Claims

1. Mixed crystalline form of agomelatine, its X-ray diffraction diagram having the following values for Bragg angle 2θ:

2θ°
9.493
9.809
10.815
11.171
11.879
12.770
13.811
14.939
15.315
16.085
17.544
18.491
19.065
19.538
19.774
20.801
21.156
21.807
22.499
23.032
23.780
24.610
25.419
27.075
31.931

including crystals whose peak diffraction angles are within 2θ±0.2° of the above.

2. Mixed crystalline form of agomelatine, its X-ray diffraction diagram having the following values for interplanar crystal spacing d, Bragg angle 2θ and relative intensity:

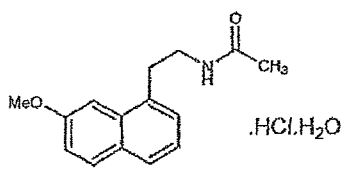
2θ°	d (Å)	Relative intensity (I%)
9.493	9.3085	12.86
9.809	9.0096	15.62
10.815	8.1735	13.10
11.171	7.9141	17.53

11.879	7.4439	64.67
12.770	6.9264	17.90
13.811	6.4065	17.10
14.939	5.9255	12.14
15.315	5.7808	10.48
16.085	5.5057	19.89
17.544	5.0510	48.47
18.491	4.7943	66.41
19.065	4.6512	24.02
19.538	4.5398	99.39
19.774	4.4861	100.00
20.801	4.2668	50.35
21.156	4.1961	30.66
21.807	4.0722	37.31
22.499	3.9486	22.63
23.032	3.8583	31.18
23.780	3.7387	39.67
24.610	3.6144	21.02
25.419	3.5011	30.30
27.075	3.2906	14.67
31.931	2.8004	14.14

including crystals whose peak diffraction angles are within 2θ±0.2° of the above.

3. The mixed crystalline form of agomelatine according to claim 1 or 2, characterised by: its DSC change-in-absorption diagram, the onset value range being 97-98°C, the endothermic peak area being no lower than 90%, with the preferable ratio being 95-99%.

4. The preparation method for the mixed crystalline form of agomelatine according to any of claims 1-3, wherein agomelatine compounds of formula (II) are dissolved in acetic acid, to which sodium acetate is then added, followed by the dropwise addition of water to this reaction mixture, which is then agitated at a temperature of 7-13°C in order to bring about crystallization, with the crystals then being separated from the solution



(II)

5. The preparation method according to claim 4, wherein the molar ratio of agomelatine compounds of formula (II) and sodium acetate is of the order of 1 : 1-1.5, most optimally 1 : 1-1.1.

6. The preparation method according to claim 4 or 5, wherein the ratio of volume of acetic acid to water is 1:15-30.

7. The preparation method according to any of claims 4-6, wherein when the temperature of the resulting reaction mixture reaches 12-18°C, and in particular when 15°C, water is added dropwise in order to bring about crystallization.

8. The preparation method according to any of claims 4-7, wherein water is added dropwise to the resulting reaction mixture which is then agitated at a temperature of 10°C in order to bring about crystallization.

9. The preparation method according to any of claims 4-8, wherein following the addition of the sodium acetate, the reaction mixture is heated to 40-80°C; the said solution is then left to cool on its own, and water is added dropwise in order to bring about crystallization.

10. A pharmaceutical composition, including the mixed crystalline form of agomelatine according to any of claims 1-3 and pharmaceutically acceptable adjuvants or excipients.

11. The pharmaceutical composition according to claim 10, used in the preparation of a medicament, with this medicament being used to treat diseases of the melatoninergic system.

12. The pharmaceutical composition according to claim 10, used in the preparation of a medicament, with this medicament being used to treat sleep disorders, stress, anxiety, seasonal affective disorder, severe depression, cardiovascular diseases, digestive system diseases, insomnia and fatigue brought on by jet lag, schizophrenia, phobias, or depression.

13. The pharmaceutical application of the mixed form of agomelatine according to any of claims 1-3, wherein the said pharmaceutical application relates to the treatment of diseases of the melatoninergic system.

