



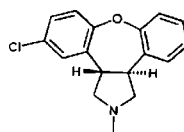
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(54) **Title:** NEW CRYSTAL FORMS OF THE SALT OF TRANS-5-CHLORO-2-METHYL-2,3,3A,12b-TETRAHYDRO-1H-DIBENZO[2,3:6,7]OXEPINO[4,5-c]PYRROLE WITH MALEIC ACID

*trans-(I)*

(57) **Abstract:** The present invention relates to two new crystal forms of the salt of trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenzo[2,3:6,7]oxepino[4,5-c]pyrrole with maleic acid, processes for preparing thereof and compositions comprising thereof. These new crystal forms of the salt of trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenzo[2,3:6,7]oxepino[4,5-c]pyrrole with maleic acid are stable under micronization and show an improved water solubility when compared to other asenapine maleate crystalline forms described in the prior art, such as the orthorhombic form (form L) and the monoclinic form (form H).

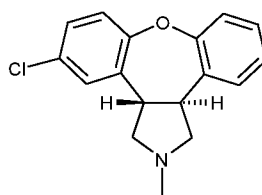
NEW CRYSTAL FORMS OF THE SALT OF *TRANS*-5-CHLORO-2-METHYL-2,3,3a,12b-TETRAHYDRO-1*H*-DIBENZO[2,3:6,7]OXEPINO[4,5-*c*]PYRROLE WITH MALEIC ACID

- 5 This invention relates to new crystal forms of the salt of *trans*-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*c*]pyrrole with maleic acid.

Background of the invention

- 10 Asenapine (compound *trans*-(I)) is the international commonly accepted non-proprietary name (INN) for *trans*-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*c*]pyrrole, and has an empirical formula of C₁₇H₁₆ClNO and a molecular weight of 285.77. The molecule has two chiral centers but the name asenapine is used to designate the racemic mixture of the *trans* isomer.

15



trans-(I)

- The maleic acid salt (1:1) of asenapine (designated in this specification as asenapine maleate) is known to be therapeutically useful and is commercially marketed for the treatment of schizophrenia and acute manic or mixed episodes associated with bipolar 1 disorder. Asenapine maleate exhibits high affinity and potency for blocking dopamine, serotonin, α -adrenergic and histamine receptors, and no appreciable activity at muscarinic and cholinergic receptors. The rank order of receptor affinity for asenapine maleate reveals a unique human receptor binding signature, characterized by strong serotonergic properties, when compared to other antipsychotic drugs. In the United States, asenapine maleate is marketed under the name SaphrisTM. In Europe, asenapine maleate is marketed under the name SycrestTM.
- 20
- 25
- 30 Asenapine maleate was first disclosed in U.S. Patent No. 4,145,434 ("the '434 patent"). Example IV of the '434 patent described asenapine maleate to have a melting point of 141 °C. However, no specific crystallization conditions were reported.

It is known that solid asenapine maleate shows polymorphism. Polymorphism is the existence of different crystal forms of the same chemical compound. The different crystal polymorphs of a molecule may differ (and frequently do) in their chemical and physical properties, such as their melting point, solubility, and crystal habit. These properties in turn may influence the stability, bioavailability and flow behaviour of the compound. So, companies face a larger number of compounds that are either poorly soluble, difficult to crystallize or problematic with respect to desired physical chemical properties hindering successful drug development.

Regulatory agencies worldwide require that, as part of any significant filing, a company has to demonstrate that it has made a reasonable effort to identify the polymorphs of their drug substance and has checked for polymorph inter-conversions. Due to the unpredictable behaviour of polymorphs and their respective differences in physicochemical properties, companies also have to demonstrate consistency in manufacturing between batches of the same product. Proper understanding of the polymorph landscape and nature of the polymorphs will contribute to manufacturing consistency.

High polymorphic purity is therefore often required and the presence of other polymorphs can cause processing problems. Hence understanding polymorphism is highly important to many industries that work with crystalline particles such as the pharmaceutical and chemical industries.

Arzneim.-Forsch. Drug Res. 1990, 40, 536 described the physicochemical properties of a monoclinic crystalline form of asenapine maleate having a melting point in the range of 141 to 145 °C (form H) which comprised crystalline particles over 100 µm in size. Aqueous solubility of this monoclinic form is described to be 3 g/L (at 21 °C).

The marketed product (SaphrisTM, SycrestTM) is currently available in the form of tablets for sublingual administration. Since asenapine maleate is administered as sublingual tablets, its particle size and solubility are of outstanding importance and physical forms having an increased in vitro dissolution rate, but being stable over the time and easy to handle, would be desirable.

European Patent EP 1 710 245 A1 describes that asenapine maleate with a small particle size is desired, preferably having a d_{95} of 100 μm or less, more preferably 50 μm or less, and most preferably 30 μm or less. This patent application also describes that a micronization step is applied to reduce the particle size of the crystals, but that it is difficult to obtain a drug substance with high polymorph purity by micronization of the monoclinic form (form H) of asenapine maleate, since the outcome of the micronization process is very unpredictable when crystals of the monoclinic form of asenapine maleate are subjected to such a process. Particularly, analyses of the crystals following micronization of the monoclinic form revealed the presence of a second polymorph (orthorhombic form L) in addition to the known monoclinic form in the starting material. This second polymorph (form L) has a melting point in the range of 138 to 142 $^{\circ}\text{C}$. Either the monoclinic form, or the orthorhombic form, or a mixture of both polymorphs was obtained after micronization starting from the monoclinic form. It is known that the difference in crystal structure can lead to differences in physicochemical parameters such as stability, rate of dissolution, bioavailability, and the like. Hence, a mixture of polymorphic forms of a compound frequently has physicochemical parameters which differ from those of the pure forms that form the mixture. This is all the more important since in practice it is difficult to make each batch of a mixture of polymorphs of a compound identical in respect of its composition. As a consequence of these differences, it is often undesirable to incorporate a mixture of polymorphs of a compound in medicaments which typically demand that only one of the polymorphs is used.

European Patent EP 1 710 245 A1 also discloses that the orthorhombic form of asenapine maleate (form L) is obtainable with a smaller particle size (based on d_{95}) than the monoclinic form (form H) by means of crystallization techniques. Furthermore, it is said that micronization of the orthorhombic form of asenapine maleate reproducibly results in microcrystalline asenapine maleate of the orthorhombic form.

Therefore, the teaching from EP 1 710 245 A1 is that a suitable and stable composition of crystalline asenapine maleate for sublingual or buccal administration can only be obtained from the orthorhombic form of asenapine maleate (form L) which shows high polymorphic purity after micronization.

Moreover, European Patent EP 1 710 245 A1 describes the preparation of the monoclinic form of asenapine maleate (form H) by crystallization from ethanolic solutions and the preparation of the orthorhombic form of asenapine maleate (form L) by crystallization from 9:1 v/v ethanol:water solutions. Additionally, this patent and
5 International patent application number WO 2008/003460 A1 describe the preparation of the orthorhombic form of asenapine maleate (form L) by seeding a solution of asenapine maleate in a 3:1 v/v acetone/heptane mixture with the desired orthorhombic form, followed by the addition of more heptane up to a solvent ratio of 1:1.2 v/v acetone/heptane.

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A teaching from EP 1 710 245 A1 is that asenapine maleate form H is obtained by crystallization from ethanol and that asenapine maleate form L is obtained by crystallization from mixtures of ethanol/water.

15 Patent application WO 2011/159903 A2 relates to a monoclinic form of asenapine maleate, which is stable to micronization. This asenapine maleate monoclinic form apparently matches with previously described monoclinic form H. This patent application discloses the preparation of this asenapine maleate monoclinic form by crystallization from 1-propanol or 2-propanol, optionally seeding with asenapine
20 maleate monoclinic form. This patent application also describes the micronization of this asenapine maleate monoclinic form using a Midas Micronizer 50, using nitrogen gas with pressures of 4-6 kg/cm². This micronization conditions are very similar to those reported in EP 1 710 245 A1: Chrispro MC200 stainless steel JetMill, using nitrogen as the gas carrier and a micronization pressure of 7 bars.

25

The asenapine maleate used herein as starting material to obtain asenapine maleate form M and/or form T as disclosed herein can be obtained by any of the processes described in the prior art.

30 *Research Disclosure* 523012 discloses solvent / anti-solvent recrystallization processes for the preparation of monoclinic asenapine maleate (form H). The mixtures of solvents used for the preparation of monoclinic asenapine maleate are: acetone:methyl *tert*-butyl ether (MTBE) (1:10 v/v, rt, 0°C), methanol:diisopropyl ether (1:10 v/v, rt, -78°C), acetone:diisopropyl ether (1:5 v/v, rt), acetone:n-heptane (1:10 v/v, rt and fast addition
35 or at reflux), ethanol:n-heptane (1:5 v/v, reflux), ethyl acetate:MTBE (12:25 v/v, during

cooling after reflux), 2-propanol/n-heptane (1:10 v/v, 76°C), 1-propanol/n-heptane (1:40 v/v, rt) and nitromethane:diethyl ether (1:20 v/v, rt). It also discloses the preparation of monoclinic asenapine maleate (form H) by recrystallization from ethanol, chloroform with evaporation at air, 1-propanol, 2-propanol, 1-butanol, 2-butanol, chlorobenzene, ethanol with cooling to -20 °C and toluene (around 57°C). Moreover, it also discloses that mixtures of asenapine maleate forms H and L are obtained by recrystallization from ethyl acetate and toluene, by recrystallization with evaporation at air from acetonitrile, methanol and acetone, and with the following solvent / anti-solvent mixtures: acetone:n-heptane (1:10 v/v, rt and slow addition), 1,4-dioxane/diisopropyl ether (1:2 v/v, rt) and 1-butanol:n-heptane (1:40 v/v, rt). It also states that typically asenapine maleate form H is obtained by recrystallization from alcoholic solvents.

IP.com 208816D published on July 19th, 2011 discloses form A of asenapine maleate, which is obtained by crystallization from acetone/diethyl ether or from acetone/methyl *tert*-butyl ether (MTBE) at -5 to -10 °C. This form A apparently matches with the asenapine maleate form M reported herein. It also discloses form B of asenapine maleate, which is obtained by crystallization from acetone/diethyl ether at -20 to -30 °C. Finally, it also discloses form C of asenapine maleate, which is obtained by crystallization from acetone/diethyl ether, acetone/MTBE and isopropanol at temperatures above 20 °C.

IP.com 210074D published on August 25th, 2011 discloses form S of asenapine maleate, which is substantially equivalent to form C as disclosed in *IP.com* 208816D, and which is obtained by treating a solution of asenapine base in isopropanol with maleic acid at 50 °C and cooling to room temperature.

IP.com 214225D published on January 18th 2012 discloses forms I, II, III and IV of asenapine maleate. Form IV is substantially equivalent to form A as disclosed in *IP.com* 208816D and consequently matches with the asenapine maleate form M reported herein. Forms I, II and IV are obtained by mixing an ethanolic solution of asenapine maleate with MTBE using different procedures for the mixing step, solvent ratios, temperatures and stirring times. Form III was obtained by crystallization from an ethanol/water mixture.

A well known problem associated with the micronization of crystalline products having more than one polymorphic form is that the high energy input associated with the micronization process for the reduction of particle size can promote the polymorphic transition from a less stable form to a more stable one. Generally, the most stable polymorph is known to have the lowest solubility value.

The orthorhombic form of asenapine maleate (form L) shows reduced water solubility when compared to the monoclinic form (form H), which is detrimental for its use in pharmaceutical formulations that are required to have high water solubility such as tablets for sublingual administration. Therefore, there is a need for new polymorphic forms of asenapine maleate that do not transform to the less soluble orthorhombic form (form L) during the micronization process, and that show an improved water solubility when compared to other asenapine maleate crystalline forms described in the prior art, such as the orthorhombic form (form L) and the monoclinic form (form H).

15 **Detailed description of the Invention**

In aspects, the present invention provides crystalline polymorphic forms of asenapine maleate, which are designated herein as "form M" and "form T".

20 Applicants have now identified new crystalline polymorphic forms of asenapine maleate (form M and form T), which can be micronized to a suitable particle size without a substantial conversion into the orthorhombic form (form L) and which show an improved water solubility when compared to the other polymorphic forms described in the prior art, for example the orthorhombic form (form L) and the monoclinic form (form H). Moreover, crystalline asenapine maleate form M and form T show excellent properties in term of stability, bioavailability, solubility and flowability, which contributes to a successful drug development.

30 In addition, the inventors of the present invention have found that these crystalline polymorphic forms M and form T are suitable to be formulated, for example in the form of tablets for sublingual or buccal administration. Moreover, the inventors of the present invention have found that these crystalline polymorphic form M and/or form T are surprisingly stable, for example in terms of chemical stability as well as in terms of polymorphic stability both as isolated products and when incorporated into

compositions, for example in the form of tablets for sublingual or buccal administration, and additionally show a suitable dispersion and dissolution profile.

The first aspect of the invention provides crystalline asenapine maleate form M.

- 5 Crystalline asenapine maleate form M as herein disclosed may be characterized using XRD techniques. Preferably the XRPD pattern of the crystalline asenapine maleate form M as herein disclosed comprises at least the following peaks (2-theta, 2θ) at 5.5, 12.6 and 19.9° (± 0.2 degrees), more preferably at 5.5, 12.6, 19.1, 19.9 and 25.2° (± 0.2 degrees), and even more preferably at 5.5, 9.9, 11.0, 12.6, 13.7, 14.6, 16.7, 17.3, 18.5, 10 19.1, 19.9, 20.8, 21.6, 22.0, 23.4, 24.2, 25.2, 25.9, 26.7, 27.7, 28.7, 29.3, 29.8, 30.6, 33.4, 34.4, 34.9, 38.8, 39.2 and 40.2° (± 0.2 degrees). Figure 1 shows a X-Ray Powder Diffraction pattern of crystalline asenapine maleate form M as herein disclosed.

- In additional embodiment of the present invention, it is provided asenapine maleate form M, which contains 20% (w/w) or less of another crystalline form, preferably 10% (w/w) or less of another crystalline form, more preferably 5% (w/w) or less of another crystalline form, and even more preferably 1% (w/w) or less of another crystalline form. Namely, the present invention provides asenapine maleate wherein at least 80% (w/w) of the asenapine maleate is crystalline asenapine maleate form M, preferably at least 15 90% (w/w) of the asenapine maleate is crystalline asenapine maleate form M, more preferably at least 95% (w/w) of the asenapine maleate is crystalline asenapine maleate form M. Even more preferably the asenapine maleate as herein disclosed consists essentially of crystalline asenapine maleate form M, namely, the asenapine maleate contains more than 99% (w/w) of the crystalline asenapine maleate form M, 20 99.5% (w/w) of the crystalline asenapine maleate form M, more preferably the asenapine maleate contains more than 99.9% (w/w) of the crystalline asenapine maleate form M. 25 99.9% (w/w) of the crystalline asenapine maleate form M.

- In additional embodiment, the present invention provides asenapine maleate form M wherein less than 20% (w/w) of the asenapine maleate is asenapine maleate 30 amorphous form, preferably less than 10% (w/w) of the asenapine maleate is asenapine maleate amorphous form, more preferably less than 5% (w/w) of the asenapine maleate is asenapine maleate amorphous form, and even more preferably less than 1% (w/w) of the asenapine maleate is asenapine maleate amorphous form.

In a further embodiment, the present invention further provides asenapine maleate form M that is microcrystalline.

5 In the present specification asenapine maleate form M is considered to be microcrystalline when it has a particle size distribution characterized by a d_{90} of 100 μm or less, preferably a d_{90} of 50 μm or less, even more preferably a d_{90} of 30 μm or less. The notation d_x [also written as $d(v, 0.X)$] means that X% of the particles have a diameter less than a specified diameter d . Thus a d_{90} [or $D(v, 0.9)$] of 100 μm means that 90% of the particles have a diameter less than 100 μm .

10

Yet another aspect of the present invention relates to a process for the preparation of crystalline asenapine maleate form M as herein disclosed. In a first embodiment, the process comprises crystallization of asenapine maleate from a solvent or mixture of solvents and seeding with crystalline asenapine maleate form M.

15

The term "seeding with crystalline asenapine maleate form M" when used hereinafter refers to the addition of crystalline asenapine maleate form M to facilitate obtaining crystalline asenapine maleate form M.

