

GLP1 TABLET COMPOSITIONS

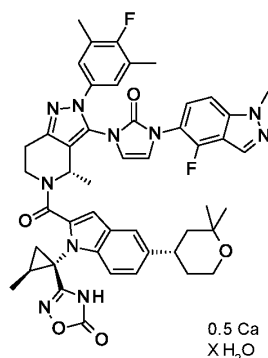
The present invention relates to oral tablet compositions of a GLP-1 receptor agonist, 3-[(1S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methylindazol-5-yl)-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one (herein, GLP1RA), or a pharmaceutically acceptable salt thereof. Compositions disclosed herein can be useful for the treatment of type 2 diabetes mellitus (T2D) and in weight management.

Diabetes mellitus is a chronic disorder characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. In T2D, the combined effects of impaired insulin secretion and insulin resistance are associated with elevated blood glucose levels. T2D is an increasingly prevalent disease that frequently leads to declining health and quality of life for patients. Effective oral treatments to manage T2D and/or for use in weight management are desired.

GLP1RA, that 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, or a pharmaceutically acceptable salt thereof, is described and claimed in US10,858,356. The US10,858,356 patent generally describes oral compositions.

GLP1RA may be prepared as a pharmaceutically acceptable salt. One salt of GLP1RA is a hemi-calcium hydrate, 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, (herein “GLP1RA-Ca”) with the structure as shown below.

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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.

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:

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

5 a pH modifier.

In an embodiment, the tablet composition disclosed herein is an oral solid composition.

In an embodiment is a composition wherein a 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.

In an embodiment is a solid oral tablet composition comprising

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; 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, sodium carbonate hydrate, magnesium hydroxide, and anhydrous magnesium hydroxide.

In an embodiment, a pH modifier is sodium carbonate. In an embodiment, a pH modifier is anhydrous. In an embodiment, a pH modifier is anhydrous sodium carbonate.

In an embodiment, a pH modifier is sodium carbonate hydrate.

In an embodiment, a pH modifier is sodium bicarbonate. In an embodiment, a pH modifier is anhydrous. In an embodiment, a pH modifier is anhydrous sodium bicarbonate.

In an embodiment is a tablet composition comprising 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; wherein the pH modifier is anhydrous sodium carbonate.

In an embodiment is a tablet composition wherein the composition comprises

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;

- 5 a pH modifier; and
 a super disintegrant.

In an embodiment, a super disintegrant is selected from the group consisting of croscarmellose sodium, crospovidone, sodium starch glycolate, and a mixture thereof. In an embodiment, a super disintegrant is selected from the group consisting of

- 10 croscarmellose sodium and crospovidone.

In an embodiment is a tablet composition wherein the composition comprises

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-

- 15 1,2,4-oxadiazol-5-one, or a pharmaceutically acceptable salt thereof;

 a pH modifier; and
 a lubricant.

In an embodiment, a lubricant is selected from the group consisting of calcium stearate, magnesium stearate, polyethylene glycol, sodium stearyl fumarate, stearic acid, talc, and a mixture thereof. In an embodiment, a lubricant comprises magnesium stearate. In an embodiment, a lubricant is magnesium stearate.

In an embodiment is a tablet composition wherein the composition comprises

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-

- 25 1,2,4-oxadiazol-5-one, or a pharmaceutically acceptable salt thereof;

 a pH modifier;
 a super disintegrant; and
 a lubricant.

- 30 In an embodiment is a tablet composition wherein the composition comprises

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 selected from the group consisting of croscarmellose sodium

5 and crospovidone; and

a lubricant which is magnesium stearate.

In an embodiment is a tablet composition wherein the composition comprises

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-
10 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

crospovidone.

In an embodiment, a tablet composition comprises an enteric coating. In an
15 embodiment, a tablet composition comprises an immediate release coating. In an
embodiment, a tablet composition comprises both an immediate release coating and an
enteric coating.

In an embodiment, a tablet composition comprises 3-[(1S,2S)-1-[5-[(4S)-2,2-
dimethyloxan-4-yl]-2-[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-
20 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 a pH modifier.

In an embodiment, a tablet composition comprises 3-[(1S,2S)-1-[5-[(4S)-2,2-
dimethyloxan-4-yl]-2-[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-
25 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; in an
amount of about 0.5 to about 75 mg per tablet composition.

In an embodiment, a tablet composition comprises 3-[(1S,2S)-1-[5-[(4S)-2,2-
dimethyloxan-4-yl]-2-[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-
30 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; in an
amount of about 0.5 to about 60 mg; or more specifically, about 0.5 to about 45 mg; or

more specifically, about 0.5 to about 36 mg; or even more specifically, about 0.8 to about 36 mg; per tablet composition.

In an embodiment, a tablet composition comprises 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 0.5 to about 82 mg; or more specifically, about 0.5 to about 75 mg; or more specifically, about 0.5 to about 60 mg; or more specifically, about 0.5 to about 45 mg; or more specifically, about 0.8 to about 45 mg; or even more specifically, about 1 to about 36 mg; (all amounts are on free acid basis); per tablet composition.

As described herein, the conversion factor for GLP1RA/GLP1RA-Ca (i.e., the hemicalcium salt hydrate of GLP1RA) is assumed to be around 0.91. As a skilled artisan readily appreciates, the exact conversion rate may change slightly depending on the actual content of the hydrate.

In an embodiment is a tablet composition wherein the composition comprises 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);

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 5 mg to about 15 mg;

a super disintegrant selected from the group consisting of croscarmellose sodium and crospovidone; in an amount of about 2 mg to about 25 mg; and

a lubricant selected from the group consisting of calcium stearate, magnesium stearate, polyethylene glycol, sodium stearyl fumarate, stearic acid, talc, and a mixture thereof; in an amount of about 0.5 mg to about 5 mg.

In an embodiment is a tablet composition wherein the composition comprises 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 0.7 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 5 mg to about 15 mg;

a super disintegrant selected from the group consisting of croscarmellose sodium and crospovidone; in an amount of about 2 mg to about 25 mg; and

a lubricant which is magnesium stearate; in an amount of about 0.5 mg to about 5 mg.

10 In an embodiment is a tablet composition wherein the composition comprises
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
15 about 0.8 mg to about 45 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 5 mg to about 15 mg;

a super disintegrant selected from the group consisting of croscarmellose sodium and crospovidone; in an amount of about 2 mg to about 17.5 mg; and

a lubricant which is magnesium stearate; in an amount of about 1 mg to about 2.5 mg.

In an embodiment is a tablet composition wherein the composition comprises
3-[(1S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-[(4S)-2-(4-fluoro-3,5-
25 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 1 to about 36 mg (on a free acid basis);

a pH modifier selected from the group consisting of calcium carbonate, sodium bicarbonate, sodium carbonate, sodium carbonate hydrate, and magnesium hydroxide, and a mixture thereof; in an amount of about 5 mg to about 10 mg;

a super disintegrant selected from the group consisting of croscarmellose sodium and crospovidone; in an amount of about 5 mg to about 20 mg; and

a lubricant which is magnesium stearate; in an amount of about 1 mg to about 2.5 mg.

In an embodiment is a tablet composition wherein the composition comprises

3-[(1S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-[(4S)-2-(4-fluoro-3,5-
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 1 mg to about 30 mg (on a free acid basis);

a pH modifier selected from the group consisting of anhydrous calcium carbonate,
10 anhydrous sodium bicarbonate, anhydrous sodium carbonate, sodium carbonate hydrate,
and anhydrous magnesium hydroxide; in an amount of about 6 mg to about 8 mg;

a super disintegrant selected from the group consisting of croscarmellose sodium
and crospovidone; in the amount of about 10 mg to about 18 mg; and

a lubricant which is magnesium stearate; in an amount of about 1.5 mg to about 2
15 mg.

In an embodiment is a tablet composition wherein the composition comprises

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-
20 1,2,4-oxadiazol-5-one, 0.5 Ca hydrate; in an amount of about 0.8 mg to about 45 mg (on a
free acid basis);

a pH modifier which is anhydrous sodium carbonate; in an amount of about 8 mg;

a super disintegrant which is crospovidone; in an amount of about 17.5 mg; and

a lubricant which is magnesium stearate; in an amount of about 2 mg.

25 In an embodiment is a tablet composition wherein the composition comprises

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 1 mg to about 36 mg (on a
30 free acid basis);

a pH modifier which is anhydrous sodium carbonate; in an amount of about 8 mg;

a super disintegrant which is crospovidone; in an amount of about 17.5 mg; and

a lubricant which is magnesium stearate; in an amount of about 2 mg.

In an embodiment is a tablet composition wherein the composition comprises
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 45 mg to about 60 mg (on a
free acid basis);

a pH modifier which is anhydrous sodium carbonate; in an amount of about 8 mg;
a super disintegrant which is crospovidone; in an amount of about 17.5 mg; and
a lubricant which is magnesium stearate; in an amount of about 2 mg.

In an embodiment, GLP1RA or a pharmaceutically acceptable salt thereof is
prepared into a spray dried dispersion (SDD) for use as the active drug in a tablet
composition. In an embodiment, an SDD of GLP1RA or a pharmaceutically acceptable
salt thereof is prepared under the conditions as described in Preparation 2 and Preparation
3 below.

In an embodiment, the GLP1RA (“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 GLP1RA-Ca (“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”) is present as an SDD preparation in a composition described herein.

In general, an SDD preparation disclosed herein comprises GLP1RA, or a
pharmaceutically acceptable salt thereof, and a polymer as a balance component to
maintain an amorphous state of the GLP1RA, or a pharmaceutically acceptable salt
thereof. In an embodiment, the polymer is selected from the group consisting of
polyvinyl pyrrolidone (also known as “povidone” or “PVP”) and polyvinyl pyrrolidone
vinyl acetate (also known as “copovidone” or “PVP-VA”). In an embodiment, the
polymer is PVP-VA. In an embodiment, the polymer is PVP.

In an embodiment where the weight percentage of the GLP1RA, or a
pharmaceutically acceptable salt thereof, in an SDD preparation is specified, the balance
component of the SDD is a polymer selected from PVP and PVP-VA, that is, the total
weight percentage of the GLP1RA, or a pharmaceutically acceptable salt thereof, and the

polymer is 100 wt%. In an embodiment, the polymer is PVP-VA. In an embodiment, the polymer is PVP.