14. The pharmaceutical application of the mixed crystalline form of agomelatine according to any of claims 1-3, wherein the said pharmaceutical application relates to the treatment of sleep disorders, stress, anxiety, seasonal affective disorder, severe depression, cardiovascular diseases, digestive system diseases, insomnia and fatigue brought on by jet lag, schizophrenia, phobias, or depression.

The claims defining the invention are as follows:

1. Mixed crystalline form of agomelatine, its X-ray diffraction diagram having the following values for Bragg angle 2θ:

2θ°
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10.815
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including crystals whose peak diffraction angles are within 2θ±0.2° of the above.

2. Mixed crystalline form of agomelatine, its X-ray diffraction diagram having the following values for interplanar crystal spacing d, Bragg angle 2θ and relative intensity:

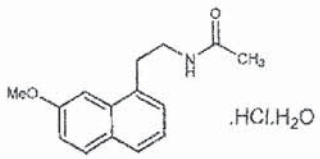
2θ°	d (Å)	Relative intensity (I%)
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24.610	3.6144	21.02
25.419	3.5011	30.30
27.075	3.2906	14.67
31.931	2.8004	14.14

including crystals whose peak diffraction angles are within $2\theta \pm 0.2°$ of the above.

3. The mixed crystalline form of agomelatine according to claim 1 or 2, characterised by: its DSC change-in-absorption diagram, the onset value range being 97-98°C, the endothermic peak area being no lower than 90%, with the preferable ratio being 95-99%.

4. A method for the preparation of the mixed crystalline form of agomelatine according to any one of claims 1 to 3, wherein agomelatine compounds of formula (II) are dissolved in acetic acid, to which sodium acetate is then added, followed by the dropwise addition of water to this reaction mixture, which is then agitated at a temperature of 7-13°C in order to bring about crystallization, with the crystals then being separated from the solution



(II)

5. The preparation method according to claim 4, wherein the molar ratio of agomelatine compounds of formula (II) and sodium acetate is of the order of 1 : 1-1.5.

6. The preparation method according to claim 5, wherein the molar ratio of agomelatine compounds of formula (II) and sodium acetate is of the order of 1 : 1-1.1.

7. The preparation method according to any one of claims 4 to 6, wherein the ratio of volume of acetic acid to water is 1:15-30.

8. The preparation method according to any one of claims 4 to 7, wherein when the temperature of the resulting reaction mixture reaches 12-18°C, water is added dropwise in order to bring about crystallization.

9. The preparation method according to claim 8, wherein the temperature of the resulting reaction mixture is 15°C.

10. The preparation method according to any one of claims 4 to 9, wherein water is added dropwise to the resulting reaction mixture which is then agitated at a temperature of 10°C in order to bring about crystallization.

11. The preparation method according to any one of claims 4 to 10, wherein following the addition of the sodium acetate, the reaction mixture is heated to 40-80°C; the said solution is then left to cool on its own, and water is added dropwise in order to bring about crystallization.

12. A pharmaceutical composition comprising the mixed crystalline form of agomelatine according to any one of claims 1 to 3 and a pharmaceutically acceptable adjuvant or excipient.

13. Use of the mixed crystalline form of agomelatine according to any one of claims 1 to 3 or the pharmaceutical composition according to claim 12, in the preparation of a medicament for the treatment of diseases of the melatoninergic system.

14. The use according to claim 13, for the treatment of sleep disorders, stress, anxiety, seasonal affective disorder, severe depression, cardiovascular diseases, digestive system diseases, insomnia and fatigue brought on by jet lag, schizophrenia, phobias, or depression.

15. A method for the treatment of diseases of the melatoninergic system in a patient, the method comprising administering an effective amount of the mixed form of agomelatine according to any one of claims 1 to 3, or the pharmaceutical composition according to claim 12.

16. The method according to claim 15, for the treatment of sleep disorders, stress, anxiety, seasonal affective disorder, severe depression, cardiovascular diseases, digestive system diseases, insomnia and fatigue brought on by jet lag, schizophrenia, phobias, or depression.