Title: A PROCESS FOR THE PREPARATION OF N-[2-(7-METHOXY-1-NAPHTHYL) ETHYL] ACETAMIDE CRYSTALLINE FORM I

Abstract: The present invention provides a cost-effective, reproducible and industrial process for the preparation of N-[2-(7-methoxy- 1-naphthyl) ethyl] acetamide crystalline form I and pharmaceutical compositions thereof.
A PROCESS FOR THE PREPARATION OF N-[2-(7-METHOXY-1-NAPHTHYL) ETHYL] ACETAMIDE CRYSTALLINE FORM I

BACKGROUND OF THE INVENTION

1. **Technical field:**

The present invention relates to a process for the preparation of N-[2-(7-methoxy-1-naphthyl) ethyl] acetamide crystalline form I. More specifically, the present invention relates to a cost-effective, reproducible, and industrial process for synthesis of the N-[2-(7-methoxy-1-naphthyl) ethyl] acetamide crystalline form I.

**Brief description of the related art:**

Agomelatine is an agonist of melatonergic system receptors and an antagonist of the 5-HT2C receptor. Those properties confer activity in the central nervous system and, more especially, in the treatment of severe depression, seasonal affective disorders, sleep disorders, cardiovascular pathologies, and pathologies of the digestive system, insomnia and fatigue resulting from jetlag, appetite disorders and obesity. Agomelatine is under regulatory review in US and is being approved in EU for the treatment of major depressive disorder. It is marketed under the trade names Valdoxan, Melitor, Thymanax in the form of tablets in dosage strength 25 mg. Agomelatine is chemically described as N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide (herein after referred by generic name agomelatine) and is represented by the structural formula I.

![Structural formula](attachment:image.png)


US '442 in example 1 also discloses a process for the preparation of agomelatine. In this process agomelatine is obtained by recrystallization from isopropyl ether. No information on the polymorph form obtained therein can be found except the melting point as 109-110°C.
obtained according to the process described above. It is, in fact, important to be able to obtain a well defined and perfectly reproducible crystalline form.

U.S. Patent No. 5,225,442, EP 0 447 285 and Yous et al. (Journal of Medicinal Chemistry, 1992, 35 (8), 1484-1486) allows N-[2-(7-methoxy-l-naphthyl)ethyl] acetamide to be obtained in a particular crystalline form which has been described in Tinant et al. (Acta Cryst., 1994, C50, 907-910).

S. Yous et al. in J. Med. Chem. 1992, 35, 1484-1486 describe a process for the preparation of agomelatine, wherein agomelatine is obtained from a biphasic medium of water and chloroform. Bernard Tinant and Jean-Paul Declercq in Acta Cryst. (1994), C50, 907-910 disclose a full crystallographic investigation of the agomelatine produced by Yous et al. The polymorph form of the product obtained by Yous et al. and analyzed by Tinant and Declercq is designated as the polymorph form I of agomelatine. Tinant and Declercq provide the full crystal data of this polymorph form, and regarding the identification of the polymorph form I of agomelatine, it is explicitly referred to Bernard Tinant and Jean-Paul Declercq in Acta Cryst. (1994), C50, 907-910. The crystal data is as follows:

Mr = 243.30 ; Orthorhombic ; Pca2₁
a = 31.1501 (4) A; b = 9.5280 (10) A; c = 17.906 (2) A.

European application publication EP 23 19827A1 describes a process for the preparation of agomelatine Form I by using water miscible solvents and water in solvent - antisolvent technique.

The density is D = 1.203 Mg · m⁻³, and the number of molecules in one cell is Z = 16.

The known processes for obtaining the polymorphic form I of agomelatine are considered as providing the polymorphic form I of agomelatine not in a sufficiently reproducible and well-defined manner and with only poor filtrability (US 2005/0182276) . Furthermore, the known methods of preparation of polymorph form I of agomelatine use solvents which can be problematic and which should be avoided in medicaments. In particular, chloroform, that has been used by Yous et al. for the preparation of agomelatine of polymorphic form I, is a class II solvent with a concentration limit of only 60 ppm in pharmaceutical products. It is very difficult to remove the hazardous solvent to the required extent from the agomelatine.

