

CLAIMS

What is claimed is:

1. A pharmaceutical granulation comprising a plurality of coated granules, wherein, the coated granules comprise a core and a functional coating surrounding the core; the core comprises greater than 85 wt% of an active pharmaceutical ingredient, wherein the active pharmaceutical ingredient has an aqueous solubility greater than 100 mg/mL; and wt% is based on the total weight of the core; and the functional coating comprises a plasticizer.
2. The pharmaceutical granulation of claim 1, wherein the pharmaceutical granulation comprises from 50 wt% to 90 wt% of the active pharmaceutical ingredient, wherein wt% is based on the total weight of the pharmaceutical granulation.
3. The pharmaceutical granulation of any one of claims 1 to 2, wherein the functional coating comprises a controlled release coating.
4. The pharmaceutical granulation of any one of claims 1 to 3, wherein the functional coating comprises from 60 wt% to 85 wt% of a matrix polymer, wherein wt% is based on the total weight of the functional coating.
5. The pharmaceutical granulation of claim 4, wherein the matrix polymer comprises a water-insoluble polymer.
6. The pharmaceutical granulation of claim 5, wherein the water-insoluble polymer comprises ethylcellulose.
7. The pharmaceutical granulation of any one of claims 1 to 6, wherein the functional coating comprises from 0.5 wt% to 20 wt% of a water-soluble polymer, wherein wt% is based on the total weight of the matrix polymer.
8. The pharmaceutical granulation of claim 7, wherein the water-soluble polymer comprises hydroxypropyl cellulose.

9. The pharmaceutical granulation of any one of claims 4 to 8, wherein the matrix polymer comprises from 92 wt% to 98 wt% of a water-insoluble polymer and from 2 wt% to 8 wt% of a water-soluble polymer, wherein wt% is based on the total weight of the matrix polymer.

10. The pharmaceutical granulation of any one of claims 1 to 9, wherein the functional coating comprises from 3 wt% to 13 wt% of the plasticizer, wherein wt% is based on the total weight of the functional coating.

11. The pharmaceutical granulation of claim 10, wherein the plasticizer comprises dibutyl sebacate.

12. The pharmaceutical granulation of any one of claims 1 to 11, wherein the functional coating comprises from 10 wt% to 20 wt% an antistatic agent, wherein wt% is based on the total weight of the functional coating.

13. The pharmaceutical granulation of claim 12, wherein the antistatic agent comprises talc.

14. The pharmaceutical granulation of any one of claims 1 to 13, wherein the functional coating comprises:

from 60 wt% to 85 wt% of a matrix polymer;

from 10 wt% to 20 wt% of an antistatic agent; and

from 3 wt% to 13 wt% of the plasticizer,

wherein wt% is based on the total weight of the functional coating.

15. The pharmaceutical granulation of any one of claims 1 to 14, wherein the coated granules comprise:

from 55 wt% to 90 wt% of the core; and

from 10 wt% to 45 wt% of the functional coating,

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

16. The pharmaceutical granulation of any one of claims 1 to 15, wherein the functional coating has a thickness from 5 μm to 30 μm .

17. The pharmaceutical granulation of any one of claims 1 to 16, wherein the pharmaceutical granulation has a water content less than 1 wt%, wherein wt% is based on the total weight of the pharmaceutical granulation.

18. The pharmaceutical granulation of any one of claims 1 to 17, wherein, the coated granules comprise a seal coating surrounding the core; and the functional coating surrounds the seal coating.

19. The pharmaceutical granulation of claim 18, wherein the seal coating comprises hydroxypropyl cellulose.

20. The pharmaceutical granulation of any one of claims 18 to 19, wherein the coated granules comprise from 2 wt% to 15 wt% of the seal coating, wherein wt% is based on the total weight of the granules.

21. The pharmaceutical granulation of any one of claims 18 to 20, wherein the seal coating has a thickness from 0.5 μm to 5 μm .