In an embodiment, the SDD preparation comprises about 20 wt% to about 40 wt% of GLP1RA or GLP1RA-Ca and the balance is composed of PVP-VA. In an embodiment, the SDD preparation comprises about 30 wt% to about 35 wt% of GLP1RA or GLP1RA-Ca and the balance is composed of PVP-VA. In an embodiment, the SDD preparation comprises about 30 wt% of GLP1RA or GLP1RA-Ca and the balance is composed of PVP-VA. In an embodiment, the SDD preparation comprises about 30 wt% of GLP1RA-Ca and the balance is composed of PVP-VA.

In an embodiment, the mean particle size of the GLP1RA or GLP1RA-Ca SDD is about 5 µm to about 150 µm in diameter. In an embodiment, the mean particle size of the SDD is about 5 µm to about 113 µm in diameter. In an embodiment, the mean particle size of the SDD is about 40 µm to about 65 µm in diameter. In an embodiment, the mean particle size of the SDD is about 40 µm to about 50 µm in diameter. In an embodiment, the mean particle size of the SDD is about 5 µm to about 25 µm in diameter.

In an embodiment is a tablet composition comprising:

an SDD comprising 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 an embodiment, 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. In an embodiment, the pH modifier is sodium bicarbonate. In an embodiment, the pH modifier is sodium carbonate. In an embodiment, the pH modifier is anhydrous sodium carbonate.

In an embodiment is a tablet composition comprising:

an SDD of about 20 wt% to about 40 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; 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 an embodiment is a tablet composition comprising:

an 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; and

a pH modifier selected from the group consisting of sodium bicarbonate and sodium carbonate.

In an embodiment is a tablet composition comprising:

an 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; wherein the SDD has a mean particle size of about 5 μm to about 113 μm in diameter; and

a pH modifier selected from the group consisting of sodium bicarbonate and sodium carbonate.

In an embodiment is a tablet composition comprising:

an 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, 0.5 Ca hydrate; and the balance is composed of a polymer selected from PVP-VA and PVP; wherein the SDD has a mean particle size of about 5 μm to about 113 μm in diameter; and

a pH modifier selected from the group consisting of sodium bicarbonate and sodium carbonate.

In an embodiment is a tablet composition comprising:

an 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, 0.5

5 Ca hydrate; in an amount of about 0.5 mg to about 60 mg (on a free acid basis); and the balance is composed of a polymer selected from PVP-VA and PVP; and

a pH modifier selected from the group consisting of sodium bicarbonate and sodium carbonate.

In an embodiment is a tablet composition comprising:

10 an 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, 0.5

15 Ca hydrate; in an amount of about 0.8 mg to about 45 mg (on a free acid basis); and the balance is composed of a polymer which is PVP-VA; and

a pH modifier selected from the group consisting of sodium bicarbonate and sodium carbonate.

In an embodiment is a tablet composition comprising:

an SDD of about 30 wt% to about 35 wt% 3-[(1S,2S)-1-[5-[(4S)-2,2-

20 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 0.5 mg to about 60 mg (on a free acid basis); and the balance is composed of a polymer which is PVP-VA; and

25 a pH modifier selected from the group consisting of sodium bicarbonate and sodium carbonate; in an amount of about 1 mg to about 100 mg.

In an embodiment of the tablet compositions described above, the SDD has a mean particle size of about 5 μ m to about 113 μ m in diameter; and

the pH modifier is sodium carbonate.

30 In an embodiment of the tablet compositions described above, the composition further comprises:

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

a lubricant.

In an embodiment of the tablet compositions described above, the super disintegrant is croscopovidone in an amount of about 2 mg to about 250 mg; and

the lubricant is magnesium stearate in an amount of about 0.1 mg to about 10 mg.

5 In an embodiment, disclosed herein is a tablet composition selected from the group consisting of composition 1 (Comp. 1), composition 2 (Comp. 2), composition 3 (Comp. 3), composition 4 (Comp. 4), composition 5 (Comp. 5), composition 6 (Comp. 6), composition 7 (Comp. 7), and composition 8 (Comp. 8), as shown in the following table, wherein the amount of each ingredient of a particular composition is shown as the target
10 amount for that composition. In one embodiment, GLP1RA-Ca is used as the active ingredient and the amount of each GLP1RA in the compositions is on the free acid basis.

Ingredient	Target Amount and Variable Ranges in Parenthesis (mg/tablet)			
	Comp. 1 60 mg GLP1RA (A: 54-66 mg) (B: 57-63 mg)	Comp. 2 45 mg GLP1RA (A: 40-50 mg) (B: 42-47 mg)	Comp. 3 30 mg GLP1RA (A: 27-33 mg) (B: 28-32 mg)	Comp. 4 20 mg GLP1RA (A: 18-22 mg) (B: 19-21 mg)
SDD (30 wt% of GLP1RA)	200 (A: 180-220) (B: 190-210)	150 (A: 135-165) (B: 143-158)	100 (A: 90-110) (B: 95-105)	67 (A: 60-73) (B: 63-70)
Filler	332 (A: 265-400) (B: 299-365)	382 (A: 305-458) (B: 344-420)	282 (A: 226-338) (B: 254-310)	188 (A: 150-225) (B: 169-207)
Disintegrant	121 (A: 97-145) (B: 109-134)	121 (A: 97-145) (B: 109-134)	87 (A: 70-105) (B: 109-134)	58 (A: 47-70) (B: 52-64)
pH Modifier	57 (A: 46-69) (B: 51-63)	57 (A: 46-69) (B: 51-63)	41 (A: 33-49) (B: 37-45)	27 (A: 22-33) (B: 25-30)
Lubricant	3.6 (A: 2.9-4.3) (B: 3.2-3.9)	3.6 (A: 2.9-4.3) (B: 3.2-3.9)	2.6 (A: 2.1-3.1) (B: 2.3-2.8)	1.7 (A: 1.4-2.1) (B: 1.6-1.9)
Glidant (optional)	0-20	0-20	0-15	0-10
Total tab. wt.	714 mg	714 mg	513 mg	342 mg
Ingredient	Target Amount and Variable Ranges in Parenthesis (mg/tablet)			
	Comp. 5 10 mg (A: 9-11 mg) (B: 9.5-10.5 mg)	Comp. 6 5 mg (A: 4.5-5.5 mg) (B: 4.6-5.3 mg)	Comp. 7 2.5 mg (A: 2.2-2.8 mg) (B: 2.3-2.6 mg)	Comp. 8 0.8 mg (A: 0.6-1 mg) (B: 0.7-0.9 mg)
SDD (30 wt% of GLP1RA)	33 (A: 30-36) (B: 31-34)	16.7 (A: 15-18) (B: 16-17)	8.3 (A: 7.5-9.1) (B: 7.8-8.6)	2.8 (A: 2.1-3.3) (B: 2.3-3.0)

Filler	94 (A: 75-113) (B: 85-103)	47 (A: 38-56) (B: 42-52)	61 (A: 49-7.3) (B: 55-67)	67 (A: 53-80) (B: 60-73)
Disintegrant	29 (A: 23-35) (B: 26-32)	14.5 (A: 12-17) (B: 13-16)	8.5 (A: 6.8-10) (B: 7.7-9.4)	8.5 (A: 6.8-10) (B: 7.7-9.4)
pH Modifier	14 (A: 11-16) (B: 12-15)	6.8 (A: 5.5-8.2) (B: 6.2-7.5)	6.8 (A: 5.4-8.2) (B: 6.2-7.5)	6.8 (A: 5.4-8.2) (B: 6.2-7.5)
Lubricant	0.8 (A: 0.7-1.0) (B: 0.7-0.9)	0.4 (A: 0.3-0.5) (B: 0.35-0.4)	0.4 (A: 0.3-0.5) (B: 0.35-0.4)	0.4 (A: 0.3-0.5) (B: 0.35-0.4)
Glidant (optional)	0-10	0-5	0-5	0-5
Total tab. wt.	171 mg	85 mg	85 mg	85 mg

As one skilled in pharmaceutical formulation can appreciate, the amount of one or more ingredients of a composition can be changed within certain limits while the desired properties of a composition can be maintained. Additionally, when the amount of one ingredient is changed, the amount of one or more other ingredients can be adjusted accordingly within certain ranges to keep the total weight of a composition constant and maintain the desired properties of the composition.

In an embodiment of a particular composition shown in the above table, the amount of each ingredient is within the respective variable A range as indicated in parenthesis from the target amount while the desired properties of the corresponding composition are maintained.

In an embodiment of a particular composition shown in the above table, the amount of each ingredient is within the respective variable B range as indicated in parenthesis from the target amount while the desired properties of the corresponding composition are maintained.

In an embodiment is a process for preparing a composition as claimed herein comprising a spray dried dispersion process.

In an embodiment is a tablet composition wherein the composition comprises:

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 0.5 mg to about 75 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 1 mg to about 150 mg;

5 a super disintegrant selected from the group consisting of croscarmellose sodium and crospovidone; in an amount of about 1 mg to about 250 mg; and

a lubricant which is magnesium stearate; in an amount of about 0.1 mg to about 10 mg.

In an embodiment is a tablet composition as claimed by Claim 21 wherein the composition comprises:

10 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;

15 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

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

In an embodiment is a tablet composition wherein the composition comprises:

25 an 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 an embodiment is a tablet composition wherein the composition comprises:

30 an 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.

5 In an embodiment is a tablet composition wherein the composition comprises:

an 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
10 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.

In an embodiment is a tablet composition wherein the composition comprises:

15 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, 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
20 SDD is composed of PVP-VA; wherein the SDD is between about 2 wt% to about 25 wt% of the total tablet weight; and

a 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.

25 In an embodiment is a tablet composition 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
30 between about 1.7 mg to about 14.3 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 16.9 wt% of the total tablet weight; and

a pH modifier which is sodium carbonate; in an amount of about 6.8 mg; wherein the pH modifier is about 8 wt% of the total tablet weight.

