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(54) Benevnelse **CO-CRYSTALS OF AGOMELATINE AND P-TOLUENESULPHONIC ACID, METHOD FOR PREPARING SAME AND THE PHARMACEUTICAL COMPOSITIONS CONTAINING SAME**

(56) Anførte publikasjoner CN-A- 102 702 041

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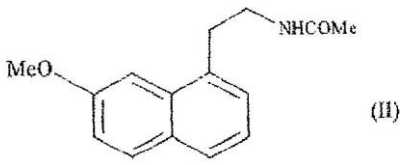
The present invention relates to new forms of co-crystals of agomelatine and *p*-toluenesulphonic acid, to a process for their preparation, and to pharmaceutical compositions containing them.

Agomelatine, or *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide, has the structure of formula (II):



(II)

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Agomelatine is marketed by the French company Servier under the trade name Valdoxan® or Thymanax® as an agonist of receptors of the melatoninergic system and an antagonist of the 5-HT_{2C} receptor. It is the first antidepressant of the melatoninergic type, for use in the treatment of major depression, improving sleep and sexual function.

Agomelatine, its preparation and its use in therapeutics have been described in European patents EP 0 447 285 and EP 1 564 202.

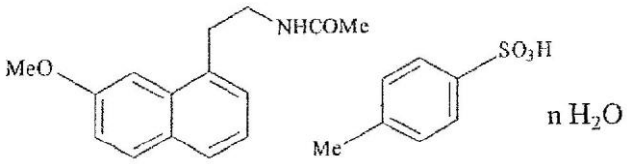
In view of its pharmaceutical value, it is important to be able to produce agomelatine or a complex thereof with improved purity, solubility and reproducibility.

A process for the preparation of the agomelatine/*p*-toluenesulphonic acid co-crystal has been reported in patent application CN102702041, in which the structure of the co-crystal was identified by ^{1}H-NMR, the product obtained being amorphous.

The amorphous form has a number of disadvantages as a pharmaceutical product, such as adherence to walls, poor flow properties, low stability, and it is accordingly still valuable to have available a well defined crystalline form of a chemical entity.

The object of the present invention is to prepare new crystalline forms of co-crystals of agomelatine and *p*-toluenesulphonic acid which have excellent properties in terms of solubility, stability and purity, allowing their use in the manufacture of pharmaceutical compositions comprising agomelatine to be envisaged.

The present invention relates to crystalline forms of co-crystals of agomelatine and *p*-toluenesulphonic acid having the structure of formula (I):



(I)

wherein n represents 0 or 1.

The preferred compounds according to the invention are the following co-crystals of agomelatine and *p*-toluenesulphonic acid:

- agomelatine/*p*-toluenesulphonic acid (1/1) monohydrate co-crystal,
- agomelatine/*p*-toluenesulphonic acid (1/1) co-crystal.

The agomelatine/*p*-toluenesulphonic acid (1/1) monohydrate co-crystal is characterised by its X-ray powder diffraction diagram shown in Figure 1, measured using a Panalytical Xpert Pro MPD diffractometer (copper anticathode). The principal lines are 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) and are listed in Table 1:

Table 1: Table of the diffraction peaks of the agomelatine/*p*-toluenesulphonic acid (1/1) monohydrate co-crystal

2-Theta (°) exp.	d (Å) exp.	Intensity (%)
6.9631	12.6846	77.52
9.4831	9.31871	16.21
12.8823	6.86648	100
13.9527	6.34201	23.16
14.1761	6.24258	16.06
15.1817	5.83128	13.38
15.379	5.75689	25
15.5788	5.68351	46.24
16.7156	5.29947	94.46
17.2926	5.12391	37.98
18.4671	4.80058	92.47
18.6356	4.75756	22.34
19.199	4.6192	25.69
19.6747	4.50857	35.74
20.1398	4.4055	28.53
21.6248	4.1062	14.93
22.0586	4.02643	52.23

22.2859	3.98587	99.09
23.2175	3.82799	15.22
23.9607	3.71092	32.37
25.1733	3.53485	42.09
26.0152	3.42233	16.64
27.7148	3.2162	39.29
28.23	3.15866	11.25
28.4033	3.13979	16.33

When the co-crystal of the present invention is characterised by X-ray diffraction measurement, there may be errors of measurement of the identified peaks which are sometimes attributable to the equipment or to the conditions used. More especially, the 2 theta values can have an error of approximately ± 0.2 and sometimes an error of approximately ± 0.1, even if sophisticated equipment is used. The measurement error must accordingly be taken into account when identifying the structure of the co-crystal.

