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- (71) **Applicant (for all designated States except US):** SANDOZ AG [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).
- (72) **Inventors; and**
- (71) **Applicants (for US only):** WIESER, Josef [AT/AT]; c/o Sandoz GmbH, Biochemiestrasse 10, A-6250 Kundl (AT). PICHLER, Arthur [AT/AT]; c/o Sandoz GmbH, Biochemiestrasse 10, A-6250 Kundl (AT). NOISTERNIG, Michael [AT/AT]; c/o Sandoz GmbH, Biochemiestrasse 10, A-6250 Kundl (AT).
- (74) **Agent:** KLUSCHANZOFF, Harald; Hexal AG, IP Department, Industriestrasse 25, 83607 Holzkirchen (DE).
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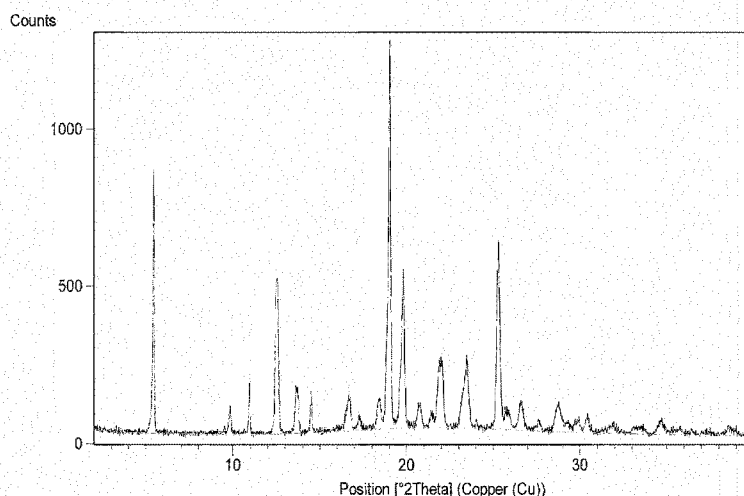


Figure 1

(57) **Abstract:** The present invention relates to a form of Asenapine Maleate with XRPD peaks at about 5.5, 12.5, 19.0 and 25.3 and to methods for the preparation thereof. Furthermore the invention relates to a reproducible process for the preparation of pure monoclinic form of Asenapine Maleate in crystalline form and to pharmaceutical compositions comprising the pure monoclinic form of asenapine maleate.

CRYSTAL FORM OF ASENAPINE MALEATE

FIELD OF THE INVENTION

5 The present invention relates to a new crystal form of Asenapine Maleate (form S) and to methods for the preparation thereof. Furthermore the invention relates to a reproducible process for the preparation of pure monoclinic form of Asenapine Maleate in crystalline form and to pharmaceutical compositions comprising the pure monoclinic form of asenapine maleate.

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BACKGROUND OF THE INVENTION

Asenapine maleate (trans-5-Chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole maleate; CAS Registry Nr. 85650-56-2) is approved in the US both for the acute treatment of schizophrenia and the manic and mixed episodes
15 associated with bipolar I disorder with or without psychotic features in adults.

The preparation of asenapine is disclosed in the United States Patent No. 4,145,434. The maleic acid salt is prepared from the free base and maleic acid in ethanol as solvent (i.e. production example 3 in EP2166012) or in isopropanol as solvent (i.e. example 3 in
20 WO2008/3460). For further purification, the salt is recrystallized from 90% aqueous ethanol (i.e. example 6 in WO2008/3460) or acetone and heptane (i.e. example 17 in US2007/27134).

Two non solvated polymorphic forms have been reported for Asenapine maleate, the
25 monoclinic form H and the orthorhombic form L. The physico-chemical properties of the monoclinic form H are described by Funke et al. (Arzneim.-Forsch./Drug Res. 40 (1999), 536-539), while patent application WO2006/106135 discloses the orthorhombic crystalline form L of asenapine maleate.

30 Asenapine is described to show low bioavailability caused by extensive first-pass metabolism when taken up via the gastrointestinal tract (see WO95/23600). For this reason, asenapine maleate is marketed as a sublingual tablet (Saphris ®, USA, Sycrest ® Europe) which contains 5 mg or 10 mg of the active substance in gelatin and mannitol. The drug product contains the orthorhombic form L, no monoclinic form H and between ~10% amorphous
35 asenapine maleate (10 mg strength) and ~24% amorphous asenapine maleate (5 mg strength). The orthorhombic form of asenapine maleate, form L, is the more stable crystalline

form of asenapine maleate and has a lower solubility than the monoclinic form of asenapine maleate, form H. Form L is used in the marketed sublingual tablet, as described above.

The reason for the use of form L - despite its lower solubility - is that for sublingual or buccal administration, a drug substance with a small particle size is desired (see page 2, lines 8 to 16 of WO2006/106135 A1). This is because when drug substance particles are small it takes only short periods of time for the small particles to dissolve and thus to achieve high concentrations in the saliva. WO2006/106135 A1 discloses that only form L can be reproducibly obtained by micronization in high polymorph purity whereas micronization of monoclinic form H resulted in a non reproducible product (page 2, lines 22 to 32 and examples 9 and 10 of WO2006/106135 A1).

Thus, there is a need for a simple and reproducible production of the pure monoclinic form of asenapine maleate in form of small crystalline particles.

SUMMARY OF THE INVENTION

The present invention relates to a new crystalline form of asenapine maleate which is a useful intermediate in the production of polymorphically pure monoclinic form of asenapine maleate.

Therefore, in one aspect, the invention relates to crystalline asenapine maleate having an X-ray powder diffraction pattern (XRPD) obtained with Cu K-alpha radiation comprising peaks at 2-theta angles of $5.5 \pm 0.2^\circ$, $12.5 \pm 0.2^\circ$, $19.0 \pm 0.2^\circ$ and $25.3 \pm 0.2^\circ$ (Asenapine maleate form S).

Alternatively Asenapine maleate form S can be described by having an attenuated total reflectance infrared spectrum comprising absorption bands at wavenumbers of about $3035 \text{ cm}^{-1} \pm 2 \text{ cm}^{-1}$, $2976 \text{ cm}^{-1} \pm 2 \text{ cm}^{-1}$, $1476 \text{ cm}^{-1} \pm 2 \text{ cm}^{-1}$, $1447 \text{ cm}^{-1} \pm 2 \text{ cm}^{-1}$, $1351 \text{ cm}^{-1} \pm 2 \text{ cm}^{-1}$, $1246 \text{ cm}^{-1} \pm 2 \text{ cm}^{-1}$, $1232 \text{ cm}^{-1} \pm 2 \text{ cm}^{-1}$, $1080 \text{ cm}^{-1} \pm 2 \text{ cm}^{-1}$, $867 \text{ cm}^{-1} \pm 2 \text{ cm}^{-1}$ and $768 \text{ cm}^{-1} \pm 2 \text{ cm}^{-1}$.

In another aspect the present invention provides a process for the production of Asenapine maleate form S.

Asenapine maleate form S of the present invention enables the preparation of monoclinic form of asenapine maleate with high polymorphic purity, the monoclinic crystalline material having a particle size distribution characterized by a d95 of at most 50 μm , preferably at most 30 μm .

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The present invention therefore, in another aspect, relates to a process for preparing the monoclinic form of asenapine maleate with high polymorphic purity starting from Asenapine maleate form S and, in yet another aspect, the use of Asenapine maleate form S of the present invention for the preparation of monoclinic asenapine maleate.

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In another aspect the present invention relates to the monoclinic form of Asenapine maleate in the form of crystalline material having a particle size distribution characterized by a d95 of at most 50 μm comprising less than 10% w/w of the orthorhombic crystalline form of asenapine maleate in relation to the total amount of Asenapine maleate.

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In yet another aspect the present invention relates to the use of the monoclinic form of Asenapine maleate for the preparation of a pharmaceutical composition intended for sublingual or buccal administration and, in yet another aspect, to a pharmaceutical composition comprising the monoclinic form of asenapine maleate in the form of crystalline material having a particle size distribution characterized by a d95 of at most 50 μm .

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BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: XRPD pattern of the form S of trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]-oxepino[4,5-c]pyrrole (Z)-2-butenedioate (Asenapine maleate)

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Figure 2: IR spectrum of the form S of Asenapine maleate

Figure 3: XRPD pattern of monoclinic Asenapine maleate in the form of crystalline material having a particle size distribution characterized by a d95 of 34.9 μm obtained from example 3.

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Figure 4: XRPD pattern of micronized monoclinic Asenapine maleate in the form of crystalline material having a particle size distribution characterized by a d95 of 10.0 μm obtained from example 5.

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Figure 5: (a) PSD of pure monoclinic Asenapine maleate as obtained from example 3; (b) PSD of pure monoclinic Asenapine maleate as obtained from example 5.

Figure 6: XRPD pattern of monoclinic Asenapine maleate in the form of crystalline material having a particle size distribution characterized by a d95 of 34.9 μm obtained from example 3 to which 5% (a) or 10% (b) of the orthorhombic Asenapine Maleate have been added.

DETAILED DESCRIPTION OF THE INVENTION

In the course of crystallization experiments carried out with Asenapine maleate it was found that the maleate salt in general crystallizes as the monoclinic form of asenapine maleate, herein sometimes also referred to as form H, under a variety of conditions in the form of large crystals, as described in WO2006/106135A1. For example crystallization experiments by cooling from solutions of asenapine maleate in ethanol, isopropanol, n-butanol, methylisobutylketon, tetrahydrofuran, ethylacetate or isopropylacetate as solvent provided form H with typical d95 values between 100 μm and 300 μm . Evaporation and cooling crystallization experiments sometimes led to amorphous samples or sometimes no solid at all. Antisolvent crystallization of asenapine maleate from ethanol or isopropanol by the addition of diethyl ether or hexane gave also form H.

