COMPOSITIONS, METHODS & SYSTEMS FOR RESPIRATORY DELIVERY OF THREE OR MORE ACTIVE AGENTS

Technical Field

[0001] The present disclosure relates generally to compositions, methods and systems suitable for respiratory delivery of three or more active agents. In certain embodiments, the present disclosure relates to compositions, methods, and systems suitable for respiratory delivery of three active agents, wherein the active agents include a long-acting muscarinic antagonist (LAMA), a long-acting β_2 adrenergic agonist (LABA), and an inhaled corticosteroid (ICS).

Summary

[0001A] In one aspect, the present invention provides a suspension composition for respiratory delivery of a long-acting muscarinic antagonist (LAMA), a long-acting β2 adrenergic agonist (LABA), and an inhaled corticosteroid (ICS) from a metered dose inhaler (MDI) to a patient, the composition comprising: a suspension medium comprising a pharmaceutically acceptable propellant; a first species of respirable active agent particles comprising the LABA active agent; a second species of respirable active agent particles comprising the LAMA active agent; a third species of respirable active agent particles comprising the ICS active agent; and a plurality of respirable suspending particles, wherein the plurality of suspending particles are formed of a material that is substantially insoluble in the suspension medium, and the ICS active agent and LABA active agent are included in the suspension composition such that the ICS:LABA delivered dose ratio is at least 5:1 per actuation of the MDI.

Brief Description of the Drawings

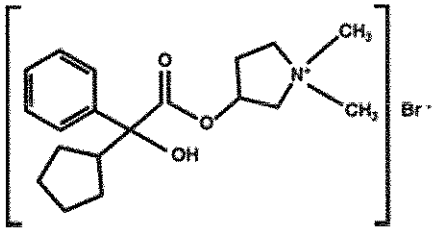
[0002] Figure 1 provides cascade impaction data for mometasone furoate delivered from three different triple cosuspension compositions described in Example 1.

[0003] Figure 2 provides a graph illustrating the fine particle mass (FPM) of mometasone furoate, glycopyrrolate, and formoterol fumarate delivered from three different triple cosuspension compositions described in Example 1.

[0004] Figure 3 provides cascade impaction data for mometasone furoate, glycopyrrolate, and formoterol fumarate delivered from cosuspenion compositions described in Example 1, with Figure 3A providing cascade impaction data for the composition formulated to provide a delivered dose of 100 µg mometasone furoate per MDI actuation, Figure 3B providing cascade impaction data for the composition formulated to provide a delivered dose of 200 µg mometasone furoate per MDI actuation, and Figure 3C providing cascade impaction data for the composition formulated to provide a delivered dose of 300 µg mometasone furoate per MDI actuation.

[0005] Figure 4 provides cascade impaction data illustrating dose linearity for each of the mometasone furoate, glycopyrrolate, and formoterol fumarate actives delivered from three different triple cosuspension compositions described in Example 1, with Figure 4A providing cascade impaction data for mometasone furoate delivered from each of the three compositions, Figure 4B

or amine salts, or as acid addition salts), esters or solvate (hydrates). Suitable counter ions of glycopyrronium include, for example, fluoride, chloride, bromide, iodide, nitrate, sulfate, phosphate, formate, acetate, trifluoroacetate, propionate, butyrate, lactate, citrate, tartrate, malate, maleate, succinate, benzoate, p-chlorobenzoate, diphenyl-acetate or triphenylacetate, o-hydroxybenzoate, p-hydroxybenzoate, 1-hydroxynaphthalene-2-carboxylate, 3-hydroxynaphthalene-2-carboxylate, methanesulfonate and benzenesulfonate. In particular embodiments, the compositions described herein include the bromide salt of glycopyrronium, namely (3-[(cyclopentylhydroxyphenylacetyl)oxy]-1, 1-dimethyl-pyrrolidium, bromide). The bromide salt of glycopyrronium is commonly referred to as glycopyrrolate. Glycopyrrolate is commercially available and can be prepared according to the procedures set out in U.S. Pat. No. 2,956,062, the contents of which are incorporated herein by reference. The structure of glycopyrronium bromide is shown below:



[0073] Where the compositions described herein include glycopyrrolate, in certain embodiments, the compositions may include sufficient glycopyrrolate to provide a delivered dose selected from between about 1 µg and about 100 µg, about 15 µg and about 100 µg, about 5µg and about 80 µg, and about 2 µg and about 40 µg per actuation of an MDI. In other such embodiments, the formulations include sufficient glycopyrrolate to provide a delivered dose selected from up to about 100 µg, up to about 80 µg, up to about 40 µg, up to about 20 µg, up to about 10 µg per actuation, up to about 5 µg of an MDI. In yet further embodiments, the formulations include sufficient glycopyrrolate to provide a delivered dose selected from about 2 µg, 5 µg, 9 µg, 18 µg, 36 µg and 72 µg per actuation of the MDI.

[0074] The compositions described herein include an ICS. The ICS can be selected, for example, from beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, methyl-prednisolone, mometasone, prednisone and

between about 2.5:1 and about 75:1, between about 2.5:1 and about 50:1, between about 2.5:1 and about 35:1, between about 2.5:1 and about 25:1, between about 2.5:1 and about 15:1, between about 2.5:1 and about 10:1, and between about 2.5:1 and about 5:1. In yet further embodiments, the ratio of the total mass of the suspending particles to the total mass of the active agent particles may be selected from between about 5:1 and about 75:1, between about 5:1 and about 50:1, between about 5:1 and about 35:1, between about 5:1 and about 25:1, between about 5:1 and about 15:1, and between about 5:1 and about 10:1.

[0082] Phospholipids from both natural and synthetic sources may be used in preparing suspending particles suitable for use in the compositions described herein. In particular embodiments, the phospholipid chosen will have a gel to liquid crystal phase transition of greater than about 40°C. Exemplary phospholipids are relatively long chain (*i.e.*, C_{16}-C_{22}) saturated lipids and may comprise saturated phospholipids, such as saturated phosphatidylcholines having acyl chain lengths of 16 C or 18 C (palmitoyl and stearoyl). Exemplary phospholipids include phosphoglycerides such as dipalmitoylphosphatidylcholine, disteroylphosphatidylcholine, diarachidoylphosphatidylcholine, dibehenoylphosphatidylcholine, diphosphatidyl glycerol, short-chain phosphatidylcholines, long-chain saturated phosphatidylethanolamines, long-chain saturated phosphatidylserines, long-chain saturated phosphatidylglycerols, and long-chain saturated phosphatidylinositols. In specific embodiments, the suspending particles are formed using 1,2 distearoyl-sn-glycero-3-phosphocholine (DSPC) as a phospholipid material. In such embodiments, the ~~DPSC~~ DSPC suspending particles may additionally include calcium chloride ($CaCl_2$). Methods suitable for preparing suspending particles as described herein using DSPC are described, for example, in US Patent No. 8,324,266 and in *Cosuspensions of microcrystals and engineered microparticles for uniform and efficient delivery of respiratory therapeutics from pressurized metered dose inhalers*, Vehring, R, Lechuga-Ballesteros, D, Joshi, V, Noga, B, Dwivedi, SK: *Langmuir* 2012, 28(42):15015-23. Additional excipients are disclosed in International Patent Publication No. WO 96/32149 and U.S. Patent Nos. 6,358,530, 6,372,258 and 6,518,239.

wherein the composition is formulated to provide a delivered dose less than or equal to 5.0 µg of the pharmaceutically acceptable salt, ester, or isomer of formoterol per actuation of the MDI,

wherein the composition is formulated to provide a delivered dose less than or equal to 7.5 µg of the pharmaceutically acceptable salt, ester, or isomer of glycopyrronium per actuation of the MDI, and

wherein the ICS:LABA delivered dose ratio is at least 30:1 and the ICS:LAMA delivered dose ratio is at least 20:1.

[00107] In each of the compositions described herein, including in compositions according to the twelve example compositions, the pharmaceutically acceptable salt, ester, or isomer of formoterol may be formoterol fumarate, and the pharmaceutically acceptable salt, ester, or isomer of glycopyrronium may be the bromide salt of glycopyrronium, namely (3-[(cyclopentylhydroxyphenylacetyl)oxy]-1, 1-dimethyl-pyrrolidium, bromide).