In an embodiment is a tablet composition wherein the composition comprises:

an SDD of about 30 wt% of 3-[(1S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-
5 [(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 16.7 mg to about 120 mg of the SDD; and the balance of the SDD is composed of PVP-VA; wherein the SDD is about 19.5 wt% of the total tablet weight; and
10 the pH modifier which is sodium carbonate; in an amount of between about 6.8 mg to about 49.2 mg; wherein the pH modifier is about 8 wt% of the total tablet weight.

In an embodiment is a tablet composition 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
15 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

20 a 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.

In an embodiment of the tablet compositions as described above, the SDD has a mean particle size of about 5 μ m to about 113 μ m in diameter.

In an embodiment is a tablet composition, wherein the composition further
25 comprises: a super disintegrant selected from the group consisting of croscarmellose sodium and crospovidone.

In an embodiment is a tablet composition 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
30 the total tablet weight.

In an embodiment is a tablet composition 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.

In an embodiment is a tablet composition, wherein the composition further comprises:

5 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.

In an embodiment is a tablet composition, wherein the composition comprises:

an SDD of about 30 wt% of 3-[(1S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-
10 [(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 about 19.5 wt% of the total tablet weight;

15 a 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 about 55 wt% of the total tablet weight.

20 In an embodiment is a tablet composition 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; and the balance of
25 the SDD is composed of PVP-VA; wherein the SDD is about 25 wt% of the total tablet weight;

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

30 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 about 49.5 wt% of the total tablet weight.

In an embodiment is a tablet composition 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; and the balance of the SDD is composed of PVP-VA; wherein the SDD is about 21 wt% of the total tablet weight;

a 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 about 53.5 wt% of the total tablet weight.

In an embodiment is a tablet composition 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; and the balance of the SDD is composed of PVP-VA; wherein the SDD is about 16.9 wt% of the total tablet weight;

a 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 about 64.6 wt% of the total tablet weight.

In an embodiment is a tablet composition 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; and the balance of the SDD is composed of PVP-VA; wherein the SDD is about 11.8 wt% of the total tablet weight;

a 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 about 69.7 wt% of the total tablet weight.

In an embodiment is a tablet composition wherein the composition comprises:

5 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; and the balance of the SDD is composed of PVP-VA; wherein the SDD is about 9.8 wt% of the total tablet weight;

a 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

15 a filler which is MCC; wherein the filler is about 71.7 wt% of the total tablet weight.

In an embodiment is a tablet composition 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; and the balance of the SDD is composed of PVP-VA; wherein the SDD is about 3.9 wt% of the total tablet weight;

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

25 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 about 77.6 wt% of the total tablet weight.

In an embodiment is a tablet composition 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; and the balance of

the SDD is composed of PVP-VA; wherein the SDD is about 3.2 wt% of the total tablet weight;

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

5 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 about 78.3 wt% of the total tablet weight.

In an embodiment is a tablet composition wherein the composition comprises:

an SDD of about 30 wt% of 3-[(1S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-
10 [(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 about 2.7 wt% of the total tablet weight;

15 a 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 about 78.8 wt% of the total tablet weight.

20 In an embodiment is a tablet composition 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; and the balance of
25 the SDD is composed of PVP-VA; wherein the SDD is about 2.0 wt% of the total tablet weight;

a 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
30 10 wt% of the total tablet weight; and

a filler which is MCC; wherein the filler is about 79.5 wt% of the total tablet weight.

In an embodiment is a tablet composition as described above wherein the composition further comprises a lubricant which is magnesium stearate; wherein the lubricant is about 0.5 wt% of the total tablet weight.

5 In an embodiment is a composition as described above wherein the composition further comprises an immediate release coating.

In an embodiment is a tablet composition as described above wherein the composition further comprises an enteric coating over the immediate release coating.

Pharmaceutical compositions using amorphous forms of an active, have been prepared using spray dried dispersions (SDD), to develop dosage forms for poorly soluble
10 drugs. However, this SDD approach is complicated by the presence of polymeric functional excipients that may be required to maintain the drug in an amorphous state. Compositions providing acceptable pharmacokinetic performance and desired food effects profile can be especially challenging for molecules possessing strong pH dependent solubility profiles. GLP1RA and GLP1RA-Ca exhibit such pH dependent
15 solubility profile. Weak acids can present challenges in ensuring dissolution of the active substance is achieved in the desired portion of the gastrointestinal tract, particularly the stomach, where low pH could retard dissolution of weakly acidic drugs. Certain excipients may become unstable when added to a tablet composition described herein. In an embodiment, an excipient is stable in a tablet composition with pH modifier.

20 As used herein, a pH modifier means an inorganic basic salt including, but not limited to, calcium carbonate, magnesium carbonate, sodium bicarbonate, sodium carbonate, magnesium hydroxide, calcium hydroxide, magnesium oxide including both anhydrous and hydrated forms of the respective salts capable of raising the micro pH during tablet disintegration and dissolution.

25 In an embodiment, a GLP1RA or a pharmaceutically acceptable salt composition comprises a pH modifier that is sodium carbonate. In an embodiment, a GLP1RA or a pharmaceutically acceptable salt composition comprises a pH modifier that is sodium carbonate in its anhydrous form.

30 In an embodiment is a composition comprising GLP1RA, or a pharmaceutically acceptable salt thereof, and a pH modifier that is selected from the group consisting of calcium carbonate, sodium bicarbonate, sodium carbonate, magnesium hydroxide, and a mixture thereof.

In an embodiment is a composition comprising GLP1RA, or a pharmaceutically acceptable salt thereof, and a pH modifier 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.

In an embodiment, a tablet composition comprising GLP1RA or a pharmaceutically acceptable salt thereof, and a pH modifier is uncoated.

In an embodiment, a tablet composition is prepared as an immediate release (IR) dosage form that releases GLP1RA or a pharmaceutically acceptable salt thereof in the gastric compartment. Excessive amounts of pH modifier in the tablet may affect absorption of a co-administered medicine whose absorption is pH sensitive. In an embodiment, a pH modifier is in sufficiently low amounts such that it will not raise the bulk gastric pH during dissolution but sufficient to facilitate the dissolution of the GLP1RA or a pharmaceutically acceptable salt thereof. An immediate release dosage form with sufficiently low amount of a pH modifier may be desired to minimize potential for elevated stomach pH and drug-drug interaction (DDI) with a co-administered drug.

In an embodiment, a tablet composition comprising GLP1RA or a pharmaceutically acceptable salt thereof, and a pH modifier is coated with an immediate release coating.

As used herein, the term “immediate release coating” means a coating that is intended primarily for aesthetics and is not intended to alter disintegration and/or dissolution of the tablet. As used herein, appropriate immediate release coatings may be selected from known coatings, for example, but not limited to, Opadry® Clear (03K19229) (Colorcon Inc). As is common for moisture sensitive SDD based formulations, protection from moisture may be desired, to ensure product functionality and elegance throughout shelf life. This protection may be achieved through packaging, as well as utilization of coating materials to minimize moisture uptake of the tablet. One known immediate release coating with this functionality is Opadry® ambII (Colorcon).

In an embodiment is a composition comprising GLP1RA, or a pharmaceutically acceptable salt thereof; a pH modifier; and an immediate release coating.

In an embodiment, a tablet composition comprising GLP1RA, or a pharmaceutical salt thereof, and a pH modifier is prepared as a delayed release (DR) dosage form further comprising an enteric coating. A composition further comprising an enteric coating may

release in the intestine at a pH of 5.5 or greater. Release in the intestine may be desired for GLP1RA, or a pharmaceutical salt thereof, to limit risks potentially associated with the presence of a pH modifier in the tablet. A DR composition may minimize potential food effect, and may have other favorable effects to the pharmacokinetic profile, for example, but not limited to, overall exposure and modulation of C_{max}.

As used herein, “enteric coating” means a functional coating that is intended to prevent tablet disintegration and/or dissolution in the gastric environment but dissolve in the intestinal environment.

In an embodiment is a composition comprising GLP1RA, or a pharmaceutically acceptable salt thereof; a pH modifier; and an enteric coating.

In an embodiment is a tablet composition comprising GLP1RA, or a pharmaceutical salt thereof; a pH modifier; and a super disintegrant.

In an embodiment is a tablet composition comprising GLP1RA, or a pharmaceutical salt thereof; a pH modifier; a super disintegrant; and a lubricant.

In an embodiment is a tablet composition comprising GLP1RA, or a pharmaceutically acceptable salt thereof; a pH modifier; a super disintegrant; and an enteric coating on the tablet.

In an embodiment is a tablet composition comprising GLP1RA, or a pharmaceutically acceptable salt thereof; a pH modifier; a super disintegrant; and an immediate release coating on the tablet.

As used herein, terms “super disintegrant” and “disintegrant” are interchangeable and mean an excipient to facilitate desirable dissolution of the GLPRA, or pharmaceutical salt thereof, including but not limited to, croscarmellose sodium and crospovidone. The term “super disintegrant” refers to an excipient that preferably facilitates dissolution of the GLP1RA, or pharmaceutical salt thereof, within 30 to about 60 minutes. In an embodiment, a tablet composition comprising GLP1RA, or a pharmaceutical salt thereof; a pH modifier; and a super disintegrant selected from the group consisting of croscarmellose sodium and crospovidone.

In an embodiment is a tablet composition comprising GLP1RA, or a pharmaceutical salt thereof; a pH modifier, and crospovidone.

In an embodiment, a desired tablet composition provides reliable PK performance, in a patient friendly dosage form. Patient friendly tablet composition dosage forms are desired with acceptable size to facilitate swallowing during daily administration, have

minimal potential for drug-drug interactions (DDI) with other concomitant medication, and have minimal use restrictions, including minimizing food effects, avoiding restrictions on time of administration, and avoiding restriction on the volume of liquid used to aid in swallowing.

5 Tablet compositions may release either in the gastric compartment or intestine (enteric) through an erosional mechanism. A dosage form of this invention provides the potential to improve absorption/ PK performance. Dosage forms provided herein can reduce undesired drug-drug interactions.

