84
985	84
957	85
934	63
923	78
895	62
876	45
841	93
785	8
779	10
753	6
738	33
730	26
698	7
654	82
630	51
618	76
605	30
595	60
575	80
558	53
543	70
506	39
497	52
457	88
443	77

Form VI can be anhydrous.

Crystalline Form VI of Perampanel may be characterized by each of the above characteristics alone and/or by all possible combinations. For example, crystalline Form VI of

Perampanel may be characterized by a PXRD pattern as depicted in Figure 1 and also by a DSC showing a melting peak at about 181 degrees Celsius $\pm$ 3 degrees Celsius.

As discussed above, depending on which other solid state form it is compared with, Form VI of Perampanel may have advantageous properties selected from at least one of: chemical or polymorphic purity, flowability, solubility, wettability, dissolution rate, bioavailability, morphology or crystal habit, stability - such as chemical stability as well as thermal and mechanical stability with respect to polymorphic conversion, stability towards dehydration and/or storage stability, a lower degree of hygroscopicity, low content of residual solvents, adhesive tendencies and advantageous processing and handling characteristics such as compressibility, or bulk density. Particularly, crystalline Form VI of Perampanel of the present disclosure is for example, thermodynamically more stable than anhydrous form II described in US 8,772,497. Pharmaceutical molecules may display solid to solid phase transformations, transformations between polymorphs or between unsolvated and solvated form, which may be detected for example by competitive slurry experiments, or by DSC analysis. A thermodynamically stable polymorph (which does not convert to other form or a mixture of forms), facilitates the handling and formulation of the API, and thus enables a reliable and reproducible formulation manufacturing processing. As a result the formulation process enables readily reproducible formulations in terms of solubility, bioavailability, etc.

The present disclosure also provides the use of the solid state form of Perampanel described above for preparing other solid state forms of Perampanel or other Perampanel salts, and their solid state forms.

The present disclosure further encompasses a process for preparing other Perampanel salts or solid state forms thereof. The process comprises preparing the Perampanel solid state form of the present disclosure, and converting it to Perampanel salt.

In another embodiment, the present disclosure encompasses the above described solid state form of Perampanel for use in the preparation of pharmaceutical compositions, preferably for the treatment of epilepsy and diabetic neuropathy.

In another embodiment, the present disclosure encompasses the use of the above described solid state form of Perampanel thereof for the preparation of pharmaceutical compositions and/or formulations.

5 The present disclosure further provides pharmaceutical compositions comprising the solid state form of Perampanel according to the present disclosure.

The present disclosure comprises a process for preparing the above mentioned pharmaceutical compositions.

10 In yet another embodiment, the present disclosure encompasses pharmaceutical formulations comprising the above described solid state form of Perampanel and at least one pharmaceutically acceptable excipient.

The present disclosure encompasses a process to prepare said formulations of Perampanel comprising combining the above solid state form and at least one pharmaceutically acceptable excipient.

15 The solid state form as defined herein, as well as the pharmaceutical compositions or formulations of Perampanel can be used as medicaments, particularly for the treatment of epilepsy and diabetic neuropathy.

20 The present disclosure also provides a method of treating epilepsy and diabetic neuropathy, comprising administering a therapeutically effective amount of the solid state form of Perampanel of the present disclosure and/or combinations thereof, or at least one of the above pharmaceutical compositions or formulations, to a subject suffering from epilepsy and diabetic neuropathy, or otherwise in need of the treatment.

The present disclosure also provides the use of the solid state form of Perampanel of the present disclosure, or at least one of the above pharmaceutical compositions or formulations for the manufacture of a medicament for treating epilepsy and diabetic neuropathy.

25 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 illustrated by reference to the following examples

describing in detail the preparation of the composition and methods of use 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.

Powder X-ray diffraction pattern ("PXRD") method:

5 Powder X-ray Diffraction was performed on an X-Ray powder diffractometer PanAlytical X'pert Pro; CuK α radiation ($\lambda = 1.5419$); X'Celerator detector with active length 2.122 degrees 2-theta; laboratory temperature 25 ± 3 °C; zero background sample holders. Prior to analysis, the samples were gently ground using a mortar and pestle to obtain a fine powder. Optionally, silicon powder can be added in a suitable amount as internal standard in order to
10 calibrate the positions of the diffractions with precision of 0.1 degrees 2-theta. The ground sample was adjusted into a cavity of the sample holder and the surface of the sample was smoothed using a cover glass.

Measurement parameters:

Scan range	3 - 40 degrees 2-theta
15 Scan mode	continuous
Step size	0.0167 degrees
Step size	42 s
Sample spin	60 rpm
Sample holder	zero background silicon plate

20 ^{13}C Solid state NMR method:

Solid-state ^{13}C NMR spectra were recorded with variable amplitude cross polarization, magic angle spinning and high power proton decoupling using a BRUKER Avance 11+ spectrometer operating at 125 MHz and controlled temperature of 0 °C. A probe using 4 mm o.d. zirconia rotors was employed. The operation conditions were: contact time 2 ms; acquisition
25 time, recycle delay: 50 s, 128 scans; spin rate: 11 kHz. Chemical shifts were referenced via a replacement sample of glycine (carboxyl carbon chemical shift assigned as 176.03 ppm relative to the signal of tetramethylsilane).

Differential scanning calorimetry (DSC) method:

DSC measurements were performed on a differential scanning calorimeter DSC823e (Mettler Toledo). Aluminum crucibles 40 μ i with pin-holed lids were used for sample preparation. Typical sample weight was between 1 and 5 mg.

- 5 Program parameters: temperature range at least 30 - 200 °C; heating rate 10 °C/min; nitrogen flow 50 ml/min.

Raman spectroscopy method:

Powder samples were filled into 5 mm NMR tube and Raman spectrum was recorded on Nicolet 6700 FT-IR spectrometer with NXR FT-Raman module, equipped with 1064 nm

- 10 Nd:YVO₄ excitation laser, CaF₂ beam splitter and Ge detector.

Instrument parameters:

- | | | |
|----|-------------------|---------------------------|
| | Spectral range: | 4000-150 cm ⁻¹ |
| | Resolution: | 4.0 cm ⁻¹ |
| | Number of scans: | 128 |
| 15 | Sample gain: | auto |
| | Optical velocity: | 0.4747 |
| | Aperture: | 58.84 |
| | Laser power: | 1 W |

FT-IR spectroscopy method:

- 20 KBr pellet was prepared and FTIR spectrum was recorded on Nicolet 380 spectrometer, equipped with KBr beam splitter and DTGS KBr detector.