It has been surprisingly been found that dissolving asenapine maleate at defined concentrations in isopropanol and then adding defined relative amounts of methyl tert-butyl ether or diisopropyl ether, preferably at room temperature, afforded a new crystalline form of asenapine maleate after allowing sufficient time for crystallization. As a further surprise, the new crystalline form of Asenapine maleate enabled the reproducible production of crystalline monoclinic form of Asenapine maleate in the form of crystalline material having a particle size distribution characterized by a d95 of at most 50 μm , comprising less than 10% w/w of the orthorhombic crystalline form of asenapine maleate in relation to the total amount of Asenapine maleate, in high polymorphic purity, whereas the micronization of monoclinic form H with relatively high d95 values has been described to result in a non reproducible product (page 2, lines 22 to 32 and examples 9 and 10 of WO2006/106135 A1).

For the purposes of the present invention the following definitions apply.

w/w: weight per weight

PSD: Particle size distribution as determined by the laser diffraction spectroscopy method detailed in the experimental section

d95 as used throughout this disclosure means that 95% of the particles (based on volume) are smaller than or equal to the indicated size.

- 5 XRPD : X-ray powder diffraction pattern obtained with Cu-K α radiation at a wavelength of 0,15419 nm.

DSC: differential scanning calorimetry

- 10 Monoclinic form of asenapine maleate: the crystalline form of asenapine maleate named "form H" or "monoclinic form" as characterized in WO2006/106135 by the two most characteristic peaks at 9.6° and 26.8° 2-Theta. According to page 4, lines 17-20 of WO2006/106135, the monoclinic form of asenapine maleate can be further characterized by peaks at 2-theta of 9.6°, 20.4°, 22.0°, 23.4°, 25.2° and 26.8°. The monoclinic form of
15 asenapine maleate can also be characterized by the crystal structure belonging to the monoclinic form consisting of the space group P2₁/n and 4 molecules in the unit cell.

- Orthorhombic form of asenapine maleate: the crystalline form of asenapine maleate named "form L" or "orthorhombic form" as characterized in WO2006/106135 by the two most
20 characteristic peaks at 10.5° and 15.7° 2-Theta. According to page 4, lines 22-25 of WO2006/106135, the orthorhombic form of asenapine maleate can be further characterized by peaks at 2-theta of 10.5°, 15.7°, 18.3°, 19.0°, 22.2°, 23.2° and 27.5°. The orthorhombic form of asenapine maleate can also be characterized by the crystal structure belonging to the orthorhombic form consisting of the space group Pca2₁ and 8 molecules in the unit cell.

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Batch (or Lot)

- A specific quantity of material produced by a process or a series of processes to a final homogeneous state with specified limits and identified by a batch number and a material number. In the case of continuous production a batch may correspond to a defined fraction of
30 the production. The batch size may be defined either by a fixed quantity or the amount produced in a fixed time interval.

Batch Number (or Lot Number)

- A unique combination of numbers, letters, and/or symbols that identifies a batch (or lot) and
35 from which the production and distribution history can be determined.

The present invention thus, in a first aspect, relates to a new crystalline form of Asenapine maleate (form S).

Crystalline asenapine maleate of the invention can be characterized by an X-ray powder diffraction pattern (XRPD) obtained with Cu K-alpha radiation comprising peaks at 2-theta angles of $5.5 \pm 0.2^\circ$, $12.5 \pm 0.2^\circ$, $19.0 \pm 0.2^\circ$ and $25.3 \pm 0.2^\circ$, optionally further comprising peaks at 2-theta angles $10.9 \pm 0.2^\circ$, $13.7 \pm 0.2^\circ$, $14.5 \pm 0.2^\circ$, $19.8 \pm 0.2^\circ$ and $23.5 \pm 0.2^\circ$, optionally comprising peaks at all those 2-theta angles listed in Table 1 with a relative intensity of above 10%, and further optionally comprising peaks at all 2-theta angles listed in Table 1. An example of a characteristic X-ray powder diffraction pattern of form S of Asenapine maleate is shown in Figure 1.

Table 1: X-Ray Powder Diffraction (XRPD) pattern of Asenapine maleate

Angle [$2\text{-theta} \pm 0.2^\circ$]	relative intensity [%]
5.5	69
9.8	7
10.9	13
12.5	41
13.7	12
14.5	10
16.7	9
18.4	8
19.0	100
19.8	41
22.0	17
23.5	18
25.3	47
26.6	7
28.7	7
30.4	4

The main characteristics of diffraction line profiles are 2θ position, peak height, peak area and shape (characterised by, for example, peak width or asymmetry, analytical function, empirical representation). In addition to the diffraction peaks, an X-ray diffraction experiment

also generates a more-or-less uniform background, upon which the peaks are superimposed. Besides specimen preparation, other factors contribute to the background, for instance the sample holder, diffuse scattering from air and equipment, other instrumental parameters such as detector noise, general radiation from the X-ray tube, etc. The peak-to-background ratio can be increased by minimising background and by choosing prolonged exposure times. In the context of the present invention, the term "peak" denotes a particular 2θ position, wherein the signal-to-noise ratio (calculated according to item 2.2.46 of the European Pharmacopoeia) is greater than 3/1.

Alternatively, or additionally, Asenapine maleate form S of the present invention may be characterized by an attenuated total reflectance infrared spectrum comprising absorption bands at wavenumbers of about $3035\text{ cm}^{-1} \pm 2\text{ cm}^{-1}$, $2976\text{ cm}^{-1} \pm 2\text{ cm}^{-1}$, $1476\text{ cm}^{-1} \pm 2\text{ cm}^{-1}$, $1447\text{ cm}^{-1} \pm 2\text{ cm}^{-1}$, $1351\text{ cm}^{-1} \pm 2\text{ cm}^{-1}$, $1246\text{ cm}^{-1} \pm 2\text{ cm}^{-1}$, $1232\text{ cm}^{-1} \pm 2\text{ cm}^{-1}$, $1080\text{ cm}^{-1} \pm 2\text{ cm}^{-1}$, $867\text{ cm}^{-1} \pm 2\text{ cm}^{-1}$ and $768\text{ cm}^{-1} \pm 2\text{ cm}^{-1}$. The interval $\pm 2\text{ cm}^{-1}$ is a usual deviation for these bands. An example of a typical IR spectrum is shown in Figure 2.

Asenapine free base can be obtained from the marketed product Sycrest or it can be prepared, for example, according to US 4,145,434.

The crystalline asenapine maleate form S of the present invention can be prepared by the following process comprising the following steps:

- (a) dissolving trans-5-chloro-2,3,3a,12b-tetrahydro-2-methyl-1H-dibenz [2,3:6,7] oxepino [4,5-c] pyrrole (asenapine) in a solvent selected from isopropanol or methanol to obtain a solution with a concentration of 1g asenapine per 3 ml to 10 ml of solvent, optionally per 4 ml to 6 ml of solvent;
- (b) adding maleic acid to the solution obtained in step (a), wherein from 0.8 mol to 1.2 mol of maleic acid is added per 1 mol of asenapine, preferably wherein about 1 mol of maleic acid is added per 1 mol of asenapine;
- (c) adding an ether to the solution obtained in step (b) in an amount sufficient to induce crystallization of asenapine maleate; and
- (d) allowing asenapine maleate to crystallize, and optionally (e) isolating the crystalline Asenapine maleate form S, for example by filtration,

which process forms another aspect of the present invention.

Steps (a) and (b) can be performed as one step (a'), for example if crystalline asenapine maleate instead of asenapine is dissolved at the above concentration in the above-

mentioned solvent. Steps (a) and (b) are typically performed at room temperature or slightly elevated temperatures in order to facilitate dissolution of asenapine and maleic acid (steps (a) and (b)) or of asenapine maleate (Step (a')). Temperatures are typically from 10°C to 80°C, more preferably from 15°C to 50°C. After dissolution of asenapine and maleic acid (steps (a) and (b)) or of asenapine maleate (Step (a')) the resulting solution can optionally be filtered in order to remove any solids which might still be present.

It is to be understood that the volumes provided in process step (a) are only given for correct determination of the concentrations to be used, and they are not intended to limit the process to be carried out in any one particular total volume. A total volume of 1l or even 10l or 100l for large scale technical production of the crystalline form S of asenapine maleate of the present invention is within the scope of the inventive process described above. It is apparent to the skilled person that in such a higher total volume a correspondingly higher total amount of asenapine and maleic acid or asenapine maleate need to be employed in order to reach the concentration specified in step (a).

An ether or a mixture of ethers is typically added as an antisolvent in step (c) in order to induce crystallization. Examples of ethers are C₄- to C₈- ethers, with Methyl tert-butylether (MTBE) and diisopropylether being particular examples. The antisolvent should be added fast and under rapid mixing so that a clear solution is obtained immediately after addition of the antisolvent in step (c). Fast in this context in particular means that the ether addition takes place within 5 minutes, in particular within 2 minutes. Rapid mixing in this context in particular means the application of a means for mixing which is sufficient to generate a homogeneous mixture after ether addition within 2 minutes, preferably within 30 seconds.

Preferred combinations of the solvent for step (a) or step (a') and the antisolvent for step (c) are methanol (step a') and an ether selected from methyl tert-butyl ether and diisopropylether (step c), or isopropanol (step a) and an ether selected from methyl tert-butyl ether and diisopropylether (step c).

In a preferred embodiment MTBE is added in step (c), optionally in an amount of from 3 to 10 volumes of MTBE per volume of the solution obtained after step (b).

Optionally, the ether is added at the same temperature as described for steps (a) and (b). Optionally after addition of the ether in step (c), seed crystals of asenapine maleate form S can be added in order to facilitate crystallization.

Crystallization of asenapine maleate form S from the mixture obtained from step (c) needs the allowance of sufficient time, for example from 60 min to 7 days, more particularly from 1 hour to 2 days, and should optionally be facilitated by cooling. Optionally, step (d) can be performed at a temperature of from -20°C to 15°C, optionally of from -5°C to 10°C. The crystallization step is typically carried out while only slowly stirring the mixture or without agitation. The skilled person will be able to easily determine combinations of time and temperature best suitable for optimal recovery of asenapine maleate as crystalline material and the examples provide information about suitable combinations.

