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(54) Benevnelse **New co-crystals of agomelatin**

(56) Anførte publikasjoner

REMENAR J F ET AL: "Crystal engineering of novel cocrystals of a tiazole drug with 1,4-dicarboxylic acids", JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC; US, vol. 125, 1 juin 2003 (2003-06-01), pages 8456-8457, XP002973472, ISSN: 0002-7863, DOI: 10.1021/JA035776P

TRASK A V ET AL: "Physical stability enhancement of theophylline via cocrystallization", INTERNATIONAL JOURNAL OF PHARMACEUTICS, ELSEVIER BV, NL, vol. 320, no. 1-2, 31 août 2006 (2006-08-31), pages 114-123, XP025113479, ISSN: 0378-5173, DOI: 10.1016/J.IJPHARM.2006.04.018 [extrait le 2006-08-31]

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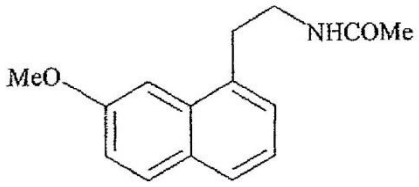
The present invention relates to new co-crystals of agomelatine or *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide of formula (I):



(I)

to a process for their preparation and to pharmaceutical compositions containing them.

Agomelatine, or *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide, has valuable pharmacological properties.

It has the double feature of being on the one hand an agonist of the receptors of the melatoninergic system and on the other hand an antagonist of the 5-HT_{2C} receptor. These properties impart thereto an activity in the central nervous system and more especially in the treatment of major depression, seasonal affective disorder, sleep disorders, cardiovascular pathologies, pathologies of the digestive system, insomnia and fatigue due to jet-lag, appetite disorders and obesity.

Agomelatine, its preparation and its use in therapeutics have been described in European patent EP 0 447 285.

In view of the pharmaceutical value of this compound, many research works have been carried out and have made it possible to isolate different polymorphic forms having various advantages, especially of purity, stability, reproducibility, formulation..., allowing prolonged storage without particular conditions of temperature, light, humidity or oxygen level.

In addition, as is the case for any active ingredient which is to be administered to humans, it is very important to be able to control its dissolution rate in order to promote rapid or, on the contrary, slow diffusion.

The applicant has now developed new co-crystals of agomelatine which allow the dissolution rate of the active ingredient to be modified. The co-crystals according to the invention have a dissolution rate which is accelerated or retarded as compared with the form available on the market described in patent EP1564202 and marketed under the trade mark Valdoxan®. These new co-crystals with a modified dissolution profile thus allow new formulations to be envisaged according to the desired use.

There is found in the prior art WO2005/002562 a claim relating to a co-crystal of agomelatine with tartaric acid. This prior art does not put forward any characterisation or any mode of preparation.

Sai-Li Zheng *et al*. (Crystal Growth and Design, 2011, 11, 466-471) describe a co-crystal of agomelatine obtained with acetic acid, but the study of this co-crystal has shown that it is very unstable and corresponds to a very labile solvate.

A co-crystal is a crystalline complex composed of at least two neutral molecules which are bonded together in a crystal lattice by non-covalent interactions. The main difference between solvates and co-crystals is linked to the physical state of the pure components: if one of the constituents is liquid at ambient temperature, then the molecular complex is a solvate; if all the components are solid at ambient temperature, then the complex is designated by the term co-crystal. The major difference between a solvate and a co-crystal is the far greater stability of the co-crystal compared with the solvate. A co-crystal is characterised by a preparation process and an ordered three-dimensional structure demonstrated by X-ray diffraction diagrams, for example. It is not possible *a priori* to know if two given constituents are going to be able to form a co-crystal having a particular three-dimensional structure or simply give rise to a juxtaposition of the two powders. This particular three-dimensional structure is related directly to the dissolution rate of the entity so formed.

The invention relates more especially to new co-crystals composed of agomelatine on the one hand and an organic acid on the other hand. The co-crystals according to the invention comprise organic acids which are in the solid state at ambient temperature.

The organic acids according to the invention are linear acids containing from 2 to 10 carbon atoms. They have one or more acid COOH functions, and more preferably one, two or three acid functions. They can generally have, in addition to their acid

function(s), one or more ketone functions, one or more hydroxy functions, one or more unsaturated bonds.

The organic acids which are constituents of the co-crystals according to the invention are para-hydroxybenzoic acid, gallic acid, malonic acid, glutaric acid, glycolic acid, ketoglutaric acid...

