[0025] Furthermore, any method of manufacture must be readily reproducible, and provide batch to batch consistency.

[0026] It is a first object of this invention to provide psilocybin, of consistent polymorphic form, for administration to human subjects.

[0027] It is another object of this invention to provide chemically pure psilocybin, of consistent polymorphic form, for administration to human subjects.

[0028] It is yet a further object to provide chemically pure psilocybin, in large scale batch quantities since for commercial use, the pure psilocybin must be produced at scale.

[0029] It is yet a further object of the invention to provide a method of crystallising psilocybin in a desired polymorphic form.

[0030] It is yet a further object of the present invention to provide a scalable method for manufacturing psilocybin, from psilocin or 4 hydroxy-indole.

[0031] In developing suitable methodology Applicant experienced numerous problems and difficulties which they had to be overcome, and it is a separate, independent, object to overcome those problems identified at each step, and use the inventions either alone or in combination.

[0032] It is yet a further object of the invention to formulate the psilocybin of the invention in a form suitable for administration to human subjects and use it in medicine, particularly in the treatment of central nervous system disorders (CNS), and more particularly, but not exclusively, in the treatment of depression, particularly, drug resistant depression either alone or in combination with a digital health product or digital solution.

BRIEF SUMMARY

[0032a] In an aspect of the present disclosure, there is provided a crystalline psilocybin characterized by X-ray powder diffraction (XRPD) peaks at 11.5±0.1, 12.0±0.1, 14.5±0.1, 17.5±0.1, and 19.7±0.1 °2θ, wherein the crystalline psilocybin has a chemical purity of greater than 98% and no single impurity of greater than 1% as determined by high-performance liquid chromatography (HPLC) analysis.

[0032b] In another aspect of the present disclosure, there is provided a crystalline psilocybin characterized by X-ray powder diffraction (XRPD) peaks at 11.5±0.1, 12.0±0.1, 14.5±0.1, 17.5±0.1 and 19.7±0.1 °2θ, wherein the crystalline psilocybin has a chemical purity of greater than 97% as determined by high-performance liquid chromatography (HPLC) analysis.

[0032c] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a therapeutically effective amount of the crystalline psilocybin disclosed herein and a pharmaceutically acceptable excipient.

~~BRIEF~~ SUMMARY OF THE DISCLOSURE

[0033] In accordance with a first aspect of the present inventions there is provided crystalline psilocybin in the form Polymorph A or Polymorph A', characterised by one or more of:

a. peaks in an XRPD diffractogram at 11.5, 12.0 and 14.5 °2θ±0.1°2θ;
b. peaks in an XRPD diffractogram at 11.5, 12.0 and 14.5 °2θ±0.1°2θ, further characterised by at least one further peak at 19.7, 20.4, 22.2, 24.3 or 25.7 °2θ±0.1°2θ;
c. an XRPD diffractogram as substantially illustrated in Figure 7a or 7b; or
d. an endothermic event in a DSC thermogram having an onset temperature of between 205 and 220°C substantially as illustrated in Figure 8a or 8b.

Polymorph A

[0034] In accordance with a preferred embodiment of the present invention there is provided crystalline psilocybin in the form Polymorph A, characterised by one or more of:

CLAIMS

~~1. Crystalline psilocybin in the form Polymorph A or Polymorph A', characterised by one or more of:~~

~~a. peaks in an XRPD diffractogram at 11.5, 12.0 and 14.5 °2θ±0.1°2θ;~~

~~b. peaks in an XRPD diffractogram at 11.5, 12.0 and 14.5 °2θ±0.1°2θ, further characterised by at least one further peak at 19.7, 20.4, 22.2, 24.3 or 25.7 °2θ±0.1°2θ;~~

~~c. an XRPD diffractogram as substantially illustrated in Figure 7a or 7b; or~~

~~d. an endothermic event in a DSC thermogram having an onset temperature of between 205 and 220°C substantially as illustrated in Figure 8a or 8b.~~

~~2. Crystalline psilocybin in the form Polymorph A or Polymorph A', according to claim 1 further characterised by an endothermic event in a DSC thermogram having an onset temperature of between 210 and 215°C.~~

