SUMMARY

In one aspect there is provided a method for making inhalable composite particles comprising a pharmaceutically-active agent, the method comprising: a) dry milling a composition comprising a solid pharmaceutically active agent and a millable grinding matrix in a mill, for a time period sufficient to produce composite particles comprising the millable grinding matrix and the solid pharmaceutically active agent~~providing composite particles comprising a millable grinding matrix and a solid pharmaceutically-active agent~~, wherein the pharmaceutically-active agent has a~~n~~ median particle size on a volume average basis between 50 nm and 3 μm; and b) milling the composite particles in a mill without milling bodies for a time period sufficient to produce inhalable composite particles having a mass median aerodynamic diameter between 1 μm and 20 μm.

In various embodiments: inhalable composite particles comprise a solid pharmaceutically-active agent having a median particle on a volume average basis between 50 nm and 3 μm; the inhalable composite particles have a median particle size on a volume average size less than or equal to 10,000 nm; the inhalable composite particles have a D90, determined on a particle volume basis, less than or equal to 15,000 nm; the inhalable composite particles have a D90, determined on a particle volume basis, greater than or equal to 2000 nm; the inhalable composite particles have a volume weighted mean (D4,3) less than or equal to 10,000 nm; the inhalable composite particles have a volume weighted mean (D4,3) greater than or equal to 1000 nm; the inhalable composite particles are capable of providing an aerosol with a mass median aerodynamic diameter (MMAD) of the inhalable composite particles between 1 μm and 10 μm when delivered from a dry powder inhaler; the inhalable composite particles are capable of providing an aerosol with a fine particle fraction (FPF) of emitted dose of the pharmaceutically active agent of greater than or equal to about 10% when delivered from a dry powder inhaler; the inhalable composite particles are capable of providing an aerosol with a related standard deviation (RSD) of the FPF of emitted dose of the pharmaceutically active agent of less than or equal to about 10%; the inhalable composite particles are capable of providing an aerosol with a fine particle fraction (FPF) of total recovered dose of the pharmaceutically active agent of greater than or equal to about 30% when delivered from a dry powder inhaler; the inhalable composite particles when delivered from a dry powder inhaler are capable of providing an aerosol with a mass median aerodynamic diameter (MMAD) of the inhalable composite particles from about 1 μm to about 10 μm and a FPF of the pharmaceutically active agent of at least about 10%.

Poloxamer 188, leucine, L-leucine, isoleucine, lysine, valine, methionine, phenylalanine, glycine, arginine, aspartic acid, glutamic acid, cysteine, alanine, and serine.

In various embodiments: the composite particle further comprises a second pharmaceutically active agent, the method producing composite particles of the matrix having the solid pharmaceutically active agent and the second pharmaceutically active agent dispersed therein; the composite particles have a fine particle fraction ratio of the first pharmaceutically active agent and second pharmaceutically active agent less than or equal to about 1.2 when delivered from a dry powder inhaler and analyzed with a NGI with an induction port and a preseparator; the composite particles have a MMAD uniformity ratio of less than or equal to about 1.2 when delivered from a dry powder inhaler and analyzed with a NGI with an induction port and a preseparator, wherein the distribution of each of the first and second pharmaceutically active agent is assayed and each is used to calculate an MMAD for the composite particle.

In one aspect there is provided an inhalable composition of pharmaceutically-active composite particles produced by any of the methods described above.

In one aspect there is provided an inhalable pharmaceutically-active composition comprising: a plurality of inhalable composite particles comprising a millable grinding matrix and a solid pharmaceutically-active agent, wherein the composite particles of the millable grinding matrix and the solid pharmaceutically-active agent have a mass median aerodynamic diameter (MMAD) of ~~from about~~no smaller than 1 μm ~~to about~~and no larger than 20 μm; and wherein the solid pharmaceutically-active agent within the composite particles has an average particle size, determined on a particle number basis, of ~~from about~~no smaller than 50 nm ~~to about~~and no larger than 3 μm.

In various embodiments of this inhalable composition: the inhalable composite particles comprise a solid pharmaceutically-active agent having a median particle on a volume average basis between 50 nm and 3 μm; the inhalable composite particles have a median particle size on a volume average size less than or equal to 10,000 nm; the inhalable composite particles have a D90, determined on a particle volume basis, less than or equal to 15,000 nm; the inhalable composite particles have a D90, determined on a particle volume basis, greater than or equal to 2000 nm; the inhalable composite particles have a volume weighted mean (D4,3) less than or equal to 10,000 nm; the inhalable composite particles have a volume weighted mean (D4,3) greater than or equal to 1000 nm; the inhalable composite particles are capable of providing an aerosol with a mass median aerodynamic diameter (MMAD) of the inhalable

