preparation of a crystalline form of the free base of 6-*O*-(4-Dimethylaminoethoxy)cinnamoyl fumagillol does not appear to be disclosed in the art.

[0005] Polymorphism is the ability of a substance to crystallize in more than one crystal lattice arrangement. Crystallization, or polymorphism, can influence many aspects of solid state properties of a drug substance. A crystalline substance may differ considerably from an amorphous form, and different crystal modifications of a substance may differ considerably from one another in many respects including solubility, dissolution rate and/or bioavailability. Generally, it is difficult to predict whether or not a given compound will form various crystalline solid state forms. It is even more difficult to predict the physical properties of these crystalline solid state forms. Further, it can be advantageous to have a crystalline form of a therapeutic agent for certain formulations, e.g., formulations suitable for subcutaneous use.

SUMMARY

[0006] *In an embodiment, provided herein is a composition comprising a crystalline* form of 6-*O*-(4-dimethylaminoethoxy)cinnamoyl fumagillol.

[0006a] In an aspect, provided herein is a crystalline form of 6-O-(4-dimethylaminoethoxy)cinnamoyl fumagillol, free base, characterized by a powder X-ray diffraction pattern having a characteristic peak in degrees 2θ at about 13.3, 17.4, and 19.9.

[0006b] A crystalline form of 6-*O*-(4-dimethylaminoethoxy)cinnamoyl fumagillol, free base, is also provided herein, characterized by a powder X-ray diffraction pattern having a characteristic peak in degrees 2θ at about 13.3, or for example, characterized by a powder X-ray diffraction pattern having characteristic peaks in degrees 2θ at 13.3, 17.4, and 19.9, or for example, characterized by a powder X-ray diffraction pattern having characteristic peaks in degrees 2θ at 7.1, 13.3, 16.3, 17.4, 18.6, 19.4, and 19.9, or for example, characterized by a powder X-ray diffraction pattern having characteristic peaks in degrees 2θ at 5.2, 7.1, 10.4, 13.3, 14.2, 16.3, 17.4, 18.6, 19.4, and 19.9, e.g., characterized by the crystallization pattern shown in Figure 1. In some embodiments, the powder X-ray diffraction pattern may be obtained using Cu Kα radiation.

[0007] In another aspect, also~~Also~~ provided herein is a crystalline form of 6-*O*-(4-dimethylaminoethoxy)cinnamoyl fumagillol, free base, having a space group of $P2_12_12_1$.

[0008] In one embodiment, the crystalline form of 6-*O*-(4-dimethylaminoethoxy)cinnamoyl fumagillol, free base, in solution may have a ^1H NMR spectrum substantially in accordance with the pattern shown in Figure 6.

[0009] Also provided herein is a process for preparing a crystalline form of 6-*O*-(4-dimethylaminoethoxy)cinnamoyl fumagillol, (e.g., form A) comprising:

a) preparing a solution of 6-*O*-(4-dimethylaminoethoxy)cinnamoyl fumagillol, e.g., amorphous 6-*O*-(4-dimethylaminoethoxy)cinnamoyl fumagillol, in a solvent. For example, a solvent may be a secondary ether, e.g., diisopropyl ether, or maybe e.g., a solvent/antisolvent system, e.g., a toluene:*n*-heptane mixture, e.g., with a ratio of *n*-heptane to toluene of about 4:1;

b) heating the solution, e.g., to about 40°C to about 60°C, e.g., to about 50°C, to substantially or completely dissolve the 6-*O*-(4-dimethylaminoethoxy)cinnamoyl fumagillol;

c) adjusting the temperature so that solid precipitates out of the solution; and

d) isolating the crystalline form of 6-*O*-(4-dimethylaminoethoxy)cinnamoyl fumagillol. Such a process that includes adjusting temperature may comprise cooling the solution to about 4°C or less, or to about 2°C to about 10°C.

