(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 August 2014 (28.08.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/127786 A1

(51) International Patent Classification:
A61K 9/00 (2006.01) *A61K 9/20* (2006.01)
A61K 31/407 (2006.01)

(21) International Application Number:
PCT/EP2013/000516

(22) International Filing Date:
22 February 2013 (22.02.2013)

(25) Filing Language: English

(26) Publication Language: English

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *with international search report (Art. 21(3))*

WO 2014/127786 A1

(54) Title: ORALLY DISINTEGRATING PHARMACEUTICAL COMPOSITION COMPRISING ASENAPINE

(57) Abstract: An orally disintegrating pharmaceutical composition comprising Asenapine, pharmaceutically acceptable salt or crystalline forms thereof, and at least one pharmaceutically acceptable excipient, which is free from binder, and a process for manufacturing the same, which comprises the following steps: a) mixing asenapine, pharmaceutically acceptable salt or crystalline forms thereof, the first part of a disintegrant, at least one diluent, at least one glidant, optionally a sweetener and /or a flavoring agent, b) wet granulation of the blend obtained in step a), c) screening and drying the granules, d) mixing the dried granules obtained in step c) with the second part of the disintegrant, at least one glidant, and optionally with a sweetener and/or flavoring agent, e) the blend obtained in step d) is lubricated with a lubricant, optionally flavoring agent is added, and f) optionally compressing the mixture obtained in step e) to form a tablet.

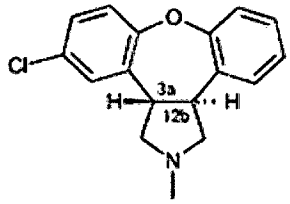
Orally disintegrating pharmaceutical composition comprising asenapine

Field of technique

The present invention relates to an orally disintegrating pharmaceutical composition comprising Asenapine, pharmaceutically acceptable salt or crystalline forms thereof, which is free from binder, and a method for manufacturing thereof by wet granulation.

State of the art

Asenapine, (3aR,12bR)-rel-5-chloro-2,3,3a,12b-tetrahydro-2-methyl-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole



or a pharmaceutically acceptable non-toxic salts, specifically maleate salt, or nitrogen oxide thereof are described in the patent US4145434B.

Asenapine is a well-known psychopharmacologic agent with high affinity and potency for blocking dopamine, serotonin, α-adrenergic and histamine receptors, and no appreciable activity at muscarinic cholinergic receptors and is indicated for the treatment of moderate to severe manic episodes associated with bipolar I disorder in adults.

Asenapine maleate occurs in two different crystalline forms, monoclinic and orthorhombic forms which are described in EP1710245B (ORGANON). The preferred crystalline form is orthorhombic form.

The development of the marketed product Sycrest was based on 'Zydis' technology, in which the active substance is mixed in a solution of gelatine and mannitol, and subsequently dispensed by weight into blister pockets before freeze-drying and blister sealing. The dissolved drug substance is quickly frozen and lyophilized, allowing for amorphous asenapine to be present in the final drug product. The drug substance that does not dissolve in the matrix remains crystalline. The drug product formulation

is a fast dissolving tablet for sublingual administration as the bioavailability after sublingual dosing is much higher (approximately 35%) than after oral dosing (<2% in tablet formulation).

A sublingual or buccal pharmaceutical composition prepared by using freeze-drying process is described in the patent application WO95/23600A (Akzo Nobel). The prepared sublingual tablets are fragile and require special packaging.

An orally disintegrating sublingual composition prepared by direct compression, dry granulation or wet granulation is described in the international application WO2012/038975A (MSN). The pharmaceutical composition comprises diluent(s), binding agent(s), solvents or binding fluids, disintegrating agent(s), lubricant(s), sweetener(s), flavoring agent(s) and optionally colouring agent(s). According to the description the orally disintegrating tablet has low friability that is not more than 1%, preferable 0.5%, tablet hardness from 20 N to 50 N, diameter of a tablet ranging from 5 mm to 7 mm, and disintegration time from 35 s to 60 s.

An orally disintegrating tablet (ODT) is a solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue. The ODTs disintegrate or dissolve rapidly on contact with saliva, without the need to chew the tablet, swallow an intact tablet, or take the tablet with liquids. According to the Food and Drug Administration's (FDA's) Guidance for Industry (December 2008) ODTs are considered solid oral preparations that disintegrate rapidly in the oral cavity, with an in-vitro disintegration time of approximately 30 seconds or less, when based on the United States Pharmacopeia (USP) disintegration test method or alternative.

Surprisingly, it has been found that it is possible to prepare stable orally disintegrating pharmaceutical composition comprising Asenapine, pharmaceutically acceptable salt or crystalline forms thereof, and at least one pharmaceutically acceptable excipient by wet granulation process without using a binder, which disintegrates rapidly. The disintegration time of the composition according to the invention is below 30 seconds.