deviation (RSD) less than or equal to about 5.0%; the inhalable composite particles have a roughness by surface area ratio greater than or equal to a ratio of about 1.1 (wherein the specific surface area is measured using nitrogen absorption wherein the surface area is calculated from the spherical equivalent size determined by dry powder laser diffraction); the composite particles have a Rrms greater than or equal to a height selected about 15 nm and wherein the Rrms is measured using atomic force microscopy; the composite particles have a Rrms greater than or equal to a height selected from about 15 nm and when the Rrms is measured using white light interferometry; the composite particles have a median of force adhesion (F[50]) less than or equal to about 150 nN when measured by atomic force microscopy; the weight of composite particles when dispensed from an automated or semi-automated filing machine deviates from the average weight dispensed by a percentage less than or equal to about 10%; the RSD from the average weight is less than or equal to about 10% when the number of samples measured is greater than or equal to 100 samples delivered from an automated or semi-automated filing machine; the composite particle further comprises a second pharmaceutically active agent, the method producing composite particles of the matrix having the solid pharmaceutically active agent and the second pharmaceutically active agent dispersed therein; the composite particles have a fine particle fraction ratio of the first pharmaceutically active agent and second pharmaceutically active agent less than or equal to about 1.2 when delivered from a dry powder inhaler and analyzed with a NGI with an induction port and a preseparator; the composite particles have a MMAD uniformity ratio of less than or equal to about 1.2 when delivered from a dry powder inhaler and analyzed with a NGI with an induction port and a preseparator, wherein the distribution of each of the first and second pharmaceutically active agent is assayed and each is used to calculate an MMAD for the composite particle.

Also described is any of the forgoing pharmaceutical compositions formulated in a unit dosage form. In various embodiments: the pharmaceutical composition comprises a gelatin capsule, the composition is suitable for use in a dry powder inhaler.

In one aspect there is provided a dry powder inhaler comprising the inhalable pharmaceutically active composition described above.

Figure 1 shows representative SEM data of batch 4J (10,000x magnification).

Figure 2 shows representative SEM data of batch 4J (100,000x magnification).

1. A method for making inhalable composite particles comprising a pharmaceutically-active agent, the method comprising:

a) providing composite particles comprising a millable grinding matrix and a solid pharmaceutically-active agent, wherein the pharmaceutically-active agent has an median particle size on a volume average basis between 50 nm and 3 μm; and

b) milling the composite particles in a mill without milling bodies for a time period sufficient to produce inhalable composite particles having a mass median aerodynamic diameter between 1 μm and 20 μm.

2. The method of claim 1, wherein the inhalable composite particles comprise a solid pharmaceutically-active agent having a median particle on a volume average basis between 50 nm and 3 μm.

3. The method of claim 1, wherein the inhalable composite particles have a median particle size on a volume average size less than or equal to 10,000 nm.

4. The method of claim 1, wherein the inhalable composite particles have a D90, determined on a particle volume basis, less than or equal to 15,000 nm.

5. The method of claim 1, wherein the inhalable composite particles have a D90, determined on a particle volume basis, greater than or equal to 2000 nm.

6. The method of claim 1, wherein the inhalable composite particles have a volume weighted mean (D4,3) less than or equal to 10,000 nm.

7. The method of claim 1, wherein the inhalable composite particles have a volume weighted mean (D4,3) greater than or equal to 1000 nm.

8. The method of claim 1, wherein the inhalable composite particles are capable of providing an aerosol with a mass median aerodynamic diameter (MMAD) of the inhalable composite particles between 1 μm and 10 μm when delivered from a dry powder inhaler.

9. The method of claim 1, wherein the inhalable composite particles are capable of providing an aerosol with a fine particle fraction (FPF) of emitted dose of the pharmaceutically active agent of greater than or equal to about 10% when delivered from a dry powder inhaler.

10. The method of claim 1, wherein the inhalable composite particles are capable of providing an aerosol with a related standard deviation (RSD) of the FPF of emitted dose of the pharmaceutically active agent of less than or equal to about 10%.

11. The method of claim 1, wherein the inhalable composite particles are capable of providing an aerosol with a fine particle fraction (FPF) of total recovered dose of the pharmaceutically active agent of greater than or equal to about 30% when delivered from a dry powder inhaler.

12. The method of claim 1, wherein the inhalable composite particles when delivered from a dry powder inhaler are capable of providing an aerosol with a mass median aerodynamic diameter (MMAD) of the inhalable composite particles from about 1 μm to about 10 μm and a FPF of the pharmaceutically active agent of at least about 10%.

13. The method of claims 8 or 12, wherein the inhalable composite particles are capable of providing an aerosol with a mass median aerodynamic diameter (MMAD) of the inhalable composite particles between 1 μm and 7 μm when delivered from a dry powder inhaler.

14. The method of claims 8 or 12, wherein the inhalable composite particles are capable of providing an aerosol with a mass median aerodynamic diameter (MMAD) of the inhalable composite particles between 1.5 μm and 5 μm when delivered from a dry powder inhaler.

15. The method of claims 8 or 12, wherein the inhalable composite particles are capable of providing an aerosol with a mass median aerodynamic diameter (MMAD) of the inhalable composite particles is between 2 μm and 5 μm when delivered from a dry powder inhaler.

16. The method of claims 8 or 12, wherein the inhalable composite particles are capable of providing an aerosol with a mass median aerodynamic diameter (MMAD) of the inhalable composite particles is between 2 μm and 4 μm when delivered from a dry powder inhaler.

17. The method of claim 1, wherein the inhalable composite particles are capable of providing an aerosol with an emitted dose (ED) of greater than or equal to about 70% when delivered from a dry powder inhaler.

18. The method of claim 1, wherein the composite particles are capable of providing an aerosol with an related standard deviation (RSD) of less than or equal to about 10% when determined on at least three samples delivered from a dry powder inhaler.