20 Another embodiment of the present invention relates to a process for preparing crystalline asenapine maleate form M comprising at least the following steps:

i) dissolving asenapine maleate in a solvent or a mixture of solvents at a temperature between 5°C and 80°C, more preferably between 30°C and 60°C, even more preferably
25 between 40°C and 56°C;

ii) optionally filtering the solution prepared in step (i);

iii) combining the solution prepared in step (i) or in step (ii) with an antisolvent while maintaining the temperature between 40°C and 100°C;

iv) cooling the mixture prepared in step (iii) to a temperature between -20°C and 39°C,
30 preferably between -10°C and 25°C,

wherein the solvent or the mixture of solvents comprises a ketone, preferably acetone, methyl ethyl ketone or methyl isobutyl ketone, and the antisolvent comprises an alkane or a mixture of alkanes such as pentane, hexane, cyclohexane, methylcyclohexane,
35 heptane or mixtures thereof. It is noted that the temperatures within the above ranges

need to be selected taking into consideration the specific and/or antisolvents employed so that it is avoided to work at temperatures above the boiling points of these solvents and/or antisolvents.

- 5 In a preferred embodiment the solvent or the mixture of solvents is selected from the group consisting of ketones, preferably acetone, methyl ethyl ketone or methyl isobutyl ketone and mixtures thereof, and the antisolvent is selected from the group consisting of alkanes such as pentane, hexane, cyclohexane, methylcyclohexane, heptane and mixtures thereof.

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In a preferred embodiment the above mentioned process is conducted either without any seeding step or seeding at any time after step (ii) with crystalline asenapine maleate form M.

- 15 The term “combining the solution prepared in step (i) or in step (ii) with an antisolvent” as used herein comprises the addition of the solution prepared in step (i) or in step (ii) over the antisolvent, or the addition of the antisolvent over the solution prepared in step (i) or in step (ii), or the simultaneous addition of the solution prepared in step (i) or in step (ii) and the antisolvent into a receiving vessel.

20

Preferably, the mixtures of solvent or mixture of solvents and antisolvent have a solvent or mixture of solvents/antisolvent volume/volume ratio from 3:1 to 1:5, more preferably from 2:1 to 1:2, even more preferably from 1.2:1 to 1:1.2.

- 25 Crystalline asenapine maleate form M as herein disclosed is preferably obtained by a process which comprises at least the following steps:

- i) dissolving asenapine maleate in acetone at a temperature between 30°C and 56°C;
ii) optionally filtering the solution prepared in step (i);
30 iii) combining the solution prepared in step (i) or in step (ii) with hexane, heptane or mixtures thereof, while maintaining the temperature between 40°C and 98°C;
iv) cooling the mixture prepared in step (iii) to a temperature between -20°C and 39°C, preferably between -10°C and 25°C.

In a preferred embodiment the above mentioned process is conducted either without any seeding step or seeding at any time after step (ii) with crystalline asenapine maleate form M.

- 5 In another preferred embodiment of the present invention asenapine maleate form M is obtained by a process which comprises at least the following steps:

- i) dissolving asenapine maleate in acetone at a temperature between 30°C and 56°C;
- ii) optionally filtering the solution prepared in step (i);
- 10 iii) combining the solution prepared in step (i) or in step (ii) with hexane while maintaining the mixture between 40°C and 60°C;
- iv) cooling the mixture prepared in step (iii) to a temperature between -20°C and 39°C, preferably between -10°C and 25°C.

- 15 In a preferred embodiment the above mentioned process is conducted either without any seeding step or seeding at any time after step (ii) with crystalline asenapine maleate form M.

- 20 Preferably, the mixtures of acetone and hexane used for the preparation of asenapine maleate form M as herein disclosed have an acetone/hexane volume/volume ratio from 3:1 to 1:5, more preferably from 2:1 to 1:2, even more preferably from 1.2:1 to 1:1.2.

Preferably, hexane is added over the solution of asenapine maleate in acetone at a temperature between 40°C and 60°C.

25

In another preferred embodiment of the present invention asenapine maleate form M is obtained by a process which comprises at least the following steps:

- i) dissolving asenapine maleate in acetone at a temperature between 30°C and 56°C;
- 30 ii) optionally filtering the solution prepared in step (i);
- iii) combining the solution prepared in step (i) or in step (ii) with heptane while maintaining the temperature between 40°C and 98°C;
- iv) cooling the mixture prepared in step (iii) to a temperature between -20°C and 39°C, preferably between -10°C and 25°C.

35

In a preferred embodiment the above mentioned process is conducted either without any seeding step or seeding at any time after step (ii) with crystalline asenapine maleate form M.

- 5 Preferably, the mixtures of acetone and heptane used for the preparation of asenapine maleate form M as herein disclosed have an acetone/heptane volume/volume ratio from 3:1 to 1:5, more preferably from 2:1 to 1:2, even more preferably from 1.2:1 to 1:1.2.
- 10 Preferably, heptane is added over the solution of asenapine maleate in acetone at a temperature between 40°C and 98°C.

In another aspect of the present invention crystalline asenapine maleate form M is obtained by a process which comprises suspending asenapine maleate in a solvent or
15 mixture of solvents wherein asenapine maleate remains at least partially undissolved and seeding with crystalline asenapine maleate form M.

The solvent or mixture of solvents in which asenapine maleate is suspended comprises C1-C4 alkyl alcohols such as methanol, ethanol, propanol and butanol, more preferably
20 isopropanol and still more preferably the solvent is isopropanol alone.

In a preferred embodiment, the crystalline asenapine maleate form M obtained according to the precesses disclosed herein is preferably isolated by filtration.

25 The asenapine maleate form M that is microcrystalline as herein disclosed can be obtained by any conventional mechanical process of reducing the size of particles of asenapine maleate form M. Non-limiting examples of mechanical processes of reducing the size of particles of asenapine maleate form M are cutting, chipping, micronizing, milling, crushing, grinding and triturating.

30

Typically by carrying out milling comprises air-jet milling or pin milling.

Micronizing and/or air-jet milling can be preferably carried out in any commercially available micronizer and/or mill working at a gas pressure from 1 bar to 15 bar.

35 Preferably gas pressure comprises air pressure or nitrogen pressure.

Pin milling can be preferably carried out in any commercially available pin mill working from 3000 rpm to 14000 rpm.

5 Alternatively the asenapine maleate form M that is microcrystalline as herein disclosed can also be directly obtained by means of the crystallization and/or slurring processes as herein disclosed without the need of including an additional step of reducing the particle size of the asenapine maleate form M.

10 Particle size of the microcrystalline asenapine maleate form M as herein disclosed is determined by laser diffraction using a Malvern Mastersizer instrument as explained in the experimental section.

A further aspect of the present invention provides pharmaceutical compositions
15 comprising the crystalline asenapine maleate form M, alone or in combination with at least one additional polymorphic and/or amorphous form of asenapine maleate, and at least one pharmaceutically acceptable carrier.

The pharmaceutical compositions as herein disclosed may contain from 0.005 mg to
20 500 mg of crystalline asenapine maleate form M, preferably from 1 mg to 250 mg of crystalline asenapine maleate form M, more preferably the pharmaceutical compositions as herein disclosed contain from 3 mg to 150 mg of crystalline asenapine maleate form M.

25 The invention further relates to the use of crystalline asenapine maleate form M for the manufacture of a sublingual or buccal pharmaceutical composition for treating mental disorders such as psychosis, schizophrenia and bipolar disorders.

A further aspect of the invention provides new crystalline asenapine maleate form T.
30

Crystalline asenapine maleate form T as herein disclosed may be characterized using X-Ray diffraction (XRD) techniques. Preferably the XRPD pattern of the crystalline asenapine maleate form T as herein disclosed comprises at least the following peaks (2-theta, 2θ) at 7.6, 10.4 and 19.1° (± 0.2 degrees), more preferably at 7.6, 9.5, 10.4,
35 19.1, 19.5 and 20.0° (± 0.2 degrees), and even more preferably at 7.6, 8.3, 9.5, 10.4,

11.2, 12.6, 13.3, 13.9, 15.7, 16.3, 16.7, 17.1, 17.4, 17.8, 18.6, 19.1, 19.5, 20.0, 20.9, 21.7, 22.5, 22.9, 23.5, 24.4, 24.9, 25.3, 26.7, 28.0, 28.3, 29.1, 29.6 and 31.9° (± 0.2 degrees). Figure 2 shows a X-Ray Powder Diffraction pattern of crystalline asenapine maleate form T as herein disclosed.

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In additional embodiment of the present invention, it is provided asenapine maleate form T, which contains 20% (w/w) or less of another crystalline form, preferably 10% (w/w) or less of another crystalline form, more preferably 5% (w/w) or less of another crystalline form, and even more preferably 1% (w/w) or less of another crystalline form.

10 Namely, the present invention provides asenapine maleate wherein at least 80% (w/w) of the asenapine maleate is crystalline asenapine maleate form T, preferably at least 90% (w/w) of the asenapine maleate is crystalline asenapine maleate form T, more preferably at least 95% (w/w) of the asenapine maleate is crystalline asenapine maleate form T. Even more preferably the asenapine maleate as herein disclosed
15 consists essentially of crystalline asenapine maleate form T, namely, the asenapine maleate contains more than 99% (w/w) of the crystalline asenapine maleate form T, preferably the asenapine maleate contains more than 99.5% (w/w) of the crystalline asenapine maleate form T, more preferably the asenapine maleate contains more than 99.9% (w/w) of the crystalline asenapine maleate form T.

20

In additional embodiment, the present invention provides asenapine maleate form T wherein less than 20% (w/w) of the asenapine maleate is asenapine maleate amorphous form, preferably less than 10% (w/w) of the asenapine maleate is asenapine maleate amorphous form, more preferably less than 5% (w/w) of the
25 asenapine maleate is asenapine maleate amorphous form, and even more preferably less than 1% (w/w) of the asenapine maleate is asenapine maleate amorphous form.

In a further embodiment, the present invention further provides asenapine maleate form T that is microcrystalline.

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In the present specification the asenapine maleate form T is considered to be microcrystalline when it has a particle size distribution characterized by a d_{90} of 100 μm or less, preferably a d_{90} of 50 μm or less, even more preferably a d_{90} of 30 μm or less. The notation d_x [also written as $d(v, 0.X)$] means that X% of the particles have a

diameter less than a specified diameter d . Thus a d_{90} [or $D(v, 0.9)$] of 100 μm means that 90% of the particles have a diameter less than 100 μm .

Yet another aspect of the present invention relates to a process for the preparation of crystalline asenapine maleate form T as herein disclosed. In a first embodiment, the process comprises crystallization of asenapine maleate from a solvent or mixture of solvents and seeding with crystalline asenapine maleate form T.

The term "seeding with crystalline asenapine maleate form T" when used hereinafter refers to the addition of crystalline asenapine maleate form T to facilitate obtaining crystalline asenapine maleate form T.

Another embodiment of the present invention relates to a process for preparing crystalline asenapine maleate form T comprising at least the following steps:

- i) dissolving asenapine maleate in a solvent or a mixture of solvents at a temperature between 5°C and 80°C, more preferably between 15°C and 40°C, even more preferably between 20°C and 25°C;
- ii) optionally filtering the solution prepared in step (i);
- iii) combining the solution prepared in step (i) or in step (ii) with an antisolvent while maintaining the mixture at a temperature between -20°C and 35°C, more preferably between -10°C and 25°C,

wherein the solvent or the mixture of solvents comprises a ketone, preferably acetone, methyl ethyl ketone or methyl isobutyl ketone, and the antisolvent comprises an alkane or a mixture of alkanes such as pentane, hexane, cyclohexane, methylcyclohexane, heptane or mixtures thereof. It is noted that the temperatures within the above ranges need to be selected taking into consideration the specific and/or antisolvents employed so that it is avoided to work at temperatures above the boiling points of these solvents and/or antisolvents.

In a preferred embodiment the solvent or the mixture of solvents is selected from the group consisting of ketones, preferably acetone, methyl ethyl ketone or methyl isobutyl ketone and mixtures thereof, and the antisolvent is selected from the group consisting

of alkanes such as pentane, hexane, cyclohexane, methylcyclohexane, heptane and mixtures thereof.

In a preferred embodiment the above mentioned process is conducted either without
5 any seeding step or seeding at any point in time after step ii) with crystalline asenapine maleate form T.

The term "combining the solution prepared in step (i) or in step (ii) with an antisolvent" as used herein comprises the addition of the solution prepared in step (i) or in step (ii)
10 over the antisolvent, or the addition of the antisolvent over the solution prepared in step (i) or in step (ii), or the simultaneous addition of the solution prepared in step (i) or in step (ii) and the antisolvent into a receiving vessel.

Preferably, the solvent or mixture of solvents and the antisolvent have a solvent or
15 mixture of solvents/antisolvent volume/volume ratio from 3:1 to 1:10, more preferably from 2:1 to 1:6, even more preferably from 1:1 to 1:5.

In a preferred embodiment, the process for preparing crystalline asenapine maleate form T comprises at least the following steps:

- 20
- i) dissolving asenapine maleate in a solvent or a mixture of solvents at a temperature between 5°C and 80°C, more preferably between 15°C and 40°C, even more preferably between 20°C and 25°C;
 - ii) optionally filtering the solution prepared in step (i);
 - 25 iii) combining the solution prepared in step (i) or in step (ii) with an antisolvent while maintaining the mixture at a temperature between 20°C and 25°C,

wherein the solvent or the mixture of solvents comprises a ketone, preferably acetone, methyl ethyl ketone or methyl isobutyl ketone, and the antisolvent comprises an alkane
30 or a mixture of alkanes such as pentane, hexane, cyclohexane, methylcyclohexane, heptane or mixtures thereof.

In a preferred embodiment the above mentioned process is conducted either without
35 any seeding step or seeding at any time after step ii) with crystalline asenapine maleate form T.

In another preferred embodiment of the present invention asenapine maleate form T is obtained by a process which comprises at least the following steps:

- 5 i) dissolving asenapine maleate in methyl ethyl ketone at a temperature between 20°C and 25°C;
ii) optionally filtering the solution prepared in step (i);
iii) combining the solution prepared in step (i) or in step (ii) with cyclohexane while maintaining the mixture at a temperature between 20°C and 25°C.

10

In a preferred embodiment the above mentioned process is conducted either without any seeding step or seeding at any point in time after step ii) with crystalline asenapine maleate form T.

- 15 Preferably, the mixtures of methyl ethyl ketone and cyclohexane used for the preparation of asenapine maleate form T as herein disclosed have a methyl ethyl ketone/cyclohexane volume/volume ratio from 3:1 to 1:10, more preferably from 1:2 to 1:6, even more preferably from 1.2:1 to 1:2.5.

- 20 Preferably, the solution of asenapine maleate in methyl ethyl ketone is added over the cyclohexane while maintaining the mixture at a temperature between 20°C and 25°C, or the cyclohexane is added over the solution of asenapine maleate in methyl ethyl ketone while maintaining the mixture at a temperature between 20°C and 25°C.

- In another preferred embodiment of the present invention asenapine maleate form T is
25 obtained by a process which comprises at least the following steps:

- i) dissolving asenapine maleate in acetone at a temperature between 20°C and 25°C;
ii) optionally filtering the solution prepared in step (i);
iii) combining the solution prepared in step (i) or in step (ii) with cyclohexane while
30 maintaining the mixture at a temperature between 20°C and 25°C.

In a preferred embodiment the above mentioned process is conducted either without any seeding step or seeding at any point in time after step ii) with crystalline asenapine maleate form T.

35

Preferably, the mixtures of acetone and cyclohexane used for the preparation of asenapine maleate form T as herein disclosed have an acetone/cyclohexane volume/volume ratio from 3:1 to 1:10, more preferably from 1:2 to 1:6, even more preferably from 1:3.1 to 1:3.5.

5

Preferably, the solution of asenapine maleate in acetone is added over the cyclohexane while maintaining the mixture at a temperature between 20°C and 25°C.

