Claims

1. A pharmaceutical composition deliverable from a metered dose inhaler, the pharmaceutical composition comprising:

a plurality of a first species of active agent particle;

a plurality of a second species of active agent particle;

a plurality of a third species of active agent particle;

a plurality of a fourth species of active agent particle;

a plurality of phospholipid particles comprising perforated microstructures; and

a pharmaceutically acceptable propellant;

wherein the first, second, third and fourth species of active agents are each independently selected from a long-acting muscarinic antagonist (LAMA), a long-acting β2-agonists (LABA), a short-acting beta-agonists (SABA), an inhaled corticosteroid (ICS), and a non-corticosteroid anti-inflammatory agent.

2. The pharmaceutical composition according to claim 2, wherein:

the LAMA is selected from glycopyrrolate, dexpirronium, tiotropium, trospium, aclidinium, umeclidinium, and darotropium; or a pharmaceutically acceptable salt or solvate thereof;

the LABA is selected from bambuterol, clenbuterol, formoterol, salmeterol, carmoterol, milveterol, indacaterol, vilanterol, and saligenin- or indole-containing and adamantyl-derived β_2 agonists; or a pharmaceutically acceptable salt or solvate thereof;

the SABA is selected from bitolterol, carbuterol, fenoterol, hexoprenaline, isoprenaline (isoproterenol), levosalbutamol, orciprenaline (metaproterenol), pirbuterol, procaterol, rimiterol, albuterol (salbutamol), terbutaline, tulobuterol, reproterol, and epinephrine; or a pharmaceutically acceptable salt or solvate thereof;

the ICS is selected from beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, methylprednisolone, mometasone, prednisone and triamcinolone; or a pharmaceutically acceptable salt or solvate thereof; and

the non-corticosteroid anti-inflammatory agent is selected from roflumilast, apremilast, crisaborole, ruxolitinib, tofacitinib, oclacitinib, baricitinib, peficitinib, fedratinib, and upadacitinib; or a pharmaceutically acceptable salt or solvate thereof.

3. The pharmaceutical composition according to claim 1 or 2, wherein the LAMA is glycopyrrolate or a pharmaceutically acceptable salt or solvate thereof.

4. The pharmaceutical composition according to any one of claims 1 to 3, wherein the LABA is formoterol or a pharmaceutically acceptable salt or solvate thereof.

5. The pharmaceutical composition according to any one of claims 1 to 4, wherein the SABA is albuterol or a pharmaceutically acceptable salt or solvate thereof.

6. The pharmaceutical composition according to any one of claims 1 to 5, wherein the ICS is budesonide or a pharmaceutically acceptable salt or solvate thereof.

7. The pharmaceutical composition according to any one of claims 1 to 6, wherein the non-corticosteroid anti-inflammatory agent is roflumilast or a pharmaceutically acceptable salt or solvate thereof.

8. The pharmaceutical composition according to any one of claims 1 to 7, wherein the LAMA is present at a concentration in the range of about 0.04 mg/mL to about 2.25 mg/mL.

9. The pharmaceutical composition according to any one of claims 1 to 8, wherein the LABA is present at a concentration in the range of about 0.01 mg/mL to about 1 mg/mL.

10. The pharmaceutical composition according to any one of claims 1 to 9, wherein the ICS is present at a concentration in the range of about 0.1 mg/mL to about 20 mg/mL.

11. The pharmaceutical composition according to any one of claims 1 to 10, wherein the SABA is present at a concentration in the range of about 0.1 mg/mL to about 20 mg/mL.

12. The pharmaceutical composition according to any one of claims 1 to 11, wherein the non-corticosteroid anti-inflammatory agent is present at a concentration in the range of about 0.03 mg/mL to about 3 mg/mL

13. The pharmaceutical composition according to any one of claims 1 to 12, wherein the perforated microstructures comprise 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC) and calcium chloride.

14. The pharmaceutical composition according to any one of claims 1 to 13, wherein the phospholipid particles are present at a concentration in the range of about 0.1 mg/mL to about 10 mg/mL.

15. The pharmaceutical composition according to any one of claims 1 to 14, comprising:

a plurality of glycopyrrolate particles;
a plurality of formoterol particles;
a plurality of budesonide particles;
a plurality of roflumilast particles; and
a plurality of phospholipid particles comprising perforated microstructures; and
a pharmaceutically acceptable propellant.

