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	Utpekte samarbeidende stater	BA ; ME
(73)	Innehaver	Les Laboratoires Servier, 35, Rue de Verdun, 92284 Suresnes, Frankrike Shanghai Institute Of Pharmaceutical Industry, No.1320 West Beijing Road Jing'an District, Shanghai 200040, Kina
(72)	Oppfinner	SHAN, Hanbin, 24 DongfangxincunGaoan, GaoanJiangxi 330800, Kina SHEN, Yuhui, Room 603 Lane 358n° 30 Sanmen Road, Shanghai 200439, Kina LUO, Ying, Room 803 Unit 4 J1 BuildingXian Shi Garden, Nan ChangJiangxi 300006, Kina LETELLIER, Philippe, 25 Rue du Faubourg Saint Jean, 45000 Orléans, Frankrike LYNCH, Michael, 74 Rue des Chaises, 45140 Saint Jean de la Ruelle, Frankrike
(74)	Fullmektig	OSLO PATENTKONTOR AS, Hoffsveien 1A, 0275 OSLO, Norge

(54) Benevnelse **COMPLEXES OF AGOMELATINE AND SULPHONIC ACIDS, METHOD FOR PREPARING SAME AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM**

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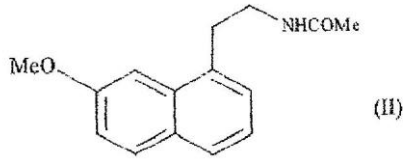
NEW COMPLEXES OF AGOMELATINE AND SULPHONIC ACIDS, A PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

The present invention relates to new complexes of agomelatine and sulphonic acids, 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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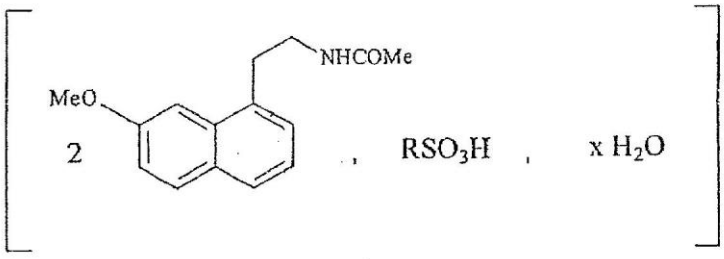
Agomelatine is marketed by the French company Servier under the trade name Valdoxan® or Thymanax® as an agonist of receptors of the melatoninergic system and an antagonist of the 5-HT_{2C} receptor. It is the first antidepressant of the melatoninergic type, for use in the treatment of major depression, 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.

European patent EP 2 517 700 describes co-crystals of agomelatine with citric acid, benzenesulphonic acid and maleic acid of stoichiometry 1/1.

The object of the present invention is to prepare complexes of agomelatine and sulphonic acids having the particular stoichiometry of 2 molar equivalents of agomelatine for 1 molar equivalent of sulphonic acids. These complexes have excellent properties in terms of solubility, stability and purity, allowing their use in the manufacture of pharmaceutical compositions comprising agomelatine to be envisaged. In addition, the stoichiometry of the complexes according to the present invention confers a weight advantage in favour of the active ingredient of the complex, i.e. agomelatine, allowing pharmaceutical compositions containing smaller amounts of complex to be prepared.

The present invention relates to complexes of agomelatine and sulphonic acids having the structure of formula (I):



(I)

wherein x represents 0 or 1, and RSO_3H represents 1,5-naphthalenedisulphonic acid or benzenesulphonic acid.

The preferred compounds according to the invention are the following complexes of agomelatine and sulphonic acids:

- agomelatine/1,5-naphthalenedisulphonic acid (2/1) complex,
- agomelatine/1,5-naphthalenedisulphonic acid (2/1) monohydrate complex,
- agomelatine/benzenesulphonic acid (2/1) complex.

The agomelatine/1,5-naphthalenedisulphonic acid (2/1) complex 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/1,5-naphthalenedisulphonic acid (2/1) complex

2-Theta (°) exp.	d (Å) exp.	Intensity (%)
6.3716	13.87229	18.97
11.3804	7.77552	17.98
11.9227	7.42299	36.06
12.5064	7.07784	100.00
12.6590	6.99288	13.75
14.5508	6.08767	44.17

15.5658	5.69292	11.96
16.2029	5.47051	42.63
16.9421	5.23346	25.85
17.6267	5.03171	18.67
19.4300	4.56857	49.04
20.2146	4.39301	22.77
21.4353	4.14550	17.80
21.6713	4.10090	22.84
22.2180	4.00121	64.19
22.4174	3.96607	10.83
24.0749	3.69664	29.61
24.5048	3.63275	13.33
25.1744	3.53763	20.58
25.7599	3.45853	23.59

When the complex 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 complex.

The crystalline structure of the agomelatine/1,5-naphthalenedisulphonic acid (2/1) complex was determined and the following parameters were identified:

- Space group: P 1 21/c 1 (14)
- Lattice parameters: a = 8.4970(3)Å, b = 8.0873(3)Å, c = 27.7107(9)Å; $\alpha = 90°$, $\beta = 93.059(2)°$, $\gamma = 90°$
- Volume of the lattice: $V_{unit\ cell} = 1901.51100Å^3$

The agomelatine/1,5-naphthalenedisulphonic acid (2/1) complex is also characterised by DSC (differential scanning calorimetry) in the spectrum shown in Figure 2, which shows

an endotherm corresponding to the melting of the complex at a temperature of approximately 237°C.