The crystalline structure of the agomelatine/*p*-toluenesulphonic acid (1/1) monohydrate co-crystal was determined and the following parameters were identified:

- Space group: P 21 21 21 (19)
- Lattice parameters: a = 13.7359(3)Å, b = 25.3716(6)Å, c = 6.4487(1)Å; α = 90°, β = 90(2)°, γ = 90°
- Volume of the lattice: $V_{unit\ cell}$ = 2247.4Å^3

The agomelatine/*p*-toluenesulphonic acid (1/1) monohydrate co-crystal is also characterised by DSC (differential scanning calorimetry) in the spectrum shown in Figure 2, which shows a broad endotherm corresponding to the dehydration of the co-crystal and the melting thereof at a temperature of approximately 78°C (and a temperature peak at approximately 87°C).

The invention relates also to the agomelatine/*p*-toluenesulphonic acid (1/1) co-crystal which is characterised by its X-ray powder diffraction diagram shown in Figure 3, measured using a Panalytical Xpert Pro MPD diffractometer (copper anticathode). The principal lines are 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) and are listed in Table 2:

Table 2: Table of the diffraction peaks of the agomelatine/*p*-toluenesulphonic acid (1/1) co-crystal

2-Theta (°) exp.	d (Å) exp.	Intensity (%)
11.2964	7.82664	21.53
11.6596	7.58367	20.45
13.4436	6.58103	61.31
15.2416	5.80848	18.42
16.0185	5.52847	30.89
17.3473	5.10789	41.39
17.8289	4.97096	54.3
18.2535	4.85629	100
20.4891	4.33118	19.84
20.6912	4.28932	45.12
20.9516	4.23659	36.73
21.3088	4.16638	14.93
22.2998	3.98342	33.92
23.129	3.84244	24.66
23.4107	3.79685	12.89
23.6474	3.75938	12.34
23.9983	3.7052	12.8

When the co-crystal of the present invention is characterised by X-ray diffraction measurement, there may be errors of measurement of the identified peaks which are sometimes attributable to the equipment or to the conditions used. More especially, the 2 theta values can have an error of approximately ± 0.2 and sometimes an error of approximately ± 0.1, even if sophisticated equipment is used. The measurement error must accordingly be taken into account when identifying the structure of the co-crystal.

The crystalline structure of the agomelatine/*p*-toluenesulphonic acid (1/1) co-crystal was determined and the following parameters were identified:

- Space group: P $2_12_12_1$ (19)
- Lattice parameters: a = 8.6683(3) Å, b = 30.360(1) Å, c = 8.0982(4) Å; α = 90°, β = 90°, γ = 90°
- Volume of the lattice: $V_{unit\ cell}$ = 2131.2 Å^3

The agomelatine/*p*-toluenesulphonic acid (1/1) co-crystal is also characterised by DSC (differential scanning calorimetry) in the spectrum shown in Figure 4, which shows an endotherm corresponding to the melting of the complex at a temperature of approximately 105°C.

The invention relates also to a process for obtaining co-crystals of agomelatine and *p*-toluenesulphonic acid, wherein:

- agomelatine and *p*-toluenesulphonic acid monohydrate are mixed in an organic or aqueous-organic solvent in the desired proportions;
- the solution obtained is stirred and optionally heated at a temperature not greater than the boiling point of the chosen solvent;
- the mixture is cooled, with stirring, and the complex precipitates naturally or precipitates after being taken up in a second solvent;
- the precipitate obtained is filtered and dried;
- optionally, the precipitate is dried by heating.

In the process according to the invention, the solvent used is preferably an ether such as, for example, diisopropyl ether, tetrahydrofuran, dioxane or methyl *tert*-butyl ether; or an aromatic hydrocarbon such as, for example, toluene. When a second solvent is used in order to promote precipitation of the complex, the solvent chosen is an alcohol such as, for example, methanol, ethanol or *tert*-butanol; an alkane such as, for example, n-hexane or n-heptane; or benzonitrile.

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, ethers such as, for example, diisopropyl ether, or methyl *tert*-butyl ether. Alcohols such as, for example, methanol or tert-butanol can also be used.
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 5 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.

The co-crystals of agomelatine and *p*-toluenesulphonic acid that are obtained have a solubility that is increased very significantly relative to agomelatine *per se*, which renders them more suitable for the preparation of pharmaceutical formulations. The co-crystals of agomelatine and *p*-toluenesulphonic acid according to the invention additionally exhibit advantageous properties of stability, purity and solubility. They are, moreover, obtained by a simple process which does not include any difficult steps.