Instrument parameters:

- | | | |
|----|-------------------|---------------------------|
| | Spectral range: | 4000-400 cm ⁻¹ |
| | Resolution: | 4.0 cm ⁻¹ |
| 25 | Number of scans: | 64 |
| | Sample gain: | 1 |
| | Optical velocity: | 0.6329 |

Aperture: 100

Thermogravimetric analysis (TGA) method:

TGA measurements were performed on a Thermogravimetric analyzer TGA851e (Mettler Toledo). Alumina crucibles 70 μ i were used for sample preparation. Usual sample weight was between 5 and 15 mg.

Program parameters: temperature range at least 30 - 200 °C; heating rate 10 °C/min; nitrogen flow 50 ml/min.

Examples

Reference examples:

10 The starting material Perampanel form I can be prepared according to the US patent No. 8,772,497 B2, Example 7:

A 1-L vessel was charged with 8 g of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one (Hydrate). Ethyl acetate (480 mL) was added to the vessel and the mixture was stirred at heating under reflux (in an oil bath) to effect dissolution. Heating was stopped and the stirring was allowed to continue while the vessel was in the oil bath (under gradual cooling). At the point that the internal temperature reached 50.9° C , 0.2 g of seed crystals [3-(2-cyanophenyl)-5-(2-pyridyl)-1 -phenyl- 1,2-dihydropyridin-2-one (anhydrous crystal) was added to the mixture. Subsequently, stirring continued until the internal temperature reached 31.3° C. The mixture was stirred for additional 2 hours in an ice bath. The precipitated crystals were collected by filtration and dried under aeration (50° C./18 hours) to give 5.8 g of anhydrous crystals of 3-(2-cyanophenyl)-5-(2-pyridyl)- 1-phenyl- 1,2-dihydropyridin-2-one.

¹HNMR (400 MHz, DMSO-d₆): δ 8.58 (d, 1H), 8.53 (d, 1H), 8.47 (d, 1H), 8.01 (d, 1H), 7.93 (d, 1H), 7.83 (ddd, 1H), 7.78 (d, 1H), 7.72 (d, 1H), 7.61-7.48 (m, 6H), 7.32-7.27 (m, 1H).

Alternatively form I of Perampanel may be prepared according to the following procedure:

Perampanel (11.2 g) was charged into 1L mL flask followed by addition of 2-propanol (672 mL). The mixture was heated at reflux until complete dissolution, subsequently treated with charcoal (5 % w/w) at the same temp. Afterwards, the mixture was filtered on celite bed and then left to spontaneously cool down to room temp. Afterwards, the mixture was cooled in ice-water bath for 30 min. and filtered. The filtration cake was washed with cold (5-10 °C) 2-propanol and dried at room temperature. The sample was analyzed by PXRD, and form I was identified.

The starting Perampanel form II can be prepared according to the US Patent No. 8,772,497 B2, reference example 1:

In the same manner as the procedure after reaction work-up that are described in Example 7 in WO 01/96308, the production was carried out below. The synthetic method for 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one [alternative name: 2-(2-oxo-1-phenyl-5-(pyridin-2-yl)-1,2-dihydropyridin-3-yl)benzonitrile] is described in Example 7 in WO 01/96308.

Ethyl acetate (400 mL) was added to 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one (8 g). The mixture was heated at 60° C. in a warm bath. Additional acetate (160 mL) was added to the mixture and the solids were dissolved by heating at 70° C. in the warm bath. After n-hexane (80 mL) was added to this solution, the solvent was evaporated under reduced pressure to give 7.7 g of a pale yellow powder.

¹HNMR (400 MHz, DMSO-d₆): δ 8.59-8.57 (m, 1H), 8.53 (d, 1H), 8.47 (d, 1H), 8.01 (d, 1H), 7.92 (d, 1H), 7.83 (ddd, 1H), 7.80-7.76 (m, 1H), 7.73-7.71 (d-like, 1H), 7.61-7.48 (m, 6H), 7.30 (dd, 1H).

Working examples:

Example 1: Preparation of Perampanel form VI

Perampanel form I (5 g) was charged in 250 mL flask followed by addition of n-butyl acetate (125 mL). The mixture was stirred at 40 °C for 1 hour, and then cooled to RT and stirred for 3 hours, followed by heating of the mixture to 40 °C and by stirring for additional 2 hours at 40 °C. Afterwards, the mixture was allowed to reach to RT, stirred for 22 hours and filtered. The

filtration cake was washed with methyl tert-butyl ether (2 x 100 mL) and dried with suction at RT for 2 h. The sample was analyzed by PXRD, and form VI was identified.

Example 2: Preparation of Perampanel form VI

Perampanel form II (15 g) was charged into 500 mL jacketed reactor equipped with
5 thermometer followed by addition of n-butyl acetate (375 mL). The mixture was heated at 110-115 °C until complete dissolution. Afterwards, the mixture was cooled to 85 °C followed by addition of Perampanel form VI seeds. The mixture was then stirred at 80 °C for 2 hours, cooled to 25 °C during 5 hours (linear temperature ramp) and then stirred at the same temperature for 20
10 hours. Afterwards, the mixture was cooled to -5 °C, stirred at the same temperature for 15 minutes and filtered. The filtration cake was washed with cold (10-15 °C) methyl t-butyl ether (2 x 100 mL) and dried in the inert gas flow at room temperature for 4 h. The sample was analyzed by PXRD, and form VI was identified. A PXRD pattern and DSC thermogram are shown in figures 1 and 2, respectively; weight loss determined by TGA: lower than 0.05 % (w/w).