[0009a] In an aspect, also provided herein is a process for preparing the crystalline form as defined above, comprising:

a) preparing a solution of 6-O-(4-dimethylaminoethoxy)cinnamoyl fumagillol in a solvent comprising at least one of diisopropyl ether, toluene, and n-heptane;

b) heating the solution to completely dissolve the 6-O-(4-dimethylaminoethoxy)cinnamoyl fumagillol;

c) adjusting the temperature so that solid precipitates out of the solution; and

d) isolating the crystalline form of 6-O-(4-dimethylaminoethoxy)cinnamoyl fumagillol.

[0010] In another aspect, a~~A~~ pharmaceutical composition comprising the crystalline form provided herein and a pharmaceutically acceptable excipient is provided~~contemplated~~, for example, a composition that is a suspension formulation suitable for subcutaneous injection. Provided herein, in an embodiment, is a drug substance comprising at least a detectable amount of the provided crystalline form.

[0011] A method of treating obesity in a patient in need thereof is also provided that includes administering to the patient an effective amount of a crystalline form provided herein. Also provided herein is a method of treating obesity in patient in need thereof, comprising subcutaneously administering a composition comprising a crystalline form of 6-*O*-(4-dimethylaminoethoxy)cinnamoyl fumagillol (free base).

[0012] Still another aspect of the present disclosure~~invention~~ provides a kit comprising the~~a~~ disclosed ~~a~~ crystalline form.

BRIEF DESCRIPTION OF THE FIGURES

[0013] Figure 1 depicts the X-ray diffraction pattern of Form A.

[0014] Figure 2 is a micrograph of Form A.

[0015] Figure 3 depicts the characterization of Form A by differential scanning calorimetry (DSC).

[0016] Figure 4 depicts the characterization of Form A by thermogravimetric/differential thermal analysis (TG/DTA).

1. A crystalline form of 6-*O*-(4-dimethylaminoethoxy)cinnamoyl fumagillol, free base, characterized by a powder X-ray diffraction pattern having a characteristic peak in degrees 2θ at about 13.3.

2. The crystalline form of claim 1, characterized by a powder X-ray diffraction pattern having characteristic peaks in degrees 2θ at about 13.3, 17.4, and 19.9.

3. The crystalline form of claim 2, characterized by a powder X-ray diffraction pattern having characteristic peaks in degrees 2θ at about 7.1, 13.3, 16.3, 17.4, 18.6, 19.4, and 19.9.

4. The crystalline form of claim 3, characterized by a powder X-ray diffraction pattern having characteristic peaks in degrees 2θ at 5.2, 7.1, 10.4, 13.3, 14.2, 16.3, 17.4, 18.6, 19.4, and 19.9.

5. The crystalline form of any one of claims 1-4, comprising the powder X-ray diffraction pattern shown in Figure 1.

6. The crystalline form of any one of claims 1-5, wherein the powder X-ray diffraction pattern was obtained using Cu Kα radiation.

7. A crystalline form of 6-*O*-(4-dimethylaminoethoxy)cinnamoyl fumagillol, free base, having a space group of $P2_12_12_1$.

8. The crystalline form of any one of claims 1-7, having a ^{1}H NMR spectrum substantially in accordance with the pattern shown in Figure 6, wherein the crystalline form is in solution.

9. A process for preparing the crystalline form of any one of claims 1-8, comprising:

a) preparing a solution of 6-*O*-(4-dimethylaminoethoxy)cinnamoyl fumagillol in a solvent;

b) heating the solution to completely dissolve the 6-*O*-(4-dimethylaminoethoxy)cinnamoyl fumagillol;

c) adjusting the temperature so that solid precipitates out of the solution; and

d) isolating the crystalline form of 6-*O*-(4-dimethylaminoethoxy)cinnamoyl fumagillol.

10. The process of claim 9, wherein the solvent is diisopropyl ether.

11. The process of claim 9, wherein the solvent comprises toluene.

12. The process of claim 9 or 11, wherein the solvent comprises *n*-heptane.

13. The process of claim 9, wherein the solvent comprises a toluene:*n*-heptane mixture.

14. The process of claim 13, wherein the ratio of *n*-heptane to toluene is about 4:1.

15. The process of any one of claims 9-14, wherein heating the solution comprises heating the solution to about 40°C to about 60°C.