Description

The invention relates to an orally disintegrating pharmaceutical composition comprising Asenapine, pharmaceutically acceptable salt or crystalline forms thereof, and at least one pharmaceutically acceptable excipient, which is free form binder.

The described orally disintegrating pharmaceutical composition disintegrates within 30 seconds, preferable form 10 to 20 seconds.

In the preferred embodiment of the invention the pharmaceutical composition comprises Asenapine, pharmaceutically acceptable salt or crystalline forms thereof in an amount of from 10 to 35% w/w. Asenapine, pharmaceutically acceptable salt or crystalline forms thereof have a particle size D_{90} preferable less than 30 microns.

The orally disintegrating pharmaceutical composition preferable comprises Asenapine maleate, essentially the monoclinic crystalline form (also known as Form H) thereof, wherein the content of other crystalline form of Asenapine maleate is less than 5 % w/w.

The orally disintegrating pharmaceutical composition is in the form of granules or tablet, preferable in the form of a fast disintegating tablet for sublingual application.

The orally disintegrating pharmaceutical composition in the form of granules or tablet comprises Asenapine, pharmaceutically acceptable salt or crystalline forms thereof, one or more disintegrant(s), one or more diluents(s), one or more glidant(s), optionally one or more sweetener(s), flavouring agent(s) or combinations thereof.

Disintegrants with wicking and/or swelling properties according to the present invention may be selected from various useful disintegrants including but not limited to carmellose calcium (Gotoku Yakuhin Co., Ltd.), carboxymethylstarch sodium (Matsutani Kagaku Co., Ltd., Kimura Sangyo Co., Ltd., etc.), croscarmellose sodium (FMC-Asahi Chemical Industry Co., Ltd.), crospovidone, examples of commercially available crospovidone products including but not limited to crosslinked povidone, Kollidon.TM CL [manufactured by BASF (Germany)], Polyplasdone.TM XL, XI-10, and INF-10 [manufactured by ISP Inc. (USA)], and low-substituted hydroxypropylcellulose, examples of low-substituted hydroxypropylcellulose include but are not limited to low-substituted hydroxypropylcellulose LH11, LH21, LH31, LH22, LH32, LH20, LH30, LH32 and LH33 (all manufactured by Shin-Etsu Chemical Co., Ltd.). Other useful disintegrants include sodium starch glycolate, colloidal silicon dioxide, and starch. The preferred disintegrant is croscarmellose sodium.

Diluents may be selected from various useful diluents including but not limited to starches, mannitol, lactose, cellulose derivatives, sorbitol, dextrate, dextrin, maltodextrins, and dextrose.

Different grades of lactose include but are not limited to lactose monohydrate, lactose DT (direct tableting), and lactose anhydrous, Tablettose, Flowlac.TM (available from Meggle Products), Pharmatose.TM (available from DMV).

Different grades of starches include but are not limited to maize starch, potato starch, rice starch, wheat starch, pregelatinized starch (commercially available as PCS PC10 from Signet Chemical Corporation) and Starch 1500, Starch 1500 LM grade (low moisture content grade) from Colorcon, fully pregelatinized starch (commercially available as National 78-1551 from Essex Grain Products).

Different mannitol grades can be used alone or in combination with other pharmaceutically acceptable excipients. Examples of mannitol range products include but are not limited to Pearlitol Flash, Pearlitol C, Pearlitol DC, Pearlitol PF, Pearlitol SD (from Roquette).

Different cellulose compounds that can be used include crystalline cellulose and powdered cellulose. Examples of crystalline cellulose products include but are not limited to CEOLUS.TM KG801, Avicel.TM PH 101, PH102, PH301, PH302 and PH-F20, microcrystalline cellulose 114, and microcrystalline cellulose 112.

Other useful diluents include but are not limited to Ludiflash, F-melt, modified chitosan with silicon dioxide, Orocell 200 & 400, Mannogem EZ, Advantose, Galen IQ, sugar alcohols such as mannitol, sorbitol and xylitol, calcium carbonate, magnesium carbonate, dibasic calcium phosphate, and tribasic calcium phosphate.

The preferred diluents are selected from mannitol, starch, combination of mannitol and starch (Pearlitol Flash®), lactose, microcrystalline cellulose or combinations thereof.

Glidants may be selected from various useful glidants or antisticking agents including but not limited to talc, silica derivatives, colloidal silicon dioxide. The preferred glidant is fumed silica (Aerosil®).

Lubricants may be selected from magnesium stearate, calcium stearate, talcum, sodium stearyl fumarate, macrogol or hydrogenated esters of fatty acids with glycerine and stearic acid. The preferred lubricants are sodium stearyl fumarate and magnesium stearate.