Further aspects and embodiments of the present invention are set out in the following
15 numbered paragraphs :

1. A crystalline form of Perampanel characterized by an X-ray powder diffraction pattern having peaks at 9.6, 14.4, 15.5, 16.2 and 20.6 degrees 2-theta $\pm$ 0.1 degrees 2-theta and having one, two, three, four or five additional peaks selected from: 4.8, 7.8, 10.3, 15.0 and
20 18.4 degrees two theta $\pm$ 0.1 degrees two theta.
2. A crystalline form of Perampanel characterized by an X-ray powder diffraction pattern having peaks at 9.6, 14.4, 15.5, 16.2 and 20.6 degrees 2-theta $\pm$ 0.1 degrees 2-theta and having one additional peak selected from: 4.8, 7.8, 10.3, 15.0 and 18.4 degrees two theta $\pm$ 0.1 degrees two theta.
- 25 3. A crystalline form of Perampanel characterized by an X-ray powder diffraction pattern having peaks at 9.6, 14.4, 15.5, 16.2, 18.4 and 20.6 degrees 2-theta $\pm$ 0.1 degrees 2-theta
4. A crystalline form of Perampanel according to any of Paragraphs 1, 2 or 3, characterized by an X-ray powder diffraction pattern having peaks at 9.6, 14.4, 15.5, 16.2, 18.4 and 20.6

degrees 2-theta $\pm$ 0.1 degrees 2-theta, and one, two three or four additional peaks at 4.8, 7.8, 10.3 and 15.0 degrees two theta $\pm$ 0.1 degrees two theta.

5. A crystalline form of Perampanel according to any of Paragraphs 1, 2, 3 or 4, characterized by an X-ray powder diffraction pattern having peaks at: 4.8, 7.8, 9.6, 10.3, 14.4, 15.0, 15.5, 16.2, 18.4 and 20.6 degrees 2-theta $\pm$ 0.1 degrees 2-theta.
6. A crystalline form of Perampanel according to any of Paragraphs 1, 2, 3, 4 or 5, characterized by an X-ray powder diffraction pattern as depicted in Figure 1.
7. A crystalline form of Perampanel according to any of Paragraphs 1, 2, 3, 4, 5 or 6, further characterized by having orthorhombic structure, preferably with the largest unit cell dimension $a = 37.85 \text{ \AA}$, obtained by LeBail refinement of the laboratory powder diffraction pattern.
8. A crystalline form of Perampanel according to any of Paragraphs 1, 2, 3, 4, 5, 6 or 7 further characterized by a solid state ^{13}C NMR spectrum having peaks at 127.4, 125.9, 120.8, 114.2 and $107.2 \text{ ppm} \pm 0.2 \text{ ppm}$.
9. A crystalline form of Perampanel according to any of Paragraphs 1, 2, 3, 4, 5, 6 or 7 characterized by solid state ^{13}C NMR spectrum having peaks at: 159.9, 152.3, 151.9, 149.0, 141.2, 140.7, 137.6, 136.9, 134.8, 133.7, 131.0, 129.4, 128.3, 127.4, 126.6, 125.9, 120.8, 117.9, 114.2 and $107.2 \pm 0.2 \text{ ppm}$.
10. A crystalline form of Perampanel according to any of Paragraphs 1, 2, 3, 4, 5, 6 or 7 characterized by solid state ^{13}C NMR spectrum as depicted in Figure 3.
11. A crystalline form of Perampanel according to any of Paragraphs 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, further characterized by one or more of the following:
 - a. a DSC showing a melting peak maximum at about 181 degrees Celsius $\pm$ 3 degrees Celsius;
 - b. a DSC thermogram as depicted in Figure 2;
 - c. Raman spectrum having peaks at 1622, 1157, 279, 266 and $191 \text{ cm}^{-1} \pm 1 \text{ cm}^{-1}$;
 - d. Raman spectrum as depicted in any one of figures 4a or 4b;

- e. FT-IR spectrum having peaks at 1156, 934, 895, 779 and 698 $\text{cm}^{-1} \pm 1 \text{ cm}^{-1}$;
 - f. FT-IR spectrum as depicted in any one of figures 5a or 5b; and
 - g. combinations of a-f.
12. The crystalline form of Perampanel according to any of Paragraphs 1, 2, 3, 4, 5, 6, 7, 8, 9,
5 10, or 11, wherein the crystalline form is an anhydrous form.
13. A pharmaceutical composition comprising a crystalline form according to any of Paragraphs 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.
14. Use of the crystalline form according to any one of Paragraphs 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12, in the manufacture of pharmaceutical compositions and/or formulations.
- 10 15. A pharmaceutical formulation comprising a crystalline form according to any of Paragraphs 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12, or the pharmaceutical composition according to Paragraph 13, and at least one pharmaceutically acceptable excipient.
16. A process for preparing the pharmaceutical formulation according to Paragraph 14, comprising combining a crystalline form according to any of Paragraphs 1, 2, 3, 4, 5, 6, 7,
15 8, 9, 10, 11 or 12, or a pharmaceutical composition according to Paragraph 13, with at least one pharmaceutically acceptable excipient.
17. The crystalline form, according to any of Paragraphs 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12, a pharmaceutical composition according to Paragraph 13, or a pharmaceutical formulation according to Paragraph 15, for use as a medicament.
- 20 18. The crystalline form, according to any of Paragraphs 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12, a pharmaceutical composition according to Paragraph 13, or a pharmaceutical formulation according to Paragraph 15, for use in the treatment of epilepsy and diabetic neuropathy.
19. A method of treating epilepsy and diabetic neuropathy, comprising administering a therapeutically effective amount of a crystalline form according to any of Paragraphs 1, 2,
25 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12, a pharmaceutical composition according to Paragraph 13, or a pharmaceutical formulation according to Paragraph 15, to a subject suffering from epilepsy or diabetic neuropathy, or otherwise in need of the treatment.

20. Use of crystalline form of Perampanel according to any of Paragraphs 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12, in the preparation of another solid state form of Perampanel, or a Perampanel salt or solid state form thereof.
21. A process for preparing Perampanel salt or a solid state form thereof comprising preparing
5 a crystalline form of Perampanel according to any of Paragraphs 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12, and converting it to Perampanel salt.
22. A crystalline form of Perampanel according to any of Paragraphs 1, 2, 3, 4, 5, 6, 7, 8, 9, 10,
11 or 12, the pharmaceutical composition according to Paragraph 13, or the pharmaceutical
10 formulation according to Paragraph 15, for the manufacture of a medicament for treating epilepsy and diabetic neuropathy.