- 10 The crystalline asenapine maleate form S of the present invention obtainable from the processes described in examples 1 and 2 crystallizes in the form of relatively small needles.

The present inventors have surprisingly found that the crystalline form S of asenapine maleate transforms to the monoclinic form of asenapine maleate upon contact with isopropanol. Furthermore, it has been surprisingly found that the monoclinic form of asenapine maleate becomes reproducibly available in the form of crystalline material having a particle size distribution characterized by a d₉₅ of at most 50 µm, the crystalline material comprising less than 10% w/w of the orthorhombic crystalline form of asenapine maleate in relation to the total amount of Asenapine maleate due to the present invention.

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Thus, in a further aspect, the present invention relates to a process for preparing the monoclinic form of asenapine maleate, comprising the steps of:

- (a) providing a suspension of the crystalline form S of Asenapine maleate in isopropanol, and
25 (b) allowing the crystalline form S of Asenapine maleate to transform to the monoclinic form of asenapine maleate.

Typically crystalline asenapine maleate form S of the present invention is suspended at a ratio of about 1g crystalline asenapine maleate form S per every 5ml of isopropanol. This concentration provides a slurry which can be stirred and which allows transformation to the monoclinic form of asenapine maleate in high yield.

It is to be understood that the volume of 5ml provided for process step (a) above is only given for correct determination of the ratio of crystalline asenapine maleate and isopropanol to be used for slurry preparation, and it is not intended to limit the process to be carried out in any one particular total volume. A total volume of 1l or even 10l or 100l for large scale technical production of the monoclinic form of asenapine maleate from asenapine maleate

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form S is within the scope of the inventive process described above. It is apparent to the skilled person that in such a higher total volume a correspondingly higher total amount of asenapine maleate form S is to be employed in order to reach the ratio of about 1g crystalline form S per 5ml of isopropanol.

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Step (b) is typically performed at a temperature of at most 50°C, with lower temperatures of from -20°C to 40°C, and optionally from 0°C to 30°C being preferred.

The typical length of step (b) is at least 30 minutes, optionally from 90 minutes to 3 days.

10 Gentle stirring can be applied during step (b). After the transformation, the monoclinic form of asenapine maleate can be isolated from the slurry, for example by simple means like filtration or centrifugation. The isolated material can be washed with isopropanol and can be further dried, e.g. by the application of a vacuum.

15 Isopropanol is the preferred solvent for the transformation of form S to the monoclinic form of asenapine maleate, since the monoclinic form is stable in isopropanol and does not convert to the orthorhombic form when kept in isopropanol. A suspension of the monoclinic form H in isopropanol was polymorphically stable for two weeks at 27°C.

20 The monoclinic form of asenapine maleate of the present invention can further be prepared by following the above-disclosed process for preparing the crystalline asenapine maleate form S and using isopropanol instead of an ether to directly induce crystallization of monoclinic asenapine maleate via the form S. In particular, in a further aspect, the present invention relates to a process for preparing the monoclinic form of asenapine maleate,
25 comprising the steps of:

- (a) dissolving trans-5-chloro-2,3,3a,12b-tetrahydro-2-methyl-1H-dibenz [2,3:6,7] oxepino [4,5-c] pyrrole (asenapine) in isopropanol to obtain a solution with a concentration of 1g asenapine per 3 ml to 10 ml of solvent, optionally per 4 ml to 6 ml of solvent;
- (b) adding maleic acid to the solution obtained in step (a), wherein from 0.8 mol to 1.2 mol
30 of maleic acid is added per 1 mol of asenapine, preferably wherein about 1 mol of maleic acid is added per 1 mol of asenapine;
- (c) adding isopropanol to the solution obtained in step (b) in an amount sufficient to induce crystallization of asenapine maleate;
- (d) allowing asenapine maleate to crystallize, and optionally (e) isolating the monoclinic
35 form of asenapine maleate, for example by filtration; and
- (e) optionally after step (a), (b) or (c), seed crystals of asenapine maleate form S are added in order to facilitate crystallization.

The form S of asenapine maleate of the present invention is thus a useful intermediate, allowing for the first time the reproducible preparation of monoclinic form of Asenapine maleate in the form of crystalline material having a particle size distribution characterized by a d95 of at most 50 μm , the crystalline material comprising less than 10% w/w of the orthorhombic crystalline form of asenapine maleate in relation to the total amount of Asenapine maleate. Thus, in another aspect, the present invention relates to the use of the crystalline form S of Asenapine Maleate for the preparation of the monoclinic form of Asenapine Maleate, in particular the monoclinic form of Asenapine maleate in the form of crystalline material having a particle size distribution characterized by a d95 of at most 50 μm , the crystalline material comprising less than 10% w/w of the orthorhombic crystalline form of asenapine maleate in relation to the total amount of Asenapine maleate.

The monoclinic form of Asenapine maleate in the form of crystalline material having a particle size distribution characterized by a d95 of at most 50 μm , the crystalline material comprising less than 10% w/w of the orthorhombic crystalline form of asenapine maleate in relation to the total amount of Asenapine maleate, in turn, allows the preparation of pharmaceutical compositions comprising it. Thus, in a preferred aspect, the present invention relates to the use of the crystalline form S of Asenapine Maleate for the preparation of the monoclinic form of Asenapine Maleate in the form of crystalline material having a particle size distribution characterized by a d95 of at most 50 μm , the crystalline material comprising less than 10% w/w of the orthorhombic crystalline form of asenapine maleate in relation to the total amount of Asenapine maleate, wherein the monoclinic form of Asenapine Maleate is further used in the preparation of a pharmaceutical composition, optionally for sublingual or buccal administration.

For the above use the monoclinic form of Asenapine maleate is preferably in the form of crystalline material having a particle size distribution characterized by a d95 of at most 50 μm , preferably at most 30 μm , more preferably at most 25 μm .

As described in WO2006/106135A1 on page 1, line 24 to page 2, line 32, which disclosure is herein explicitly incorporated by reference, the monoclinic form of asenapine maleate (also called form H) is typically comprised of large crystalline particles over 100 μm in size. This finding was confirmed in reference examples 1 and 2, where a preparation of the monoclinic form of asenapine maleate by recrystallization from ethanol had a mean particle size of 90 μm and a d95 of more than 200 μm (see reference example 2), while the monoclinic form prepared from asenapine free base and maleic acid in ethanol with addition of crystal seeds

and diethyl ether had a mean particle size of 51µm and a d95 of 128µm (see reference example 1).

When it was previously attempted (WO2006/106135A1) to generate smaller crystalline particles by micronization of the large crystals of the monoclinic form H, highly variable and unpredictable results were obtained even when the starting material was taken from the same batch of the monoclinic form of asenapine maleate. The polymorphic form of the micronized crystals was either one of two alternatives (i.e. different polymorphs) or a mixture of both and one particular product could not be reproducibly obtained by micronization of the large crystals of the monoclinic form of asenapine maleate (see WO2006/106135A1, in particular examples 9 and 10 of WO2006/106135A1).

However, for the development of sublingual or buccal formulations, crystalline asenapine maleate with a small average particle size is desired in order to facilitate quick dissolution of asenapine maleate in the saliva. Moreover, this crystalline material should at the same time be polymorphically pure, as a mixture of polymorphic forms has different physicochemical characteristics than the pure forms that are comprised in the mixture, making it hard to produce pharmaceutical compositions with reproducible characteristics based on such mixtures of polymorphs (see also WO2006/106135A1 page 2, line 34 to page 3, line 10 for a discussion of the disadvantages of polymorph mixtures).

WO2006/106135A1 proposed the highly pure orthorhombic form of asenapine maleate as a solution to the above problem. However, the monoclinic form of asenapine maleate is more readily soluble than the orthorhombic form, when two samples of the different polymorphic forms with the same particle size distribution are compared, and thus, the monoclinic form of asenapine maleate would be highly desirable as a potentially more bioavailable form of asenapine maleate, provided that it was reproducibly available in the form of small crystals, such as in the form of crystalline material having a particle size distribution characterized by a d95 of at most 50 µm, with high polymorphic purity. The present invention solves this objective by reproducibly providing this material.

In a further aspect, therefore, the present invention relates to monoclinic form of Asenapine Maleate in the form of crystalline material having a particle size distribution characterized by a d95 of at most 50 µm, the crystalline material comprising less than 10% w/w of the orthorhombic crystalline form of asenapine maleate in relation to the total amount of Asenapine maleate, preferably the crystalline material comprising less than 5% of the

orthorhombic crystalline form of asenapine maleate, and most preferably comprising no detectable amount of the orthorhombic crystalline form of asenapine maleate.

5 The relative amount of the crystalline orthorhombic form of asenapine maleate in relation to the total amount of asenapine maleate can be determined by mixing defined amounts of pure crystalline orthorhombic form of asenapine, for example obtainable according to example 5 of WO2006/106135, with defined amounts of pure crystalline monoclinic form of asenapine maleate, for example obtainable according to example 3 of the present invention. In such a manner reference mixtures comprised of 10% w/w orthorhombic form of asenapine maleate and 90% w/w crystalline monoclinic form of asenapine maleate or 5% w/w orthorhombic form of asenapine maleate and 95% w/w crystalline monoclinic form of asenapine maleate or 1% w/w orthorhombic form of asenapine maleate and 99% w/w crystalline monoclinic form of asenapine maleate can be prepared. The content w/w of crystalline orthorhombic form of asenapine maleate can then be determined by taking an XRPD of the test sample and
15 comparing it with the XRPDs of the reference mixtures.