1. Crystalline psilocybin characterized by X-ray powder diffraction (XRPD) peaks at 11.5±0.1, 12.0±0.1, 14.5±0.1, 17.5±0.1, and 19.7±0.1 °2θ, wherein the crystalline psilocybin has a chemical purity of greater than 98% and no single impurity of greater than 1% as determined by high-performance liquid chromatography (HPLC) analysis.
2. The crystalline psilocybin of claim 1, further characterized by XRPD peaks at least one of 20.4±0.1, 22.2±0.1, 24.3±0.1, or 25.7±0.1 °2θ.
3. The crystalline psilocybin of claim 1, further characterized by a XRPD diffraction pattern that is substantially the same as shown in FIG. 7a.
4. The crystalline psilocybin of claim 1, having a chemical purity of greater than 99%.
5. The crystalline psilocybin of claim 1, further characterized by a water content of <0.5% w/w as determined by Karl Fisher Titration.
6. The crystalline psilocybin of claim 1, having less than 1% psilocin as determined by HPLC analysis.
7. The crystalline psilocybin of claim 1, having less than 0.5% psilocin as determined by HPLC analysis.
8. The crystalline psilocybin of claim 1, having less than 1% phosphoric acid as determined by ^{31}P nuclear magnetic resonance (^{31}P NMR).
9. The crystalline psilocybin of claim 1, having less than 0.5% phosphoric acid as determined by ^{31}P NMR.
10. The crystalline psilocybin of claim 1, further characterized by a <0.5% w/w loss in the thermogravimetric analysis (TGA) thermogram between 25° C and 200° C.
11. The crystalline psilocybin of claim 1, further characterized by an endothermic event in a differential scanning calorimetry (DSC) thermogram having an onset temperature of between 205° C and 220° C.
12. The crystalline psilocybin of claim 1, further characterized by an endothermic event in a DSC thermogram having an onset temperature of between 145° C and 155° C.

13. The crystalline psilocybin of claim 1, further characterized by one or more of the following:

a) a loss on drying of no more than 2% w/w;

b) residue on ignition of no more than 0.5% w/w;

c) assay (on a dry basis) of 95-103% by weight as measured by HPLC;

d) residual solvent content of no more than 3000 ppm methanol, 5000 ppm ethanol, 720 ppm tetrahydrofuran (THF), and 890 ppm toluene, as measured by high resolution gas chromatography (HRGC);

e) Inductively Coupled Plasma Mass Spectrometry (ICP-MS) elemental analysis of:

i. no more than 1.5 ppm cadmium (Cd);

ii. no more than 1.5 ppm lead (Pb);

iii. no more than 4.5 ppm arsenic (As);

iv. no more than 9.0 ppm mercury (Hg);

v. no more than 15 ppm cobalt (Co);

vi. no more than 30 ppm vanadium (V);

vii. no more than 60 ppm nickel (Ni);

viii. no more than 165 ppm lithium (Li); and

ix. no more than 30 ppm lead (Pd).

14. The crystalline psilocybin of claim 1, comprising crystals with a size ranging from 50 to 200 microns.

15. A pharmaceutical composition comprising a therapeutically effective amount of the crystalline psilocybin of claim 1 and a pharmaceutically acceptable excipient.

16. The pharmaceutical composition of claim 15, wherein the pharmaceutical composition is a capsule.

17. The pharmaceutical composition of claim 15, wherein the pharmaceutical composition is a tablet.

18. The pharmaceutical composition of claim 15, comprising about 1 mg to about 40 mg of the crystalline psilocybin.

19. The pharmaceutical composition of claim 15, comprising about 1 mg of the crystalline psilocybin.

20. The pharmaceutical composition of claim 15, comprising about 25 mg of the crystalline psilocybin.

21. The pharmaceutical composition of claim 15, wherein the crystalline psilocybin has a chemical purity of greater than 99%.

22. The pharmaceutical composition of claim 15, wherein the crystalline psilocybin has content of <0.5% w/w as determined by Karl Fisher Titration.