CLAIMS:

1. A crystalline form of Perampanel designated as Form VI, characterized by data selected from one or more of the following:
 - a. orthorhombic structure, with the largest unit cell dimension $a = 37.85 \text{ \AA}$, obtained by LeBail refinement of the laboratory powder diffraction pattern in combination with a PXRD pattern having peaks at 9.6, 14.4, 15.5, 16.2 and 20.6 degrees 2-theta ± 0.1 degrees 2-theta or a PXRD pattern as depicted in Figure 1;
 - b. a solid state ^{13}C NMR spectrum with peaks at 127.4, 125.9, 120.8, 114.2 and 107.2 ppm ± 0.2 ppm;
 - c. a solid state ^{13}C NMR spectrum having the following chemical shift absolute differences from a peak at 149.0 ppm ± 1 ppm of 21.6, 23.1, 28.2, 34.8 and 41.8 ppm ± 0.1 ppm;
 - d. a solid state ^{13}C NMR spectrum having chemical shift difference from a peak at 107.2 ppm ± 1 ppm of 18.7 ppm ± 0.1 ppm;
 - e. a solid state ^{13}C NMR spectrum having chemical shift difference from a peak a peak at 107.2 ppm ± 1 ppm of 13.6 ppm ± 0.1 ppm;
 - f. a solid state ^{13}C NMR spectrum as depicted in Figure 3; and
 - g. combinations of these data.
2. The crystalline Form VI of Perampanel according to claim 1, characterized by orthorhombic structure with the largest unit cell dimension of $a = 37.85 \text{ \AA}$, obtained by LeBail refinement of the laboratory powder diffraction pattern, and an X-ray powder diffraction pattern having peaks at 9.6, 14.4, 15.5, 16.2 and 20.6 degrees 2-theta ± 0.1 degrees 2-theta and also having one, two, three, four or five additional peaks selected from: 4.8, 7.8, 10.3, 15.0 and 18.4 degrees two theta ± 0.1 degrees two theta.
3. The crystalline Form VI of Perampanel according to any one of claim 1 or claim 2, characterized by solid state ^{13}C NMR spectrum having peaks at: 159.9, 152.3, 151.9,

149.0, 141.2, 140.7, 137.6, 136.9, 134.8, 133.7, 131.0, 129.4, 128.3, 127.4, 126.6, 125.9, 120.8, 117.9, 114.2 and 107.2 ± 0.2 ppm.

4. The crystalline Form VI of Perampanel according to any one of claims 1 to 3, further characterized by one or more of the following:
 - a. a DSC showing a melting peak maximum at about 181 degrees Celsius ± 3 degrees Celsius;
 - b. a DSC thermogram as depicted in Fig. 2;
 - c. Raman spectrum having peaks at 1622, 1157, 279, 266 and $191 \text{ cm}^{-1} \pm 1 \text{ cm}^{-1}$;
 - d. Raman spectrum as depicted in any one of figures 4a or 4b;
 - e. FT-IR spectrum having peaks at 1156, 934, 895, 779 and $698 \text{ cm}^{-1} \pm 1 \text{ cm}^{-1}$;
 - f. FT-IR spectrum as depicted in any one of figures 5a or 5b; and
 - g. combinations of these data.
5. The crystalline Form VI of Perampanel according to any one of claims 1 to 4, wherein the crystalline form is an anhydrous form.
6. A pharmaceutical composition comprising a crystalline form according to any one of claims 1 to 5.
7. Use of the crystalline form according to any one of claims 1 to 5 in the manufacture of pharmaceutical compositions and/or formulations.
8. A pharmaceutical formulation comprising a crystalline form according to any one of claims 1 to 5 or the pharmaceutical composition of claim 6, and at least one pharmaceutically acceptable excipient.
9. A process for preparing the pharmaceutical formulation according to claim 8, comprising combining a crystalline form according to any one of claims 1 to 5 or the pharmaceutical composition of claim 6, with at least one pharmaceutically acceptable excipient.
10. The crystalline form, according to any one of claims 1 to 5, the pharmaceutical composition according to claim 6, or the pharmaceutical formulation according to claim 8, for use as a medicament.

11. The crystalline form, according to any one of claims 1 to 5, the pharmaceutical composition according to claim 6, or the pharmaceutical formulation according to claim 8, for use in the treatment of epilepsy and diabetic neuropathy.
12. A method of treating epilepsy and diabetic neuropathy, comprising administering a therapeutically effective amount of a crystalline form according to any one of claims 1 to 5, the pharmaceutical composition according to claim 6, or the pharmaceutical formulation according to claim 8, to a subject suffering from epilepsy or diabetic neuropathy, or otherwise in need of the treatment.
13. Use of crystalline Form VI of Perampanel according to any one of claims 1 to 5 in the preparation of another solid state form of Perampanel, or a Perampanel salt or solid state form thereof.
14. A process for preparing Perampanel salt or a solid state form thereof comprising preparing crystalline form VI of Perampanel, and converting it to Perampanel salt.
15. The crystalline form, according to any one of claims 1 to 5, the pharmaceutical composition according to claim 6, or the pharmaceutical formulation according to claim 8, for the manufacture of a medicament for treating epilepsy and diabetic neuropathy.