The necessary amount of lubricant, in the pharmaceutical composition comprising Asenapine, pharmaceutically acceptable salt or crystalline forms thereof having a particle size D_{90} less than 30 microns, is up to 5% w/w. This amount of lubricant improves tabletting properties during compression while the disintegration time of the prepared tablet is maintained below 30 s.

Sweeteners may be selected from artificial, natural or synthetic or semi-synthetic sweeteners like Neotame, aspartame, acesulfame potassium, cyclamate, sucralose, saccharine, sugars and others. The preferred sweetener is Neotame.

The suitable flavoring agents according to the invention include but are not limited to natural or synthetic or semi-synthetic flavors like menthol, Bitter blocker, fruit flavors, peppermint flavors, citrus oils, peppermint oil, spearmint oil, oil of wintergreen (methyl salicylate). The preferred flavouring agent is peppermint flavor, Bitter blocker or combination thereof.

The orally disintegrating pharmaceutical composition preferable is an orally disintegrating tablet having a two-phase structure consisting of:
a) an inner phase comprising Asenapine, pharmaceutically acceptable salt or crystalline forms thereof, at least one disintegrant, optionally one or more pharmaceutically acceptable excipient(s), and
b) an outer phase comprising at least one disintegrant, at least one lubricant, and optionally one or more pharmaceutically acceptable excipient(s).

In the preferred embodiment of the invention the orally disintegrating tablet has a two-phase structure consisting of:
a) an inner phase comprising Asenapine, pharmaceutically acceptable salts or crystalline forms thereof, at least one disintegrant, at least one diluent, at least one glidant, optionally a flavoring agent and/or a sweetener, and
b) an outer phase comprising at least one disintegrant, at least one glidant, at least one lubricant, optionally a sweetener and/or a flavouring agent.

In other preferred embodiment of the invention the orally disintegrating tablet has a two-phase structure consisting of:
a) an inner phase comprising Asenapine maleate, at least one disintegrant, at least one diluent, at least one glidant, optionally a flavoring agent and/or a sweetener, and
b) an outer phase comprising at least one disintegrant, at least one glidant, at least one lubricant, optionally a sweetener and/or a flavouring agent.

In the more preferred embodiment of the invention the orally disintegrating tablet with a two-phase structure comprises:
a) an inner phase comprising Asenapine maleate, croscarmellose sodium, mannitol, fumed silica, bitter blocker and neotame, and

b) an outer phase comprising croscarmellose sodium, fumed silica, sodium stearyl fumarate or magnesium stearate, neotame and peppermint flavor.

In another aspect the invention relates to a process for manufacturing the orally disintegrating pharmaceutical composition comprising Asenapine, pharmaceutically acceptable salt or crystalline forms thereof, and at least one pharmaceutically acceptable excipient by wet granulation process without using a binder.

The orally disintegrating tablets according to the invention are prepared by wet granulation, followed by compression the granules into tablets. In the preferred embodiment purified water is used as granulation liquid.

A process for preparation of the orally disintegrating tablets comprises the following steps:
a) mixing asenapine, pharmaceutically acceptable salt or crystalline forms thereof, the first part of a disintegrant, at least one diluent, at least one glidant, optionally a sweetener and /or a flavoring agent,
b) wet granulating the blend obtained in step a),
c) screening and drying the granules,
d) mixing the dried granules obtained in step c) with the second part of the disintegrant, at least one glidant, and optionally with a sweetener and/or flavoring agent,
e) the blend obtained in step d) is lubricated with a lubricant, optionally flavoring agent is added, and
f) optionally compressing the mixture obtained in step e) to form a tablet.

Description of the figures:

Fig. 1: dissolution profile of the composition prepared according to example 1 compared to the reference product

Fig. 2: dissolution profile of the composition prepared according to example 2 compared to the reference product

Fig. 3: dissolution profile of the composition prepared according to example 3 compared to the reference product

Fig. 4: dissolution profile of the composition prepared according to example 4 compared to the reference product

Examples

Example 1: Asenapine sublingual tablets 10 mg

No.	Ingredients	Quantity/tab [mg]
	Inner phase	
1	Asenapine Maleate (equivalent to 10 mg of Asenapine)	14.06
2	Mannitol SD 200	14.00
3	Alpha-lactose monohydrate (Tablettose)	36.34
4	Crosscormallose sodium	3.00
5	Purified Water	Q.S
	Outer phase	
6	Crosscormallose sodium	3.00
7	Neotame	2.40
8	Fumed silica (Aerosil®)	2.40
9	Bitter Blocker	0.40
10	Peppermint flavor	0.40
11	Sodium stearyl fumarate	4.00
	Tablet weight	80.00

Asenapine maleate and Mannitol SD 200 were sifted through 40 mesh sieve. Tablettose and Croscarmellose Sodium were co-sifted along with Asenapine maleate blend through 40 mesh screen. The sifted mixture was blended for 10 minutes in rapid mixture granulator and the blend was granulated with purified water. The obtained wet mass was passed through 20 mesh screen and dried in tray dryer at 105 °C until the LOD reached less than 2% w/w. The dried granules were sifted through 30 mesh screen. Croscarmellose sodium, Neotame, Fumed silica, Bitter Blocker and Peppermint flavor were sifted through 30 mesh screen then blended with the dried granules for 5 minutes, and lubricated with sodium stearyl fumarate for 5 minutes to get a uniform mass. The obtained mixture was compressed into tablets with suitable punches and packed.

