WHAT IS CLAIMED IS:

1. A method of making microcrystalline fumaryl diketopiperazine (FDKP) particles, each of the FDKP partcles having a substantially hollow spherical structure, the structure comprising a shell having FDKP crystallites that do not self-assemble, the method comprising the steps of:

dissolving FDKP in aqueous ammonia to form a first solution;

feeding the first solution and a second solution comprising acetic acid concurrently to a high shear mixer under high pressure of about 2,000 psi;

homogenizing a mixture of the first solution and the second solution to form a precipitate of microcrystalline FDKP in suspension;

concentrating and washing the precipitate with deionized water; and

spray-drying the precipitate to form a dry powder of microcrystalline FDKP particles.

2. The method of claim 1 further comprising the step of adding a third solution comprising one or more active ingredients to the mixture of the first solution and the second solution.

3. The method of claim 2 wherein the one or more active ingredients is any one or any combination of the following: a peptide, a protein, a nucleic acid molecule, and a small organic molecule.

4. The method of claim 3 wherein the peptide is an endocrine hormone.

5. The method of claim 4 wherein the endocrine hormone is any one of the following: insulin, parathyroid hormone, calcitonin, glucagon, glucagon-like peptide 1, oxyntomodulin, peptide YY, leptin, and an analog of the endocrine hormone.

61. A ~~crystalline diketopiperazine~~ composition comprising a plurality of microcrystalline FDKP particles substantially uniform in size, each of the plurality of microcrystalline FDKP particles having a substantially hollow spherical structure, and wherein ~~and comprising~~ the structure comprises a shell, and the shell ~~comprising~~ comprises FDKP crystallites ~~of the diketopiperazine~~ that do not self-assemble~~, wherein the particles have a volumetric median geometric diameter less than 5 µm~~.

72. The ~~crystalline diketopiperazine~~ composition of claim 61, wherein up to 92% of the microcrystalline FDKP particles have a volumetric median geometric diameter of < 5.8 µm.

8. The composition of claim 6 wherein the microcrystalline FDKP particles have a volumetric median geometric diameter of < 5 µm.

93. The ~~crystalline diketopiperazine~~ composition of any one of claims 6 to 8 ~~1,~~ wherein the microcrystalline FDKP particles further comprises one or more active ingredients.

104. The ~~crystalline diketopiperazine~~ composition of claim 93, wherein the one or more active ingredients is any one or any combination of the following: a peptide, a protein, a nucleic acid molecule, ~~or~~ and a small organic molecule.

115. The ~~crystalline diketopiperazine~~ composition of claim 104, wherein the peptide is an endocrine hormone.

126. The ~~crystalline diketopiperazine~~ composition of claim 115, wherein the endocrine hormone is any one of the following: insulin, parathyroid hormone, calcitonin, glucagon, glucagon-like peptide 1, oxyntomodulin, peptide YY, leptin, ~~or~~ and an analog of ~~said~~ the endocrine hormone.

~~7. The crystalline diketopiperazine composition of claim 1 , 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, malonyl, and glutaryl, or a salt thereof.~~

~~8. The crystalline diketopiperazine composition of claim 7, wherein the diketopiperazine is 3,6-bis(N-fumaryl-4-aminobutyl)-2,5- diketopiperazine.~~

13. The composition of claim 10 for use in the treatment of a disease or a disorder.

14. Use of the composition of claim 12 in the manufacture of a medicament for treating hyperglycemia and/or diabetes in a patient in need of treatment.

15. A dry powder comprising the composition of claim 6.

16. The dry powder of claim 15 further comprising one or more active agents and wherein the one or more active agents is any one or any combination of the following: a peptide, a protein, a nucleic acid molecule, a small organic molecule, and an analog thereof.

17~~9~~. A method of making microcrystalline fumaryl diketopiperazine (FDKP) particles, each of the FDKP particles having a substantially hollow spherical structure, the structure comprising a shell having FDKP crystallites that do not self-assemble, the method comprising the steps of~~suitable for pulmonary administration as a dry powder comprising~~:

dissolving a FDKP salt in a water solution in an amount from about 0.2% to about 6% (w/w) to form a first solution, the water solution comprising a surfactant;

combining the first solution with a second solution comprising from about 8% to about 12% (w/w) acetic acid concurrently in a high shear mixer at an approximate pH of less than 6.0 under high pressure;

homogenizing the first solution and the second solution to form a suspension, the suspension comprising crystallites of the FDKP in the suspension, the FDKP crystallites having a bimodal distribution in particle sizes ranging from about 0.05 µm to about 10 µm in diameter;

~~a) forming diketopiperazine particles in a suspension having a bimodal distribution in the particle sizes which range from about 0.05 µm to about 10 µm;~~

~~b)~~ atomizing the suspension using a spray dryer under an air or gas stream, and

~~c)~~ reforming the FDKP particles by spray-drying into a dry powder, the dry powder comprising the microcrystalline ~~diketopiperazine~~ FDKP particles ~~having a substantially hollow spheres~~.

