

CLAIMS

What is claimed is:

1. A granulation comprising a plurality of granules, wherein,
the granules comprise greater than 95 wt% of an active pharmaceutical ingredient (API),
wherein wt% is based on the total weight of the granulation; and
the active pharmaceutical ingredient comprises an aqueous solubility greater than 100 mg/mL.
2. The granulation of claim 1, wherein the active pharmaceutical ingredient is characterized by a particle size distribution characterized by a D90 less than 30 μm .
3. The granulation of any one of claims 1 to 2, wherein the active pharmaceutical ingredient is characterized by a specific surface area from 200 m^2/kg to 1200 m^2/kg , wherein the specific surface area is determined using laser diffraction.
4. The granulation of any one of claims 1 to 3, wherein the active pharmaceutical ingredient is characterized by a bulk density from 0.1 g/mL to 0.4 g/mL, wherein the bulk density is determined according to USP 616, Method 1.
5. The granulation of any one of claims 1 to 4, wherein the active pharmaceutical ingredient has a bulk density from 0.15 g/mL to 0.35 g/mL, wherein the bulk density is determined using USP 616, Method I.
6. The granulation of any one of claims 1 to 5, wherein the active pharmaceutical ingredient has an aqueous solubility from 100 mg/mL to 1,000 mg/mL.
7. The granulation of any one of claims 1 to 6, wherein the granules comprise from 96 wt% to 99.5 wt% of the active pharmaceutical ingredient, wherein wt% is based on the total weight of the granules.
8. The granulation of any one of claims 1 to 7, wherein the granulation is characterized by a particle size distribution (PSD) characterized by a D50 from 150 μm to 500 μm , wherein the particle size distribution is determined by laser diffraction or by sieve analysis.

9. The granulation of any one of claims 1 to 7, wherein the granulation is characterized by a particle size distribution D50 from 200 μm to 400 μm , wherein the particle size distribution is determined by laser diffraction or by sieve analysis.

10. The granulation of any one of claims 1 to 7, wherein the granulation is characterized by:

a particle size distribution D10 from 50 μm to 250 μm ; and
a particle size distribution D90 from 400 μm to 750 μm ,
wherein the particle size distribution is determined by laser diffraction or by sieve analysis.

11. The granulation of any one of claims 1 to 7, wherein the granulation is characterized by:

a particle size distribution D10 from 80 μm to 120 μm ; and
a particle size distribution D90 from 510 μm to 650 μm ,
wherein the particle size distribution is determined by laser diffraction or by sieve analysis.

12. The granulation of any one of claims 1 to 11, wherein the granulation has a bulk density from 0.50 g/mL to 1.20 g/mL, wherein bulk density is determined according to USP 616, Method I.

13. The granulation of any one of claims 1 to 12, wherein the granulation has a bulk density from 0.40 g/mL to 0.80 g/mL, wherein bulk density is determined according to USP 616, Method I.

14. The granulation of any one of claims 1 to 13, wherein the granulation is characterized by a loss on drying (LOD) from 0.05 wt% to 1.5 wt%, where wt% is based on the weight of the granulation after drying.

15. The granulation of any one of claims 1 to 13, wherein the granulation is characterized by a loss on drying (LOD) from 0.2 wt% to 1.2 wt%, where wt% is based on the weight of the granulation after drying.

16. The granulation of any one of claims 1 to 15, wherein the granulation is characterized by a friability less than 2 wt%, wherein wt% is based on the total weight of the granulation, and the friability is determined using a sieve shaker according to the method described in the examples.

17. The granulation of any one of claims 1 to 15, wherein the granulation is characterized by a friability less than 1.10 wt%, wherein wt% is based on the total weight of the granulation, and the friability is determined using a sieve shaker according to the method described in the examples.

18. The granulation of any one of claims 1 to 15, wherein the granulation is characterized by a friability of less than 1.02 wt%, wherein wt% is based on the total weight of the granulation, and the friability is determined using a sieve shaker according to the method described in the examples.

19. The granulation of any one of claims 1 to 18, wherein the granules are characterized by a sphericity from 0.90 to 1.00, wherein sphericity is determined by dynamic image analysis.

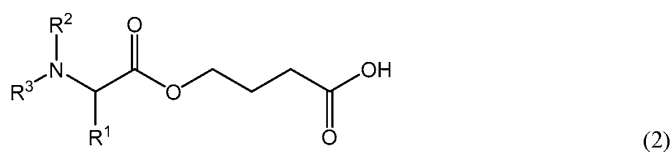
20. The granulation of any one of claims 1 to 19, wherein the granules are characterized by a surface roughness as substantially shown in FIGS. 9B-9E.

21. The granulation of any one of claims 1 to 19, wherein the granules are characterized by a surface roughness as substantially shown in FIGS. 19-20.