23. The pharmaceutical composition of claim 15, having less than 1% psilocin as determined by HPLC analysis.

24. The pharmaceutical composition of claim 15, having less than 1% phosphoric acid as determined by ^{31}P NMR.

25. The pharmaceutical composition of claim 19, wherein the crystalline psilocybin has a chemical purity of greater than 99%.
26. The pharmaceutical composition of claim 19, having less than 1% psilocin as determined by HPLC analysis.
27. The pharmaceutical composition of claim 19, having less than 1% phosphoric acid as determined by ^{31}P NMR.
28. The pharmaceutical composition of claim 20, wherein the crystalline psilocybin has a chemical purity of greater than 99%.
29. The pharmaceutical composition of claim 20, having less than 1% psilocin as determined by HPLC analysis.
30. The pharmaceutical composition of claim 20, having less than 1% phosphoric acid as determined by ^{31}P NMR.

~~3.~~31. Crystalline psilocybin ~~in the form Polymorph A, according to claim 1 or 2 characterised~~ characterized by X-ray powder diffraction (XRPD) peaks at 11.5±0.1, 12.0±0.1, 14.5±0.1, 17.5±0.1 and 19.7±0.1 °2θ, wherein the crystalline psilocybin has a chemical purity of greater than 97% as determined by high-performance liquid chromatography (HPLC) analysis.~~one or more of:~~

~~a. peaks in an XRPD diffractogram at 11.5, 12.0,14.5, and 17.5, °2θ±0.1°2θ;~~
~~b. peaks in an XRPD diffractogram at 11.5, 12.0, 14.5 and 17.5, °2θ±0.1°2θ, further characterised by at least one further peak at 19.7, 20.4, 22.2, 24.3 or 25.7 °2θ±0.1°2θ;~~
~~c. an XRPD diffractogram as substantially illustrated in Figure 7a; or~~
~~d. an endothermic event in a DSC thermogram having an onset temperature of between 205 and 220°C substantially as illustrated in Figure 8a.~~

~~4.~~32. The crystalline psilocybin of claim 31, further characterized by XRPD peaks at least one of 20.4±0.1, 22.2±0.1, 24.3±0.1, or 25.7±0.1 °2θ~~Crystalline psilocybin in the form Polymorph A, according to claim 3 wherein the peak at 17.5 °2θ±0.1°2θ has a relative intensity compared to the peak at 14.5 °2θ±0.1°2θ of at least 5%~~.

~~5. Crystalline psilocybin in the form Polymorph A', according to claim 1 or 2 characterised by one or more of:~~

~~a. peaks in an XRPD diffractogram at 11.5, 12.0 and 14.5 °2θ±0.1°2θ, but absent or substantially absent of a peak at 17.5 °2θ±0.1°2θ;~~
~~b. peaks in an XRPD diffractogram at 11.5, 12.0 and 14.5 °2θ±0.1°2θ, but absent or substantially absent of a peak at 17.5 °2θ±0.1°2θ, further characterised by at least one further peak at 19.7, 20.4, 22.2, 24.3 or 25.7 °2θ±0.1°2θ;~~
~~c. an XRPD diffractogram as substantially illustrated in Figure 7b; or~~
~~d. an endothermic event in a DSC thermogram having an onset temperature of between 205 and 220°C substantially as illustrated in Figure 8b.~~

33. The crystalline psilocybin of claim 31, further characterized by a XRPD diffraction pattern that is substantially the same as shown in FIG. 7a.
34. The crystalline psilocybin of claim 31, having a chemical purity of greater than 98%.

~~6. Crystalline psilocybin in the form Polymorph A' according to claim 5 wherein any peak at 17.5 °2θ±0.1°2θ has a relative intensity compared to the peak at 14.5 °2θ±0.1°2θ of less than 5%.~~

~~7.~~35. The crystalline psilocybin of claim 31, further characterized by a water content of <0.5% w/w as determined by Karl Fisher Titration.~~Crystalline psilocybin in the form Polymorph A or Polymorph A', according to any of claims 1 to 6 further characterised by having either:~~

~~(i) a water content of <0.5% w/w; or~~

~~(ii) <0.5% w/w loss in the TGA thermogram between ambient temperature, such as 25°C, and 200°C.~~

36. The crystalline psilocybin of claim 31, having less than 1% psilocin as determined by HPLC analysis.

37. The crystalline psilocybin of claim 31, having less than 0.5% psilocin as determined by HPLC analysis.

38. The crystalline psilocybin of claim 31, having less than 1% phosphoric acid as determined by ^{31}P nuclear magnetic resonance (NMR).