The pharmacological studies of the co-crystals according to the invention show that they can be used for the treatment of disorders of the melatoninergic system and, more especially, 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 invention relates also to pharmaceutical compositions comprising as active ingredient a co-crystal of agomelatine and *p*-toluenesulphonic acid according to the invention together with one or more adjuvants or 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 varied 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.

Representative examples of the present invention are illustrated with the corresponding figures in order better to evaluate the subject-matter, features and advantages thereof.

Figure 1: X-ray powder diffraction diagram of the agomelatine/*p*-toluenesulphonic acid (1/1) monohydrate co-crystal.
Figure 2: DSC thermogram of the agomelatine/*p*-toluenesulphonic acid (1/1) monohydrate co-crystal.
Figure 3: X-ray powder diffraction diagram of the agomelatine/*p*-toluenesulphonic acid (1/1) co-crystal.
Figure 4: DSC thermogram of the agomelatine/*p*-toluenesulphonic acid (1/1) co-crystal.

<u>Example 1</u>: Agomelatine/*p*-toluenesulphonic acid (1/1) monohydrate co-crystal

<u>Procedure 1</u>

Agomelatine (5.00 g, 1 eq.) and *p*-toluenesulphonic acid monohydrate (3.92 g, 1 eq.) are placed in a reactor. 40 ml of tetrahydrofuran and 20 ml of hexane are added. The suspension is stirred under reflux for 0.5 hour until it becomes clear (if it does not become clear, further tetrahydrofuran is added until it is clear). The solution is cooled naturally to 5°C and stirred for 0.5 hour, and then the suspension is filtered. The cake is dried for one hour *in vacuo*. 8.53 g of a white solid are obtained.

Yield: 95.8%
Melting point: 78°C

Procedure 2

Agomelatine (5.00 g , 1 eq.) and *p*-toluenesulphonic acid monohydrate (3.952 g, 1 eq.) are introduced into a reactor. 40 ml of acetone and 10 ml of hexane are added. The suspension is stirred under reflux for 0.5 hour until it becomes clear (if it does not become clear, further acetone is added until it is clear). The solution is cooled naturally to 5°C and stirred for 0.5 hour, and the suspension is then filtered. The cake is dried for one hour *in vacuo*. 8.06 g of a white solid are obtained.
Yield: 90.4%
Melting point: 78°C

Procedure 3

Agomelatine (0.5 g) and *p*-toluenesulphonic acid monohydrate (0.392) are placed in a 50-ml non-oxidisable jar. Two stainless steel balls of 12 mm diameter are added and the jar is closed. Vibrations with a frequency of 30 Hz are applied for 15 minutes to yield, after drying overnight at ambient temperature, 0.881 g of solid.
Melting point: 78°C

Procedure 4

Agomelatine (0.5 g) and *p*-toluenesulphonic acid monohydrate (0.392) are placed in a 50-ml non-oxidisable jar. Two stainless steel balls of 12 mm diameter are added and the jar is closed. 100 µl of methyl *tert*-butyl ether are added. Vibrations with a frequency of 30 Hz are applied for 30 minutes to yield, after drying overnight at ambient temperature, 0.883 g of solid.
Melting point: 78°C

Procedure 5

Agomelatine (5 g) and *p*-toluenesulphonic acid monohydrate (3.92 g) are placed in a 100-ml non-oxidisable jar. Two stainless steel balls of 12 mm diameter are added and the jar is closed. 100 µl of methyl *tert*-butyl ether are added. Vibrations with a frequency of 30 Hz are applied for 30 minutes to yield, after drying overnight at ambient temperature, 8.83 g of solid.
Melting point: 78°C

Example 2: Agomelatine/*p*-toluenesulphonic acid (1/1) co-crystal

2 g of the agomelatine/*p*-toluenesulphonic acid (1/1) monohydrate co-crystal obtained in Example 1 are heated at 85°C for 4 hours. A white solid is obtained.
Yield: 100%
Melting point: 105°C

In the examples above it is possible to use commercially available agomelatine or agomelatine prepared by one of the methods described in the prior art.