19. The method of claim 1, wherein the pharmaceutically-active agent within the provided composite particles has a median size of from about 50 nm to about 1000 nm.

20. The method of claim 1, wherein the provided composite particles further comprise a milling aid.

21. The method of claim 1, wherein the millable grinding matrix is crystalline.

22. The method of claim 1, wherein the pharmaceutically-active agent is crystalline.

23. The method of claim 1, wherein the content uniformity of the solid pharmaceutically active agent dispersed in the composite particle varies from the average content by a percentage less than or equal to about 5.0%.

24. The method of claim 1, wherein the content uniformity of the pharmaceutically active agent throughout the blend has a percent relative standard deviation (RSD) less than or equal to about 5.0%.

25. The method of claim 1, wherein the inhalable composite particles have a roughness by surface area ratio greater than or equal to a ratio of about 1.1;

wherein the specific surface area is measured using nitrogen absorption; and,

wherein the surface area is calculated from the spherical equivalent size determined by dry powder laser diffraction.

26. The method of claim 1, wherein the composite particles have a Rrms greater than or equal to a height selected about 15 nm and wherein the Rrms is measured using atomic force microscopy.

27. The method of claim 1, wherein the composite particles have a Rrms greater than or equal to a height selected from about 15 nm and when the Rrms is measured using white light interferometry.

28. The method of claim 1, wherein the composite particles have a median of force adhesion (F[50]) less than or equal to about 150 nN when measured by atomic force microscopy.

29. The method of claim 1, wherein the weight of composite particles when dispensed from an automated or semi-automated filing machine deviates from the average weight dispensed by a percentage less than or equal to about 10%.

30. The method of claim 1, wherein the RSD from the average weight is less than or equal to about 10% when the number of samples measured is greater than or equal to 100 samples delivered from an automated or semi-automated filing machine.

31. The method of claim 1 wherein the step of providing composite particles comprises dry milling a composition comprising: a solid pharmaceutically active agent and a millable grinding matrix in a mill comprising a plurality of milling bodies for a time period sufficient to produce composite particles comprising grinding matrix and solid pharmaceutically active agent.

32. The method of claim 31, wherein the dry milling comprises milling in a mill with a plurality of milling bodies.

33. The method of claim 1, wherein the mill without milling bodies is selected from a cutter mill, end-runner mill, roller mill, hammer mill, fluid energy mill, pin mill, impact mill, mechanofusion mill, beater mill, jet mill and air jet mill.

34. The method of claim 1, wherein the millable grinding matrix comprises one or more materials selected from an organic acid, organic base, polyol, peptide, protein, fat, fatty acid, amino acid, carbohydrate, phospholipid, triglyceride, detergent, polymer, or a pharmaceutically acceptable salt, solvate, hydrate, or polymorph thereof.

35. The method of claim 34, wherein the carbohydrate is selected from mannitol, sorbitol, xylitol, maltitol, lactitol, erythritol, arabitol, ribitol, glucose, fructose, mannose, galactose, lactose, sucrose, raffinose, ribitol, maltose, sorbose, cellobiose, sorbose, trehalose, maltodextrins, dextrans, inulin, 1-O-alpha-D-glucopyranosyl-D-mannitol (Isomalt), or a pharmaceutically acceptable solvate, hydrate, or polymorph thereof.

36. The method of claim 34, wherein the amino acid is selected from aspartic acid, glutamic acid, leucine, L-leucine, isoleucine, lysine, valine, methionine, phenylalanine, glycine, arginine, aspartic acid, glutamic acid, cysteine, alanine, serine, phenylalanine, lysine, N-acetyl-L-cysteine, or a pharmaceutically acceptable salt, solvate, hydrate, or polymorph thereof.

37. The method of claim 34, wherein the millable grinding matrix comprises lactose monohydrate and optionally one or more material selected from sodium chloride, anhydrous lactose, mannitol, glucose, sucrose, trehalose, sorbitol, 1-O-alpha-D-glucopyranosyl-D-mannitol (Isomalt), xylitol, maltitol, lactitol, erythritol, arabitol, ribitol, fructose, mannose, galactose, raffinose, ribitol, maltose, sorbose, cellobiose, sorbose, inulin, sodium citrate, sodium ascorbate. lecithin, soy lecithin, dipalmitoyl phosphatidylcholine, phosphatidylglycerol, dipalmitoyl phosphatidyl ethanolamine, dipalmitoyl phosphatidylinositol, phospatidylcholines, phosphatidylethanolamine, phosphatidylglycerols, phosphatidylinositol, phosphatidylserine, sodium lauryl sulphate, magnesium lauryl sulphate; PEG 6000, PEG 3000 Tween 80, Poloxamer 188, leucine, L-leucine, isoleucine, lysine, valine, methionine, phenylalanine, glycine, arginine, aspartic acid, glutamic acid, cysteine, alanine, and serine.

38. The method of claim 1, wherein the composite particle further comprises a second pharmaceutically active agent, the method producing composite particles of the matrix having the solid pharmaceutically active agent and the second pharmaceutically active agent dispersed therein.

39. The method of claim 38, wherein the composite particles have a fine particle fraction ratio of the first pharmaceutically active agent and second pharmaceutically active agent less than or equal to about 1.2 when delivered from a dry powder inhaler and analyzed with a NGI with an induction port and a preseparator.