 Certain abbreviations are defined as follows: “cfm” refers to cubic feet/minute;
10 “Cmax” refers to the maximum plasma concentration that a drug achieves in tested area after the drug has been administered and prior to the administration of a second dose; “DDI” refers to drug-drug interactions; “DR” refers to delayed release; “EtOH” refers to ethanol or ethyl alcohol; “FaSSiF” refers to fasted state simulated intestinal fluid; “FaSSGF” refers to fasted state simulated gastric fluid; “FeSSiF” refers to fed state simulated intestinal fluid;
15 “hr” refers to hour; “hrs” refers to hours; “IR” refers to immediate release; “PK” refers to pharmacokinetics; “MeOH” refers to methanol or methyl alcohol; “rpm” refers to revolutions per minute; “PVP-VA” refers to polyvinylpyrrolidone/vinyl acetate copolymer; “SDD” refers to spray dried dispersion “SIF” refers to simulated intestinal fluid; “T2D” refers to type 2 diabetes; “THF” refers to tetrahydrofuran; “USP” refers to United States
20 Pharmacopeia; “wt%” refers to mass of desired material/total mass; and XRPD refers to X-ray powder diffraction. As used herein “prep” means to preparation.

 A skilled artisan may prepare 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, spray dried dispersion (SDD)
25 preparation under a variety of processing conditions and with varying equipment to produce material of suitable quality and critical characteristics.

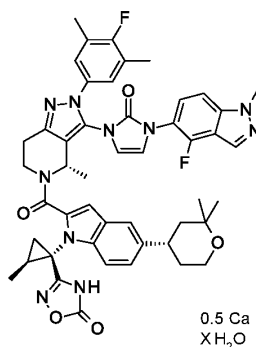
 In an embodiment, a GLP1RA or GLP1RA-Ca in an SDD preparation is amorphous as measured via XRPD, of the desired wt% of drug (30%) and PVP-VA (70%), and of a
30 particle size that can be isolated and forward processed and is acceptably free of process related impurities and excessive residual solvents.

In an embodiment, amorphous solid dispersion may be used in the preparation process. In an embodiment, the particle size is from about 5 to about 113 μm for use in the preparing the tablet composition.

Capsules are prepared for assays herein, utilizing conventional encapsulation methods.

Preparation 1

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



Example 1 may be prepared as described in WO18/056453.

The title compound has alternative names. For example, it is also known as the hemicalcium salt hydrate of orforglipron.

Another name for the title compound is 1,2,4-oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]-, calcium salt (2:1), hydrate.

Preparation 2

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, SDD preparation

30% 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 SDD is prepared by dissolving 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 (8.7 g, 92% potency) and PVP-VA, (also known as copovidone, CAS# 25086-89-9;) (18.7 g) in EtOH (200 mL) at room temperature. Following dissolution of the solids the solution is spray dried on a conventional spray dryer with a pressure nozzle. The following parameters in Table 1 are used to create the dispersion using a laboratory scale spray drier. Spray drying can begin when the spray dryer temperature is above 33 °C. Collect the material and dry under vacuum at 50 °C overnight to give the title compound (21.99 g, 7.0 g, 92% potency, 80% recovery) and observe via photomicroscopy that the material is microscopically non birefringent particles that are approximately 5-25 µm in diameter.

SDD Parameters

Table 1

Process Parameter	Value
Aspirator	100%
Nebulization Flow	37 mm (~400 L/hr)
Solution flow rate	40% (12.5 mL/min)
Chiller Temperature	-20 °C
Drying Gas Inlet Temperature	120 °C
Spray Dryer Outlet Temperature (°C)	75 °C

Preparation 3

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, SDD preparation

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, is dissolved in EtOH, and denatured with MeOH (5% v/v or w/w). A 20% w/w solids solution is prepared with 30% w/w of the solid fraction composed of the title compound; (on a free acid basis) and the balance composed of PVP-VA. This translates to 6% of the title compound (on a free acid basis), 14% PVP-VA and 80% of denatured EtOH SDA-3A – all fractions as w/w. After spray drying, the solids that form are composed of 30% w/w of the solid fraction composed of the title compound (on a free acid basis) and the balance composed of PVP-VA. The % values are shown in Table 2 below.

Formulation of Preparation 3 SDD

Table 2

	Solution (mass fractions)	Amorphous SDD (mass fraction)
Title compound	6%	30.0%
PVP-VA	14%	70.0%
EtOH SDA-3A	80%	
EtOH	76%	
MeOH	4%	

Once the solution is prepared, the solution is pumped to a spray dryer where the solution atomizes upon entry. Heated drying gas enters co-current to the atomized liquid at the top of the spray drying chamber at an approximate ratio of 0.044 kg/kg of spray solution to drying gas. The inlet temperature is adjusted to provide an outlet temperature of 35 to 45 °C. The solids formed in the spray dryer are collected from a cyclone as well as a filter housing on the gas stream. The gas is passed over a condenser maintained at -3 °C to remove (to a dewpoint of -3 °C) solvent. The gas is then heated to the inlet temperature and passed back to the spray dryer.

Preparation 4

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

Capsule Preparation

Capsules are prepared by first adding sodium bicarbonate (600 mg) to a size 0 hypromellose capsule followed by Preparation 3 SDD (54 mg)

Quantitative Capsule Composition, Preparation 4

Table 3

Capsule	Wt%	mg/tablet
Preparation 3 SDD	8.26	54
Sodium bicarbonate (anhydrous)	91.74	600
Total	100	654

Preparation 5

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, tablet formulation

Core Tablet Composition Preparation

To prepare core tablets, 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 (13.3 % w/w) SDD and excipients, (as set forth in Examples 1 through 7), except magnesium stearate, are screened through a 600 µm sieve before use. The materials are added to a vessel (1000 mL) and mixed with a mixer at 32 rpm for about 10 min. The mixture blend is passed through sieve (600 µm) and mixed with mixer a 2nd time at 32 rpm for about 10 min. Magnesium stearate is added and the mixture is mixed at 32 rpm for about 3 min. The

mixture blend is compressed using a 14.10 x 7.75 mm oval tablet tooling on a single station tablet press to produce tablets (400.0 mg) with a hardness of 30 kP.

Tablet compositions are prepared substantially as described herein above, using parameters of the following Tables 4 through 10, to prepare corresponding Examples 1 through 7 (Compositions T1, T2, A, B, C, D, and E). Examples 1 to 7 each include an IR coating substantially as described herein and additionally may include an enteric coating for tablets in Examples 1-6. A tablet of Example 7 includes only an IR coating.

Example 1 Tablet Composition T1

10 Table 4

Component	Function	Example 1 Composition T1		
		% w/w	mg/tablet	Quantity/ 300 g batch (g)
Prep 2 SDD (30 wt%)	Drug	13.3	53.3 *(16)	39.5 (40)
Microcrystalline cellulose	Filler	56.7	226.7	170.5 (170)
Na ₂ CO ₃ anhydrous	pH modifier	10	40	30
Crospovidone XL-10	disintegrant	17.5	70	52.5
Silicon dioxide	Glidant	2	8	6
Magnesium stearate	Lubricant	0.50	2.00	1.5
Total		100	400	300

Example 2 Tablet Composition T2

Table 5

Component	Function	Example 2 Composition T2		
		% w/w	mg/tablet	Quantity/ 300 g batch (g)
Prep 2 SDD (30 wt%)	Drug	13.3	53.3 (16)	40
Microcrystalline cellulose	Filler	72.17	288.67	216.5
Na ₂ CO ₃ anhydrous	pH modifier	10	40	30
Crospovidone XL-10	disintegrant	2	8	6
Silicon dioxide	Glidant	2	8	6
Magnesium stearate	lubricant	0.5	2	1.5
Total		100	400	300

Example 3 Tablet Composition A

Table 6

Component	Function	Example 3 Composition A		
		% w/w	mg/tablet	Quantity/ 300 g batch (g)
Prep 2 SDD (30 wt%)	Drug	13.3	53.3 (16)	38.9
Microcrystalline cellulose	Filler	61.7	246.7	186.1
Na ₂ CO ₃ anhydrous	pH modifier	5	20	15
Crospovidone XL-10	disintegrant	17.5	70	52.5
Silicon dioxide	Glidant	2	8	6
Magnesium stearate	lubricant	0.5	2	1.5
Total		100	400	300

5

Example 4 Tablet Composition B

Table 7

Component	Function	Example 4 Composition B		
		% w/w	mg/tablet	Quantity/ 300 g batch (g)
Prep 2 SDD (30 wt%)	Drug	13.3	53.3 (16)	38.9
Microcrystalline cellulose	Filler	51.7	206.7	156
Na ₂ CO ₃ anhydrous	pH modifier	15	60	45
Crospovidone XL-10	disintegrant	17.5	70	52.5
Silicon dioxide	Glidant	2	8	6
Magnesium stearate	Lubricant	0.5	2	1.5
Total		100	400	300

Example 5 Tablet Composition C

Table 8

Component	Function	Example 5 Composition C		
		% w/w	mg/tablet	Quantity/ 300 g batch (g)
Prep 2 SDD (30 wt%)	Drug	13.3	53.3 (16)	38.9
Microcrystalline cellulose	Filler	69.2	276.7	208.6
Na ₂ CO ₃ anhydrous	pH modifier	15	60	45
Silicon dioxide	Glidant	2	8	6
Magnesium stearate	Lubricant	0.5	2	1.5
Total		100	400	300

Example 6 Tablet Composition D

Table 9

Component	Function	Example 6 Composition D		
		% w/w	mg/tablet	Quantity/ 300 g batch (g)
Prep 2 SDD (30 wt%)	Drug	13.3	53.3 (16)	40
Microcrystalline cellulose	Filler	79.2	316.7	20
Na ₂ CO ₃ anhydrous	pH modifier	5	20	8
Silicon dioxide	Glidant	2	8	2
Magnesium stearate	Lubricant	0.5	2	400
Total		100	400	300

5

Example 7 Tablet Composition E

Table 10

Component	Function	Example 7 Composition E		
		% w/w	mg/tablet	Quantity/ 300 g batch (g)
Prep 2 SDD (30 wt%)	Drug	13.3	53.3 (16)	38.9
Microcrystalline cellulose	Filler	56.7	226.7	171
Na ₂ CO ₃ anhydrous	pH modifier	10	40	30
Crospovidone XL-10	Disintegrant	17.5	70	52.5
Silicon dioxide	Glidant	2	8	6
Magnesium stearate	Lubricant	0.5	2	1.5
Total		100	400	300

*Numbers in () indicate theoretical targets of GLP1RA.

