

A HIGH BIOAVAILABILITY PHARMACEUTICAL COMPOSITION OF GLP AGONIST FOR ORAL ADMINISTRATION.

The present invention relates to a pharmaceutical composition for oral
5 administration comprising a GLP receptor agonist or pharmaceutically acceptable
salt or derivatives thereof, one or more medium chain fatty acid based permeation
enhancers with aromatic functional group, and one or more medium chain fatty acid
based permeation enhancers without aromatic functional group. The
pharmaceutical composition may optionally further comprise a basifier.

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BACKGROUND OF INVENTION

Peptides are large macromolecules mainly made up of amino acids (AAs)
attached to each other. Peptides are the major therapeutic compounds used for the
15 treatment of various disease or disorder. Peptides are majorly administered as
injection which poses major patient compliance challenge as it is cumbersome for
the patients requiring repeated administration.

There have been multiple attempts to delivery peptides by oral route.
20 However, majority of them has been unsuccessful largely due to susceptibility of
peptide to gastrointestinal tract (GIT) enzymes. Permeability of these large
macromolecules from GIT poses further challenge to development of oral therapy
for such macromolecules.

Therefore, there is an urgent need for the improved oral delivery therapy
25 with pharmaceutical composition comprising peptides or pharmaceutically
acceptable salts or derivatives thereof. It is surprisingly found that the composition
as per invention can deliver peptide through oral route effectively.

DESCRIPTION OF DRAWINGS

Figure 1: Plasma concentration time profile curve for example 1 vs Rybelsus 7 mg tablets in human volunteers.

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Figure 2: Dissolution profile of the composition as per example 1 performed in Phosphate Buffer with pH 6.8.

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DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a pharmaceutical composition for oral administration comprising a GLP receptor agonist or pharmaceutically acceptable salt or derivatives thereof, one or more medium chain fatty acid based permeation enhancers with aromatic functional group, and one or more medium chain fatty acid based permeation enhancers without aromatic functional group. The pharmaceutical composition may optionally further comprise a basifier.

“Therapeutically effective amount” or “effective amount” refers to the amount of a pharmaceutically active agent when administered, is sufficient to affect such prevention or treatment. The therapeutically effective amount will vary depending on the disease and its severity, and the age, weight, and other conditions of the patient to be treated. The pharmaceutical composition as per present invention are useful for the treatment of disease involving GLP receptors including but not limited to type 2 diabetes and obesity.

“Medium chain fatty acid” refers to fatty acids with C6 to C12 carbon chain. Examples of medium chain fatty acid includes caproic acid (C6), caprylic acid(C8), capric acid (C10), and lauric acid(C10).

In an embodiment, the present invention relates to a pharmaceutical composition
5 for oral administration comprising

- a. a therapeutically effective amount of GLP receptor agonist or pharmaceutically acceptable salt or derivatives thereof
- b. one or more medium chain fatty acid based permeation enhancers with aromatic functional group, and
- 10 c. one or more medium chain fatty acid based permeation enhancers without aromatic functional group.

In an another embodiment, the present invention relates to a pharmaceutical composition for oral administration comprising

- a. a therapeutically effective amount of GLP receptor agonist or
15 pharmaceutically acceptable salt or derivatives thereof,
- b. one or more medium chain fatty acid based permeation enhancers with aromatic functional group,
- c. one or more medium chain fatty acid based permeation enhancers without aromatic functional group, and
- 20 d. one or more basifier.

In an another embodiment, the present invention relates to a pharmaceutical composition for oral administration comprising

- a. a therapeutically effective amount of semaglutide,
- b. one or more medium chain fatty acid based permeation enhancers with
25 aromatic functional group,

- c. one or more medium chain fatty acid based permeation enhancers without aromatic functional group, and
- d. one or more basifier.

5 In a specific embodiment, medium chain fatty acid based permeation enhancers with aromatic functional group is Salcaprozate sodium. In a more specific embodiment, Salcaprozate sodium is in amount of 25 mg to 200mg.

In an another specific embodiment, the present invention relates to a pharmaceutical composition for oral administration comprising

- a. a therapeutically effective amount of semaglutide,
- 10 b. salcaprozate sodium,
- c. sodium caprate or sodium caprylate or combinations thereof, and
- d. calcium carbonate.

In an another embodiment, the pharmaceutical composition as per present invention is tablet and are prepared by direct compression method. In one embodiments, tablet
15 does not contains binder.

In one or more embodiments, AUC_{0-t} (ngxh/mL) for one or more pharmaceutical composition as per present invention is 1.5 times or more compare to AUC_{0-t} (ngxh/mL) for reference product Rybelsus in single dose fasted study in human volunteers. In one or more embodiments, AUC_{0-t} (ngxh/mL) for one or more
20 pharmaceutical composition as per present invention is 2 times or more compare to AUC_{0-t} (ngxh/mL) for reference product Rybelsus in single dose fasted study in human volunteers. In one or more embodiments, the ratio of AUC_{0-t} (ngxh/mL) of reference product Rybelsus to AUC_{0-t} (ngxh/mL) of one or more pharmaceutical composition as per present invention in single dose fasted study in human
25 volunteers is 1:1.5 to 1:6.

