CLAIMS

That which is claimed is:

1. A solid dispersion comprising Compound I molecularly dispersed within a polymer matrix formed by an ionic polymer in its solid state.

2. A solid dispersion according to claim 1, wherein said ionic polymer is selected from the group consisting of hydroxypropylmethyl cellulose acetate succinate, hydroxypropylmethyl cellulose, hydroxypropyl methyl cellulose phthalate and methacrylic acid copolymers.

3. A solid dispersion according to claim 2, wherein said ionic polymer is selected from the group consisting of hydroxypropylmethyl cellulose acetate succinate, hydroxypropylmethyl cellulose and methacrylic acid copolymers.

4. A solid dispersion according to any of the preceding claims, wherein said polymer is hydroxypropylmethyl cellulose acetate succinate (HPMCAS).

5. A solid dispersion according to any of claims 1 to 3, wherein said polymer comprises a methacrylic acid copolymer.

6. A solid dispersion according to claim 1, wherein said polymer comprises EUDRAGIT® L 100-55.

7. A solid dispersion according any of the preceding claims, wherein the ratio of the amount by weight of Compound I within the solid dispersion to the amount by weight of the ionic polymer therein is from about 1:9 to about 1:1.

8. A solid dispersion according any of the preceding claims, wherein the ratio of the amount by weight of Compound I within the solid dispersion to the amount by weight of the ionic polymer therein is from about 2:8 to about 4:6.

9. A solid dispersion according any of the preceding claims, wherein the ratio of the amount by weight of Compound I within the solid dispersion to the amount by weight of the ionic polymer therein is about 3:7.

10. A solid dispersion according to any of the preceding claims, wherein Compound I is primarily in amorphous form.

11. A solid dispersion according to claim 4, wherein hydroxypropylmethyl cellulose acetate succinate (HPMCAS) is present in an amount of not less than about 20%, by weight, of the solid dispersion.

12. A solid dispersion according to claim 11, wherein hydroxypropylmethyl cellulose acetate succinate is present in an amount of from about 20% to about 95% by weight of the solid dispersion.

13. A solid dispersion according to claim 11, wherein hydroxypropylmethyl cellulose acetate succinate is present in an amount of about 20% to about 70% by weight of the solid dispersion.

14. A composition comprising a solid dispersion according to any of the preceding claims, and a pharmaceutically-acceptable carrier.

15. A formulation comprising the solid dispersion according to any of claims 1-13 or a composition according to claim 14 suspended in an aqueous vehicle.

16. A formulation according to claim 15 further comprising colloidal silicon dioxide.

17. A formulation according to claim 16, wherein said colloidal silicon dioxide is present in an amount of at least 0.5% by weight of the composition.

18. A formulation according to any of claims 15-17, wherein said aqueous vehicle contains 2% by weight hydroxypropylcellulose.

19. A method for making a solid dispersion according to any of claims 1-13, said method comprising microprecipitating Compound I and an ionic polymer.

20. A method according to claim 19, wherein Compound I and the ionic polymer simultaneously precipitate out to form a molecular dispersion of Compound I in said ionic polymer.

21. A method according to claim 19, wherein the solid dispersion is prepared by spray drying.

22. A method according to claim 19, wherein the solid dispersion is prepared by hot melt extrusion..

23. A method according to claim 19, wherein said method comprises the method step of a solvent controlled precipitation.

24. A method according to any of claims 19-23, wherein said polymer is hydroxypropylmethyl cellulose acetate succinate.

25. A method according to claim 24, wherein Compound I and hydroxypropylmethyl cellulose acetate succinate are dissolved in an organic solvent.

26. A method according to claim 25, wherein said solvent is selected from the group consisting of dimethylformamide, dimethylacetamide, dimethyl sulfoxide, and N-methyl pyrrolidone.

27. A method according to any of claims 25 and 26, wherein the resulting solution is added into water, whereby Compound I and hydroxypropylmethyl cellulose acetate succinate simultaneously precipitate out to form a solid molecular complex containing Compound I embedded in a matrix formed by said polymer.