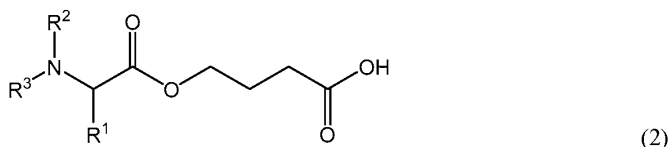
22. The pharmaceutical granulation of any one of claims 1 to 21, wherein the active pharmaceutical ingredient has an aqueous solubility greater than 100 mg/mL.

23. The pharmaceutical granulation of any one of claims 1 to 21, wherein the active pharmaceutical ingredient has an aqueous solubility from 100 mg/mL to 1,000 mg/mL.

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

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

26. The pharmaceutical granulation of any one of claims 1 to 23, 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, C_{3-6} cycloalkoxy, and C_{3-6} cycloalkoxycarbonyl.

27. The pharmaceutical granulation of any one of claims 1 to 23, 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;

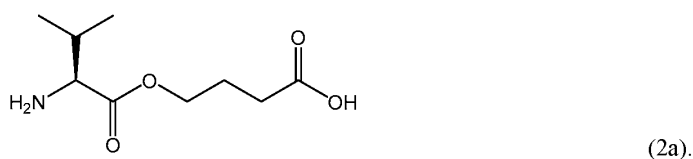
4-(((ethoxycarbonyl)-*D*-valyl)oxy)butanoic acid;

4-(((*L*-valyl)oxy)butanoic acid;

a pharmaceutically acceptable salt of any of the foregoing; and

a combination of any of the foregoing.

28. The pharmaceutical granulation of any one of claims 1 to 23, wherein the active pharmaceutical ingredient comprises 4-(((*L*-valyl)oxy)butanoic acid (2a) or a pharmaceutically acceptable salt thereof:



29. The pharmaceutical granulation of any one of claims 1 to 28, wherein the coated granules are characterized by a particle size distribution (PSD) (D_{50}) from 150 μm to 500 μm , wherein the particle size distribution is determined by laser diffraction.

30. The pharmaceutical granulation of any one of claims 1 to 29, wherein from 35% to 85% of the active pharmaceutical ingredient is released from the pharmaceutical granulation within 2

hours when tested in a USP Type 2 dissolution apparatus in a buffered solution at pH 4.5 at a temperature of 37 °C and a paddle speed of 75 rpm.

31. The pharmaceutical granulation of any one of claims 1 to 30, wherein from 70% to 95% of the active pharmaceutical ingredient is released from the pharmaceutical granulation within 4 hours when tested in a USP Type 2 dissolution apparatus in a buffered solution at pH 4.5 at a temperature of 37 °C and a paddle speed of 75 rpm.

32. The pharmaceutical granulation of any one of claims 1 to 31, wherein from 80% to 100% of the active pharmaceutical ingredient is released from the pharmaceutical granulation within 6 hours when tested in a USP Type 2 dissolution apparatus in a buffered solution at pH 4.5 at a temperature of 37 °C and a paddle speed of 75 rpm.

33. A pharmaceutical composition comprising the pharmaceutical granulation of any one of claims 1 to 32.

34. The pharmaceutical composition of claim 33, wherein the pharmaceutical composition is an oral formulation.

35. The pharmaceutical composition of claim 34, wherein the oral formulation comprises an oral suspension.

36. The pharmaceutical composition of any one of claims 31 to 35, wherein the pharmaceutical composition comprises:

a controlled release portion, wherein the controlled release portion comprises the pharmaceutical granulation; and
an immediate release portion, an extended release portion, or a combination thereof.

37. The pharmaceutical composition of any one of claims 31 to 36, wherein the immediate release portion comprises immediate release granules, wherein,
the immediate release granules comprise a seal coating surrounding a core; and
the core comprises greater than 85 wt% of the active pharmaceutical ingredient.

38. The pharmaceutical composition of any one of claims 31 to 37, wherein the pharmaceutical composition is a BID formulation.

39. The pharmaceutical composition of any one of claims 31 to 38, wherein the pharmaceutical composition is a QD formulation.

40. The pharmaceutical composition of any one of claims 31 to 39, wherein the pharmaceutical composition comprises from 500 mg equivalents to 12 g equivalents of γ -hydroxybutyric acid.