The invention relates also to the agomelatine/1,5-naphthalenedisulphonic acid (2/1) monohydrate complex 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/1,5-naphthalenedisulphonic acid (2/1) monohydrate complex

2-Theta (°) exp.	d (Å) exp.	Intensity (%)
9.6680	9.14852	12.45
12.4885	7.08796	57.23
12.6164	7.01639	28.61
14.5042	6.10715	57.42
16.2684	5.44863	25.67
16.4624	5.38484	32.93
16.8967	5.24739	90.90
19.3772	4.58091	10.50
22.4767	3.95573	100.00
23.4111	3.79992	20.49
23.5330	3.78051	44.02
23.6735	3.75840	21.92
24.0477	3.70076	13.67
24.5716	3.62303	13.43
25.1240	3.54460	12.46
26.6602	3.34374	19.10
28.1333	3.16930	12.07
28.2443	3.15971	22.49

When the complex 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 complex.

The crystalline structure of the agomelatine/1,5-naphthalenedisulphonic acid (2/1) monohydrate complex was determined and the following parameters were identified:

- Space group: P -1 (2)
- Lattice parameters: a = 9.5673(3) Å, b = 9.7223(3) Å, c = 11.4632(3) Å; α = 76.967(2)°, β = 75.339(1)°, γ = 78.675(2)°
- Volume of the lattice: $V_{unit\ cell}$ = 993.93800 $Å^3$

The agomelatine/1,5-naphthalenedisulphonic acid (2/1) monohydrate complex is also characterised by DSC (differential scanning calorimetry) in the spectrum shown in Figure 4, which shows two endotherms: one at approximately 116°C corresponding to the dehydration of the complex, the other at approximately 238°C corresponding to the melting of the complex.

The invention relates also to the agomelatine/benzenesulphonic acid (2/1) complex which is characterised by its X-ray powder diffraction diagram shown in Figure 5, 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 3:

Table 3: Table of the diffraction peaks of the agomelatine/benzenesulphonic acid (2/1) complex

2-Theta (°) exp.	d (Å) exp.	Intensity (%)
8.0711	10.95469	35.25
12.6820	6.98026	68.37
12.7706	6.93203	65.37
13.0114	6.80427	15.18
13.3054	6.65458	31.84
14.9475	5.92700	19.42
15.1121	5.86283	70.19
15.4873	5.72160	14.16
16.1644	5.48344	12.98
17.2360	5.14486	21.06
18.1046	4.89993	36.33
18.6255	4.76406	10.91
18.8009	4.72001	33.43
20.0908	4.41978	30.26
20.4742	4.33788	42.37
20.6921	4.29270	56.78
20.8640	4.25771	26.42
21.7142	4.09289	13.88
23.3683	3.80679	15.16
23.6410	3.76349	100.00
24.9314	3.57154	26.81
25.6543	3.47253	10.71
27.5599	3.23660	14.00

When the complex 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 complex.

The crystalline structure of the agomelatine/benzenesulphonic acid (2/1) complex was determined and the following parameters were identified:

- Space group: P -1 (2)
- Lattice parameters: a = 15.5878(8) Å, b = 15.7088(6) Å, c = 7.2091(3) Å; α = 100.445(2)°, β = 99.470(2)°, γ = 89.054(3)°
- Volume of the lattice: $V_{unit\ cell}$ = 1712.18900 Å

The agomelatine/benzenesulphonic acid (2/1) complex is also characterised by DSC (differential scanning calorimetry) in the spectrum shown in Figure 6, which shows an endotherm at approximately 116°C corresponding to the melting of the complex.

The invention relates also to a process for obtaining complexes of agomelatine and sulphonic acids, wherein:

- the two constituents 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.

In the process according to the invention, the solvent used is preferably a ketone such as, for example, acetone; an ether such as, for example, diisopropyl ether, tetrahydrofuran 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, ketones such as, for example, acetone; or ethers such as, for example, diisopropyl ether, or methyl *tert*-butyl ether. Alcohols such as, for example, methanol, ethanol or tert-butanol can also be used.
The grinding is advantageously carried out using stainless steel 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 complexes of agomelatine and sulphonic acids 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 complexes of agomelatine and sulphonic acids according to the invention additionally exhibit excellent stability and very good purity. They are, moreover, obtained by a simple process which does not include any difficult steps.

The pharmaceutical forms comprising the complexes according to the invention will 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 complex of agomelatine and sulphonic acids 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/1,5-naphthalenedisulphonic acid (2/1) complex of Example 1.

Figure 2: DSC thermogram of the agomelatine/1,5-naphthalenedisulphonic acid (2/1) complex of Example 1.

Figure 3: X-ray powder diffraction diagram of the agomelatine/1,5-naphthalenedisulphonic acid (2/1) monohydrate complex of Example 2.

Figure 4: DSC thermogram of the agomelatine/1,5-naphthalenedisulphonic acid (2/1) monohydrate complex of Example 2.

Figure 5: X-ray powder diffraction diagram of the agomelatine/benzenesulphonic acid (2/1) complex of Example 3.