40. The method of claim 38, wherein the composite particles have a MMAD uniformity ratio of less than or equal to about 1.2 when delivered from a dry powder inhaler and analyzed with a NGI with an induction port and a preseparator, wherein the distribution of each of the first and second pharmaceutically active agent is assayed and each is used to calculate an MMAD for the composite particle.

41. An inhalable composition of pharmaceutically-active composite particles produced by the method of claim 1.

42. An inhalable pharmaceutically-active composition comprising:
a plurality of composite particles comprising a millable grinding matrix and a solid pharmaceutically-active agent, wherein the composite particles of the grinding matrix and the pharmaceutically-active agent have a mass median aerodynamic diameter of from about 1 μm to about 20 μm; and wherein the pharmaceutically-active agent within the composite particles has an average particle size of from about 50 nm to about 3 μm.

43. The inhalable pharmaceutical composition of claim 42, wherein the inhalable composite particles comprise a solid pharmaceutically-active agent having a median particle on a volume average basis between 50 nm and 3 μm.

44. The inhalable pharmaceutical composition of claim 42, wherein the inhalable composite particles have a median particle size on a volume average size less than or equal to 10,000 nm.

45. The inhalable pharmaceutical composition of claim 42, wherein the inhalable composite particles have a D90, determined on a particle volume basis, less than or equal to 15,000 nm.

46. The inhalable pharmaceutical composition of claim 42, wherein the inhalable composite particles have a D90, determined on a particle volume basis, greater than or equal to 2000 nm.

47. The inhalable pharmaceutical composition of claim 42, wherein the inhalable composite particles have a volume weighted mean (D4,3) less than or equal to 10,000 nm.

48. The inhalable pharmaceutical composition of claim 42, wherein the inhalable composite particles have a volume weighted mean (D4,3) greater than or equal to 1000 nm.

49. The inhalable pharmaceutical composition of claim 42, wherein the inhalable composite particles are capable of providing an aerosol with a mass median aerodynamic diameter (MMAD) of the inhalable composite particles between 1 μm and 10 μm when delivered from a dry powder inhaler.

50. The inhalable pharmaceutical composition of claim 42, wherein the inhalable composite particles are capable of providing an aerosol with a fine particle fraction (FPF) of emitted dose of the pharmaceutically active agent of greater than or equal to about 10% when delivered from a dry powder inhaler.

51. The inhalable pharmaceutical composition of claim 42, wherein the inhalable composite particles are capable of providing an aerosol with a related standard deviation (RSD) of the FPF of emitted dose of the pharmaceutically active agent of less than or equal to about 10%.

52. The inhalable pharmaceutical composition of claim 42, wherein the inhalable composite particles are capable of providing an aerosol with a fine particle fraction (FPF) of total recovered dose of the pharmaceutically active agent of greater than or equal to about 30% when delivered from a dry powder inhaler.

53. The inhalable pharmaceutical composition of claim 49, wherein the inhalable composite particles when delivered from a dry powder inhaler are capable of providing an aerosol with a mass median aerodynamic diameter (MMAD) of the inhalable composite particles from about 1 μm to about 10 μm and a FPF of the pharmaceutically active agent of at least about 10%.

54. The inhalable pharmaceutical composition of claim 49, wherein the inhalable composite particles are capable of providing an aerosol with a mass median aerodynamic diameter (MMAD) of the inhalable composite particles between 1 μm and 7 μm when delivered from a dry powder inhaler.

55. The inhalable pharmaceutical composition of claim 49, wherein the inhalable composite particles are capable of providing an aerosol with a mass median aerodynamic diameter (MMAD) of the inhalable composite particles between 1.5 μm and 5 μm when delivered from a dry powder inhaler.

56. The inhalable pharmaceutical composition of claim 49, wherein the inhalable composite particles are capable of providing an aerosol with a mass median aerodynamic diameter (MMAD) of the inhalable composite particles is between 2 μm and 5 μm when delivered from a dry powder inhaler.

57. The inhalable pharmaceutical composition of claim 49, wherein the inhalable composite particles are capable of providing an aerosol with a mass median aerodynamic diameter (MMAD) of the inhalable composite particles is between 2 μm and 4 μm when delivered from a dry powder inhaler.

58. The inhalable pharmaceutical composition of claim 42, wherein the inhalable composite particles are capable of providing an aerosol with an emitted dose (ED) of greater than or equal to about 70% when delivered from a dry powder inhaler.

59. The inhalable pharmaceutical composition of claim 42, wherein the composite particles are capable of providing an aerosol with an related standard deviation (RSD) of less than or equal to about 10% when determined on at least three samples delivered from a dry powder inhaler.

60. The inhalable pharmaceutical composition of claim 42, wherein the pharmaceutically-active agent within the provided composite particles has a median size of from about 50 nm to about 1000 nm.

61. The inhalable pharmaceutical composition of claim 42, wherein the provided composite particles further comprise a milling aid.

62. The inhalable pharmaceutical composition of claim 42, wherein the millable grinding matrix is crystalline.

63. The inhalable pharmaceutical composition of claim 42, wherein the pharmaceutically-active agent is crystalline.

64. The inhalable pharmaceutical composition of claim 42, wherein the content uniformity of the solid pharmaceutically active agent dispersed in the composite particle varies from the average content by a percentage less than or equal to about 5.0%.