None of these processes produced the polymorphic form I of agomelatine, but different new polymorphic forms of agomelatine were obtained.
The processes reported for making crystalline Form-I of N-[2-(7-methoxy-l-naphthyl) ethyl] acetamide are not reproducible and do not comply with industrial requirements in terms of cost and the environment.

In view of the pharmaceutical value of this compound, a polymorph form of agomelatine for use in a medicament should have excellent properties, such as crystallinity, polymorphic stability, chemical stability and process ability to pharmaceutical compositions.

Therefore, there exists a need in the art for a process for reliably and reproducibly producing the polymorphic form I of agomelatine with good filterability, in particular for a process in which solvents are used which are better pharmaceutically acceptable than the solvents used in the prior art processes for obtaining the polymorphic form I of agomelatine. Furthermore, the polymorph form I of agomelatine should be provided in a very high chemical and polymorph purity.

It has been also important to be able to obtain N-[2-(7-methoxy-l-naphthyl) ethyl] acetamide with well defined crystalline form, perfectly reproducible, which as a result exhibits valuable characteristics in terms of filtration and ease of formulation.

The Applicant has now developed a process for obtaining N-[2-(7-methoxy-l-naphthyl) ethyl] acetamide crystalline form I in a well-defined, perfectly reproducible, crystalline form and which as a result exhibits valuable characteristics in terms of filtration and ease of formulation.

The process for making crystalline Form I of present invention is simple, eco-friendly, cost effective, reproducible, and robust and feasible on an industrial scale.

**SUMMARY OF THE INVENTION**

The present invention relates to process for the preparation of N-[2-(7-methoxy-l-naphthyl) ethyl] acetamide crystalline form I. More specifically the present invention relates to cost-effective, reproducible process for synthesis of the N-[2-(7-methoxy-l-naphthyl) ethyl] acetamide crystalline form I.

In one aspect, the present invention provides a cost-effective, reproducible and industrial process for the preparation of N-[2-(7-methoxy-l-naphthyl) ethyl] acetamide crystalline form I comprising:

a) providing a solution of a N-[2-(7-methoxy-l-naphthyl) ethyl] acetamide in a solvent or mixture of solvents or aqueous mixtures thereof; and
b) evaporation of the solvents or by cooling to obtain
the substantially pure crystalline form I of N-[2-(7-methoxy-1-naphthyl)-ethyl] acetamide characterized by XRPD depicted by fig. 1 and DSC as depicted by fig. 2.

The crystalline form I obtained by the process of present invention is characterized by XRPD with characteristic peaks at about 10.8, 11.2, 11.9, 13.8, 14.6, 14.9, 15.4, 15.8, 17.0, 17.5, 18.4, 19.5, 19.8, 20.5, 21.0, 21.3, 21.8, 22.6, 23.0, 24.0, 24.6, 25.4, 26.0, 26.4, 27.1, 27.7, 28.8, 30.1, 31.6, 31.9, 33.0, 33.7, 34.5 and 36.0 ± 0.2 degrees two-theta, which is substantially in accordance with Fig. Land further characterized by differential scanning calorimetry (DSC) with an endotherm curve at about 108.62°C measured at 0.2 °C/min. ramp, and is substantially in accordance with Fig. 2.

In another aspect, the present invention encompasses a pharmaceutical composition comprising therapeutically effective amount of highly pure agomelatine crystalline Form I obtained by the process of present invention and at least a pharmaceutically acceptable carrier.

**BRIEF DESCRIPTION OF THE DRAWINGS**

Fig. 1: is an X-ray powder diffraction pattern of agomelatine crystalline Form-I.

Fig. 2: is a Differential Scanning Calorimetry endotherm of agomelatine crystalline Form-I.

**DETAILED DESCRIPTION OF THE INVENTION**

The present invention is directed to a process for the preparation of N-[2-(7-methoxy-1-naphthyl)-ethyl] acetamide crystalline form I.

In an embodiment of the present invention, there is provided a cost-effective, reproducible and industrial process for the preparation of N-[2-(7-methoxy-1-naphthyl)-ethyl] acetamide crystalline form I comprising:

a) providing a solution of a N-[2-(7-methoxy-1-naphthyl)-ethyl] acetamide in a solvent or mixture of solvents or aqueous mixtures thereof; and

b) evaporation of the solvents or by cooling to obtain the substantially pure crystalline form I of N-[2-(7-methoxy-1-naphthyl)-ethyl] acetamide.