Figure 6: DSC thermogram of the agomelatine/benzenesulphonic acid (2/1) complex of Example 3.

Example 1: Agomelatine/1,5-naphthalenedisulphonic acid (2/1) complex

Procedure 1

Agomelatine (5.00 g, 1 eq.) and anhydrous 1,5-naphthalenedisulphonic acid (2.96 g, 1 eq.) are placed in a reactor. 20 ml of acetone are added. The suspension is stirred under reflux for 1 hour and then immediately filtered. The cake is washed twice with acetone and then dried for 1 hour. 25 g of a white solid corresponding to the title compound are obtained.

Yield: 78.5%

Melting point: 237°C

Procedure 2

Agomelatine (2.98 g, 2 eq.) and 1,5-naphthalenedisulphonic acid tetrahydrate (2.18 g, 1 eq.) are introduced into a 250-ml flask. 100 ml of acetone are added, and the reaction mixture is heated at reflux for 3 hours (crystallisation occurs after approximately one hour). The suspension is cooled to ambient temperature and stirred for 1 hour. 4.03 g of a white solid corresponding to the title compound are isolated by filtration and dried *in vacuo* (10 mbar) at 40°C for 15 hours.

Yield: 85.0%

Melting point: 237°C

Procedure 3

Agomelatine (5.00 g, 2 eq.) and anhydrous 1,5-naphthalenedisulphonic acid (2.96 g, 1 eq.) are placed in a reactor. 40 ml of methyl tert-butyl ether are added. The suspension is stirred under reflux for 3 hours and then immediately filtered. The cake is washed twice with methyl tert-butyl ether and then dried for 1 hour. 5.28 g of a white solid corresponding to the title product are obtained.

Yield: 66.3%

Melting point: 237°C

Example 2: Agomelatine/1,5-naphthalenedisulphonic acid (2/1) monohydrate complex

Procedure 1

Agomelatine (5.00 g, 1 eq.) and anhydrous 1,5-naphthalenedisulphonic acid (5.92 g, 1 eq.) are placed in a reactor. 10 ml of ethanol and 20 ml of water are added. The suspension is stirred under reflux for 0.5 hour so that it becomes clear. The mixture is then cooled naturally, with stirring, for 0.5 hour, and the suspension is filtered. The cake is washed with ethanol and water and then dried for 1 hour. 5.15 g of a white solid are obtained.

Yield: 63.2%

Melting point: 116°C (dehydration endotherm), 238°C

Procedure 2

Agomelatine (5.00 g, 1 eq.) and 1,5-naphthalenedisulphonic acid tetrahydrate (7.40 g, 1 eq.) are introduced into a reactor. 10 ml of ethanol and 20 ml of water are added. The suspension is stirred under reflux for 0.5 hour so that it becomes clear. The mixture is then cooled naturally, with stirring, for 0.5 hour, and the suspension is filtered. The cake is washed with ethanol and water and then dried for 1 hour. 4.90 g of a white solid are obtained.

Yield: 60.2%

Melting point: 116°C (dehydration endotherm), 238°C

Procedure 3

Agomelatine (0.5 g) and 1,5-naphthalenedisulphonic acid tetrahydrate (0.370 g) 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, 0.805 g of solid.

Melting point: 116°C (dehydration endotherm), 238°C

Procedure 4

Agomelatine (0.5 g) and 1,5-naphthalenedisulphonic acid tetrahydrate (0.370 g) 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, 0.803 g of solid.

Melting point: 116°C (dehydration endotherm), 238°C

Example 3: Agomelatine/benzenesulphonic acid (2/1) complex

Agomelatine (5.00 g, 2 eq.) and benzenesulphonic acid (1.62 g, 1 eq.) are introduced into a reactor. 10 ml of ethanol and 15 ml (10 ml + 5 ml) of toluene are added. The suspension is stirred under reflux for 0.5 hour so that it becomes clear (if the solution is not clear, further ethanol is added until it becomes clear). The mixture is then cooled naturally to 5°C, with stirring, for 0.5 hour, and the suspension is filtered. The cake is dried for 1 hour. 4.31 g of a white solid corresponding to the title product are obtained.

Yield: 65.2%

Melting point: 116°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.

<u>Example 4</u>: Pharmaceutical compositions: capsules containing a dose of 25 mg of agomelatine

Pharmaceutical composition containing the compound of Example 1

Formulation for the preparation of 1000 capsules each containing 25 mg of agomelatine	
Compound of Example 1	39.8 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

Pharmaceutical composition containing the compound of Example 2

Formulation for the preparation of 1000 capsules each containing 25 mg of agomelatine	
Compound of Example 2	40.7 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

Pharmaceutical composition containing the compound of Example 3

Formulation for the preparation of 1000 capsules each containing 25 mg of agomelatine	
Compound of Example 3	33.1 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 5: 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	39.8 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	40.7 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

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

Compound of Example 3	33.1 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 Example 1.

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 the invention all have purities greater than or equal to 99%.

2. Stability

Samples of the compounds of Examples 1, 2 and 3 are placed in incubators under denaturing conditions, and the stability is determined by DSC measurement over 2 months. The results are presented in Table 4:

Table 4

	25°C, 60% RH OB	50°C CB	70°C CB
Compound of Example 1	stable	stable	stable
Compound of Example 2	stable	stable	stable
Compound of Example 3	stable	stable	stable

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

The compounds of the invention are stable under highly denaturing conditions, which is beneficial to their use in pharmaceutical compositions.