65. The inhalable pharmaceutical composition of claim 42, wherein the content uniformity of the pharmaceutically active agent throughout the blend has a percent relative standard deviation (RSD) less than or equal to about 5.0%.

66. The inhalable pharmaceutical composition of claim 42, wherein the inhalable composite particles have a roughness by surface area ratio greater than or equal to a ratio of about 1.1;

wherein the specific surface area is measured using nitrogen absorption; and,

wherein the surface area is calculated from the spherical equivalent size determined by dry powder laser diffraction.

67. The inhalable pharmaceutical composition of claim 42, wherein the composite particles have a Rrms greater than or equal to a height selected about 15 nm and wherein the Rrms is measured using atomic force microscopy.

68. The inhalable pharmaceutical composition of claim 42, wherein the composite particles have a Rrms greater than or equal to a height selected from about 15 nm and when the Rrms is measured using white light interferometry.

69. The inhalable pharmaceutical composition of claim 42, wherein the composite particles have a median of force adhesion (F[50]) less than or equal to about 150 nN when measured by atomic force microscopy.

70. The inhalable pharmaceutical composition of claim 42, wherein the weight of composite particles when dispensed from an automated or semi-automated filing machine deviates from the average weight dispensed by a percentage less than or equal to about 10%.

71. The inhalable pharmaceutical composition of claim 42, wherein the RSD from the average weight is less than or equal to about 10% when the number of samples measured is greater than or equal to 100 samples delivered from an automated or semi-automated filing machine.

72. The inhalable pharmaceutical composition of claim 42, wherein the composite particle further comprises a second pharmaceutically active agent, the method producing composite particles of the matrix having the solid pharmaceutically active agent and the second pharmaceutically active agent dispersed therein.

73. The inhalable pharmaceutical composition of claim 42, wherein the composite particles have a fine particle fraction ratio of the first pharmaceutically active agent and

second pharmaceutically active agent less than or equal to about 1.2 when delivered from a dry powder inhaler and analyzed with a NGI with an induction port and a preseparator.

74. The inhalable pharmaceutical composition of claim 42, wherein the composite particles have a MMAD uniformity ratio of less than or equal to about 1.2 when delivered from a dry powder inhaler and analyzed with a NGI with an induction port and a preseparator, wherein the distribution of each of the first and second pharmaceutically active agent is assayed and each is used to calculate an MMAD for the composite particle.

75. The pharmaceutical composition of any of claims 41 to 74, wherein the composition is formulated in a unit dosage form.

76. The pharmaceutical composition of claim 75 comprising a gelatin capsule.

77. The pharmaceutical composition of claim 75 wherein the composition suitable for use with a dry powder inhaler.

78. A dry powder inhaler comprising the pharmaceutical composition of any of claims 41 to 74.

79. A dry powder inhaler comprising the pharmaceutical composition of claim 76.

Claims

1. A method for making inhalable composite particles comprising a pharmaceutically active agent, the method comprising:

a) dry milling a composition comprising a solid pharmaceutically active agent and a millable grinding matrix in a mill, for a time period sufficient to produce composite particles comprising the millable grinding matrix and the solid pharmaceutically active agent, wherein the pharmaceutically active agent has a median particle size on a volume average basis between 50 nm and 3 μm; and

b) milling the composite particles in a mill without milling bodies for a time period sufficient to produce inhalable composite particles having a mass median aerodynamic diameter between 1 μm and 20 μm.

2. The method of claim 1, wherein the pharmaceutically active agent has a median particle size on a volume average basis between 50 nm and 1000 nm.

3. The method of claim 1, wherein after step (b), the inhalable composite particles comprise a solid pharmaceutically active agent having a median particle size on a volume average basis between 50 nm and 3 μm.

4. The method of claim 1, wherein the inhalable composite particles have a median particle size on a volume average basis less than or equal to 10,000 nm.

5. The method of claim 1, wherein the inhalable composite particles have a D90, determined on a particle volume basis, less than or equal to 15,000 nm.

6. The method of claim 1, wherein the inhalable composite particles have a D90, determined on a particle volume basis, greater than or equal to 2000 nm.

7. The method of claim 1, wherein the inhalable composite particles have a volume weighted mean diameter (D4,3) less than or equal to 10,000 nm.

8. The method of claim 1, wherein the inhalable composite particles have a volume weighted mean diameter (D4,3) greater than or equal to 1000 nm.

9. The method of claim 1, wherein the inhalable composite particles are capable of providing an aerosol with a mass median aerodynamic diameter (MMAD) of the inhalable composite particles between 1 μm and 10 μm when delivered from a dry powder inhaler.

10. The method of claim 1, wherein the inhalable composite particles are capable of providing an aerosol with a fine particle fraction (FPF) of emitted dose of the pharmaceutically active agent of greater than or equal to about 10% when delivered from a dry powder inhaler.

11. The method of claim 1, wherein the inhalable composite particles are capable of providing an aerosol with a relative standard deviation (RSD) of the fine particle fraction (FPF) of emitted dose of the pharmaceutically active agent of less than or equal to about 10%.

12. The method of claim 1, wherein the inhalable composite particles are capable of providing an aerosol with a fine particle fraction (FPF) of total recovered dose of the pharmaceutically active agent of greater than or equal to about 30% when delivered from a dry powder inhaler.

