of the inhalation system allows the deagglomeration mechanism of the inhaler to produce respirable fractions greater than 50%; that is, more than half of the powder contained in the inhaler (cartridge) is emitted as particles of less than 5.8 μm. The inhalers can discharge greater than 85% of a powder medicament contained within a container during dosing. In certain embodiments, the inhalers can discharge greater than 85% of a powder medicament contained in a single inhalation. In one embodiment, the inhalers can discharge greater that 90% of the cartridge contents or container contents in less than 3 seconds at pressure differentials between 2 and 5 kPa with fill masses ranging up to 30 mg.

[0014] Embodiments disclosed herein also include methods. In one embodiment, a method of treating an endocrine-related disease or disorder comprising administering to a person in need thereof a dry powder formulation comprising FDKP microparticles comprising an FDKP trans isomer content of about 45 to about 65% and a drug suitable to treat said disease or disorder. One embodiment includes a method of treating an insulin-related disorder comprising administering a dry powder comprising microparticles of FDKP described above to a person in need thereof. The method comprises administering to a subject a dry powder formulation comprising microparticles of fumaryl diketopiperazine having a trans isomer content ranging from about 45% to 65% or from about 45% to about 63%. In various embodiments an insulin-related disorder can specifically include or exclude any or all of pre-diabetes, type 1 diabetes mellitus (honeymoon phase, post-honeymoon phase, or both), type 2 diabetes mellitus, gestational diabetes, hypoglycemia, hyperglycemia, insulin resistance, secretory dysfunction, impaired early-phase release of insulin, loss of pancreatic β-cell function, loss of pancreatic β-cells, and metabolic disorder. In one embodiment, the dry powder comprises insulin. In other embodiments, the dry powder comprises glucagon, an exendin, or GLP-1.

[0015] In another embodiment there is provided the use of a dry powder formulation in the manufacture of a medicament for treating an endocrine-related disease or disorder, wherein the dry powder formulation comprises fumaryl diketopiperazine (FDKP) microparticles comprising an FKDP transisomer content of about 45% to about 65% and an endocrine hormone suitable to treat said disease or disorder.

[0015a] Another embodiment disclosed herein includes a method of making microparticles suitable for pulmonary administration as a dry powder comprising: a) synthesizing an FDKP compound having a trans isomer content from about 45% to

about 65%; b) determining the trans isomer content of the FDKP compound to assess that the trans isomer content range is from about 45% to about 65%; c) dissolving the FDKP compound of step b) in a solution having a basic pH to form an FDKP solution; d) providing a solution of a volatile acid, and e) mixing the FDKP solution with the solution of a volatile acid together in a high-shear mixer to produce the microparticles. In one embodiment, the step of determining the trans isomer content of the FDKP compound is performed using high pressure liquid chromatography (HPLC). In alternative embodiments, isomer content is determined subsequent to particle formation.

WHAT IS CLAIMED IS:

1. A fumaryl diketopiperazine (FDKP) composition comprising a trans isomer content of about 45% to about 65%.

2. The FDKP composition according to claim 1, wherein said trans isomer content is from about 50% to about 65%.

3. The FDKP composition according to claim 1, wherein said trans isomer content is from about 53% to about 63%.

4. Fumaryl diketopiperazine (FDKP) microparticles comprising the FDKP composition of claim 1.

5. FDKP microparticles according to claim 4, wherein said trans isomer content is from about 50% to about 65%.

6. FDKP microparticles according to claim 4, wherein said trans isomer content is from about 53% to about 63%.

7. FDKP microparticles according to claim 4, further comprising a drug or an active agent.

8. FDKP microparticles according to claim 7, wherein said drug or active agent is a peptide or protein.

9. FDKP microparticles according to claim 8, wherein said peptide is an endocrine hormone.

10. FDKP microparticles according to claim 9, wherein said endocrine hormone is insulin, parathyroid hormone, calcitonin, glucagon, glucagon-like peptide 1, oxyntomodulin, an analog or active fragment of said endocrine hormone.

11. The microparticles of claim 4, wherein the drug is present in an amount greater than 0.01 wt% of the microparticles.

12. A dry powder comprising the microparticles of claim 4.

13. A dry powder comprising the microparticles of claim 7.

14. Use of a dry powder formulation in the manufacture of a medicament for treating an endocrine-related disease or disorder, wherein the dry powder formulation comprises fumaryl diketopiperazine (FDKP) microparticles comprising an FDKP trans

isomer content of about 45% to about 65% and an endocrine hormone suitable to treat said disease or disorder.