39. The crystalline psilocybin of claim 31, having less than 0.5% phosphoric acid as determined by ^{31}P NMR.

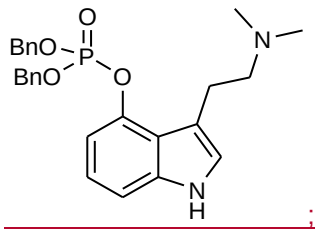
40. The crystalline psilocybin of claim 31, further characterized by a <0.5% w/w loss in the TGA thermogram between 25° C and 200° C.

41. The crystalline psilocybin of claim 31, further characterized by an endothermic event in a differential scanning calorimetry (DSC) thermogram having an onset temperature of between 205° C and 220° C.

42. The crystalline psilocybin of claim 31, further characterized by an endothermic event in a DSC thermogram having an onset temperature of between 145° C and 155° C.

43. The crystalline psilocybin of claim 31, comprising crystals with a size ranging from 50 to 200 microns.

44. The crystalline psilocybin of claim 31, comprising less than 1% of:



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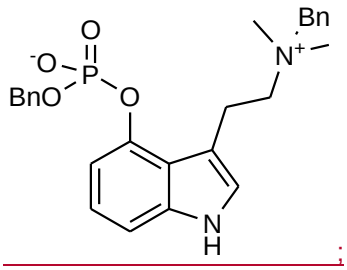

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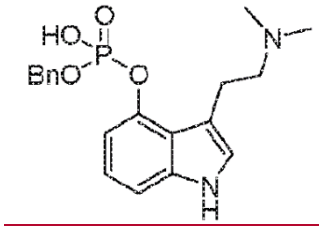

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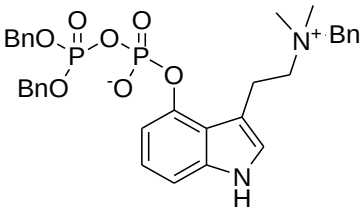

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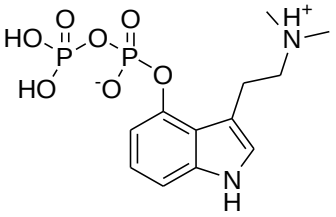

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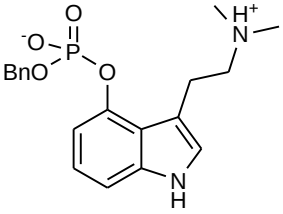
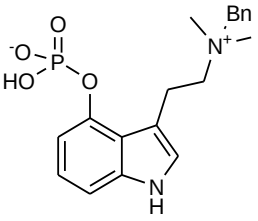


; or



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~~8. Crystalline psilocybin in the form Polymorph A or Polymorph A', according to any preceding claim, having a chemical purity of greater than 97% by HPLC, and no single impurity of greater than 1% including phosphoric acid as measured by ^{31}P NMR, and psilocin as measured by HPLC.~~

~~9. Crystalline psilocybin in the form Polymorph A or Polymorph A' according to any preceding claims wherein the crystalline psilocybin is a white to off white solid.~~

~~10. Crystalline psilocybin in the form Polymorph A or Polymorph A' according to any preceding claim comprising spectra that conforms with any one or more of Figs 10 to 13.~~

~~11. Crystalline psilocybin in the form Polymorph A or Polymorph A' according to any preceding claim comprising the acceptance criteria of one or more quality attributes of Table 9, points 6 to 13.~~

~~12. A batch of crystalline psilocybin Polymorph A, as claimed in claim 1 to 4 or 7 to 11 comprising at least 100g.~~

~~13.~~45. A pharmaceutical composition comprising a therapeutically effective amount of the crystalline psilocybin of claim 31 and a pharmaceutically acceptable excipient~~A~~

~~pharmaceutical formulation comprising crystalline psilocybin in the form Polymorph A or Polymorph A' as claimed in any preceding claim~~.

~~14.~~46. The pharmaceutical composition of claim 45, wherein the pharmaceutical composition is a capsule~~A pharmaceutical formulation as claimed in claim 13 which is an oral dosage form~~.