In a preferred embodiment, the process for preparing crystalline asenapine maleate form T comprises at least the following steps:

i) dissolving asenapine maleate in a solvent or a mixture of solvents at a temperature between 5°C and 80°C, more preferably between 15°C and 40°C, even more preferably between 20°C and 25°C;

15 ii) optionally filtering the solution prepared in step (i);

iii) combining the solution prepared in step (i) or in step (ii) with an antisolvent while maintaining the mixture at a temperature between 0°C and 10°C, preferably 5°C,

wherein the solvent or the mixture of solvents comprises a ketone, preferably acetone, methyl ethyl ketone or methyl isobutyl ketone, and the antisolvent comprises an alkane or a mixture of alkanes such as pentane, hexane, cyclohexane, methylcyclohexane, heptane or mixtures thereof.

In a preferred embodiment the above mentioned process is conducted either without any seeding step or seeding at any point in time after step ii) with crystalline asenapine maleate form T.

In another preferred embodiment of the present invention asenapine maleate form T is obtained by a process which comprises at least the following steps:

30

i) dissolving asenapine maleate in methyl ethyl ketone at a temperature between 20°C and 25°C;

ii) optionally filtering the solution prepared in step (i);

iii) combining the solution prepared in step (i) or in step (ii) with heptane while maintaining the mixture at a temperature between 0°C and 10°C, preferably 5°C.

35

In a preferred embodiment the above mentioned process is conducted either without any seeding step or seeding at any point in time after step ii) with crystalline asenapine maleate form T.

5

Preferably, the mixtures of methyl ethyl ketone and heptane used for the preparation of asenapine maleate form T as herein disclosed have a methyl ethyl ketone/heptane volume/volume ratio from 3:1 to 1:10, more preferably from 1:1 to 1:6, even more preferably from 1:2.1 to 1:2.5.

10

Preferably, the heptane is added over the solution of asenapine maleate in methyl ethyl ketone while maintaining the mixture at a temperature between 0°C and 10°C, preferably 5°C.

15 In a preferred embodiment, the process for preparing crystalline asenapine maleate form T comprises at least the following steps:

i) dissolving asenapine maleate in a solvent or a mixture of solvents at a temperature between 5°C and 80°C, more preferably between 15°C and 40°C, even more preferably
20 between 20°C and 25°C;

ii) optionally filtering the solution prepared in step (i);

iii) combining the solution prepared in step (i) or in step (ii) with an antisolvent while maintaining the mixture at a temperature between -10°C and -5°C,

25 wherein the solvent or the mixture of solvents comprises a ketone, preferably acetone, methyl ethyl ketone or methyl isobutyl ketone, and the antisolvent comprises an alkane or a mixture of alkanes such as pentane, hexane, cyclohexane, methylcyclohexane, heptane or mixtures thereof.

30 In a preferred embodiment the above mentioned process is conducted either without any seeding step or seeding at any point in time after step ii) with crystalline asenapine maleate form T.

In another preferred embodiment of the present invention asenapine maleate form T is
35 obtained by a process which comprises at least the following steps:

- i) dissolving asenapine maleate in acetone at a temperature between 20°C and 25°C;
ii) optionally filtering the solution prepared in step (i);
iii) combining the solution prepared in step (i) or in step (ii) with hexane while
5 maintaining the mixture at a temperature between -10°C and -5°C.

In a preferred embodiment the above mentioned process is conducted either without any seeding step or seeding at any point in time after step ii) with crystalline asenapine maleate form T.

10

Preferably, the mixtures of acetone and hexane used for the preparation of asenapine maleate form T as herein disclosed have an acetone/hexane volume/volume ratio from 3:1 to 1:10, more preferably from 1:2 to 1:6, even more preferably from 1:3.1 to 1:3.5.

- 15 Preferably, the solution of asenapine maleate in acetone is added over the hexane while maintaining the mixture at a temperature between -10°C and -5°C.

In another preferred embodiment of the present invention asenapine maleate form T is obtained by a process which comprises at least the following steps:

20

- i) dissolving asenapine maleate in acetone at a temperature between 20°C and 25°C;
ii) optionally filtering the solution prepared in step (i);
iii) combining the solution prepared in step (i) or in step (ii) with heptane while
maintaining the mixture at a temperature between -10°C and -5°C.

25

In a preferred embodiment the above mentioned process is conducted either without any seeding step or seeding at any point in time after step ii) with crystalline asenapine maleate form T.

- 30 Preferably, the mixtures of acetone and heptane used for the preparation of asenapine maleate form T as herein disclosed have an acetone/heptane volume/volume ratio from 3:1 to 1:10, more preferably from 1:2 to 1:6, even more preferably from 1:3.1 to 1:3.5.

- Preferably, the solution of asenapine maleate in acetone is added over the heptane
35 while maintaining the mixture at a temperature between -10°C and -5°C.

In another preferred embodiment of the present invention asenapine maleate form T is obtained by a process which comprises at least the following steps:

- 5 i) dissolving asenapine maleate in acetone at a temperature between 20°C and 25°C;
 ii) optionally filtering the solution prepared in step (i);
 iii) combining the solution prepared in step (i) or in step (ii) with methylcyclohexane while maintaining the mixture at a temperature between -10°C and -5°C.
- 10 In a preferred embodiment the above mentioned process is conducted either without any seeding step or seeding at any point in time after step ii) with crystalline asenapine maleate form T.

Preferably, the mixtures of acetone and methylcyclohexane used for the preparation of
15 asenapine maleate form T as herein disclosed have an acetone/methylcyclohexane volume/volume ratio from 3:1 to 1:10, more preferably from 1:2 to 1:6, even more preferably from 1:3.1 to 1:3.5.

Preferably, the solution of asenapine maleate in acetone is added over the
20 methylcyclohexane while maintaining the mixture at a temperature between -10°C and -5°C.

In another preferred embodiment of the present invention asenapine maleate form T is obtained by a process which comprises at least the following steps:

- 25 i) dissolving asenapine maleate in methyl ethyl ketone at a temperature between 20°C and 25°C;
 ii) optionally filtering the solution prepared in step (i);
 iii) combining the solution prepared in step (i) or in step (ii) with hexane while
30 maintaining the mixture at a temperature between -10°C and -5°C.

In a preferred embodiment the above mentioned process is conducted either without any seeding step or seeding at any point in time after step ii) with crystalline asenapine maleate form T.

Preferably, the mixtures of methyl ethyl ketone and hexane used for the preparation of asenapine maleate form T as herein disclosed have an methyl ethyl ketone /hexane volume/volume ratio from 3:1 to 1:10, more preferably from 1:2 to 1:6, even more preferably from 1:2.1 to 1:2.5.

5

Preferably, the solution of asenapine maleate in methyl ethyl ketone is added over the hexane while maintaining the mixture at a temperature between -10°C and -5°C.

In another preferred embodiment of the present invention asenapine maleate form T is
10 obtained by a process which comprises at least the following steps:

i) dissolving asenapine maleate in methyl ethyl ketone at a temperature between 20°C and 25°C;

ii) optionally filtering the solution prepared in step (i);

15 iii) combining the solution prepared in step (i) or in step (ii) with heptane while maintaining the mixture at a temperature between -10°C and -5°C.

In a preferred embodiment the above mentioned process is conducted either without any seeding step or seeding at any point in time after step ii) with crystalline asenapine maleate form T.

20 Preferably, the mixtures of methyl ethyl ketone and heptane used for the preparation of asenapine maleate form T as herein disclosed have an methyl ethyl ketone/heptane volume/volume ratio from 3:1 to 1:10, more preferably from 1:2 to 1:6, even more preferably from 1:2.1 to 1:2.5.

25 Preferably, the solution of asenapine maleate in methyl ethyl ketone is added over the heptane while maintaining the mixture at a temperature between -10°C and -5°C.

In another preferred embodiment of the present invention asenapine maleate form T is obtained by a process which comprises at least the following steps:

30

i) dissolving asenapine maleate in methyl ethyl ketone at a temperature between 20°C and 25°C;

ii) optionally filtering the solution prepared in step (i);

35 iii) combining the solution prepared in step (i) or in step (ii) with methylcyclohexane while maintaining the mixture at a temperature between -10°C and -5°C.

In a preferred embodiment the above mentioned process is conducted either without any seeding step or seeding at any point in time after step ii) with crystalline asenapine maleate form T.

5

Preferably, the mixtures of methyl ethyl ketone and methylcyclohexane used for the preparation of asenapine maleate form T as herein disclosed have an methyl ethyl ketone /methylcyclohexane volume/volume ratio from 3:1 to 1:10, more preferably from 1:2 to 1:6, even more preferably from 1:2.1 to 1:2.5.

10

Preferably, the solution of asenapine maleate in methyl ethyl ketone is added over the methylcyclohexane while maintaining the mixture at a temperature between -10°C and -5°C.

15 In a preferred embodiment, the process for preparing crystalline asenapine maleate form T comprises at least the following steps:

i) dissolving asenapine maleate in methyl ethyl ketone at a temperature between 5°C and 80°C, more preferably between 15°C and 40°C, even more preferably between 20°C and 25°C;

20

ii) optionally filtering the solution prepared in step (i);

iii) combining the solution prepared in step (i) or in step (ii) with an antisolvent comprising an ether such as diethyl ether, diisopropyl ether, methyl *tert*-butyl ether, cyclopentyl methyl ether or mixtures thereof, while maintaining the mixture at a temperature between -10°C and -5°C.

25

In a preferred embodiment the antisolvent is selected from the group consisting of ethers, preferably diethyl ether, diisopropyl ether, methyl *tert*-butyl ether, cyclopentyl methyl ether or mixtures thereof.

30

In a preferred embodiment the above mentioned process is conducted either without any seeding step or seeding at any point in time after step ii) with crystalline asenapine maleate form T.

Preferably, the mixtures of methyl ethyl ketone and ether used for the preparation of asenapine maleate form T as herein disclosed have an methyl ethyl ketone/ether volume/volume ratio from 3:1 to 1:10, more preferably from 1:2 to 1:6, even more preferably from 1:2.1 to 1:2.5.

5

In another preferred embodiment of the present invention asenapine maleate form T is obtained by a process which comprises at least the following steps:

- 10 i) dissolving asenapine maleate in methyl ethyl ketone at a temperature between 20°C and 25°C;
 - ii) optionally filtering the solution prepared in step (i);
 - iii) combining the solution prepared in step (i) or in step (ii) with methyl *tert*-butyl ether while maintaining the mixture at a temperature between -10°C and -5°C.
- 15 In a preferred embodiment the above mentioned process is conducted either without any seeding step or seeding at any point in time after step ii) with crystalline asenapine maleate form T.

20 Preferably, the mixtures of methyl ethyl ketone and methyl *tert*-butyl ether used for the preparation of asenapine maleate form T as herein disclosed have an methyl ethyl ketone / methyl *tert*-butyl ether volume/volume ratio from 3:1 to 1:10, more preferably from 1:2 to 1:6, even more preferably from 1:2.1 to 1:2.5.

Preferably, the solution of asenapine maleate in methyl ethyl ketone is added over the methyl *tert*-butyl ether while maintaining the mixture at a temperature between -10°C
25 and -5°C.

In another preferred embodiment of the present invention asenapine maleate form T is obtained by a process which comprises at least the following steps:

- 30 i) dissolving asenapine maleate in methyl ethyl ketone at a temperature between 20°C and 25°C;
- ii) optionally filtering the solution prepared in step (i);
- iii) combining the solution prepared in step (i) or in step (ii) with cyclopentyl methyl ether while maintaining the mixture at a temperature between -10°C and -5°C.

35

In a preferred embodiment the above mentioned process is conducted either without any seeding step or seeding at any point in time after step ii) with crystalline asenapine maleate form T.

- 5 Preferably, the mixtures of methyl ethyl ketone and cyclopentyl methyl ether used for the preparation of asenapine maleate form T as herein disclosed have an methyl ethyl ketone / cyclopentyl methyl ether volume/volume ratio from 3:1 to 1:10, more preferably from 1:2 to 1:6, even more preferably from 1:2.1 to 1:2.5.
- 10 Preferably, the solution of asenapine maleate in methyl ethyl ketone is added over the cyclopentyl methyl ether while maintaining the mixture at a temperature between -10°C and -5°C.

In a preferred embodiment, the process for preparing crystalline asenapine maleate form T comprises at least the following steps:

- 15 i) dissolving asenapine maleate in acetone at a temperature between 20°C and 25°C;
ii) optionally filtering the solution prepared in step (i);
iii) combining the solution prepared in step (i) or in step (ii) with cyclopentyl methyl ether while maintaining the mixture at a temperature between -10°C and -5°C.

In a preferred embodiment the above mentioned process is conducted either without any seeding step or seeding at any point in time after step ii) with crystalline asenapine maleate form T.

25

Preferably, the mixtures of acetone and cyclopentyl methyl ether used for the preparation of asenapine maleate form T as herein disclosed have an acetone / cyclopentyl methyl ether volume/volume ratio from 3:1 to 1:10, more preferably from 1:2 to 1:6, even more preferably from 1:3.1 to 1:3.5.

30

Preferably, the solution of asenapine maleate in acetone is added over the cyclopentyl methyl ether while maintaining the mixture at a temperature between -10°C and -5°C.

The crystalline asenapine maleate form T obtained according to the processes disclosed herein is preferably isolated by filtration at a temperature between -20°C and 35°C, preferably between -10°C and 25°C.

- 5 In another aspect of the present invention crystalline asenapine maleate form T is obtained by a process which comprises suspending asenapine maleate in a solvent or mixture of solvents wherein asenapine maleate remains at least partially undissolved and seeding with crystalline asenapine maleate form T.
- 10 The asenapine maleate form T that is microcrystalline as herein disclosed can be obtained by any conventional mechanical process of reducing the size of particles of asenapine maleate form T. Non-limiting examples of mechanical processes of reducing the size of particles of asenapine maleate form T are cutting, chipping, micronizing, milling, crushing, grinding and triturating.
- 15 Typically by carrying out milling comprises air-jet milling or pin milling.
- Micronizing and/or air-jet milling can be preferably carried out in any commercially available micronizer and/or mill working at a gas pressure from 1 bar to 15 bar.
- 20 Preferably gas pressure comprises air pressure or nitrogen pressure.
- Pin milling can be preferably carried out in any commercially available pin mill working from 3000 rpm to 14000 rpm.
- 25 Alternatively the asenapine maleate form T that is microcrystalline as herein disclosed can also be directly obtained by means of the crystallization and/or slurring processes as herein disclosed without the need of including an additional step of reducing the particle size of the asenapine maleate form T.
- 30 Particle size of the microcrystalline asenapine maleate form T as herein disclosed is determined by laser diffraction using a Malvern Mastersizer instrument as explained in the experimental section.
- A further aspect of the present invention provides pharmaceutical compositions
- 35 comprising the crystalline asenapine maleate form T, alone or in combination with at

least one additional polymorphic and/or amorphous form of asenapine maleate, and at least one pharmaceutically acceptable carrier.

The pharmaceutical compositions as herein disclosed may contain from 0.005 mg to 500 mg of crystalline asenapine maleate form T, preferably from 1 mg to 250 mg of crystalline asenapine maleate form T, more preferably the pharmaceutical compositions as herein disclosed contain from 3 mg to 150 mg of crystalline asenapine maleate form T.

10 The invention further relates to the use of crystalline asenapine maleate form T for the manufacture of a sublingual or buccal pharmaceutical composition for treating mental disorders such as psychosis, schizophrenia and bipolar disorders.

The term "pharmaceutically acceptable carrier" refers to a excipient, diluent, adjuvant, or carrier with which a compound of the invention is administered.

As used herein, the term "alkane" is used to designate fully saturated, linear or branched hydrocarbon compounds which may be monocyclic or non-cyclic. Non-cyclic alkanes have empiric formula C_nH_{2n+2} wherein n is an integer. Examples of non-cyclic alkanes are pentane, hexane and heptane. Non-cyclic alkanes may be branched or non-branched. Thus, the term hexane encompasses any isomer of formula C_6H_{14} such as hexane, 2-methylpentane, 3-methylpentane, 2,3-dimethylbutane, 2,2-dimethylbutane and mixtures thereof. Similarly, the term heptanes encompasses any isomer of formula C_7H_{16} such as n-heptane, 2-methylhexane, 3-methylhexane, 2,2-dimethylpentane, 2,3-dimethylpentane, 2,4-dimethylpentane, 3,3-dimethylpentane, 3-ethylpentane, 2,2,3-trimethylbutane and mixtures thereof. Monocyclic alkanes have empiric formula C_nH_{2n} wherein n is an integer. Cyclic alkanes may be branched or non-branched. Thus, for example, both cyclohexane and methylcyclohexane will be considered cycloalkanes.