Fig. 1
PXRD pattern of Perampanel Form VI

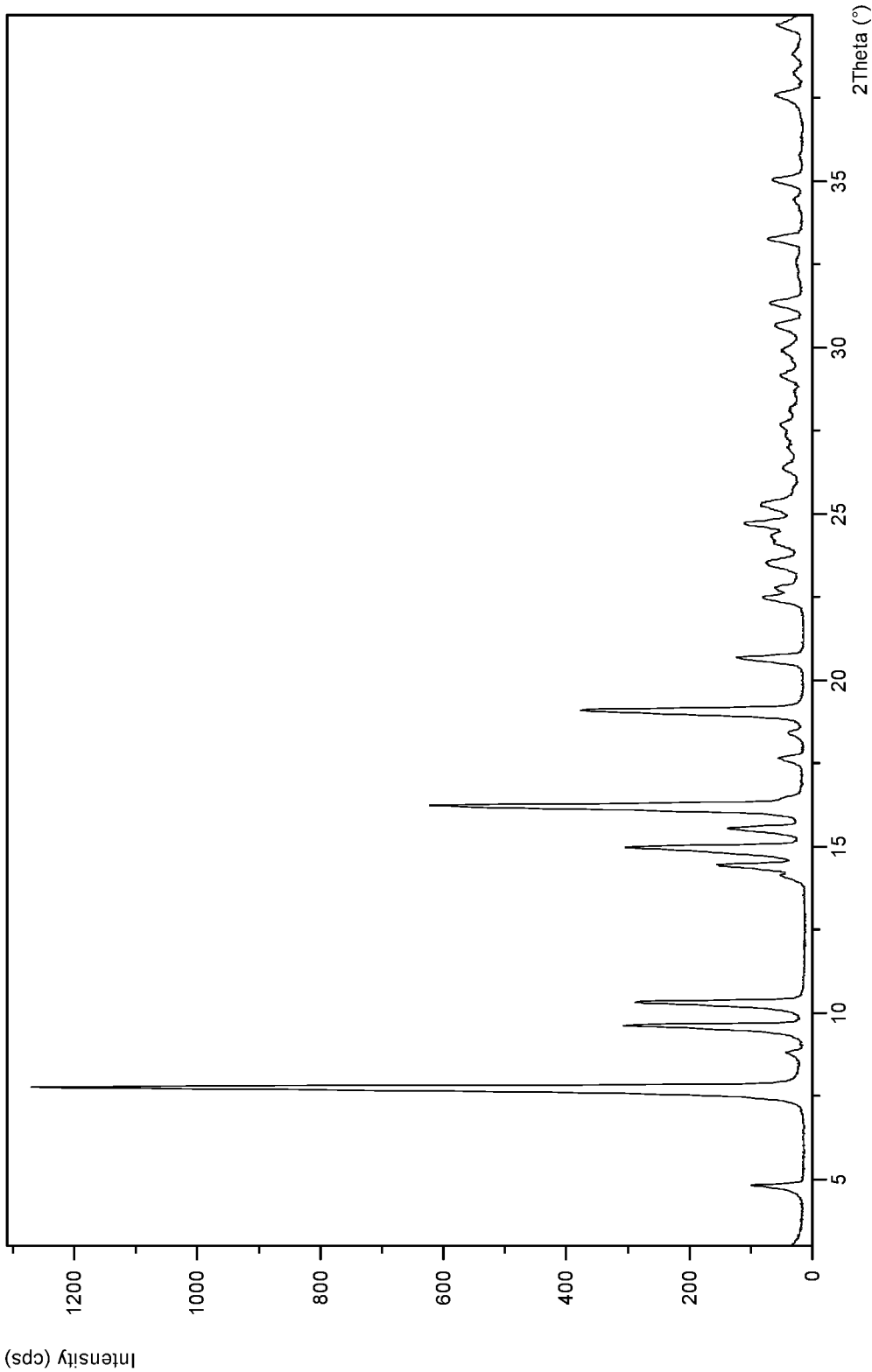


Fig. 2
DSC thermogram of Perampanel Form VI

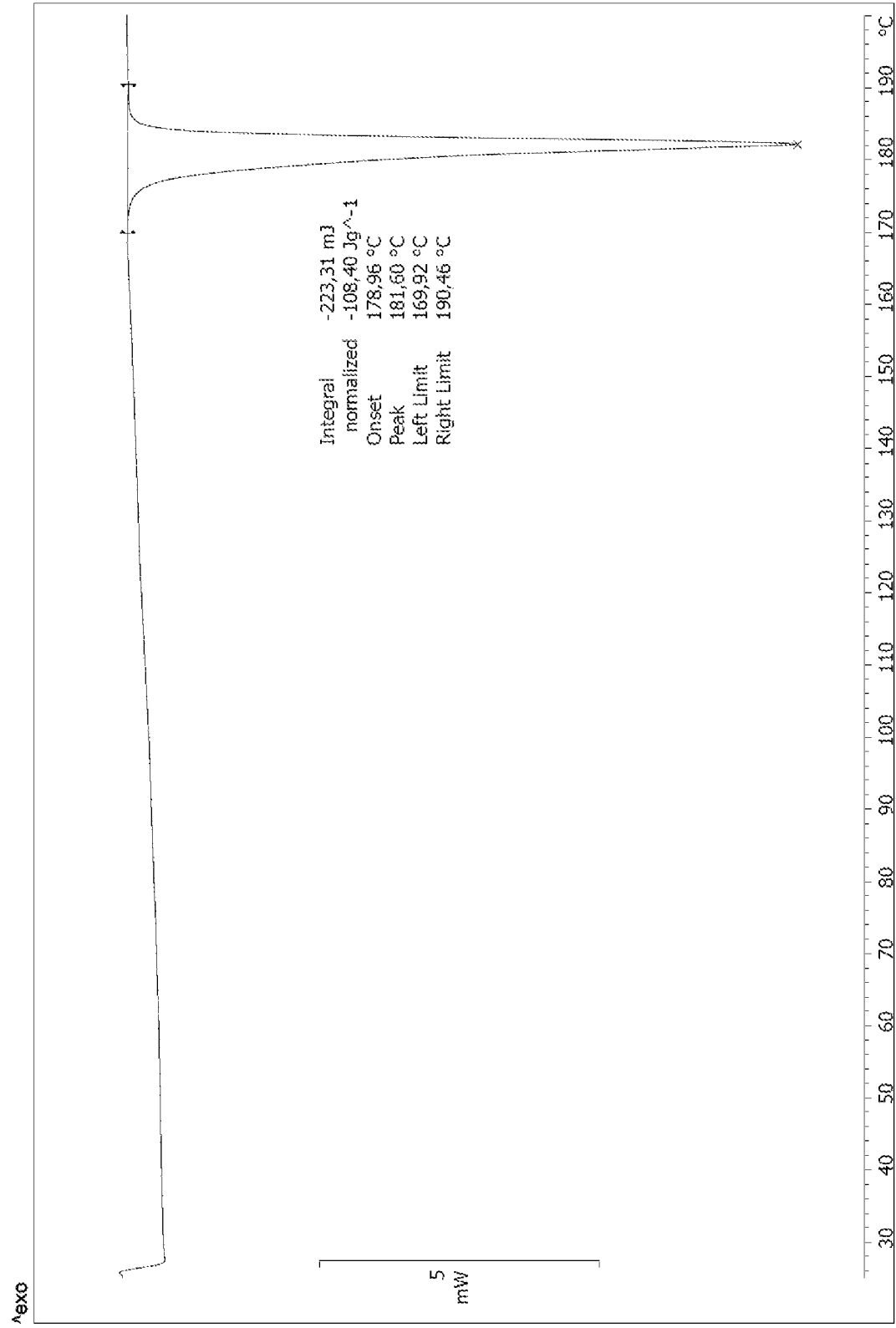


Fig. 3

A solid state ^{13}C NMR spectrum of Perampanel Form VI.

