SUMMARY

~~Described herein is~~In one aspect there is provided 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.

In various ~~aspects~~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%.

In various embodimentsaspects: 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; 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; 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; 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; 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; 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; the pharmaceutically-active agent within the provided composite particles has a median size of from about 50 nm to about 1000 nm.

In various embodimentsaspects, the provided composite particles further comprise a milling aid; the millable grinding matrix is crystalline; the pharmaceutically-active agent is crystalline; 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%; 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%; 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).

In various embodimentsaspects: 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 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; the dry milling comprises milling in a mill with a plurality of milling bodies; 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.

In various embodimentsaspects, the millable grinding matrix comprises one or more materials selected from an organic acid, organic base, polyol, peptide, protein, fat, fatty acid, amino acid (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), carbohydrate (e.g., 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., phospholipid, triglyceride, detergent, polymer, or a pharmaceutically acceptable salt, solvate, hydrate, or polymorph thereof.

In various embodimentsaspects: 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.

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

Also described isIn one aspect there is provided 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.

In various embodimentsaspects 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~~aspects~~: the pharmaceutical composition comprises a gelatin capsule, the composition is suitable for use in a dry powder inhaler.

~~Also described is~~In one aspect there is provided a dry powder inhaler comprising the pharmaceutical 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).