[00108] The compositions described herein, including compositions according to the twelve example compositions, may be provided with an amount of suspending particles that provides a desired ratio of the total mass of the suspending particles to the total mass of the active agent particles. For instance, where the example compositions described herein are formulated to provide an ICS:LABA delivered dose ratio of at least 20:1 and an ICS:LAMA delivered dose ratio of at least 15:1, the ratio of the total mass of the suspending particles to the total mass of the active agent particles may be selected from between about 0.5:1 and about 5:1, such as between about 0.5:1 and about 3:1, between about 0.5:1 and about 2:1, between about 0.75:1 and about 5:1, between about 0.75:1 and about 3:1, and between about 0.75:1 and about 2:1. Alternatively, where the example compositions are formulated to provide an ICS:LABA delivered dose ratio of at least 15:1 and a ICS:LAMA delivered dose ratio of at least 10:1, the ratio of the total mass of the suspending particles to the total mass of the active agent particles may be selected from between about 1:1 and about 10:1, such as between about 1:1 and about 7.5:1, between about 1:1 and about 5:1, between about 1:1 and about 2.5:1, between about 2.5:1 and about 10:1, between about 2.5:1 and about 7.5:1, and between about 2.5:1 and 5:1. Further, where the example

compositions are formulated to provide an ICS:LABA delivered dose ratio of at least 5:1 and an ICS:LAMA delivered dose ratio of at least 5:1, the ratio of the total mass of the suspending particles to the total mass of the active agent particles may be selected from between about 2:1 and about 15:1, such as between about 1:1 and about 7.5:1, between about 1:1 and about 5:1, between about 1:1 and about 2.5:1, between about 2.5:1 and about 10:1, between about 2.5:1 and about 7.5:1, and between about 2.5:1 and 5:1.

[00109] In a specific example, a composition according to the present description includes:

(i) a suspension medium including a pharmaceutically acceptable HFA propellant;

(ii) a first species of respirable active agent particles formed using formoterol fumarate;

(iii) a second species of respirable active agent particles formed using (3-[(cyclopentylhydroxyphenylacetyl)oxy]-1, 1-dimethyl-pyrrolidium, bromide)

(iv) a third species of respirable active agent particles formed using a pharmaceutically acceptable salt, ester, or isomer of budesonide ; and

(v) a plurality of phospholipid suspending particles formed separately from each of the different species of active agent particles,

wherein the composition is formulated to provide a delivered dose of the pharmaceutically acceptable salt, ester, or isomer of formoterol that is less than or equal to 7.5 µg per actuation of the MDI and a delivered dose of the pharmaceutically acceptable salt, ester, or isomer of glycopyrronium that is less than or equal to 10 µg per actuation of the MDI,

wherein the ICS:LABA delivered dose ratio is at least 5:1 and the ICS:LAMA delivered dose ratio is at least 5:1, and

wherein the ratio of the total mass of the suspending particles to the total mass of the active agent particles may be selected from between about 2:1 and about 15:1, such as between about 1:1 and about 7.5:1, between about 1:1 and about 5:1, between about 1:1 and about 2.5:1, between about 2.5:1 and about 10:1, between about 2.5:1 and about 7.5:1, or between about 2.5:1 and 5:1.

[00110] In another specific example, a composition according to the present description includes:

(i) a suspension medium including a pharmaceutically acceptable HFA propellant;

(ii) a first species of respirable active agent particles formed using formoterol fumarate;

(iii) a second species of respirable active agent particles formed using (3-[(cyclopentylhydroxyphenylacetyl)oxy]-1, 1-dimethyl-pyrrolidium, bromide);

(iv) a third species of respirable active agent particles formed using a pharmaceutically acceptable salt, ester, or isomer of budesonide; and

(v) a plurality of phospholipid suspending particles formed separately from each of the different species of active agent particles,

wherein the composition is formulated to provide a delivered dose of the pharmaceutically acceptable salt, ester, or isomer of formoterol that is less than or equal to 7.5 µg per actuation of the MDI and a delivered dose of the pharmaceutically acceptable salt, ester, or isomer of glycopyrronium that is less than or equal to 10 µg per actuation of the MDI,

wherein the ICS:LABA delivered dose ratio is at least 10:1 and the ICS:LAMA delivered dose ratio is at least 7.5:1, and

wherein the ratio of the total mass of the suspending particles to the total mass of the active agent particles may be selected from between about 2:1 and about 15:1, such as between about 1:1 and about 7.5:1, between about 1:1 and about 5:1, between about 1:1 and about 2.5:1, between about 2.5:1 and about 10:1, between about 2.5:1 and about 7.5:1, or between about 2.5:1 and 5:1.

[00111] In another specific example, a composition according to the present description includes:

(i) a suspension medium including a pharmaceutically acceptable HFA propellant; (ii) a first species of respirable active agent particles formed using formoterol fumarate;

(iii) a second species of respirable active agent particles formed using (3-[(cyclopentylhydroxyphenylacetyl)oxy]-1, 1-dimethyl-pyrrolidium, bromide);

(iv) a third species of respirable active agent particles formed using a pharmaceutically acceptable salt, ester, or isomer of budesonide ; and

(v) a plurality of phospholipid suspending particles formed separately from each of the different species of active agent particles,

wherein the composition is formulated to provide a delivered dose of the pharmaceutically acceptable salt, ester, or isomer of formoterol that is less than or equal to 7.5 µg per actuation of the MDI and a delivered dose of the pharmaceutically acceptable salt, ester, or isomer of glycopyrronium that is less than or equal to 10 µg per actuation of the MDI,

wherein the ICS:LABA delivered dose ratio is at least 15:1 and the ICS:LAMA delivered dose ratio is at least 10:1, and

wherein the ratio of the total mass of the suspending particles to the total mass of the active agent particles may be selected from between about 1:1 and about 10:1, such as between about 1:1 and about 7.5:1, between about 1:1 and about 5:1, between about 1:1 and about 2.5:1, between about 2.5:1 and about 10:1, between about 2.5:1 and about 7.5:1, or between about 2.5:1 and 5:1.

[00112] In another specific example, a composition according to the present description includes:

(i) a suspension medium including a pharmaceutically acceptable HFA propellant;

(ii) a first species of respirable active agent particles formed using formoterol fumarate;

(iii) a second species of respirable active agent particles formed using (3-[(cyclopentylhydroxyphenylacetyl)oxy]-1, 1-dimethyl-pyrrolidium, bromide) ;

(iv) a third species of respirable active agent particles formed using a pharmaceutically acceptable salt, ester, or isomer of budesonide; and

(v) a plurality of phospholipid suspending particles formed separately from each of the different species of active agent particles,

wherein the composition is formulated to provide a delivered dose of the pharmaceutically acceptable salt, ester, or isomer of formoterol that is less than or equal to 7.5 µg per actuation of the MDI and a delivered dose of the

pharmaceutically acceptable salt, ester, or isomer of glycopyrronium that is less than or equal to 10 µg per actuation of the MDI,

wherein the ICS:LABA delivered dose ratio is at least 20:1 and the ICS:LAMA delivered dose ratio is at least 15:1, and

wherein the ratio of the total mass of the suspending particles to the total mass of the active agent particles may be selected from between about 0.5:1 and about 5:1, such as between about 0.5:1 and about 3:1, between about 0.5:1 and about 2:1, between about 0.75:1 and about 5:1, between about 0.75:1 and about 3:1, or between about 0.75:1 and about 2:1..

[00113] In another specific example, a composition according to the present description includes:

(i) a suspension medium including a pharmaceutically acceptable HFA propellant;

(ii) a first species of respirable active agent particles formed using formoterol fumarate;

(iii) a second species of respirable active agent particles formed using (3-[(cyclopentylhydroxyphenylacetyl)oxy]-1, 1-dimethyl-pyrrolidium, bromide);

(iv) a third species of respirable active agent particles formed using a pharmaceutically acceptable salt, ester, or isomer of budesonide; and

(v) a plurality of phospholipid suspending particles formed separately from each of the different species of active agent particles,

wherein the composition is formulated to provide a delivered dose of the pharmaceutically acceptable salt, ester, or isomer of formoterol that is less than or equal to 7.5 µg per actuation of the MDI and a delivered dose of the pharmaceutically acceptable salt, ester, or isomer of glycopyrronium that is less than or equal to 10 µg per actuation of the MDI,

wherein the ICS:LABA delivered dose ratio is at least 25:1 and the ICS:LAMA delivered dose ratio is at least 20:1, and

wherein the ratio of the total mass of the suspending particles to the total mass of the active agent particles may be selected from between about 0.5:1 and about 5:1, such as between about 0.5:1 and about 3:1, between about 0.5:1 and about 2:1, between about 0.75:1 and about 5:1, between about 0.75:1 and about 3:1, or between about 0.75:1 and about 2:1.

