SPOOR & FISHER

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FULL NAMES OF INVENTORS

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EARLIEST PRIORITY CLAIMED

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TITLE OF INVENTION

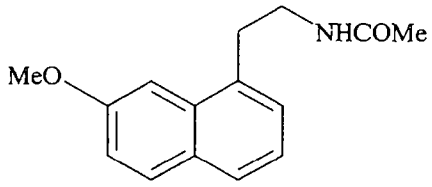
54	CRYSTALLINE FORM V OF AGOMELATINE, A PROCESS FOR ITS PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING IT

57	ABSTRACT (NOT MORE THAT 150 WORDS)	NUMBER OF SHEETS	12

If no classification is finished, Form P.9 should accompany this form.
The figure of the drawing to which the abstract refers is attached.

ABSTRACT

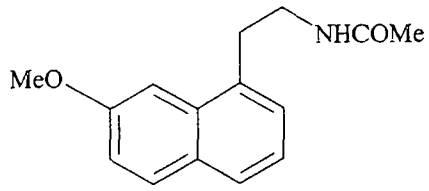
Crystalline form V of the compound of formula (I) :



(I)

characterised by its powder X-ray diffraction diagram.

The present invention relates to a new crystalline form V of agomelatine, or *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide, of formula (I) :



(I)

a process for its preparation and pharmaceutical compositions containing it.

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

Indeed it has the double feature of being, on the one hand, an agonist of melatoninergic system receptors and, on the other hand, an antagonist of the 5-HT_{2C} 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, pathologies of the digestive system, insomnia and fatigue resulting from jetlag, appetite disorders and obesity.

Agomelatine, its preparation and its therapeutic use have been described in European Patent Specification EP 0 447 285.

In view of the pharmaceutical value of this compound, it has been important to be able to obtain it with excellent purity, with well defined crystalline form, perfectly reproducible, which as a result exhibits valuable characteristics in terms of dissolution and formulation and sufficiently stable to allow its storage for long periods without particular requirements for temperature, light, humidity or oxygen level.

Patent Specification EP 0 447 285 describes the preparation of agomelatine in eight steps, starting from 7-methoxy-1-tetralone. However, that document does not specify the conditions for obtaining agomelatine in a form that exhibits those characteristics in a reproducible manner.

The Applicant has now developed a new synthesis process that allows agomelatine to be obtained in a well defined, perfectly reproducible crystalline form that especially exhibits valuable characteristics for dissolution and formulation.

More specifically, the present invention relates to the crystalline form V of the compound of formula (I), characterised by the following powder X-ray diffraction diagram, measured using a Siemens D5005 diffractometer (copper anticathode) and expressed in terms of inter-planar distance d, Bragg's angle 2 theta, intensity and relative intensity (expressed as a percentage of the most intense ray) :

2-Theta (°) exp.	d (Å) exp.	Intensité (%)
9.84	8.979	17
12.40	7.134	15
13.31	6.646	19
15.14	5.848	18
15.98	5.543	18
16.62	5.329	19
17.95	4.939	100
18.88	4.697	65
20.49	4.332	24
20.99	4.228	34
23.07	3.852	39
23.44	3.792	36
24.28	3.663	58
25.10	3.545	19
26.02	3.422	15
26.82	3.322	19
27.51	3.239	16

The invention relates also to a process for the preparation of the crystalline form V of the compound of formula (I), which process is characterised in that agomelatine is subjected to a mechanical grinding which is said to be "of high energy".

In the crystallisation process according to the invention it is possible to use the compound of formula (I) obtained by any process.

The invention relates also to another process for the preparation of the crystalline form V of the compound of formula (I), which process is characterised in that agomelatine is heated until complete melting, then immediately put at room temperature and simultaneously a small quantity of crystalline form V of compound of formula (I) freshly prepared is added, and the mixture is cooled until crystallisation is complete.

Preferably, in that second crystallisation process according to the invention, agomelatine will be melted at 110°C.

The amount of crystalline form V added in that second process according to the invention will be preferably contained between 1/100 and 1/50 of agomelatine weight.

In that second crystallisation process according to the invention, it is possible to use the compound of formula (I) obtained by any process.

An advantage of obtaining that crystalline form is that it allows the preparation of pharmaceutical formulations having a consistent and reproducible composition, which as a result exhibits valuable characteristics in terms of dissolution which is especially advantageous when the formulations are to be used for oral administration.

A pharmacological study of the form V so obtained has demonstrated that it has substantial activity in respect of the central nervous system and in respect of microcirculation, enabling it to be established that the crystalline form V of agomelatine is useful in the treatment of stress, sleep disorders, anxiety, severe depression, seasonal affective disorders, cardiovascular pathologies, pathologies of the digestive system, insomnia and fatigue due to jetlag, 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 in cerebral circulation disorders. In another field of activity, it appears that the crystalline V form of agomelatine can be used in the treatment of sexual dysfunction, that it has ovulation-inhibiting and immunomodulating properties and that it lends itself to use in the treatment of cancers.

The crystalline form V of agomelatine will preferably be used in the treatment of severe depression, seasonal affective disorders, sleep disorders, cardiovascular pathologies, insomnia and fatigue due to jetlag, appetite disorders and obesity.