The prepared tablets were subjected to disintegration test and dissolution test.

Disintegration time of the prepared asenapine sublingual tablets (ST) 10 mg:

Asenapine ST 10mg	Disintegration Time [Seconds]
Tablet-1	12
Tablet-2	14
Tablet-3	14
Average	**13**

Dissolution profile test:

Comparative dissolution test was carried out with the above prepared tablet and the reference product Sycrest. Figure 1 and the results presented in Table 1 show the reference product and the tested product are equivalent.

Dissolution medium: 500 ml of pH 4.5 Acetate Buffer

Dissolution apparatus: USP II Paddle type, RPM: 50

Table 1:

Time [minutes]	5	10	15	30	45	60
Reference Product (Sycrest)	80	85	87	88	88	88
Tested Product	68	93	96	97	97	97

Example 2: Asenapine sublingual tablets 10 mg

No.	**Ingredients**	**Quantity/tab** [mg]
	Inner phase	
1	Asenapine maleate (equivalent to 10 mg of Asenapine)	14.06
2	Bitter blocker	1.60
3	Mannitol and starch (Pearlitol flash®)	47.54
4	Croscarmellose sodium	2.40
5	Fumed silica (Aerosil®)	1.60
6	Neotame	1.60
7	Purified water	Q.S
	Outer phase	
8	Croscarmellose sodium	3.20
9	Neotame	1.60
10	Fumed silica (Aerosil®)	2.00
11	Sodium stearyl fumarate	4.00
12	Peppermint flavor	0.40
	Tablet weight	80.00

Asenapine maleate, Bitter blocker, Neotame, Fumed silica (Aerosil®), and ½ amount of mannitol (Pearlitol flash®) were sifted through 30 mesh sieve and then mixed in a rapid mixture granulator for

5 minutes. Croscarmellose sodium and ½ amount of mannitol (Pearlitol flash®) were sifted through 30 mesh sieve, were added to the rapid mixture granulator and mixed for 5 more minutes. The uniform dry mix was then granulated with purified water. The obtained wet mass was passed through 14 mesh screen and dried at 55°C until the LOD reached less than 2%w/w. The dried granules were sifted through 30 mesh screen.

Croscarmellose sodium, Neotame and Fumed Silica were sifted through 30 mesh screen, and blended with the dried granules for 10 minutes. Peppermint flavour and sodium stearyl fumarate were sifted through 60 mesh screen, added to the blender for lubrication 5 more minutes. The obtained mixture was compressed into tablets with suitable punches and packed.

The prepared tablets were subjected to disintegration test and dissolution test.

Disintegration time of the prepared asenapine sublingual tablets (ST) 10 mg

Asenapine ST 10mg	**Disintegration Time** [Seconds]
Tablet-1	20
Tablet-2	18
Tablet-3	20
Average	**19**

Dissolution profile test:

Comparative dissolution test was carried out with the above prepared tablet and the reference product Sycrest. Figure 2 and the results presented in Table 2 show the reference product and the tested product are equivalent.

Dissolution medium: 500 ml of pH 4.5 Acetate Buffer

Dissolution apparatus: USP II Paddle type, RPM: 50

Table 2:

Time [minutes]	5	10	15	30	45	60
Reference Product (Sycrest)	80	85	87	88	88	88
Tested product	73	91	93	94	95	95

Example 3: Asenapine sublingual tablets 10 mg

No.	**Ingredients**	**Quantity/tab** [mg]
	Inner phase	

1	Asenapine maleate	14.06
2	Bitter blocker	0.80
3	Mannitol and starch (Pearlitol flash®)	49.74
4	Croscarmellose sodium	3.00
5	Fumed silica (Aerosil®)	2.40
6	Neotame	1.20
7	Purified water	Q.S
	Outer phase	
8	Croscarmellose sodium	3.00
9	Neotame	1.20
10	Fumed silica (Aerosil®)	2.40
11	Magnesium stearate	2.00
12	Peppermint flavor	0.20
	Tablet weight	80.00

Asenapine maleate, Bitter blocker, Neotame, Fumed silica (Aerosil®), and ½ amount of mannitol (Pearlitol flash®) were sifted through 30 mesh sieve and then mixed in a rapid mixture granulator for 5 minutes. Croscarmellose sodium and ½ amount of mannitol (Pearlitol flash®) were sifted through 30 mesh sieve, were added to the rapid mixture granulator and mixed for 5 more minutes. The uniform dry mix was then granulated with purified water. The obtained wet mass was passed through 14 mesh screen and dried at 55°C until the LOD reached less than 2%w/w. The dried granules were sifted through 30 mesh screen.

