CLAIMS

1. A composition for manufacturing a spray-dried dispersion, the composition comprising 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one; a solvent; and hypromellose acetate succinate; wherein the hypromellose acetate succinate is dissolved in the solvent.

2. The composition of claim 1, wherein the ratio of 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one to hypromellose acetate succinate is between 1:9 and 2:1.

3. The composition of claim 1 or 2, wherein the ratio of 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one to hypromellose acetate succinate is about 1:3.

4. The composition of any one of claims 1-3, wherein the hypromellose acetate succinate has an acetyl content of 5-14%, a succinoyl content of 4-18%, a methoxyl content of 20-26%, and a hydroxypropoxy content of 5-10%.

5. The composition of any one of claims 1-3, wherein the hypromellose acetate succinate has an acetyl content of 7-12%, a succinoyl content of 7-15%, a methoxyl content of 21-25%, and a hydroxypropoxy content of 5-9%.

6. The composition of any one of claims 1-5, wherein the solvent is acetone, methyl ethlyketone, ethyl acetate, isopropyl alcohol, dioxane, acetonitrile, ethanol, water, methanol, dichloromethane, tetrahydrofuran, or a combination of any of them.

7. The composition of claim 6, wherein the solvent is a combination of methanol and dichloromethane.

8. The composition of claim 7, wherein the ratio of dichloromethane to methanol is 30:70 to 60:40.

9. The composition of claim 8, wherein the ratio of dichloromethane to methanol is about 60:40.

10. A method of manufacturing a spray-dried dispersion, comprising the step of spray-drying the composition of any one of claims 1-9.

11. The method of claim 10, wherein the temperature of a nozzle through which the composition is spray-dried is between 20°C and 60 °C.

12. The method of claim 11, wherein the temperature of the nozzle is between 35 °C and 40 °C.

13. The method of any one of claims 10-12, wherein the step of spray drying is performed at an atomization pressure of between 1.0 and 10.0 bars.

14. The method of claim 13, wherein the step of spray drying is performed at an atomization pressure of between 2.0 and 4.0 bars.

15. A spray-dried dispersion comprising 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one; and hypromellose acetate succinate.

16. The spray-dried dispersion of claim 15, wherein the 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one is in an amorphous form.

17. The spray-dried dispersion of claim 15 or 16, wherein the ratio of 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one to hypromellose acetate succinate is between 1:9 and 2:1.

18. The spray-dried dispersion of any one of claims 15-17, wherein the ratio of 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one to hypromellose acetate succinate is about 1:3.

19. The spray-dried dispersion of any one of claims 15-18, wherein the hypromellose acetate succinate has an acetyl content of 5-14%, a succinoyl content of 4-18%, a methoxyl content of 20-26%, and a hydroxypropoxy content of 5-10%.

20. The spray-dried dispersion of any one of claims 15-19, wherein the hypromellose acetate succinate has an acetyl content of 5-11%, a succinoyl content of 10-18%, a methoxyl content of 20-25%, and a hydroxypropoxy content of 5-9%.

21. A solid dosage form comprising the spray-dried dispersion of any one of claims 15-20, and one or more of a filler, a disintegrant, a lubricant, a glidant, and a stabilizer.

22. The solid dosage form of claim 21, wherein the filler comprises one or more of mannitol, lactose, or microcrystalline cellulose.

23. The solid dosage form of claim 22, wherein the filler comprises mannitol and microcrystalline cellulose.

24. The solid dosage form of claim 23, wherein the ratio of mannitol to microcrystalline cellulose is between 1:3 and 3:1.

25. The solid dosage form of claim 24, wherein the ratio of mannitol to microcrystalline cellulose is 1:1 to 1:1.3.

26. The solid dosage form of any one of claims 21-25, wherein the average particle size of the microcrystalline cellulose is between 5 µm and 80 µm.

27. The solid dosage form of claim 26, wherein the average particle size of the microcrystalline cellulose is between 10 µm and 50 µm.

28. The solid dosage form of any one of claims 21-27, wherein the disintegrant is croscarmellose sodium.

29. The solid dosage form of claim 28, wherein the croscarmellose sodium is present at between 3% and 15% w/w.

30. The solid dosage form of claim 29, wherein the croscarmellose sodium is present at about 6% w/w.

31. The solid dosage form of any one of claims 21-30, wherein the lubricant is stearyl fumarate sodium.

32. The solid dosage form of claim 31, wherein the stearyl fumarate sodium is present at between 0.5 and 5% w/w.

33. The solid dosage form of claim 32, wherein the stearyl fumarate sodium is present at about 1% w/w or about 0.95% w/w.