The crystalline form I obtained by the process of present invention is characterized by XRPD with characteristic peaks at about 10.8, 11.2, 11.9, 13.8, 14.6, 14.9, 15.4, 15.8, 17.0, 17.5, 18.4, 19.5, 19.8, 20.5, 21.0, 21.3, 21.8, 22.6, 23.0, 24.0, 24.6, 25.4, 26.0, 26.4, 27.1, 27.7, 28.8, 30.1, 31.6, 31.9, 33.0, 33.7, 34.5 and 36.0 ± 0.2 degrees two-theta, which is substantially in accordance with Fig. Land further characterized by differential scanning calorimetry (DSC)
with an endotherm curve at about 108.62°C measured at 0.2 °C/min. ramp, and is substantially in accordance with Fig. 2.

The crystalline Form-I here in emphasized was referred by the crystalline Form-II patent US 7250531 B2.

The solvents that can be used for solubilizing or dissolving the agomelatine in step (a) above, include but are not limited to water, alcohols such as methanol, ethanol, isopropyl alcohol, n-butanol, isobutyl alcohol, tertiary butyl alcohol and the like ketonic solvents such as acetone, methyl ethyl ketone, methyl isobutyl ketone, 2-butanone and the like; aprotic polar solvents such as N,N-dimethyl formamide (DMF), dimethyl sulfoxide (DMSO), dimethyl acetamide, N-methyl pyrrolidone (NMP), acetonitrile and the like; hydrocarbons such as toluene, xylene, cyclohexane, n-hexane and the like; ethers such as 1,4-dioxane, tetrahydrofuran, diisopropylether as single solvents or water miscible solvents described above can be combined with water in any proportion or mixtures of water immiscible solvents. Preferably, water or ethanol or toluene or acetonitrile or DMF as single solvent and DMF or ethanol or ketone or acetonitrile in combination with water in any proportion.

As used herein a mixture of solvents refers to a composition comprising more than one solvent.

The volume of the solvent may be from about 5 to about 150 volumes. The volume of the suitable organic solvent may be from about 50 to about 130 volumes. The volume of the suitable organic solvent may be from about 80 to about 120 volumes. The mixture may be heated to a temperature sufficient to obtain partial dissolution. The mixture may be heated to a temperature sufficient to obtain complete dissolution.

According to the invention the broad range of solvent/water ratios from 1 : 100 up to 100: 1 (v/v), preferably at ratios from 1:20 up to 20:1 (v/v), more preferably at ratios from 1:2 to 2:1 (v/v) at a temperature of 25°C.

According to the invention it was also unexpectedly found that a very high reproducibility of the product characteristics and a very good filterability can be obtained by using a sufficiently high excess of water. Preferably the solvent/water ratio in process step b) of the process of the present invention is at least 1 : 2, more preferably at least 1 : 3 and most preferably at least 1 : 4.

The amount of water can be significantly higher than the amount of solvent for agomelatine, but for practical reasons it is generally sufficient, if the solvent/water ratio is 1 :
10 or less or 1:8 or less or 1:6 or less. Thus, preferred solvent/water ratios are in the range from 1:2 to 1:10, preferably 1:3 to 1:8 and most preferred from 1:4 to 1:6.

The temperature for obtaining a clear and homogenous solution can range from about 25°C to about 100°C or the boiling point of the solvent/s used, preferably from about 50°C to about boiling point of the solvent/s used.

The solution obtained is optionally filtered through celite or diatomaceous earth to separate the extraneous matter present or formed in the solution by using conventional filtration techniques known in the art.

Evaporation or removal of solvent(s) is accomplished by, for example, substantially complete evaporation of the solvent, concentrating the solution, cooling to obtain crystalline form and filtering the solid under inert atmosphere. Alternatively, the solvent may also be removed by evaporation. Evaporation can be achieved at sub-zero temperatures by the lyophilisation or freeze-drying technique. The solution may also be completely evaporated in, for example, a pilot plant rota vapor, a vacuum paddle dryer or in a conventional reactor under vacuum above about 720 mm Hg by flash evaporation techniques by using an agitated thin film dryer (ATFD), or evaporated by spray drying to obtain a dry amorphous powder. Preferably, the methods for evaporation or removal of solvents are distillation under reduced pressure.