13. The method of claim 1, wherein the inhalable composite particles when delivered from a dry powder inhaler are capable of providing an aerosol with a mass median aerodynamic diameter (MMAD) of the inhalable composite particles from about 1 μm to about 10 μm and a fine particle fraction (FPF) of the pharmaceutically active agent of at least about 10%.

14. The method of claims 9 or 13, wherein the inhalable composite particles are capable of providing an aerosol with a mass median aerodynamic diameter (MMAD) of the inhalable composite particles between 1 μm and 7 μm when delivered from a dry powder inhaler.

15. The method of claims 9 or 13, wherein the inhalable composite particles are capable of providing an aerosol with a mass median aerodynamic diameter (MMAD) of the inhalable composite particles between 1.5 μm and 5 μm when delivered from a dry powder inhaler.

16. The method of claims 9 or 13, wherein the inhalable composite particles are capable of providing an aerosol with a mass median aerodynamic diameter (MMAD) of the inhalable composite particles of between 2 μm and 5 μm when delivered from a dry powder inhaler.

17. The method of claims 9 or 13, wherein the inhalable composite particles are capable of providing an aerosol with a mass median aerodynamic diameter (MMAD) of the inhalable composite particles of between 2 μm and 4 μm when delivered from a dry powder inhaler.

18. The method of claim 1, wherein the inhalable composite particles are capable of providing an aerosol with an emitted dose (ED) of greater than or equal to about 70% when delivered from a dry powder inhaler.

19. The method of claim 1, wherein the composite particles are capable of providing an aerosol with an relative standard deviation (RSD) of less than or equal to about 10% when determined on at least three samples delivered from a dry powder inhaler.

20. The method of claim 1, wherein the pharmaceutically active agent within the provided composite particles has a median size of from about 50 nm to about 1000 nm.

21. The method of claim 1, wherein the provided composite particles further comprise a milling aid.

22. The method of claim 1, wherein the millable grinding matrix is crystalline.

23. The method of claim 1, wherein the pharmaceutically active agent is crystalline.

24. The method of claim 1, wherein the content uniformity of the solid pharmaceutically active agent dispersed in the composite particle varies from the average content by a percentage less than or equal to about 5.0%.

25. The method of claim 1, wherein the content uniformity of the pharmaceutically active agent throughout the composition has a percent relative standard deviation (RSD) less than or equal to about 5.0%.

26. The method of claim 1, wherein the inhalable composite particles have a roughness by surface area ratio greater than or equal to a ratio of about 1.1;

wherein the specific surface area is measured using nitrogen absorption; and,

wherein the surface area is calculated from the spherical equivalent size determined by dry powder laser diffraction.

27. The method of claim 1, wherein the composite particles have a Roughness – root mean square (Rrms) greater than or equal to a height selected from about 15 nm and wherein the Rrms is measured using atomic force microscopy.

28. The method of claim 1, wherein the composite particles have a Roughness – root mean square (Rrms) greater than or equal to a height selected from about 15 nm and when the Rrms is measured using white light interferometry.

29. The method of claim 1, wherein the composite particles have a median of force adhesion (F[50]) less than or equal to about 150 nN when measured by atomic force microscopy.

30. The method of claim 1, wherein the weight of composite particles when dispensed from an automated or semi-automated filing machine deviates from the average weight dispensed by a percentage less than or equal to about 10%.

31. The method of claim 1, wherein the relative standard deviation (RSD) from the average weight is less than or equal to about 10% when the number of samples measured is greater than or equal to 100 samples delivered from an automated or semi-automated filing machine.

32. The method of claim 1, wherein the dry milling comprises milling in a mill with a plurality of milling bodies.

33. The method of claim 1, wherein the mill without milling bodies is selected from a cutter mill, end-runner mill, roller mill, hammer mill, fluid energy mill, pin mill, impact mill, mechanofusion mill, beater mill, jet mill and air jet mill.

34. The method of claim 1, wherin the mill without milling bodies is selected from a jet mill and an air jet mill.

35. The method of claim 1, wherein the millable grinding matrix comprises one or more materials selected from an organic acid, organic base, polyol, peptide, protein, fat, fatty acid, amino acid, carbohydrate, phospholipid, triglyceride, detergent, polymer, or a pharmaceutically acceptable salt, solvate, hydrate, or polymorph thereof.

36. The method of claim 1, wherein the millable grinding matrix comprises a carbohydrate or an amino acid.

37. The method of claim 35, wherein the carbohydrate is selected from mannitol, sorbitol, xylitol, maltitol, lactitol, erythritol, arabitol, ribitol, glucose, fructose, mannose, galactose, lactose, sucrose, raffinose, ribitol, maltose, sorbose, cellobiose, sorbose, trehalose, maltodextrins, dextrans, inulin, 1-O-alpha-D-glucopyranosyl-D-mannitol (Isomalt), or a pharmaceutically acceptable solvate, hydrate, or polymorph thereof.

38. The method of claim 35, wherein the amino acid is selected from aspartic acid, glutamic acid, leucine, L-leucine, isoleucine, lysine, valine, methionine, phenylalanine, glycine, arginine, aspartic acid, glutamic acid, cysteine, alanine, serine, phenylalanine, lysine, N-acetyl-L-cysteine, or a pharmaceutically acceptable salt, solvate, hydrate, or polymorph thereof.