30 As used herein, the term "excipient" refers to any pharmaceutically acceptable ingredient that is commonly used in the pharmaceutical technology for preparing granulate and/or solid oral dosage formulations. Examples of categories of excipients include, but are not limited to, binders, disintegrants, lubricants, glidants, stabilizers, fillers and diluents. One of ordinary skill in the art may select one or more of the

aforementioned excipients with respect to the particular desired properties of the granulate and/or solid oral dosage form by routine experimentation and without any undue burden. The amount of each excipient used may vary within ranges conventional in the art. The following references, which are all hereby incorporated by
5 reference discloses techniques and excipients used to formulate oral dosage forms. See The Handbook of Pharmaceutical Excipients, 4th edition, Rowe et al., Eds., American Pharmaceuticals Association (2003); and Remington: the Science and Practice of Pharmacy, 20th edition, Gennaro, Ed., Lippincott Williams & Wilkins (2000).

10 In the present description the term "diluent" refers to an excipient which fills out the size of a tablet or capsule, making it practical to produce and convenient for the consumer to use. Suitable diluents include e.g. pharmaceutically acceptable inert fillers, such as microcrystalline cellulose, lactose, dibasic calcium phosphate sugar, sugar alcohols, corn starch, sucrose, silicic anhydride, polysaccharides, N-methyl pyrrolidone
15 (Pharmasolve (ISP)) and mixtures thereof. The term sugar and sugar alcohols comprises mannitol, lactose, fructose, sorbitol, xylitol, maltodextrin, dextrates, dextrans, lactitol and mixtures thereof.

As used herein the term "adjuvant" refers to any component which improves the body's
20 response to a pharmaceutical composition.

The term "carrier" refers to a compound that facilitates the incorporation of an active ingredient into the body.

25 Preferably the pharmaceutical compositions as herein disclosed are sublingual or buccal tablets.

The pharmaceutical compositions as herein disclosed can be preferably prepared as disclosed in US patent No 5,763,476 and as described in example 16 of European Patent application EP 1,710,245 A1.

30

All documents referred to herein, including patents, patent applications, and printed publications, are hereby incorporated by reference in their entirety in this disclosure.

Description of the figures

35

Figure 1: X-Ray Powder Diffraction pattern of asenapine maleate Form M as obtained in Ex. 2.

Figure 2: X-Ray Powder Diffraction pattern of asenapine maleate Form T as obtained in Ex. 10.

5 Figure 3: X-Ray Powder Diffraction pattern of asenapine maleate Form H with traces of Form L as obtained in Comp. Ex. 1.

Figure 4: X-Ray Powder Diffraction pattern of asenapine maleate Form H with traces of Form L as obtained in Comp. Ex. 2.

10 Figure 5: X-Ray Powder Diffraction pattern of asenapine maleate Form H as obtained in Ref. Ex. 1.

Figure 6: X-Ray Powder Diffraction pattern of asenapine maleate Form L as obtained in Ref. Ex. 3.

Figure 7: X-Ray Powder Diffraction pattern of asenapine maleate Form M as obtained in Ex. 30.

15 Figure 8: X-Ray Powder Diffraction pattern of asenapine maleate Form T as obtained in Ex. 32.

Experimental examples

20 The asenapine maleate forms M and T as herein disclosed can be characterized, and thus distinguished from the prior art forms, by several analytical techniques known in the art such as Infrared Spectroscopy, Raman Spectroscopy, Solid State Nuclear Magnetic Resonance Spectroscopy, Differential Scanning Calorimetry, X-Ray Powder Diffraction patterns (XRPD), Electron Diffraction and the like. Such techniques may be
25 applied individually or in combination.

The asenapine maleate used herein as starting material to obtain asenapine maleate form M or form T as disclosed herein can be obtained by any of the processes described in the prior art.

30

General Methods

X-Ray Powder Diffraction (XRPD)

XRPD patterns were recorded on a Siemens D5000 diffractometer equipped with two symmetrically mounted vertical goniometers (Bragg-Brentano geometry) with horizontal sample stages, a X-ray tube, a high voltage generator (working at 45 kV and 35 mA) and standard scintillation detectors. Ni-filtered Cu-anode source was used and diffracted radiation was further monochromatized with a graphite crystal to avoid fluorescence effects [$\lambda(K_{\alpha}) = 1.54056 \text{ \AA}$]. Routine diffraction patterns were recorded including values of 2θ that range from 4 to 50° with a sampling rate of 0.02° per second and a step time of 0.5 seconds or 1 second per step. Powdered samples were pressed between two glass plates, forming a film. DIFFRAC Plus measurement software with EVA evaluation software (Bruker) was used to record the data and for a primary analysis of the diffraction patterns. The equipment was periodically calibrated using quartz and silicon.

HPLC method 1:

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The chromatographic separation was carried out in a Phenomenex Prodigy ODS-3, 5 μm , 4.6 x 250 mm column at 30°C .

The mobile phase A was prepared by adjusting the pH of a water / acetonitrile / methanol / methanesulfonic acid (60 : 18 : 22 : 0.1) v/v/v/v to 2.5 with diethylamine. The mobile phase B was acetonitrile.

The chromatograph was programmed as follows: initial 0-4 min 0 % mobile phase B, 4-18 min linear gradient to 15 % mobile phase B, 18-60 min isocratic 15% mobile phase B, 60-65 min linear gradient to 0 % mobile phase B and 65-70 min equilibration with 0 % mobile phase B.

The chromatograph was equipped with a 210 nm detector and the flow rate was 1.5 mL per minute. 10 μL of the test samples were injected. The samples were prepared by dissolving the appropriate amount of sample in mobile phase A, to obtain a concentration of 1.5 mg per mL. The chromatogram was run for at least 50 min. The approximate retention time for asenapine was found to be 18 min.

HPLC method 2:

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The chromatographic separation was carried out in a Kromasil 100 C18, 5 μ m, 4.6 x 250 mm column at 30 °C.

The mobile phase A was prepared by adjusting the pH of a 0.1% methanesulfonic acid solution in water to 2.5 with diethylamine. The mobile phase B was acetonitrile.

The chromatograph was programmed as follows: initial 0-3 min 25 % mobile phase B, 3-50 min linear gradient to 65 % mobile phase B, 50-55 min isocratic 65 % mobile phase B, 55-70 min linear gradient to 90 % mobile phase B, 70-100 min isocratic 90 % mobile phase B, 100-105 min linear gradient to 25 % mobile phase B and 105-110 min equilibration with 25 % mobile phase B.

The chromatograph was equipped with a 210 nm detector and the flow rate was 1.0 mL per minute. 10 μ L of the test samples were injected. The samples were prepared by dissolving the appropriate amount of sample in methanol, to obtain a concentration of 0.5 mg per mL. The chromatogram was run for at least 100 min. The approximate retention time for asenapine was found to be 17.4 min.

Particle Size Distribution method:

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The particle size parameters measured in the present invention have been obtained by means of laser light diffraction technique, and specifically by means of a Malvern Mastersizer 1000 equipped with a 2 milliwatt Helium/Neon laser (633 nm wavelength) and a Fourier Transform lens system. The sample unit was a MS1 Small Volume Sample Dispersion Unit stirred cell. The dispersant was Isopar G. The sample particle size distribution was assumed to follow a normal distribution.

Analysis model: Polydisperse. Optical properties: Particle R.I.= (1.9000, 0.1), Dispersant R.I.= 1.42.

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Sample dispersant (5% solution of soybean lecithin in Isopar G) was prepared by adding 2.5 g of soybean lecithin to 50 mL of Isopar G, and mixing gently until lecithin dissolved.

Samples for analysis were prepared by wetting a weighed amount of asenapine maleate (approximately 60 mg) with 20 mL of sample dispersant (5% solution of soybean lecithin in Isopar G). The samples were sonicated for 2 minutes, and were delivered dropwise to the previously background and corrected measuring cell filled with dispersant until the obscuration reached the desired level (approximately 15-17%).

Volume distributions were obtained for at least six measures. For characterization, the values of D_{10} , D_{50} and D_{90} (by volume), $D[4,3]$ (mean diameter by volume) and $D[3,2]$ (mean diameter by surface area to volume, or Sauter diameter) were specifically listed, each one being the mean of the six values available for each characterization parameter.

Solubility method:

1 g of asenapine maleate was suspended in 40 mL of deionized water at 25 °C. The resulting suspension was stirred at 300 rpm. 0.50 mL aliquots were taken and filtered through a 0.20 µm filter after stirring times from 1 to 180 minutes. The filtered aliquots were diluted to 20 mL with methanol and analyzed by HPLC (method 2). The amount of dissolved asenapine maleate in the aliquots was determined by comparing the area % of the asenapine peak as measured by HPLC with a calibration curve obtained from 7 samples of asenapine maleate having known concentrations between 0 mg/mL and 0.5 mg/mL.

Comparative Example 1: Synthesis of asenapine maleate

This Comparative Example is a partial reproduction of Example 3 (step D+E), process 1 of International patent application number WO2008/003460 A1, which discloses the crystallization of asenapine maleate from isopropanol in a first step.

512 mg of asenapine (free base, 1.79 mmol) were dissolved in 2 mL of isopropanol. The resulting solution was vacuum distilled to remove the solvent and to leave asenapine as a yellowish oil. Maleic acid (229.4 mg, 1.98 mmol) was dissolved in isopropanol (3.6 mL) at 45-50 °C. This solution was added to the yellow oil at 45-50 °C. The solution was cooled to 10 °C over 3 hours and held at 10 °C for 2 hours. The resulting solid was filtered and washed with 2.6 mL of cold (0-5 °C) isopropanol. The

solid was dried at 40 °C under vacuum for 2 h to afford a white solid. XRPD (step time: 0.5 seconds): Form H with traces of form L (see Figure 3).

Comparative Example 2: Synthesis of asenapine maleate

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This Comparative Example is a partial reproduction of Example 1 (step D+E), process 3 of International patent application number WO2008/003460 A1, which discloses the crystallization of asenapine maleate from isopropanol / water.

- 10 675.6 mg of asenapine (free base, 2.36 mmol) were dissolved in 0.9 mL of isopropanol, whereupon a solution of maleic acid (314.1 mg; 2.71 mmol) in isopropanol (6.1 mL) and water (0.16 mL) was added under stirring at room temperature. After stirring for 19 hours at room temperature the crystals of asenapine maleate were collected and dried under vacuum at 40 °C for 2 hours to afford a white solid. XRPD (step time: 0.5
- 15 seconds): Form H with traces of form L (see Figure 4).

Reference Example 1: Synthesis of asenapine maleate form H

- 19.51 g of asenapine base were dissolved in 136.5 mL of isopropanol. The solution
- 20 was filtered through a nylon filter (pore size 0.20 µm) and the collected liquors were heated to 30°C. 8.55 g of maleic acid were added, and the resulting mixture was heated to 45-50 °C and stirred for 1 h 20 min at this temperature. The obtained suspension was cooled to 25 °C over 1 h, filtered, and the solid washed twice with 20 mL of isopropanol. The collected solid was dried in the filter under vacuum for 1 h and
- 25 then transferred to a vacuum oven at 40 °C. Yield: 19.29 g (70%). XRPD (step time: 1 second): Form H (see Figure 5). Particle Size Distribution: D₁₀ 6.5 µm, D₅₀ 28.5 µm, D₉₀ 60.3 µm.

Reference Example 2: Synthesis of asenapine maleate form H

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- 19.03 g of asenapine base were dissolved in 133 mL of isopropanol. The solution was filtered through a nylon filter (pore size 0.20 µm) and the collected liquors were heated to 30°C. 8.49 g of maleic acid were added, and the resulting mixture was heated to 45-50°C and stirred for 1 h at this temperature. The obtained suspension was cooled to
- 35 25°C over 1 h 15 minutes, filtered, and the solid washed twice with 20 mL of

isopropanol. The collected solid was dried in the filter under vacuum for 30 minutes and then transferred to a vacuum oven at 40°C. Yield: 23.04 g (86.2%). XRPD (step time: 1 second): Form H (substantially equivalent to Figure 5).

5 Reference Example 3: Micronization of asenapine maleate form H

Asenapine maleate form H as obtained in Reference Example 1 was micronized in a Rina-jet turbomicronizer from Riera Nadeu S.A. using compressed air at 20-25 °C. Conditions: venturi at 3 bar, grinding chamber at 2 bar. XRPD (step time: 1 second):
10 Form L (see Figure 6). Particle Size Distribution: D₁₀ 1.5 µm, D₅₀ 5.2 µm, D₉₀ 10.0 µm.

Example 1: Synthesis of asenapine maleate form M

2.28 g of asenapine maleate were dissolved in 13.3 mL of acetone at 52-53 °C. 15.7
15 mL of heptane (mixture of isomers) were added dropwise over the solution while keeping reflux temperature. Precipitation of a white solid was observed during the addition. The suspension was stirred at reflux temperature for 1 hour and cooled to 10 °C. After stirring at this temperature for 1 hour, the solid was isolated by filtration and dried at 60 °C under vacuum to obtain 1.83 g of asenapine maleate as a white solid
20 (yield: 80.3 %). XRPD (step time: 1 second): Form M (substantially equivalent to Figure 1).

Example 2: Synthesis of asenapine maleate form M

25 7.12 g (53.4 mmol) of aluminum trichloride and 3.55 g (93.5 mmol) of lithium aluminum hydride were suspended in 200 mL of anhydrous tetrahydrofuran below 10 °C. The resulting suspension was stirred at 0°C for 15 minutes. A solution of 10.0 g (33.4 mmol) of *trans*-11-chloro-2,3,3a,12b-tetrahydro-2-methyl-1*H*-dibenz[2,3:6,7]oxepino[4,5-*c*]pyrrol-1-one in 100 mL of anhydrous tetrahydrofuran was added dropwise while
30 keeping the temperature below 15 °C. The resulting mixture was stirred at 10 °C for 1 hour, and the consumption of *trans*-11-chloro-2,3,3a,12b-tetrahydro-2-methyl-1*H*-dibenz[2,3:6,7]oxepino[4,5-*c*]pyrrol-1-one was checked by TLC. 110 mL of a 0.6M aqueous solution of sodium hydroxide was added dropwise while keeping the temperature below 10 °C. The resulting mixture was stirred at 20 °C for 20 minutes.
35 150 mL of toluene and 100 mL of water were added, and the resulting mixture was

stirred for 20 minutes. Phases were separated and the aqueous phase was washed with 2 x 100 mL of toluene. The combined organic phases were washed with 2 x 300 mL of brine, and dried with anhydrous sodium sulfate. Asenapine base was isolated after removing the solvent under reduced pressure. Then, asenapine base was dissolved in 66 mL of isopropanol. The resulting solution was filtered and heated to 30 °C. At this temperature, 4.26 g (36.7 mmol) of maleic acid were added. The resulting mixture was heated to 46 °C and stirred at 45-50 °C for 1 hour. After cooling to room temperature, the suspension was filtered and the cake was washed with 50 mL of cooled isopropanol. The filtered solid was dried under reduced pressure to obtain 6.5 g of asenapine maleate (yield: 48.4 %).

The above obtained asenapine maleate was dissolved in 38 mL of acetone at reflux temperature. 45 mL of hexane (mixture of isomers) were added over the solution at this temperature, and the resulting mixture was stirred at 51 °C for 1 hour. After cooling to 10 °C and stirring at this temperature for 1 hour, the resulting suspension was filtered and the solid was washed with 6.6 mL of an acetone/hexane 1:1 mixture (v/v) to obtain 4.8 g of asenapine maleate as a white solid. Following the same procedure, 15.7 g of additional asenapine maleate was obtained.

The combined solids (20.5 g of asenapine maleate) were dissolved in 120 mL of acetone at 34 °C. After heating to reflux temperature, 40 mL of hexane (mixture of isomers) were added dropwise. Further, additional 100 mL of hexane (mixture of isomers) were added dropwise over 1 hour. Optionally, the resulting mixture can be seeded at this point with asenapine maleate form M. The resulting mixture was cooled and a white solid precipitated off at 35 °C. After cooling to 10 °C and stirring at this temperature for 1 hour, the resulting suspension was filtered and the solid was washed with 21 mL of an acetone/hexane 1:1 mixture (v/v) to obtain 17.5 g of asenapine maleate as a white solid after drying under reduced pressure at 40 °C for 5 hours. Yield: 85.4 %. Purity (HPLC): 99.5 %. XRPD (step time: 1 second): Form M (see Figure 1).