Crystal growth may be promoted by cooling the solution to a temperature between about 0°C to about 50°C. Crystal growth may be promoted by cooling the solution to a temperature between about 0°C to about 30°C. Crystal growth may be promoted by cooling the solution to a temperature between about 0°C to about 15°C.

The cooling of the solution in step (b) can be from about -10 to about 25°C, preferably from about -5°C to about 5°C.

The crystalline Form I obtained by the process of present invention is stable with good flow properties, which make them well suitable for formulating agomelatine in any dosage form.

Recovery of agomelatine crystalline Form I obtained can be achieved by any conventional methods known in the art, for example filtration.

The agomelatine substantially in crystalline form I obtained by the above process may be further dried in, for example, vacuum tray dryer, rotocon vacuum dryer, vacuum paddle dryer or pilot plant rotavapor, to further lower residual solvents. When implemented, the preferred instrument is a vacuum tray dryer.
The crystalline form I of agomelatine obtained by the process of present invention can be optionally dried at a temperature range from about 30°C to about 75°C, preferably from about 35°C to about 55°C.

Polymorphs of a molecule can be obtained by a number of methods known in the art. Such methods include, but are not limited to, recrystallization, melt recrystallization, melt cooling, solvent recrystallization (including using single or multiple solvents), precipitation, anti-solvent precipitation, evaporation, rapid evaporation, slurrying, slurry ripening, suspension equilibration, desolvation, dehydration, vapor diffusion, liquid-liquid diffusion, sublimation, grinding, milling, crystallization from the melt, heat induced transformations, desolvation of solvates, salting out, pH change, lyophilization, distillation, drying, rapid cooling, slow cooling, and combinations thereof.

Polymorphs can be detected, identified, classified and characterized using well-known techniques such as, but not limited to, differential scanning calorimetry (DSC), thermogravimetry (TGA), powder X-ray diffractometry (PXRD), single crystal X-ray diffractometry, vibrational spectroscopy, solution calorimetry, solid state nuclear magnetic resonance (NMR), infrared (IR) spectroscopy, Raman spectroscopy, hot stage optical microscopy, scanning electron microscopy (SEM), electron crystallography, quantitative analysis, solubility, and rate of dissolution.

The crystalline form I of agomelatine obtained by the process of present invention was characterized by using Diffractometer Make Bruker AXS, Model D8 FOCUS Goniometer

Type : Theta-2Theta
X-Ray source : Copper Ka
Detector : Lynx Eye Detector

Approximately 1 g of sample was gently flattened on a sample holder and scanned from 2 to 50° two theta, at 0.03° two theta per step and a step time of 0.4 seconds. The sample was simply placed on the sample holder. The sample was rotated at 30rpm at a voltage 40 KV and current 35 mA.

Optionally seeding of the crystalline Form I is being used to obtain the desired polymorph with purity and consistently by adding to the solution of agomelatine.

The compound agomelatine used herein as starting material can be of any polymorph reported or may be crude agomelatine resulting from synthetic processes known in the art. Illustratively, U.S. Patent No. 5,225,442 incorporated herein for reference.
In yet another embodiment there is provided pharmaceutical compositions comprising at least a therapeutically effective amount of highly pure agomelatine crystalline Form I obtained by the process of present invention and at least a pharmaceutically acceptable excipient. Such pharmaceutical compositions may be administered to a mammalian patient for the treatment or prevention of major depressive episodes in adults in a dosage form, e.g., solid, liquid, powder, elixir, aerosol, syrups, injectable solution, etc. Dosage forms may be adapted for administration to the patient by oral, buccal, parenteral, ophthalmic, rectal and transdermal routes or any other acceptable route of administration. Oral dosage forms include, but are not limited to, tablets, pills, capsules, syrup, troches, sachets, suspensions, powders, lozenges, elixirs and the like. The highly pure agomelatine or a pharmaceutically acceptable salt thereof substantially free of hydrazine impurity may also be administered as suppositories, ophthalmic ointments and suspensions, and parenteral suspensions, which are administered by other routes.