The presence of the orthorhombic form of asenapine maleate can be detected by the presence of an XRPD peak at $10.5^{\circ} \pm 0.2^{\circ}$ 2-Theta and/or the presence of an XRPD peak at $15.7^{\circ} \pm 0.2^{\circ}$ 2-Theta. Thus, optionally the monoclinic form of Asenapine Maleate in the form of crystalline material having a particle size distribution characterized by a d95 of at most 50 μm , preferably at most 30 μm , more preferably at most 25 μm , of the present invention can be characterized by the absence of an XRPD peak at $10.5^{\circ} \pm 0.2^{\circ}$ 2-Theta and/or absence of an XRPD peak at $15.7^{\circ} \pm 0.2^{\circ}$ 2-Theta. "Absence of a peak" is herein defined as a peak having an intensity of at most 1%, such as 0.5% or 0.2%, of the highest
25 peak in an XRPD of a sample of crystalline asenapine maleate, more preferably no detectable XRPD peak above background signals. An example of a characteristic X-ray powder diffraction pattern of monoclinic Asenapine maleate to which 5% or 10% of the orthorhombic Asenapine Maleate have been added is shown in Figure 6.

30 Thus in a preferred aspect, the present invention relates to crystalline asenapine maleate in form of crystalline material having a particle size distribution characterized by a d95 of at most 50 μm , optionally at most 30 μm , such as at most 25 μm , having an XRPD comprising peaks at 2-theta angles of 9.6° and 26.8° , characterized by the absence of peaks at 2-theta angles of $10.5^{\circ} \pm 0.2^{\circ}$ and $15.7^{\circ} \pm 0.2^{\circ}$. Optionally, the particle size distribution is
35 characterized by a d95 of between 1 μm and 50 μm , 1 μm and 30 μm , or 1 μm and 25 μm .

Such monoclinic form of asenapine maleate is obtainable by the process for monoclinic form production starting from asenapine maleate form S.

Thus, in a further aspect, the present invention relates to the monoclinic form of asenapine maleate obtainable by

- 5 (a) providing a suspension of crystalline form S of Asenapine maleate in an C_1 to C_6 alcohol, optionally in isopropanol, and
- (b) allowing the crystalline form S of Asenapine maleate to transform to the monoclinic form of asenapine maleate, in particular obtainable by any one of the particular
10 embodiments described herein for this process, such as the monoclinic form of asenapine maleate obtainable from the process described in detail in example 3.

The present invention thus enables the preparation of the monoclinic form of Asenapine Maleate in the form of crystalline material having a particle size distribution characterized by a d95 of at most 50 μm , with high polymorphic purity, making the monoclinic form of
15 asenapine maleate useful for the preparation of pharmaceutical compositions for sublingual or buccal administration. The monoclinic form of Asenapine Maleate in the form of crystalline material having a particle size distribution characterized by a d95 of at most 50 μm , with high polymorphic purity, of the present invention is suitable for further micronization such that the
20 particle size distribution of the monoclinic form of asenapine maleate of the present invention is not limited by the particle size distribution of asenapine maleate form S of the present invention. Without wishing to be bound to any theory, it is speculated that the large crystals of the monoclinic form of asenapine maleate of the prior art might contain some seeds of the orthorhombic form of asenapine maleate, leading to polymorphic transformation upon
25 micronization, while the high degree of polymorphic purity for the monoclinic form of asenapine maleate of the present invention could, in contrast, allow the further micronization.

In a further aspect, the present invention relates to at least two, more preferably three, such as four or even five, subsequent batches of the monoclinic form of Asenapine Maleate in the form of crystalline material having a particle size distribution characterized by a d95 of at
30 most 50 μm , the crystalline material comprising less than 10% w/w of the orthorhombic crystalline form of asenapine maleate in relation to the total amount of Asenapine maleate, preferably the crystalline material comprising less than 5% of the orthorhombic crystalline form of asenapine maleate, and most preferably comprising no detectable amount of the orthorhombic crystalline form of asenapine maleate. Preferably all of the at least two, more
35 preferably all of the three, such as all of the four or even all of the five subsequent batches comprise no detectable amount of the orthorhombic crystalline form of asenapine maleate. Subsequent batches can be identified via batch numbers and information on the batch

production history. An example for five subsequent batches of "M=Monoclinic Asenapine maleate" is the uninterrupted sequence M, M, M, M, M, where no batch of asenapine maleate with a different end product "O= Orthorhombic Asenapine" or "O/M=Mixture of Orthorhombic and Monoclinic Asenapine maleate" intervenes the sequence.

5

In a further aspect, the present invention relates to the use of the monoclinic form of Asenapine maleate for the preparation of a pharmaceutical composition intended for sublingual or buccal administration. The preferred monoclinic form of Asenapine maleate for this use is monoclinic asenapine maleate in the form of crystalline material having a particle
10 size distribution characterized by a d95 of at most 50 μm , preferably at most 30 μm , such as at most 20 μm , and comprising less than 10% w/w of the orthorhombic crystalline form of asenapine maleate in relation to the total amount of Asenapine maleate, preferably less than 5% of the orthorhombic crystalline form of asenapine maleate, and most preferably no detectable amount of the orthorhombic crystalline form of asenapine maleate. Preferred
15 combinations of particle size distribution and polymorphic purity are:

The combination of a particle size distribution characterized by a d95 of at most 50 μm and comprising less than 10% w/w of the orthorhombic crystalline form of asenapine maleate in relation to the total amount of Asenapine maleate, preferably less than 5% of the orthorhombic crystalline form of asenapine maleate, and most preferably no detectable
20 amount of the orthorhombic crystalline form of asenapine maleate;

the combination of a particle size distribution characterized by a d95 of at most 30 μm and comprising less than 10% w/w of the orthorhombic crystalline form of asenapine maleate in relation to the total amount of Asenapine maleate, preferably less than 5% of the orthorhombic crystalline form of asenapine maleate, and most preferably no detectable
25 amount of the orthorhombic crystalline form of asenapine maleate; and

the combination of a particle size distribution characterized by a d95 of at most 25 μm and comprising less than 10% w/w of the orthorhombic crystalline form of asenapine maleate in relation to the total amount of Asenapine maleate, preferably less than 5% of the orthorhombic crystalline form of asenapine maleate, and most preferably no detectable
30 amount of the orthorhombic crystalline form of asenapine maleate.

In a further aspect the present invention relates to pharmaceutical composition comprising the monoclinic form of asenapine maleate of the present invention, in particular monoclinic form of Asenapine Maleate in the form of crystalline material having a particle size
35 distribution characterized by a d95 of at most 50 μm , the crystalline material comprising less than 10% w/w of the orthorhombic crystalline form of asenapine maleate in relation to the total amount of Asenapine maleate, preferably less than 5% of the orthorhombic crystalline

form of asenapine maleate, and most preferably no detectable amount of the orthorhombic crystalline form of asenapine maleate.

Preferred are pharmaceutical composition for sublingual or buccal administration, such as orally disintegrating tablets, such as sublingual tablets or orally dispersible tablets. Sublingual tablets may be prepared, for example, according to examples 1, 2, 3, 4, 5, 6 or 7 of WO 95/23600, replacing the asenapine maleate in the examples by the monoclinic form of Asenapine maleate in the form of crystalline material having a particle size distribution characterized by a d95 of at most 50 μm , the crystalline material comprising less than 10% w/w of the orthorhombic crystalline form of asenapine maleate in relation to the total amount of Asenapine maleate of the present invention, and oral dispersible tablets can be prepared according to examples 1 or 2 of US2007/0036852A1, by replacing the ondansetron hydrochloride dehydrate in the examples with by the monoclinic form of Asenapine maleate in the form of crystalline material having a particle size distribution characterized by a d95 of at most 50 μm , the crystalline material comprising less than 10% w/w of the orthorhombic crystalline form of asenapine maleate in relation to the total amount of Asenapine maleate of the present invention.

Other objects, features, advantages and aspects of the present invention will become apparent to those of skill from the following description. It should be understood, however, that the description and the following specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only. Various changes and modifications within the spirit and scope of the disclosed invention will become readily apparent to those skilled in the art from reading the description and the other parts of the present disclosure.

The present invention is illustrated in the following examples, which should not be construed as limiting.

EXAMPLES

The X-ray powder diffraction patterns (XRPD) was obtained with a PANalytical X'Pert PRO diffractometer equipped with a theta/theta coupled goniometer in transmission geometry, Cu-K α 1,2 radiation (wavelength 0,15419 nm) with a focusing mirror and a solid state PIXcel detector. The patterns were recorded at a tube voltage of 40 kV, tube current of 40 mA, applying a stepsize of 0.007° 2-theta with 80s per step (255 channels) in the angular range of 2° to 40° 2-theta at ambient conditions. A typical precision of the 2-theta values is in the

range of $\pm 0.2^\circ$ 2-theta. Thus a diffraction peak that appears at 5.0° 2-theta can appear between 4.8 and 5.2° 2-theta on most X-ray diffractometers under standard conditions.

Infrared spectra (IR) were recorded on a MKII Golden Gate™ Single Reflection Diamond ATR (attenuated total reflection) cell with a Bruker Tensor 27 FTIR spectrometer with 4 cm^{-1} resolution. To collect a spectrum a spatula tip of a sample was applied to the surface of the diamond in powder form. Then the sample was pressed onto the diamond with a sapphire anvil and the spectrum was recorded. A spectrum of the clean diamond was used as background spectrum. A typical precision of the wavenumber values is in the range of $\pm 2\text{ cm}^{-1}$. Thus, an infrared peak that appears at 1716 cm^{-1} can appear between 1714 and 1718 cm^{-1} on most infrared spectrometers under standard conditions.

Differential scanning calorimetry (DSC) was performed on a Mettler Polymer DSC R instrument. About $1 - 2\text{ mg}$ sample were heated in $40\text{ }\mu\text{l}$ aluminium pans with pierced aluminium lids from room temperature to 250°C at a rate of $10^\circ\text{C}/\text{min}$. Nitrogen (purge rate $50\text{ ml}/\text{min}$) was used as purge gas.