[00114] In another specific example, a composition according to the present description includes:

(i) a suspension medium including a pharmaceutically acceptable HFA propellant;

(ii) a first species of respirable active agent particles formed using formoterol fumarate;

(iii) a second species of respirable active agent particles formed using (3-[(cyclopentylhydroxyphenylacetyl)oxy]-1, 1-dimethyl-pyrrolidium, bromide);

(iv) a third species of respirable active agent particles formed using a pharmaceutically acceptable salt, ester, or isomer of budesonide; and

(v) a plurality of phospholipid suspending particles formed separately from each of the different species of active agent particles,

wherein the composition is formulated to provide a delivered dose of the pharmaceutically acceptable salt, ester, or isomer of formoterol that is less than or equal to 7.5 µg per actuation of the MDI and a delivered dose of the pharmaceutically acceptable salt, ester, or isomer of glycopyrronium that is less than or equal to 10 µg per actuation of the MDI,

wherein the ICS:LABA delivered dose ratio is at least 30:1 and the ICS:LAMA delivered dose ratio is at least 20:1, and

wherein the ratio of the total mass of the suspending particles to the total mass of the active agent particles may be selected from between about 0.5:1 and about 5:1, such as between about 0.5:1 and about 3:1, between about 0.5:1 and about 2:1, between about 0.75:1 and about 5:1, between about 0.75:1 and about 3:1, or between about 0.75:1 and about 2:1.

[00115] In another specific example, a composition according to the present description includes:

(i) a suspension medium including a pharmaceutically acceptable HFA propellant;

(ii) a first species of respirable active agent particles formed using formoterol fumarate;

(iii) a second species of respirable active agent particles formed using (3-[(cyclopentylhydroxyphenylacetyl)oxy]-1, 1-dimethyl-pyrrolidium, bromide);

(iv) a third species of respirable active agent particles formed using a pharmaceutically acceptable salt, ester, or isomer of budesonide; and

(v) a plurality of phospholipid suspending particles formed separately from each of the different species of active agent particles,

wherein the composition is formulated to provide a delivered dose of the pharmaceutically acceptable salt, ester, or isomer of formoterol that is less than or equal to 7.5 µg per actuation of the MDI and a delivered dose of the pharmaceutically acceptable salt, ester, or isomer of glycopyrronium that is less than or equal to 10 µg per actuation of the MDI,

wherein the ICS:LABA delivered dose ratio is at least 5:1 and the ICS:LAMA delivered dose ratio is at least 5:1, and

wherein the ratio of the total mass of the suspending particles to the total mass of the active agent particles may be selected from between about 2:1 and about 15:1, such as between about 1:1 and about 7.5:1, between about 1:1 and about 5:1, between about 1:1 and about 2.5:1, between about 2.5:1 and about 10:1, between about 2.5:1 and about 7.5:1, or between about 2.5:1 and 5:1.

[00116] In another specific example, a composition according to the present description includes:

(i) a suspension medium including a pharmaceutically acceptable HFA propellant;

(ii) a first species of respirable active agent particles formed using formoterol fumarate;

(iii) a second species of respirable active agent particles formed using (3-[(cyclopentylhydroxyphenylacetyl)oxy]-1, 1-dimethyl-pyrrolidium, bromide);

(iv) a third species of respirable active agent particles formed using a pharmaceutically acceptable salt, ester, or isomer of budesonide; and

(v) a plurality of phospholipid suspending particles formed separately from each of the different species of active agent particles,

wherein the composition is formulated to provide a delivered dose of the pharmaceutically acceptable salt, ester, or isomer of formoterol that is less than or equal to 5.0 µg per actuation of the MDI and a delivered dose of the

pharmaceutically acceptable salt, ester, or isomer of glycopyrronium that is less than or equal to 7.5 µg per actuation of the MDI,

wherein the ICS:LABA delivered dose ratio is at least 10:1 and the ICS:LAMA delivered dose ratio is at least 7.5:1, and

wherein the ratio of the total mass of the suspending particles to the total mass of the active agent particles may be selected from between about 2:1 and about 15:1, such as between about 1:1 and about 7.5:1, between about 1:1 and about 5:1, between about 1:1 and about 2.5:1, between about 2.5:1 and about 10:1, between about 2.5:1 and about 7.5:1, or between about 2.5:1 and 5:1.

[00117] In another specific example, a composition according to the present description includes:

(i) a suspension medium including a pharmaceutically acceptable HFA propellant;

(ii) a first species of respirable active agent particles formed using formoterol fumarate;

(iii) a second species of respirable active agent particles formed using (3-[(cyclopentylhydroxyphenylacetyl)oxy]-1, 1-dimethyl-pyrrolidium, bromide);

(iv) a third species of respirable active agent particles formed using a pharmaceutically acceptable salt, ester, or isomer of budesonide; and

(v) a plurality of phospholipid suspending particles formed separately from each of the different species of active agent particles,

wherein the composition is formulated to provide a delivered dose of the pharmaceutically acceptable salt, ester, or isomer of formoterol that is less than or equal to 5.0 µg per actuation of the MDI and a delivered dose of the pharmaceutically acceptable salt, ester, or isomer of glycopyrronium that is less than or equal to 7.5 µg per actuation of the MDI,

wherein the ICS:LABA delivered dose ratio is at least 15:1 and the ICS:LAMA delivered dose ratio is at least 10:1, and

wherein the ratio of the total mass of the suspending particles to the total mass of the active agent particles may be selected from between about 1:1 and about 10:1, such as between about 1:1 and about 7.5:1, between about 1:1 and about 5:1, between about 1:1 and about 2.5:1, between about 2.5:1

and about 10:1, between about 2.5:1 and about 7.5:1, or between about 2.5:1 and 5:1.

[00118] In another specific example, a composition according to the present description includes:

(i) a suspension medium including a pharmaceutically acceptable HFA propellant;

(ii) a first species of respirable active agent particles formed using formoterol fumarate ;

(iii) a second species of respirable active agent particles formed using (3-[(cyclopentylhydroxyphenylacetyl)oxy]-1, 1-dimethyl-pyrrolidium, bromide);

(iv) a third species of respirable active agent particles formed using a pharmaceutically acceptable salt, ester, or isomer of budesonide I; and

(v) a plurality of phospholipid suspending particles formed separately from each of the different species of active agent particles,

wherein the composition is formulated to provide a delivered dose of the pharmaceutically acceptable salt, ester, or isomer of formoterol that is less than or equal to 5.0 µg per actuation of the MDI and a delivered dose of the pharmaceutically acceptable salt, ester, or isomer of glycopyrronium that is less than or equal to 7.5 µg per actuation of the MDI,

wherein the ICS:LABA delivered dose ratio is at least 20:1 and the ICS:LAMA delivered dose ratio is at least 15:1, and

wherein the ratio of the total mass of the suspending particles to the total mass of the active agent particles may be selected from between about 0.5:1 and about 5:1, such as between about 0.5:1 and about 3:1, between about 0.5:1 and about 2:1, between about 0.75:1 and about 5:1, between about 0.75:1 and about 3:1, or between about 0.75:1 and about 2:1.

[00119] In another specific example, a composition according to the present description includes:

(i) a suspension medium including a pharmaceutically acceptable HFA propellant;

(ii) a first species of respirable active agent particles formed using formoterol fumarate;

(iii) a second species of respirable active agent particles formed using (3-[(cyclopentylhydroxyphenylacetyl)oxy]-1, 1-dimethyl-pyrrolidium, bromide) ;

(iv) a third species of respirable active agent particles formed using a pharmaceutically acceptable salt, ester, or isomer of budesonide ; and

(v) a plurality of phospholipid suspending particles formed separately from each of the different species of active agent particles,

wherein the composition is formulated to provide a delivered dose of the pharmaceutically acceptable salt, ester, or isomer of formoterol that is less than or equal to 5.0 µg per actuation of the MDI and a delivered dose of the pharmaceutically acceptable salt, ester, or isomer of glycopyrronium that is less than or equal to 7.5 µg per actuation of the MDI,

wherein the ICS:LABA delivered dose ratio is at least 25:1 and the ICS:LAMA delivered dose ratio is at least 20:1, and

wherein the ratio of the total mass of the suspending particles to the total mass of the active agent particles may be selected from between about 0.5:1 and about 5:1, such as between about 0.5:1 and about 3:1, between about 0.5:1 and about 2:1, between about 0.75:1 and about 5:1, between about 0.75:1 and about 3:1, or between about 0.75:1 and about 2:1.