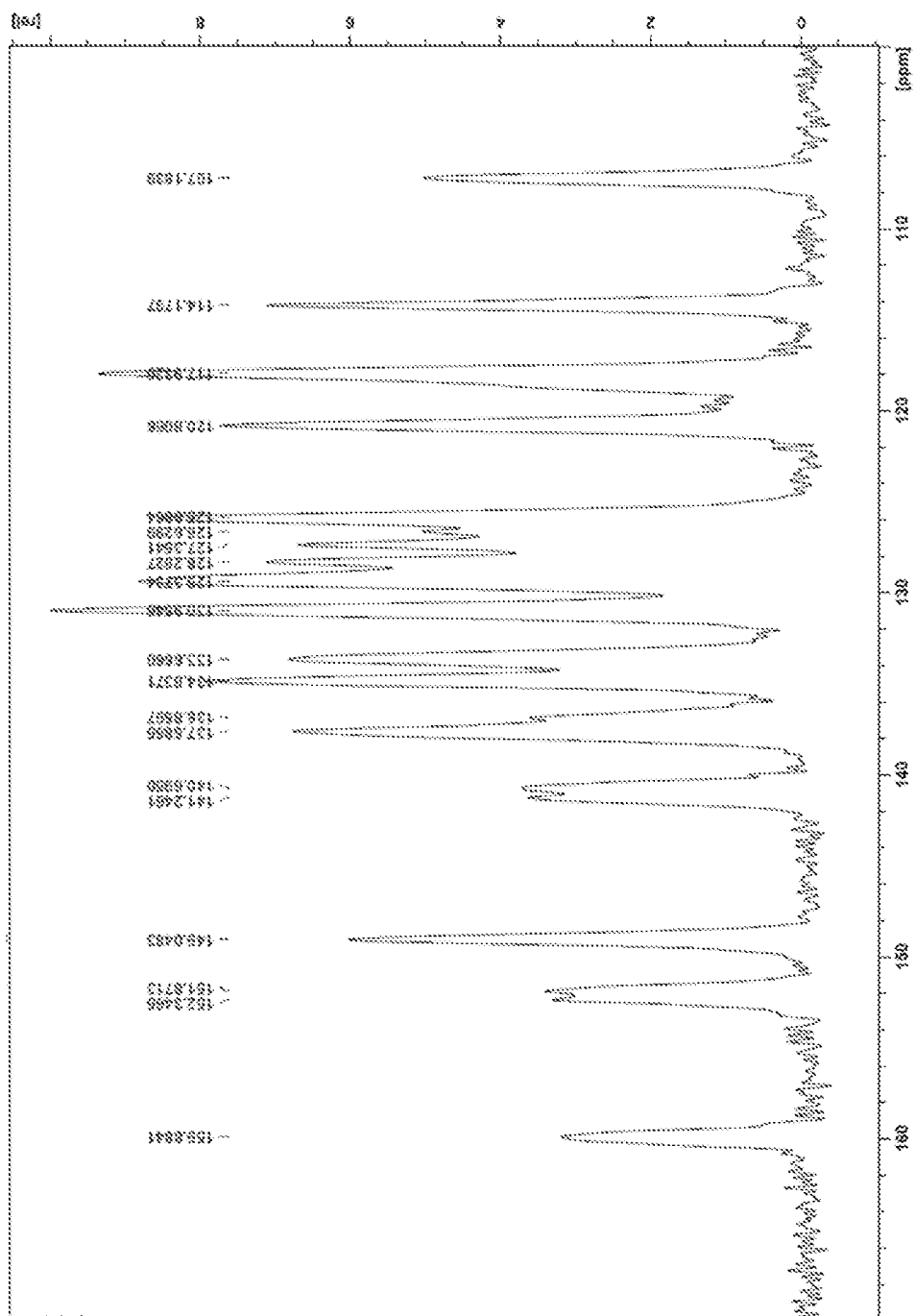


Fig. 4a

A Raman spectrum of Perampanel Form VI, range: 4000-150 cm^{-1} .