For the determination of the particle size distribution (PSD) the laser diffraction spectroscopy (LDS) method as described in WO2006/106135 on page 9 under the header "LDS method" was used. A Mastersizer 2000 (Malvern, UK-Worcestershire) equipped with a Hydro SM Small Sample Dispersion unit (Malvern, UK-Worcestershire) was used for PSD-Analysis. Further equipment used are: XS1003S analytical balance (Mettler Toledo, CH-Greifensee), SONOREX ultrasoniq bath (Bandelin, D-Berlin) and $0.22\text{ }\mu\text{m}$ and $0.45\text{ }\mu\text{m}$ membrane filters used with an 25 mm glass micronalysis vacuum filter holder (Millipore, Billerica, MA, USA).

Reference Example 1

Preparation of monoclinic Form H of Asenapine Maleate from the base similar to the method disclosed in WO2006/106135.

trans-5-chloro-2,3,3a,12b-tetrahydro-2-methyl-1H-dibenz [2,3:6,7]oxepino[4,5-c] pyrrole (Asenapine) was prepared according to Example 3 of WO2008/003460 by Ullman cyclisation of trans-N-methyl-2-(2-hydroxyphenyl)-3-(2-bromo-5-chlorophenyl)-pyrrolidine. The crude base compound was purified by chromatography using a mixture of dichloromethane and methanol (20:1 v/v) as eluent.

45.23 g of the purified base (HPLC: 97%+) were dissolved in 100 ml ethanol and the solution was added dropwise to a solution of 18.37 g maleic acid in 22.0 ml Ethanol at 60°C .

After stirring at 60°C for another 15 min the solution was cooled down spontaneously to RT. At about 30°C seed crystals of form H were added and product started to precipitate immediately. Then 375 ml ethyl ether was added dropwise and the suspension was stirred at RT for 3h. The suspension was cooled down to 10 °C within 10-15 minutes and stirred for one hour at 10 °C. The solid was filtered off, washed with 20ml ethyl ether and dried at 40°C overnight to yield 53.26 g of asenapine maleate (HPLC: 99%+).

XRPD: complies to reference of monoclinic polymorph

DSC: peak at 144.4°C

Particle size distribution: $d(0.1) = 1.6$, $d(0.5) = 50.6$, $d(0.9) = 115.2$ and $d(0.95) = 128.2$

Reference Example 2

Preparation of monoclinic Form H of Asenapine Maleate by recrystallization similar to the method disclosed in Example 2 of WO2006/106135.

10 g Asenapine maleate prepared according to the procedure described in reference example 1 were heated in 24 ml 99% ethanol using the Easy Max System of Mettlet Toledo. The turbid solution was filtered and the clear filtrate was cooled down to 20°C. After stirring for one hour at 20°C the reaction mixture was cooled to -10° C and stirred for another two hours. The precipitated crystals were filtered and dried in vacuum at room temperature to yield 8.45 g form H of Asenapine Maleate. No further washing steps were conducted.

XRPD: complies to reference of monoclinic polymorph

DSC: peak at 144.8°C

Particle size distribution: $d(0.1) = 2.7$, $d(0.5) = 90.3$, $d(0.9) = 211$ and $d(0.95) = 244.7$

Example 1

Preparation of seeds of crystalline form S of Asenapine Maleate

500 mg Asenapine maleate of reference example 1 and 1.5 ml methanol were briefly heated in a reaction tube until almost all of the Asenapine maleate was dissolved. The solution was clarified by filtration and 8.5 ml methyl tert-butyl ether (MTBE) were added to the filtrate in one portion. The mixture was put in a refrigerator at 5°C without agitation for three days. The precipitated crystals were collected by filtration and then dried at room temperature in a vacuum oven to yield 285 mg of Asenapine maleate in form of white needles.

Crystalline form S obtained according to example 1 displayed an X-ray powder diffraction spectrum as shown in Figure 1. Characteristic XRPD angles and relative intensities are shown in Table X.

- 5 Crystalline form S of Asenapine maleate obtained above had an attenuated total reflectance IR spectrum with absorption bands 3035, 2976, 1476, 1447, 1351, 1246, 1232, 1080, 867 and 768 cm⁻¹ (± 2 cm⁻¹; Figure 2).

Table X: Angles 2 theta, d-values and relative intensities of form S of Asenapine Maleate

10

Angle [2-Theta °]	Relative intensity [%]
5.5	69
9.8	7
10.9	13
12.5	41
13.7	12
14.5	10
16.7	9
17.3	4
18.4	8
19.0	100
19.8	41
20.7	6
21.4	3
22.0	17
23.5	18
25.3	47
25.8	4
26.6	7
27.6	3
28.7	7
30.4	4

Example 2

Preparation of crystalline form S of Asenapine Maleate

7.14 g of asenapine free base, trans-5-chloro-2,3,3a,12b-tetrahydro-2-methyl-1H-dibenz [2,3:6,7]oxepino[4,5-c] pyrrole (yellow oil, 0.025 mol), was dissolved in 30 ml of methanol and 2.9 g of solid maleic acid was added. The reaction mixture was stirred at room temperature until a clear solution was obtained. The solution was filtered dust free. Under strong stirring 150 ml of methyl tert-butyl ether (MTBE) was added. The reaction mixture was then cooled in an ice bath to 0 °C (ice/water mixture) and seeded with 0.1 g of Asenapine maleate form S obtained from example 1.

After standing without agitation for 5 hours the precipitated crystals were filtered. The crystals were washed with 30 ml MTBE. The wet crystals were dried under vacuum (30 – 40 mbar) at room temperature over night to afford 8.2 g of Asenapine Maleate, form S.

XRPD and FT-IR: did comply to polymorphic form S of example 1

Example 3

Transformation of form S of Asenapine Maleate to the monoclinic polymorph H

38.56 g crystalline form S of Asenapine maleate prepared according to the procedure described in example 2 were suspended in 193 ml isopropanol and stirred with a standard mechanical stirrer (170 rpm) at room temperature. After 3 hours a small amount of material was removed, filtered and dried at room temperature while stirring of the bulk sample was continued. The small amount of solids isolated after 3 hours of stirring was found to correspond to the monoclinic form H of Asenapine Maleate as judged by XRPD analysis (see Figure 3).

The crystals from the bulk sample were collected by filtration after stirring the mixture for a total of 28 hours and dried in vacuum at room temperature over night.

Yield: 34.1 g of monoclinic form H of Asenapine Maleate

DSC: peak at 145.1°C

Particle size distribution: d(0.1) = 1.5, d(0.5) = 7.7, d(0.9) = 27.0 and d(0.95) = 34.9

Example 4

Transformation of form S of Asenapine Maleate to the monoclinic polymorph H

113 g crystalline form S of Asenapine maleate prepared according to the procedure

described in example 2 were suspended in 570 ml isopropanol and stirred at room temperature for a total of 28 hours. The solid crystalline material was isolated by filtration and dried in vacuum at room temperature over night.

5 Yield: 101.7 g of monoclinic form H of Asenapine Maleate.

Particle size distribution: $d(0.1) = 1.5$, $d(0.5) = 7.0$, $d(0.9) = 21.1$ and $d(0.95) = 25.1$

Example 5

Micronization of monoclinic polymorph H of example 4

10

33 g of the product of example 4 were micronized in a Hosokawa spiral Jet Mill 50 AS, using a micronization pressure of 3.5 bar. The micronized product was characterized as the monoclinic polymorph. Forms S and the orthorhombic form L of Asenapine Maleate could not be detected by XRPD, as judged by the absence of XRPD peaks at 2-theta angles (± 0.2) of 5.5 (a characteristic peak for form S) and 10.5 and/or 15.7 (characteristic peaks of 15 orthorhombic form L as characterized in WO2006/106135) (see Figure 4). The peaks at 10.4 and/or 15.6 depicted in Figure 6 (XRPD pattern of monoclinic Asenapine maleate in the form of crystalline material obtained from example 3 to which 5% (a) or 10% (b) of the orthorhombic Asenapine Maleate have been added) correspond to the two most 20 characteristic peaks at $10.5^\circ \pm 0.2^\circ$ and $15.7^\circ \pm 0.2^\circ$ 2-Theta of the orthorhombic Asenapine Maleate as characterized in WO2006/106135.

Particle size distribution: $d(0.1) = 1.1$, $d(0.5) = 3.9$, $d(0.9) = 8.5$ and $d(0.95) = 10.0$

CLAIMS

1. Crystalline Asenapine maleate having an X-ray powder diffraction pattern (XRPD) obtained with $\text{CuK}\alpha$ radiation comprising peaks at 2-theta angles of $5.5 \pm 0.2^\circ$, $12.5 \pm 0.2^\circ$, $19.0 \pm 0.2^\circ$ and $25.3 \pm 0.2^\circ$, optionally further comprising peaks at 2-theta angles $10.9 \pm 0.2^\circ$, $13.7 \pm 0.2^\circ$, $14.5 \pm 0.2^\circ$, $19.8 \pm 0.2^\circ$ and $23.5 \pm 0.2^\circ$, in particular having an XRPD substantially in accordance with Figure 1.
2. Crystalline form of Asenapine maleate, optionally according to claim 1, having an attenuated total reflectance infrared spectrum comprising absorption bands at wavenumbers of about $3035 \text{ cm}^{-1} \pm 2 \text{ cm}^{-1}$, $2976 \text{ cm}^{-1} \pm 2 \text{ cm}^{-1}$, $1476 \text{ cm}^{-1} \pm 2 \text{ cm}^{-1}$, $1447 \text{ cm}^{-1} \pm 2 \text{ cm}^{-1}$, $1351 \text{ cm}^{-1} \pm 2 \text{ cm}^{-1}$, $1246 \text{ cm}^{-1} \pm 2 \text{ cm}^{-1}$, $1232 \text{ cm}^{-1} \pm 2 \text{ cm}^{-1}$, $1080 \text{ cm}^{-1} \pm 2 \text{ cm}^{-1}$, $867 \text{ cm}^{-1} \pm 2 \text{ cm}^{-1}$ and $768 \text{ cm}^{-1} \pm 2 \text{ cm}^{-1}$, in particular substantially in accordance with Figure 2.
3. The crystalline form according to any one of claims 1 or 2, wherein the crystalline form of Asenapine maleate contains less than 10% of the orthorhombic crystalline form of asenapine maleate in relation to the total amount of Asenapine maleate, optionally containing less than 5% of the orthorhombic crystalline form of asenapine maleate, optionally containing no detectable amount of the orthorhombic crystalline form of asenapine maleate.
4. A process for the preparation of the crystalline Asenapine maleate according to any one of claims 1 to 3, comprising the following steps:
 - (a) dissolving trans-5-chloro-2,3,3a,12b-tetrahydro-2-methyl-1H-dibenz [2,3:6,7] oxepino [4,5-c] pyrrole (asenapine) in methanol to obtain a solution with a concentration of 1g asenapine per 3 ml to 10 ml of methanol, optionally per 4 ml to 6 ml of methanol;
 - (b) adding maleic acid to the solution obtained in step (a), wherein from 0.8 mol to 1.2 mol of maleic acid is added per 1 mol of asenapine, preferably wherein about 1 mol of maleic acid is added per 1 mol of asenapine;
 - (c) adding an ether to the solution obtained in step (b) in an amount sufficient to induce crystallization of asenapine maleate; and