Example 3: Pharmaceutical compositions: capsules containing a dose of 25 mg of agomelatine

Formulation for the preparation of 1000 capsules each containing 25 mg of agomelatine	
Compound of Example 1	44.5 g
Lactose (Spherolac 100)	85.2 g
Starch 1500	25.5 g
CMS-Na	8.5 g
Ac-Di-Sol® (FMC)	17 g
Stearic acid	3.4 g

Formulation for the preparation of 1000 capsules each containing 25 mg of agomelatine	
Compound of Example 2	42.7 g
Lactose (Spherolac 100)	85.2 g
Starch 1500	25.5 g
CMS-Na	8.5 g
Ac-Di-Sol® (FMC)	17 g
Stearic acid	3.4 g

Example 4: Pharmaceutical compositions: tablets each containing a dose of 25 mg of agomelatine

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

Compound of Example 1	44.5 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

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

Compound of Example 2	42.7 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

Detection methods and results

1. Purity of the samples

Chromatography conditions: C18 column; mobile phase: phosphate buffer 10 mmol/L (adjusted to pH 7.0 with NaOH) : acetonitrile 2:7 (v/v); temperature of the column: 40°C; detection wavelength: 220 nm; internal standard method used with the compound of Examples 1 and 2.

1 mg/ml solutions of the compounds of the invention are prepared with the mobile phase. 10 µl of each solution are injected into the liquid chromatography system and the chromatograms are recorded.

The compounds of Examples 1 and 2 have purities greater than or equal to 99%.

2. Stability

Samples of the compounds of Examples 1 and 2 are placed in incubators at 40°C for 30 days in order to determine their stability by HPLC. The results are presented in Table 3:

Table 3

	25°C, 60% RH OB	40°C, 75% RH OB	50°C CB	70°C CB
Compound of Example 1	Stable	Stable	Stable	Stable
Compound of Example 2	Changes into the monohydrate	Changes into the monohydrate	Changes into the monohydrate	Stable

RH: relative humidity; OB: open bottle; CB: closed bottle

3. Solubility in water

By means of an external standard method, the compounds of Examples 1 and 2 are tested by HPLC and compared with agomelatine of form II. The results are presented in Table 4 in the form of % increase in solubility relative to the solubility of agomelatine of form II:

Table 4

Sample	Solubility (increase versus agomelatine form II)		
	in water	in 0.1N HCl	in a buffer pH 6.8
Compound of Example 1	+41%	+50%	+49%
Compound of Example 2	+35%	+45%	+60%

The results show that the co-crystals of agomelatine and *p*-toluenesulphonic acid of the present invention have greater solubility than agomelatine of form II *per se* in water, in 0.1N HCl, which is similar to human gastric fluids, or in a buffer at pH 6.8. These results show that the co-crystals have a far better potential in terms of bioavailability than agomelatine of form II.

4. DSC analyses

Approximately 5-10 mg of the compounds of Examples 1 and 2 are weighed into an aluminium crucible closed with a pierced (non-hermetic) aluminium lid, unless specified otherwise. The sample is introduced into a TA Q1000 device (equipped with a cooler), cooled and maintained at 25°C. After thermal stabilisation, the sample and the reference are heated from 200°C to 250°C at a rate of 10°C/min and the response to the heat flow is recorded. Nitrogen is used as the purge gas, at a flow rate of 100 cm^3/min.

The DSC thermograms obtained with the compounds of Examples 1 and 2 are shown in Figures 2 and 4.

5. Analysis of the crystalline structure

The conditions of measurement of the X-ray powder diffraction diagrams of the products of Examples 1 and 2 are as follows:

Approximately 50 mg of the compounds of Examples 1 and 2 are placed between two Kapton® films and fixed to the sample support. The sample is then placed in a PANALYTICAL XPERT-PRO MPD diffractometer in transmission mode under the following conditions:

Parameters of the generator: 45 kV / 40 mA

Configuration theta/theta

Anode: Cu

K-Alpha1 [Å] 1.54060

K-Alpha2 [Å] 1.54443

K-Beta [Å] 1.39225

K-A2 / K-A1 ratio 0.50000

Scanning mode: continuous from 3° to 55° (Bragg's angle 2 theta)

Step [°2Th.] 0.0170

Step duration [s] 35.5301

Starting angle [°2Th.] 3.0034

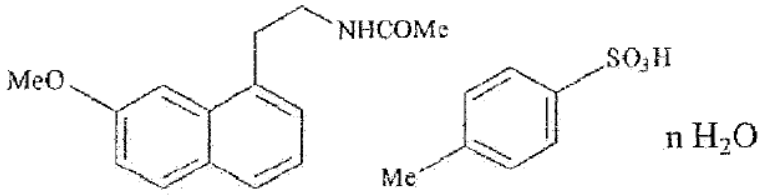
Finishing angle [°2Th.] 54.9894

Rotation: yes

The X-ray powder diffraction diagrams obtained for Examples 1 and 2 are shown in Figures 1 and 3.

Krav

1. Krystallinske former for ko-krystaller av agomelatin og p-toluensulfonsyre med formel (I):



(I)

hvor n er 0 eller 1.