The proportion of organic acid used, relative to agomelatine, varies from 0.25 to 4 molar equivalents and preferably from 0.5 to 2 molar equivalents.

The invention relates more especially to the following co-crystals: agomelatine/para-hydroxybenzoic acid (2/1) and (1/2); agomelatine/gallic acid (2/1); agomelatine/-malonic acid (1/1); agomelatine/glutaric acid (1/1); agomelatine/glycolic acid (1/1); agomelatine/ketoglutaric acid (1/1).

The invention relates also to a process for obtaining co-crystals of agomelatine and organic acids, wherein:

- the two constituents are mixed in an organic solvent in the desired proportions (1 equivalent of agomelatine per 0.25 to 4 molar equivalents of organic acid);
- the solution obtained is stirred and optionally heated at a temperature not greater than the boiling point of the selected solvent;
- the mixture is cooled, with stirring, and the co-crystal precipitates naturally or precipitates after taking up in a second solvent;
- the precipitate obtained is filtered and dried.

In the process according to the invention, the solvent used is preferably an alcohol such as, for example, methanol or *tert*-butanol; an ether such as, for example, diisopropyl ether or methyl *tert*-butyl ether; or an aromatic hydrocarbon such as, for example, toluene. When a second solvent is used to promote precipitation of the co-crystal, benzonitrile is advantageously chosen.

An alternative process comprises co-grinding the two constituents of the co-crystal. The co-grinding is preferably carried out in a steel jar. A variant of this process comprises adding an organic solvent during the grinding; in this case, the co-crystal obtained is then dried. Among the solvents used, there may be mentioned, more

especially, alcohols such as, for example, ethanol or ethers such as, for example, diisopropyl ether.
The grinding is advantageously carried out using non-oxidisable balls. The grinding is carried out using vibrations, preferably vibrations with a frequency ranging from 20 to 30 Hz. The vibrations are applied for a period which may range from 15 minutes to 3 hours.

Another alternative process comprises mixing two solutions containing each of the constituents and rapidly freezing the mixture obtained at a very low temperature, and then at that same very low temperature drying the co-crystal thereby obtained. The two constituents are advantageously mixed in an organic or aqueous-organic solvent. The freezing and drying are carried out preferably between -40°C and -60°C, and more preferably at -40°C.

Another advantageous process according to the invention comprises mixing the powders of agomelatine and of the acid in question in a mixer and then extruding the mixture by twin-screw extrusion without a die in order to obtain a solid grain directly at the outlet of the extruder. The screw profile used is preferably a high-shear profile, optionally with the use of kneader elements allowing the contact surface between the constituents to be improved. The L/D parameter of the screw may vary between 10 and 40 and the speed of rotation between 10 and 200 rpm. The temperature used varies from 40 to 100°C.

In the processes for the preparation of the co-crystals according to the invention there may be used the compound of formula (I) obtained by any process, especially by the process described in EP1564202(A1).

The co-crystals according to the invention exhibit very valuable properties in terms of stability and dissolution, two parameters which are essential in the pharmaceutical industry. The dissolution of active ingredients is an important phenomenon which can determine the rate of absorption of the active ingredients in the human body. It is an important step in the release process, which determines to a large degree the activity of a medicament. In order to cross the biological membranes or in order to be

absorbed, the active ingredient must in fact be dispersed in the molecular state in aqueous media (that is to say dissolved) at the absorption site. The dissolution rate of the active ingredient is a function of its physico-chemical characteristics as well as of the conditions of the absorption medium. It is thus important to have available forms which have a modified dissolution rate of the active ingredient, allowing more or less rapid dissolution of the active ingredient to be obtained according to the desired use: a form having improved dissolution for use in immediate release formulations, and a form having less rapid dissolution for use in retard or delayed release formulations.
The co-crystals according to the invention meet this need since it is possible to modify the dissolution rate of the agomelatine and promote or reduce its dissolution by a factor of up to 2 relative to the form currently marketed under the trade name Valdoxan®. In particular, the co-crystals according to the invention allow the dissolution rate of the active ingredient to be modified relative to the dissolution rate of the form currently marketed under the trade name Valdoxan® by at least 25% in neutral (pH 6.8) or acid (HCl 0.01N) conditions. It is thus possible to use the co-crystals according to the invention in the preparation of immediate release pharmaceutical forms in which the dissolution rate is improved relative to the form currently available on the market, as well as in delayed release forms in which the dissolution rate is retarded.