Immediate Release coating for Examples 1 through Example 7

10

Immediate Release Tablet

Coating

A core tablet composition, prepared substantially as described by each of Examples 1 to 7 is film coated to a target 3 wt% gain (with an acceptable range of 2.5 to 3.5 percent) of immediate release coating, such as Opadry® Clear (03K19229) (Colorcon Inc). Tablets are coated using conventional pan coating equipment and vendor recommended coating conditions using water as the base for the spray suspension. Composition Examples 1 to 7 are coated using this immediate release coating.

15

Example 8

Delayed Release tablet composition Coating (enteric coating)

A tablet composition of Example 1-6 is coated substantially as described above with Opadry® Clear. The Opadry® Clear coated tablets are further enterically coated to a target 6.75 wt% gain (with an acceptable range of 6.25 to 7.25 percent) with Acryl-EZE® (93A18597) (Colorcon Inc) and with PEG 8000 as a plasticizer at 8 wt% relative to Acryl-EZE. Tablets are coated using conventional pan coating equipment with vendor recommended coating conditions using water as the base for the spray suspension.

10

Example 9

Enteric Coated Tablet Compositions - Enteric coated tablets are prepared using tablet compositions substantially as described by Examples 1 to 6, except that the wt% of sodium carbonate is adjusted and compensated for by adjusting microcrystalline cellulose content. Tablets are coated with Opadry® 03K19229 (Colorcon Inc.) using 8 wt% solids in the spray suspension to a target weight gain of 3%. Tablets are coated using a benchtop pan coater with a 0.8 mm orifice spray nozzle spraygun with AntiBearding Cap, inlet airflow of 30 cfm, inlet air temperature of 70 °C, spray suspension rate of 2.3 g per minute, atomization pressure of 1.5 bar, a pattern air pressure of 0.25 bar and pan speed of 32 rpm. Tablets are then enterically coated to a wt% gain target of approximately 6.5% with Acryl-EZE 93A18597 (Colorcon Inc.) using the same equipment. The aqueous suspension is prepared at 20 wt% Acryl-EZE powder with PEG-8000 added as plasticizer at 8 wt% relative the Acryl-EZE. Coating conditions are as follows: 0.8 mm orifice spray nozzle spraygun with AntiBearding Cap, inlet airflow of 25 cfm, inlet air temperature of 60 °C, spray suspension rate of 4.1 g per minute, atomization pressure of 1.5 bar, a pattern air pressure of 0.25 bar and pan speed of 35 rpm.

20

25

Example 10

Quantitative IR Tablet Composition

30

Table 11

IR Tablet	Wt%	mg/tablet
Preparation 3 SDD	13.3	53.3
Microcrystalline cellulose 102	64.2	256.7

Sodium carbonate (anhydrous)	15	60
Crospovidone	5	20
Magnesium Stearate	0.5	2
Silicon Dioxide	2	8
Total	100	400

Example 11

Alternate Tablet Composition Super disintegrant with Croscarmellose Sodium

Table 12

	Wt%	mg/tablet
Preparation 3 SDD	13.9	55.8
Microcrystalline Cellulose 102	58	232
Sodium carbonate (anhydrous)	20	80
Croscarmellose Sodium	5	20
Magnesium Stearate	1	4
Silicon Dioxide	2	8
Total	100	400

5

Example 12

Alternate Tablet Composition Super disintegrant with Crospovidone

Table 13

	Wt%	mg/tablet
Preparation 3 SDD	13.8	55.8
Silicified microcrystalline cellulose	57	232
Sodium carbonate (anhydrous)	20	80
Crospovidone	6.2	25
Magnesium Stearate	1	4
Silicon Dioxide	2	8
Total	100	405

- 10 Tablet compositions are prepared with these super disintegrants in the formulas as shown in Tables 11 and 12. All materials are added, excluding magnesium stearate, to an amber glass jar and mixed using a rotational diffusional mixer at 22 rpm for 10 minutes. The blend is passed through a #35 mesh screen and then mixed for another 10 minutes. The magnesium stearate is passed through a #35 mesh and added to the jar and blended
- 15 for 5 minutes. The blend is compressed using a single station tablet press at 6 kN compression force using modified oval tooling. Core tablets are coated with Opadry® 03K19229 (Colorcon Inc.) using 8 wt% solids in the spray suspension to a weight gain

target of 3%. Tablets are coated using a benchtop pan coater with a 0.8 mm orifice spray nozzle spraygun with AntiBearding Cap, inlet airflow of 30 cfm, inlet air temperature of 70 °C, spray suspension rate of 2.3 g per minute, atomization pressure of 1.5 bar, a pattern air pressure of 0.25 bar and pan speed of 32 rpm. Tablets are then enterically coated to a

5 wt% gain target of 6.5 % with Acryl-Eze 93A18597 (Colorcon Inc.) using the same equipment. The aqueous suspension is prepared at 20 wt% Acryl-EZE powder with PEG-8000 added as plasticizer at 8 wt% relative the Acryl-EZE. Coating conditions are as follows: 0.8 mm orifice spray nozzle spraygun with AntiBearding Cap, inlet airflow of 25 cfm, inlet air temperature of 60 °C, spray suspension rate of 4.1 g per minute,

10 atomization pressure of 1.5 bar, a pattern air pressure of 0.25 bar and pan speed of 35 rpm.

Example 13

Tablet Composition 400 mg total weight tablet

Total weight tablets (400 mg) are prepared using the percentages in Table 14.

15 Tablets are prepared, coated with the immediate release coating, and then the enteric coating substantially as described by Example 9.

Table 14

	Wt% in a 400 mg total tablet weight					
	Example 1; T1	Example 2; T2	Example 3; A	Example 4; B	Example 5; C	Example 6; D
Preparation 3 SDD	13.3	13.3	13.3	13.3	13.3	13.3
Microcrystalline cellulose 102	57	72	62	52	69	79
Sodium carbonate (anhydrous)	10	10	5	15	15	5
Crospovidone	17.5	2	17.5	17.5	0	0
Silicon Dioxide	2	2	2	2	2	2
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5
Total	100	100	100	100	100	100

20

Example 14

Tablet Compositions 9-30

Core tablet compositions 9-30 (Comp. 9 – Comp. 30) are prepared using the percentages in the following table and processes as described earlier. Core tablets are

prepared, coated with the immediate release coating, and optionally, can be further coated with the enteric coating substantially as described in Example 9.

Ingredient	Comp. 9 75 mg GLP1RA (wt% of composition)	Comp. 10 60 mg GLP1RA (wt% of composition)	Comp. 11 45 mg GLP1RA (wt% of composition)	Comp. 12 36 mg GLP1RA (wt% of composition)
Prep 2 SDD (30 wt% of GLP1RA)	250 (25%)	200 (25%)	150 (21%)	120 (19.5%)
Microcrystalline cellulose	495 (49.5%)	396 (49.5%)	382 (53.5%)	338 (55%)
Crospovidone XL-10	170 (17%)	136 (17%)	121 (17%)	104 (17%)
Na ₂ CO ₃ anhydrous	80 (8%)	64 (8%)	57 (8%)	49 (8%)
Magnesium stearate	5 (0.5%)	4 (0.5%)	3.6 (0.5%)	3.1 (0.5%)
Total	1000 mg	800 mg	714 mg	615 mg
Ingredient	Comp. 13 30 mg GLP1RA (wt% of composition)	Comp. 14 25.7 mg GLP1RA (wt% of composition)	Comp. 15 24 mg GLP1RA (wt% of composition)	Comp. 16 20 mg GLP1RA (wt% of composition)
Prep 2 SDD (30 wt% of GLP1RA)	100 (19.5%)	85.7 (19.5%)	80 (19.5%)	67 (19.5%)
Microcrystalline cellulose	282 (55%)	242 (55%)	225 (55%)	188 (55%)
Crospovidone XL-10	87 (17%)	75 (17%)	70 (17%)	58 (17%)
Na ₂ CO ₃ anhydrous	41 (8%)	35 (8%)	33 (8%)	27 (8%)
Magnesium stearate	2.6 (0.5%)	2.2 (0.5%)	2.1 (0.5%)	1.7 (0.5%)
Total	513 mg	440 mg	410 mg	342 mg
Ingredient	Comp. 17 17 mg GLP1RA (wt% of composition)	Comp. 18 12 mg GLP1RA (wt% of composition)	Comp. 19 10 mg GLP1RA (wt% of composition)	Comp. 20 8.6 mg GLP1RA (wt% of composition)
Prep 2 SDD (30 wt% of GLP1RA)	57 (19.5%)	40 (19.5%)	33 (19.5%)	29 (19.5%)
Microcrystalline cellulose	161 (55%)	113 (55%)	94 (55%)	81 (55%)
Crospovidone XL-10	50	35	29	25

	(17%)	(17%)	(17%)	(17%)
Na ₂ CO ₃ anhydrous	23 (8%)	16 (8%)	14 (8%)	12 (8%)
Magnesium stearate	1.5 (0.5%)	1.0 (0.5%)	0.85 (0.5%)	0.73 (0.5%)
Total	293 mg	205 mg	171 mg	147 mg
Ingredient	Comp. 21 6 mg GLP1RA (wt% of composition)	Comp. 22 5 mg GLP1RA (wt% of composition)	Comp. 23 4.3 mg GLP1RA (wt% of composition)	Comp. 24 3 mg GLP1RA (wt% of composition)
Prep 2 SDD (30 wt% of GLP1RA)	20 (19.5%)	17 (19.5%)	14.3 (16.9%)	10 (11.8%)
Microcrystalline cellulose	56 (55%)	47 (55%)	55 (65%)	59 (70%)
Crospovidone XL-10	17 (17%)	10 (17%)	8.5 (10%)	8.5 (10%)
Na ₂ CO ₃ anhydrous	8.2 (8%)	6.8 (8%)	6.8 (8%)	6.8 (8%)
Magnesium stearate	0.51 (0.5%)	0.43 (0.5%)	0.43 (0.5%)	0.43 (0.5%)
Total	103 mg	100 mg	100 mg	85 mg
Ingredient	Comp. 25 2.5 mg GLP1RA (wt% of composition)	Comp. 26 2.1 mg GLP1RA (wt% of composition)	Comp. 27 1.0 mg GLP1RA (wt% of composition)	Comp. 28 0.8 mg GLP1RA (wt% of composition)
Prep 2 SDD (30 wt% of GLP1RA)	8.3 (9.8%)	7 (8.2%)	3.3 (3.9%)	2.7 (3.2%)
Microcrystalline cellulose	61 (72%)	62 (73%)	66 (78%)	67 (78%)
Crospovidone XL-10	8.5 (10%)	8.5 (10%)	8.5 (10%)	8.5 (10%)
Na ₂ CO ₃ anhydrous	6.8 (8%)	6.8 (8%)	6.8 (8%)	6.8 (8%)
Magnesium stearate	0.43 (0.5%)	0.43 (0.5%)	0.43 (0.5%)	0.43 (0.5%)
Total	85 mg	85 mg	85 mg	85 mg
Ingredient	Comp. 29 0.7 mg GLP1RA (wt% of composition)	Comp. 30 0.5 mg GLP1RA (wt% of composition)		
Prep 2 SDD (30 wt% of GLP1RA)	2.3 (2.7%)	1.7 (2.0%)		