[00120] In another specific example, a composition according to the present description includes:

(i) a suspension medium including a pharmaceutically acceptable HFA propellant;

(ii) a first species of respirable active agent particles formed using formoterol fumarate;

(iii) a second species of respirable active agent particles formed using (3-[(cyclopentylhydroxyphenylacetyl)oxy]-1, 1-dimethyl-pyrrolidium, bromide);

(iv) a third species of respirable active agent particles formed using a pharmaceutically acceptable salt, ester, or isomer of budesonide; and

(v) a plurality of phospholipid suspending particles formed separately from each of the different species of active agent particles,

wherein the composition is formulated to provide a delivered dose of the pharmaceutically acceptable salt, ester, or isomer of formoterol that is less than or equal to 5.0 µg per actuation of the MDI and a delivered dose of the

pharmaceutically acceptable salt, ester, or isomer of glycopyrronium that is less than or equal to 7.5 µg per actuation of the MDI,

wherein the ICS:LABA delivered dose ratio is at least 30:1 and the ICS:LAMA delivered dose ratio is at least 20:1, and

wherein the ratio of the total mass of the suspending particles to the total mass of the active agent particles may be selected from between about 0.5:1 and about 5:1, such as between about 0.5:1 and about 3:1, between about 0.5:1 and about 2:1, between about 0.75:1 and about 5:1, between about 0.75:1 and about 3:1, or between about 0.75:1 and about 2:1.

[00121] In each of the twelve example compositions and in each of the compositions provided by the specific examples recited herein, the compositions can be formulated to provide a desired delivered dose of the formoterol, glycopyrronium, and budesonide active agents. For example, compositions according to the twelve example compositions and the other specific examples recited herein can be formulated to provide a delivered dose of formoterol, glycopyrronium, and budesonide selected from the combinations of delivered doses defined herein for compositions including budesonide as the ICS active agent, including, *e.g.*, combinations of delivered doses selected from those defined in preceding paragraph [00078].

[00122] In each of the compositions described herein, including in each of the twelve example compositions and in each of the compositions provided by the specific examples recited herein, the suspending particles may be provided by or formed using any of the phospholipid materials and associated methods described herein, and the formoterol, glycopyrronium, and budesonide active agents utilized in the three species of active agent particles may be selected from any of the ~~the~~ formoterol, glycopyrronium, and budesonide materials described herein (including any combinations thereof). Further, in each of the compositions described herein, each of the active agent particle species and the suspending particles may be selected and/or formulated to be substantially insoluble in the suspension medium. If desired, the materials forming one, more or all of the three different species of active agent particles and the suspending particles may be selected from material(s) that is(are) substantially

Example 2

[00126] Exemplary triple cosuspension compositions deliverable from an MDI were prepared according to the present description. The compositions included a combination of budesonide (BD), glycopyrrolate (GPBr) and formoterol fumarate (FF), with each being provided as a micronized, crystalline material. The micronized BD, GPBr, and FF materials were co-suspended in HFA propellant with suspending particles (SP). The SP used in each MDI cosuspension formulation were spray-dried porous particles formed of 1,2 distearoyl-sn-glycero-3-phosphocholine (DSPC) and calcium chloride ($CaCl_2$).

[00127] Three different triple cosuspension compositions were prepared, with each of the compositions prepared to provide a delivered dose of 9 µg GPBr per MDI actuation and 4.8 µg FF per MDI actuation. The delivered dose of 9 µg GPBr provided a delivered dose of glycopyrronium (GP) of 7.2 µg per MDI actuation. Two of the triple cosuspensions, labeled ~~BFG1~~ BGF1 and BGF2, were formulated to provide a delivered dose of 160 µg BD per MDI actuation. A third triple cosuspension composition was formulated to provide a delivered dose of 40 µg BD per MDI actuation. Information regarding the materials cosuspended within the HFA propellant in each of the three triple cosuspension compositions is provided in Table 1.

[00128] In addition to the exemplary triple cosuspension compositions, a mono cosuspension composition including only BD as an active agent (BD Mono), a dual cosuspension including a combination of GPBr and FF (GFF), and a dual cosuspension including a combination of BD and FF (BFF) were prepared. Information regarding the materials cosuspended in the HFA propellant for the BD Mono, GFF, and BFF compositions is provided in Table 1. The BD Mono compostion was formulated to provide a delivered dose of 160 µg BD per MDI actuation. The GFF composition was formulated to provide a delivered dose of 7.2 µg GP per MDI actuation and a delivered dose of 4.8 µg FF per MDI actuation. The BFF composition was formulated to provide a delivered dose of 160 µg BD per MDI actuation and a delivered dose of 4.8 µg FF per MDI actuation.

distribution of the micronized, crystalline BD material included in BGF1 was relatively coarse (X_{90} of 3.34 µm, based on primary particle size as measured by Sympatec) when compared to that of the BD material included in ~~BFG2~~ BGF2 (X_{90} of 2.99 µm, based on primary particle size as measured by Sympatec). The concentration of SP included in BGF1 and BGF2 was 3.0 mg/ml, while that of the GFF cosuspension was 5.85 mg/ml, and the GFF cosuspension contained no BD, while the BGF1 and BGF2 compositions were both formulated to provide a delivered dose of 160 µg BD per MDI actuation. Despite differences in BD particle size distribution, and significant differences in both the concentration of BD and the concentration of SP included in the different cosuspension compositions, no coformulation effect was observed for FF when formulated in the exemplary triple cosuspensions. As can be appreciated by reference to Figure 5, the cascade impaction profiles for FF and the FPM, MMAD and FPF for FF were nearly identical for each of the BGF1, BGF2, and GFF compositions.

[00132] Figure 6 provides cascade impaction profiles for BD provided by the BGF1, BGF2, and ~~BFG3~~BGF3 cosuspensions. The particle size distribution of the micronized, crystalline BD material included in BGF1 was again relatively coarse compared to that of the crystalline BD material included in ~~BFG2~~BGF2. The concentration of SP included in BGF1 and BGF2 was 3.0 mg/ml, while that of the BGF3 cosuspension was 5.85 mg/ml. Moreover, the BGF1and ~~BFG2~~BGF2 compositions provided a delivered dose of 160 µg BD per MDI actuation, while BGF3 provided a delivered dose of 40 µg BD per MDI actuation. Despite such differences among the compositions, no coformulation effect was observed for BD when formulated in the exemplary triple cosuspensions. As can be appreciated by reference to Figure 6, the cascade impaction profiles for BD and the FPM, MMAD and FPF for BD were nearly identical for each of the BGF1, BGF2, and BGF3compositions.

[00133] Figure 7 provides cascade impaction profiles for GP provided by the BGF1, BGF2, and GFF cosuspensions. Again, the particle size distribution of the micronized, crystalline BD material included in BGF1 was relatively coarse compared to that of the crystalline BD material included in ~~BFG2~~BGF2. The concentration of SP included in BGF1 and BGF2 was 3.0 mg/ml, while that of

the GFF cosuspension was 5.85 mg/ml. Moreover, BGF1 and ~~BFG2~~BGF2 provided a delivered dose of 160 µg BD per MDI actuation, while the GFF composition included no BD. Despite such differences among the compositions, no coformulation effect was observed for GP when formulated in the exemplary triple cosuspensions. As can be appreciated by reference to Figure 7, the cascade impaction profiles for GP and the FPM, MMAD and FPF for GP were nearly identical for each of the BGF1, BGF2, and GFF compositions.

[00134] Figure 8 provides cascade impaction profiles for BD provided by the BGF3, BD Mono, and BFF cosuspensions. The concentration of SP included in BGF3 and BD Mono was 5.85 mg/ml, while that of the BFF cosuspension was 4.5 mg/ml. The BD Mono and BFF compositions provided a delivered dose of 160 µg BD per MDI actuation, while BGF3 provided a delivered dose of 40 µg BD per MDI actuation. Moreover, BGF3 included GPBr and FF, while BFF did not include GPBr and BD Mono did not include GPBr or FF. Despite the differences between the compositions, no coformulation effect was observed for BD when formulated in the exemplary triple cosuspensions. As can be appreciated by reference to Figure 8, the cascade impaction profiles for BD and the FPM, MMAD and FPF for BD were nearly identical for each of the BD Mono, BFF, and BGF3 compositions.

Example 3

[00135] A double-blind, four-period, six-treatment, single-dose, cross-over clinical study in healthy adult volunteers was conducted to evaluate three different triple cosuspension compositions prepared according to the present description. In particular, the pharmacokinetic (PK) performance and safety of the exemplary triple cosuspensions was evaluated.

[00136] Three different triple cosuspension compositions including BD, GPBr, and FF were prepared. Each of the active agents was provided as a micronized crystalline material, and the micronized BD, GPBr, and FF materials were co-suspended in a hydrofluoroalkane (HFA) propellant with suspending particles (SP). The HFA propellant used was HFA 134a, and the SP used in each MDI cosuspension formulation were spray-dried porous particles formed of 1,2 distearoyl-sn-glycero-3-phosphocholine (DSPC) and calcium chloride ($CaCl_2$).