28. A method according to any of claims 25 and 26, wherein the resulting solution is added into aqueous hydrochloric acid (HCl), whereby Compound I and hydroxypropylmethyl cellulose acetate succinate simultaneously precipitate out to form a solid molecular complex containing Compound I embedded in a matrix formed by said polymer.

29. A method according to any of claims 19-28, wherein the resulting solid molecular complex is washed with water to remove the organic solvent.

30. A method according to claim 19, comprising the following steps:

(a) dissolution of Compound I and HPMCAS in the same organic solvent to give one single organic phase;

(b) continuously adding the organic phase obtained under (a) into an aqueous phase which is present in a mixing chamber, said mixing chamber being equipped with a high shear

mixing unit and two additional openings which connect said mixing chamber to a closed loop wherein said aqueous phase is circulated and passes through the mixing chamber;

(c) precipitation of a mixture consisting of the amorphous form of Compound I and HPMCAS out of the aqueous phase mentioned under (b), while the high shear mixer is operating and said aqueous phase is passed through the mixing chamber in a closed loop, resulting in the formation of an aqueous suspension of the precipitate;

(d) continuously circulating the aqueous suspension through the mixing chamber while the high shear mixing unit is operating and after the organic solution prepared under (a) has been completely added to the aqueous phase until a defined particle size and/or particle size distribution is obtained;

(e) isolating the solid phase from the suspension;

(f) washing the isolated solid phase with water; and

(g) delumping and drying the solid phase.

31. A method according to claim 30, wherein

- the organic phase in (a) is a 35 % solution of Compound I and HPMCAS in DMA, the ratio of Compound I to HPMCAS being 30% to 70% (w/w); and

- the continuous adding in step (b) is achieved via an injector nozzle which is oriented at an angle between 40 and 50° to the longitudinal axis of the high shear mixer and has a distance of about 1 to about 10 mm from the rotor of said high shear mixer which is operating with a tip speed of about 15 to about 25 m/sec.

32. A crystalline polymorph Form 1 of Compound I that exhibits a powder x-ray diffraction pattern having characteristic peak locations of approximately 4.7, 9.4, 11.0, 12.5, and 15.4 degrees 2θ.

33. A crystalline polymorph according to claim 32, wherein said polymorph exhibits a powder x-ray diffraction pattern having characteristic peak locations of approximately 4.7, 9.4, 10.0, 11.0, 12.5, 14.2, 15.4, 18.6, and 22.2 degrees 2θ.

34. A crystalline polymorph according to claim 32, wherein said polymorph exhibits a powder x-ray diffraction pattern having characteristic peak locations of approximately 4.7, 9.4, 10.0, 11.0, 12.5, 14.2, 15.4, 16.1, 18.6, 19.0, 22.2 and 26.8 degrees 2θ.

35. A crystalline polymorph according to claim 32, wherein said polymorph exhibits a powder x-ray diffraction pattern substantially the same as the powder x-ray diffraction pattern of FIG. 1.

36. A method according to any of claims 19-29, wherein Compound I is the crystalline polymorph according to any of claims 32-35.

37. A purified form of the crystalline polymorph of claim 32.

38. A crystalline polymorph Form 2 of Compound I that exhibits a powder x-ray diffraction pattern having characteristic peak locations of approximately 8.8, 9.2, 13.5, 19.1 and 24.4 degrees 2θ.

39. A crystalline polymorph according to claim 38, wherein said polymorph exhibits a powder x-ray diffraction pattern having characteristic peak locations of approximately 6.7, 8.8, 9.2, 13.5, 15.0, 17.7, 19.1, 19.7, 21.4 and 24.4 degrees 2θ.

40. A crystalline polymorph according to claim 38, wherein said polymorph exhibits a powder x-ray diffraction pattern having characteristic peak locations of approximately 6.7, 8.8, 9.2, 13.5, 14.1, 14.5, 15.0, 16.2, 17.0, 17.7, 19.1, 19.7, 21.4, 22.2, 24.1, 24.4, and 28.1 degrees 2θ.