- (d) allowing asenapine maleate to crystallize, and optionally isolating the crystalline Asenapine maleate according to any one of claims 1 to 3, for example by filtration.
- 5. The process of claim 4, wherein in step (c) methyl tert-butylether (MTBE) is added, optionally in an amount of from 3 to 10 volumes of MTBE per volume of the solution obtained in step (b).
- 6. The process of any one of claims 4 to 5, wherein step (d) is performed at a temperature of from -20°C to 15°C, optionally of from -5°C to 10°C.
- 7. A process for preparing the monoclinic form of asenapine maleate, comprising the steps of:
 - (a) providing a suspension of the crystalline form of Asenapine maleate according to any one of claims 1 to 3 in isopropanol, and
 - (b) allowing the crystalline form according to any one of claims 1 to 3 to transform to the monoclinic form of asenapine maleate.
- 8. The process of claim 7, wherein step (b) is performed at a temperature of at most 50°C, optionally at a temperature from -20°C to 40°C, optionally from 0°C to 30°C.
- 9. The process of any one of claims 7 to 8, wherein step (b) is performed for at least 30 minutes, optionally for at least 90 minutes under stirring.
- 10. Use of the crystalline form of Asenapine Maleate according to any one of claims 1 to 3 for the preparation of the monoclinic form of Asenapine Maleate.
- 11. The use of claim 10, wherein the monoclinic form of Asenapine Maleate is further used in the preparation of a pharmaceutical composition, optionally for sublingual or buccal administration.
- 12. The use of any one of claims 10 to 11, wherein the monoclinic form of Asenapine maleate is in the form of crystalline material having a particle size distribution characterized by a d95 of at most 50 µm, preferably at most 30 µm.
- 13. Monoclinic form of Asenapine maleate in the form of crystalline material having a particle size distribution characterized by a d95 of at most 50 µm, preferably at most 30 µm, comprising less than 10% of the orthorhombic crystalline form of asenapine maleate in relation to the total amount of Asenapine maleate, optionally less than 5% of

the orthorhombic crystalline form of asenapine maleate, optionally no detectable amount of the orthorhombic crystalline form of asenapine maleate.

14. Monoclinic form of asenapine maleate obtainable according to the process of any one of claims 7 to 9.
15. Use of the monoclinic form of Asenapine maleate for the preparation of a pharmaceutical composition intended for sublingual or buccal administration.
16. The use of claim 15, wherein the monoclinic form of asenapine maleate is according to any one of claims 13 to 14.
17. Pharmaceutical composition comprising the monoclinic form of asenapine maleate according to any one of claims 13 to 14.
18. The pharmaceutical composition according to claim 17 which pharmaceutical composition is for sublingual or buccal administration.