Tablets and powders may also be coated with an enteric coating. The enteric-coated powder forms may have coatings containing at least phthalic acid cellulose acetate, hydroxypropylmethyl cellulose phthalate, polyvinyl alcohol phthalate, carboxy methyl ethyl cellulose, a copolymer of styrene and maleic acid, a copolymer of methacrylic acid and methyl methacrylate, and like materials, and if desired, the coating agents may be employed with suitable plasticizers and/or extending agents. A coated capsule or tablet may have a coating on the surface thereof or may be a capsule or tablet comprising a powder or granules with an enteric-coating.

The process for the preparation of agomelatine crystalline form I of the present invention is simple, eco-friendly, robust, reproducible, cost effective and well amenable on industrial scale.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

**EXAMPLES**

**Reference example**

3 gr of N-[2-(7-methoxy-1-naphthyl)ethyl] acetamide and 200 ml of isopropyl ether are introduced into a flask. This suspension is heated at boiling temperature for 10-15 min. Clear solution is formed. Then the solution is cooled to 0-5°C. During the process of cooling, seeding is given with form-I sample. Stir for 30 min at 0-5°C. Filter and wash the solid with 20
ml of isopropyl ether. Dry the material at 50-55°C for 4 hrs. The solid obtained is characterized by X-ray powder Diffraction, which has matched with crystalline Form I of Agomelatine.

**Processes for the preparation of agomelatine crystalline Form - I**

**Example -1: Preparation of agomelatine crystalline form I using water**

2.5 gr of N-[2-(7-(-methoxy -l-naphthyl)ethyl)] acetamide and 25 ml of water were charged into a clean and dry 4 neck R.B.Flask and heated to until the melting is completed. Then the product is placed at about 30°C and seeded with 0.25 gr of pure crystalline form-I of N-[2-(7-(-methoxy -l-naphthyl)ethyl)] acetamide . The resultant suspension was allowed to reach about 30°C and further cooled to about 5°C for about 10 min. The solid separated was filtered and dried to obtain pure crystalline form I. **Yield: 2.5 gr.**

**Example -2 : Preparation of agomelatine crystalline form I using isopropyl alcohol**

3 gr of N-[2-(7-(-methoxy -l-naphthyl)ethyl)] acetamide and 10 ml of isopropyl alcohol were charged into a clean and dry 4 neck R.B.Flask followed by heating to about 50°C .The resultant solution was allowed to reach about 30°C and seeded with 0.2 gr of pure crystalline form-I of N-[2-(7-(-methoxy -l-naphthyl)ethyl)] acetamide. The solution was further cooled to about 5°C for about 15 min. The solid separated was filtered and the solid obtained was dried to obtain pure crystalline form I. **Yield: 1.5 gr.**

**Example -3 : Preparation of agomelatine crystalline form I using methanol**

4 gr of N-[2-(7-(-methoxy -l-naphthyl)ethyl)] acetamide and 10 ml of methanol were charged into a clean and dry 4 neck R.B.Flask followed by heating to about 50°C .The resultant solution was allowed to reach about 30°C and then seeded with 0.3 gr of pure crystalline form-I of N-[2-(7-(-methoxy -l-naphthyl)ethyl)] acetamide. Then the solution was further cooled to about 5°C for about 20 min. The solid separated was filtered and the solid obtained was dried to obtain pure crystalline form I. **Yield: 1.5 gr.**

**Example -4 : Preparation of agomelatine crystalline form I using toluene**

3 gr of N-[2-(7-(-methoxy -l-naphthyl)ethyl)] acetamide and 15 ml of toluene were charged into a clean and dry 4 neck R.B.Flask followed by heating to reflux temperature (105-108°C). The resultant solution was allowed to reach about 30°C and seeded with crystalline form-I of N-[2-(7-(-methoxy -l-naphthyl)ethyl)] acetamide with structurally pure. This
solution was further cooled to 0-5°C for 15 min. The solid separated was filtered and dried to obtain pure crystalline form I. Yield: 3 gr.

