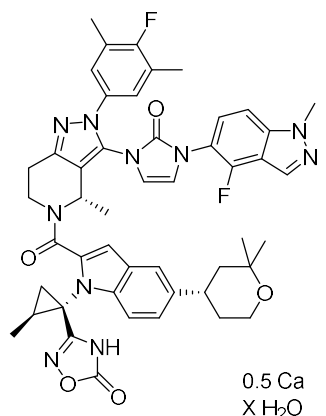




GLP1RA is a poorly permeable and poorly soluble weak acid with a pKa of 5.1. GLP1RA and its pharmaceutically acceptable salts have very low aqueous solubility across the physiologic pH range as well as in simulated physiological fluids. GLP1RA is observed to have a strong pH dependent solubility profile contributing to challenges such as variability in absorption and consequently in pharmacokinetic performance and potential food effects. There is a desire for GLP1RA, including but not limited to, GLP1RA-Ca, capsule compositions providing reliable PK performance in a patient friendly dosage form, with minimal potential for drug-drug interactions and reduced or no food effects. A GLP1RA composition to enhance solubility and dissolution rate of the active substance in a capsule dosage form may be desired. A pharmaceutically elegant dosage form to deliver an effective amount of active GLP1RA to the targeted portion of the gastrointestinal tract, while small enough to facilitate patient swallowing is desired.

Summary

In an aspect, there is provided a solid oral capsule composition comprising a spray dried dispersion (SDD) of 3-[(1S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methylindazol-5-yl)-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one, or a pharmaceutically acceptable salt thereof; and

a pH modifier selected from the group consisting of calcium carbonate, magnesium carbonate, sodium bicarbonate, sodium carbonate, magnesium hydroxide, calcium hydroxide, magnesium oxide, and a mixture thereof.

In another aspect, there is provided a composition comprising:

a spray dried dispersion (SDD) of about 30 wt% to about 35 wt% of 3-[(1S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-

5 c]pyridine-5-carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one, or a pharmaceutically acceptable salt thereof; in an amount of between about 0.7 mg to about 50 mg, on a free acid basis; and the balance of the SDD is composed of PVP-VA; and

10 a pH modifier selected from the group consisting of calcium carbonate, magnesium carbonate, sodium bicarbonate, sodium carbonate, magnesium hydroxide, calcium hydroxide, magnesium oxide, and a mixture thereof.

In another aspect, there is provided use of the composition as described herein in the manufacture of a medicament for treating type 2 diabetes.

In another aspect, there is provided use of the composition as described herein in the manufacture of a medicament for weight management.

15 In another aspect, there is provided a composition as described herein for use in therapy.

Description

Compositions described herein provide desired properties. In an aspect, the use of a sprayed dried dispersion (SDD) of the GLP1RA, or a pharmaceutically acceptable salt
20 thereof, together with a pH modifier, as described herein, contributes to the desired properties. In an aspect, the specific particle sizes of the SDD and the particular compositions as described provide the desired properties. In an aspect, compositions disclosed herein provide desirable pharmacokinetic performances and deliver an effective amount of active GLP1RA to the targeted portion of the gastrointestinal tract. In an
25 aspect, disclosed herein is an elegant dosage form that is convenient for patients to take without the limitation of food or water restrictions.

We Claim:

1. A solid oral capsule composition comprising
a spray dried dispersion (SDD) of 3-[(1S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-
2-[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methylindazol-5-yl)-2-
5 oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carbonyl]indol-1-
yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one, or a pharmaceutically acceptable
salt thereof; and

a pH modifier selected from the group consisting of calcium carbonate,
magnesium carbonate, sodium bicarbonate, sodium carbonate, magnesium hydroxide,
10 calcium hydroxide, magnesium oxide, and a mixture thereof.

2. The composition as claimed by Claim 1, wherein the pH modifier is selected
from the group consisting of calcium carbonate, anhydrous calcium carbonate, sodium
bicarbonate, anhydrous sodium bicarbonate, sodium carbonate, anhydrous sodium
15 carbonate, magnesium hydroxide, and anhydrous magnesium hydroxide.

3. The composition as claimed by Claim 1, wherein the pH modifier is sodium
bicarbonate.

20 4. The composition as claimed by Claim 3, wherein the pH modifier is anhydrous
sodium bicarbonate.

5. The composition as claimed by any one of Claims 1 to 4, wherein the
composition comprises

25 3-[(1S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-[(4S)-2-(4-fluoro-3,5-
dimethylphenyl)-3-[3-(4-fluoro-1-methylindazol-5-yl)-2-oxoimidazol-1-yl]-4-methyl-6,7-
dihydro-4H-pyrazolo[4,3-c]pyridine-5-carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-
1,2,4-oxadiazol-5-one; and
anhydrous sodium bicarbonate.

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6. The composition as claimed by any one of Claims 1 to 4, wherein the 3-[(1S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methylindazol-5-yl)-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one, or a pharmaceutically acceptable salt thereof, is

3-[(1S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methylindazol-5-yl)-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one, 0.5 Ca hydrate.

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7. The composition as claimed by claim 6, wherein the 3-[(1S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methylindazol-5-yl)-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one, or a pharmaceutically acceptable salt thereof, is

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3-[(1S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methylindazol-5-yl)-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one, 0.5 Ca hydrate in an amount of between about 1.2 to about 46 mg, on a free acid basis, per capsule composition.

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8. The composition as claimed by any one of Claims 1 to 4, wherein the 3-[(1S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methylindazol-5-yl)-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one, or a pharmaceutically acceptable salt thereof, is in an amount of between about 1 mg to about 45 mg, on a free acid basis, per capsule.