Claims

1. A suspension composition for respiratory delivery of a long-acting muscarinic antagonist (LAMA), a long-acting β_2 adrenergic agonist (LABA), and an inhaled corticosteroid (ICS) from a metered dose inhaler (MDI) to a patient, the composition comprising:

a suspension medium comprising a pharmaceutically acceptable propellant;

a first species of respirable active agent particles comprising the LABA active agent that is substantially insoluble in the suspension medium;

a second species of respirable active agent particles comprising the LAMA active agent that is substantially insoluble in the suspension medium;

a third species of respirable active agent particles comprising the ICS active agent that is substantially insoluble in the suspension medium;

a plurality of respirable suspending particles, wherein the plurality of suspending particles are formed of a material that is substantially insoluble in the suspension medium, and the ICS active agent and LABA active agent are included in the suspension composition such that the ICS:LABA delivered dose ratio is at least 5:1 per actuation of the MDI.

2. The suspension composition of claim 1, wherein the LABA active agent is selected from bambuterol, clenbuterol, formoterol, salmeterol, carmoterol, milveterol, indacaterol, and saligenin- or indole- containing and adamantyl-derived β_2 agonists.

3. The suspension composition of any one of the preceding claims, wherein the LABA active agent is a pharmaceutically acceptable salt, ester, or isomer of formoterol selected from hydrochloric, hydrobromic, sulfuric, phosphoric, fumaric, maleic, acetic, lactic, citric, tartaric, ascorbic, succinic, glutaric, gluconic, tricarballylic, oleic, benzoic, p-methoxybenzoic, salicylic, o-

and p-hydroxybenzoic, p-chlorobenzoic, methanesulfonic, p-toluenesulfonic and 3-hydroxy-2-naphthalene carboxylic acid salts.

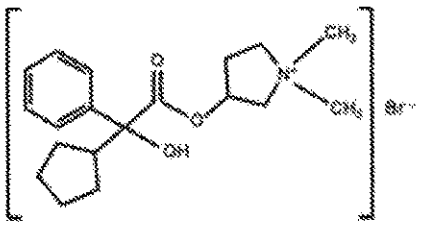
4. The suspension composition of claim 3, wherein the pharmaceutically acceptable salt of formoterol is formoterol fumarate.

5. The suspension composition of any one of the preceding claims, wherein the LAMA active agent is selected from glycopyrronium, dexipirronium, scopolamine, tropicamide, pirenzepine, dimenhydrinate, tiotropium, darotropium, aclidinium, trospium, ipatropium, atropine, benzatropin, and oxitropium.

6. The suspension composition of claim 5, wherein the LAMA active agent is a pharmaceutically acceptable salt, ester, or isomer of glycopyrronium selected from fluoride, chloride, bromide, iodide, nitrate, sulfate, phosphate, formate, acetate, trifluoroacetate, propionate, butyrate, lactate, citrate, tartrate, malate, maleate, succinate, benzoate, p-chlorobenzoate, diphenyl-acetate or triphenylacetate, o-hydroxybenzoate, p-hydroxybenzoate, 1-hydroxynaphthalene-2-carboxylate, 3-hydroxynaphthalene-2-carboxylate, methanesulfonate, and benzenesulfonate salts

7. The suspension composition of claim 6, wherein the pharmaceutically acceptable glycopyrronium salt is selected from fluoride, chloride, bromide, and iodide salts.

8. The suspension composition of claim 7, wherein the pharmaceutically acceptable salt of glycopyrronium is 3-[(cyclopentyl-hydroxyphenylacetyl)oxy]-1,1-dimethylpyrrolidinium bromide which has the following structure:



9. The suspension composition of any one of the preceding claims, wherein the ICS active agent is selected from beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, methyl-prednisolone, mometasone, prednisone, and triamcinolone.

10. The suspension composition of claim 9, wherein the ICS active agent is selected from a pharmaceutically acceptable salt, ester, or isomer of mometasone or budesonide.

11. The suspension composition of claim 10, wherein the ICS active agent is budesonide.

12. The suspension composition according to any preceding claim, wherein at least one of the first, second, and third species of active agent particle comprises a micronized crystalline material.

13. The suspension composition according to any one of the preceding claims, wherein the first species of active agent particle comprises respirable, crystalline particles of the LABA active agent.

14. The suspension composition according to any one of the preceding claims, wherein the second species of active agent particle comprises respirable, crystalline particles of the LAMA active agent.

15. The suspension composition according to any one of the preceding claims, wherein the third species of active agent particle comprises respirable, crystalline particles of the ICS active agent.

16. The suspension composition according to claim 12, wherein the first species of active agent particle comprises respirable, crystalline particles of the LABA active agent, the second species of active agent particle comprises respirable, crystalline particles of the LAMA active agent, and the third species of active agent particle comprises respirable, crystalline particles of the ICS active agent.

17. The suspension composition according to any one of the preceding claims, wherein the ICS active agent and LABA active agent are included in the suspension composition such that the ICS:LABA delivered dose ratio per actuation of the MDI is selected from about 10:1 or greater, about 15:1 or greater, about 20:1 or greater, about 35:1 or greater, and about 50:1 or greater.

18. The suspension composition according to claim 17, wherein the first species of active agent particles comprises a pharmaceutically acceptable salt, ester, or isomer of formoterol selected from hydrochloric, hydrobromic, sulfuric, phosphoric, fumaric, maleic, acetic, lactic, citric, tartaric, ascorbic, succinic, glutaric, gluconic, tricarballylic, oleic, benzoic, p-methoxybenzoic, salicylic, o- and p-hydroxybenzoic, p-chlorobenzoic, methanesulfonic, p-toluenesulfonic and 3-hydroxy-2-naphthalene carboxylic acid salts, and the third species of active agent particles comprises a pharmaceutically acceptable salt, ester, or isomer of mometasone or budesonide.

19. The suspension composition according to claim 18, wherein the first species of active agent particles comprises formoterol fumarate, the third species of active agent particles comprises a pharmaceutically acceptable salt, ester, or isomer of budesonide, and the ICS active agent and LABA active agent are included in the suspension composition such that the ICS:LABA delivered dose ratio per actuation of the MDI is selected from about 5:1 or greater, 10:1 or greater, about 15:1 or greater, about 20:1 or greater, about 35:1 or greater, and about 50:1.

20. The suspension composition according to claim 18, wherein the first species of active agent particles comprises formoterol fumarate, the third species of active agent particles comprises a pharmaceutically acceptable salt, ester, or isomer of mometasone furoate, and the ICS active agent and LABA active agent are included in the suspension composition such that the ICS:LABA delivered dose ratio per actuation of the MDI is selected from about 10:1 or greater, about 15:1 or greater, about 20:1 or greater, about 35:1 or greater, and about 50:1.

21. The suspension composition according to any preceding claim, wherein the ICS active agent and LAMA active agent are included in the suspension composition such that the ICS:LAMA delivered dose ratio per actuation of the MDI is selected from about 5:1 or greater, about 10:1 or greater, about 15:1 or greater, about 20:1 or greater, about 35:1 or greater, and about 50:1 or greater.

22. The suspension composition according to claim 21, wherein the second species of active agent particles comprise a pharmaceutically acceptable salt, ester, or isomer of glycopyrronium selected from fluoride, chloride, bromide, iodide, nitrate, sulfate, phosphate, formate, acetate, trifluoroacetate, propionate, butyrate, lactate, citrate, tartrate, malate, maleate, succinate, benzoate, p-chlorobenzoate, diphenyl-acetate or triphenylacetate, o-hydroxybenzoate, p-hydroxybenzoate, 1-hydroxynaphthalene-2-carboxylate, 3-hydroxynaphthalene-2-carboxylate, methanesulfonate, and benzenesulfonate salts, and the third species of active agent particles comprise a pharmaceutically acceptable salt, ester, or isomer of mometasone or budesonide.

23. The suspension composition according to claim 22, wherein the wherein the pharmaceutically acceptable glycopyrronium salt is selected from fluoride, chloride, bromide, and iodide salts, and the third species of active agent particles comprise a pharmaceutically acceptable salt, ester, or isomer of budesonide.

24. The suspension composition of claim 23, wherein the pharmaceutically acceptable salt of glycopyrronium is 3-[(cyclopentyl-hydroxyphenylacetyl)oxy]-1,1-dimethylpyrrolidinium bromide, and the third species of active agent particles comprise a pharmaceutically acceptable salt, ester, or isomer of budesonide.

25. The suspension composition according to claim 23, wherein the ICS active agent and LABA active agent are included in the suspension composition such that the ICS:LABA delivered dose ratio per actuation of the MDI is selected from about 5:1 or greater, 10:1 or greater, about 15:1 or greater, about 20:1 or greater, about 35:1 or greater, and about 50:1.