41. The pharmaceutical composition of any one of claims 31 to 39, wherein the active pharmaceutical ingredient comprises γ -hydroxybutyric acid or a pharmaceutically acceptable salt thereof, a derivative of γ -hydroxybutyric acid or a pharmaceutically acceptable salt thereof, a compound of Formula (2) or a pharmaceutically acceptable salt thereof, or a combination of any of the foregoing.

42. The pharmaceutical composition of any one of claims 31 to 39, wherein the active pharmaceutical ingredient comprises:

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;

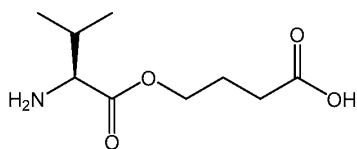
4-(((ethoxycarbonyl)-*D*-valyl)oxy)butanoic acid;

4-((*L*-valyl)oxy)butanoic acid;

a pharmaceutically acceptable salt of any of the foregoing; or

a combination of any of the foregoing.

43. The pharmaceutical composition of any one of claims 31 to 39, wherein the active pharmaceutical ingredient comprises 4-((*L*-valyl)oxy)butanoic acid (2a) or a pharmaceutically acceptable salt thereof:



(2a).

44. The pharmaceutical composition of any one of claims 40 to 43, wherein the pharmaceutical composition comprises a therapeutically effective amount of the active

pharmaceutical ingredient for treating excessive daytime sleepiness associated with narcolepsy, excessive daytime sleepiness associated with Parkinson's disease, excessive daytime sleepiness associated with multiple sclerosis, cataplexy associated with narcolepsy, fatigue in a patient with Parkinson's disease, fatigue in a patient with multiple sclerosis, or fibromyalgia.

45. A method of providing a therapeutically effective amount of γ -hydroxybutyric acid in the systemic circulation of a patient for treating a disease comprising administering to a patient in need of such treatment a therapeutically effective amount of the pharmaceutical composition of any one of claims 40 to 44 for treating the disease.

46. A method of treating a disease in a patient, wherein the disease is known to be treated by administering γ -hydroxybutyric acid, comprising administering to a patient in need of such treatment a therapeutically effective amount of the pharmaceutical composition of any one of claims 40 to 44 for treating the disease.

47. The method of any one of claim 45 to 46, wherein, following administration to the patient, the pharmaceutical composition provides a therapeutically effective amount of γ -hydroxybutyric acid in the systemic circulation of the patient for treating the disease.

48. The method of any one of claims 45 to 47, wherein administering comprises orally administering.

49. The method of any one of claims 45 to 48, wherein the disease is selected from excessive daytime sleepiness associated with narcolepsy, excessive daytime sleepiness associated with Parkinson's disease, excessive daytime sleepiness associated with multiple sclerosis, cataplexy associated with narcolepsy, fatigue in a patient with Parkinson's disease, fatigue in a patient with multiple sclerosis, and fibromyalgia.

50. A method of coating a pharmaceutical granulation comprising applying a coating composition to a pharmaceutical granulation comprising a plurality of granules, wherein the coating composition comprises:

from 4 wt% to 12 wt% solids;

greater than 10 wt% water; and

from 75 wt% to 92 wt% ethanol;

wherein wt% is based on the total weight of the coating composition; and

the granules comprise:

a core comprising no less than 90 wt% of an active pharmaceutical ingredient; and

the active pharmaceutical ingredient has an aqueous solubility greater than 100 mg/mL,

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

51. The method of claim 50, wherein the solids comprise from 3 wt% to 13 wt% of a plasticizer, wherein wt% is based on the total weight of the solids.

52. The method of any one of claims 50 to 51, wherein,
from 60 wt% to 85 wt% of a matrix polymer; and
from 10 wt% to 20 wt% of an antistatic agent,
wherein wt% is based on the total weight of the solids.

53. The method of any one of claims 50 to 52, wherein the granules comprise a seal coating surrounding the core.

54. The method of any one of claims 50 to 53, wherein applying comprises spraying.

55. The method of any one of claims 50 to 54, wherein the method comprises drying the applied coating composition.