The pharmaceutical forms comprising the co-crystals according to the invention will be used for their activity on the central nervous system and on microcirculation, in the treatment of stress, sleep disorders, anxiety disorders and especially generalised anxiety disorder, obsessive compulsive disorders, mood disorders and especially bipolar disorders, major depression, seasonal affective disorder, cardiovascular pathologies, pathologies of the digestive system, insomnia and fatigue due to jet-lag, schizophrenia, panic attacks, melancholia, appetite disorders, obesity, insomnia, pain, psychotic disorders, epilepsy, diabetes, Parkinson's disease, senile dementia, various disorders associated with normal or pathological ageing, migraine, memory loss, Alzheimer's disease, and also in cerebral circulation disorders. In another field of activity, it will be possible to use the co-crystals according to the invention in sexual

dysfunctions, as ovulation inhibitors and immunomodulators and in the treatment of cancers.

The co-crystals according to the invention will be used preferably in the treatment of major depression, seasonal affective disorder, sleep disorders, anxiety disorders, mood disorders, cardiovascular pathologies, pathologies of the digestive system, insomnia and fatigue due to jet-lag, appetite disorders and obesity.

The invention relates also to pharmaceutical compositions comprising as active ingredient a co-crystal according to the invention together with one or more suitable inert, non-toxic excipients. Among the pharmaceutical compositions according to the invention, there may be mentioned, more especially, those that are suitable for oral, parenteral (intravenous or subcutaneous) or nasal administration, tablets or dragées, granules, sublingual tablets, capsules, lozenges, suppositories, creams, ointments, dermal gels, injectable preparations, drinkable suspensions and chewing gums.

The useful dosage can be adapted according to the nature and severity of the disorder, the administration route and the age and weight of the patient. The dosage varies from 0.1 mg to 1 g of agomelatine per day in one or more administrations.

The examples below illustrate the invention but do not limit it in any way.

Example 1: Agomelatine/gallic acid (2/1) co-crystal

A solution of 300.6 mg of *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide in 15 ml of tert-butanol is added slowly to a solution of 106 mg of gallic acid in 35 ml of water in a 250 ml flask. The mixture is stirred for 10 minutes and then the solution is frozen at -40°C and dried at that same temperature for 2 days to yield the title product, which is characterised by its melting point and by the following X-ray powder diffraction diagram, measured using a Panalytical Xpert Pro MPD diffractometer (copper anticathode) and expressed in terms of interplanar distance d,

Bragg's angle 2 theta (expressed in °±0.2) and relative intensity (expressed as a percentage relative to the most intense line):

2-Theta (°) exp.	d (Å) exp.	Intensity (%)
7.4888	11.8051	13.8
9.9347	8.90352	14.42
12.456	7.10638	9.11
12.7479	6.9443	14.08
14.0965	6.28286	5.63
14.4701	6.12146	20.24
16.7302	5.29926	14.01
16.829	5.26837	13.25
17.6782	5.01714	100
19.8178	4.48005	27.73
21.2441	4.18238	14.42
21.8521	4.06737	7.02
22.3357	3.98038	39.37
23.2889	3.81958	10.11
23.9313	3.71848	64.55
24.3882	3.64985	17.32
25.1812	3.53668	5.33
27.5931	3.23278	5.39
29.6861	3.00945	7.02
30.7722	2.90566	7.71

Characteristic Bragg's angles 2 theta (expressed in °±0.2) of the X-ray powder diffraction diagram: 14.47°, 17.68°, 19.82°, 22.33°, 23.93°.

Melting point: 108-110℃

Example 2: Agomelatine/malonic acid (1/1) co-crystal

A solution of 300 mg of *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide in 15 ml of tert-butanol is added slowly to a solution of 129 mg of malonic acid in 35 ml of

water in a 250 ml flask. The mixture is stirred for 30 minutes and then the solution is frozen at -40°C and dried at that same temperature for 2 days to yield the title product, which is characterised by its melting point and by the following X-ray powder diffraction diagram, measured using a Panalytical Xpert Pro MPD diffractometer (copper anticathode) and expressed in terms of interplanar distance d, Bragg's angle 2 theta (expressed in °±0.2) and relative intensity (expressed as a percentage relative to the most intense line):