Example-5: Preparation of agomelatine crystalline form I using ethanol and water mixture

4 gr of N-[2-(7-methoxy -l-naphthyl)ethyl)] acetamide and 20 ml of ethanol/water (35/65)v/v mixture were charged into a clean and dry 4 neck R.B.Flask followed by heating to about 75°C for about 10 min. Then again 20 ml ethanol/water (35/65)v/v was charged to the hot solution. The resultant suspension was stirred at about 75°C for about 10 min. After getting homogenous solution, the solution was cooled to about 5°C and stirred for about 30 min. The solid separated was filtered and the solid obtained was washed with 20 ml of ethanol/water (35/65) v/v mixture. The solid obtained was dried at about 55°C for about 12 hrs to afford pure crystalline form I.

Example -6: Preparation of agomelatine crystalline form I using methyl isobutyl ketone

3 gr of N-[2-(7-methoxy -l-naphthyl)ethyl)] acetamide and 10 ml of methylisobutyl ketone (MIBK) were charged into a clean and dry 4 neck R.B.Flask followed by heating to about 55°C for about 15 min. The resultant homogenous solution was allowed to reach 30 °C and seeded with 0.1 gr of pure crystalline form-I of N-[2-(7-methoxy -l-naphthyl)ethyl)] acetamide. The solution was further cooled to about 0°C for about 15 min. The solid separated was filtered and the solid obtained was dried at about 55°C for overnight to afford pure crystalline form I. Yield: 1.5gr.

Example -7: Preparation of agomelatine crystalline form I using DMF and water mixture

3 gr of N-[2-(7-methoxy -l-naphthyl)ethyl)] acetamide and 15 ml of water/DMF (65/35) mixture were charged into a clean and dry 4 neck R.B.Flask followed by heating to about 75°C for about 15 min. Then again 15 ml of water/DMF (65/35) was added to the hot suspension at about 75°C. The resultant homogenous solution was allowed to reach about 30°C and seeded with 0.1 gr of pure crystalline form I of N-[2-(7-methoxy -l-naphthyl)ethyl)]acetamide . The resultant solution was further cooled to about 0°C for about 15 min. The solid separated was filtered and the solid obtained was dried at about 55°C for overnight to afford pure crystalline form I. Yield: 2 gr.
Example-8: Preparation of agomelatine crystalline form I using water and ethanol mixture

4 gr of N-[2-(7-methoxy -l-naphthyl)ethyl] acetamide and 20 ml of water + ethanol (95/5 ratio) mixture were charged into a clean and dry 4 neck R.B.Flask followed by heating to about 75°C for about 10 min. Again 20 ml of water/ethanol (95/5) mixture was added at about 75°C and stirred for about 10 min. Dissolution was not clear at this temperature. So 60 ml of water/ethanol mixture was added at about 75°C and maintained at 75°C for about 15 min. The compound melting was observed but the dissolution was not clear. Then the suspension was allowed to reach about 30°C and seeded with 0.2 gr of pure crystalline form-I of N-[2-(7-methoxy -l-naphthyl)ethyl] acetamide at about 70°C. The crystallization was observed at about 65°C and stirred for about 10 min. at about 25°C. The solid separated was filtered and dried at about 55°C for overnight to afford pure crystalline form I. Yield: 4 gr.

Example-9: Preparation of agomelatine crystalline form I using water and ethanol mixture

3 gr of N-[2-(7-methoxy -l-naphthyl)ethyl] acetamide and 15 ml of water + ethanol (40/60 ratio) mixture were charged into a clean and dry 4 neck R.B.Flask. The resultant solution was allowed to cooling and seeded with 0.1 gr of pure crystalline form-I of N-[2-(7-methoxy -l-naphthyl)ethyl] acetamide. The solution was further cooled to about 5°C for about 15 mins. The separated solid was filtered and dried at about 55°C for 12 hours to afford pure crystalline Form I. Yield: 1.5 gr.

Example-10: Preparation of agomelatine crystalline form I using xylene

3 gr of N-[2-(7-methoxy -l-naphthyl)ethyl] acetamide and 10 ml of O-xylene were charged into a clean and dry 4 neck R.B.Flask followed by heating to about 90°C. The resultant solution obtained was allowed to cooling followed by seeding 0.1 gr of pure crystalline form-I of N-[2-(7-methoxy -l-naphthyl)ethyl] acetamide at about 60°C. Then the resultant solution was cooled to about 5°C for about 15 min. The solid separated was filtered and dried at about 55°C for about 24 hrs. to afford pure crystalline Form I. Yield: 2.5 gr.