16. The process of any one of claims 9-15, wherein heating the solution comprises heating the solution to about 50°C.

17. The process of any one of claims 9-16, wherein adjusting temperature comprises cooling the solution to about 4°C or less, or to about 2°C to about 10°C.

18. A pharmaceutical composition comprising the crystalline form of any one of claims 1-8, and a pharmaceutically acceptable excipient.

19. The pharmaceutical composition of claim 18, wherein the composition is a suspension formulation for subcutaneous injections.

20. A drug substance comprising at least a detectable amount of the crystalline form of any one of claims 1-8.

21. A method of treating obesity in a patient in need thereof, comprising administering to the patient an effective amount of the crystalline form of any one of claims 1-8.

22. A method of treating obesity in patient in need thereof, comprising:

subcutaneously administering a composition comprising a crystalline form of 6-*O*-(4-dimethylaminoethoxy)cinnamoyl fumagillol.

23. A kit comprising the crystalline form of claim 1.

24. The kit of claim 23, further comprising written instructions describing preparation of a pharmaceutical composition suitable for administration to a patient from the crystalline form.

25. The kit of claim 23, further comprising written instructions describing how to administer the resulting composition to the patient.

26. The kit of any one of claims 23-25, further comprising a pharmaceutically acceptable excipient.

27. A pharmaceutically acceptable composition formed from the crystalline form of claim 1.

CLAIMS

1. A crystalline form of 6-O-(4-dimethylaminoethoxy)cinnamoyl fumagillol, free base, characterized by a powder X-ray diffraction pattern having a characteristic peak in degrees 2θ at about 13.3, 17.4, and 19.9.

2. The crystalline form of claim 1, characterized by a powder X-ray diffraction pattern having characteristic peaks in degrees 2θ at about 7.1, 13.3, 16.3, 17.4, 18.6, 19.4, and 19.9.

3. The crystalline form of claim 2, characterized by a powder X-ray diffraction pattern having characteristic peaks in degrees 2θ at 5.2, 7.1, 10.4, 13.3, 14.2, 16.3, 17.4, 18.6, 19.4, and 19.9.

4. The crystalline form of claim 1, having the powder X-ray diffraction pattern shown in FIG. 1.

5. The crystalline form of claim 1, wherein the powder X-ray diffraction pattern was obtained using Cu Kα radiation.

6. A crystalline form of 6-O-(4-dimethylaminoethoxy)cinnamoyl fumagillol, free base, having a space group of $P2_12_12_1$.

7. A process for preparing the crystalline form of claim 1, comprising:

a) preparing a solution of 6-O-(4-dimethylaminoethoxy)cinnamoyl fumagillol in a solvent comprising at least one of diisopropyl ether, toluene, and n-heptane;

b) heating the solution to completely dissolve the 6-O-(4-dimethylaminoethoxy)cinnamoyl fumagillol;

c) adjusting the temperature so that solid precipitates out of the solution; and

d) isolating the crystalline form of 6-O-(4-dimethylaminoethoxy)cinnamoyl fumagillol.

8. The process of claim 7, wherein the solvent is diisopropyl ether.

9. The process of claim 7, wherein the solvent comprises toluene.

10. The process of claim 7, wherein the solvent comprises n-heptane.

11. The process of claim 10, wherein the solvent comprises a toluene:n-heptane mixture.

12. The process of claim 11, wherein the ratio of n-heptane to toluene is about 4:1.

13. The process of claim 7, wherein heating the solution comprises heating the solution to about 40° C. to about 60° C.

14. The process of claim 7, wherein adjusting temperature comprises cooling the solution to about 2° C. to about 10° C.

15. A pharmaceutical composition comprising the crystalline form of claim 1, and a pharmaceutically acceptable excipient.

16. The pharmaceutical composition of claim 15, wherein the composition is a suspension formulation for subcutaneous injections.

17. A kit comprising the crystalline form of claim 1.

18. The kit of claim 17, further comprising written instructions describing preparation of a pharmaceutical composition suitable for administration to a patient from the crystalline form.

19. The kit of claim 18, further comprising written instructions describing how to administer the resulting composition to the patient.

20. The kit of claim 17, further comprising a pharmaceutically acceptable excipient.