2-Theta (°) exp.	d (Å) exp.	Intensity (%)
7.8661	11.23971	16.84
10.4713	8.44846	46.94
11.9502	7.406	45.62
12.7824	6.92563	9.99
14.7848	5.99187	21.65
15.3432	5.77504	19.95
16.0487	5.52273	100
16.7983	5.27793	11.99
16.9715	5.22445	13.9
17.1267	5.17745	9.19
21.0784	4.21489	9.77
22.3247	3.98233	23.32
24.0567	3.69939	6.29
24.5022	3.63313	56.82
25.0477	3.55523	23.07
25.2424	3.52825	40.38
25.7892	3.45467	10.44
26.7244	3.33585	7.17
27.3793	3.25753	20.44
27.9097	3.19682	26.63
29.4500	3.03304	10.41
34.0469	2.63332	5.16

Characteristic Bragg's angles 2 theta (expressed in °±0.2) of the X-ray powder diffraction diagram: 10.47°, 11.95°, 14.78°, 16.05°, 22.32°, 24.50°, 25.05°, 25.24°, 27.38°, 27.91°.

Melting point: 67-68°C

<u>Example 3:</u> Agomelatine/para-hydroxybenzoic acid (2/1) co-crystal

1 g of *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide and 283.8 mg of para-hydroxybenzoic acid are introduced into a 25 ml non-oxidisable jar. Two stainless steel balls having a diameter of 12 mm are added and the jar is closed. 200 µl of isopropyl ether are added. Vibrations having a frequency of 30 Hz are applied for 60 minutes to yield the title product, which is characterised by its melting point and by the following X-ray powder diffraction diagram, measured using a Panalytical Xpert Pro MPD diffractometer (copper anticathode) and expressed in terms of interplanar distance d, Bragg's angle 2 theta (expressed in °±0.2) and relative intensity (expressed as a percentage relative to the most intense line):

2-Theta (°) exp.	d (Å) exp.	Intensity (%)
10.6835	8.28111	11.39
11.9471	7.40793	8.16
12.0698	7.33288	12.04
13.1596	6.72799	22.29
14.6189	6.05948	6.29
14.7754	5.99567	11.14
14.907	5.94301	43.41
15.1499	5.84827	14.08
16.7697	5.28686	7.17
17.08	5.19149	8.17
17.2378	5.14433	10.12
17.3731	5.10456	20.24
17.5783	5.04543	16.57
18.3905	4.82442	24.81
18.7565	4.73108	11.19
18.9282	4.68855	23.85
19.0366	4.6621	21.45
19.4137	4.57238	8.15

19.6471	4.5186	20.4
19.9637	4.44765	20.12
20.1044	4.41683	19.09
20.2539	4.38456	20.62
20.9205	4.24635	10.62
21.491	4.13489	100
21.7733	4.08191	91.9
22.2831	3.98966	7.75
23.7997	3.73875	12.32
23.9912	3.70935	8.36
24.2112	3.67614	6.78
24.6151	3.61672	17.26
24.9976	3.56224	22.13
26.5573	3.35646	4.98
26.7447	3.33337	5.85
27.5321	3.2398	12.36
29.4497	3.03306	12.87

Characteristic Bragg's angles 2 theta (expressed in °±0.2) of the X-ray powder diffraction diagram: 13.16°, 14.91°, 17.37°, 18.39°, 18.93°, 19.04°, 19.65°, 19.96°, 20.25°, 21.49°, 25.00°.

Melting point: 93-95°C

Example 4: Agomelatine/para-hydroxybenzoic acid (1/2) co-crystal

1 g of *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide and 1.14 g of para-hydroxy-benzoic acid are introduced into a 25 ml non-oxidisable jar with 250 µl of diisopropyl ether. Two stainless steel balls having a diameter of 12 mm are added and the jar is closed. Vibrations having a frequency of 30 Hz are applied for 120 minutes to yield the title product, which is characterised by its melting point and by the following X-ray powder diffraction diagram, measured using a Panalytical Xpert Pro MPD diffractometer (copper anticathode) and expressed in terms of

interplanar distance d, Bragg's angle 2 theta (expressed in °±0.2) and relative intensity (expressed as a percentage relative to the most intense line):