The invention relates also to pharmaceutical compositions comprising as active ingredient the crystalline form V of agomelatine together with one or more appropriate inert, non-toxic excipients. Among the pharmaceutical compositions according to the invention there may be mentioned, more especially, those which are suitable for oral, parenteral (intravenous or subcutaneous) or nasal administration, tablets or dragées, granules, sublingual tablets, gelatin capsules, lozenges, suppositories, creams, ointments, dermal gels, injectable preparations, drinkable suspensions and disintegrable pastes.

The useful dosage can be adapted according to the nature and the 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 per day in one or more administrations.

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

Example 1 : Crystalline form V of *N*-[2-(7-Methoxy-1-naphthyl)ethyl]acetamide

100 g of *N*-[2-(7-Methoxy-1-naphthyl)ethyl]acetamide are put in a mechanical grinder of the vario-planetary mill type for about 6 hours and the solid obtained is characterised by the following powder X-ray diffraction diagram, measured using a Siemens D5005 diffractometer (copper anticathode) and expressed in terms of inter-planar distance d, Bragg's angle 2 theta, intensity and relative intensity (expressed as a percentage of the most intense ray) :

2-Theta (°) exp.	d (Å) exp.	Intensité (%)
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26.02	3.422	15
26.82	3.322	19
27.51	3.239	16

Example 2 : Crystalline form V of *N*-[2-(7-Methoxy-1-naphthyl)ethyl]acetamide

4 g of *N*-[2-(7-Methoxy-1-naphthyl)ethyl]acetamide are put in a ventilated incubator at 110°C. After 1 hour at 110°C, the product is immediately placed at room temperature and seeded with 0.05 g of crystalline form V of *N*-[2-(7-Methoxy-1-naphthyl)ethyl]acetamide structurally pure obtained by mechanical grinding of high energy. After 5 minutes, the crystallisation is complete and the solid obtained is characterised by the following powder X-ray diffraction diagram, measured using a Siemens D5005 diffractometer (copper anticathode) and expressed in terms of inter-planar distance d, Bragg's angle 2 theta, intensity and relative intensity (expressed as a percentage of the most intense ray) :

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26.82	3.322	19
27.51	3.239	16

Example 3 : **Pharmaceutical composition**

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

Compound of Example 1 or 2	25 g
Lactose monohydrate	62 g
Magnesium stearate	1.3 g
Maize starch	26 g
Maltodextrines	9 g
Silica, colloidal anhydrous	0.3 g
Sodium starch glycolate type A	4 g
Stearic acid	2.6 g

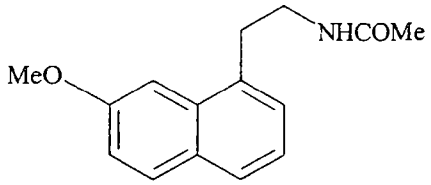
Example 4 : Pharmaceutical composition

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

Compound of Example 1 or 2	25 g
Lactose monohydrate	62 g
Magnesium stearate	1.3 g
Povidone	9 g
Silica, colloidal anhydrous	0.3 g
Sodium cellulose glycolate	30 g
Stearic acid	2.6 g

CLAIMS

1. Crystalline form V of agomelatine of formula (I) :



(I)

characterised by the following powder X-ray diffraction diagram, measured using a diffractometer (copper anticathode) and expressed in terms of inter-planar distance d, Bragg's angle 2 theta, intensity and relative intensity (expressed as a percentage with respect to the most intense ray) :

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23.44	3.792	36
24.28	3.663	58
25.10	3.545	19
26.02	3.422	15
26.82	3.322	19
27.51	3.239	16

2. Process for the preparation of the crystalline form V of the compound of formula (I) according to claim 1, characterised in that agomelatine is subjected to a mechanical grinding which is said to be "of high energy".

3. Process for the preparation of the crystalline form V of the compound of formula (I) according to claim 1, characterised in that agomelatine is heated until complete melting, then immediately put at room temperature and simultaneously a small quantity of crystalline form V of compound of formula (I) freshly prepared is added, and the mixture is cooled until crystallisation is complete.

4. A pharmaceutical composition comprising as active ingredient crystalline form V of agomelatine according to claim 1, in combination with one or more pharmaceutically acceptable, inert, non-toxic carriers.

5. Pharmaceutical composition according to claim 4 for use in the manufacture of a medicament for the treatment of melatoninergic disorders.

6. Pharmaceutical composition according to claim 4 for use in the manufacture of a medicament for the treatment of sleep disorders, stress, anxiety, seasonal affective disorders or severe depression, cardiovascular pathologies, pathologies of the digestive system, insomnia and fatigue due to jetlag, schizophrenia, panic attacks, melancholia, appetite disorders, obesity, insomnia, psychotic disorders, epilepsy, diabetes, Parkinson's disease, senile dementia, various disorders associated with normal or pathological ageing, migraine, memory loss, Alzheimer's disease, cerebral circulation disorders, and also in sexual dysfunction, as ovulation inhibitors, immunomodulators and cancers.

7. Crystalline form according to claim 1, substantially as hereinbefore described as exemplified.

8. Process according to claim 2, substantially as hereinbefore described as exemplified.

9. Pharmaceutical composition according to claim 4, substantially as hereinbefore described as exemplified.

DATED THIS 3RD DAY OF AUGUST 2006

SPOOR AND FISHER
APPLICANT'S PATENT ATTORNEYS