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9. A composition comprising:

a spray dried dispersion (SDD) of about 30 wt% to about 35 wt% of 3-[(1S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methylindazol-5-yl)-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-

5 c]pyridine-5-carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one, or a pharmaceutically acceptable salt thereof; in an amount of between about 0.7 mg to about 50 mg, on a free acid basis; and the balance of the SDD is composed of PVP-VA; and

a pH modifier selected from the group consisting of calcium carbonate, magnesium carbonate, sodium bicarbonate, sodium carbonate, magnesium hydroxide, 10 calcium hydroxide, magnesium oxide, and a mixture thereof.

10. The composition as claimed by Claim 9, wherein the composition comprises:

the SDD of about 30 wt% 3-[(1S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methylindazol-5-yl)-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one, or a pharmaceutically acceptable salt thereof; in an amount of between about 0.7 mg to about 45 mg, on a free acid basis;

a pH modifier which is sodium bicarbonate; in an amount of about 150 mg to about 650 mg;

20 optionally, a filler selected from the group consisting of a sugar alcohol, microcrystalline cellulose, methylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose, starch, dicalcium phosphate, and a mixture thereof; in an amount of about 0 mg to about 200 mg; and

optionally, a glidant selected from the group consisting of silicon oil, silicon dioxide, talc, magnesium carbonate, and a mixture thereof; in an amount of about 0 mg to about 20 mg.

11. The composition as claimed by Claim 10, wherein the composition comprises:

an SDD of about 30 wt% of 3-[(1S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methylindazol-5-yl)-2-

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oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one, 0.5 Ca hydrate; in an amount of between about 1 mg to about 36 mg, on a free acid basis; and the balance of the SDD is composed of PVP-VA;

5 a pH modifier which is sodium bicarbonate; in an amount of about 200 mg to about 600 mg;

 optionally, a filler selected from the group consisting of a sugar alcohol, microcrystalline cellulose, methylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose, starch, dicalcium phosphate, and a mixture thereof; in an amount of
10 about 0 mg to about 60 mg; and

 optionally, a glidant selected from the group consisting of silicon oil, silicon dioxide, talc, magnesium carbonate, and a mixture thereof; in an amount of about 0 mg to about 20 mg.

15 12. The composition as claimed by Claim 11, wherein:
 no filler is present; and
 the glidant is silicon oil; in an amount of about 0.1 mg to about 5 mg.

 13. The composition as claimed by any one of Claims 9-12, wherein the SDD has a
20 mean particle size of about 5 μ m to about 113 μ m in diameter.

 14. The composition as claimed by Claim 11, wherein the composition comprises:
 an SDD of about 30 wt% of 3-[(1S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-
[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methylindazol-5-yl)-2-
25 oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one, 0.5 Ca hydrate; in an amount of about 1 mg, on a free acid basis;
 a pH modifier which is sodium bicarbonate; in an amount of about 200 mg;
 a filler which is MCC PH-102; in an amount of about 40 mg to about 50 mg; and

a glidant which is silicon oil or silicon dioxide; in an amount of about 1 mg to about 5 mg;

wherein the total weight of the composition is about 250 mg.

5 15. The composition as claimed by Claim 11, wherein the composition comprises:
an SDD of about 30 wt% of 3-[(1S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-
[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methylindazol-5-yl)-2-
oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carbonyl]indol-1-
yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one, 0.5 Ca hydrate; in an amount of
10 about 6 mg, on a free acid basis; and about 70 wt% of PVP-VA in an amount of about 14
mg;

a pH modifier which is sodium bicarbonate; in an amount of about 600 mg; and
a glidant which is silicon oil; in an amount of about 1 mg to about 10 mg.

15 16. The composition as claimed by Claim 11, wherein the composition comprises:
an SDD of about 30 wt% of 3-[(1S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-
[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methylindazol-5-yl)-2-
oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carbonyl]indol-1-
yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one, 0.5 Ca hydrate; in an amount of
20 about 12 mg, on a free acid basis; and about 70 wt% of PVP-VA in an amount of about
28 mg;

a pH modifier which is sodium bicarbonate; in an amount of about 600 mg; and
a glidant which is silicon oil; in an amount of about 1 mg to about 10 mg.

25 17. The composition as claimed by Claim 11, wherein the composition comprises:
an SDD of about 30 wt% of 3-[(1S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-
[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methylindazol-5-yl)-2-
oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carbonyl]indol-1-
yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one, 0.5 Ca hydrate; in an amount of

about 36 mg, on a free acid basis; and about 70 wt% of PVP-VA in an amount of about 83 mg;

a pH modifier which is sodium bicarbonate; in an amount of about 600 mg; and
a glidant which is silicon oil; in an amount of about 1 mg to about 10 mg.

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18. The composition as claimed by any one of Claims 14-17, wherein the SDD has a mean particle size of about 5 μm to about 113 μm in diameter.

19. The composition as claimed by Claim 18, wherein the SDD has a mean particle
10 size of about 40 μm to about 65 μm in diameter.

20. The composition as claimed by any one of Claim 19, wherein the composition is in a capsule shell.

15 21. The composition as claimed by any one of Claims 20, wherein the capsule shell is an HPMC capsule shell.

22. Use of the composition as claimed by any one of Claims 1-21 in the
manufacture of a medicament for treating type 2 diabetes.

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23. Use of the composition as claimed by any one of Claims 1-21 in the
manufacture of a medicament for weight management.

24. A composition as claimed by any one of Claims 1-21 for use in therapy.
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