2-Theta (°) exp.	d (Å) exp.	Intensity (%)
6.9836	12.65784	17.63
8.4549	10.45823	6.16
9.4969	9.31293	34.61
12.2797	7.208	38.63
12.9651	6.82845	14.3
13.1503	6.7327	7.88
13.7866	6.42337	7.33
13.9951	6.32814	27.1
15.7604	5.62307	52.5
16.1791	5.4785	32.32
16.6241	5.33282	51.26
17.5572	5.05145	39.19
18.1485	4.8882	54.91
18.3819	4.82664	17.31
19.3253	4.5931	17.44
19.4415	4.56592	17.76
19.7593	4.49317	51.9
19.959	4.44867	42.09
21.0028	4.22989	45.52
21.2989	4.17175	20.42
22.0032	4.03979	60.83
22.6859	3.91973	11.33
22.9715	3.87164	20.19
23.5476	3.77821	39.55
23.7609	3.74477	93.42
24.4422	3.64191	32.21
25.3271	3.51664	19.07
25.5471	3.48685	14.62
26.0938	3.41502	100
26.8242	3.32367	21.88
26.9813	3.30467	16.4

27.9183	3.19586	6.85
28.4188	3.1407	27.49
28.7129	3.1092	30.36
29.276	3.05067	5.22
29.8536	2.99295	28.73
30.7825	2.90472	6.33
34.5702	2.59464	5.06

Characteristic Bragg's angles 2 theta (expressed in °±0.2) of the X-ray powder diffraction diagram: 9.50°, 12.28°, 14.00°, 15.76°, 16.18°, 16.62°, 17.56°, 18.15°, 19.96°, 21.00°, 21.30°, 22.00°, 22.97°, 23.55°, 23.76°, 24.44°, 26.09°, 26.82°, 28.42°, 28.71°, 29.85°.

Melting point: 116-118℃

Example 5: Agomelatine/glutaric acid (1/1) co-crystal

1 g of *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide and 555 mg of glutaric acid are introduced into a 25 ml non-oxidisable jar. Two stainless steel balls having a diameter of 12 mm are added and the jar is closed. Vibrations having a frequency of 30 Hz are applied for 60 minutes to yield the title product, which is characterised by its melting point and by the following X-ray powder diffraction diagram, measured using a Panalytical Xpert Pro MPD diffractometer (copper anticathode) and expressed in terms of interplanar distance d, Bragg's angle 2 theta (expressed in °±0.2) and relative intensity (expressed as a percentage relative to the most intense line):

2-Theta (°) exp.	**d (Å) exp.**	**Intensity (%)**
9.5919	9.22091	22.85
10.3486	8.5483	28.18
11.9618	7.39882	23.63
13.0927	6.76218	8.08
13.7395	6.44526	5.45

14.7283	6.0147	8.81
16.4376	5.39291	13.05
16.9847	5.2204	10.58
17.493	5.06987	10.05
17.6723	5.01881	6.83
18.6123	4.76741	17.35
18.9534	4.68238	15.44
19.9041	4.46083	16.48
20.5662	4.31869	20.46
21.6468	4.10548	38.05
21.9751	4.04488	5.01
22.0881	4.02444	5.94
23.3395	3.81143	100
23.7133	3.75217	6.65
24.0288	3.70362	5.71
24.6109	3.61733	5.25
25.0027	3.56152	6.82
25.863	3.44497	8.04
27.6684	3.22415	17.51
29.1279	3.06584	4.97

Characteristic Bragg's angles 2 theta (expressed in °±0.2) of the X-ray powder diffraction diagram: 9.59°, 10.35°, 11.96°, 20.57°, 21.65°, 23.34°.

Melting point: 74-75°C

Example 6: Agomelatine/ketoglutaric acid (1/1) co-crystal

1 g of *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide and 600 mg of ketoglutaric acid are introduced into a 25 ml non-oxidisable jar with 500 µl of ethanol. Two stainless steel balls having a diameter of 12 mm are added and the jar is closed. Vibrations having a frequency of 30 Hz are applied for 15 minutes to yield, after drying overnight at 40°C, the title product, which is characterised by its melting point and by the following X-ray powder diffraction diagram, measured using a Panalytical

Xpert Pro MPD diffractometer (copper anticathode) and expressed in terms of interplanar distance d, Bragg's angle 2 theta (expressed in °±0.2) and relative intensity (expressed as a percentage relative to the most intense line):

2-Theta (°) exp.	**d (Å) exp.**	**Intensity (%)**
5.2391	16.86816	18.25
6.1796	14.30283	7.39
9.6513	9.16426	12.13
10.4827	8.43926	8.6
14.2638	6.20954	5
15.3616	5.76815	45.63
16.3452	5.41872	43.96
16.5381	5.35593	59.36
17.0478	5.20123	6.44
18.3191	4.84305	8.1
19.2396	4.61337	21.8
20.5617	4.31961	7.64
21.036	4.22329	12.12
21.3726	4.15752	7.66
23.57	3.77466	36.07
23.9026	3.7229	24.64
24.4145	3.64597	100
26.4474	3.37016	6.58
29.1314	3.06548	6.73
37.1969	2.41723	5.98

Characteristic Bragg's angles 2 theta (expressed in °±0.2) of the X-ray powder diffraction diagram: 15.36°, 16.34°, 16.54°, 19.24°, 23.57°, 23.90°, 24.41°.