3. Solubility

By means of an external standard method, the compounds of Examples 1, 2 and 3 are tested by HPLC and compared with agomelatine of form II. The results are presented in Table 5 in the form of % increase in solubility relative to the solubility of agomelatine of form II:

Table 5

Sample	Solubility (increase versus agomelatine form II)		
	in water	in 0.1N HCl	in a buffer pH 6.8
Compound of Example 1	+18%	+25%	+48%
Compound of Example 2	+12%	+75%	+57%
Compound of Example 3	+22%	+32%	+46%

The results show that the complexes of agomelatine and sulphonic acids 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 complexes 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, 2 and 3 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, 2 and 3 are shown in Figures 2, 4 and 6.

5. Analysis of the crystalline structure

The conditions of measurement of the X-ray powder diffraction diagrams of the products of Examples 1, 2 and 3 are as follows:

Approximately 50 mg of the compounds of Examples 1, 2 and 3 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

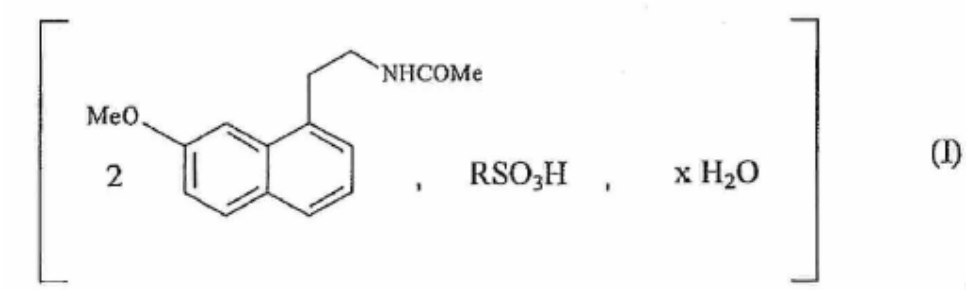
Finishing angle [°2Th.] 54.9894

Rotation: yes

The X-ray powder diffraction diagrams obtained for Examples 1, 2 and 3 are shown in Figures 1, 3 and 5.

Patentkrav

1. Komplekser av agomelatin og sulfonsyrer med formel (I):



hvor x representerer 0 eller 1, og RSO_3H representerer 1,5-naftalen-disulfonsyre eller benzensulfonsyre.

2. Kompleks av agomelatin med formel (I) ifølge krav 1, som er kompleks av agomelatin / 1,5-naftalen-disulfonsyre (2/1).

3. Kompleks av agomelatin med formel (I) ifølge krav 2 karakterisert ved dens røntgenpulverdiffraksjonsskjema uttrykt i form av inter-retikulær avstand d, Bragg 2 theta vinkel (uttrykt i °±0,2), og av relativ intensitet som følger:

2-Theta (°) exp.	d (Å) exp.	Intensitet (%)
6,3716	13,87229	18,97
11,3804	7,77552	17,98
11,9227	7,42299	36,06
12,5064	7,07784	100,00
12,6590	6,99288	13,75
14,5508	6,08767	44,17
15,5658	5,69292	11,96
16,2029	5,47051	42,63
16,9421	5,23346	25,85
17,6267	5,03171	18,67
19,4300	4,56857	49,04
20,2146	4,39301	22,77
21,4353	4,14550	17,80
21,6713	4,10090	22,84
22,2180	4,00121	64,19
22,4174	3,96607	10,83

24,0749	3,69664	29,61
24,5048	3,63275	13,33
25,1744	3,53763	20,58
25,7599	3,45853	23,59

inkludert former hvilken diffraksjonsvinkler tilsvarer ± 0,2 °.

4. Kompleks av agomelatin med formel (I) ifølge krav 1, som er kompleks av agomelatin / 1,5-naftalen-disulfonsyre (2/1) monohydrat.

5. Kompleks av agomelatin med formel (I) ifølge krav 4 karakterisert ved dens røntgenpulverdiffraksjonsskjema uttrykt i form av inter-retikulær avstand d, Bragg 2 theta vinkel (uttrykt i °±0,2), og av relativ intensitet som følger:

2-Theta (°) exp.	d (Å) exp.	Intensitet (%)
9,6680	9,14852	12,45
12,4885	7,08796	57,23
12,6164	7,01639	28,61
14,5042	6,10715	57,42
16,2684	5,44863	25,67
16,4624	5,38484	32,93
16,8967	5,24739	90,90
19,3772	4,58091	10,50
22,4767	3,95573	100,00
23,4111	3,79992	20,49
23,5330	3,78051	44,02
23,6735	3,75840	21,92
24,0477	3,70076	13,67
24,5716	3,62303	13,43
25,1240	3,54460	12,46
26,6602	3,34374	19,10
28,1333	3,16930	12,07
28,2443	3,15971	22,49

inkludert former hvilken diffraksjonsvinkler tilsvarer ± 0,2 °.