Example 3: Synthesis of asenapine maleate form M

The recrystallization of asenapine maleate in a mixture of acetone and hexane (mixture of isomers) as reported in Example 2 was repeated but including seeding with crystals

of asenapine maleate form M to obtain asenapine maleate form M. XRPD (step time: 1 second): Form M (substantially equivalent to Figure 1).

Example 4: Synthesis of asenapine maleate form M

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17.67 g (132.5 mmol) of aluminum trichloride and 8.84 g (232.9 mmol) of lithium aluminum hydride were suspended in 750 mL of anhydrous tetrahydrofuran below 10 °C. The resulting suspension was stirred at 0°C for 15 minutes. A solution of 25 g (83.5 mmol) of *trans*-11-chloro-2,3,3a,12b-tetrahydro-2-methyl-1*H*-dibenz[2,3:6,7]oxepino-
10 [4,5-*c*]pyrrol-1-one in 250 mL of anhydrous tetrahydrofuran was added dropwise while keeping the temperature below 15 °C. The resulting mixture was stirred at 10 °C for 1 hour, and the consumption of *trans*-11-chloro-2,3,3a,12b-tetrahydro-2-methyl-1*H*-dibenz[2,3:6,7]oxepino[4,5-*c*]pyrrol-1-one was checked by TLC. 275 mL of a 0.6M aqueous solution of sodium hydroxide was added dropwise while keeping the
15 temperature below 10 °C. The resulting mixture was stirred at 20 °C for 20 minutes. 450 mL of toluene and 300 mL of water were added, and the resulting mixture was stirred for 20 minutes. Phases were separated and the aqueous phase was washed with 2 x 200 mL of toluene. The combined organic phases were washed with 2 x 300 mL of brine, and dried with anhydrous sodium sulfate. Asenapine base was isolated
20 after removing the solvent under reduced pressure. Then, asenapine base was dissolved in 175 mL of isopropanol. The resulting solution was filtered and heated to 30 °C. At this temperature, 9.0 g (77.5 mmol) of maleic acid were added. The resulting mixture was heated to 46 °C and stirred at 45-50 °C for 1 hour. Then, the mixture was cooled to 0 °C and stirred at this temperature for 3 hours. The resulting suspension
25 was filtered and the cake was washed with 50 mL of cooled isopropanol.

The solid was suspended in 120 mL of acetone and heated to 52-54 °C. The resulting mixture was filtered. 120 mL of hexane (mixture of isomers) were added dropwise to the filtrate, while keeping the temperature between 52-54 °C. The resulting mixture was
30 stirred for 1 hour at 51 °C, then cooled to 10 °C and stirred at this temperature for 2 hours. The suspension was filtered and the solid was washed with 20 mL of an acetone/hexane 1:1 mixture (v/v) to obtain 15 g of asenapine maleate as a white solid. The solid was dried under reduced pressure. Yield: 44.7 %. XRPD (step time: 1 second): Form M (substantially equivalent to Figure 1).

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Example 5: Synthesis of asenapine maleate form M

7.12 g (53.4 mmol) of aluminum trichloride and 3.55 g (93.5 mmol) of lithium aluminum hydride were suspended in 200 mL of anhydrous tetrahydrofuran below 10 °C. The resulting suspension was stirred at 0°C for 15 minutes. A solution of 10 g (33.4 mmol) of *trans*-11-chloro-2,3,3a,12b-tetrahydro-2-methyl-1*H*-dibenz[2,3:6,7]oxepino[4,5-*c*]pyrrol-1-one in 100 mL of anhydrous tetrahydrofuran was added dropwise while keeping the temperature below 15 °C. The resulting mixture was stirred at 10 °C for 1 hour, and the consumption of *trans*-11-chloro-2,3,3a,12b-tetrahydro-2-methyl-1*H*-dibenz[2,3:6,7]oxepino[4,5-*c*]pyrrol-1-one was checked by TLC. 110 mL of a 0.6M aqueous solution of sodium hydroxide was added dropwise while keeping the temperature below 10 °C. The resulting mixture was stirred at 20 °C for 20 minutes. 150 mL of toluene and 100 mL of water were added, and the resulting mixture was stirred for 20 minutes. Phases were separated and the aqueous phase was washed with 2 x 100 mL of toluene. The combined organic phases were washed with 2 x 300 mL of brine, and dried with anhydrous sodium sulfate. Asenapine base was isolated after removing the solvent under reduced pressure. Then, asenapine base was dissolved in 70 mL of isopropanol. The resulting solution was filtered and heated to 30 °C. At this temperature, 4.26 g (36.7 mmol) of maleic acid were added. The resulting mixture was heated to 46 °C and stirred at 45-50 °C for 1 hour. Then, the mixture was cooled to 0 °C and stirred at this temperature for 3 hours. The resulting suspension was filtered and the cake was washed with 50 mL of cooled isopropanol. The solid was suspended in 40 mL of acetone and heated to 52-54 °C. 40 mL of hexane (mixture of isomers) were added dropwise. The resulting mixture was stirred for 1 hour at 51 °C, then cooled to 10 °C and stirred at this temperature for 1 hour. The suspension was filtered and the solid was washed with 10 mL of an acetone/hexane 1:1 mixture (v/v) to obtain 6.0 g of asenapine maleate as a white solid. The solid was dried under reduced pressure. Yield: 44.4 %. XRPD (step time: 1 second): Form M (substantially equivalent to Figure 1).

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Example 6: Synthesis of asenapine maleate form M

7.12 g (53.4 mmol) of aluminum trichloride and 3.55 g (93.5 mmol) of lithium aluminum hydride were suspended in 300 mL of anhydrous tetrahydrofuran below 10 °C. The resulting suspension was stirred at 0 °C for 15 minutes. A solution of 10 g (33.4 mmol)

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of *trans*-11-chloro-2,3,3a,12b-tetrahydro-2-methyl-1*H*-dibenz[2,3:6,7]oxepino[4,5-
c]pyrrol-1-one in 100 mL of anhydrous tetrahydrofuran was added dropwise while
keeping the temperature below 15 °C. The resulting mixture was stirred at 10 °C for 1
hour, and the consumption of *trans*-11-chloro-2,3,3a,12b-tetrahydro-2-methyl-1*H*-
5 dibenz[2,3:6,7]oxepino[4,5-*c*]pyrrol-1-one was checked by TLC. 110 mL of a 0.6M
aqueous solution of sodium hydroxide was added dropwise while keeping the
temperature below 10 °C. The resulting mixture was stirred at 20 °C for 20 minutes.
150 mL of toluene and 100 mL of water were added, and the resulting mixture was
stirred for 20 minutes. Phases were separated and the aqueous phase was washed
10 with 2 x 100 mL of toluene. The combined organic phases were washed with 2 x 300
mL of brine, and dried with anhydrous sodium sulfate. Asenapine base was isolated
after removing the solvent under reduced pressure. Then, asenapine base was
dissolved in 70 mL of isopropanol. The resulting solution was filtered and heated to 30
°C. At this temperature, 2.8 g (24.1 mmol) of maleic acid were added. The resulting
15 mixture was heated to 45-50 °C and stirred at this temperature for 1 hour. Then, the
mixture was cooled to -5 °C and stirred at this temperature for 3 hours. The resulting
suspension was filtered and the cake was washed with 50 mL of cooled isopropanol.
The solid was suspended in 40 mL of acetone and heated to 45 °C. 45 mL of hexane
(mixture of isomers) were added dropwise. The resulting mixture was stirred for 1 hour
20 at 45 °C, then cooled to 0 °C and stirred at this temperature for 3 hours. The
suspension was filtered and the solid was washed with 10 mL of an acetone/hexane
1:1 mixture (v/v) to obtain 6.9 g of asenapine maleate as a white solid. The solid was
dried under reduced pressure. Yield: 51.5 %. XRPD (step time: 1 second): Form M
(substantially equivalent to Figure 1).

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Example 7: Synthesis of asenapine maleate form M

10.0 g (32.4 mmol) of *trans*-5-chloro-2,3,3a,12b-tetrahydro-1*H*-
dibenzo[2,3:6,7]oxepino[4,5-*c*]pyrrole hydrochloride were neutralized with 1 M aqueous
30 sodium hydroxide until the pH was adjusted to above 10. The resulting mixture was
extracted with 2 x 150 mL of dichloromethane. The organic phases were combined and
the solvent was removed under reduced pressure. The residue was dissolved in a
mixture of 5.27 g (65.0 mmol) of a 37 % aqueous solution of formaldehyde, 5.1 g (97.5
mmol) of 88 % formic acid, and 100 mL of toluene. The resulting mixture was heated to
35 60 °C and stirred at this temperature for 3 hours. After cooling to room temperature, pH

was adjusted to 10 by addition of 1 M aqueous sodium hydroxide. The aqueous layer was extracted and washed with 2 x 150 mL of toluene. The organic phases were combined, washed with 100 mL of saturated sodium chloride, dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure to give asenapine (free base) as an oil, which was subsequently dissolved in 66 mL of isopropanol at 45 °C. Then, 3.77 g (32.5 mmol) of maleic acid were added. The resulting mixture was stirred at 45 °C for 30 minutes and then cooled to -5 °C. The resulting solution was seeded with asenapine maleate. 60 mL of isopropanol were added, and the resulting suspension was stirred overnight at -5 °C. The solid was filtered. The filtered solid was suspended in 45 mL of acetone and heated to 50 °C. 45 mL of hexane (mixture of isomers) were added dropwise. The resulting solution was cooled to -5 °C and stirred at this temperature for 30 minutes. The suspension was filtered and the solid was washed with 20 mL of an acetone/hexane 1:1 mixture (v/v) to obtain 5.3 g of asenapine maleate as a white solid. Additional 4.9 g were obtained from the mother liquors. Solids were combined to obtain 10.2 g of asenapine maleate. XRPD (step time: 1 second): Form M (substantially equivalent to Figure 1).

Example 8: Synthesis of asenapine maleate form M

0.75 g (2.6 mmol) of asenapine base in form of a yellow oil were dissolved in 5 mL of isopropanol. A solution of 0.42 g (3.6 mmol) of maleic acid in 5 mL of isopropanol was added dropwise. The resulting mixture was heated to 45-50 °C and stirred at this temperature for 5 minutes. After cooling to room temperature, the resulting suspension was filtered and the obtained solid was suspended in 4 mL of isopropanol. The suspension was seeded with asenapine maleate form M and was stirred for 1 hour. Then, the suspension was filtered and washed with 2 mL of isopropanol, to obtain 0.37 g of asenapine maleate as a white solid after drying under reduced pressure. Yield: 35.4 %. XRPD (step time: 1 second): Form M (substantially equivalent to Figure 1).

Example 9: Synthesis of asenapine maleate form M

3.0 g (7.5 mmol) of asenapine maleate obtained as described in Example 8 were dissolved in 17.5 mL of acetone at reflux temperature. Then, 6.0 mL of heptane (mixture of isomers) were added dropwise. The resulting mixture was seeded with asenapine maleate form M and additional 14.6 mL of heptane (mixture of isomers)

were added dropwise at reflux temperature over 5 minutes. The resulting mixture was cooled and a white solid precipitated off at 35 °C. After cooling to 10 °C and stirring at this temperature for 1 hour, the resulting suspension was filtered and the solid was washed with 3 mL of an acetone/heptane 1:1 mixture (v/v) to obtain 2.3 g of asenapine maleate as a white solid after drying under reduced pressure at 60 °C. Yield: 76.7 %. XRPD (step time: 1 second): Form M (substantially equivalent to Figure 1).

Example 10: Synthesis of asenapine maleate form T

282.2 mg of asenapine maleate were dissolved in 2.1 mL of methyl ethyl ketone at a temperature between 20 to 25 °C. The resulting solution was filtered. 5 mL of cyclohexane were added dropwise over the filtered solution, and the resulting mixture was stirred at 20-25 °C for 2 hours. A white suspension was obtained. The solid was filtered under vacuum. XRPD (step time: 0.5 seconds): Form T (see Figure 2).

Example 11: Synthesis of asenapine maleate form T

273.6 mg of asenapine maleate were dissolved in 2.1 mL of methyl ethyl ketone at a temperature between 20 to 25 °C. The resulting solution was filtered. 5 mL of cyclohexane were added dropwise over the filtered solution, and the resulting mixture was stirred at 20-25 °C for 24 hours. A white suspension was obtained. The solid was filtered under vacuum. XRPD (step time: 0.5 seconds): Form T (substantially equivalent to Figure 2).

Example 12: Synthesis of asenapine maleate form T

280.9 mg of asenapine maleate were dissolved in 2.2 mL of methyl ethyl ketone at a temperature between 20 to 25 °C. The resulting solution was filtered, and the filtered solution was added dropwise over 5 mL of cyclohexane at a temperature between 20 to 25 °C. The resulting mixture was stirred at 20-25 °C for 1.5 hours. A white suspension was obtained. The solid was filtered under vacuum. XRPD (step time: 0.5 seconds): Form T (substantially equivalent to Figure 2).

Part of this solid was dried at 40 °C under vacuum for 72 h. XRPD (step time: 0.5 seconds): Form T (substantially equivalent to Figure 2).

Example 13: Synthesis of asenapine maleate form T

260.6 mg of asenapine maleate were dissolved in 2.2 mL of methyl ethyl ketone at a temperature between 20 to 25 °C. The resulting solution was filtered, and the filtrate was added dropwise over 5 mL of methyl *tert*-butyl ether, which had been previously cooled to a temperature between -10 to -5 °C. The resulting mixture was stirred at -10 to -5 °C for 1 hour. A white suspension was obtained. The solid was filtered under vacuum. XRPD (step time: 0.5 seconds): Form T (substantially equivalent to Figure 2).

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Example 14: Synthesis of asenapine maleate form T

266.5 mg of asenapine maleate were dissolved in 2.2 mL of methyl ethyl ketone at a temperature between 20 to 25 °C. The resulting solution was filtered, and the filtrate was added dropwise over 5 mL of cyclopentyl methyl ether, which had been previously cooled to a temperature between -10 to -5 °C. The resulting mixture was stirred at -10 to -5 °C for 1 hour. A white suspension was obtained. The solid was filtered under vacuum. XRPD (step time: 0.5 seconds): Form T (substantially equivalent to Figure 2).

Example 15: Synthesis of asenapine maleate form T

267.4 mg of asenapine maleate were dissolved in 2.2 mL of methyl ethyl ketone at a temperature between 20 to 25 °C. The resulting solution was filtered, and the filtrate was added dropwise over 5 mL of n-hexane, which had been previously cooled to a temperature between -10 to -5 °C. The resulting mixture was stirred at -10 to -5 °C for 1 hour. A white suspension was obtained. The solid was filtered under vacuum. XRPD (step time: 0.5 seconds): Form T (substantially equivalent to Figure 2).

Example 16: Synthesis of asenapine maleate form T

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277.2 mg of asenapine maleate were dissolved in 2.2 mL of methyl ethyl ketone at a temperature between 20 to 25 °C. The resulting solution was filtered, and the filtrate was added dropwise over 5 mL of heptane (mixture of isomers), which had been previously cooled to a temperature between -10 to -5 °C. The resulting mixture was stirred at -10 to -5 °C for 2.5 hours. A white suspension was obtained. The solid was

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filtered under vacuum. XRPD (step time: 0.5 seconds): Form T (substantially equivalent to Figure 2).

Example 17: Synthesis of asenapine maleate form T

5 270.3 mg of asenapine maleate were dissolved in 2.2 mL of methyl ethyl ketone at a temperature between 20 to 25 °C. The resulting solution was filtered, and the filtrate was added dropwise over 5 mL of n-heptane, which had been previously cooled to a temperature between -10 to -5 °C. The resulting mixture was stirred at -10 to -5 °C for 1 hour 15 minutes. A white suspension was obtained. The solid was filtered under
10 vacuum. XRPD (step time: 0.5 seconds): Form T (substantially equivalent to Figure 2).