2. Ko-krystall av agomelatin og p-toluensulfonsyremonohydrat med formel (I) ifølge krav 1, k a r a k t e r i s e r t v e d dets røntgenpulverdiffraksjonsdiagram uttrykt som interplanar avstand d, Braggs vinkel 2 theta (uttrykt i 0 ± 0,2) og relativ intensitet, som følger:

2-Theta (°) exp.	d (Å) exp.	Intensitet (%)
6.9631	12.6846	77.52
9.4831	9.31871	16.21
12.8823	6.86648	100
13.9527	6.34201	23.16
14.1761	6.24258	16.06
15.1817	5.83128	13.38
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15.5788	5.68351	46.24
16.7156	5.29947	94.46
17.2926	5.12391	37.98
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19.6747	4.50857	35.74
20.1398	4.4055	28.53
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25.1733	3.53485	42.09

26.0152	3.42233	16.64
27.7148	3.2162	39.29
28.23	3.15866	11.25
28.4033	3.13979	16.33

inkludert formene hvis diffraksjonsvinkler samsvarer med ± 0,2 °.

3. Ko-krystall av agomelatin og p-toluensulfonsyremonohydrat med formel (I) ifølge krav 1, k a r a k t e r i s e r t v e d dets røntgenpulverdiffraksjonsdiagram uttrykt som interplanar avstand d, Braggs vinkel 2 theta (uttrykt i 0 ± 0,2) og relativ intensitet, som følger:

2-Theta (°) exp.	d (Å) exp.	Intensitet (%)
11.2964	7.82664	21.53
11.6596	7.58367	20.45
13.4436	6.58103	61.31
15.2416	5.80848	18.42
16.0185	5.52847	30.89
17.3473	5.10789	41.39
17.8289	4.97096	54.3
18.2535	4.85629	100
20.4891	4.33118	19.84
20.6912	4.28932	45.12
20.9516	4.23659	36.73
21.3088	4.16638	14.93
22.2998	3.98342	33.92
23.129	3.84244	24.66
23.4107	3.79685	12.89
23.6474	3.75938	12.34
23.9983	3.7052	12.8

inkludert formene hvis diffraksjonsvinkler samsvarer med ± 0,2 °.

4. Fremgangsmåte for å oppnå ko-krystaller av agomelatin og p-toluensulfonsyre ifølge et hvilket som helst av kravene 1 til 3, k a r a k t e r i s e r t v e d a t :

- agomelatin og p-toluensulfonsyremonohydrat blandes i et organisk eller vandig-organisk løsningsmiddel i de ønskede mengdeforholdene;
- den oppnådde oppløsningen røres og eventuelt oppvarmes ved en temperatur som ikke er større enn kokepunktet for det valgte løsningsmiddelet;
- blandingen avkjøles, under omrøring, og komplekset utfeller naturlig eller utfeller etter opptak i et andre løsningsmiddel;
- den oppnådde utfellingen blir filtrert og tørket;
- eventuelt, tørkes utfellingen ved oppvarming.

5. Fremgangsmåte for fremstilling av ko-krystaller av agomelatin og p-toluensulfonsyre ifølge et hvilket som helst av kravene 1 til 3, k a r a k t e r i s e r t v e d a t de to bestanddelene er sammalt.

6. Fremgangsmåte for fremstilling av ko-krystaller av agomelatin og p-toluensulfonsyre ifølge et hvilket som helst av kravene 1 til 3, k a r a k t e r i s e r t v e d a t de to bestanddeler blandes i et organisk eller vandig-organisk løsningsmiddel og deretter fryses og tørkes ved en meget lav temperatur.

7. Fremgangsmåte for fremstilling av ko-krystaller av agomelatin og p-toluensulfonsyre ifølge et hvilket som helst av kravene 1 til 3, k a r a k t e r i s e r t v e d a t pulverene av agomelatin og nevnte syre blandes i en mikser og blandingen ekstruderes deretter ved hjelp av tvillingskrue-ekstrudering uten en dyse for å oppnå et fast korn direkte ved ekstruderens utløp.

8. Farmasøytiske sammensetninger omfattende som aktiv ingrediens en av ko-krystallene av agomelatin og p-toluensulfonsyre ifølge et hvilket som helst av kravene 1 til 3, i kombinasjon med en eller flere inerte, ikke-toksiske, farmasøytisk akseptable bærere.