26. The suspension composition according to claim 22, wherein the third species of active agent particles comprises a pharmaceutically acceptable salt, ester, or isomer of mometasone, and the ICS active agent and LABA active agent are included in the suspension composition such that the ICS:LABA delivered dose ratio per actuation of the MDI is selected from about 10:1 or greater, about 15:1 or greater, about 20:1 or greater, about 35:1 or greater, and about 50:1.

27. The suspension composition according to any one of the preceding claims, wherein a ratio of total mass of the suspending particles to total mass of the first, second, and third active agent particles is selected from between about 0.5:1 and about 75:1, between about 0.5:1 and about 50:1, between about 0.5:1 and about 35:1, between about 0.5:1 and about 25:1, between about 0.5:1 and about 15:1, between about 0.5:1 and about 10:1, and between about 0.5:1 and about 5:1.

28. The suspension composition according to any one of claims 1-26, wherein a ratio of total mass of the suspending particles to total mass of the first, second, and third active agent particles is selected from between about 1.5:1 and about 75:1, between about 1.5:1 and about 50:1, between about

1.5:1 and about 35:1, about 1.5:1 and about 25:1, about 1.5:1 and about 15:1, about 1.5:1 and about 10:1, and between about 1.5:1 and about 5:1.

29. The suspension composition according to any one of claims 1-26, wherein a ratio of total mass of the suspending particles to total mass of the first, second, and third active agent particles is selected from between about 2.5:1 and about 75:1, between about 2.5:1 and about 50:1, between about 2.5:1 and about 35:1, between about 2.5:1 and about 25:1, between about 2.5:1 and about 15:1, between about 2.5:1 and about 10:1, and between about 2.5:1 and about 5:1.

30. The suspension composition of claim 27, wherein the first species of active agent particles comprises a pharmaceutically acceptable salt, ester, or isomer of formoterol, the second species of active agent particles comprises a pharmaceutically acceptable salt, ester, or isomer of glycopyrronium, the third species of active agent particles comprises a pharmaceutically acceptable salt, ester, or isomer of budesonide, the ICS active agent and LABA active agent are included in the suspension composition such that the ICS:LABA delivered dose ratio per actuation of the MDI is selected from about 5:1 or greater, about 10:1 or greater, about 15:1 or greater, about 20:1 or greater, about 35:1 or greater, and about 50:1, and the ICS active agent and LABA active agent are included in the suspension composition such that the ICS:LABA delivered dose ratio per actuation of the MDI is selected from about 5:1 or greater, about 10:1 or greater, about 15:1 or greater, about 20:1 or greater, about 35:1 or greater, and about 50:1.

31. The suspension composition of claim 28, wherein the first species of active agent particles comprises a pharmaceutically acceptable salt, ester, or isomer of formoterol, the second species of active agent particles comprises a pharmaceutically acceptable salt, ester, or isomer of glycopyrronium, the third species of active agent particles comprises a pharmaceutically acceptable salt, ester, or isomer of budesonide, the ICS active agent and LABA active agent are included in the suspension composition such that the ICS:LABA delivered dose

ratio per actuation of the MDI is selected from about 5:1 or greater, about 10:1 or greater, about 15:1 or greater, about 20:1 or greater, about 35:1 or greater, and about 50:1, and the ICS active agent and LABA active agent are included in the suspension composition such that the ICS:LABA delivered dose ratio per actuation of the MDI is selected from about 5:1 or greater, about 10:1 or greater, about 15:1 or greater, about 20:1 or greater, about 35:1 or greater, and about 50:1.

32. The suspension composition of claim 29, wherein the first species of active agent particles comprises a pharmaceutically acceptable salt, ester, or isomer of formoterol, the second species of active agent particles comprises a pharmaceutically acceptable salt, ester, or isomer of glycopyrronium, the third species of active agent particles comprises a pharmaceutically acceptable salt, ester, or isomer of budesonide, the ICS active agent and LABA active agent are included in the suspension composition such that the ICS:LABA delivered dose ratio per actuation of the MDI is selected from about 5:1 or greater, about 10:1 or greater, about 15:1 or greater, about 20:1 or greater, about 35:1 or greater, and about 50:1, and the ICS active agent and LABA active agent are included in the suspension composition such that the ICS:LABA delivered dose ratio per actuation of the MDI is selected from about 5:1 or greater, about 10:1 or greater, about 15:1 or greater, about 20:1 or greater, about 35:1 or greater, and about 50:1.

33. The suspension composition according to any one of the preceding claims, wherein the suspending particles comprise dry particulate, perforated microstructures.

34. The suspension composition according to any one of claims 1-33, wherein the suspending particles comprise 1,2-distearoyl-sn-Glycero-3-phosphocholine (DSPC).

35. The suspension composition according to claim 34, wherein the suspending particles comprise DSPC and calcium chloride.

36. The suspension composition according to any one of the preceding claims, wherein the pharmaceutically acceptable propellant comprises an HFA propellant.

37. The suspension composition according to claim 36, wherein the suspension medium comprises a pharmaceutically acceptable HFA propellant substantially free of co-solvents and solubilizing agents.

38. A suspension composition for respiratory delivery of a long-acting muscarinic antagonist (LAMA), a long-acting β_2 adrenergic agonist (LABA), and an inhaled corticosteroid (ICS) from a metered dose inhaler (MDI) to a patient, the composition comprising:

a suspension medium comprising a pharmaceutically acceptable propellant;

a first species of respirable active agent particles comprising a pharmaceutically acceptable salt, ester, or isomer of formoterol that is substantially insoluble in the suspension medium;

a second species of respirable active agent particles comprising a pharmaceutically acceptable salt, ester, or isomer of glycopyrronium that is substantially insoluble in the suspension medium;

a third species of respirable active agent particles comprising a pharmaceutically acceptable salt, ester, or isomer of budesonide that is substantially insoluble in the suspension medium;

a plurality of respirable suspending particles, wherein the plurality of suspending particles are formed of a material that is substantially insoluble in the suspension medium, the ICS active agent and LABA active agent are included in the suspension composition such that the ICS:LABA delivered dose ratio is at least 5:1 per actuation of the MDI, and the ICS active agent and LAMA active agent are included in the suspension composition such that the ICS:LAMA delivered dose ratio is at least 5:1 per actuation of the MDI.

39. The suspension composition of claim 38, wherein the pharmaceutically acceptable salt, ester, or isomer of formoterol is formoterol fumarate and the pharmaceutically acceptable salt, ester, or isomer of glycopyrronium is 3-[(cyclopentyl-hydroxyphenylacetyl)oxy]-1,1-dimethylpyrrolidinium bromide.

40. The suspension composition according to any one of claims 38 and 39, wherein a ratio of total mass of the suspending particles to total mass of the first, second, and third active agent particles is selected from between about 0.5:1 and about 75:1, between about 0.5:1 and about 50:1, between about 0.5:1 and about 35:1, between about 0.5:1 and about 25:1, between about 0.5:1 and about 15:1, between about 0.5:1 and about 10:1, and between about 0.5:1 and about 5:1.

41. The suspension composition according to any one of claims 38 and 39, wherein a ratio of total mass of the suspending particles to total mass of the first, second, and third active agent particles is selected from between about 1.5:1 and about 75:1, between about 1.5:1 and about 50:1, between about 1.5:1 and about 35:1, between about 1.5:1 and about 25:1, between about 1.5:1 and about 15:1, between about 1.5:1 and about 10:1, and between about 1.5:1 and about 5:1.

42. The suspension composition according to any one of claims 38 and 39, wherein a ratio of total mass of the suspending particles to total mass of the first, second, and third active agent particles is selected from between about 2.5:1 and about 75:1, between about 2.5:1 and about 50:1, between about 2.5:1 and about 35:1, between about 2.5:1 and about 25:1, between about 2.5:1 and about 15:1, between about 2.5:1 and about 10:1, and between about 2.5:1 and about 5:1.

43. The suspension composition according to any one of claims 38-42, wherein the ICS active agent and LABA active agent are included in the suspension composition such that the ICS:LABA delivered dose ratio is about

10:1 or greater and the ICS active agent and LAMA active agent are included in the suspension composition such that the ICS:LAMA delivered dose ratio is at least 5:1 per actuation of the MDI

44. The suspension composition according to claim 43, wherein the ICS active agent and LABA active agent are included in the suspension composition such that the ICS:LABA delivered dose ratio is about 15:1 or greater per actuation of the MDI.

45. The suspension composition according to claim 43, wherein the ICS active agent and LABA active agent are included in the suspension composition such that the ICS:LABA delivered dose ratio is about 20:1 or greater per actuation of the MDI.

