WHAT IS CLAIMED IS:

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

2. The crystalline diketopiperazine composition of claim 1, wherein up to 92% of the microcrystalline particles have a volumetric median geometric diameter of ≤ 5.8 μm.

3. The crystalline diketopiperazine composition of claim 1, wherein the microcrystalline particles further comprise one or more active ingredients.

4. The crystalline diketopiperazine composition of claim 3, wherein the one or more active ingredients is a peptide, a protein, a nucleic acid molecule, or a small organic molecule.

5. The crystalline diketopiperazine composition of claim 4, wherein the peptide is an endocrine hormone.

6. The crystalline diketopiperazine composition of claim 5, wherein the endocrine hormone is insulin, parathyroid hormone, calcitonin, glucagon, glucagon-like peptide 1, oxyntomodulin, peptide YY, leptin, or an analog of said 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 (bis—3,6-(N-fumaryl-4-aminobutyl)-2,5- diketopiperazine.

9. A method of making microcrystalline diketopiperazine particles suitable for pulmonary administration as a dry powder comprising:

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

10. The method of claim 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 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 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.

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

13. The method of claim 9, further comprising the step of adding a solution comprising one or more active agents to the suspension in step a).

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

15. The method of claim 14, wherein the surfactant is polysorbate 80.

16. The method of claim 13, wherein the one or more active agent is a peptide, a protein, a nucleic acid molecule, or a small organic molecule.

17. The method of claim 16, wherein the peptide is an endocrine hormone.

18. The method of claim 17, wherein the endocrine hormone is insulin, parathyroid hormone, calcitonin, glucagon, glucagon-like peptide 1, oxyntomodulin, peptide YY, leptin, or an analog of said endocrine hormone.

19. The method of claims 9 or 11, wherein the diketopiperazine is a disodium, magnesium, lithium, calcium or potassium salt of the diketopiperazine.

20. 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.

21. The method of claim 19, wherein atomizing the suspension comprises utilizing an external mixing 2-fluid nozzle into a spray-dryer fitted with a high efficiency cyclone separator under nitrogen gas.

22. A method of treating a disease or disorder comprising, administering to a subject in need of treatment the crystalline diketopiperazine composition of claim 4.

23. A method of treating hyperglycemia and/or diabetes comprising administering to a patient in need of treatment the crystalline diketopiperazine composition of claim 6.

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

25. The dry powder of claim 24, 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.

WHAT IS CLAIMED IS:

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

2. The crystalline diketopiperazine composition of claim 1, wherein up to 92% of the microcrystalline particles have a volumetric median geometric diameter of < 5.8 μm.

3. The crystalline diketopiperazine composition of claim 1, wherein the microcrystalline particles further comprise one or more active ingredients.

4. The crystalline diketopiperazine composition of claim 3, wherein the one or more active ingredients is a peptide, a protein, a nucleic acid molecule, or a small organic molecule.

5. The crystalline diketopiperazine composition of claim 4, wherein the peptide is an endocrine hormone.

6. The crystalline diketopiperazine composition of claim 5, wherein the endocrine hormone is insulin, parathyroid hormone, calcitonin, glucagon, glucagon-like peptide 1, oxyntomodulin, peptide YY, leptin, or an analog of said endocrine hormone.

7. The crystalline diketopiperazine composition of claim 1, 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, 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.

9. A method of making microcrystalline diketopiperazine particles suitable for pulmonary administration as a dry powder comprising:

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

10. The method of claim 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 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.

13. The method of claim 9, further comprising the step of adding a solution comprising one or more active agents to the suspension in step a).

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

15. The method of claim 14, wherein the surfactant is polysorbate 80.

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

17. The method of claim 13, wherein the one or more active agent is a peptide, a protein, a nucleic acid molecule, or a small organic molecule.

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

19. The method of claim 18, wherein the endocrine hormone is insulin, parathyroid hormone, calcitonin, glucagon, glucagon-like peptide 1, oxyntomodulin, peptide YY, leptin, or an analog of said endocrine hormone.

20. The method of claims 9 or 1, wherein the diketopiperazine is a disodium, magnesium, lithium, calcium or potassium salt of the diketopiperazine.

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.

22. The method of claim 21, wherein atomizing the suspension comprises 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 a 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.