6. Kompleks av agomelatin med formel (I) ifølge krav 1, som er kompleks av agomelatin / benzensulfonsyre (2/1).

7. Kompleks av agomelatin med formel (I) ifølge krav 6 karakterisert ved dens røntgenpulverdiffraksjonsskjema uttrykt i form av inter-retikulær avstand d, Bragg 2 theta vinkel (uttrykt i °±0,2), og av relativ intensitet som følger:

2-Theta (°) exp.	d (Å) exp.	Intensitet (%)
8,0711	10,95469	35,25
12,6820	6,98026	68,37
12,7706	6,93203	65,37
13,0114	6,80427	15,18
13,3054	6,65458	31,84
14,9475	5,92700	19,42
15,1121	5,86283	70,19
15,4873	5,72160	14,16
16,1644	5,48344	12,98
17,2360	5,14486	21,06
18,1046	4,89993	36,33
18,6255	4,76406	10,91
18,8009	4,72001	33,43
20,0908	4,41978	30,26
20,4742	4,33788	42,37
20,6921	4,29270	56,78
20,8640	4,25771	26,42
21,7142	4,09289	13,88
23,3683	3,80679	15,16
23,6410	3,76349	100,00
24,9314	3,57154	26,81
25,6543	3,47253	10,71
27,5599	3,23660	14,00

inkludert former hvilken diffraksjonsvinkler tilsvarer ± 0,2 °.

8. Fremgangsmåte for å oppnå komplekser av agomelatin og sulfonsyrer ifølge et hvilket som helst av kravene 1 til 7, karakterisert ved at:

- agomelatin og sulfonsyrer blandes med et organisk eller vandig hydro-organisk løsningsmiddel i de ønskede proporsjoner;
- den oppnådde løsningen blir omrørt og eventuelt oppvarmet til en temperatur som er mest lik kokepunktet for det valgte løsningsmiddel;

- mediet avkjøles under omrøring og samkrystallen utfeller naturlig eller utfeller etter opptak i et andre løsningsmiddel;
- det oppnådde bunnfall blir filtrert og tørket.

9. Fremgangsmåte for fremstilling av komplekser av agomelatin og sulfonsyrer ifølge et hvilket som helst av kravene 1 til 7, karakterisert ved at de to bestanddelene er sammenmalt.

10. Fremgangsmåte for fremstilling av komplekser av agomelatin og sulfonsyrer ifølge et hvilket som helst av kravene 1 til 7, karakterisert ved at de to bestanddelene blandes i et organisk eller hydro-organisk løsningsmiddel og deretter fryses og tørkes ved veldig lav temperatur.

11. Fremgangsmåte for fremstilling av komplekser av agomelatin og sulfonsyrer ifølge et hvilket som helst av kravene 1 til 7, karakterisert ved at pulverene av agomelatin og av den vurderte syren blandes i en mikser, og deretter ekstruderes blandingen ved tvillingskrue ekstrudering uten dyse for å få et fast korn direkte ved ekstruderens utløp.

12. Farmasøytiske sammensetninger som inneholder som aktiv ingrediens et av komplekser av agomelatin og sulfonsyrer ifølge et hvilket som helst av kravene 1 til 7, i kombinasjon med en eller flere inerte, ikke-toksiske og farmasøytisk akseptable bærere.

13. Anvendelse av farmasøytiske sammensetninger ifølge krav 12 for fremstilling av medikamenter for å behandle forstyrrelser i det melatoninergiske systemet.

14. Anvendelse av farmasøytiske sammensetninger ifølge krav 12 for fremstilling av medikamenter for behandling av stress, søvnforstyrrelser, angstlidelser og spesielt generalisert angstlidelse, tvangslidelser, humørsykdommer og spesielt bipolar lidelse, alvorlig depresjon lidelse, sesongdepresjon, kardiovaskulær patologi, patologi i fordøyelsessystemet, søvnløshet og tretthet på grunn av tidsforskjeller, schizofreni, panikkanfall, melankoli, lidelser i matlyst, overvektighet, søvnløshet, smerter, psykotiske lidelser, epilepsi, diabetes, Parkinsons sykdom, senil demens, forskjellige lidelser relatert til normal eller patologisk aldring, migrene, hukommelsestap, Alzheimers sykdom, så vel som for

cerebrale sirkulasjonsforstyrrelser, så vel som for seksuelle dysfunksjoner, som eggløsningshemmere, immunmodulatorer og for behandling av kreft.

15. Komplekser av agomelatin og sulfonsyrer med formel (I) ifølge et hilket som helst av kravene 1 til 7 for behandling av forstyrrelser i det melatoninergiske systemet.

16. Komplekser av agomelatin og sulfonsyrer med formel (I) ifølge et hilket som helst av kravene 1 til 7 for behandling av stress, søvnforstyrrelser, angstlidelser og spesielt generalisert angstlidelse, tvangslidelser, humørsykdommer og spesielt bipolar lidelse, alvorlig depresjon lidelse, sesongdepresjon, kardiovaskulær patologi, patologi i fordøyelsessystemet, søvnløshet og tretthet på grunn av tidsforskjeller, schizofreni, panikkanfall, melankoli, lidelser i matlyst, overvektighet, søvnløshet, smerter, psykotiske lidelser, epilepsi, diabetes, Parkinsons sykdom, senil demens, forskjellige lidelser relatert til normal eller patologisk aldring, migrene, hukommelsestap, Alzheimers sykdom, så vel som for cerebrale sirkulasjonsforstyrrelser, så vel som for seksuelle dysfunksjoner, som eggløsningshemmere, immunmodulatorer og for behandling av kreft.