Microcrystalline cellulose	67 (79%)	68 (80%)
Crospovidone XL-10	8.5 (10%)	8.5 (10%)
Na ₂ CO ₃ anhydrous	6.8 (8%)	6.8 (8%)
Magnesium stearate	0.43 (0.5%)	0.43 (0.5%)
Total	85 mg	85 mg

Particle Size Measurement

Particle size of the SDD was determined by laser diffraction utilizing wet dispersion on the Malvern Mastersizer 3000 equipped with the Hydro MV (medium volume) liquid disperser (Malvern Instruments Ltd. UK.). Optical model: Mie model, obscuration limits: 5-30%, general purpose model. The volume-based distribution was measured and the (D10, D50, D90) quantiles were reported.

The SDDs of Preparations 2 and 3 have a mean particle size of about 40 to about 65 μm , or more specifically, about 40 to about 50 μm , in diameter, as measured by the above method.

Solubility Studies

Twenty-four Hour Aqueous Solubility of Crystalline GLP1RA-Ca at 25 °C

Table 15

Solvent	Media pH	Solubility at 25 °C (mg/mL)
Water	NM*	0.028
0.1 N HCl	1.01	< 0.001
0.01 N HCl	1.98	< 0.001
pH 4.5 acetate buffer (USP)	4.5	< 0.001
pH 6.0 phosphate buffer (USP)	5.99	< 0.001
pH 7.5 phosphate buffer (USP)	7.44	0.003
Simulated gastric fluid	1.97	0.003
Fasted state simulated intestinal fluid	6.49	0.002
Fed state simulated intestinal fluid	4.93	0.013

*Not Measured

An embodiment of the present invention is an oral tablet formulation comprising an amorphous SDD of GLP1RA-Ca. GLP1RA-Ca in its crystalline form has poor

aqueous solubility as shown in Table 15. An amorphous SDD of GLP1RA-Ca using PVP-VA as the carrier polymer has been shown to provide improved hydrophilicity and solubility as compared to the crystalline GLP1RA-Ca (Table 16).

5 Twenty-four Hour Aqueous Solubility of Preparation 3 SDD at 25 °C

Table 16

Solvent	Media pH	Solubility at 25°C (mg/mL)
Water	6.9	90.0
0.1 N HCl	1.0	0.005
0.01 N HCl	2.0	0.004
pH 4.5 acetate buffer (USP)	4.5	0.007
pH 6.0 phosphate buffer (USP)	6.0	0.100
pH 7.5 phosphate buffer (USP)	7.5	8.7
Simulated gastric fluid	2.0	0.110
Fasted state simulated intestinal fluid	6.5	0.620
Fed state simulated intestinal fluid	5.0	0.022

Twenty-four-hour Aqueous Solubility of the Preparation 3, SDD at 37 °C

Table 17

Solvent	pH	24 hr solubility at 37°C (mg/mL)
Water	6.9	86.5
0.1 N HCl	1.0	0.001
0.01 N HCl	2.0	0.001
pH 4.5 acetate buffer (USP)	4.5	0.001
pH 6.0 phosphate buffer (USP)	6.0	0.038
pH 7.5 phosphate buffer (USP)	7.5	8.4
Simulated gastric fluid	2.0	0.044
Fasted state simulated intestinal fluid	6.5	0.005
Fed state simulated intestinal fluid	5.0	0.003

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As seen in Tables 16 and 17, Preparation 3 has pH dependent solubility. With a pKa of 5.1, it is expected that solubility of the drug would begin to increase at pH values near the pKa and dissolution performance will improve at pH values at or above the pKa. To test this, capsules containing the SDD and sufficient amounts of sodium bicarbonate to raise the pH of an acidic dissolution media to around the pKa were evaluated in

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dissolution experiments compared to a tablet containing much less pH modifier. The quantitative formulations are shown in Table 11 for the tablet and Table 3 for the capsule.

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Dosage Dissolution Studies

Dosage forms are evaluated in a 2-stage dissolution test consisting of an acid stage (500 mL 0.0133N HCl/ 8.12 mM NaCl) for 1 hour followed by the addition of concentrated FaSSiF (400 mL) to convert media to the same pH and composition of conventional fasted state intestinal fluid. To prepare concentrated FaSSiF for each 1 L, sodium phosphate dibasic anhydrous (5.714 g), sodium phosphate monobasic anhydrous (2.906 g), and NaCl (12.354 g) are added together with water to make 1 L and mixed well. The pH should be about 7.0. Add SIF powder (5.6 g) (FaSSiF/FeSSiF/FaSSGF powder (Biorelevant)).

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The test is run at 100 rpm using a USP II dissolution apparatus. Aliquots are withdrawn, filtered through a 0.22 micron filter, diluted 1:1 with MeOH to prevent drug precipitation and analyzed by HPLC.

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It was surprisingly found that the IR tablet performed better in the gastric stage than the capsule formulation, despite the capsule formulation raising the pH in the media to above 5 due to the large amount of sodium bicarbonate and the tablet having no effect on the media pH, which remained at a pH of 2.

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Dissolution Comparisons of Example 10 Tablet and Preparation 4 Capsule.

Table 18

		% Dissolved						
		0.0133 N HCl/ 8.12mM NaCl			Fasted state intestinal fluid			
		0.25 hr	0.5hr	1 hr	2 hr	3 hr	5 hr	5.5 hr
Example 10 IR Tablet	R1	40.7225	34.7522	23.9687	8.9237	5.5276	6.8771	5.6406
	R2	36.3592	33.8439	24.5525	11.3698	5.8262	5.6113	4.7865
	R3	35.577	38.8444	32.1674	13.9839	8.9858	6.6275	7.5356
	Ave	37.5529	35.8135	26.8962	11.4258	6.779867	6.371967	5.987567
	StDev	2.772676	2.663835	4.574316	2.530565	1.916219	0.670474	1.40701

	RSD	7.383387	7.4380 76	17.007 3	22.147 81	28.263 38	10.522 25	23.498 86
Preparation 4 Capsule	R1	7.0103	6.5912	5.9243	8.1787	10.058 6	11.042 3	15.85
	R2	0	0	4.0373	6.8174	7.3107	8.0334	9.687
	R3	9.2946	11.467 7	9.5824	11.702 3	15.091 2	13.215 6	15.546 4
	Ave	5.434967	6.0196 33	6.5146 67	8.8994 67	10.820 17	10.763 77	13.694 47
	StDev	4.843413	5.7551 76	2.8192 97	2.5209 5	3.9457 61	2.6023 04	3.4738 86
	RSD	89.11579	95.606 76	43.276 14	28.326 98	36.466 73	24.176 52	25.367 08

StDev refers to standard deviation.

Capsule Preparation 4 and IR tablet composition Example 7 are also compared using alternate dissolution conditions. Conditions used are USP II paddle at 100 rpm with 50 mM pH 6.8 phosphate buffer with 2% sodium lauryl sulfate as the dissolution media. Samples are analyzed by HPLC.

Surprisingly, despite having a significant amount of sodium bicarbonate present that should facilitate dissolution of the SDD from the capsule, the IR tablet again released more rapidly than the capsule with 100% release achieved within 30 minutes, while the capsule only achieved 35% release at 30 minutes and did not achieve >90% release until about 75 minutes.

Preparation 4 Capsule Alternate Dissolution Conditions

Table 19

Time (minutes)	% released
10	0.40
20	14.20
30	35.20
45	71.80
60	87.00
75	94.80
90	96.20
120	96.60

Composition Example 7 Alternate Dissolution Conditions

Table 20

Time (minutes)	% released
15	90.90
30	100.50
45	100.70
60	100.70
90	100.80
120	100.80
150	100.80

The pH modifiers in both the IR and DR tablets facilitate dissolution of the weakly acidic drug by raising the local, or micro, pH of the tablet as it disintegrates. Enteric tablets are used to discover levels of pH modifier required for enteric tablet compositions. Enteric Coated Tablets, Example 9, are tested in a 2-stage dissolution test using a USP II apparatus with paddle speed of 100 rpm. An acid challenge stage is conducted first lasting 2 hours in pH 4.5 sodium acetate buffer (500 mL) after which the tablets are removed and placed into FaSSiF (Biorelevant) (500 mL). Aliquots are withdrawn, filtered through a 0.22 micron filter, diluted 1:1 with MeOH to prevent drug precipitation and analyzed by HPLC.

Unexpectedly, very high levels of pH modifier (20 wt% in the tablet) resulted in poorer dissolution behavior of the DR tablets compared to lower levels. Further, an optimal level of peak and more sustained dissolution is achieved at around 10 wt% sodium carbonate.

