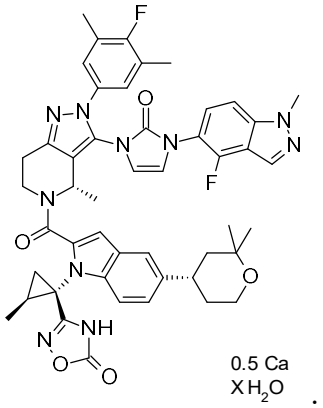


GLP1RA is a poorly permeable and poorly soluble weak acid with a pKa of 5.1. GLP1RA has very low aqueous solubility across the physiologic pH range as well as in simulated physiological fluids. GLP1RA and its pharmaceutically acceptable salts are observed to have a strong pH dependent solubility profile 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, tablet 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 tablet 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 tablet 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.

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.

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

In another aspect, there is provided a tablet composition wherein the composition comprises:

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; in an amount of between about 0.7 mg to about 60 mg, on a free acid basis;

a pH modifier selected from the group consisting of calcium carbonate, sodium bicarbonate, sodium carbonate, sodium carbonate hydrate, magnesium hydroxide, and a mixture thereof; in an amount of about 2 mg to about 100 mg;

a super disintegrant selected from the group consisting of croscarmellose sodium and crospovidone; in an amount of about 2 mg to about 200 mg; and

a lubricant which is magnesium stearate; in an amount of about 0.1 mg to about 2.5 mg.

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 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 aspect, disclosed herein is an elegant dosage form that is convenient for patients to take without the limitation of food or water restrictions.

Solid oral formulations provided herein can be useful for patients in need of treatment for T2D. Solid oral formulations provided herein can be useful for patients in need of chronic weight management.

In an embodiment is a tablet composition comprising:

We Claim:

1. A tablet 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.

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

3. The composition as claimed by Claim 2, 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 carbonate, magnesium hydroxide, and anhydrous magnesium hydroxide.

4. The composition as claimed by Claim 3 wherein the pH modifier is sodium carbonate.

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

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;

a pH modifier; and

a super disintegrant.

6. The composition as claimed by Claim 5 wherein the super disintegrant is selected from the group consisting of croscarmellose sodium and crospovidone.

7. The composition as claimed by any one of Claims 1 to 6 wherein the composition comprises:

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;

a pH modifier;

a super disintegrant; and

a lubricant.

8. The composition as claimed by any one of Claims 1 to 7 further comprising an immediate release coating.

9. The composition as claimed by any one of claims 1 to 8, 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; in an amount of between about 0.7 to about 50 mg, on a free acid basis, per tablet composition.

10. Use of the composition as claimed by any one of Claims 1 to 9 in the manufacture of a medicament for treating type 2 diabetes.

11. Use of the composition as claimed by any one of Claims 1 to 9 in the manufacture of a medicament for weight management.

12. The composition as claimed by any one of Claims 1 to 9 for use in therapy.

13. A tablet composition wherein the composition comprises:

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; in an amount of between about 0.7 mg to about 60 mg, on a free acid basis;

a pH modifier selected from the group consisting of calcium carbonate, sodium bicarbonate, sodium carbonate, sodium carbonate hydrate, magnesium hydroxide, and a mixture thereof; in an amount of about 2 mg to about 100 mg;

a super disintegrant selected from the group consisting of croscarmellose sodium and crospovidone; in an amount of about 2 mg to about 200 mg; and

a lubricant which is magnesium stearate; in an amount of about 0.1 mg to about 2.5 mg.

14. The tablet composition as claimed by Claim 1 wherein the composition comprises:

the 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-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 about 0.5 mg to about 75 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 sodium bicarbonate and sodium carbonate; in an amount of between about 1 mg to about 150 mg.

15. The tablet composition as claimed by Claim 14 wherein the composition comprises:

the 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-

c]pyridine-5-carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one, or the 0.5 Ca hydrate thereof; in an amount of between about 0.7 mg to about 60 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 sodium bicarbonate and sodium carbonate; in an amount of between about 5 mg to about 100 mg.

16. The tablet composition as claimed by Claim 14 wherein the composition comprises:

the 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, or the 0.5 Ca hydrate thereof; in an amount of between about 1.7 mg to about 250 mg of the SDD; and the balance of the SDD is composed of PVP-VA; wherein the SDD is between about 2 wt% to about 25 wt% of the total tablet weight; and

the pH modifier which is sodium carbonate; in an amount of between about 6 mg to about 100 mg; wherein the pH modifier is between about 5 wt% to about 15 wt% of the total tablet weight.

17. The tablet composition as claimed by Claim 16 wherein the composition comprises:

the 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 between about 150 mg to about 250 mg of the SDD; and the balance of the SDD is composed of PVP-VA; wherein the SDD is between about 21 wt% to about 25 wt% of the total tablet weight; and

the pH modifier which is sodium carbonate; in an amount of between about 57.1 mg to about 80 mg; wherein the pH modifier is about 8 wt% of the total tablet weight.

18. The tablet composition as claimed by any one of Claims 13-17, wherein the SDD has a mean particle size of about 5 μm to about 113 μm in diameter; and

the pH modifier is sodium carbonate.

19. The tablet composition as claimed by Claim 18, wherein the composition further comprises:

a super disintegrant selected from the group consisting of croscarmellose sodium and crospovidone.

20. The tablet composition as claimed by Claim 19, wherein:

the super disintegrant is crospovidone in an amount of between about 8.5 mg to about 170 mg; wherein the super disintegrant is between about 10 wt% to about 17 wt% of the total tablet weight.

21. The tablet composition as claimed by Claim 20, wherein the composition further comprises:

a filler which is MCC; in an amount of between about 67 mg to about 495 mg; wherein the filler is between about 49.5 wt% to about 79.5 wt% of the total tablet weight.

22. The tablet composition as claimed by Claim 21, wherein the composition further comprises:

a lubricant which is magnesium stearate; in an amount of between about 0.4 mg to about 5 mg; wherein the lubricant is between about 0.1 wt% to about 1 wt% of the total tablet weight.

23. The tablet composition as claimed by Claim 16, wherein the composition comprises:

the 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; and the balance of the SDD is composed of PVP-VA; wherein the SDD is in an amount of about 19.5 wt% to about 25 wt% of the total tablet weight;

the pH modifier which is sodium carbonate; wherein the pH modifier is about 8 wt% of the total tablet weight;

a super disintegrant which is crospovidone; wherein the super disintegrant is about 17 wt% of the total tablet weight; and

a filler which is MCC; wherein the filler is in an amount of about 49.5 wt% to about 55 wt% of the total tablet weight.

24. The tablet composition as claimed by Claim 16, wherein the composition comprises:

the 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; and the balance of the SDD is composed of PVP-VA; wherein the SDD is in an amount of about 2.0 wt% to about 16.9 wt% of the total tablet weight;

the pH modifier which is sodium carbonate; wherein the pH modifier is about 8 wt% of the total tablet weight;

a super disintegrant which is crospovidone; wherein the super disintegrant is about 10 wt% of the total tablet weight; and

a filler which is MCC; wherein the filler is in an amount of from about 64.6 wt% to about 79.5 wt% of the total tablet weight.

25. The tablet composition as claimed by Claims 23 or 24, wherein the SDD has a mean particle size of about 5 μm to about 113 μm in diameter.

26. The tablet composition as claimed by any one of Claims 13-23 wherein the composition further comprises a lubricant which is magnesium stearate; wherein the lubricant is about 0.5 wt% of the total tablet weight.

27. The tablet composition as claimed by Claim 26 wherein the composition further comprises an immediate release coating.