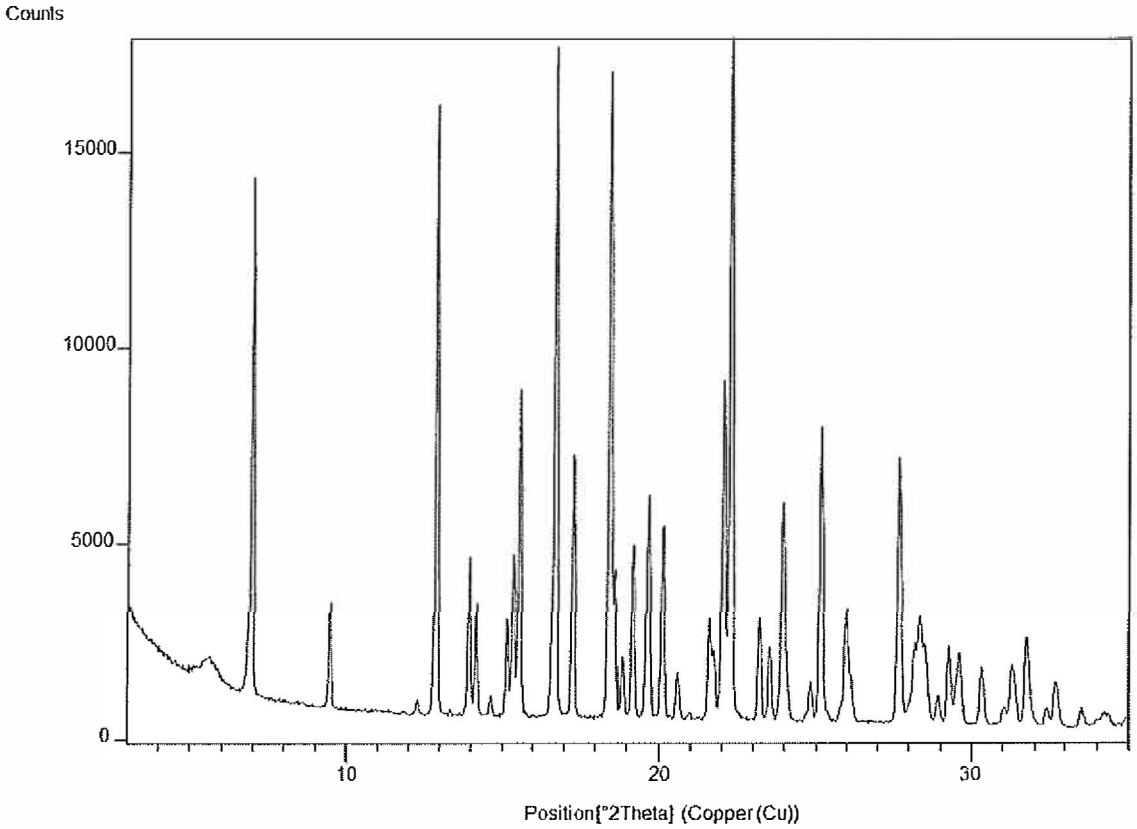
9. Anvendelse av farmasøytiske sammensetninger ifølge krav 8 for fremstilling av medikamenter for behandling av lidelser i det melatoninergiske systemet.

10. Anvendelse av farmasøytiske sammensetninger ifølge krav 8 for fremstilling av medikamenter for behandling av stress, søvnforstyrrelser, angstlidelser og spesielt generalisert angstlidelse, obsessive tvangssykdommer, humørsykdommer og spesielt bipolare lidelser, alvorlig depresjon, sesongbasert affektiv lidelse, kardiovaskulære patologier, fordøyelsessykdommer, søvnløshet og tretthet på

grunn av jetlag, skizofreni, panikkanfall, melankoli, appetittforstyrrelser, fedme, søvnløshet, smerte, psykotiske lidelser, epilepsi, diabetes, Parkinsons sykdom, senil demens, forskjellige lidelser assosiert med normal eller patologisk aldring, migrene, hukommelsestap, Alzheimers sykdom, og også i hjernesirkulasjonsforstyrrelser, og også i seksuelle dysfunksjoner, som eggløsningshemmere og immunmodulatorer og i behandling av kreft.

11. Ko-krystaller av agomelatin og p-toluensulfonsyre med formel (I) ifølge et hvilket som helst av kravene 1 til 3 for behandling av lidelser i det melatoninergiske systemet.