Croscarmellose sodium, Neotame and Fumed silica were sifted through 30 mesh screen, and blended with the dried granules for 10 minutes. Peppermint flavour and magnesium stearate were sifted through 60 mesh screen, added to the blender for lubrication for 5 more minutes. The obtained mixture was compressed into tablets with suitable punches and packed.

The prepared tablets were subjected to disintegration test and dissolution test.

Disintegration time of the prepared asenapine sublingual tablets (ST) 10 mg

Asenapine ST 10mg	**Disintegration Time** [Seconds]
Tablet-1	11
Tablet-2	10
Tablet-3	12
Average	**11**

Dissolution profile test:

Comparative dissolution test was carried out with the above prepared tablet and the reference product Sycrest. Figure 3 and the results presented in Table 3 show the reference product and the tested product are equivalent.

Dissolution medium: 500 ml of pH 4.5 Acetate Buffer

Dissolution apparatus: USP II Paddle type, RPM: 50

Table 3:

Time (minutes)	5	10	15	30	45
Reference Product [Sycrest]	80	85	87	88	88
Tested product	94	97	97	97	97

Example 4: Asenapine Sublingual tablets 5 mg

S. No.	Name of Raw Materials	Quantity/tab [mg]
	Inner phase	
1	Asenapine maleate	7.03
2	Bitter blocker	0.40
3	Mannitol and starch (Pearlitol flash®)	24.87
4	Croscarmellose sodium	1.50
5	Fumed silica (Aerosil®)	1.20
6	Neotame	0.60
7	Purified water	Q.S
	Outer phase	
8	Croscarmellose sodium	1.50
9	Neotame	0.60
10	Fumed silica (Aerosil®)	1.20
11	Magnesium stearate	1.00
12	Peppermint flavor	0.10
	Tablet weight	40.00

Asenapine maleate, Bitter blocker, Neotame, Fumed silica (Aerosil®), and ½ amount of mannitol (Pearlitol flash®) were sifted through 30 mesh sieve and then mixed in a rapid mixture granulator for 5 minutes. Croscarmellose sodium and ½ amount of mannitol (Pearlitol flash®) were sifted through 30 mesh sieve, were added to the rapid mixture granulator and mixed for 5 more minutes. The uniform

dry mix was then granulated with purified water. The obtained wet mass was passed through 14 mesh screen and dried at 55°C until the LOD reached less than 2%w/w. The dried granules were sifted through 30 mesh screen.

Croscarmellose sodium, Neotame and Fumed silica were sifted through 30 mesh screen, and blended with the dried granules for 10 minutes. Peppermint flavour and magnesium stearate were sifted through 60 mesh screen, added to the blender for lubrication for 5 more minutes. The obtained mixture was compressed into tablets with suitable punches and packed.

The prepared tablets were been subjected to disintegration test and dissolution test.

Disintegration Time of the prepared asenapine sublingual tablets (ST) 5 mg

Asenapine ST 10mg	**Disintegration Time** [Seconds]
Tablet-1	11
Tablet-2	10
Tablet-3	10
Average	**10**

Dissolution profile test:

Comparative dissolution test was carried out with the above prepared tablet and the reference product Sycrest. Figure 4 and the results presented in Table 4 show the reference product and the tested product are equivalent.

Dissolution medium: 500 ml of pH 4.5 Acetate Buffer

Dissolution apparatus: USP II Paddle type, RPM: 50

Table 4:

Time [minutes]	5	10	15	30	45
Reference Product (Sycrest)	88	99	99	99	99
Tested product	90	95	96	97	97

Claims:

1. An orally disintegrating pharmaceutical composition comprising Asenapine, pharmaceutically acceptable salt or crystalline forms thereof, and at least one pharmaceutically acceptable excipient, which is free from binder.

2. The orally disintegrating pharmaceutical composition according to claim 1, characterized in that a disintegration time of said composition is less than 30 seconds.

3. The orally disintegrating pharmaceutical composition according to claim 2, characterized in that a disintegration time of said composition is between 10 and 20 seconds.

4. The orally disintegrating pharmaceutical composition according to claims 1 to 3, characterized in that it comprises Asenapine, pharmaceutically acceptable salt or crystalline forms thereof in an amount of from 10 to 35% w/w.

5. The orally disintegrating pharmaceutical composition according to claims 1 to 4, characterized in that it comprises Asenapine maleate.