Dissolution Studies for Delayed Release Tablet

Table 21

Example #	% Na ₂ CO ₃	Replicate	% Dissolved in Simulated fasted intestinal fluid						
			0.5 hr	1 hr	2 hr	3 hr	4 hr	5 hr	5.5 hr
Example 9a	0	R1	5.7	10.0	12.3	10.0	6.6	5.8	7.0
		R2	3.5	8.3	12.6	10.4	7.0	6.5	7.0
		R3	4.3	7.9	13.7	11.1	6.7	5.5	5.8
		Ave	4.5	8.7	12.9	10.5	6.8	6.0	6.6
		StDev	1.1	1.1	0.7	0.6	0.2	0.5	0.7
		RSD	24.8	12.6	5.5	5.5	3.2	8.8	10.3
Example 9b	5	R1	62.0	60.2	47.6	15.1	7.1	5.2	4.9
		R2	55.8	58.8	53.8	34.5	10.8	6.8	6.7
		R3	57.6	58.9	48.4	21.8	8.2	5.8	5.8

		Ave	58.5	59.3	49.9	23.8	8.7	5.9	5.8
		StDev	3.2	0.8	3.4	9.9	1.9	0.8	0.9
		RSD	5.5	1.3	6.7	41.6	21.6	13.6	15.2
Example 9c	10	R1	43.9	64.4	73.6	65.9	44.9	16.1	12.0
		R2	49.2	69.2	76.1	72.9	61.8	34.7	20.0
		R3	50.9	70.1	75.8	67.3	43.9	14.1	13.1
		Ave	48.0	67.9	75.2	68.7	50.2	21.6	15.0
		StDev	3.6	3.0	1.4	3.7	10.1	11.4	4.3
		RSD	7.6	4.5	1.8	5.4	20.1	52.6	28.6
Example 9d	15	R1	57.6	56.8	51.5	23.3	nm	5.6	4.9
		R2	57.2	55.3	58.3	30.5	nm	6.2	6.5
		R3	66.2	70.6	58.6	24.0	nm	5.4	4.2
		Ave	60.3	60.9	56.1	25.9	nm	5.7	5.2
		StDev	5.1	8.4	4.0	4.0	nm	0.4	1.2
		RSD	8.4	13.8	7.1	15.3	nm	7.4	22.6
Example 9e	20	R1	25.4	42.4	57.9	28.0	9.6	7.1	5.7
		R2	22.4	41.7	60.8	34.5	12.2	7.5	7.0
		R3	30.3	44.3	60.3	27.3	10.0	6.8	6.5
		Ave	26.1	42.8	59.7	29.9	10.6	7.1	6.4
		StDev	4.0	1.3	1.6	4.0	1.4	0.3	0.7
		RSD	15.3	3.1	2.6	13.3	13.2	4.4	10.3

nm = not measured

Tablets of Example 11 and Example 12 are tested in a 2-stage dissolution test using a USP II: apparatus with paddle speed of 100 rpm. The acid challenge stage is 2 hours in pH 4.5 sodium acetate buffer (500 mL) after which the tablets are removed and placed into FaSSiF (Biorelevant) (500 mL). Aliquots are withdrawn, filtered through a 0.22 micron filter, diluted 1:1 with MeOH to prevent drug precipitation and analyzed by HPLC.

It was surprisingly found that croscarmellose sodium as used in Example 11 is not able to afford the desired release profile whereas crospovidone as used in Example 12 affords the desired release profile.

Two Stage Dissolution Testing of Tablets

Table 22

		% Dissolved in Simulated fasted intestinal fluid					
		0.5 hr	1 hr	2 hr	3 hr	5 hr	5.5 hr
	R1	4.0	23.3	64.6	78.1	79.9	83.1

Croscarmellose Sodium Example 11	R2	4.1	12.7	79.4	70.4	85.2	82.5
	R3	7.0	18.7	69.3	77.5	84.7	80.8
	Ave	5.0	18.2	71.1	75.3	83.3	82.2
	RSD	34.5	29.2	10.6	5.6	3.5	1.4
Crospovidone Tablet, Example 12	R1	31.9	68.6	80.0	82.1	80.6	82.0
	R2	19.2	73.5	81.7	81.3	74.8	70.9
	R3	23.1	76.4	80.4	86.0	69.5	57.5
	Ave	24.8	72.8	80.7	83.2	75.0	70.1
	RSD	26.4	5.4	1.1	3.1	7.4	17.5

In a further embodiment, the rate of release from the enterically coated tablets may be controlled to affect specific aspects of the PK profile, such as C_{max} or the peak to trough plasma concentrations as these may be beneficial to the patient to help with tolerability and/or efficacy.

Controlled release from tablets is often achieved using rate controlling polymers such as hypromellose as in hydrophilic sustained release matrix tablets. The challenge with hypromellose or similar polymers is that they tend to work over several hours through diffusional and/or erosional mechanisms. This time span may be too long for low permeability molecules, where not maximizing drug concentration in the intestinal lumen, if the drug is released gradually over many hours, may result in decreased flux across the intestinal epithelium and subsequently lower absorption.

It was surprising found that controlling the amount of super disintegrant in the enterically coated dosage forms enables a significant degree of control of the rate of release over the desired time of complete release within 30 minutes

Tablets T1 and T2 are evaluated in a 2-stage dissolution test substantially similar to what has already been described, except the pH 4.5 sodium acetate acid stage is set to 1 hour followed by transfer of the tablet to FaSSiF (Biorelevant). The results are shown in Table 23.

Surprisingly, simply modulating the disintegrant levels can achieve a controlled level of release in the FaSSiF.

Two stage Dissolution Study of Tablets T1 and T2 at pH 4.5

Table 23

Media	Time (min)	Percent dissolved	
		Example 1; T1	Example 2; T2
	30	0.0	0.0

pH 4.5 sodium acetate buffer	60	0.0	0.0
Fasted state intestinal fluid	90	82.2	2.9
	120	85.5	9.8
	180	86.0	66.1
	240	84.8	81.2
	300	76.3	69.8
	330	67.6	58.0

Another lever to modulate the release of the drug from the enteric tablets is to alter the amount of sodium carbonate. The tablets are subjected to dissolution in pH 6.8 phosphate buffer with 2% sodium lauryl sulfate as described herein. Results of this study demonstrate that there is a synergy between the level of disintegrant and the amount of pH modifier that can be used to control release of drug from the tablet. Further, the release is controlled to within the desired range of within 30 minutes to not more than 3 hours to model the approximate in-vivo transit time through the small intestine where most drug absorption is expected to occur. The results are shown in Table 24.

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Dissolution Time Study of Composition Tablets, T1, T2, A, B, C, D at pH 6.8
Table 24

Percent dissolved in pH 6.8 phospahte buffer with 2% sodium lauryl sulfate						
Time (min)	Example 1; T1	Example 2; T2	Example 3; A	Example 4; B	Example 5; C	Example 6; D
15	94.4	8.0	89.9	58.9	2.2	1.5
30	97.4	25.1	99.4	88.5	5.5	9.4
45	97.5	44.9	99.6	95.0	14.2	24.8
60	97.4	75.7	99.6	98.3	25.5	53.6
90	97.4	99.1	99.5	98.5	56.5	83.0
120	97.5	99.3	99.5	98.6	87.2	90.8
150	97.5	99.2	99.4	98.5	99.6	97.5

Clinical Trial

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A multiple-ascending dose study was conducted to characterize and compare the pharmacokinetics (PK) of prototype formulations of Preparation 4 (capsule), Example 1 (DR Tablet composition T1 with enteric coating prepared as in Example 9, referred to below as T1 DR Tablet), and Example 7 (IR Tablet Composition E with immediate

release coating, referred to below as E IR Tablet). The study was conducted in two parts: A and B.

- Part A evaluated the safety, tolerability, and PK of multiple oral doses of GLP1RA formulation prototypes T1 and E in healthy participants versus the reference capsule Preparation 4. A dose titration period was from Day 1 through Day 18, where participants received increasing doses of GLP1RA in a capsule for dose titration. Within-treatment dose escalation was every 6 days and reached a maximum dose of 16 mg of GLP1RA once daily (QD) on Day 19. On Days 19 to 24, participants received reference capsule Preparation 4 (16 mg QD) before entering the test phase, from Days 25 to 36.
- During test period-1, the participants were administered GLP1RA a prototype tablet (16 mg QD) formulations as per their randomization. The participants were then crossed over on Day 31 for period-2 and received the second prototype tablet (16 mg QD) through Day 36.

Table 25. Geometric Mean (Geometric CV%) Plasma Pharmacokinetic Parameters for GLP1RA Following Single and Multiple Oral Doses of GLP1RA to Healthy Male and Female Participants

Dose Period Dose Level Status No. of Participants Parameter	Reference Period- Preparation 4 Capsule Fasted n=10	Test Period 1 and 2 – T1, DR tablet Fasted n=10	Test Period 1 and 2- E, IR tablet Fasted n=10
Single (1 st) Dose Day	19	25 or 31	25 or 31
T _{max} ^a (h)	8.00 (4.00-23.87)	8.00 (4.00-23.97)	8.00 (4.00-12.05)
C _{max} (ng/mL)	59.7 (64.5)	89.7 (80.0)	82.5 (86.8)
AUC(0-24) (ng.h/mL)	869 (51.7)	1230 (72.3)	1180 (64.3)
Multiple (6 th) Dose Day	24	30 or 36	30 or 36
T _{max} ^a (h)	7.02 (4.00-8.00)	8.00 (4.00-16.00)	8.00 (4.00-16.10)
C _{max} (ng/mL)	66.2 (77.4)	111 (81.2)	97.4 (58.9)
AUC(0-24) (ng.h/mL)	988 (66.9)	1480 (75.2)	1400 (51.2)
Frel C _{max} (%)	N/A	167 (38.8)	147 (36.6)
Frel AUC(0-24) (%)	N/A	150 (25.0)	141 (23.8)

Abbreviations: AUC(0-24) = area under the curve from time 0 to 24 hours post dose;
 C_{max} = maximum observed concentration; Frel AUC(0-24) = relative bioavailability
 based on AUC(0-24); Frel C_{max} = relative bioavailability based on C_{max}; h = hour;
 N/A = not applicable

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The results of Part A indicate that the average peak and overall exposure levels (as measured by C_{max} and AUC(0-24)) for 16 mg, DR Tablet T1 were approximately 67% and 50% higher, respectively, than those for 16 mg reference Preparation 4 capsule. These increases were statistically significant at the 10% significance level ($p < .001$ for both C_{max} and AUC(0-24)).

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Similarly, for 16 mg Tablet E IR tablet, the average peak and overall exposure levels (as measured by C_{max} and AUC(0-24)) were approximately 47% and 41% higher, respectively, than those for 16 mg reference capsule. These increases were statistically significant at the 10% significance level ($p = .007$ and $p < .001$ for C_{max} and AUC(0-24), respectively).