34. The solid dosage form of any one of claims 21-33, wherein the glidant is colloidal silicon dioxide.

35. The solid dosage form of claim 34, wherein the silicon dioxide is present at between 0.1 to 5% w/w.

36. The solid dosage form of claim 34, wherein the silicon dioxide is present at about 1% w/w.

37. The solid dosage form of any one of claims 21-36, wherein the spray-dried dispersion is present at between 3% to 60% w/w.

38. The solid dosage form of claim 37, wherein the spray-dried dispersion is present at about 50% w/w.

39. The solid dosage form of claim 37, wherein the spray-dried dispersion is present at about 16.7% w/w.

40. The solid dosage form of claim 37, wherein the spray-dried dispersion is present at about 3.33% w/w.

41. The solid dosage form of any one of claims 21-40, wherein the 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one is present at 0.75%-15% w/w.

42. The solid dosage form of claim 21, consisting essentially of:

a. 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one;
b. hypromellose acetate succinate;
c. mannitol;
d. microcrystalline cellulose;
e. croscarmellose sodium;
f. stearyl fumarate sodium; and
g. colloidal silicon dioxide.

43. The solid dosage form of claim 42, consisting essentially of:

a. 0.75%-40.0% (w/w) 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one;

b. 2.0%-54.0% (w/w) hypromellose acetate succinate;

c. 3.75%-42.3% (w/w) mannitol;

d. 3.75%-50.0% (w/w) microcrystalline cellulose;

e. 3.0%-15% (w/w) croscarmellose sodium;

f. 0.5%-5.0% (w/w) stearyl fumarate sodium; and

g. 0.1%-5.0% (w/w) colloidal silicon dioxide,

wherein:

the ratio of 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one to hypromellose acetate succinate is between 1:9 and 2:1;

the sum of the amounts of 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one and hypromellose acetate succinate is between 3% and 60% w/w of the solid dosage form;

the ratio of mannitol to microcrystalline cellulose is between 1:3 and 3:1; and

the sum of the amounts of mannitol and microcrystalline cellulose is between 15.0 and 90% w/w of the solid dosage form.

44. The solid dosage form of claim 43, consisting essentially of:

a. 20 mg of 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one;

b. 60 mg of hypromellose acetate succinate;

c. 33.6 mg of mannitol;

d. 33.6 mg of microcrystalline cellulose;

e. 9.6 mg of croscarmellose sodium;

f. 1.6 mg stearyl fumarate sodium; and

g. 1.6 mg colloidal silicon dioxide.

45. The solid dosage form of claim 43, consisting essentially of:

a. 100 mg of 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one;

b. 300 mg of hypromellose acetate succinate;

c. 168 mg of mannitol;

d. 168 mg of microcrystalline cellulose;

e. 48 mg of croscarmellose sodium;

f. 8 mg stearyl fumarate sodium; and

g. 8 mg colloidal silicon dioxide.

46. The solid dosage form of claim 43, consisting essentially of:

a. 5 mg of 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one;

b. 15 mg of hypromellose acetate succinate;

c. 39.2 mg of mannitol;

d. 51.2 mg of microcrystalline cellulose;

e. 7.2 mg of croscarmellose sodium;

f. 1.1 mg of stearyl fumarate sodium; and

g. 1.2 mg of colloidal silicon dioxide.

47. The solid dosage form of claim 43, consisting of:

a. 1 mg of 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one;

b. 3 mg of hypromellose acetate succinate;

c. 47.2 mg of mannitol;

d. 59.2 mg of microcrystalline cellulose;

e. 7.2 mg of croscarmellose sodium;

f. 1.1 mg of stearyl fumarate sodium; and

g. 1.2 mg of colloidal silicon dioxide.

48. The solid dosage form of any of claims 21-47, wherein the solid dosage form is a tablet.

49. The solid dosage form of any of claims 22-47, wherein the solid dosage form is a capsule.

50. The solid dosage form of claim 48 or 49, wherein the amount of 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one in the tablet or capsule is 1-200 mg.

51. The solid dosage form of claim 50, wherein the amount of 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one in the tablet or capsule is about 5 mg.

52. The solid dosage form of claim 50, wherein the amount of 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one in the tablet or capsule is about 20 mg.

53. The solid dosage form of claim 50, wherein the amount of 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one in the tablet or capsule is about 100 mg.

54. The solid dosage form of claim 50, wherein the amount of 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one in the tablet or capsule is about 1 mg.