22. The granulation of any one of claims 1 to 21, wherein the active pharmaceutical ingredient comprises γ -hydroxybutyric acid or a pharmaceutically acceptable salt thereof.

23. The granulation of any one of claims 1 to 21, wherein the active pharmaceutical ingredient comprises a derivative of γ -hydroxybutyric acid or a pharmaceutically acceptable salt thereof.

24. The granulation of any one of claims 1 to 21, wherein the active pharmaceutical ingredient comprises a compound of Formula (2):



or a pharmaceutically acceptable salt thereof, wherein,

R^1 is selected from hydrogen and C_{1-6} alkyl; and

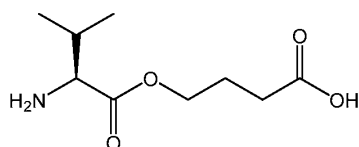
each of R^2 and R^3 is independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, carbonyl, and C_{3-6} cycloalkoxy, carbonyl.

25. The granulation of any one of claims 1 to 21, wherein the active pharmaceutical ingredient is selected from:

4-(((*tert*-butoxycarbonyl)glycyl)oxy)butanoic acid;

4-(glycyloxy)butanoic acid;
4-((*D*-valyl)oxy)butanoic acid;
4-((*L*-alanyl)oxy)butanoic acid;
4-(((ethoxycarbonyl)glycyl)oxy)butanoic acid;
4-(((isopropoxycarbonyl)glycyl)oxy)butanoic acid;
4-(((cyclohexyloxy)carbonyl)glycyl)oxy)butanoic acid;
4-(((ethoxycarbonyl)-*D*-valyl)oxy)butanoic acid;
4-((*L*-valyl)oxy)butanoic acid;
a pharmaceutically acceptable salt of any of the foregoing; and
a combination of any of the foregoing.

26. The granulation of any one of claims 1 to 21, wherein the active pharmaceutical ingredient is 4-((*L*-valyl)oxy)butanoic acid (2a) or a pharmaceutically acceptable salt thereof:



(2a).

27. The granulation of any one of claims 1 to 26, wherein the granules further comprise:
a binder; and
an antistatic agent.

28. The granulation of claim 27, wherein the granules comprise no more than 2 wt% of the binder, wherein wt% is based on the total weight of the granules.

29. The granulation of any one of claims 27 to 28, wherein the granules comprise no more than 1.5 wt% of the antistatic agent, wherein wt% is based on the total weight of the granules.

30. The granulation of any one of claims 27 to 29, wherein the granules comprise:
from 98 wt% to 99 wt% of the active pharmaceutical ingredient;
from 0.25 wt% to 0.75 wt% of the binder; and
from 0.5 wt% to 1.5 wt% of the antistatic agent,
wherein wt% is based on the total weight of the granules.

31. The granulation of any one of claims 27 to 29, wherein the granules comprise:
greater than 98.5 wt% of the active pharmaceutical ingredient;
less than or equal to 0.5 wt% of the binder; and
less than or equal to 1.0 wt% of the antistatic agent,

wherein wt% is based on the total weight of the granules.

32. The granulation of any one of claims 27 to 31, wherein the binder comprises hydroxypropyl cellulose.

33. The granulation of claim 32, wherein the hydroxypropyl cellulose comprises a size distribution characterized by a D10 from 10 μm to 35 μm ; a D50 from 45 μm to 90 μm ; and a D90 from 100 μm to 300 μm .

34. The granulation of any one of claims 32 to 33, wherein the hydroxypropyl cellulose comprises a weight average molecular weight from 50,000 Daltons to 110,000 Daltons.

35. The granulation of any one of claims 32 to 34, wherein the hydroxypropyl cellulose comprises a viscosity from 300 mPa $\times$ sec to 600 mPa $\times$ sec as determined using a Brookfield viscometer with at 25 $^{\circ}\text{C}$.

36. The granulation of any one of claims 30 to 35, wherein the antistatic agent comprises hydrophilic fumed silica.

37. The granulation of claim 36, wherein the hydrophilic fumed silica has an SiO_2 content greater than 99.8% based on ignited material.

38. The granulation of any one of claims 36 to 37, wherein the hydrophilic fumed silica has a specific surface area (BET) from 175 m^2/g to 225 m^2/g .

39. The granulation of any one of claims 36 to 37, wherein the hydrophilic fumed silica has a pH value from 3.7 to 4.5 in a 4% aqueous dispersion.

40. The granulation of any one of claims 36 to 37, wherein the hydrophilic fumed silica has a LOD of less than 1.5 wt%.

41. The granulation of any one of claims 36 to 37, wherein the hydrophilic fumed silica has a tapped density from 30 g/L to 70 g/L.

42. The granulation of any one of claims 1 to 41, wherein the granules comprise a coating.

43. The granulation of claim 42, wherein the granules comprise from 1 wt% to 10 wt% of the coating, wherein wt% is based on the total weight of the granules.