18~~10~~. The method of claim 17 ~~9~~, wherein a first peak of particles of the bimodal distribution in particle sizes has an average of about 0.2 µm to about 2.4 µm and a second peak of particles of the bimodal distribution in particle sizes has an average size of about 2.1 µm to about 2.4 µm~~;~~.

~~11. The method of claim 9, wherein the diketopiperazine is of the formula 3,6-bis(N-X-4-aminobutyl)-2,5-diketopiperazine, wherein X is selected from the group consisting of fumaryl, succinyl, maleyl, malonyl, and glutaryl.~~

~~12. The method of claim 11, wherein the diketopiperazine is 3,6-bis(N-fumaryl-4-aminobutyl)-2,5-diketopiperazine.~~

19~~13~~. The method of claim 17~~9~~ or claim 18, further comprising the step of adding a third solution comprising one or more active agents to the suspension, prior to the step of atomizing the suspension ~~the suspension in step a)~~.

~~14. The method of claim 9, further comprising the step of adding a surfactant to the solution or suspension.~~

20~~15~~. The method of any one of claim~~s 14~~ 17 to 19, wherein the surfactant is polysorbate 80.

~~16. The composition of claim 1, wherein composition further comprises polysorbate 80.~~

21~~17~~. The method of claim ~~13~~ 19, wherein the one or more active agent is any one or any combination of the following: a peptide, a protein, a nucleic acid molecule, ~~or~~ and a small organic molecule.

22~~18~~. The method of claim ~~17~~ 21, wherein the peptide is an endocrine hormone.

23~~19~~. The method of claim ~~18~~22, wherein the endocrine hormone is any one of the following: insulin, parathyroid hormone, calcitonin, glucagon, glucagon-like peptide 1, oxyntomodulin, peptide YY, leptin, ~~or~~and an analog of ~~said~~ the endocrine hormone.

24~~20~~. The method of any one of claims ~~9 or 1~~ 17 to 23, wherein the ~~diketopiperazine~~ FDKP salt is any one of the following: a disodium, magnesium, lithium, calcium ~~or~~ and potassium salt of the ~~diketopiperazine~~ FDKP.

~~21. A method for making a dry powder composition, comprising:~~

~~dissolving a diketopiperazine salt in water comprising a surfactant in an amount from about 0.2% to about 6% (w/w) to form a first solution;~~

~~combining the first solution with a second solution comprising from about 8% to about 12% (w/w) acetic acid concurrently in a high shear mixer at an approximate pH of less than 6.0 under high pressure;~~

~~homogenizing the first solution and second solution to form a suspension comprising crystallites of the diketopiperazine in the suspension, wherein the suspension has a bimodal distribution of crystallites having particle sizes ranging from about 0.05 µm to about 10 µm in diameter;~~

~~atomizing the suspension under an air or gas stream; and~~

~~reforming the particles by spray-drying into a dry powder comprising the microcrystalline particles having substantially hollow spheres.~~

25~~22~~. The method of any one of claims 17~~21~~ to 24, wherein the step of atomizing the suspension further comprises the step of utilizing an external mixing 2-fluid nozzle into a spray-dryer fitted with a high efficiency cyclone separator under nitrogen gas.

~~23. The crystalline diketopiperazine composition of claim 4 for use in the treatment of a disease or disorder.~~

~~24. Use of the crystalline diketopiperazine composition of claim 6 in the manufacture of a medicament for treating hyperglycemia and/or diabetes in a patient in need of treatment.~~

~~25. A dry powder comprising the crystalline diketopiperazine composition of claim 1.~~

~~26. The dry powder of claim 25, further comprising one or more active agents and wherein the one or more active agents is a peptide, a protein, a nucleic acid molecule, or a small organic molecule, or an analog thereof.~~