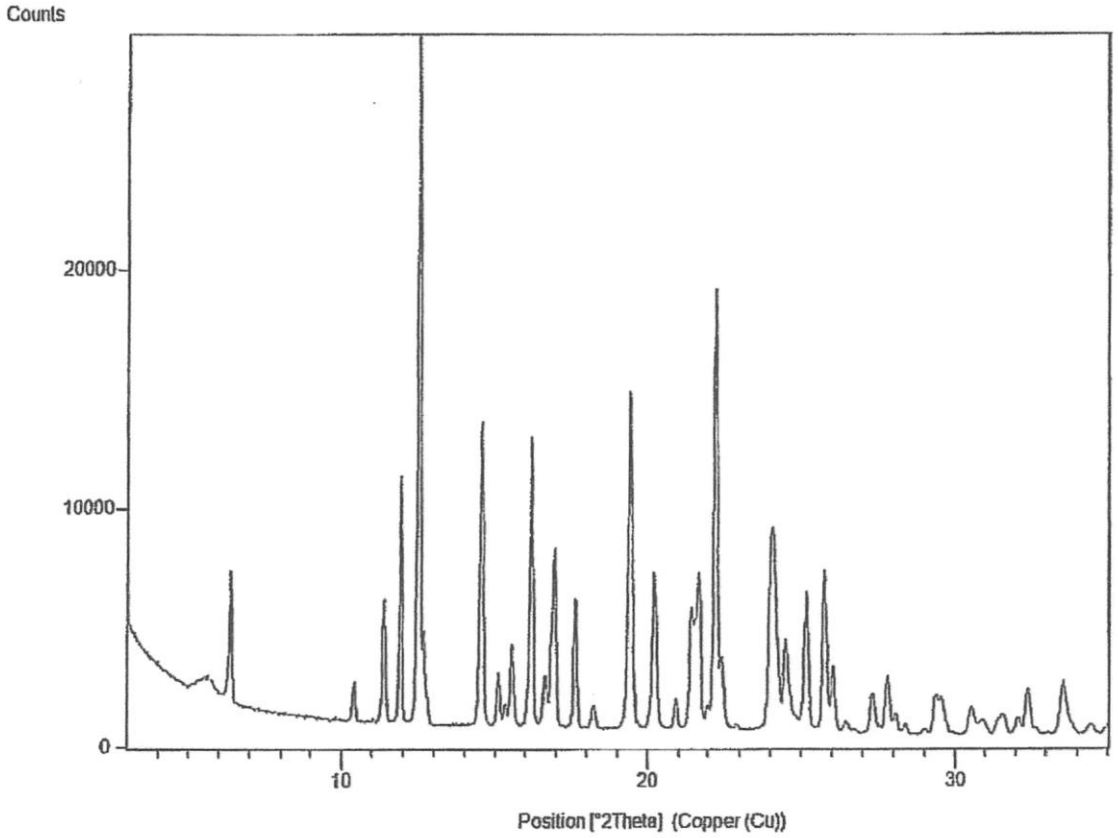

Counts
20000
10000
0
10
20
30
Position [°2Theta] (Copper (Cu))

Fig. 1

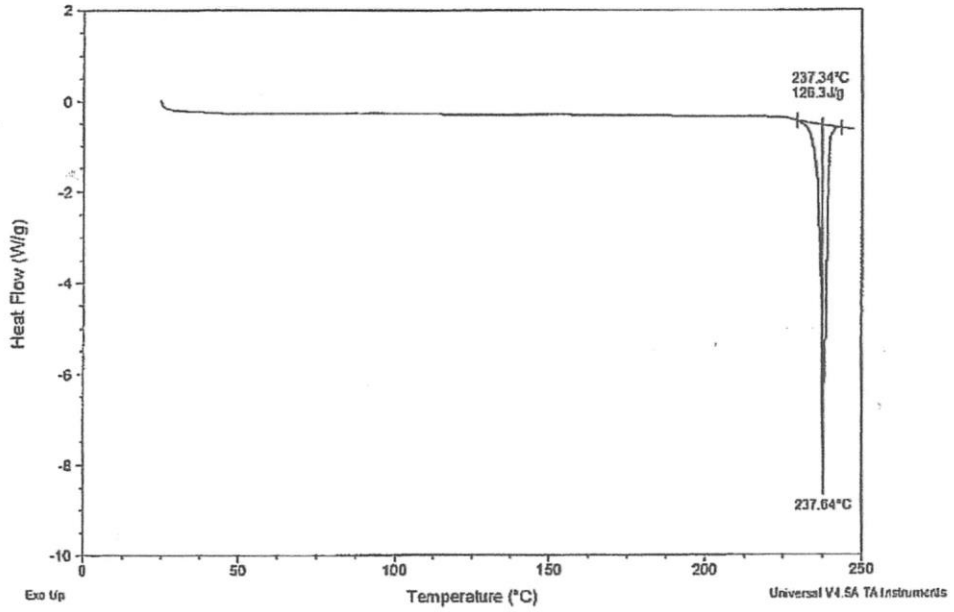

2
0
-2
-4
-6
-8
-10
Heat Flow (W/g)
237.34°C
126.3J/g
237.64°C
0
50
100
150
200
250
Exo Up
Temperature (°C)
Universal V4.5A TA Instruments