39. The method of claim 35, wherein the millable grinding matrix comprises lactose monohydrate and optionally one or more materials selected from sodium chloride, anhydrous lactose, mannitol, glucose, sucrose, trehalose, sorbitol, 1-O-alpha-D-glucopyranosyl-D-

mannitol (Isomalt), xylitol, maltitol, lactitol, erythritol, arabitol, ribitol, fructose, mannose, galactose, raffinose, ribitol, maltose, sorbose, cellobiose, sorbose, inulin, sodium citrate, sodium ascorbate. lecithin, soy lecithin, dipalmitoyl phosphatidylcholine, phosphatidylglycerol, dipalmitoyl phosphatidyl ethanolamine, dipalmitoyl phosphatidylinositol, phospatidylcholines, phosphatidylethanolamine, phosphatidylglycerols, phosphatidylinositol, phosphatidylserine, sodium lauryl sulphate, magnesium lauryl sulphate; PEG 6000, PEG 3000 Tween 80, Poloxamer 188, leucine, L-leucine, isoleucine, lysine, valine, methionine, phenylalanine, glycine, arginine, aspartic acid, glutamic acid, cysteine, alanine, and serine.

40. The method of claim 1, wherein the composite particles further comprise a second pharmaceutically active agent, the method for producing composite particles of the matrix having the solid pharmaceutically active agent and the second pharmaceutically active agent dispersed therein.

41. The method of claim 40, wherein the composite particles have a fine particle fraction ratio of the first pharmaceutically active agent and second pharmaceutically active agent less than or equal to about 1.2 when delivered from a dry powder inhaler and analyzed with a next generation impactor (NGI) with an induction port and a preseparator.

42. The method of claim 41, wherein the composite particles have a mass median aerodynamic diameter (MMAD) uniformity ratio of less than or equal to about 1.2 when delivered from a dry powder inhaler and analyzed with a next generation impactor (NGI) with an induction port and a preseparator, wherein the distribution of each of the first and second pharmaceutically active agents is assayed and each is used to calculate an MMAD for the composite particles.

43. An inhalable composition of pharmaceutically active composite particles produced by the method of any one of claims 1 to 42.

44. An inhalable pharmaceutically active composition comprising:
a plurality of inhalable composite particles comprising a millable grinding matrix and a solid pharmaceutically active agent, wherein the composite particles of the millable grinding matrix

and the solid pharmaceutically active agent have a mass median aerodynamic diameter (MMAD) of no smaller than 1 μm and no larger than 20 μm; and wherein the solid pharmaceutically active agent within the composite particles has an average particle size, determined on a particle number basis, of no smaller than 50 nm and no larger than 3 μm.

45. The inhalable pharmaceutically active composition of claim 44, wherein the solid pharmaceutically active agent has a median particle size, determined on a volume average basis of no smaller than 50 nm and no larger than 3 μm.

46. The inhalable pharmaceutically active composition of claim 44, wherein the inhalable composite particles have a median particle size, determined on a volume average basis less than or equal to 10,000 nm.

47. The inhalable pharmaceutically active composition of claim 44, wherein the inhalable composite particles have the 90^{th} percentile (D90), determined on a particle volume basis, less than or equal to 15,000 nm.

48. The inhalable pharmaceutically active composition of claim 44, wherein the inhalable composite particles have a D90, determined on a particle volume basis, greater than or equal to 2000 nm.

49. The inhalable pharmaceutically active composition of claim 44, wherein the inhalable composite particles have a volume weighted mean (D4,3) less than or equal to 10,000 nm.

50. The inhalable pharmaceutically active composition of claim 44, wherein the inhalable composite particles have a volume weighted mean (D4,3) greater than or equal to 1000 nm.

51. The inhalable pharmaceutically active composition of claim 44, wherein the inhalable composite particles are capable of providing an aerosol with a mass median aerodynamic diameter (MMAD) of the inhalable composite particles no smaller than 1 μm and no larger than10 μm when delivered from a dry powder inhaler.

52. The inhalable pharmaceutically active composition of claim 44, wherein the inhalable composite particles are capable of providing an aerosol with a fine particle fraction (FPF) of emitted dose of the solid pharmaceutically active agent of greater than or equal to about 10% when delivered from a dry powder inhaler.

53. The inhalable pharmaceutically active composition of claim 44, wherein the inhalable composite particles are capable of providing an aerosol with a relative standard deviation (RSD) of the fine particle fraction (FPF) of emitted dose of the solid pharmaceutically active agent of less than or equal to about 10%.

54. The inhalable pharmaceutically active composition of claim 44, wherein the inhalable composite particles are capable of providing an aerosol with a fine particle fraction (FPF) of total recovered dose of the solid pharmaceutically active agent of greater than or equal to about 30% when delivered from a dry powder inhaler.

55. The inhalable pharmaceutically active composition of claim 51, wherein the inhalable composite particles when delivered from a dry powder inhaler are capable of providing an aerosol with a mass median aerodynamic diameter (MMAD) of the inhalable composite particles of no smaller than 1 μm and no larger than 10 μm and a fine particle fraction (FPF) of the solid pharmaceutically active agent of at least about 10%.

56. The inhalable pharmaceutically active composition of claim 51, wherein the inhalable composite particles are capable of providing an aerosol with a mass median aerodynamic diameter (MMAD) of the inhalable composite particles of no smaller than 1 μm and no larger than 7 μm when delivered from a dry powder inhaler.