Example 18: Synthesis of asenapine maleate form T

264.5 mg of asenapine maleate were dissolved in 2.2 mL of methyl ethyl ketone at a
15 temperature between 20 to 25 °C. The resulting solution was filtered, and the filtrate was added dropwise over 5 mL of n-heptane, which had been previously cooled to a temperature between -10 to -5 °C. The resulting mixture was stirred at -10 to -5 °C for 24 hours. A white suspension was obtained. The solid was filtered under vacuum. XRPD (step time: 0.5 seconds): Form T (substantially equivalent to Figure 2).

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Example 19: Synthesis of asenapine maleate form T

268.0 mg of asenapine maleate were dissolved in 2.2 mL of methyl ethyl ketone at a temperature between 20 to 25 °C. The resulting solution was filtered, and the filtrate
25 was cooled to 5 °C. 5 mL of n-heptane were added dropwise over the solution, and the resulting mixture was stirred at 5 °C for 1.5 hours. A white suspension was obtained. The solid was filtered under vacuum. XRPD (step time: 0.5 seconds): Form T (substantially equivalent to Figure 2).

30 **Example 20: Synthesis of asenapine maleate form T**

272.5 mg of asenapine maleate were dissolved in 2.2 mL of methyl ethyl ketone at a temperature between 20 to 25 °C. The resulting solution was filtered, and the filtrate was cooled to 5 °C. 5 mL of n-heptane were added dropwise over the solution, and the
35 resulting mixture was stirred at 5 °C for 24 hours. A white suspension was obtained.

The solid was filtered under vacuum. XRPD (step time: 0.5 seconds): Form T (substantially equivalent to Figure 2).

Example 21: Synthesis of asenapine maleate form T

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5.97 g of asenapine maleate were dissolved in 70 mL of methyl ethyl ketone at a temperature between 20 to 25 °C. The resulting solution was filtered, and the filtrate was cooled to 5 °C. 140 mL of n-heptane were added dropwise over the solution, and the resulting mixture was stirred at 5 °C for 24 hours. A white suspension was
10 obtained. The solid was filtered under vacuum. XRPD (step time: 0.5 seconds): Form T (substantially equivalent to Figure 2).

Example 22: Synthesis of asenapine maleate form T

15 267.5 mg of asenapine maleate were dissolved in 2.2 mL of methyl ethyl ketone at a temperature between 20 to 25 °C. The resulting solution was filtered, and the filtrate was added dropwise over 5 mL of methylcyclohexane, which had been previously cooled to a temperature between -10 to -5 °C. The resulting mixture was stirred at -10 to -5 °C for 2.5 hours. A white suspension was obtained. The solid was filtered under
20 vacuum. XRPD (step time: 0.5 seconds): Form T (substantially equivalent to Figure 2).

Example 23: Synthesis of asenapine maleate form T

260.2 mg of asenapine maleate were dissolved in 1.5 mL of acetone at a temperature
25 between 20 to 25 °C. The resulting solution was added dropwise over 5 mL of n-hexane, which had been previously cooled to a temperature between -10 to -5 °C. The resulting mixture was stirred at -10 to -5 °C for 1.5 hours. A white suspension was obtained. The solid was filtered under vacuum. XRPD (step time: 0.5 seconds): Form T (substantially equivalent to Figure 2).

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Example 24: Synthesis of asenapine maleate form T

278.8 mg of asenapine maleate were dissolved in 1.5 mL of acetone at a temperature
between 20 to 25 °C. The resulting solution was added dropwise over 5 mL of
35 n-heptane, which had been previously cooled to a temperature between -10 to -5 °C.

The resulting mixture was stirred at -10 to -5 °C for 1h 45 min. A white suspension was obtained. The solid was filtered under vacuum. XRPD (step time: 0.5 seconds): Form T (substantially equivalent to Figure 2).

5 **Example 25: Synthesis of asenapine maleate form T**

262.0 mg of asenapine maleate were dissolved in 1.5 mL of acetone at a temperature between 20 to 25 °C. The resulting solution was filtered, and the filtrate was added dropwise over 5 mL of heptane (mixture of isomers), which had been previously cooled
10 to a temperature between -10 to -5 °C. The resulting mixture was stirred at -10 to -5 °C for 2 hours. A white suspension was obtained. The solid was filtered under vacuum. XRPD (step time: 0.5 seconds): Form T (substantially equivalent to Figure 2).

Example 26: Synthesis of asenapine maleate form T

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271.0 mg of asenapine maleate were dissolved in 1.5 mL of acetone at a temperature between 20 to 25 °C. The resulting solution was filtered, and the filtrate was added dropwise over 5 mL of cyclohexane. The resulting mixture was stirred at 20 to 25 °C for 2.5 hours. A white suspension was obtained. The solid was filtered under vacuum.
20 XRPD (step time: 0.5 seconds): Form T (substantially equivalent to Figure 2).

Example 27: Synthesis of asenapine maleate form T

257.0 mg of asenapine maleate were dissolved in 1.5 mL of acetone at a temperature
25 between 20 to 25 °C. The resulting solution was filtered, and the filtrate was added dropwise over 5 mL of methylcyclohexane, which had been previously cooled to a temperature between -10 to -5 °C. The resulting mixture was stirred at -10 to -5 °C for 2 hours. A white suspension was obtained. The solid was filtered under vacuum. XRPD (step time: 0.5 seconds): Form T (substantially equivalent to Figure 2).

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Example 28: Synthesis of asenapine maleate form T

273.7 mg of asenapine maleate were dissolved in 1.5 mL of acetone at a temperature between 20 to 25 °C. The resulting solution was filtered, and the filtrate was added
35 dropwise over 5 mL of cyclopentyl methyl ether, which had been previously cooled to a

temperature between -10 to -5 °C. The resulting mixture was stirred at -10 to -5 °C for 1.5 hours. A white suspension was obtained. The solid was filtered under vacuum. XRPD (step time: 0.5 seconds): Form T (substantially equivalent to Figure 2).

5 **Example 29: Homogenization of asenapine maleate form M**

Asenapine maleate form M as obtained in Examples 4, 5, 6 and 7 was mixed and blended to obtain a homogeneous solid mixture. XRPD (step time: 1 second): Form M (substantially equivalent to Figure 1). Particle Size Distribution: D₁₀ 1.3 µm, D₅₀ 4.3 µm, D₉₀ 28.9 µm.

Example 30: Micronization of asenapine maleate form M

Part of the homogeneous solid mixture of asenapine maleate form M obtained in Example 29 was micronized in a Rina-jet turbomiconizer from Riera Nadeu S.A. using compressed air at 20-25 °C. Conditions: venturi at 5 bar, grinding chamber at 3 bar. The obtained material was micronized for three additional times under the same conditions. XRPD (step time: 1 second): Form M (see Figure 7). Particle Size Distribution: D₁₀ 1.0 µm, D₅₀ 2.2 µm, D₉₀ 4.3 µm.

Example 31: Micronization of asenapine maleate form M

Part of the homogeneous solid mixture of asenapine maleate form M obtained in Example 29 was micronized in a Rina-jet turbomiconizer from Riera Nadeu S.A. using nitrogen at 20-25 °C. Conditions: venturi at 3 bar, grinding chamber at 2 bar. XRPD (step time: 0.5 seconds): Form M (substantially equivalent to Figure 7). Particle Size Distribution: D₁₀ 1.4 µm, D₅₀ 4.3 µm, D₉₀ 10.5 µm.

Example 32: Micronization of asenapine maleate form T

Asenapine maleate form T as obtained in Example 21 was micronized in a Rina-jet turbomiconizer from Riera Nadeu S.A. using nitrogen at 20-25 °C. Conditions: venturi at 3 bar, grinding chamber at 2 bar. XRPD (step time: 0.5 seconds): Form T (see Figure 8). Particle Size Distribution: D₁₀ 1.0 µm, D₅₀ 1.9 µm, D₉₀ 3.5 µm.

Example 33: Use of asenapine maleate form M in the preparation of a pharmaceutical composition

143.3 mg of gelatin and 106.8 mg of mannitol were dispersed in 3.2 mL of water while stirring and heating at 80 °C. 100.4 mg of asenapine maleate form M as obtained in Example 29 were added and the mixture was stirred. The mixture was frozen using an external acetone / CO₂ bath (-78 °C) and dried using a freeze dryer.

Example 34: Use of asenapine maleate form T in the preparation of a pharmaceutical composition

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142.7 mg of gelatin and 107.2 mg of mannitol were dispersed in 3.2 mL of water while stirring and heating at 80 °C. 100.4 mg of asenapine maleate form T as obtained in Example 17 were added and the mixture was stirred. The mixture was frozen using an external acetone / CO₂ bath (-78 °C) and dried using a freeze dryer.

15

Example 35: Water solubility of asenapine maleate form M

The thermodynamic water solubility of asenapine maleate form M was determined by applying the solubility method herein described to micronized asenapine maleate form M as obtained in Example 31. A solubility plateau was reached after stirring for 90 minutes. The water solubility obtained from aliquots taken between 90 and 180 minutes of stirring (7 samples taken at time intervals of 15 minutes) was 8.7 ± 0.4 mg/mL.

25

Example 36: Water solubility of asenapine maleate form T

The thermodynamic water solubility of asenapine maleate form T was determined by applying the solubility method herein described to micronized asenapine maleate form T as obtained in Example 32. A solubility plateau was observed after stirring for 10 minutes. The water solubility obtained from aliquots taken between 10 and 105 minutes of stirring (5 samples taken at time intervals of 5 minutes between 10 and 30 minutes of stirring, and 5 samples taken at time intervals of 15 minutes between 30 and 105 minutes of stirring) was 10.2 ± 1.7 mg/mL.

Example 37: Water solubility of asenapine maleate form H

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The thermodynamic water solubility of asenapine maleate form H was determined by applying the solubility method herein described to asenapine maleate form H as obtained in Reference Example 2. A solubility plateau was reached after stirring for 10 minutes. The water solubility obtained from aliquots taken between 10 and 180 minutes of stirring (5 samples taken at time intervals of 5 minutes between 10 and 30 minutes of stirring, and 10 samples taken at time intervals of 15 minutes between 30 and 180 minutes of stirring) was 6.9 ± 1.0 mg/mL.

Example 38: Water solubility of asenapine maleate form L

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The thermodynamic water solubility of asenapine maleate form L was determined by applying the solubility method herein described to micronized asenapine maleate form L as obtained in Reference Example 3. A solubility plateau was reached after stirring for 105 minutes. The water solubility obtained from aliquots taken between 105 and 180 minutes of stirring (6 samples taken at time intervals of 15 minutes) was 3.9 ± 0.2 mg/mL.

Claims

1. Crystalline form of asenapine maleate characterized by an XRPD pattern comprising at least the following peaks (2-theta, 2 θ) at 5.5, 12.6 and 19.9° (\pm 0.2 degrees).
- 5
2. Crystalline form of asenapine maleate according to claim 1 characterized by an XRPD pattern further comprising the following peaks (2-theta, 2 θ) at 19.1 and 25.2° (\pm 0.2 degrees).
- 10
3. Crystalline form of asenapine maleate according to claim 2 characterized by an XRPD pattern further comprising the following peaks (2-theta, 2 θ) at 9.9, 11.0, 13.7, 14.6, 16.7, 17.3, 18.5, 20.8, 21.6, 22.0, 23.4, 24.2, 25.9, 26.7, 27.7, 28.7, 29.3, 29.8, 30.6, 33.4, 34.4, 34.9, 38.8, 39.2 and 40.2° (\pm 0.2 degrees).
- 15
4. Crystalline form according to claim anyone of claims 1 to 3, wherein the particle size distribution of the crystalline asenapine maleate is characterized by a d₉₀ of 100 μ m or less.
5. Process for preparing the crystalline form according to anyone of claims 1 to 3
- 20 comprising the following steps:
 - i) dissolving asenapine maleate in a solvent or a mixture of solvents at a temperature between 5°C and 80°C;
 - ii) optionally filtering the solution prepared in step (i);
 - 25 iii) combining the solution prepared in step (i) or in step (ii) with an antisolvent while maintaining the temperature of the mixture between 40°C and 100°C;
 - iv) cooling the mixture prepared in step (iii) to a temperature between -20°C and 39°C.
- wherein the solvent or the mixture of solvents comprises a ketone, preferably acetone,
- 30 methyl ethyl ketone or methyl isobutyl ketone, and the antisolvent comprises an alkane or a mixture of alkanes such as pentane, hexane, cyclohexane, methylcyclohexane, heptane or mixtures thereof.
6. The process according to claim 5 wherein the solvent is acetone and the antisolvent
- 35 is hexane.

7. The process according to claim 5 wherein the solvent is acetone and the antisolvent is heptane.

5 8. The process according to any one of claims 5 to 7, wherein the volume/volume ratio of the solvent/antisolvent mixture is from 3:1 to 1:5.

9. Process for preparing the crystalline form of claim 1 to 3 comprising suspending asenapine maleate in a solvent or mixture of solvents wherein asenapine maleate
10 remains at least partially undissolved and comprising seeding with crystalline asenapine maleate of claims 1 to 3, wherein the solvent or mixture of solvents comprises C1-C4 alkyl alcohols.

10. Crystalline form of asenapine maleate characterized by an XRPD pattern
15 comprising at least the following peaks (2-theta, 2 θ) at 7.6, 10.4 and 19.1° (± 0.2 degrees).

11. Crystalline form of asenapine maleate according to claim 10 characterized by an XRPD pattern further comprising the following peaks (2-theta, 2 θ) at 9.5, 19.5 and
20 20.0° (± 0.2 degrees).

12. Crystalline form of asenapine maleate according to claim 11 characterized by an XRPD pattern further comprising the following peaks (2-theta, 2 θ) at 8.3, 11.2, 12.6, 13.3, 13.9, 15.7, 16.3, 16.7, 17.1, 17.4, 17.8, 18.6, 20.9, 21.7, 22.5, 22.9, 23.5, 24.4,
25 24.9, 25.3, 26.7, 28.0, 28.3, 29.1, 29.6 and 31.9° (± 0.2 degrees).

13. Crystalline form according to anyone of claims 10 to 12, wherein the particle size distribution of the crystalline asenapine maleate is characterized by a d_{90} of 100 μm or less.

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14. Process for preparing the crystalline form according to anyone of claims 10 to 13 comprising at least the following steps:

i) dissolving asenapine maleate in a solvent or a mixture of solvents at a suitable
35 temperature between 5°C and 80°C;

- ii) optionally filtering the solution prepared in step (i);
- iii) combining the solution prepared in step (i) or in step (ii) with an antisolvent while maintaining the mixture at a temperature between -20°C and 35°C,

5 wherein the solvent or the mixture of solvents comprises a ketone, preferably acetone, methyl ethyl ketone or methyl isobutyl ketone, and the antisolvent comprises an alkane or a mixture of alkanes such as pentane, hexane, cyclohexane, methylcyclohexane, heptane or mixtures thereof.

10 15. The process according to any one of claims 14 wherein the solution prepared in step (i) or in step (ii) is combined with the antisolvent while maintaining the mixture at a temperature between 20°C and 25°C.

15 16. The process according to claim 15, wherein the solvent is methyl ethyl ketone or acetone and the antisolvent is cyclohexane.

17. The process according to claim 14 wherein the solution prepared in step (i) or in step (ii) is combined with the antisolvent while maintaining the mixture at a temperature between 0°C and 10°C.

20

18. The process according to claim 17, wherein the solvent is methyl ethyl ketone and the antisolvent is heptane.

25 19. The process according to claim 14 wherein the solution prepared in step (i) or in step (ii) is combined with the antisolvent while maintaining the mixture at a temperature between -10°C and -5°C.

20. The process according to claim 19 wherein the solvent is methyl ethyl ketone or acetone and the antisolvent is hexane, heptane or methylcyclohexane or mixtures thereof.