44. The granulation of any one of claims 42 to 43, wherein the coating comprises a seal coating, a controlled release coating, or a combination thereof.

45. A pharmaceutical composition comprising the granulation of any one of claims 1 to 44.

46. The pharmaceutical composition of claim 45, wherein the pharmaceutical composition comprises an oral formulation.

47. The pharmaceutical composition of any one of claims 45 to 46, wherein the oral formulation comprises an oral suspension.

48. The pharmaceutical composition of any one of claims 45 to 47, wherein the pharmaceutical composition comprises an immediate release formulation.

49. The pharmaceutical composition of any one of claims 45 to 48, wherein the pharmaceutical composition comprises a controlled release formulation.

50. A method of preparing the granulation of any one of claims 1 to 44, comprising:
combining the active pharmaceutical ingredient, a binder, and an antistatic agent to form a dry mixture;

wet granulating the dry mixture to provide a wet granulation;

wet massing the wet granulation to provide a wet massed granulation; and

drying the wet massed granulation to provide the granulation.

51. The method of claim 50, wherein wet granulating the dry mixture comprises wet granulating for from 5 minutes to 10 minutes.

52. The method of any one of claims 50 to 51, wherein wet granulating comprises adding from 5 wt% to 20 wt% total water, wherein wt% is based on the total weight of the active pharmaceutical ingredient.

53. The method of any one of claims 50 to 52, wherein during wet granulating the temperature of the wet granulation at a temperature from 20 °C to 25 °C.

54. The method of any one of claims 50 to 53, wherein wet massing the wet granulation comprises wet massing for from 30 minutes to 60 minutes.

55. The method of any one of claims 50 to 54, wherein the method comprises repeating the step of wet granulating and the step of wet massing one or more times before the step of drying.

56. The method of any one of claims 50 to 55, wherein the method comprises repeating the step of wet granulating and the step of wet massing one or more times before the step of drying until the specific density of the granulation does not significantly increase.

57. The method of any one of claims 50 to 56, wherein wet granulating comprises:
granulating the dry mixture for from 5 minutes to 15 minutes at a mixer speed from 800 rpm to 900 rpm and a chopper speed from 3200 rpm to 4000 rpm;
adding water at a rate from 0.0025 wt%/min to 0.0075 wt%/min, wherein wt% is based on the total weight of the dry mixture; and
maintaining the temperature of the wet granulation during wet granulation at a temperature from 20 °C to 25 °C.

58. The method of any one of claims 50 to 57, wherein wet granulating comprises:
granulating for from 5 minutes to 60 minutes at a mixer speed of 850 rpm and a chopper speed from 3600 rpm;
adding water at a rate of 0.005 wt%/min, wherein wt% is based on the total weight of the mixture; and
maintaining the temperature of the wet granulation from 20 °C to 25 °C.

59. The method of any one of claims 50 to 58, wherein wet massing comprises:
wet massing for from 30 minutes to 60 minutes at a mixer speed of 550 rpm and a chopper speed from 1,500 rpm to 2,100 rpm; and
maintaining the temperature of the wet granulation at a temperature from 15 °C to 25 °C.

60. The method of any one of claims 50 to 58, wherein wet massing comprises:
wet massing for from 30 minutes to 60 minutes at a mixer speed from 500 rpm to 600 rpm and a chopper speed from 1800 rpm; and
maintaining the temperature of the wet granulation from 20 °C to 25 °C.

61. The method of any one of claims 50 to 58, wherein the binder comprises hydroxypropyl cellulose.

62. The method of any one of claims 50 to 58, wherein the antistatic agent comprises hydrophilic fumed silica.

63. The method of any one of claims 50 to 58, wherein the mixture comprises:
greater than 95 wt% of the active pharmaceutical ingredient;
greater than 0.25 wt% of a binder; and
greater than 0.5 wt% an antistatic agent, wherein wt% is based on the total weight of the mixture.

64. The method of any one of claims 50 to 58, wherein the mixture comprises:
from 98 wt% to 99 wt% of the active pharmaceutical ingredient;
from 0.25 wt% to 0.75 wt% of a binder; and
from 0.5 wt% to 1.5 wt% of an antistatic agent,
wherein wt% is based on the total weight of the mixture.

65. The method of any one of claims 50 to 58, wherein the mixture comprises:
from 98.2 wt% to 98.8 wt% of the active pharmaceutical ingredient;
0.3 wt% to 0.7 wt% of a binder; and
from 0.8 wt% to 1.2 wt% of an antistatic agent,
wherein wt% is based on the total weight of the mixture.

66. The method of any one of claims 50 to 65, wherein, after drying, the wet granulation comprises from 0.025 wt% to 0.075 wt% water, wherein wt% is based on the total weight of the wet granulation.

67. The method of any one of claims 50 to 66, wherein, after drying, the wet granulation comprises 0.05 wt% water, wherein wt% is based on the total weight of the wet granulation.