41. A crystalline polymorph according to claim 38, wherein said polymorph exhibits a powder x-ray diffraction pattern substantially the same as the powder x-ray diffraction pattern of FIG. 2.

42. A method according to any of claims 19-29, wherein Compound I is the crystalline polymorph according to any of claims 38-41.

43. A purified form of the crystalline polymorph of claim 38.

44. A composition comprising an amorphous form of Compound I.

45. A mesylate salt of Compound I.

46. A tosylate salt of Compound I.

47. A malcate salt of Compound I.

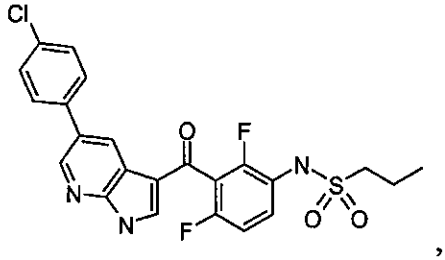
48. An oxalate salt of Compound I.

49. A dichloroacetate salt of Compound I.

50. The novel polymorphs, salts and compositions of Compound I, and the methods of making them, substantially as described hercin before.

CLAIMS:

1. A solid dispersion comprising Compound I having the formula:



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wherein Compound I is molecularly dispersed within a polymer matrix formed by an ionic polymer in its solid state and wherein Compound I is present in an amorphous form.

2. The solid dispersion according to claim 1, wherein said ionic polymer is selected from the group consisting of hydroxypropylmethyl cellulose acetate succinate, hydroxypropylmethyl cellulose, hydroxypropyl methyl cellulose phthalate and methacrylic acid copolymers.

3. The solid dispersion according to claim 2, wherein said ionic polymer is selected from the group consisting of hydroxypropylmethyl cellulose acetate succinate, hydroxypropylmethyl cellulose and methacrylic acid copolymers.

4. The solid dispersion according to any one of claims 1 to 3, wherein said polymer is hydroxypropylmethyl cellulose acetate succinate (HPMCAS).

5. The solid dispersion according to any one of claims 1 to 3, wherein said polymer comprises a methacrylic acid copolymer.

6. The solid dispersion according to claim 1, wherein said polymer comprises EUDRAGIT® L 100-55.

7. The solid dispersion according to any one of claims 1 to 6, wherein the ratio of the amount by weight of Compound I within the solid dispersion to the amount by weight of the ionic polymer therein is from about 1:9 to about 1:1.

8. The solid dispersion according to any one of claims 1 to 6, wherein the ratio of the amount by weight of Compound I within the solid dispersion to the amount by weight of the ionic polymer therein is from about 2:8 to about 4:6.

9. The solid dispersion according to any one of claims 1 to 6, wherein the ratio of the amount by weight of Compound I within the solid dispersion to the amount by weight of the ionic polymer therein is about 3:7.

10. The solid dispersion according to any one of claims 1 to 9, wherein Compound I is primarily in amorphous form.

11. The solid dispersion according to claim 4, wherein hydroxypropylmethyl cellulose acetate succinate (HPMCAS) is present in an amount of not less than about 20%, by weight, of the solid dispersion.

12. The solid dispersion according to claim 11, wherein hydroxypropylmethyl cellulose acetate succinate is present in an amount of from about 20% to about 95% by weight of the solid dispersion.

13. The solid dispersion according to claim 11, wherein hydroxypropylmethyl cellulose acetate succinate is present in an amount of about 20% to about 70% by weight of the solid dispersion.

14. A composition comprising the solid dispersion defined in any one of claims 1 to 13, and a pharmaceutically-acceptable carrier.

15. A formulation comprising the solid dispersion defined in any one of claims 1 to 13 or the composition according to claim 14 suspended in an aqueous vehicle.