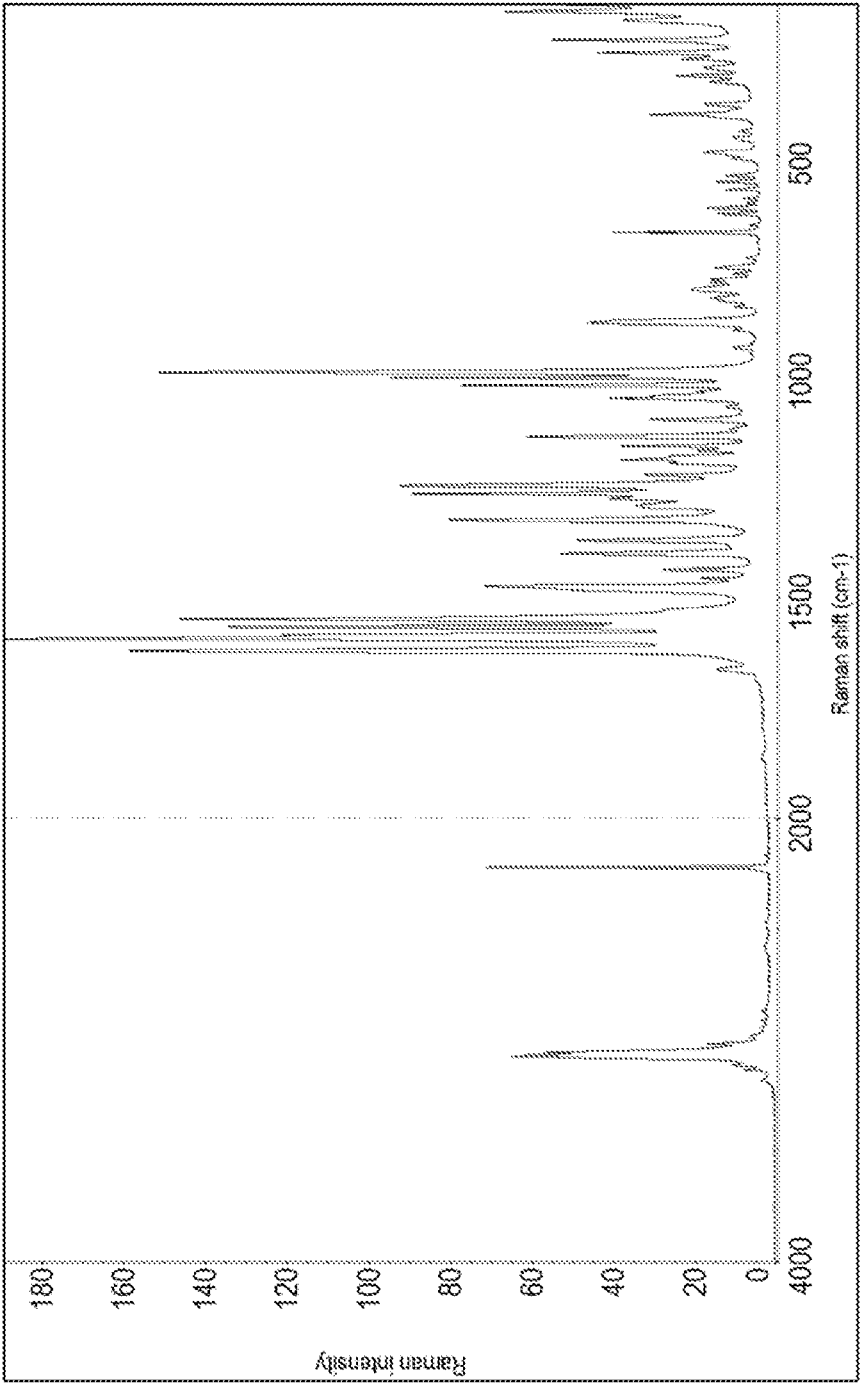
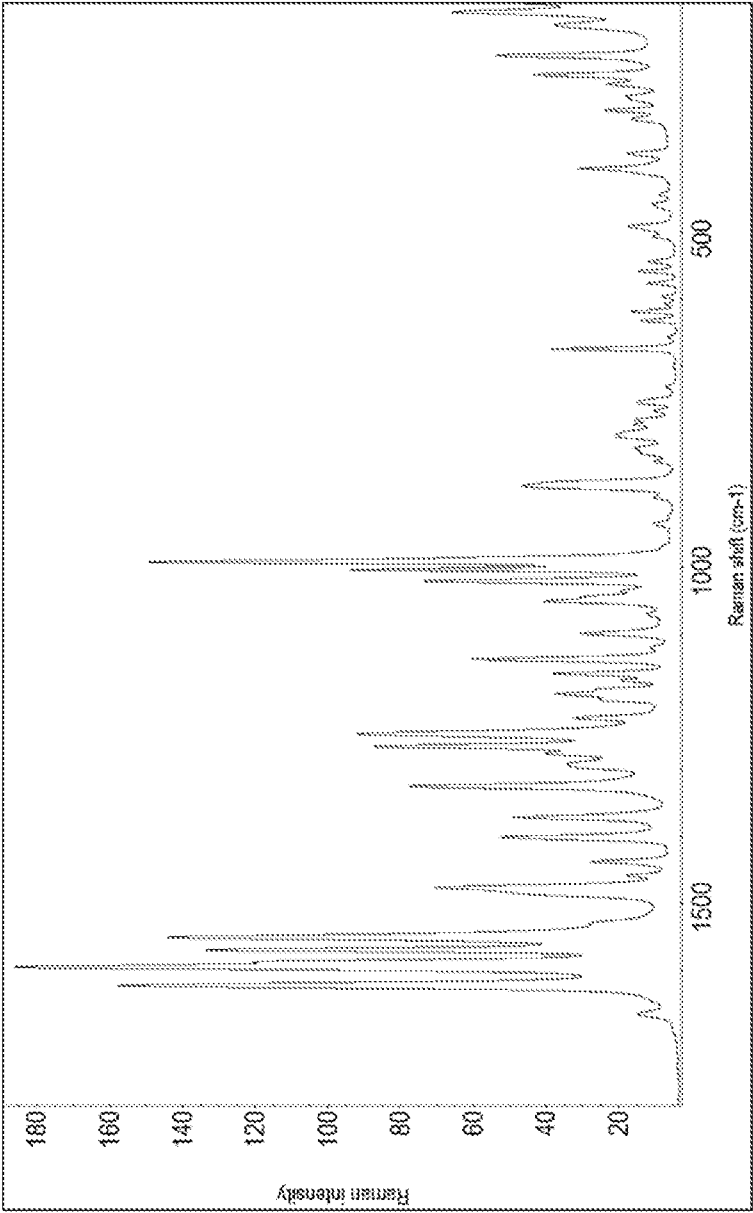


Fig. 4b

A Raman spectrum of Perampanel Form VI, range: 1800 to 160 cm^{-1} .