16. The pharmaceutical composition according to any one of the preceding claims, wherein the glycopyrrolate particles are in the propellant at a concentration sufficient to provide a delivered dose of glycopyrrolate per actuation of the metered dose inhaler selected from between about 5 µg and about 50 µg per actuation, between about 2 µg and about 25 µg per actuation, and between about 6 µg and about 15 µg per actuation.

17. The pharmaceutical composition according to any one of the preceding claims, wherein the glycopyrrolate particles comprise micronized and crystalline glycopyrronium bromide.

18. The pharmaceutical composition according to any one of the preceding claims, wherein the formoterol particles are included in the composition at a concentration

sufficient to provide a delivered dose of formoterol selected from between about 1 µg and about 30 µg, between about 0.5 µg and about 10 µg, between about 2 µg and 5 µg, between about 3 µg and about 10 µg, between about 5 µg and about 10 µg, and between 3 µg and about 30 µg per actuation of the metered dose inhaler.

19. The pharmaceutical composition according to any one of the preceding claims, wherein the formoterol particles comprise micronized and crystalline formoterol fumarate.

20. The pharmaceutical composition according to any one of the preceding claims, wherein the budesonide particles are included in the composition at a concentration sufficient to provide a delivered dose of budesonide selected from between about 50 µg and about 400 µg, between about 20 µg and about 600 µg, between about 30 µg and 100 µg, between about 50 µg and about 200 µg, and between about 150 µg and about 350 µg per actuation of the metered dose inhaler.

21. The pharmaceutical composition according to any one of the preceding claims, wherein the budesonide particles comprise micronized budesonide.

22. The pharmaceutical composition according to any one of the preceding claims, wherein the roflumilast particles comprise micronized and crystalline roflumilast.

23. The pharmaceutical composition according to any one of the preceding claims, wherein the roflumilast particles are included in the composition at a concentration sufficient to provide a delivered dose of budesonide selected from between about 1 µg and about 100 µg, about 5 µg and about 80 µg, about 5 µg and about 50 µg, about 5 µg and about 25 µg, about 10 µg and 25 µg, about 50 µg and about 400 µg, between about 20 µg and about 600 µg, between about 30 µg and 100 µg, between about 50 µg and about 200 µg, and between about 150 µg and about 350 µg per actuation of the metered dose inhaler.

24. The pharmaceutical composition according to any one of the preceding claims, wherein the phospholipid particles are included in the composition at a concentration

sufficient to provide a delivered dose of the phospholipid particles selected from between about 50 µg and about 400 µg.

25. The pharmaceutical composition according to any of claims 1 to 24, wherein the pharmaceutically acceptable propellant is selected from HFA, HFC, HFO, and a combination thereof.

26. A metered dose inhaler comprising a canister with an outlet valve including an actuator for dispensing a metered amount of a pharmaceutical composition according to any one of claims 1 through 25, wherein the canister contains the pharmaceutical composition.

27. The metered dose inhaler according to claim 26, wherein the outlet valve comprises a neck gasket and at least one seat gasket; and the neck gasket or the at least one seat gasket is composed of bromobutyl material.

28. The metered dose inhaler according to claim 26 or 27, exhibiting less than about 10%, 9%, 8%, 7%, 6%, or 5% reduced shot weight per actuation throughout emptying of the canister.

29. The metered dose inhaler according to any one of claims 26 to 28, exhibiting less than about 1.0%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% weight loss at 25°C/60% RH per year.

30. The metered dose inhaler according to any one of claims 26 to 29, which exhibits a delivered dose uniformity (DDU) for the pharmaceutical formulation selected from a DDU of ± 20%, or better, a DDU of ± 15%, or better, and a DDU of ± 10%, or better, throughout emptying of the canister.

31. Use of a pharmaceutical composition according to any one of claims 1 to 25 in the manufacture of a medicament for treating a pulmonary disease or disorder in a patient, wherein the pharmaceutical composition is to be administered to the patient by

actuating a metered dose inhaler; wherein the metered dose inhaler contains the pharmaceutical composition.

32. The use according to claim 31, wherein the pulmonary disease or disorder is asthma or COPD.

33. The use according to claim 31 or 32, wherein the metered dose inhaler is described according to any one of the claims 21 to 25.

34. The pharmaceutical composition according to any one of claims 1 to 25 for use in therapy.

35. The pharmaceutical composition according to any one of claims 1 to 25 for use in the treatment of a pulmonary disease or disorder.