6. The orally disintegrating pharmaceutical composition according to claims 1 to 5, characterized in that it comprises essentially Asenapine maleate in monoclinic crystalline form.

7. The orally disintegrating pharmaceutical composition according to claim 6, characterized in that it comprises less than 5 % w/w of another crystalline form of Asenapine maleate.

8. The orally disintegrating pharmaceutical composition according to claims 1 to 7, characterized in that Asenapine, pharmaceutically acceptable salt or crystalline forms thereof has a particle size D90 less than 30 microns.

9. The orally disintegrating pharmaceutical composition according to claims 1 to 8, characterized in that it is in the form of granules or tablet.

10. The orally disintegrating pharmaceutical composition according to claims 1 to 9, characterized in that it is in the form of a fast disintegrating tablet for sublingual application.

11. The orally disintegrating pharmaceutical composition according to claims 1 to 10, characterized in that it comprises Asenapine, pharmaceutically acceptable salt or crystalline

forms thereof, one or more disintegrant(s), one or more diluents(s), one or more glidant(s), one or more lubricant(s), optionally one or more flavoring agent(s), sweetener(s) or combination thereof.

12. The orally disintegrating pharmaceutical composition according to claims 1 to 11, characterized in that the disintegrant is selected from croscarmellose sodium, carmellose calcium, carboxymethylstarch sodium, crospovidone, low-substituted hydroxypropylcellulose, sodium starch glycolate, colloidal silicon dioxide, and starch or any combinations thereof.

13. The orally disintegrating pharmaceutical composition according to claim 12, characterized in that the disintegrant is croscarmellose sodium.

14. The orally disintegrating pharmaceutical composition according to claims 1 to 11, characterized in that the diluent is selected from mannitol, sorbitol, xylitol, F-melt, starch, lactose, cellulose derivatives, calcium carbonate, magnesium carbonate, dibasic calcium phosphate, tribasic calcium phosphate or any combinations thereof.

15. The orally disintegrating pharmaceutical composition according to claim 14, characterized in that the diluent is mannitol, starch, microcrystalline cellulose, lactose or any combination thereof.

16. The orally disintegrating pharmaceutical composition according to claims 1 to 11, characterized in that the glidant is selected from fumed silica, talc, colloidal silicone dioxide or any combinations thereof.

17. The orally disintegrating pharmaceutical composition according to claim 16, characterized in that the glidant is fumed silica.

18. The orally disintegrating pharmaceutical composition according to claims 1 to 11, characterized in that the lubricant is selected from magnesium stearate, calcium stearate, talc, sodium stearyl fumarate, macrogol or hydrogenated esters of fatty acids with glycerine and stearic acid.

19. The orally disintegrating pharmaceutical composition according to claim 18, characterized in that the lubricant is magnesium stearate or sodium stearyl fumarate.

20. The orally disintegrating pharmaceutical composition according to claims 1 to 11, characterized in that the sweetener is selected from artificial sweeteners Neotame, aspartame, acesulfame potassium, cyclamate, sucralose, saccharine or natural sugars.

21. The orally disintegrating pharmaceutical composition according to claim 20, characterized in that the sweetener is Neotame.

22. The orally disintegrating pharmaceutical composition according to claims 1 to 11, characterized in that the flavoring agent is selected from menthol, Bitter blocker, fruit flavours, peppermint flavor, citrus oil, peppermint oil, spearmint oil, methyl salicylate.

23. The orally disintegrating pharmaceutical composition according to claim 22, characterized in that the flavoring agent is peppermint flavour, bitter blocker or combinations thereof.

24. The orally disintegrating pharmaceutical composition according to claims 1 to 23, characterized in that has a two-phase structure consisting of:
a) an inner phase comprising Asenapine, pharmaceutically acceptable salts or crystalline forms thereof, at least one disintegrant, at least one diluent, at least one glidant, and optionally a flavoring agent and a sweetener, and
b) an outer phase comprising at least one disintegrant, at least one glidant, at least one lubricant, and optionally a sweetener and a flavouring agent.

25. The orally disintegrating pharmaceutical composition according to claim 22, characterized in that it has a two-phase structure consisting of:
a) an inner phase comprising Asenapine maleate, croscarmellose sodium, mannitol, fumed silica, bitter blocker and neotame, and
b) an outer phase comprising croscarmellose sodium, fumed silica, sodium stearyl fumarate, neotame and peppermint flavor.

26. A process for manufacturing the orally disintegrating pharmaceutical composition according to claims 1 to 25 characterized in that it comprises the following steps:
a) mixing asenapine, pharmaceutically acceptable salt or crystalline forms thereof, the first part of a disintegrant, at least one diluent, at least one glidant, optionally a sweetener and /or a flavoring agent,
b) wet granulation of the blend obtained in step a),
c) screening and drying the granules,
d) mixing the dried granules obtained in step c) with the second part of the disintegrant, at

least one glidant, and optionally with a sweetener and/or flavoring agent,

e) the blend obtained in step d) is lubricated with a lubricant, optionally flavoring agent is added, and

f) optionally compressing the mixture obtained in step e) to form a tablet.