15. The use of claim 14, wherein the endocrine hormone is insulin, parathyroid hormone, calcitonin, glucagon, glucagon-like peptide 1, oxyntomodulin, or an analog of said endocrine hormone.

16. The use of claim 14, wherein the endocrine-related disease is diabetes.

WHAT IS CLAIMED IS:

1. A fumaryl diketopiperazine (FDKP) composition comprising a trans isomer content of about 45% to about 65%.

2. The FDKP composition according to claim 1, wherein said trans isomer content is from about 50% to about 65%.

3. The FDKP composition according to claim 1, wherein said trans isomer content is from about 53% to about 63%.

4. Fumaryl diketopiperazine (FDKP) microparticles comprising the FDKP composition of claim 1.

5. FDKP microparticles according to claim 4, wherein said trans isomer content is from about 50% to about 65%.

6. FDKP microparticles according to claim 4, wherein said trans isomer content is from about 53% to about 63%.

7. FDKP microparticles according to claim 4, further comprising a drug or an active agent.

8. FDKP microparticles according to claim 7, wherein said drug or active agent is a peptide or protein.

9. FDKP microparticles according to claim 8, wherein said peptide is an endocrine hormone.

10. FDKP microparticles according to claim 9, wherein said endocrine hormone is insulin, parathyroid hormone, calcitonin, glucagon, glucagon-like peptide 1, oxyntomodulin, an analog or active fragment of said endocrine hormone.

11. The microparticles of claim 4, wherein the drug is present in an amount greater than 0.01 wt% of the microparticles.

12. A dry powder comprising the microparticles of claim 4.

13. A dry powder comprising the microparticles of claim 7.

14. A method of treating an endocrine-related disease or disorder comprising administering to a person in need thereof a dry powder formulation comprising fumaryl diketopiperazine (FDKP) microparticles comprising an FDKP trans isomer content of about 45% to about 65% and an endocrine hormone suitable to treat said disease or disorder.

15. The method of claim 14, wherein the endocrine hormone is insulin, parathyroid hormone, calcitonin, glucagon, glucagon-like peptide 1, oxyntomodulin, or an analog of said endocrine hormone.

16. The method of claim 14, wherein the endocrine-related disease is diabetes.

17. A method of making microparticles suitable for pulmonary administration as a dry powder comprising:

a) synthesizing an FDKP compound having an FDKP trans isomer content of about 45% to about 65%;

b) dissolving the FDKP compound in a solution having a basic pH to form an FDKP solution;

c) providing a solution of a volatile acid, and

d) mixing the solutions together in a high-shear mixer to produce said microparticles in a suspension.

18. The method of claim 17, further comprising determining the trans isomer content of the FDKP.

19. The method of claim 18, wherein the step of determining the trans isomer content of the FDKP is performed using high pressure liquid chromatography.

20. The method of claim 17, further comprising mixing said microparticles with a solution comprising a drug.

21. The method of claim 17, wherein the drug is an endocrine hormone.

22. The method of claim 21, wherein the drug is insulin, parathyroid hormone, calcitonin, glucagon, glucagon-like peptide 1, oxyntomodulin, or an analog of said drug.

23. A method for synthesizing a diketopiperazine having a trans isomer content of about 45% to about 65% comprising:

a) saponifying an ester of a diketopiperazine in a mixture of water and a water-miscible solvent at a basic pH; and

b) recrystallizing the diketopiperazine in a reaction mixture comprising trifluoroacetic acid and glacial acid at a resultant ratio ranging from about 0.4 to about 0.7.

24. The method of claim 23, wherein the water-miscible solvent is an alcohol, tetrahydrofuran, dioxane, and acetonitrile.

25. The method of claim 24, wherein the alcohol is methanol, ethanol, or isopropanol.

26. The method of claim 25, wherein the methanol is in a water:methanol ratio ranging from 1:1 to about 3:1.

27. The method of claim 23, further comprising the step of determining the trans isomer content of the diketopiperazine.

28. The method of claim 23, wherein the diketopiperazine is of the formula 2,5-diketo-3,6-bis(N-X-4-aminobutyl)piperazine, wherein X is selected from the group consisting of fumaryl, succinyl, maleyl, and glutaryl.

29. The method of claim 23, wherein the diketopiperazine is 2,5-diketo-3,6-bis(N-fumaryl-4-aminobutyl)piperazine.

30. The method of claim 23, wherein the reaction mixture in the recrystallizing step is held for a period of about 4 hours or greater than 4 hours.