46. The suspension composition according to claim 43, wherein the ICS active agent and LABA active agent are included in the suspension composition such that the ICS:LABA delivered dose ratio is about 35:1 or greater per actuation of the MDI.

47. The suspension composition according to claim 43, wherein the ICS active agent and LABA active agent are included in the suspension composition such that the ICS:LABA delivered dose ratio is about 50:1 or greater per actuation of the MDI.

48. The suspension composition according to any one of claims 38-47, wherein the ICS active agent and LAMA active agent are included in the suspension composition such that the ICS:LAMA delivered dose ratio is about 5:1 or greater per actuation of the MDI.

49. The suspension composition according to claim 48, wherein the ICS active agent and LAMA active agent are included in the suspension composition such that the ICS:LAMA delivered dose ratio is about 10:1 or greater per actuation of the MDI.

50. The suspension composition according to claim 48, wherein the ICS active agent and LAMA active agent are included in the suspension composition such that the ICS:LAMA delivered dose ratio is about 15:1 or greater per actuation of the MDI.

51. The suspension composition according to claim 48, wherein the ICS active agent and LAMA active agent are included in the suspension composition such that the ICS:LAMA delivered dose ratio is about 20:1 or greater per actuation of the MDI.

52. The suspension composition according to claim 48, wherein the ICS active agent and LAMA active agent are included in the suspension composition such that the ICS:LAMA delivered dose ratio is about 35:1 or greater per actuation of the MDI.

53. The suspension composition according to claim 48, wherein the ICS active agent and LAMA active agent are included in the suspension composition such that the ICS:LAMA delivered dose ratio is about 50:1 or greater per actuation of the MDI.

54. The suspension composition according to any one of claims 38-52, wherein at least one of the first, second, and third species of active agent particle comprises a micronized crystalline material.

55. The suspension composition according to claim 53, wherein the first species of active agent particles comprises respirable, crystalline particles of the pharmaceutically acceptable salt, ester, or isomer of formoterol, the second species of active agent particles comprises respirable, crystalline particles of the pharmaceutically acceptable salt, ester, or isomer of glycopyrronium, and the third species of active agent particles comprises respirable, crystalline particles of the pharmaceutically acceptable salt, ester, or isomer of budesonide.

56. The suspension composition according to any one of claims 38-53, wherein the suspending particles comprise dry particulate, perforated microstructures.

57. The suspension composition according to any one of claims 38-53, wherein the suspending particles comprise 1,2-distearoyl-sn-Glycero-3-phosphocholine (DSPC).

58. The suspension composition according to claim 56, wherein the suspending particles comprise DSPC and calcium chloride.

59. The suspension composition according to any one of claims 38-57, wherein the pharmaceutically acceptable propellant comprises an HFA propellant.

60. The suspension composition according to claim 58, wherein the suspension medium comprises a pharmaceutically acceptable HFA propellant substantially free of co-solvents and solubilizing agents.

61. A method for treating a pulmonary disease or disorder in a patient, the method comprising:

providing an MDI containing a suspension composition according to any one of claims 1-59; and

administering a therapeutically effective amount of a suspension composition to the patient by actuating the MDI.

62. The method of claim 61, wherein the pulmonary disease or disorder is selected from the group consisting of asthma, COPD, allergic rhinitis, sinusitis, pulmonary vasoconstriction, inflammation, allergies, impeded respiration, respiratory distress syndrome, pulmonary hypertension, pulmonary inflammation experienced with cystic fibrosis, and pulmonary obstruction experienced with cystic fibrosis.

63. The method of claim 61, wherein the pulmonary disease or disorder is COPD.

64. The method of claim 61, wherein the pulmonary disease or disorder is asthma.

65. A suspension composition for use in treatment of a pulmonary disease or disorder selected from the group consisting of asthma, COPD, allergic rhinitis, sinusitis, pulmonary vasoconstriction, inflammation, allergies, impeded respiration, respiratory distress syndrome, pulmonary hypertension, pulmonary inflammation experienced with cystic fibrosis, and pulmonary obstruction experienced with cystic fibrosis, the suspension composition comprising a suspension composition according to any one of claims 1-59.

66. The composition according to claim 65 for use in treatment of COPD.

67. The composition according to claim 65 for use in treatment of asthma.

Claims

1. A suspension composition for respiratory delivery of a long-acting muscarinic antagonist (LAMA), a long-acting β_2 adrenergic agonist (LABA), and an inhaled corticosteroid (ICS) from a metered dose inhaler (MDI) to a patient, the composition comprising:

a suspension medium comprising a pharmaceutically acceptable propellant;

a first species of respirable active agent particles comprising the LABA active agent;

a second species of respirable active agent particles comprising the LAMA active agent;

a third species of respirable active agent particles comprising the ICS active agent; and

a plurality of respirable suspending particles, wherein the plurality of suspending particles are formed of a material that is substantially insoluble in the suspension medium, and the ICS active agent and LABA active agent are included in the suspension composition such that the ICS:LABA delivered dose ratio is at least 5:1 per actuation of the MDI.

2. The suspension composition of claim 1, wherein the LABA active agent is selected from bambuterol, clenbuterol, formoterol, salmeterol, carmoterol, milveterol, indacaterol, and saligenin- or indole- containing and adamantyl-derived β_2 agonists.

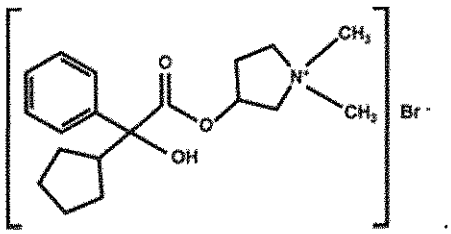
3. The suspension composition of claim 2, wherein the LABA active agent is formoterol fumarate.

4. The suspension composition of any one of the preceding claims, wherein the LAMA active agent is selected from glycopyrronium, dexipirronium, scopolamine, tropicamide, pirenzepine, dimenhydrinate, tiotropium,

darotropium, aclidinium, trospium, ipatropium, atropine, benzatropin, and oxitropium.

5. The suspension composition of claim 4, wherein the pharmaceutically acceptable glycopyrronium salt is selected from fluoride, chloride, bromide, and iodide salts.

6. The suspension composition of claim 5, wherein the pharmaceutically acceptable salt of glycopyrronium is 3-[(cyclopentyl-hydroxyphenylacetyl)oxy]-1,1-dimethylpyrrolidinium bromide which has the following structure:



7. The suspension composition of any one of the preceding claims, wherein the ICS active agent is selected from beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, methyl-prednisolone, mometasone, prednisone, and triamcinolone.

8. The suspension composition of claim 7, wherein the ICS active agent is selected from a pharmaceutically acceptable salt, ester, or isomer of mometasone or budesonide.

9. The suspension composition of claim 8, wherein the ICS active agent is budesonide.

10. The suspension composition according to any one of the preceding claims, wherein the ICS active agent and LABA active agent are included in the suspension composition such that the ICS:LABA delivered dose ratio per actuation of the MDI is selected from about 10:1 or greater, about 15:1

or greater, about 20:1 or greater, about 35:1 or greater, and about 50:1 or greater.

11. The suspension composition according to any preceding claim, wherein the ICS active agent and LAMA active agent are included in the suspension composition such that the ICS:LAMA delivered dose ratio per actuation of the MDI is selected from about 5:1 or greater, about 10:1 or greater, about 15:1 or greater, about 20:1 or greater, about 35:1 or greater, and about 50:1 or greater.

12. The suspension composition according to any one of the preceding claims, wherein a ratio of total mass of the respirable suspending particles to total mass of the first, second, and third respirable active agent particles is selected from between about 0.5:1 and about 75:1, between about 0.5:1 and about 50:1, between about 0.5:1 and about 35:1, between about 0.5:1 and about 25:1, between about 0.5:1 and about 15:1, between about 0.5:1 and about 10:1, and between about 0.5:1 and about 5:1.

13. A suspension composition according to any one of the preceding claims, wherein:

the suspension medium comprises a pharmaceutically acceptable propellant;

the first species of respirable active agent particles comprises a LABA active agent, wherein the LABA active agent is a pharmaceutically acceptable salt, ester, or isomer of formoterol that is substantially insoluble in the suspension medium;

the second species of respirable active agent particles comprises a LAMA active agent, wherein the LAMA active agent is a pharmaceutically acceptable salt, ester, or isomer of glycopyrronium that is substantially insoluble in the suspension medium;

the third species of respirable active agent particles comprises an ICS active agent, wherein the ICS active agent is a pharmaceutically acceptable

salt, ester, or isomer of budesonide that is substantially insoluble in the suspension medium; and

the ICS active agent and LABA active agent are included in the suspension composition such that the ICS:LABA delivered dose ratio is at least 10:1 per actuation of the MDI, and the ICS active agent and LAMA active agent are included in the suspension composition such that the ICS:LAMA delivered dose ratio is at least 5:1 per actuation of the MDI.