27. A process for manufacturing the orally disintegrating pharmaceutical composition according to claim 26, characterized in that wet granulation is carried out by purified water as granulation liquid.

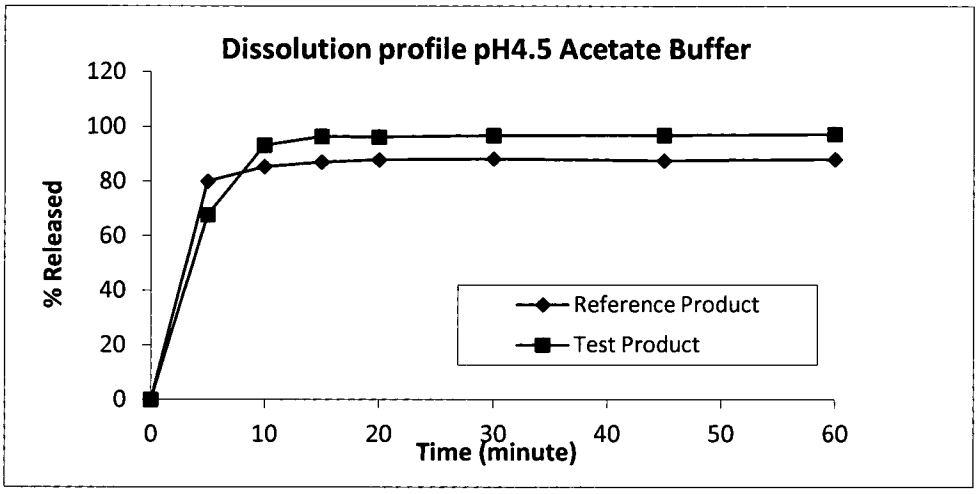

Dissolution profile pH4.5 Acetate Buffer
% Released
120
100
80
60
40
20
0
0
10
20
30
40
50
60
Time (minute)
Reference Product
Test Product

Fig. 1

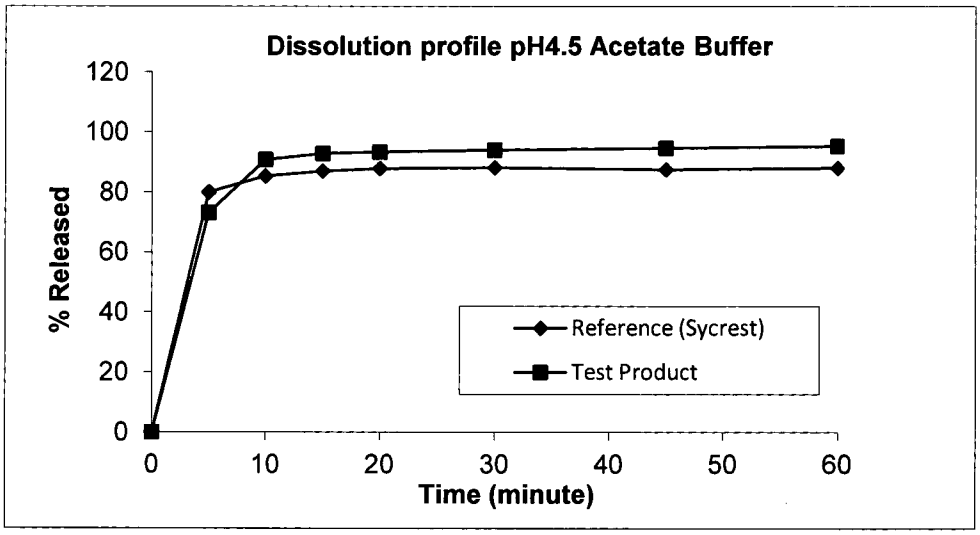

Dissolution profile pH4.5 Acetate Buffer
% Released
120
100
80
60
40
20
0
0
10
20
30
40
50
60
Time (minute)
Reference (Sycrest)
Test Product