Melting point: 94-96℃

Example 7: **Agomelatine/glycolic acid (1/1) co-crystal**

1 g of *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide and 319 mg of glycolic acid are introduced into a 25 ml non-oxidisable jar. Two stainless steel balls having a diameter of 12 mm are added and the jar is closed. Vibrations having a frequency of 30 Hz are applied for 15 minutes to yield, after drying overnight at 40°C, the title product, which is characterised by its melting point and by the following X-ray powder diffraction diagram, measured using a Panalytical Xpert Pro MPD diffractometer (copper anticathode) and expressed in terms of interplanar distance d, Bragg's angle 2 theta (expressed in °±0.2) and relative intensity (expressed as a percentage relative to the most intense line):

2-Theta (°) exp.	d (Å) exp.	Intensity (%)
10.2906	8.59638	45.79
13.9365	6.35459	5.32
14.1139	6.27513	31.57
14.2265	6.22572	24.57
14.3625	6.16708	11.84
17.9846	4.93237	90.49
18.617	4.76622	10.66
18.8288	4.71308	89.79
19.19	4.62519	9.61
19.5137	4.54918	30.43
19.941	4.45266	6.52
20.6101	4.30959	66.27
20.9906	4.23232	8.23
22.8209	3.89685	6.31
23.6248	3.76604	5.61
23.9623	3.71375	26.41
24.2171	3.67524	17.2
24.3906	3.64949	100
26.4458	3.37037	27.5
28.1154	3.1739	29.75
28.4808	3.134	5.71

28.6849	3.11217	6.41
28.9288	3.08648	5.75
29.518	3.02621	29.2
32.2458	2.77386	14.35

Characteristic Bragg's angles 2 theta (expressed in °±0.2) of the X-ray powder diffraction diagram: 10.29°, 14.11°, 14.23°, 17.98°, 18.83°, 19.51°, 20.61°, 23.96°, 24.39°, 26.44°, 28.11°, 29.52°.

Melting point: 75-77°C

Example 8: Measurement of the dissolution rate of the co-crystals

The dissolution rates of the co-crystals obtained are measured by means of a μDiss analysis apparatus (pION) in acid and neutral medium at 37°C at a stirring speed of 700 rpm. The results obtained are collected in the following tables and are expressed as the percentage increase in the dissolution rate of the co-crystal compared with the dissolution rate obtained for the agomelatine of form II contained in the commercial form Valdoxan®:

$$\% = \frac{\text{(Dissolution rate co-crystal)- (Dissolution rate Valdoxan)}}{\text{(Dissolution rate Valdoxan)}} \text{ x } 100$$

	HCl 0.01 N	Buffer pH 6.8
Compound of Example 1	+37%	+29%
Compound of Example 3	+97%	+89%
Compound of Example 4	+19%	+46%

The results obtained shown an increase in the dissolution rate of the co-crystals ranging from 29% to 97% in at least one of the two acid or neutral conditions tested.

	HCl 0.01 N	Buffer pH 6.8
Compound of Example 2	-55%	-21%
Compound of Example 5	-42%	-29%
Compound of Example 6	-47%	-32%
Compound of Example 7	-30%	-30%

The results obtained show a decrease in the dissolution rate of the co-crystals ranging from 21% to 55% in at least one of the two acid or neutral conditions tested.

Example 9: Accelerated release pharmaceutical composition

Formulation for the preparation of 1000 tablets each containing 25 mg of agomelatine:

Compound of Example 3..... 50 g
Lactose monohydrate..... 115 g
Magnesium stearate..... 2 g
Maize starch..... 33 g
Maltodextrins..... 15 g
Anhydrous colloidal silica..... 1 g
Pregelatinised maize starch type A..... 9 g

Example 10: Delayed release pharmaceutical composition

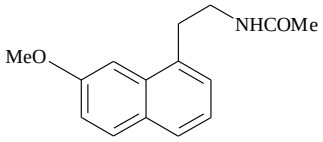
Formulation for the preparation of 1000 tablets each containing 25 mg:

Compound of Example 6..... 50 g
Lactose monohydrate..... 100 g
Magnesium stearate..... 2 g
Povidone..... 12 g
Anhydrous colloidal silica..... 1 g
Hypromellose..... 85 g

Patentkrav

1. Ko-krystall av agomelatin, k a r a k t e r i s e r t v e d at den er satt sammen av:

- agomelatin, eller *N*-[2-(7-metoksy-1-naftyl)etyl]acetamid med formel (I)



(I),

og

- en organisk syre valgt fra para-hydroksybenzosyre, gallussyre, malonsyre, glutarsyre, glykolsyre og ketoglutarsyre.