55. A method of manufacturing a solid dosage form of 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one, comprising the steps of:

a. blending a spray-dried dispersion of any one of claims 15-20 with one or more of: a first filler, a first disintegrant, a first lubricant, a first glidant, and a first stabilizer to form a first solid mixture;

b. roller compacting and milling the first solid mixture; and

c. optionally blending the roller compacted and milled first solid mixture with one or more of a second filler, a second disintegrant, a second lubricant, a second glidant, and a second stabilizer to form a second solid mixture; and

d. converting the first or the second solid mixture into the solid dosage form of 4-chloro-5-(4-(4-fluoro-2-(trifluoromethyl)phenoxy)-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)pyridazin-3(2H)-one.

56. The method of claim 55, wherein:

the first and second filler are selected from mannitol, microcrystalline cellulose of a combination thereof;

the first and second disintegrant is croscarmellose sodium;

the first and second lubricant is sodium stearyl fumarate; and

the first and second glidant is silicon dioxide.

57. The method of claim 55, wherein in step c. the roller compacted and milled solid mixture is blended with a second filler, a second disintegrant and a second lubricant.

58. The method of any one of claims 55-57, wherein the solid dosage form is a tablet formed by compressing the first solid mixture or the second solid mixture.

59. The method of any one of claims 55-57, wherein the solid dosage form is a filled capsule formed by filling a capsule with the first solid mixture or the second solid mixture.

60. Use of the spray-dried dispersion of any of claims 15-20 or solid dosage form of any one of claims 21-54 in the preparation of a medicament for the treatment of a kidney disease or a nephropathy associated with a disease or condition.

61. The use of claim 60, wherein the kidney disease or the nephropathy associated with a disease or condition is Focal Segmental Glomerulosclerosis (FSGS), Diabetic nephropathy, Alport syndrome, hypertensive kidney disease, nephrotic syndrome, steroid-resistant nephrotic syndrome, minimal change disease, membranous nephropathy, idiopathic membranous

nephropathy, membranoproliferative glomerulonephritis (MPGN), immune complex-mediated MPGN, complement-mediated MPGN, Lupus nephritis, postinfectious glomerulonephritis, thin basement membrane disease, mesangial proliferative glomerulonephritis, amyloidosis (primary), c1q nephropathy, rapidly progressive GN, anti-GBM disease, C3 glomerulonephritis, hypertensive nephrosclerosis, IgA nephropathy, IgG4 nephropathy, proteinuric kidney disease, microalbuminuria, macroalbuminuria kidney disease, transplant-related FSGS, transplant-related nephrotic syndrome, transplant-related proteinuria, nodular glomerulonephritis, NASR disease (proliferative glomerulonephritis with monoclonal IgG deposits), polycystic kidney disease, autosomal dominant polycystic kidney disease (ADPKD), or an nephropathy associated with any one of obesity, insulin resistance, Type II diabetes, prediabetes, metabolic syndrome, dyslipidemia, pulmonary arterial hypertension, cancer, cholestatic liver disease, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH) or Fabry's disease.

62. The use of claim 61, wherein the kidney disease or the nephropathy associated with a disease or condition is Focal Segmental Glomerulosclerosis (FSGS), Diabetic nephropathy, Alport syndrome, hypertensive kidney disease, obesity-related nephropathy, nephrotic syndrome, steroid-resistant nephrotic syndrome, minimal change disease, membranous nephropathy, membranoproliferative glomerulonephritis (MPGN), Lupus nephritis, postinfectious glomerulonephritis, thin basement membrane disease, mesangial proliferative glomerulonephritis, amyloidosis (primary), c1q nephropathy, anti-GBM disease, C3 glomerulonephritis, hypertensive nephrosclerosis, IgA nephropathy, IgG4 nephropathy, dyslipidemia-associated nephropathy, nodular glomerulonephritis, NASR disease (proliferative glomerulonephritis with monoclonal IgG deposits), polycystic kidney disease, or kidney complications due to Fabry's disease.

63. The use of claim 62, wherein the kidney disease is hypertensive nephropathy, a nephropathy associated with metabolic syndrome, a nephropathy associated with obesity, a nephropathy associated with dyslipidemia, diabetic nephropathy, nephrotic syndrome, FSGS, or minimal change disease.

64. The use of claim 63, wherein the kidney disease is diabetic nephropathy, FSGS, or minimal change disease.

65. Use of the spray-dried dispersion of any one of claims 15-20 or the solid dosage form of any one of claims 21-54 in the preparation of a medicament for the treatment of pain, anxiety, or depression.