12. Ko-krystaller av agomelatin og p-toluensulfonsyre med formel (I) ifølge et hvilket som helst av kravene 1 til 3 for behandling av stress, søvnforstyrrelser, angstlidelser og spesielt generalisert angstlidelse, obsessive tvangssykdommer, humørsykdommer og spesielt bipolare lidelser, alvorlig depresjon, sesongbasert affektiv lidelse, kardiovaskulære patologier, fordøyelsessykdommer, søvnløshet og tretthet på grunn av jetlag, skizofreni, panikkanfall, melankoli, appetittforstyrrelser, fedme, søvnløshet, smerte, psykotiske lidelser, epilepsi, diabetes, Parkinsons sykdom, senil demens, forskjellige lidelser assosiert med normal eller patologisk aldring, migrene, hukommelsestap, Alzheimers sykdom, og også i hjernesirkulasjonsforstyrrelser, og også i seksuelle dysfunksjoner, som eggløsningshemmere og immunmodulatorer og i behandling av kreft.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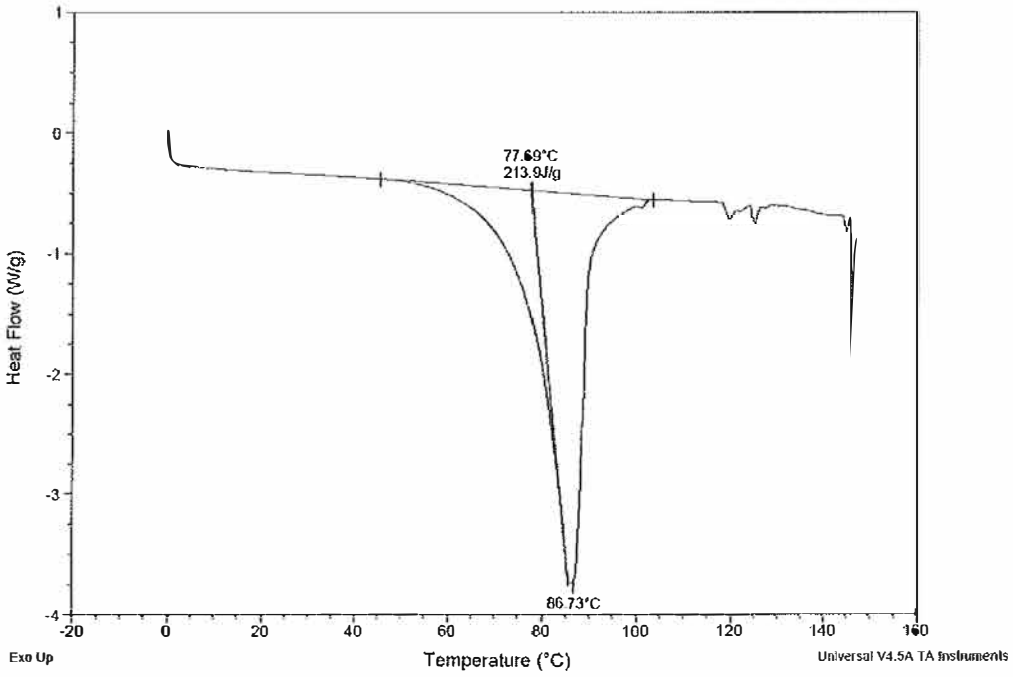
10000
5000
0
10
20
30
Position[°2Theta] (Copper (Cu))