Example-11: Preparation of agomelatine crystalline form I using water and DMF mixture

2 gr of N-[2-(7-methoxy -l-naphthyl)ethyl] acetamide and 10 ml of water + DMF (v/v) (40/60 ratio) mixture were charged into a clean and dry 4 neck R.B.Flask followed by heating
to about 40°C. The solution obtained was allowed to cool and seeded with 0.1 gr of pure crystalline form-I of N-[2-(7-methoxy -1-naphthyl)ethyl] acetamide at about 35°C. This solution was further cooled to about 5°C for about 15 min. The solid separated was filtered and dried at about 55°C for about 20 hrs. to afford pure crystalline Form I. Yield: 1 gr.
We Claim:

1) A cost-effective, reproducible and industrial process for the preparation of N-[2-(7-methoxy-l-naphthyl) ethyl] acetamide crystalline form I comprising:
   a) providing a solution of aN-[2-(7-methoxy-l-naphthyl) ethyl] acetamide in a solvent or mixture of solvents or aqueous mixtures thereof; and
   b) evaporation of the solvents or by cooling to obtain the substantially pure crystalline form I of N-[2-(7-methoxy-l-naphthyl) ethyl] acetamide.

2) The process of claim 1, wherein the solvent(s) is selected from the group consisting of water, alcohols like as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, and tertiary butyl alcohol, ketonic solvents like acetone, methyl ethyl ketone, methyl isobutyl ketone, 2-butanone, aprotic polar solvents like N,N-dimethyl formamide (DMF), dimethyl sulfoxide (DMSO), dimethyl acetamide, N-methyl pyrrolidone (NMP) acetonitrile, hydrocarbons like toluene, xylene, cyclohexane, n-hexane, ethers like 1,4-dioxane, tetrahydrofuran, diisopropyl ether and mixtures thereof in various proportions without limitation.

3) The process of claim 2, wherein the solvents used are water or ethanol or toluene or acetonitrile or DMF as single solvent and DMF or ethanol or ketone or acetonitrile in combination with water in any proportion.

4) The process of claim 1, wherein the solution formed in step a) is optionally seeded with pure crystalline form I.

5) The process of claim 1, wherein the temperature for obtaining a solution is from about 25°C to about 75°C or the boiling point of the solvent/s used, preferably from about 50°C to about boiling point of the solvents used.

6) The process of claim 1, wherein the solution obtained is optionally filtered through celite or diatomaceous earth to separate the extraneous matter present or formed in the solution by using conventional filtration techniques known in the art.

7) The process of claim 1, wherein the removal of solvent(s) is by dry distillation under vacuum or concentrating the solution to afford substantially pure crystalline Form -1.

8) The agomelatine crystalline form I obtained by the process of preceding claims is optionally
dried at a temperature range from about 30°C to about 75°C, preferably from about 35°C to about 55°C.

9) The process of preceding claims, wherein the crystalline form I obtained has XRPD substantially in accordance with Fig. 1 and endotherm curve by differential scanning calorimetry (DSC) which is substantially in accordance with Fig. 2.

10) A pharmaceutical composition comprising N-[2-(7-methoxy-1-naphthyl) ethyl] acetamide agomelatine crystalline form I obtained by the process described above and at least one pharmaceutically acceptable carrier.
INTERNATIONAL SEARCH REPORT

PCT/IN 1/00503

A. CLASSIFICATION OF SUBJECT MATTER

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category" Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No.


Y US 2007/0197829 A1 (Souvie et al.) 23 August 2007 (23.08.2007) para [0061], [0064], [0070], [0088]-[0099] 10

Further documents are listed in the continuation of Box C.

Date of the actual completion of the international search

05 March 2012 (05.03.2012)

Date of mailing of the international search report

2 T MAR 2012

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-3201

Authorized officer: Lee W. Young
PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)
This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. **Claims Nos.**
   - because they relate to subject matter not required to be searched by this Authority, namely:

2. **Claims Nos.**
   - because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. **Claims Nos.: 8-9**
   - because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

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