

etc. The term clathrate refers to drug in the form of a crystal lattice that contains spaces (e.g., channels) that have a guest molecule (e.g., a solvent or water) trapped within.

Polymorphic and pseudo-polymorphic forms occur where the same composition of matter crystallizes in a different lattice arrangement resulting in different thermodynamic properties and stabilities specific to the particular polymorph form. In cases where two or more polymorph substances can be produced, it is desirable to have a method to make both polymorphs in pure form. In deciding which polymorph is preferable, the numerous properties of the polymorphs must be compared and the preferred polymorph chosen based on the many physical property variables. It is entirely possible that one polymorph form can be preferable in some circumstances where certain aspects such as ease of preparation, stability, etc. are deemed to be critical. In other situations, a different polymorph may be preferred for greater or lesser solubility and/or superior pharmacokinetics. A particular crystalline form of a compound may have physical properties that differ from those of other polymorphic forms and such properties may influence markedly the physico-chemical and pharmaceutical processing of the compound, particularly when the compound is prepared or used on a commercial scale.

There are strict regulatory requirements for drugs intended for pharmaceutical use which mandate, among other things, a definitive knowledge of the polymorphic or pseudo-polymorphic form of the active pharmaceutical ingredient ("API") in the dosage form. The importance of recognizing and controlling for solid form changes during drug development is recognized in the art. See, for example, the recent review by Newman and Wenslow (AAPS Open (2016)2:2). Accordingly, there is a need for the characterization and control of the polymorphic and/or pseudo-polymorphic form of the API in the dosage form both to meet regulatory requirements and to ensure the quality and consistency of the final dosage form.

This application describes the identification and characterization of newly discovered pseudo-polymorphic forms of the hemisuccinate salt of 2,4,6-trifluoro-N-[6-(1-methyl-piperidine-4-carbonyl)-pyridin-2-yl]-benzamide, and how to control their presence in solid dosage forms.

SUMMARY

The present disclosure relates to pseudo-polymorphic forms of the hemi-succinate salt of 2,4,6-trifluoro-N-[6-(1-methyl-piperidine-4-carbonyl)-pyridin-2-yl]-benzamide, also

referred to herein as Compound I, or lasmitidan hemisuccinate. The pseudo-polymorphic forms of Compound I described here unexpectedly occurred during the process of manufacturing for commercial scale pharmaceutical production. The pseudo-polymorphic forms described here are useful for activating 5-HT_{1F} receptors and for the treatment or prevention of migraine headache.

In one aspect of the present disclosure, there is provided a di-hydrate of the hemisuccinate salt of 2,4,6-trifluoro-N-[6-(1-methyl-piperidine-4-carbonyl)-pyridin-2-yl]-benzamide (Form D) characterized by an X-ray diffraction pattern is substantially similar to that set forth in Figure 1A.

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the di-hydrate disclosed herein and a pharmaceutically acceptable carrier.

In a further aspect of the present disclosure, there is provided a di-hydrate disclosed herein for use in treating migraine in a mammal in need thereof.

In another aspect of the present disclosure, there is provided a use of a di-hydrate disclosed herein in the manufacture of a medicament for treating migraine in a mammal in need thereof.

In a further aspect of the present disclosure, there is provided a tri-hydrate of the hemisuccinate salt of 2,4,6-trifluoro-N-[6-(1-methyl-piperidine-4-carbonyl)-pyridin-2-yl]-benzamide (Form F) characterized by an X-ray diffraction pattern is substantially similar to that set forth in Figure 1B.

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the tri-hydrate disclosed herein and a pharmaceutically acceptable carrier.

In a further aspect of the present disclosure, there is provided a tri-hydrate disclosed herein for use in treating migraine in a mammal in need thereof.

In another aspect of the present disclosure, there is provided a tri-hydrate disclosed herein in the manufacture of a medicament for treating migraine in a mammal in need thereof.

In a further aspect of the present disclosure, there is provided a dehydrated hydrate of Form D of the hemisuccinate salt of 2,4,6-trifluoro-N-[6-(1-methyl-piperidine-4-carbonyl)-pyridin-2-yl]-benzamide (Form E) characterized by an X-ray diffraction pattern is substantially similar to that set forth in Figure 1C.

In another aspect of the present disclosure, there is provided A pharmaceutical composition comprising a mixture of polymorphic forms of Compound I selected from the group consisting of a mixture of Forms A and D, a mixture of Forms A and E, a mixture of Forms D and E, and a mixture of Forms A, D, and E.

In embodiments, the disclosure provides Compound I in the form of a solvate. In embodiments, the solvate is a hydrate. In embodiments, the hydrate is a di-hydrate or a tri-hydrate. In embodiments, the disclosure provides a hydrate or dehydrated hydrate characterized by an X-ray powder diffraction (XRPD) pattern substantially similar to one of those set forth in Figure 1.

Figure 1A shows an XRPD pattern of Form D, a di-hydrate, also referred to as Hydrate 1, using Cu-K α radiation. In embodiments, the XRPD pattern for Form D includes at least peaks at about 18.7, 26.5, 27.0, 27.5 and 27.8 degrees 2 θ , +/- 0.2 degrees. In embodiments, the XRPD pattern of Form D includes one or more additional peaks as set forth in Table 2. In embodiments, the disclosure provides Form D characterized by having unit cell parameters at 100 Kelvin of about $a = 25.08 \text{ \AA}$, $b = 10.08 \text{ \AA}$, $c = 20.84 \text{ \AA}$, $\alpha = 90^\circ$, $\beta = 123.71$, and γ angle = 90° .

Figure 1B shows an XRPD pattern of Form F, a tri-hydrate. In embodiments, the XRPD pattern of Form F includes the peaks as set forth in Table 4.