Fig. 2

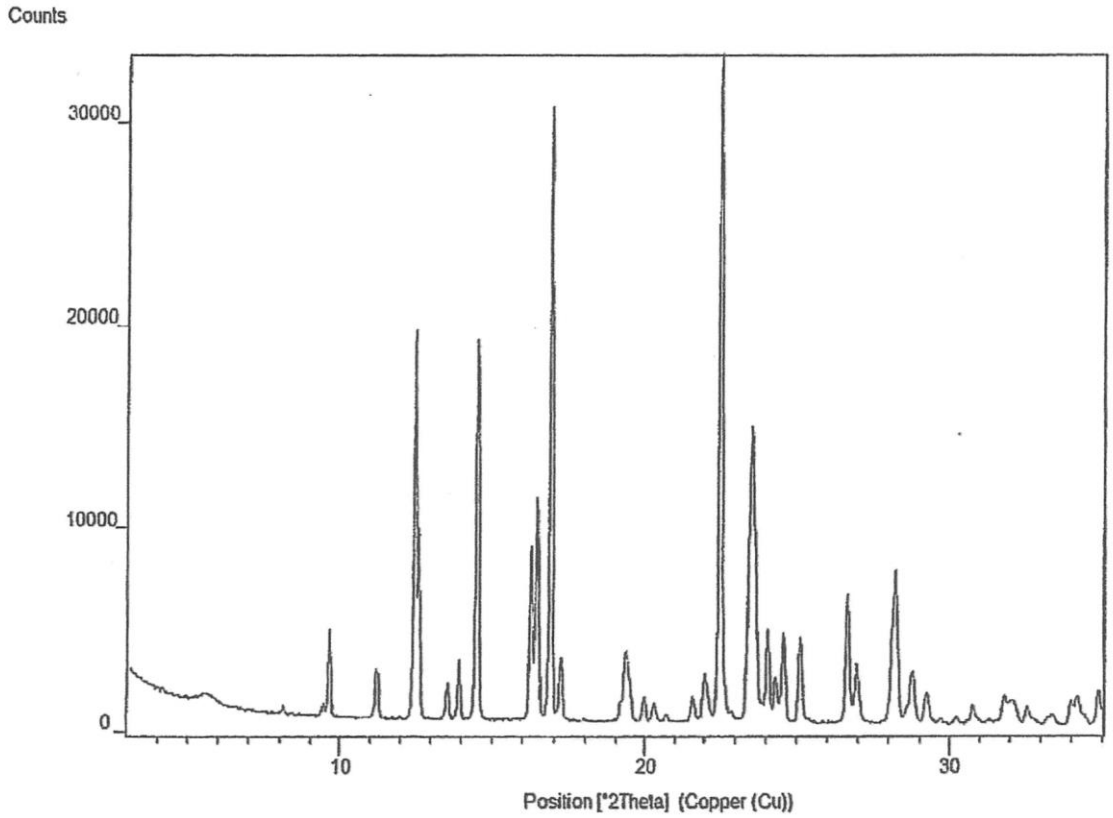

Counts
30000
20000
10000
0
10
20
30
Position [°2Theta] (Copper (Cu))

Fig. 3

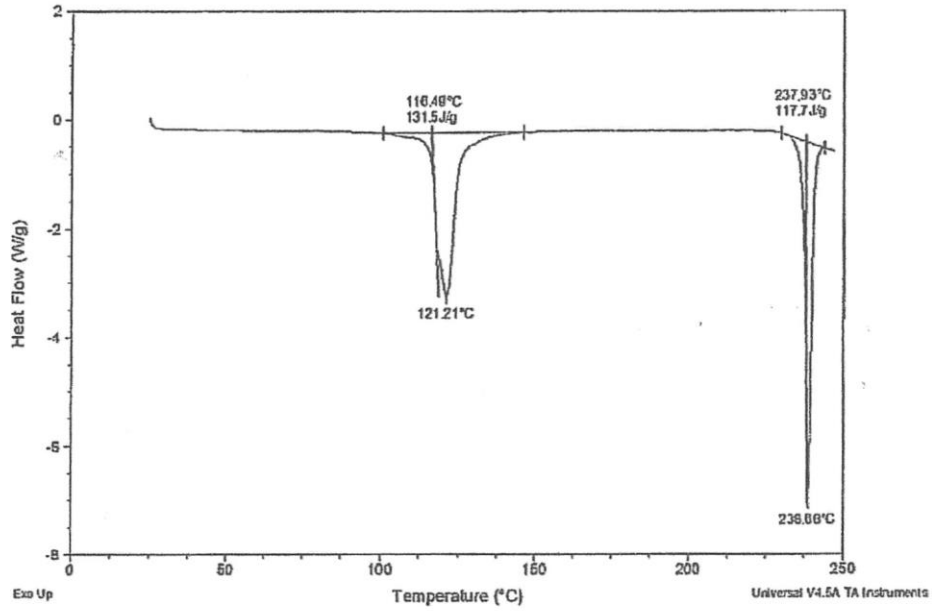

2
0
-2
-4
-6
-8
Heat Flow (W/g)
116.49°C
131.5J/g
121.21°C
237.93°C
117.7J/g
236.66°C
0
50
100
150
200
250
Exo Up
Temperature (°C)
Universal V4.5A TA Instruments