Fig. 2

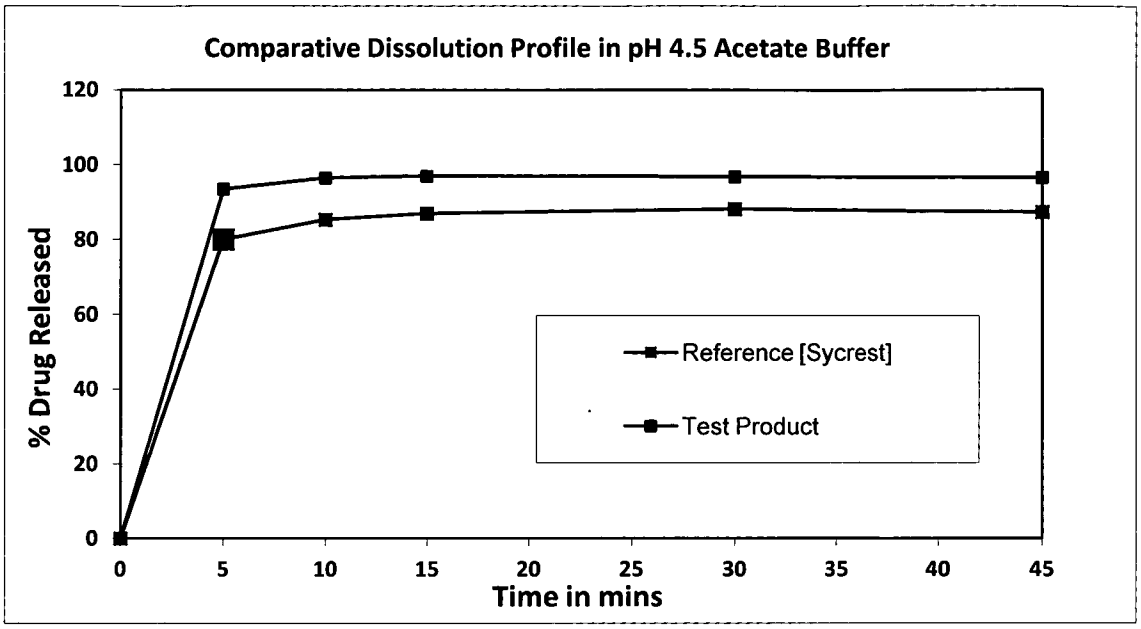

Comparative Dissolution Profile in pH 4.5 Acetate Buffer
% Drug Released
120
100
80
60
40
20
0
0
5
10
15
20
25
30
35
40
45
Time in mins
Reference [Sycrest]
Test Product

Fig. 3

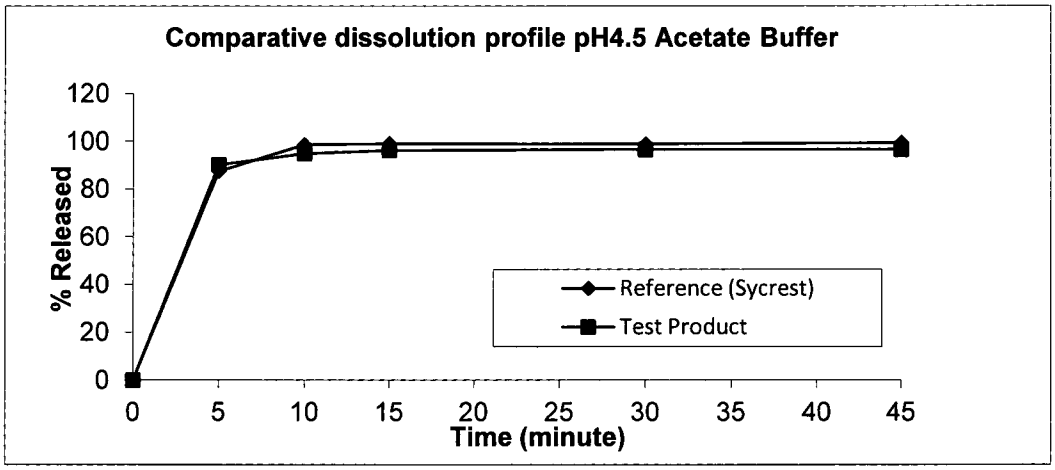

Comparative dissolution profile pH4.5 Acetate Buffer
% Released
120
100
80
60
40
20
0
0
5
10
15
20
25
30
35
40
45
Time (minute)
Reference (Sycrest)
Test Product

Fig. 4

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/000516

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K31/407 A61K9/20
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)
A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95/23600 A1 (AKZO NOBEL NV [NL]; DELBRESSINE LEONARDUS PETRUS C [NL]; WIERINGA JOHA) 8 September 1995 (1995-09-08) page 3, line 5 - page 3, line 30 -----	1-27
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[X] Further documents are listed in the continuation of Box C.

[X] 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

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"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	Date of mailing of the international search report
23 May 2013	13/06/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Schifferer, Hermann

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/000516

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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T	Anonymous: "Excipient", Wikipedia, the free encyclopedia , 22 May 2013 (2013-05-22), XP002697564, Retrieved from the Internet: URL:http://en.wikipedia.org/wiki/Excipient [retrieved on 2013-05-22] page 2, line 1 - page 2, line 21	1-27

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2013/000516

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