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Fig. 5a

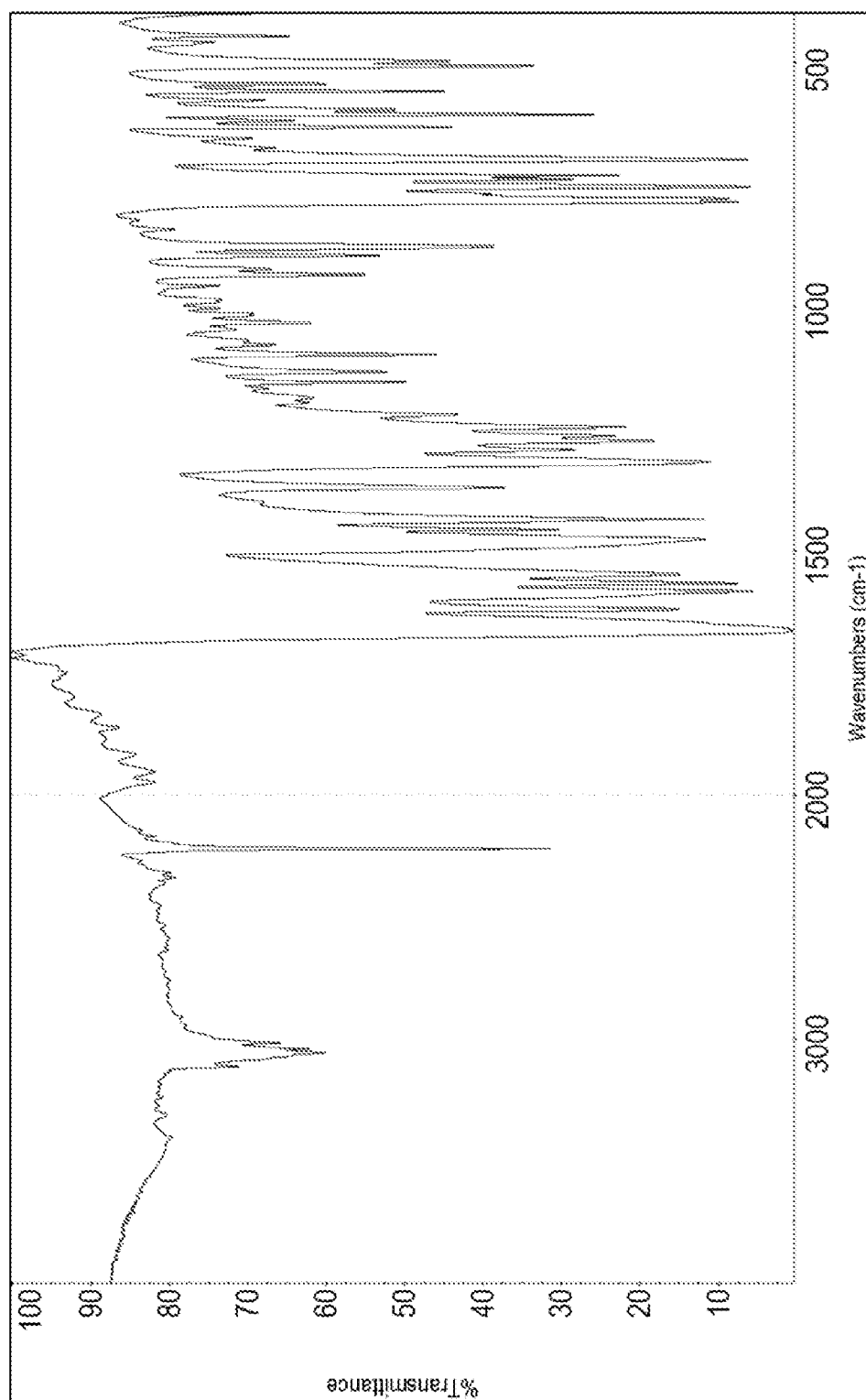
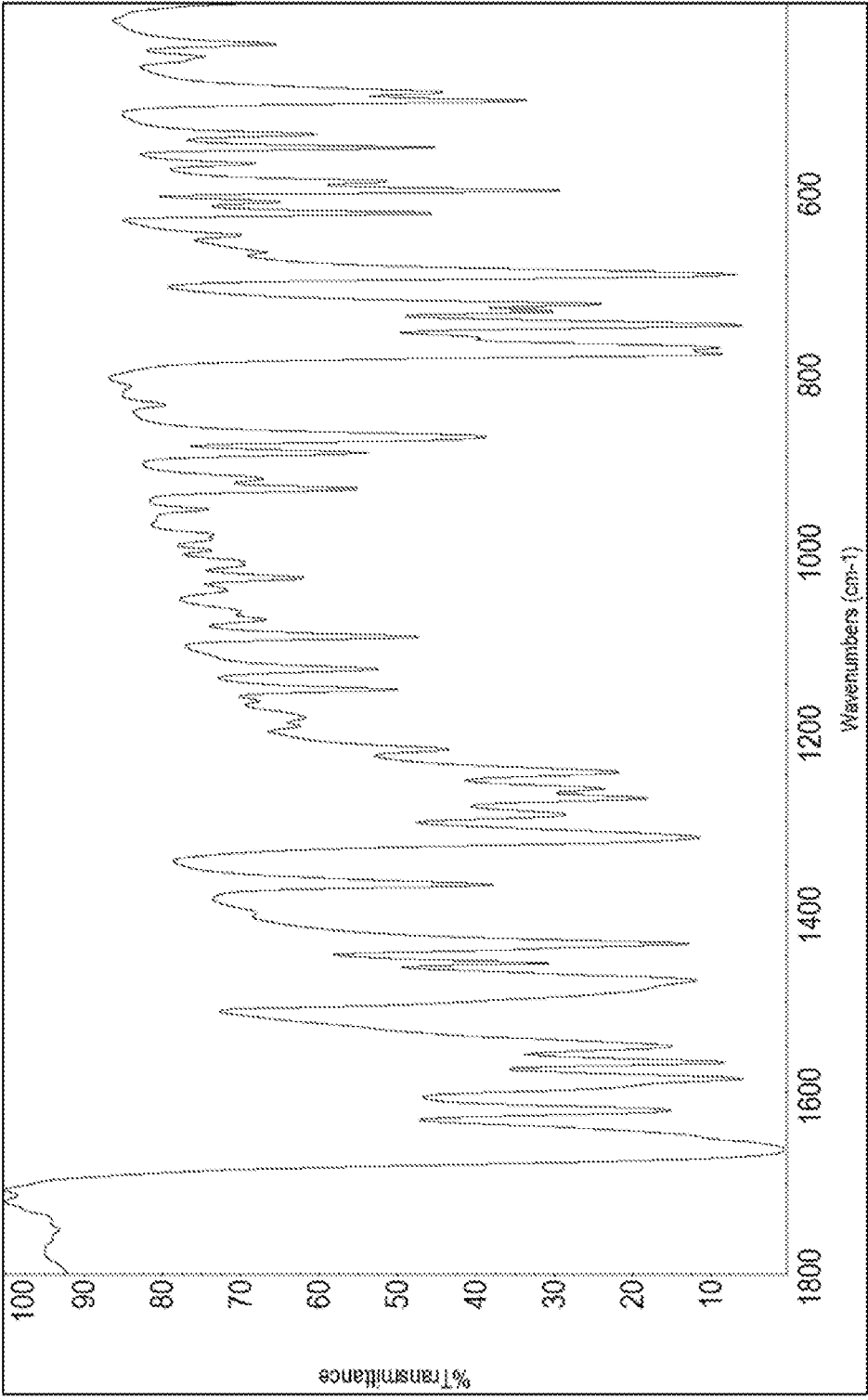
An FT-IR spectrum of Perampanel form VI, range: 4000 to 400 cm^{-1} 

Fig. 5b
An FT-IR spectrum of Perampanel form VI, range: 1800 to 400 cm^{-1}



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/028628

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/64 A61K31/4412 A61P25/08
ADD.

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)
C07D A61K

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 practicable, search terms used)

EPO-Internal , WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	US 2009/088574 AI (URAWA YOSHIO [JP] ET AL) 2 April 2009 (2009-04-02) abstract figures 1-4 claims 1-3 -----	1-15
X	CN 104 292 153 A (CRYSTAL PHARMATECH CO LTD) 21 January 2015 (2015-01-21) abstract page 6 - page 8; tables 1-3 figures 1-3 claims 1,2 ----- -/- .	1-15



Further documents are listed in the continuation of Box C.



See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search

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Date of mailing of the international search report

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Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/028628

C(Continuation). 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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Information on patent family members

International application No

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