30

21. Process for preparing the crystalline form according to anyone of claims 10 to 12 comprising at least the following steps:

- i) dissolving asenapine maleate in methyl ethyl ketone at a temperature between 5°C and 80°C;
 - ii) optionally filtering the solution prepared in step (i);
 - iii) combining the solution prepared in step (i) or in step (ii) with an antisolvent
- 5 comprising an ether such as diethyl ether, diisopropyl ether, methyl *tert*-butyl ether, cyclopentyl methyl ether or mixtures thereof while maintaining the mixture at a temperature between -10°C and -5°C.
22. Process according to claim 21 wherein the antisolvent is methyl *tert*-butyl ether,
- 10 cyclopentyl methyl ether or mixtures thereof.
23. Process for preparing the crystalline form according to anyone of claims 10 to 12 comprising at least the following steps:
- 15 i) dissolving asenapine maleate in acetone at a temperature between 5°C and 80°C;
 - ii) optionally filtering the solution prepared in step (i);
 - iii) combining the solution prepared in step (i) or in step (ii) with cyclopentyl methyl ether while maintaining the mixture at a temperature between -10°C and -5°C;
- 20 24. Pharmaceutical composition comprising the crystalline form of claims 1 to 3, and/or the crystalline form of claims 10 to 12 and at least one pharmaceutically acceptable carrier.

Fig. 1. X-Ray Powder Diffraction pattern of Form M as obtained in Ex. 2

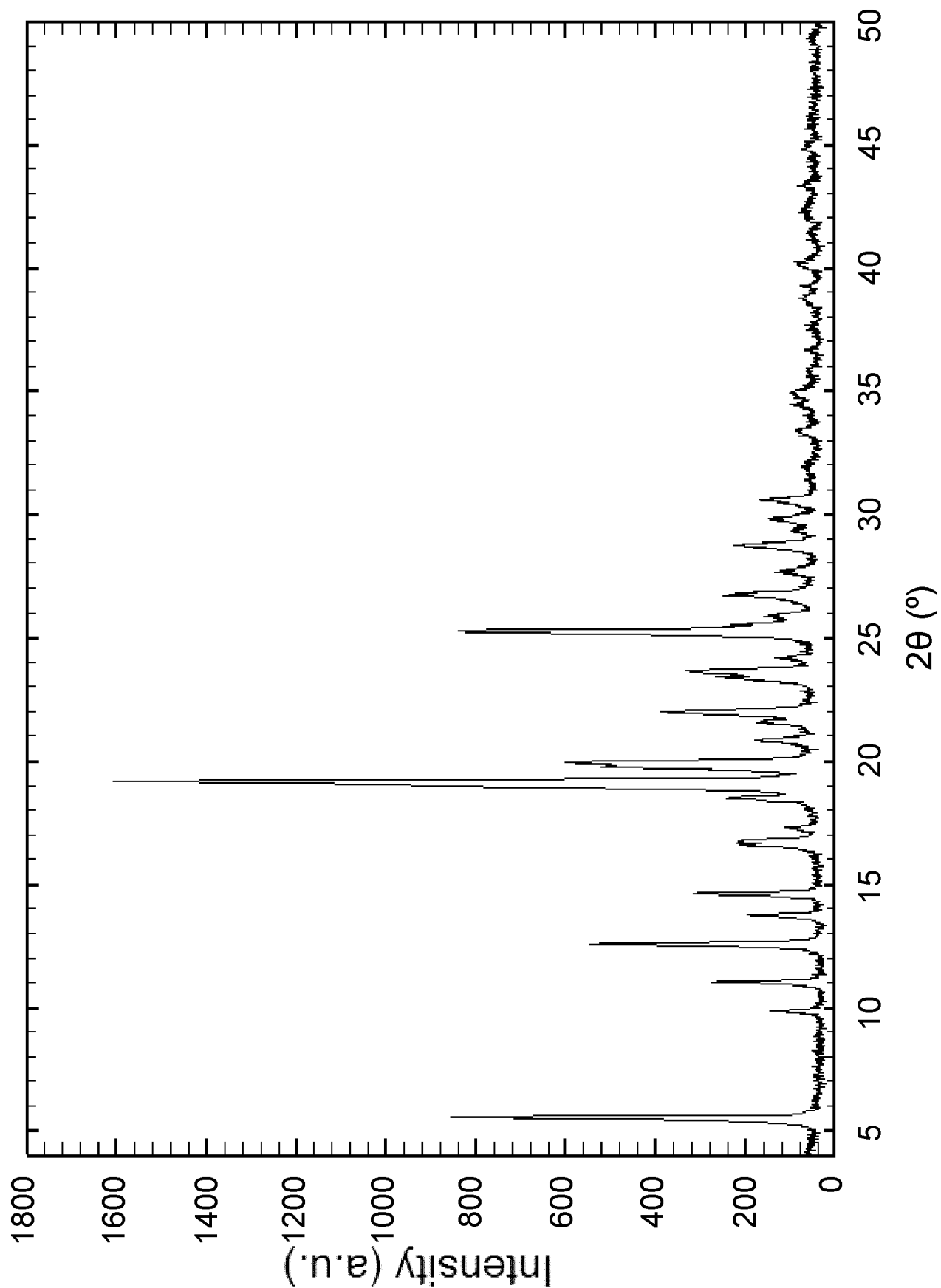


Fig. 2. X-Ray Powder Diffraction pattern of Form T as obtained in Ex.10

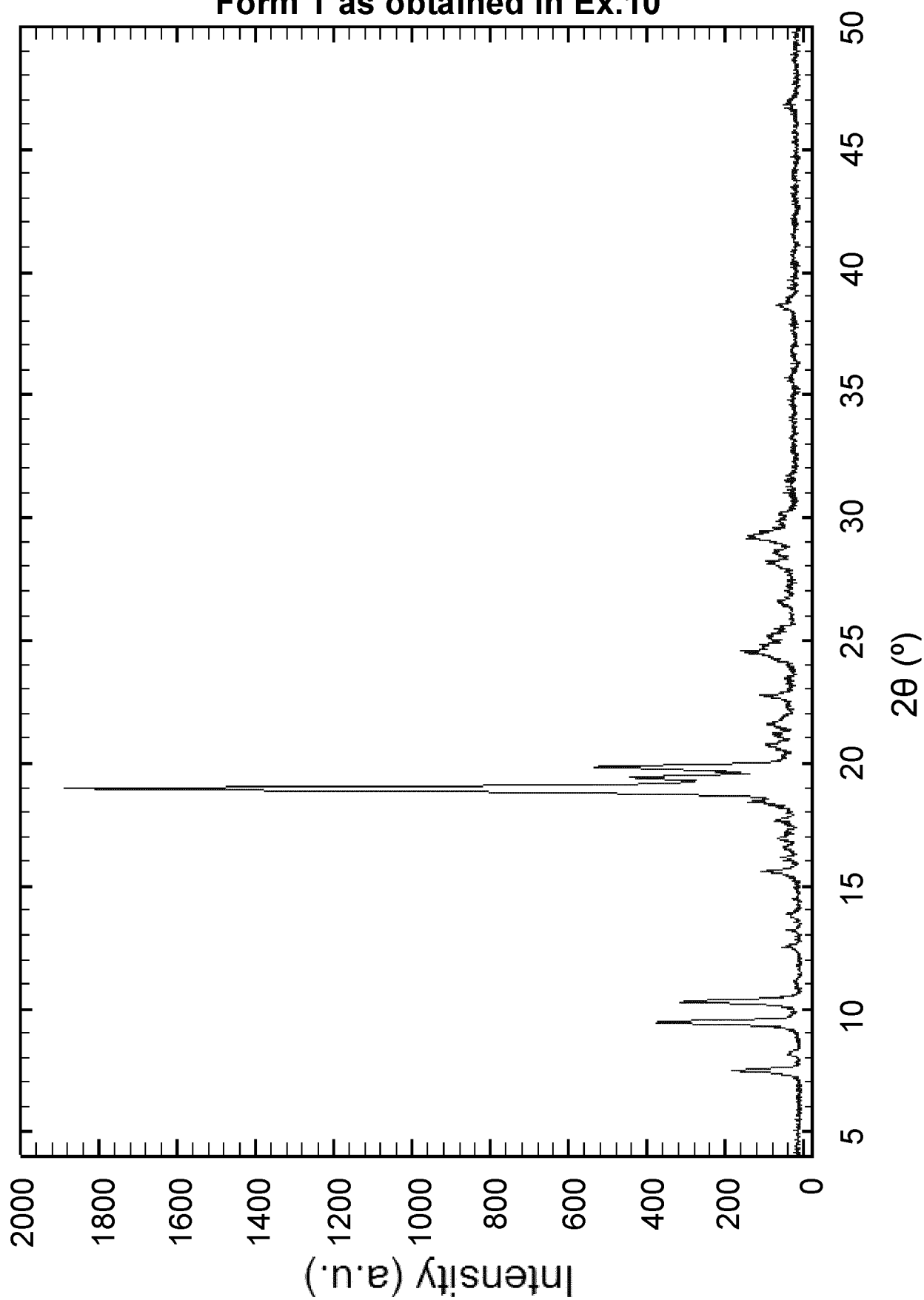


Fig. 3. X-Ray Powder Diffraction pattern of Form H with traces of Form L as obtained in Comp. Ex. 1.

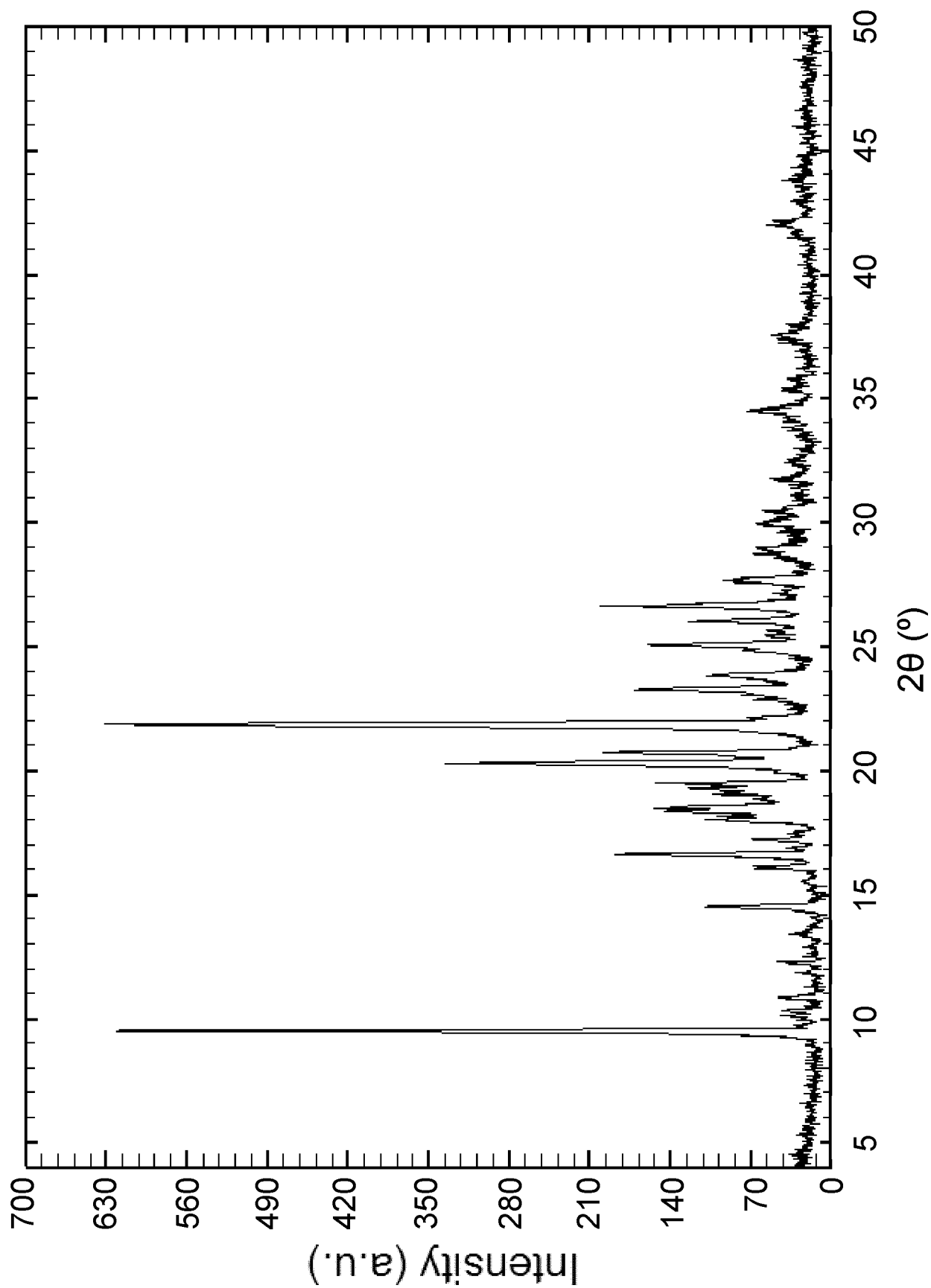


Fig. 4. X-Ray Powder Diffraction pattern of Form H with traces of Form L as obtained in Comp. Ex. 2