14.A suspension composition according to any one of the preceding claims, wherein

the suspension medium comprises a pharmaceutically acceptable HFA propellant;

the first species of respirable active agent particles comprises formoterol fumarate;

the second species of respirable active agent particles comprises (3-[(cyclopentylhydroxyphenylacetyl)oxy]-1, 1-dimethyl-pyrrolidium, bromide);

the third species of respirable active agent particles comprises a pharmaceutically acceptable salt, ester, or isomer of budesonide;

the plurality of suspending particles include a plurality of phospholipid suspending particles formed separately from each of the different species of active agent particles;

the composition is formulated to provide a delivered dose of the pharmaceutically acceptable salt, ester, or isomer of formoterol that is less than or equal to 7.5 μg per actuation of the MDI and a delivered dose of the pharmaceutically acceptable salt, ester, or isomer of glycopyrronium that is less than or equal to 10 μg per actuation of the MDI;

the ICS:LABA delivered dose ratio is at least 15:1 and the ICS:LAMA delivered dose ratio is at least 10:1; and

the ratio of the total mass of the suspending particles to the total mass of the active agent particles may be selected from between about 1:1 and about 10:1, such as between about 1:1 and about 7.5:1, between about 1:1 and about 5:1, between about 1:1 and about 2.5:1, between about 2.5:1 and about 10:1, between about 2.5:1 and about 7.5:1, or between about 2.5:1 and 5:1.

15. A suspension composition according to any one of claims 1-13, wherein

the suspension medium comprises a pharmaceutically acceptable HFA propellant;

the first species of respirable active agent particles comprises formoterol fumarate;

the second species of respirable active agent particles comprises (3-[(cyclopentylhydroxyphenylacetyl)oxy]-1, 1-dimethyl- pyrrolidium, bromide)

the third species of respirable active agent particles comprises a pharmaceutically acceptable salt, ester, or isomer of budesonide;

the plurality of suspending particles include a plurality of phospholipid suspending particles formed separately from each of the different species of active agent particles;

the composition is formulated to provide a delivered dose of the pharmaceutically acceptable salt, ester, or isomer of formoterol that is less than or equal to 7.5 μg per actuation of the MDI and a delivered dose of the pharmaceutically acceptable salt, ester, or isomer of glycopyrronium that is less than or equal to 10 μg per actuation of the MDI;

the ICS:LABA delivered dose ratio is at least 20:1 and the ICS:LAMA delivered dose ratio is at least 15:1; and

the ratio of the total mass of the suspending particles to the total mass of the active agent particles may be selected from between about 0.5:1 and about 5:1, such as between about 0.5:1 and about 3:1, between about 0.5:1 and about 2:1, between about 0.75:1 and about 5:1, between about 0.75:1 and about 3:1, or between about 0.75:1 and about 2:1.

16. A suspension composition according to any one of claims 1-13, wherein

the suspension medium comprises a pharmaceutically acceptable HFA propellant;

the first species of respirable active agent particles comprises formoterol fumarate;

the second species of respirable active agent particles comprises (3-[(cyclopentylhydroxyphenylacetyl)oxy]-1, 1-dimethyl- pyrrolidium, bromide)

the third species of respirable active agent particles comprises a pharmaceutically acceptable salt, ester, or isomer of budesonide;

the plurality of suspending particles include a plurality of phospholipid suspending particles formed separately from each of the different species of active agent particles;

the composition is formulated to provide a delivered dose of the pharmaceutically acceptable salt, ester, or isomer of formoterol that is less than or equal to 5.0 µg per actuation of the MDI and a delivered dose of the pharmaceutically acceptable salt, ester, or isomer of glycopyrronium that is less than or equal to 7.5 µg per actuation of the MDI;

the ICS:LABA delivered dose ratio is at least 15:1 and the ICS:LAMA delivered dose ratio is at least 10:1; and

the ratio of the total mass of the suspending particles to the total mass of the active agent particles may be selected from between about 1:1 and about 10:1, such as between about 1:1 and about 7.5:1, between about 1:1 and about 5:1, between about 1:1 and about 2.5:1, between about 2.5:1 and about 10:1, between about 2.5:1 and about 7.5:1, or between about 2.5:1 and 5:1.

17. A suspension composition according to any one of claims 1-13, wherein

the suspension medium comprises a pharmaceutically acceptable HFA propellant;

the first species of respirable active agent particles comprises formoterol fumarate;

the second species of respirable active agent particles comprises (3-[(cyclopentylhydroxyphenylacetyl)oxy]-1, 1-dimethyl- pyrrolidium, bromide)

the third species of respirable active agent particles comprises a pharmaceutically acceptable salt, ester, or isomer of budesonide;

the plurality of suspending particles include a plurality of phospholipid suspending particles formed separately from each of the different species of active agent particles;

the composition is formulated to provide a delivered dose of the pharmaceutically acceptable salt, ester, or isomer of formoterol that is less than or equal to 5.0 µg per actuation of the MDI and a delivered dose of the

pharmaceutically acceptable salt, ester, or isomer of glycopyrronium that is less than or equal to 7.5 µg per actuation of the MDI;

the ICS:LABA delivered dose ratio is at least 20:1 and the ICS:LAMA delivered dose ratio is at least 15:1; and

the ratio of the total mass of the suspending particles to the total mass of the active agent particles may be selected from between about 0.5:1 and about 5:1, such as between about 0.5:1 and about 3:1, between about 0.5:1 and about 2:1, between about 0.75:1 and about 5:1, between about 0.75:1 and about 3:1, or between about 0.75:1 and about 2:1.

18. A suspension composition according to any one of claims 1-13, wherein

the suspension medium comprises a pharmaceutically acceptable HFA propellant;

the first species of respirable active agent particles comprises formoterol fumarate;

the second species of respirable active agent particles comprises (3-[(cyclopentylhydroxyphenylacetyl)oxy]-1, 1-dimethyl- pyrrolidium, bromide)

the third species of respirable active agent particles comprises a pharmaceutically acceptable salt, ester, or isomer of budesonide;

the plurality of suspending particles include a plurality of phospholipid suspending particles formed separately from each of the different species of active agent particles;

the composition is formulated to provide a delivered dose of the pharmaceutically acceptable salt, ester, or isomer of formoterol that is less than or equal to 5.0 µg per actuation of the MDI and a delivered dose of the pharmaceutically acceptable salt, ester, or isomer of glycopyrronium that is less than or equal to 7.5 µg per actuation of the MDI;

the ICS:LABA delivered dose ratio is at least 25:1 and the ICS:LAMA delivered dose ratio is at least 20:1; and

the ratio of the total mass of the suspending particles to the total mass of the active agent particles may be selected from between about 0.5:1 and about 5:1, such as between about 0.5:1 and about 3:1, between about

0.5:1 and about 2:1, between about 0.75:1 and about 5:1, between about 0.75:1 and about 3:1, or between about 0.75:1 and about 2:1.

19. A suspension composition according to any one the preceding claims, wherein at least one of the first, second, and third species of respirable active agent particles comprises a micronized, crystalline material.

20. A suspension composition according to any one the preceding claims, wherein the first species of respirable active agent particle comprises micronized, crystalline particles of the LABA active agent, the second species of respirable active agent particle comprises micronized, crystalline particles of the LAMA active agent, and the third species of respirable active agent particle comprises micronized, crystalline particles of the ICS active agent.

21. A suspension composition according to any one the preceding claims, wherein the respirable suspending particles comprise dry particulate, perforated microstructures.

22. A suspension composition according to any one the preceding claims, wherein the respirable suspending particles comprise 1,2-distearoyl-sn-Glycero-3-phosphocholine (DSPC).

23. A suspension composition according to any one the preceding claims, wherein the respirable suspending particles comprise DSPC and calcium chloride.

24. A suspension composition for use in treatment of a pulmonary disease or disorder selected from the group consisting of asthma, COPD, allergic rhinitis, sinusitis, pulmonary vasoconstriction, inflammation, allergies, impeded respiration, respiratory distress syndrome, pulmonary hypertension, pulmonary inflammation experienced with cystic fibrosis, and pulmonary obstruction experienced with cystic fibrosis, the suspension composition comprising a suspension composition according to any one of claims 1-23.

25. The suspension composition according to claim 24 for use in treatment of COPD.

26. The suspension composition according to claim 24 for use in treatment of asthma.