Figure 1

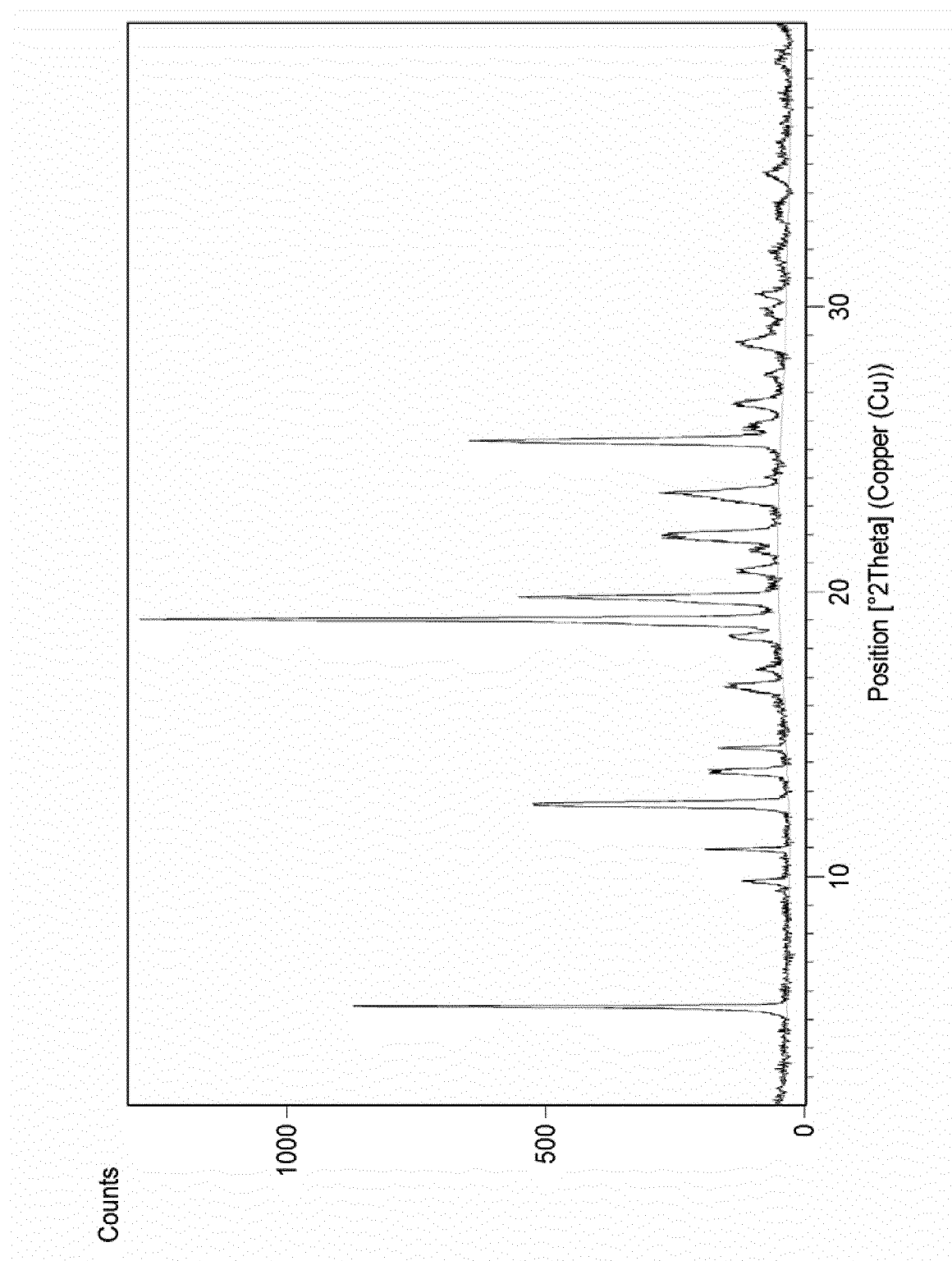


Figure 2

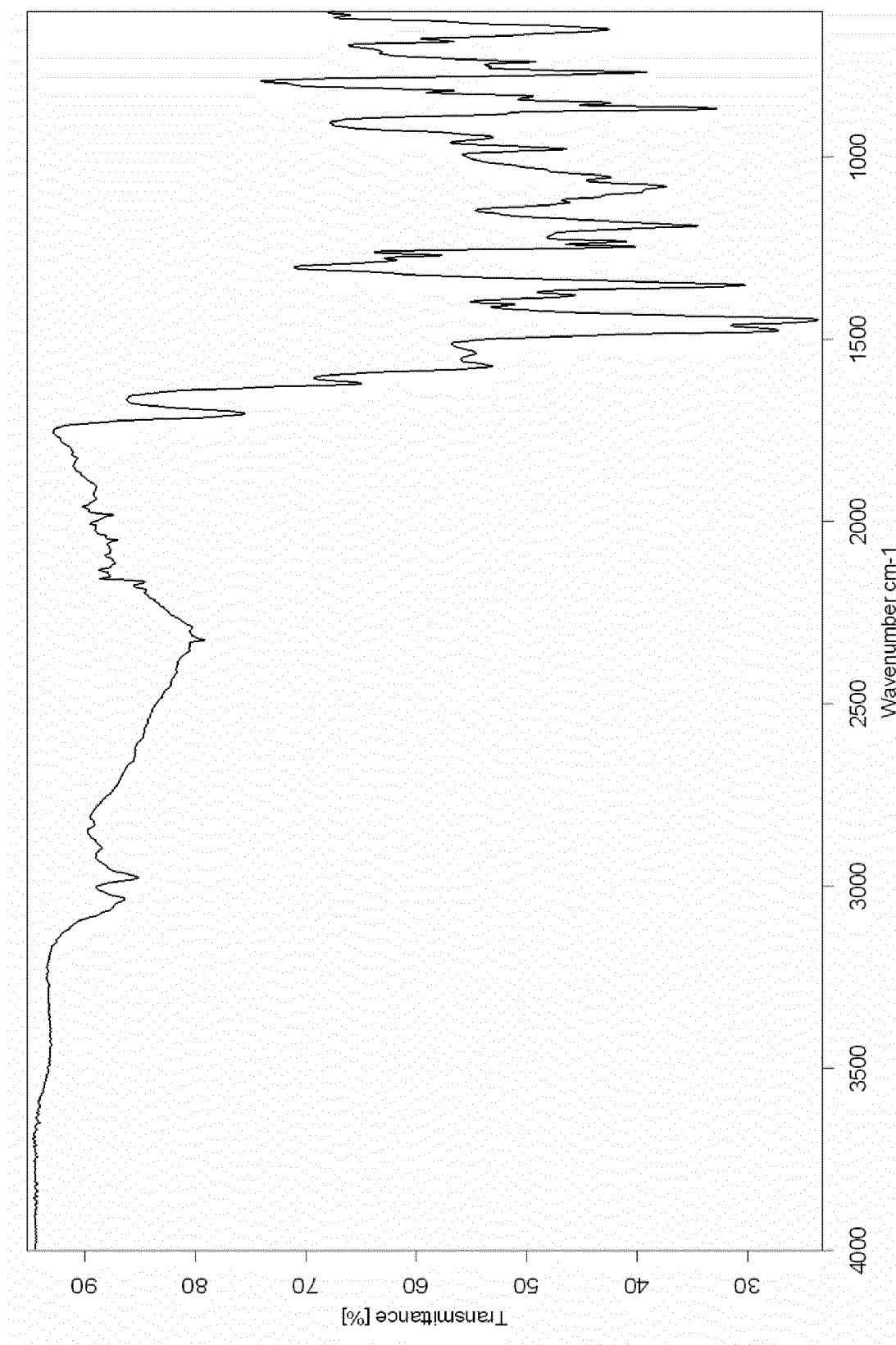


Figure 3

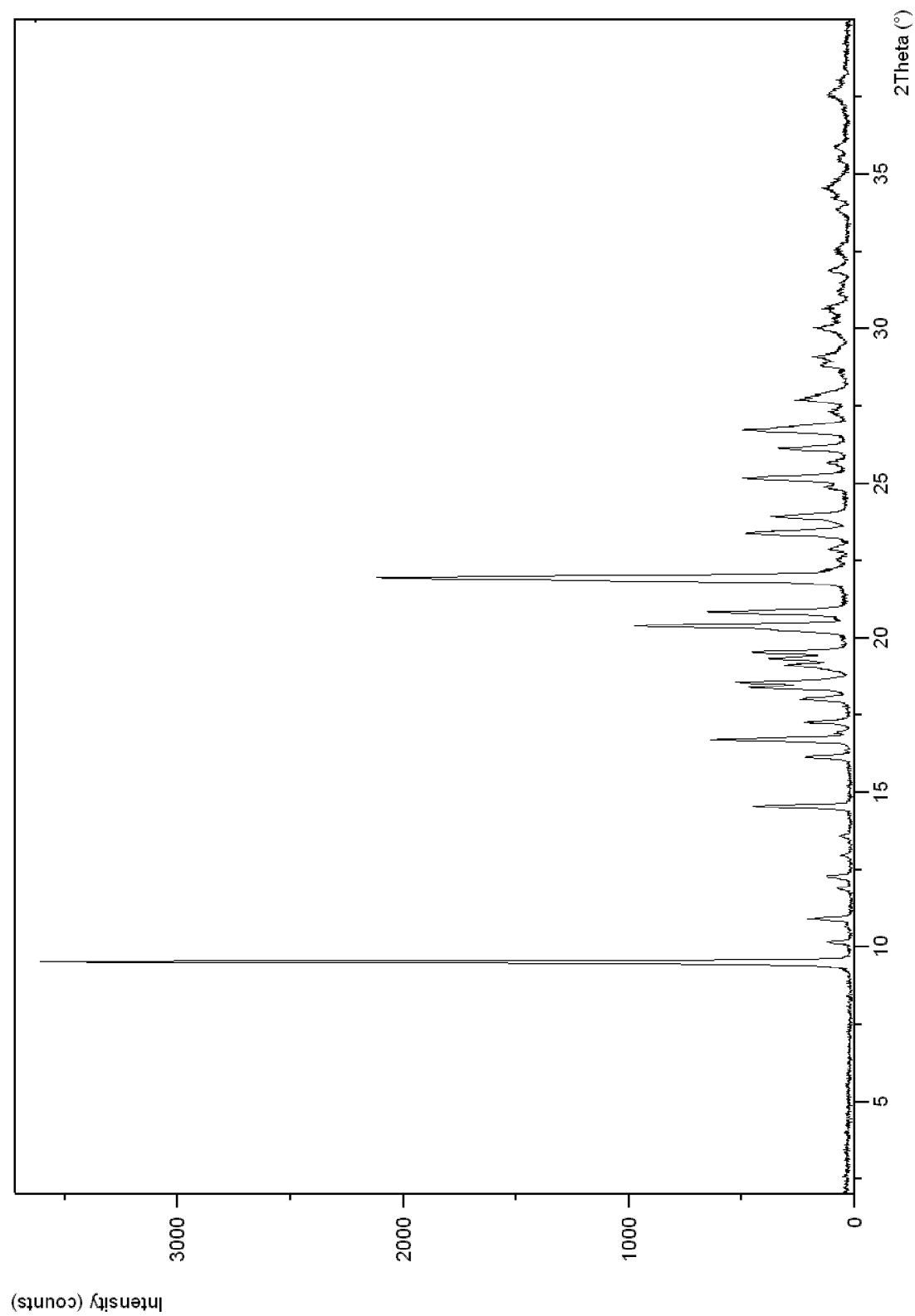


Figure 4

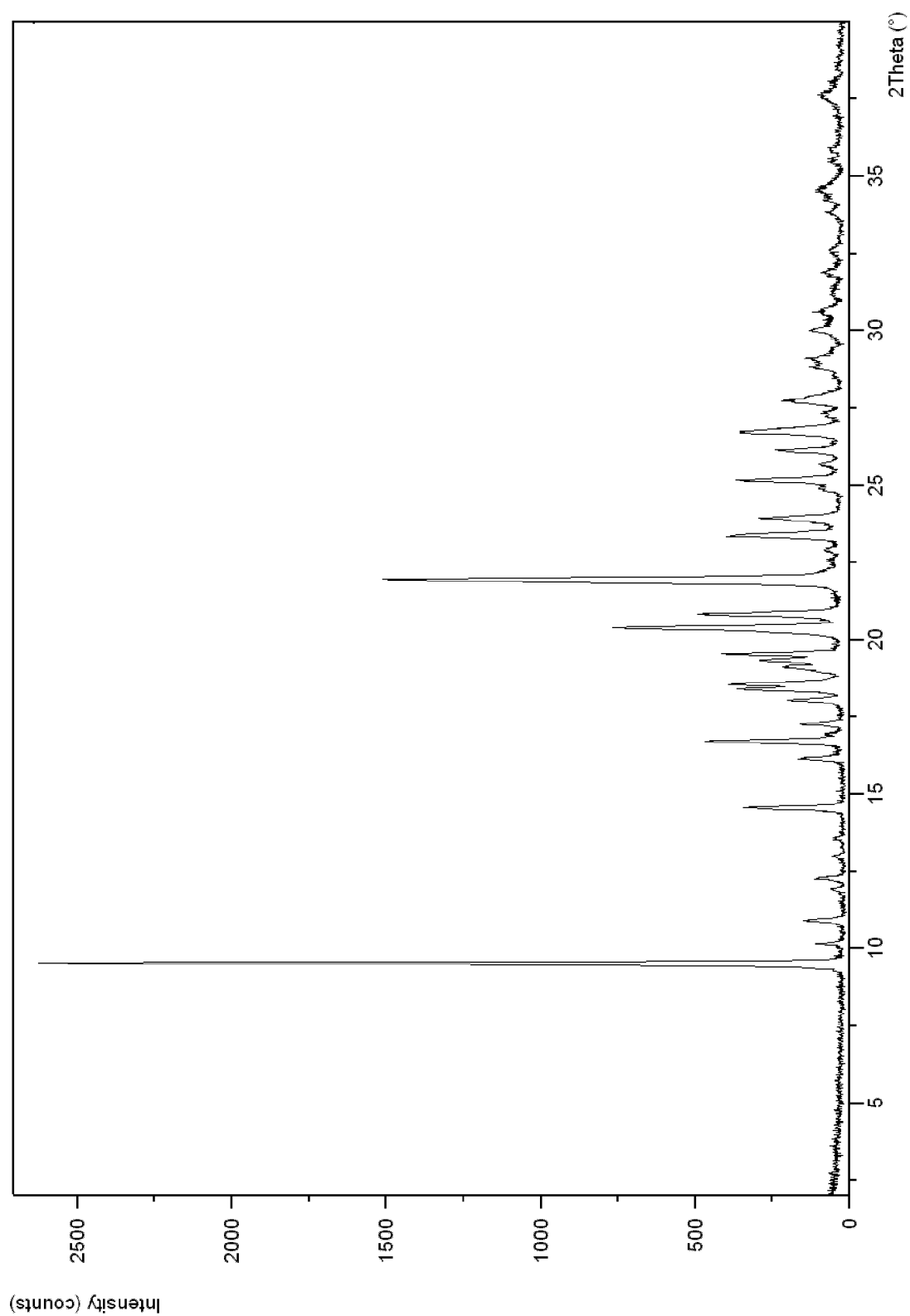


Figure 5 (a)