47. The pharmaceutical composition of claim 45, wherein the pharmaceutical composition is a tablet.

48. The pharmaceutical composition of claim 45, comprising about 1 mg to about 40 mg of the crystalline psilocybin.

49. The pharmaceutical composition of claim 45, comprising about 1 mg of the crystalline psilocybin.

50. The pharmaceutical composition of claim 45, comprising about 25 mg of the crystalline psilocybin.

51. The pharmaceutical composition of claim 45, wherein the crystalline psilocybin has a chemical purity of greater than 98%.

52. The pharmaceutical composition of claim 45, wherein the crystalline psilocybin has content of <0.5% w/w as determined by Karl Fisher Titration.

53. The pharmaceutical composition of claim 45, having less than 1% psilocin as determined by HPLC analysis.

54. The pharmaceutical composition of claim 45, having less than 1% phosphoric acid as determined by ^{31}P NMR.

55. The pharmaceutical composition of claim 48, having less than 1% psilocin as determined by HPLC analysis.

56. The pharmaceutical composition of claim 48, having less than 0.5% psilocin as determined by HPLC analysis.

57. The pharmaceutical composition of claim 49, having less than 1% psilocin as determined by HPLC analysis.

58. The pharmaceutical composition of claim 49, having less than 0.5% psilocin as determined by HPLC analysis.

59. The pharmaceutical composition of claim 50, having less than 1% psilocin as determined by HPLC analysis.

60. The pharmaceutical composition of claim 50, having less than 0.5% psilocin as determined by HPLC analysis.

~~15. A pharmaceutical formulation as claimed in claim 13 or 14 wherein the crystalline psilocybin in the form Polymorph A or Polymorph A' is present in an amount providing a dose of from 0.01mg/kg to 1mg/kg.~~

~~16. A pharmaceutical formulation as claimed in any of claims 13 to 15 which comprises one or more excipients.~~

~~17. A pharmaceutical formulation as claimed in claim 16 wherein the one or more excipients comprise microcrystalline cellulose or starch.~~

18. A pharmaceutical formulation as claimed in claim 16 wherein the one or more excipients comprises silicified microcrystalline cellulose.
19. Crystalline psilocybin in the form Polymorph A or Polymorph A' as claimed in claims 1 to 11 for use in medicine.
20. Crystalline psilocybin in the form Polymorph A or Polymorph A' as claimed in claims 1 to 11 for use in treating a central nervous disorder.
21. Crystalline psilocybin in the form Polymorph A or Polymorph A' as claimed in claims 1 to 11 for use in treating drug resistant depression.
22. A method for large scale manufacture of psilocybin (12) in the form Polymorph A characterised in that the method comprises subjecting psilocybin (12) to a water crystallization step, with controlled drying, to produce a crystalline psilocybin Polymorph A of any of claims 1 to 4 or 7 to 11.
23. Crystalline psilocybin in the form Polymorph A (12A) for use in medicine.
24. Crystalline psilocybin in the form Polymorph A (12A) for use in in treating drug resistant depression.
25. A method of treating drug resistant depression comprising administering to a subject in need thereof an effective dose of crystalline psilocybin in the form Polymorph A (12A).
26. A method for large scale manufacture of psilocybin (12) in the form Polymorph A (12A) characterised in that it comprises subjecting psilocybin (12) to a water crystallization step, with controlled drying, to produce crystals characterised by one or more of:
    a. peaks in an XRPD diffractogram at 11.5, 12.0,14.5, and 17.5, °2θ±0.1°2θ;
    b. peaks in an XRPD diffractogram at 11.5, 12.0, 14.5 and 17.5, °2θ±0.1°2θ, further characterised by at least one further peak at 19.7, 20.4, 22.2, 24.3 or 25.7 °2θ±0.1°2θ;
    c. an XRPD diffractogram as substantially illustrated in Figure 7a; or
    d. an endothermic event in a DSC thermogram having an onset temperature of between 205 and 220°C substantially as illustrated in Figure 8a.
27. A method as claimed in claim 26, wherein the psilocybin is recrystallized in about 10-20 volumes of water, heated with agitation to a temperature of at least 70ºC, polish filtered, seeded at a temperature of about 70ºC, and cooled to about 5ºC over a period of more than 2 hours.