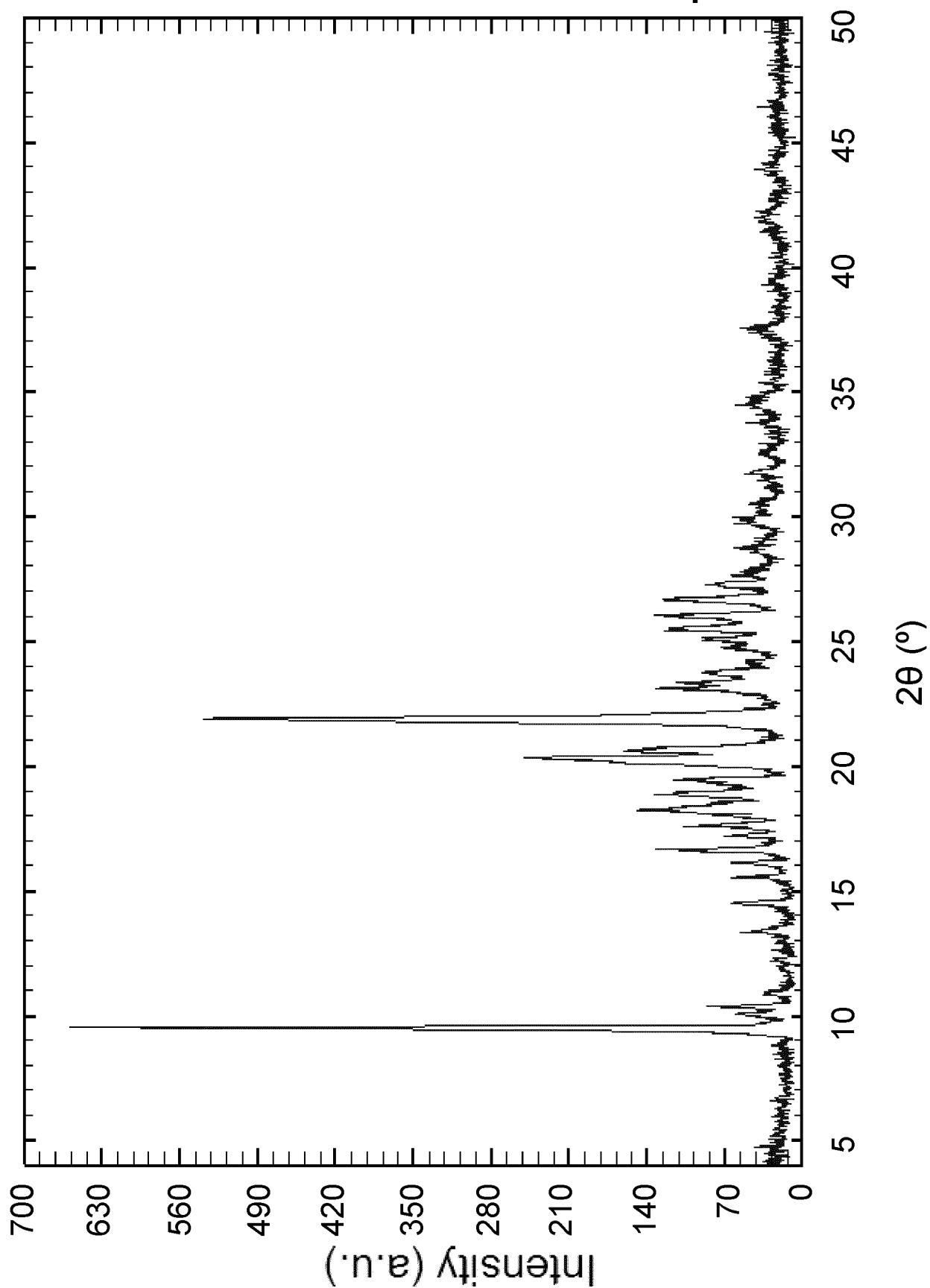


Fig. 5. X-Ray Powder Diffraction pattern of Form H as obtained in Ref. Ex. 1

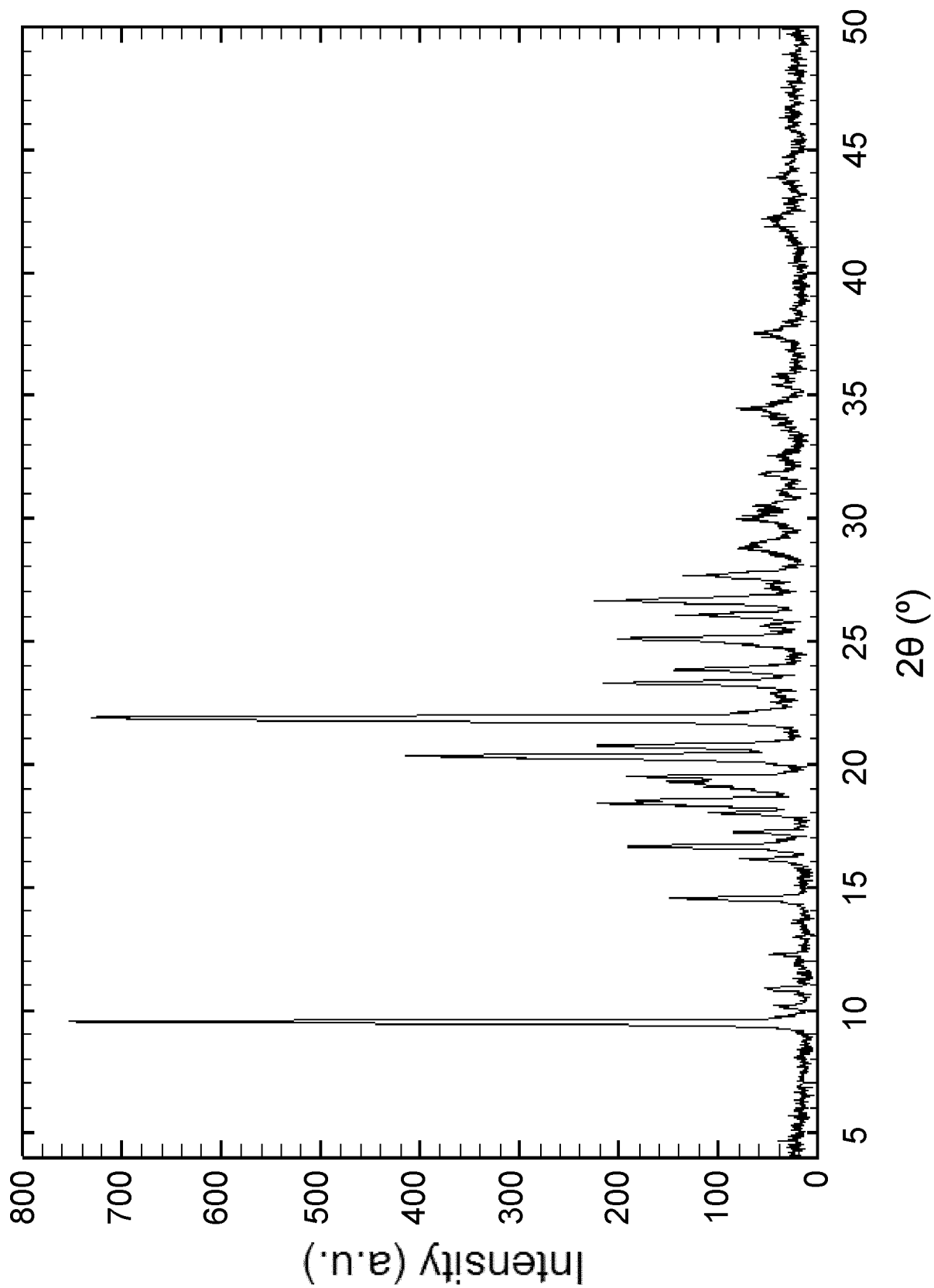


Fig. 6. X-Ray Powder Diffraction pattern of Form L as obtained in Ref. Ex. 3

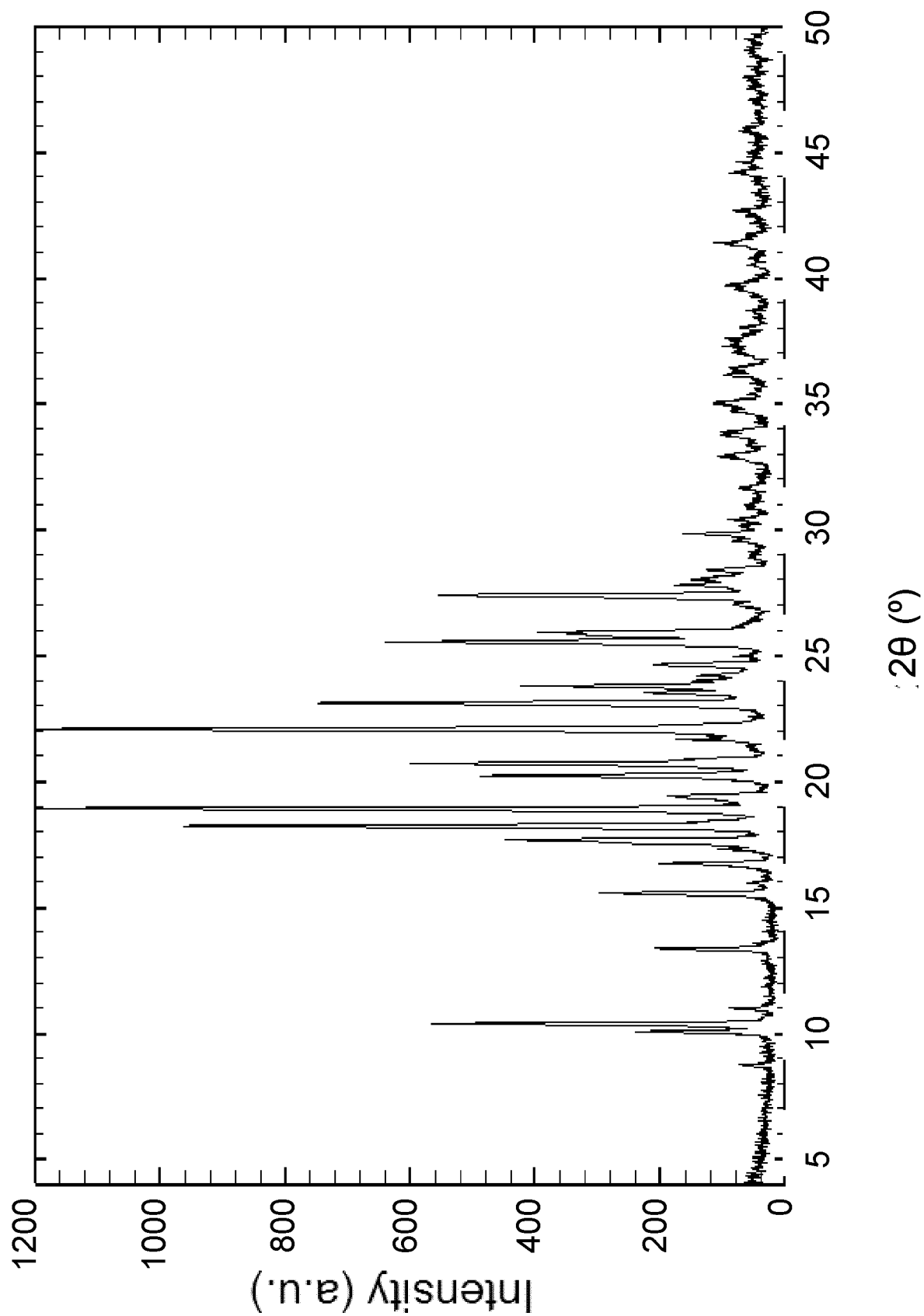


Fig. 7. X-Ray Powder Diffraction pattern of Form M as obtained in Ex. 30

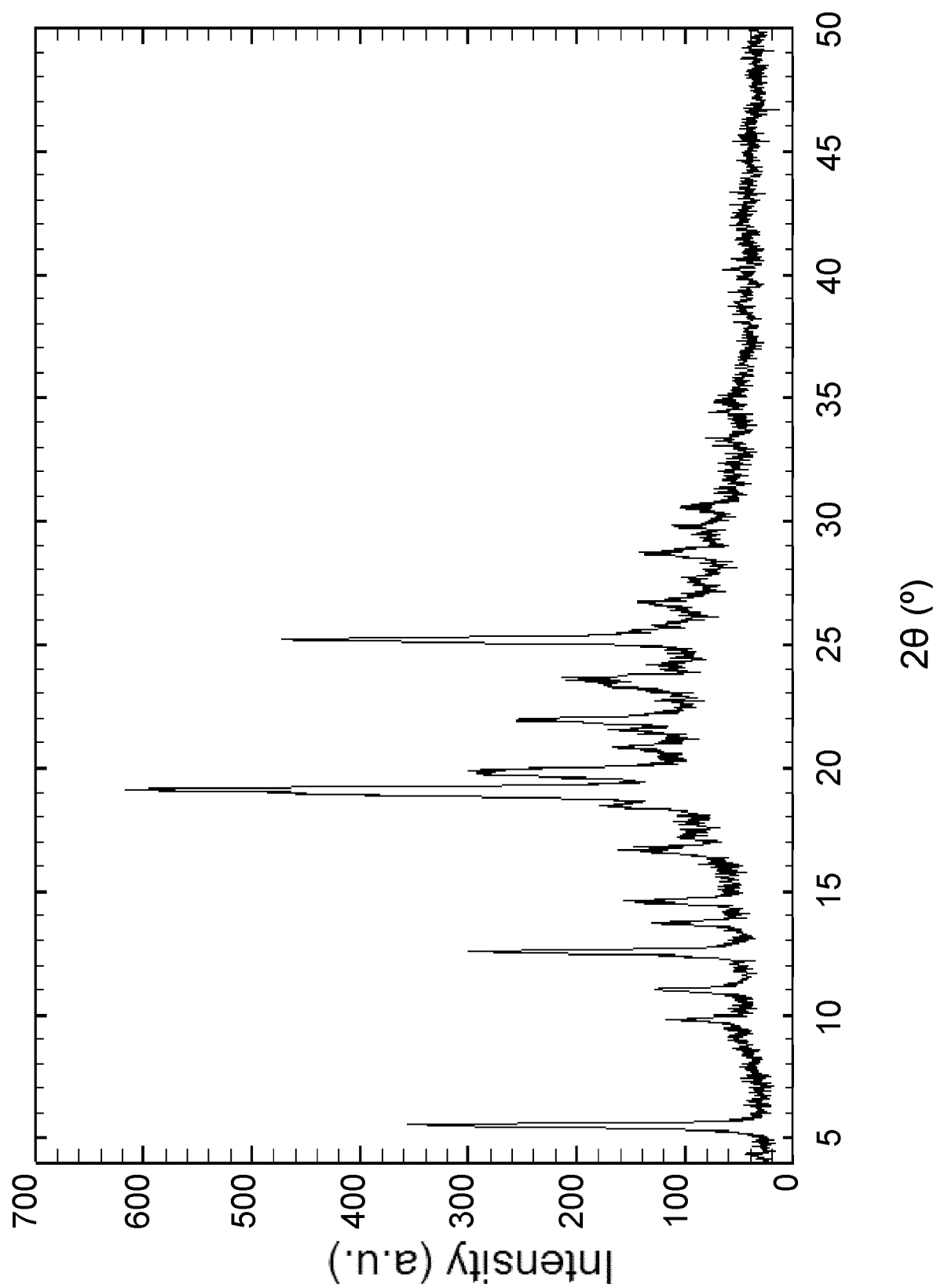
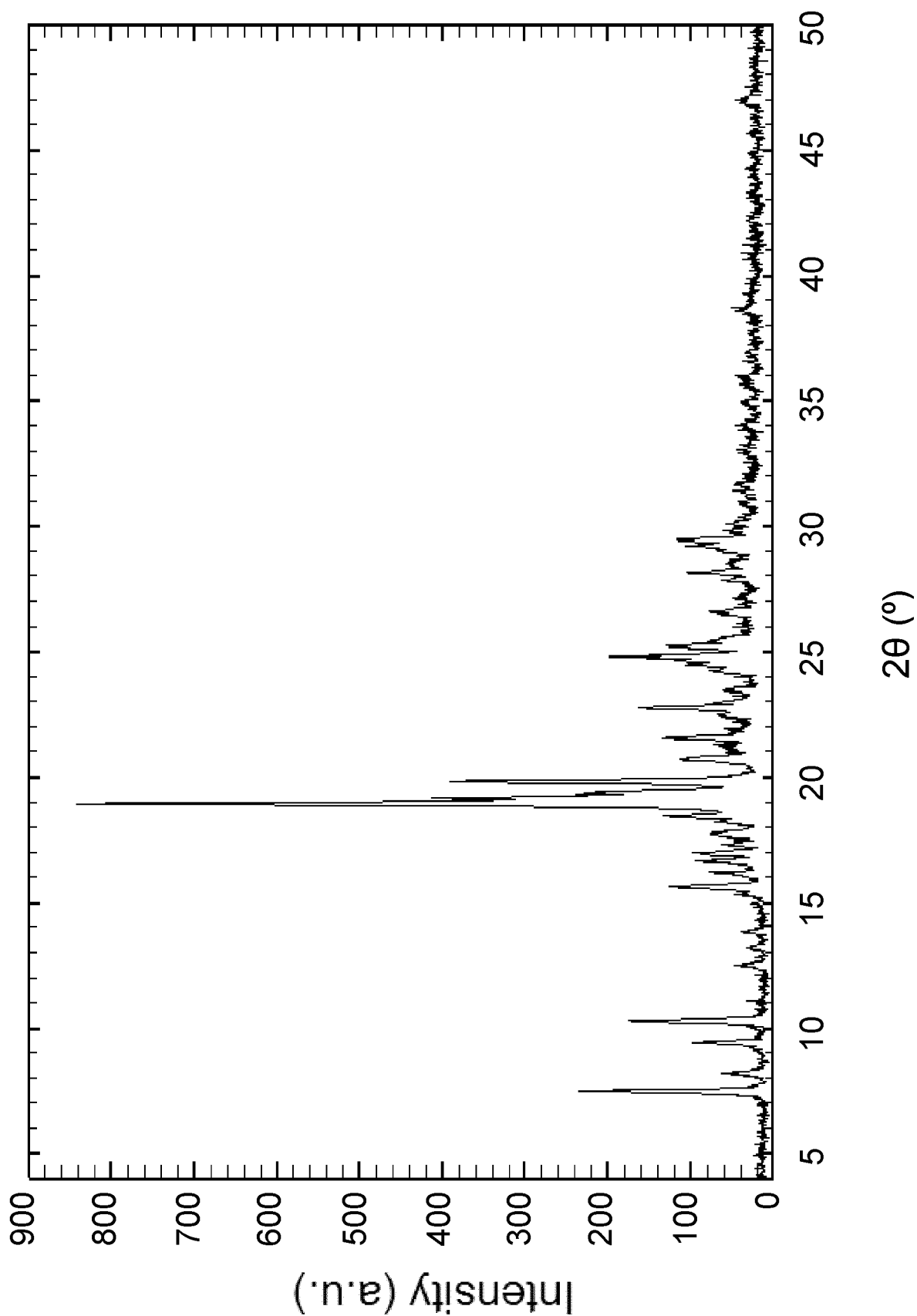


Fig. 8. X-Ray Powder Diffraction pattern of Form T as obtained in Ex. 32



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/053988

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D491/044 A61K31/407 A61P25/18
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

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, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	EP 1 710 245 A1 (ORGANON IRELAND LTD [IE] ORGANON NV [NL]) 11 October 2006 (2006-10-11) cited in the application claims 5, 9	1-24



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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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/053988

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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X,P	<p>DATABASE IP.com prior art database [Online]</p> <p>18 January 2012 (2012-01-18), Disclosed Anonymously: "Polymorphic forms of asenapine maleate", XP002676657, Database accession no. IPCOM000214225D cited in the application Form IV, table 4</p> <p>-----</p>	1
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2012/053988

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