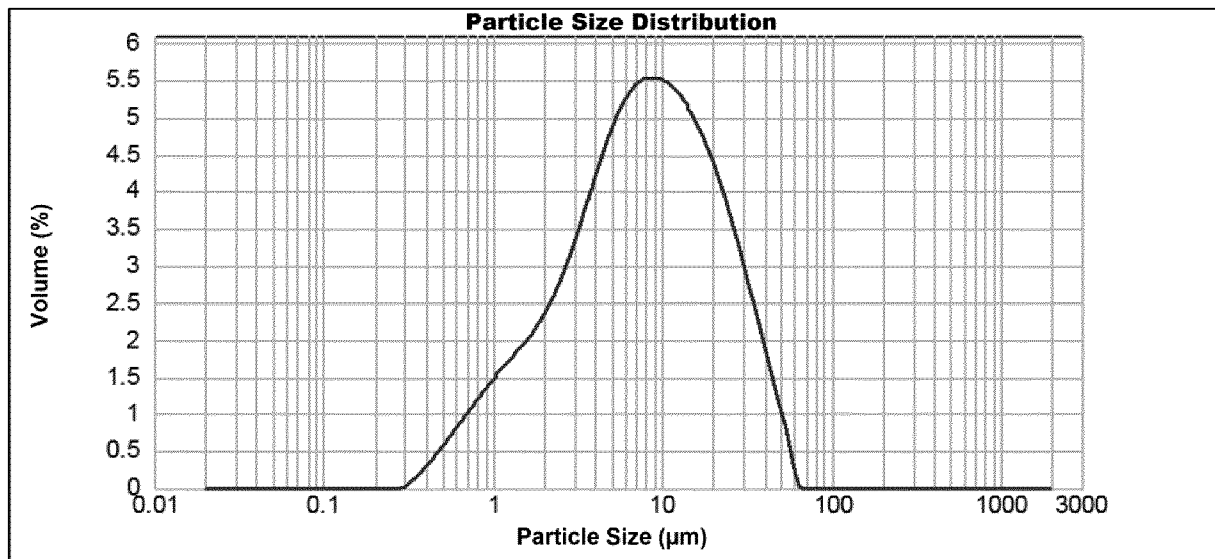


Figure 5 (b)

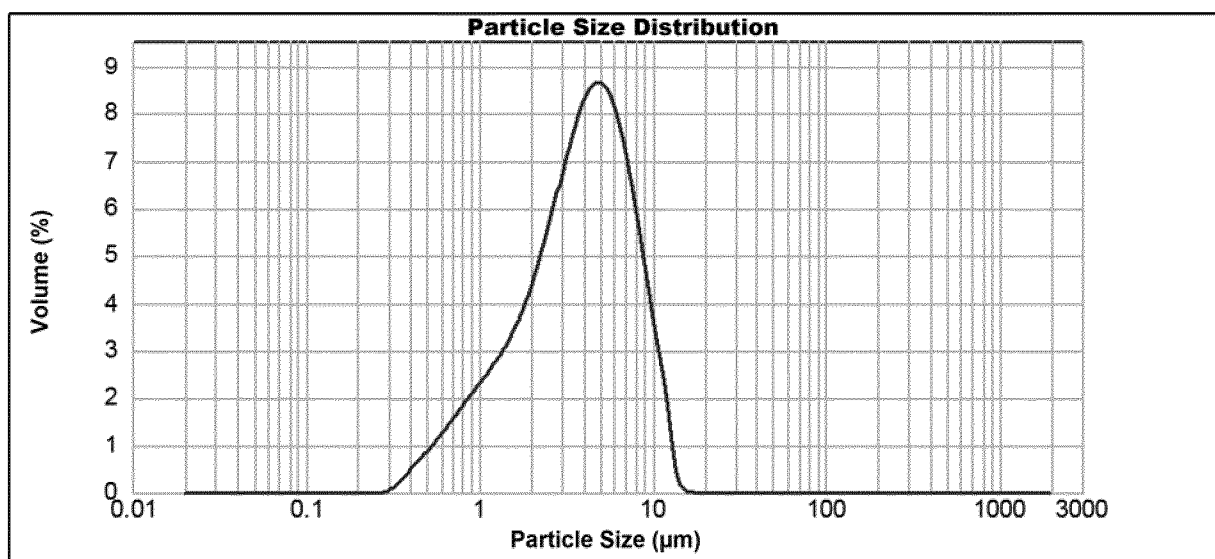
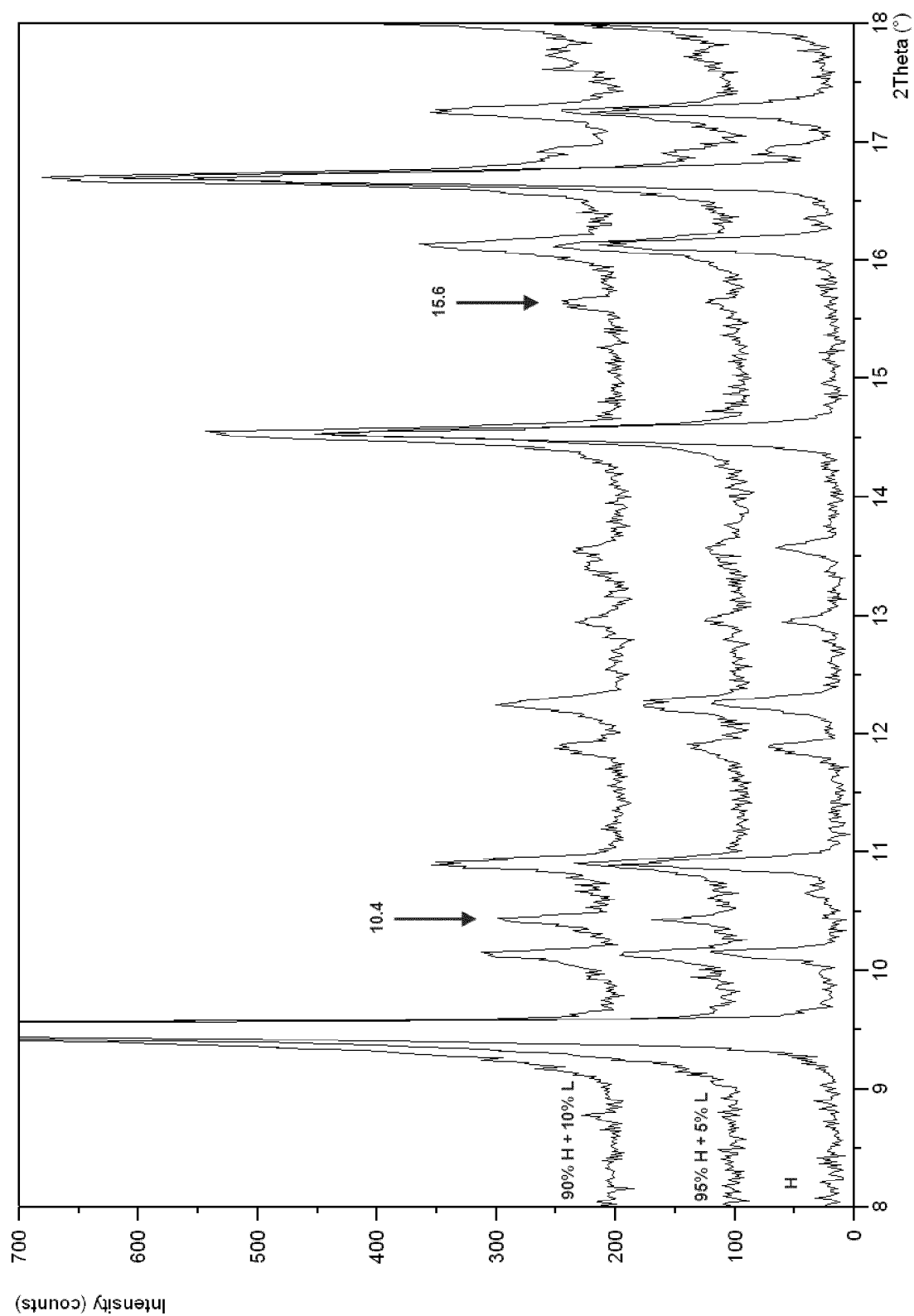


Figure 6



INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2012/068503

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 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	"POLYMORPHIC FORMS OF ASENAPINE MALEATE", IP.COM JOURNAL, IP.COM INC., WEST HENRIETTA, NY, US, 19 July 2011 (2011-07-19), XP013147549, ISSN: 1533-0001 page 3, line 8 - line 12; figure 1; table 1 page 9, lines 3,4,19 page 16, paragraph sixth; examples 2-9 page 8 ----- -/--	1-6



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

3 December 2012

Date of mailing of the international search report

08/03/2013

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Skulj, Primoz

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/068503

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SYNTHON BV: "Crystallisation method for the monoclinic form of asenapine maleate", RESEARCH DISCLOSURE, MASON PUBLICATIONS, HAMPSHIRE, GB, vol. 523, no. 12, 1 November 2007 (2007-11-01), page 1093, XP007137721, ISSN: 0374-4353 page 1, last paragraph; figure 4 pages 2,3 -----	2-5
E	WO 2012/123325 A1 (MEDICHEM SA [ES]; XU MINGLI [CN]; DURAN LOPEZ ERNESTO [ES]; BENITO VEL) 20 September 2012 (2012-09-20) the whole document -----	1
T	BRITTAİN H G ED - BRITTAİN H G: "Methods for the Characterization of Polymorphs and Solvates", POLYMORPHISM IN PHARMACEUTICAL SOLIDS, 1999, XP008098996, ISBN: 978-0-8247-0237-9 -----	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2012/068503

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-6

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-6

The polymorph of the asenapine maleate as defined in claim 1 (hereinafter form S) and its preparation process.

2. claims: 7-11(completely); 12, 14, 16-18(partially)

The use of the polymorph of the asenapine maleate as defined in claim 1 (hereinafter form S) as an intermediate in preparation of another (monoclinic) polymorph as well as this another polymorph in as far as its preparation process renders it distinguishable from the same (monoclinic) polymorph of the prior art.

3. claims: 13, 15(completely); 12, 14, 16-18(partially)

The monoclinic polymorph (in as far as it is independent from its preparation process and can not be distinguished from said polymorph of the prior art) of the asenapine maleate with a defined particle size.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2012/068503

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2012123325	A1	20-09-2012	NONE