Fig. 1


1
0
-1
-2
-3
-4
Heat Flow (W/g)
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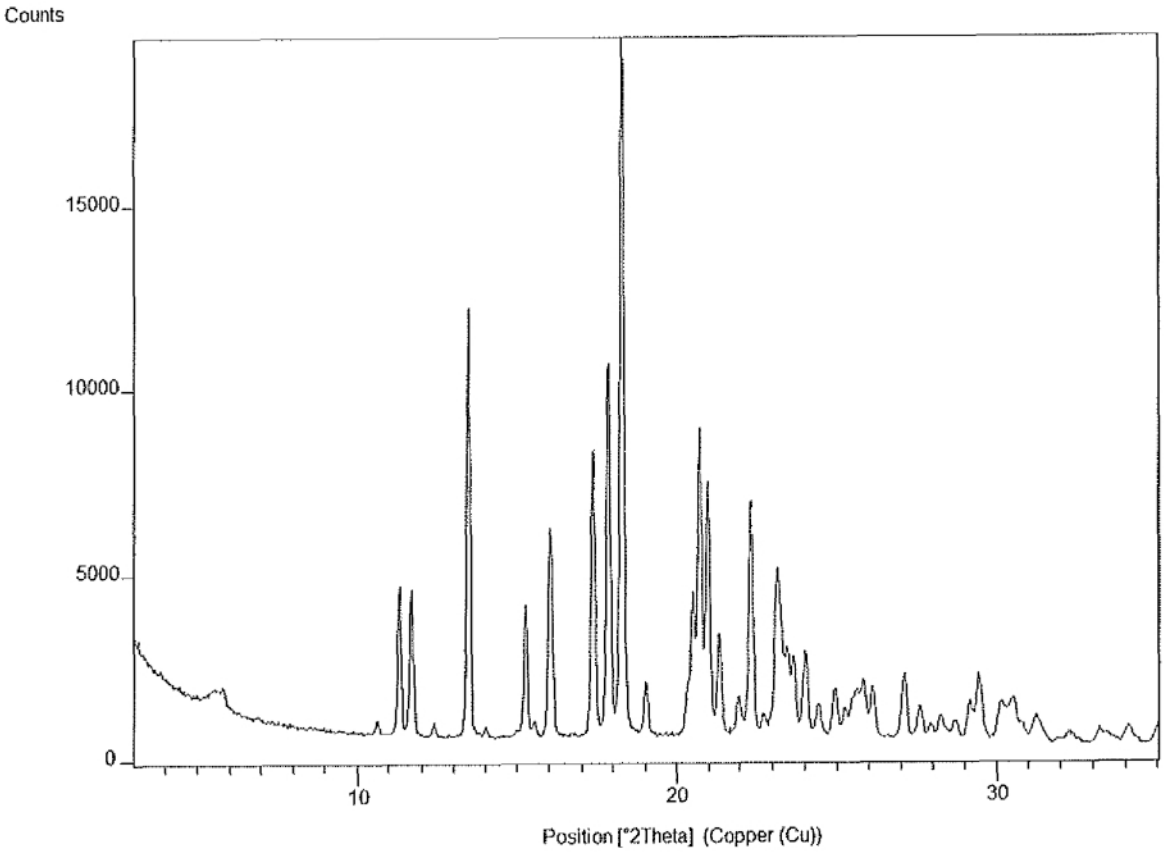
213.9J/g
86.73°C
-20
0
20
40
60
80
100
120
140
160
Exo Up
Temperature (°C)
Universal V4.5A TA Instruments

Fig. 2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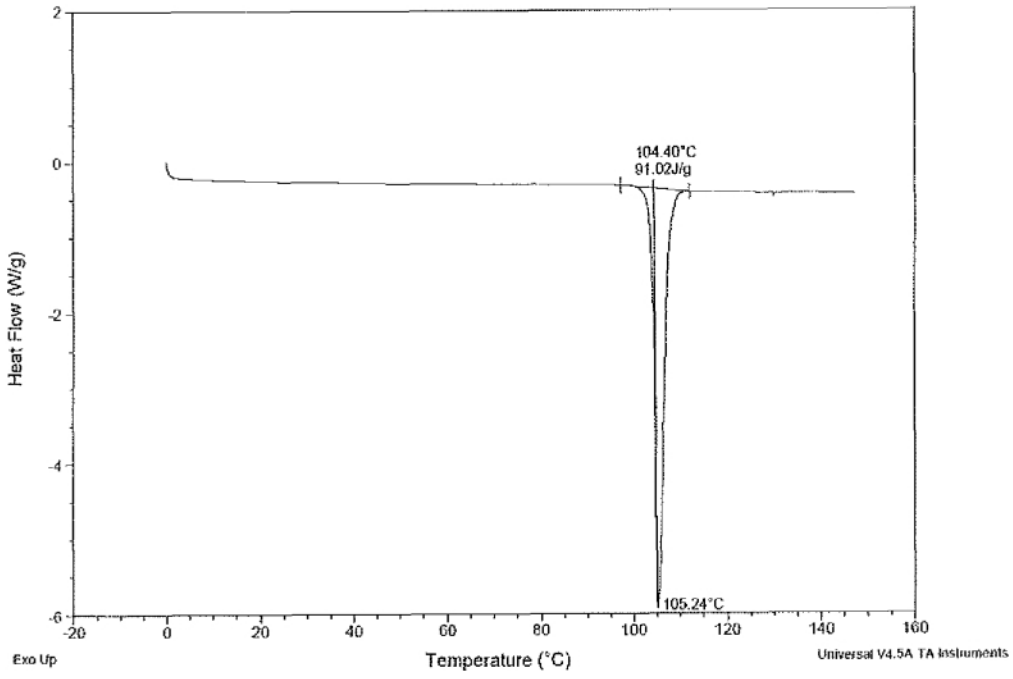
10
20
30
Position [°2Theta] (Copper (Cu))

Fig. 3


2
0
-2
-4
-6
Heat Flow (W/g)
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91.02J/g
105.24°C
-20
0
20
40
60
80
100
120
140
160
Exo Up
Temperature (°C)
Universal V4.5A TA Instruments

Fig. 4