2. Ko-krystall ifølge krav 1, k a r a k t e r i s e r t v e d at den modifiserer oppløsningshastigheten av den aktive ingrediens sammenlignet med krystallinsk form II.

3. Ko-krystall ifølge enten krav 1 eller krav 2, k a r a k t e r i s e r t v e d at den tilveiebringer en modifikasjon av oppløsningshastigheten av den aktive ingrediens sammenlignet med oppløsningshastigheten av krystallinsk form II på minst 25% under nøytrale (pH 6,8) eller sure (0,01N HCl) betingelser.

4. Ko-krystall ifølge et av kravene 1 til 3 som er *N*-[2-(7-metoksy-1-naftyl)-etyl]acetamid/para-hydroksybenzosyre (2/1), k a r a k t e r i s e r t v e d sitt røntgenpulverdiffraksjonsdiagram ifølge Braggs vinkler 2 theta (uttrykt i ° ± 0,2) 13,16°, 14,91°, 17,37°, 18,39°, 18,93°, 19,04°, 19,65°, 19,96°, 20,25°, 21,49°, 25,00°.

5. Ko-krystall ifølge et av kravene 1 til 3 som er *N*-[2-(7-metoksy-1-naftyl)-etyl]acetamid/para-hydroksybenzosyre (1/2), k a r a k t e r i s e r t v e d sitt røntgenpulverdiffraksjonsdiagram ifølge Braggs vinkler 2 theta (uttrykt i ° ± 0,2) 9,50°, 12,28°, 14,00°, 15,76°, 16,18°, 16,62°, 17,56°, 18,15°, 19,96°, 21,00°,

21,30°, 22,00°, 22,97°, 23,55°, 23,76°, 24,44°, 26,09°, 26,82°, 28,42°, 28,71°, 29,85°.

6. Ko-krystall ifølge et av kravene 1 til 3 som er *N*-[2-(7-metoksy-1-naftyl)-etyl]acetamid/gallussyre (2/1), k a r a k t e r i s e r t v e d sitt røntgenpulverdiffraksjonsdiagram ifølge Braggs vinkler 2 theta (uttrykt i ° ± 0,2) 14,47°, 17,68°, 19,82°, 22,33°, 23,93°.

7. Ko-krystall ifølge et av kravene 1 til 3 som er *N*-[2-(7-metoksy-1-naftyl)-etyl]acetamid/malonsyre (1/1), k a r a k t e r i s e r t v e d sitt røntgenpulverdiffraksjonsdiagram ifølge Braggs vinkler 2 theta (uttrykt i ° ± 0,2) 10,47°, 11,95°, 14,78°, 16,05°, 22,32°, 24,50°, 25,05°, 25,24°, 27,38°, 27,91°.

8. Ko-krystall ifølge et av kravene 1 til 3 som er *N*-[2-(7-metoksy-1-naftyl)-etyl]acetamid/glutarsyre (1/1), k a r a k t e r i s e r t v e d sitt røntgenpulverdiffraksjonsdiagram ifølge Braggs vinkler 2 theta (uttrykt i ° ± 0,2) 9,59°, 10,35°, 11,96°, 20,57°, 21,65°, 23,34°.

9. Ko-krystall ifølge et av kravene 1 til 3 som er *N*-[2-(7-metoksy-1-naftyl)-etyl]acetamid/glykolsyre (1/1), k a r a k t e r i s e r t v e d sitt røntgenpulverdiffraksjonsdiagram ifølge Braggs vinkler 2 theta (uttrykt i ° ± 0,2) 10,29°, 14,11°, 14,23°, 17,98°, 18,83°, 19,51°, 20,61°, 23,96°, 24,39°, 26,44°, 28,11°, 29,52°.