57. The inhalable pharmaceutically active composition of claim 51, wherein the inhalable composite particles are capable of providing an aerosol with a mass median aerodynamic diameter (MMAD) of the inhalable composite particles of no smaller than 1.5 μm and no larger than 5 μm when delivered from a dry powder inhaler.

58. The inhalable pharmaceutically active composition of claim 51, wherein the inhalable composite particles are capable of providing an aerosol with a mass median aerodynamic

diameter (MMAD) of the inhalable composite particles of no smaller than 2 μm and no larger than 5 μm when delivered from a dry powder inhaler.

59. The inhalable pharmaceutically active composition of claim 51, wherein the inhalable composite particles are capable of providing an aerosol with a mass median aerodynamic diameter (MMAD) of the inhalable composite particles of no smaller than 2 μm and no larger than 4 μm when delivered from a dry powder inhaler.

60. The inhalable pharmaceutically active composition of claim 44, wherein the inhalable composite particles are capable of providing an aerosol with an emitted dose (ED) of greater than or equal to about 70% when delivered from a dry powder inhaler.

61. The inhalable pharmaceutically active composition of claim 44, wherein the composite particles are capable of providing an aerosol with an relativestandard deviation (RSD) of less than or equal to about 10% when determined on at least three samples delivered from a dry powder inhaler.

62. The inhalable pharmaceutically active composition of claim 44, wherein the pharmaceutically active agent within the provided composite particles has a median size of no smaller than 50 nm and no larger than 1000 nm.

63. The inhalable pharmaceutically active composition of claim 44, wherein the provided composite particles further comprise a milling aid.

64. The inhalable pharmaceutically active composition of claim 44, wherein the millable grinding matrix is crystalline.

65. The inhalable pharmaceutically active composition of claim 44, wherein the solid pharmaceutically active agent is crystalline.

66. The inhalable pharmaceutically active composition of claim 44, wherein the content uniformity of the solid pharmaceutically active agent dispersed in the inhalable composite particles varies from the average content by a percentage less than or equal to about 5.0%.

67. The inhalable pharmaceutically active composition of claim 44, wherein the content uniformity of the pharmaceutically active agent throughout the composition has a percent relative standard deviation (RSD) less than or equal to about 5.0%.

68. The inhalable pharmaceutically active composition of claim 44, wherein the inhalable composite particles have a roughness by surface area ratio greater than or equal to a ratio of about 1.1;

a. wherein the specific surface area is measured using nitrogen absorption; and,

b. wherein the surface area is calculated from the spherical equivalent size determined by dry powder laser diffraction.

69. The inhalable pharmaceutically active composition of claim 44, wherein the composite particles have a roughness root mean square (Rrms) greater than or equal to a height selected from about 15 nm and wherein the roughness root mean square (Rrms) is measured using atomic force microscopy.

70. The inhalable pharmaceutically active composition of claim 44, wherein the composite particles have a roughness root mean square (Rrms) greater than or equal to a height selected from about 15 nm and when the roughness root mean square (Rrms) is measured using white light interferometry.

71. The inhalable pharmaceutically active composition of claim 44, wherein the inhalable composite particles have a median of force adhesion (F[50]) less than or equal to about 150 nN when measured by atomic force microscopy.

72. The inhalable pharmaceutically active composition of claim 44, wherein the weight of inhalable composite particles when dispensed from an automated or semi-automated filling machine deviates from the average weight dispensed by a percentage less than or equal to about 10%.

73. The inhalable pharmaceutically active composition of claim 44, wherein the relative standard deviation (RSD) from the average weight is less than or equal to about 10% when

the number of samples measured is greater than or equal to 100 samples delivered from an automated or semi-automated filing machine.

74. The inhalable pharmaceutically active composition of claim 44, wherein the inhalable composite particles further comprise a second pharmaceutically active agent, the method producing composite particles of the millable grinding matrix having the first solid pharmaceutically active agent and the second pharmaceutically active agent dispersed therein.

75. The inhalable pharmaceutically active composition of claim 74, wherein the inhalable composite particles have a fine particle fraction ratio of the first pharmaceutically active agent and second pharmaceutically active agent less than or equal to about 1.2 when delivered from a dry powder inhaler and analyzed with a next generation impactor (NGI) with an induction port and a preseparator.

76. The inhalable pharmaceutically active composition of claim 74, wherein the inhalable composite particles have a mass median aerodynamic diameter (MMAD) uniformity ratio of less than or equal to about 1.2 when delivered from a dry powder inhaler and analyzed with a next generation impactor (NGI) with an induction port and a preseparator, wherein the distribution of each of the first and second pharmaceutically active agents is assayed and each is used to calculate a mass median aerodynamic diameter (MMAD) for the inhalable composite particle.

77. The inhalable pharmaceutically active composition of any of claims 44 to 76, wherein the composition is formulated in a unit dosage form.

78. The inhalable pharmaceutically active composition of claim 77 comprising a gelatin capsule.

79. The inhalable pharmaceutically active composition of claim 77 wherein the composition suitable for use with a dry powder inhaler.

80. A dry powder inhaler comprising the inhalable pharmaceutically active composition of any of claims 44 to 76.

81. A dry powder inhaler comprising the inhalable pharmaceutically active composition of claim 78.