Figure 1C shows an XRPD pattern of Form E, a dehydrated Form D. In embodiments, the XRPD pattern for Form E using Cu-K α radiation includes at least peaks at about 9.2 and 10.5 degrees 2 θ , +/- 0.2 degrees. In embodiments, the XRPD pattern of Form E includes the peaks as set forth in Table 3.

In embodiments, the disclosure provides Compound I in the form of a di-hydrate, Form D, a tri-hydrate, Form F, or a dehydrated hydrate of Form D, referred to herein as Form E. In embodiments, the disclosure provides a composition comprising a mixture of Form A and Form D, or a mixture of Form A and Form E, or a mixture of Form D and Form E, or a mixture of Form A, Form D, and Form E.

In embodiments, the disclosure provides Compound I in the form of the di-hydrate Form D characterized by a Differential Scanning Calorimetry (DSC) thermogram having a broad endotherm onset at 53.1°C (-158.2 J/g), a broad exotherm onset at 92.1°C (24.9 J/g), and a sharp endotherm onset at 197.9°C (-119.0 J/g). In embodiments, Form D exhibits a DSC thermogram substantially in accordance with Figure 2.

WE CLAIM:

1. A di-hydrate of the hemisuccinate salt of 2,4,6-trifluoro-N-[6-(1-methyl-piperidine-4-carbonyl)-pyridin-2-yl]-benzamide (Form D) characterized by an X-ray diffraction pattern is substantially similar to that set forth in Figure 1A.
2. The di-hydrate of claim 1, wherein the X-ray diffraction pattern includes peaks at about 18.7, 26.5, 27.0, 27.5 and 27.8 degrees 2θ using $\text{Cu-K}\alpha$ radiation.
3. The di-hydrate of claim 2, wherein the X-ray diffraction includes one or more additional peaks set forth in Table 2.
4. The di-hydrate of any one of claims 1-3, further characterized by a Differential Scanning Calorimetry (DSC) thermogram having a single maximum value at about $X^\circ\text{C}$. a broad endotherm onset at 53.1°C (-158.2 J/g), a broad exotherm onset at 92.1°C (24.9 J/g), and a sharp endotherm onset at 197.9°C (-119.0 J/g)
5. The di-hydrate of claim 1, further characterized by having unit cell parameters at 100 Kelvin of about $a = 25.08\text{ \AA}$, $b = 10.08\text{ \AA}$, $c = 20.84\text{ \AA}$, $\alpha = 90^\circ$, $\beta = 123.71$, and γ angle = 90°
6. The di-hydrate of claim 1, produced by a method comprising wet granulation of amorphous Compound I.
7. A pharmaceutical composition comprising the di-hydrate of claim 1 and a pharmaceutically acceptable carrier.
8. The pharmaceutical composition of claim 7, wherein said di-hydrate is substantially free from impurities.
9. The pharmaceutical composition of claim 8, wherein said di-hydrate has a chemical purity greater than 98.0% as determined by HPLC.

10. A di-hydrate of claim 1 for use in treating migraine in a mammal in need thereof.
11. Use of a di-hydrate of claim 1 in the manufacture of a medicament for treating migraine in a mammal in need thereof.
12. The di-hydrate or use of claim 10 or 11, wherein the mammal is a human.
13. A tri-hydrate of the hemisuccinate salt of 2,4,6-trifluoro-N-[6-(1-methyl-piperidine-4-carbonyl)-pyridin-2-yl]-benzamide (Form F) characterized by an X-ray diffraction pattern is substantially similar to that set forth in Figure 1B.
14. The tri-hydrate according to claim 13, wherein the X-ray diffraction pattern includes peaks as set forth in Table 4.
15. The tri-hydrate of claim 13 or claim 14, further characterized by a DSC thermogram having having a broad endotherm onset at 71.2°C (-198.4 J/g), a shallow endotherm (2 peaks) onset at 95.7°C (-6.4 J/g), a shallow exotherm (2 peaks) at 103.4°C (26.9 J/g), and a sharp endotherm onset at 197.8°C (-114.4 J/g)
16. The tri-hydrate of claim 13, further characterized by a thermogravimetry curve showing 11.4 wt% loss from 25-150°C, reflecting 3.1 mole equivalent water, with degradation beginning about 200°C
17. The tri-hydrate of claim 13, produced by a method comprising slurrying amorphous Compound I or Form A of Compound I in water alone at 5 °C, or by lyophilizing amorphous Compound I from a t-butanol/water (50/50, v/v) mixture.
18. A pharmaceutical composition comprising the tri-hydrate of claim 13 and a pharmaceutically acceptable carrier.
19. The pharmaceutical composition of claim 18, wherein said tri-hydrate is substantially free from impurities.
20. The pharmaceutical composition of claim 19, wherein said tri-hydrate has a chemical purity greater than 98.0% as determined by HPLC.

21. A tri-hydrate of claim 13 for use in treating migraine in a mammal in need thereof.
22. A tri-hydrate of claim 13 in the manufacture of a medicament for treating migraine in a mammal in need thereof.
23. The tri-hydrate or use of claim 21 or 22, wherein the mammal is a human.
24. A dehydrated hydrate of Form D of the hemisuccinate salt of 2,4,6-trifluoro-N-[6-(1-methyl-piperidine-4-carbonyl)-pyridin-2-yl]-benzamide (Form E) characterized by an X-ray diffraction pattern is substantially similar to that set forth in Figure 1C.
25. The dehydrated hydrate of claim 24, wherein the X-ray diffraction pattern includes peaks as set forth in Table 3.
26. A pharmaceutical composition comprising a mixture of polymorphic forms of Compound I selected from the group consisting of a mixture of Forms A and D, a mixture of Forms A and E, a mixture of Forms D and E, and a mixture of Forms A, D, and E.