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Part B further evaluated Tablet E IR tablet regarding food effect and DDI effect with a co-administered proton pump inhibitor (PPI). As in Part A, treatment escalation occurred every 6 days during a titration period and reached a maximum dose of 16 mg QD on Day 19. Treatment then proceeded with GLP1RA in a fasted or fed state and a fasted state with a co-administered PPI. Each option began with a 6-day reference period (16 mg QD) using Tablet E IR tablet as the reference, followed by two 6-day test periods (16 mg QD).

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Table 26: Geometric Mean (Geometric CV%) Plasma Pharmacokinetic Parameters for GLP1RA Following Single and Multiple Oral Doses of GLP1RA to Healthy Male and Female Participants

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Dose Period Dose Level Status No. of Participants Parameter	Reference Period Tablet E IR tablet Fasted n=12	Test Period 1 Tablet E IR tablet Fed n=12	Test Period 2 Tablet E IR tablet + PPI Fasted n=12
Single (1st) Dose Day	19	25	31
T _{max} ^a (h)	6.00 (4.00-8.02)	8.02 (4.02-12.02) [n=11]	6.00 (4.00-16.02) [n=11]
C _{max} (ng/mL)	63.8 (33.5)	48.0 (35.2) [n=11]	74.7 (27.1) [n=11]
AUC(0-24) (ng.h/mL)	869 (27.1)	781 (31.2) [n=11]	1080 (22.7) [n=11]

Multiple (6th) Dose Day	24	30	36
Tmax ^a (h)	8.00 (4.00-12.00)	7.00 (2.00-16.05)	7.00 (4.00-12.00)
Cmax (ng/mL)	63.4 (32.2)	56.3 (29.6)	59.6 (51.0)
AUC(0-24) (ng.h/mL)	903 (25.3)	865 (24.6)	956 (40.1)
Frel Cmax (%)	N/A	88.9 (38.1)	94.1 (36.3)
Frel AUC(0-24) (%)	N/A	95.8 (23.8)	106 (31.6)

Abbreviations: AUC(0-24) = area under the curve from time 0 to 24 hours post dose;
Cmax = maximum observed concentration; Frel AUC(0-24) = relative bioavailability
based on AUC(0-24); Frel Cmax = relative bioavailability based on Cmax; h = hour;
N/A = not applicable

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The results of Part B indicate that the average peak and overall exposure levels (as measured by Cmax and AUC(0-24)) for 16 mg Tablet E IR tablet fed were comparable (that is, fed exposure within 11% and 4% of fasted exposure for Cmax and AUC(0-24), respectively) to those for 16 mg Tablet E IR tablet fasted (p=.39 and p=.66 for Cmax and AUC(0-24), respectively).

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For 16 mg Tablet E IR tablet with PPI, the average peak and overall exposure levels (as measured by Cmax and AUC(0-24)) were also comparable (that is, 6% lower and 6% higher for Cmax and AUC(0-24), respectively) to those for 16 mg IR Tablet Composition E (p=.65 and p=.57 for Cmax and AUC(0-24), respectively).

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Although the invention has been described in considerable detail with reference to certain aspects thereof, other versions are possible. Embodiments disclosed herein are for illustration purposes only and various modifications of the embodiments and further embodiments thereof, in addition to those shown and described herein, will become apparent to those skilled in the art from the full contents of this specification.

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We Claim:

1. A tablet composition comprising:
3-[(1S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-[(4S)-2-(4-fluoro-3,5-
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.
- 10 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.
- 15 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.
- 20 4. The composition as claimed by Claim 3, wherein the pH modifier is anhydrous.
5. The composition as claimed by Claim 3 wherein the pH modifier is sodium
carbonate.
- 25 6. The composition as claimed by of Claim 5 wherein the pH modifier is
anhydrous sodium carbonate.
7. The composition as claimed by any one of Claims 1 to 6 wherein the
composition comprises:
30 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.

5

8. The composition as claimed by Claim 7 wherein the super disintegrant is selected from the group consisting of croscarmellose sodium and crospovidone.

9. The composition as claimed by Claim 8 wherein the super disintegrant is
10 crospovidone.

10. The composition as claimed by any one of Claims 1 to 9 wherein the composition comprises:

3-[(1S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-[(4S)-2-(4-fluoro-3,5-
15 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;
20 a super disintegrant; and
a lubricant.

11. The composition as claimed by Claim 10 wherein the lubricant is magnesium
stearate.

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12. The composition as claimed by any one of Claims 1 to 11 further comprising an immediate release coating.

13. The composition as claimed by any one of Claims 1 to 12 further comprising
30 an enteric coating.

14. The composition as claimed by any one of Claims 1 to 13 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 salt is:

5 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.

15 15. The composition as claimed by any one of claims 1 to 14, 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

15 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.

20 16. The composition as claimed by Claim 15 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, 0.5 Ca hydrate is in an amount of about 48 mg per tablet.

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17. The composition as claimed by any one of Claims 1 to 16 for use in treating type 2 diabetes.

30 18. The composition as claimed by any one of Claims 1 to 16 for use in weight management.

19. A process for preparing a tablet composition as claimed by any one of Claims 1 to 16 comprising a spray dried dispersion 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.

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20. The process as claimed by claim 19, wherein the spray dried dispersion 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, further comprises a PVP-VA polymer.

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21. A tablet composition wherein the composition comprises:

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 0.5 mg to about 75 mg, on a free acid basis;

15

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 1 mg to about 150 mg;

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a super disintegrant selected from the group consisting of croscarmellose sodium and crospovidone, in an amount of about 1 mg to about 250 mg; and

25

a lubricant which is magnesium stearate; in an amount of about 0.1 mg to about 10 mg.

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

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;

30

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;

5 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.

23. A tablet composition wherein the composition comprises:

10 an 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.

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24. The tablet composition as claimed by Claim 23 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
25 sodium carbonate; in an amount of between about 1 mg to about 150 mg.

25. The tablet composition as claimed by any one of Claims 23 to 24 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.

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26. The tablet composition as claimed by Claim 24 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.

27. The tablet composition as claimed by Claim 26 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 1.7 mg to about 14.3 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 16.9 wt% of the total tablet weight; and

the pH modifier which is sodium carbonate; in an amount of about 6.8 mg; wherein the pH modifier is about 8 wt% of the total tablet weight.

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28. The tablet composition as claimed by Claim 26 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
5 between about 16.7 mg to about 120 mg of the SDD; and the balance of the SDD is composed of PVP-VA; wherein the SDD is about 19.5 wt% of the total tablet weight; and the pH modifier which is sodium carbonate; in an amount of between about 6.8 mg to about 49.2 mg; wherein the pH modifier is about 8 wt% of the total tablet weight.

10 29. The tablet composition as claimed by Claim 26 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
15 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
20 mg to about 80 mg; wherein the pH modifier is about 8 wt% of the total tablet weight.

30. The tablet composition as claimed by any one of Claims 21 to 29, wherein the SDD has a mean particle size of about 5 μ m to about 113 μ m in diameter; and the pH modifier is sodium carbonate.

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31. The tablet composition as claimed by Claim 30, wherein the composition further comprises:

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

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32. The tablet composition as claimed by Claim 31, 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.

5 33. The tablet composition as claimed by Claim 32, 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.

10 34. The tablet composition as claimed by Claim 33, 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.

15 35. The tablet composition as claimed by Claim 26, 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 about 19.5 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 about 55 wt% of the total tablet weight.

30 36. The tablet composition as claimed by Claim 26, 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 about 25 wt% of the total tablet weight;

5 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 about 49.5 wt% of the total tablet weight.

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37. The tablet composition as claimed by Claim 26, 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 about 21 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;

20 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 about 53.5 wt% of the total tablet weight.

25 38. The tablet composition as claimed by Claim 26, 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 about 16.9 wt% of the total tablet weight;

30

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

5 a filler which is MCC; wherein the filler is about 64.6 wt% of the total tablet weight.

39. The tablet composition as claimed by Claim 26, wherein the composition comprises:

the SDD of about 30 wt% of 3-[(1S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-
10 [(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 about 11.8 wt% of the total tablet weight;

15 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 about 69.7 wt% of the total tablet weight.
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40. The tablet composition as claimed by Claim 26, 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-
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; and the balance of the SDD is composed of PVP-VA; wherein the SDD is about 9.8 wt% of the total tablet weight;

the pH modifier which is sodium carbonate; wherein the pH modifier is about 8
30 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 about 71.7 wt% of the total tablet weight.

41. The tablet composition as claimed by Claim 26, wherein the composition comprises:

the SDD of about 30 wt% of 3-[(1S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-
5 [(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 about 3.9 wt% of the total tablet
weight;
10 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 about 77.6 wt% of the total tablet weight.

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42. The tablet composition as claimed by Claim 26, 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-
20 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 about 3.2 wt% of the total tablet
weight;
the pH modifier which is sodium carbonate; wherein the pH modifier is about 8
25 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 about 78.3 wt% of the total tablet weight.

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43. The tablet composition as claimed by Claim 26, 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 about 2.7 wt% of the total tablet weight;

5 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 about 78.8 wt% of the total tablet weight.

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44. The tablet composition as claimed by Claim 26, 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 about 2.0 wt% of the total tablet weight;

15

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

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 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 about 79.5 wt% of the total tablet weight.

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45. The tablet composition as claimed by any one of Claims 35 to 44, wherein the SDD has a mean particle size of about 5 μ m to about 113 μ m in diameter.

46. The tablet composition as claimed by any one of Claim 44, wherein the SDD has a mean particle size of about 40 μ m to about 65 μ m in diameter

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47. The tablet composition as claimed by any one of Claims 21 to 46 wherein the composition further comprises a lubricant which is magnesium stearate; wherein the lubricant is about 0.5 wt% of the total tablet weight.

48. The tablet composition as claimed by Claim 47 wherein the composition further comprises an immediate release coating.

5 49. The tablet composition as claimed by Claim 48 wherein the composition further comprises an enteric coating over the immediate release coating.

 50. The composition as claimed by any one of Claims 21 to 49 for use in treating type 2 diabetes.

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 51. The composition as claimed by any one of Claims 21 to 49 for use in weight management.