16. The formulation according to claim 15 further comprising colloidal silicon dioxide.

17. The formulation according to claim 16, wherein said colloidal silicon dioxide is present in an amount of at least 0.5% by weight of the composition.

18. The formulation according to any one of claims 15 to 17, wherein said aqueous vehicle contains 2% by weight hydroxypropylcellulose.

19. A method for making the solid dispersion defined in any one of claims 1 to 13, said method comprising microprecipitating Compound I and an ionic polymer.

20. The method according to claim 19, wherein Compound I and the ionic polymer simultaneously precipitate out to form a molecular dispersion of Compound I in said ionic polymer.

21. The method according to claim 19, wherein the solid dispersion is prepared by spray drying.

22. A method according to claim 19, wherein the solid dispersion is prepared by hot melt extrusion.

23. The method according to claim 19, wherein said method comprises the method step of a solvent controlled precipitation.

24. The method according to any one of claims 19 to 23, wherein said polymer is hydroxypropylmethyl cellulose acetate succinate.

25. The method according to claim 24, wherein Compound I and hydroxypropylmethyl cellulose acetate succinate are dissolved in an organic solvent.

26. The method according to claim 25, wherein said solvent is selected from the group consisting of dimethylformamide, dimethylacetamide, dimethyl sulfoxide, and N-methyl pyrrolidone.

27. The method according to any one of claims 25 and 26, wherein the resulting solution is added into water, whereby Compound I and hydroxypropylmethyl cellulose acetate succinate simultaneously precipitate out to form a solid molecular complex containing Compound I embedded in a matrix formed by said polymer.

28. The method according to any one of claims 25 and 26, wherein the resulting solution is added into aqueous hydrochloric acid (HCl), whereby Compound I and hydroxypropylmethyl cellulose acetate succinate simultaneously precipitate out to form a solid molecular complex containing Compound I embedded in a matrix formed by said polymer.

29. The method according to any one of claims 19 to 28, wherein the resulting solid molecular complex is washed with water to remove the organic solvent.

30. The method according to claim 19, comprising the following steps:

(a) dissolution of Compound I and HPMCAS in the same organic solvent to give one single organic phase;

(b) continuously adding the organic phase obtained under (a) into an aqueous phase which is present in a mixing chamber, said mixing chamber being equipped with a high shear mixing unit and two additional openings which connect said mixing chamber to a closed loop wherein said aqueous phase is circulated and passes through the mixing chamber;

(c) precipitation of a mixture consisting of the amorphous form of Compound I and HPMCAS out of the aqueous phase mentioned under (b), while the high shear mixer is operating and said aqueous phase is passed through the mixing chamber in a closed loop, resulting in the formation of an aqueous suspension of the precipitate;

(d) continuously circulating the aqueous suspension through the mixing chamber while the high shear mixing unit is operating and after the organic solution prepared

under (a) has been completely added to the aqueous phase until a defined particle size and/or particle size distribution is obtained;

(e) isolating the solid phase from the suspension;

(f) washing the isolated solid phase with water; and

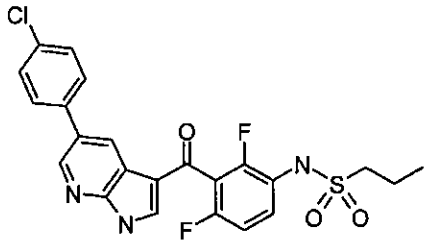
(g) delumping and drying the solid phase.

31. The method according to claim 30, wherein

- the organic phase in (a) is a 35 % solution of Compound I and HPMCAS in DMA, the ratio of Compound I to HPMCAS being 30% to 70% (w/w); and

- the continuous adding in step (b) is achieved via an injector nozzle which is oriented at an angle between 40 and 50° to the longitudinal axis of the high shear mixer and has a distance of about 1 to about 10 mm from the rotor of said high shear mixer which is operating with a tip speed of about 15 to about 25 m/sec.

32. A composition comprising an amorphous form of Compound I having the formula:



and a pharmaceutically acceptable carrier or excipient.