Fig. 4

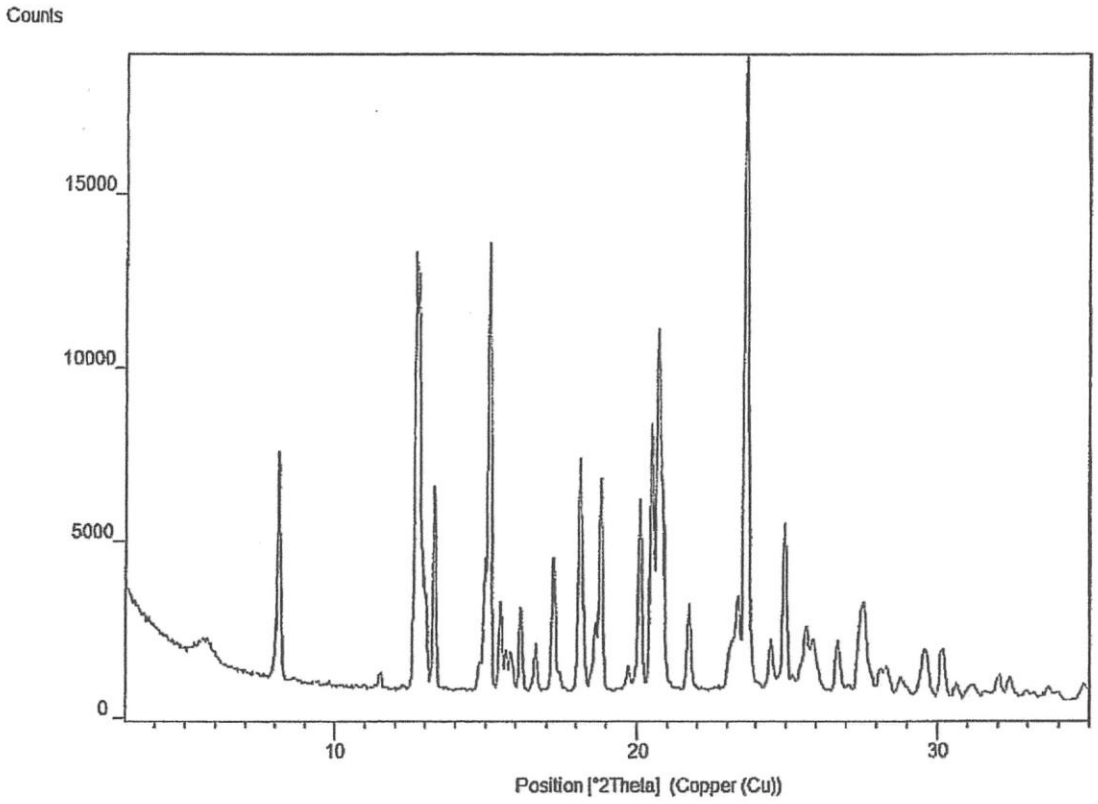

Counts
15000
10000
5000
0
10
20
30
Position [°2Theta] (Copper (Cu))

Fig. 5

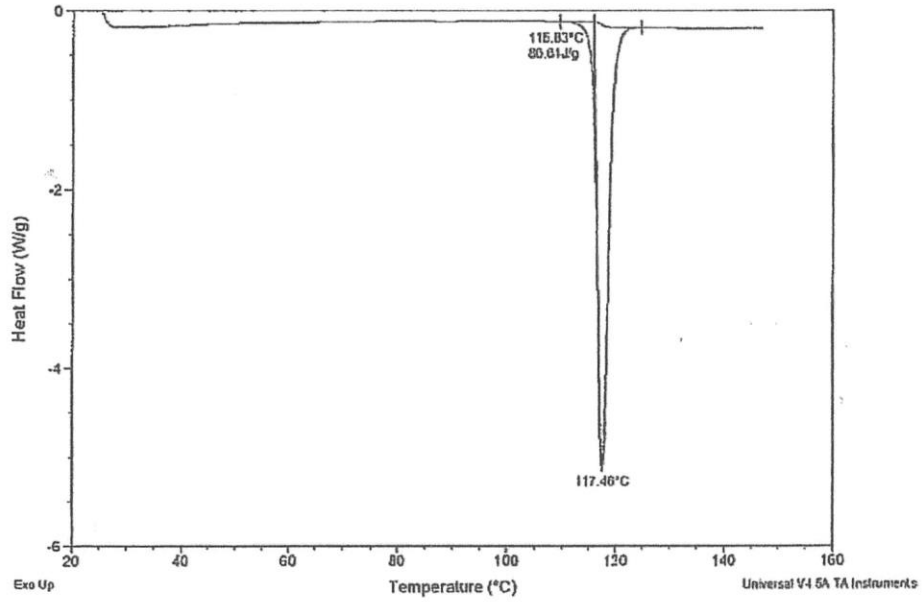

0
-2
-4
-6
Heat Flow (W/g)
115.83°C
117.46°C
20
40
60
80
100
120
140
160
Exo Up
Temperature (°C)
Universal V4.5A TA Instruments

Fig. 6