10. Ko-krystall ifølge et av kravene 1 til 3 som er *N*-[2-(7-metoksy-1-naftyl)-etyl]acetamid/ketoglutarsyre (1/1), k a r a k t e r i s e r t v e d sitt røntgenpulverdiffraksjonsdiagram ifølge Braggs vinkler 2 theta (uttrykt i ° ± 0,2) 15,36°, 16,34°, 16,54°, 19,24°, 23,57°, 23,90°, 24,41°.

11. Fremgangsmåte for å erholde en ko-krystall ifølge et av kravene 1 til 10, k a r a k t e r i s e r t v e d at:

- de to bestanddelene blandes i et organisk løsemiddel i de ønskede forhold (1 ekvivalent agomelatin per 0,25 til 4 molare ekvivalenter organisk syre);

- den dannede oppløsning omrøres og oppvarmes valgfritt ved en temperatur som ikke er høyere enn kokepunktet for det valgte løsemiddel;

- blandingen avkjøles under omrøring, og ko-krystallen felles naturlig eller felles etter å ha blitt tatt opp i et andre løsemiddel;

- den erholdte felning filtreres og tørkes.

12. Fremgangsmåte for fremstilling av en ko-krystall ifølge et av kravene 1 til 10, k a r a k t e r i s e r t v e d at de to bestanddelene males opp sammen.

13. Fremgangsmåte for fremstilling av en ko-krystall ifølge et av kravene 1 til 10, k a r a k t e r i s e r t v e d at de to bestanddelene blandes i et organisk eller vandig-organisk løsemiddel og deretter fryses og tørkes ved fra -40°C til -60°C.

14. Fremgangsmåte for fremstilling av en ko-krystall ifølge et av kravene 1 til 10, k a r a k t e r i s e r t v e d at pulvrene av agomelatin og den aktuelle syre blandes i en mikser og deretter ekstruderes blandingen ved tvillingsskrue-ekstrudering uten dyse for å erholde et fast, granulært produkt direkte i ekstruderutløpet.

15. Farmasøytisk sammensetning som som aktiv ingrediens inneholder en ko-krystall ifølge et av kravene 1 til 10, i kombinasjon med én eller flere farmasøytisk akseptable, inerte, ikke-toksiske bærere.

16. Farmasøytisk sammensetning ifølge krav 15 for anvendelse ved fremstilling av et legemiddel for å behandle forstyrrelser i det melatoninergiske system.

17. Farmasøytisk sammensetning ifølge krav 15 for anvendelse ved fremstilling av et legemiddel for å behandle stress, søvnforstyrrelser, angstforstyrrelser og spesielt generalisert angstforstyrrelse, obsessiv-kompulsive forstyrrelser, humørforstyrrelser og spesielt bipolare forstyrrelser, alvorlig depresjon, sesongavhengig depresjon, kardiovaskulære patologier, patologier i fordøyelsessystemet, søvnløshet og tretthet grunnet jet-lag, schizofreni, panikkanfall, melankoli, appetittforstyrrelser, fedme, søvnløshet, smerter, psykotiske forstyrrelser, epilepsi, diabetes, Parkinsons sykdom, senil demens, forskjellige forstyrrelser forbundet med normal eller patologisk aldring, migrene, hukommelsestap, Alzheimers sykdom, og også ved cerebrale sirkulasjonsforstyrrelser, og også ved seksuell dysfunksjon, og som ovulasjonshemmere og immunomodulatorer og ved behandling av kreft.

18. Ko-krystall ifølge et av kravene 1 til 10 for behandling av forstyrrelser i det melatoninergiske system.

19. Ko-krystall ifølge et av kravene 1 til 10 for å behandle stress, søvnforstyrrelser, angstforstyrrelser og spesielt generalisert angstforstyrrelse, obsessiv-kompulsive forstyrrelser, humørforstyrrelser og spesielt bipolare forstyrrelser, alvorlig depresjon, sesongavhengig depresjon, kardiovaskulære patologier, patologier i fordøyelsessystemet, søvnløshet og tretthet grunnet jet-lag, schizofreni, panikkanfall, melankoli, appetittforstyrrelser, fedme, søvnløshet, smerter, psykotiske forstyrrelser, epilepsi, diabetes, Parkinsons sykdom, senil demens, forskjellige forstyrrelser forbundet med normal eller patologisk aldring, migrene, hukommelsestap, Alzheimers sykdom, og også ved cerebrale sirkulasjonsforstyrrelser, og også ved seksuell dysfunksjon, og som ovulasjonshemmere og immunomodulatorer og ved behandling av kreft.