In one or more embodiments, C_{max} (ng/mL) for one or more pharmaceutical composition as per present invention is 1.5 times or more compare to C_{max} (ng/mL) for reference product Rybelsus in single dose fasted study in human volunteers. In one or more embodiments, C_{max} (ng/mL) for one or more pharmaceutical composition as per present invention is 2 times or more compare to C_{max} (ng/mL) for reference product Rybelsus in single dose fasted study in human volunteers. In one or more embodiments, the ratio of C_{max} (ng/mL) of reference product Rybelsus to C_{max} (ng/mL) of one or more pharmaceutical composition as per present invention in single dose fasted study in human volunteers is 1:1.5 to 1:6.

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GLUCAGON-LIKE PEPTIDE (GLP) RECEPTOR AGONIST

Glucagon-like Peptide (GLP) receptor agonist are agonists of the GLP receptor. GLP receptor agonist are class of compound majorly used for the treatment of type 2 diabetes. There are many other applications of GLP receptor agonist which includes weight management therapy. Without limiting, the examples of GLP receptor agonist includes Semaglutide, Exenatide, Liraglutide, Tirzepatide, Albiglutide, Dulaglutide, and Lixisenatide. The pharmaceutical composition as per present invention may contain therapeutically effective amount of GLP receptor agonist.

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SEMAGLUTIDE

Semaglutide is a Glucagon-like Peptide (GLP) receptor agonist and is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2. It is presently approved as solution for subcutaneous administration

and as tablet for oral administration. Oral tablets are approved as 3mg, 7mg and 14mg (Rybelsus) tablets which contains inactive ingredients magnesium stearate, microcrystalline cellulose, povidone and salcaprozate sodium (SNAC). The pharmaceutical composition as per present invention may contain therapeutically effective amount of semaglutide. The amount of semaglutide may range from 1 mg to 50 mg. More preferably, the amount of semaglutide may range from 1 mg to 20 mg. In one embodiment, the pharmaceutical composition of present invention contains 3mg, 7mg or 14mg of semaglutide.

10 PERMEATION ENHANCERS

Permeation enhancer are used to improve absorption of poorly permeable active pharmaceutical ingredients across the gastrointestinal tract. Permeation enhancer used in the composition as per present invention includes one or more medium chain fatty acid based permeation enhancers with aromatic functional group and one or more medium chain fatty acid based permeation enhancers with aromatic functional group.

The medium chain fatty acid based permeation enhancers with aromatic functional group may include but not limited to sodium 8-(2-hydroxybenzamido) caprylate, N-(10-[2-hydroxybenzoyl] amino) decanoic acid, N-(5-chlorosalicyloyl)-8-aminocaprylic acid. Sodium 8-(2-hydroxybenzamido) caprylate also known as Salcaprozate Sodium and is the sodium salt form of salcaprozate.

The amount of medium chain fatty acid based permeation enhancers with aromatic functional group may be in the range of 25 mg to 500 mg. In one embodiment the amount of medium chain fatty acid based permeation enhancers with aromatic functional group is 25 mg to 200mg. In one embodiment, medium

chain fatty acid based permeation enhancers with aromatic functional group is Sodium 8-(2-hydroxybenzamido) caprylate (Salcaprozate Sodium). The amount of Sodium 8-(2-hydroxybenzamido) caprylate (Salcaprozate Sodium) may be in the range of 25 mg to 500 mg. In an more specific embodiment the amount of Sodium
5 8-(2-hydroxybenzamido) caprylate (Salcaprozate Sodium) is 25 mg to 200mg.

The medium chain fatty acid based permeation enhancers without aromatic functional group may include but not limited to sodium caprylate, sodium caprate, sodium hexanoate, sodium octanoate, sodium decanoate and sodium dodecanoate.

The amount of medium chain fatty acid based permeation enhancers without
10 aromatic functional group may be in the range of 25mg to 800mg. In one embodiment, medium chain fatty acid based permeation enhancers without aromatic functional group is Sodium caprate or sodium caprylate. The amount of Sodium caprate or sodium caprylate may be in the range of 25mg to 800mg. In an more specific embodiment the amount of Sodium caprate or sodium caprylate is
15 200mg to 500mg.

In a one or more embodiments, the ratio of “medium chain fatty acid based permeation enhancers with aromatic functional group” to “medium chain fatty acid based permeation enhancers without aromatic functional group” in a pharmaceutical composition is 1:1 to 1:20. In a one or more preferred embodiments,
20 the ratio of “medium chain fatty acid based permeation enhancers with aromatic functional group” to “medium chain fatty acid based permeation enhancers without aromatic functional group” in a pharmaceutical composition is 1:1 to 1:5.

BASIFIERS

Basifier are compound that provide alkaline environment during and/or
25 after dissolution of active ingredient. The basifiers may include but not limited to calcium carbonate, sodium carbonate, sodium bicarbonate, magnesium hydroxide,

and aluminium hydroxide or combination thereof. The amount of basifier may be in the range of 25mg to 600mg. In one embodiment, basifier is Calcium carbonate.

5 The oral pharmaceutical composition as per present invention may further comprise one or more additional active ingredient. Non-limiting examples of additional active ingredients includes biguanides like metformin; glipizide or glyburide; DPP4 inhibitors like sitagliptin, alogliptin, linagliptin; SGLT2 inhibitors like dapagliflozin, canagliflozin, empagliflozin, ertugliflozin; rosiglitazone or pioglitazone; and repaglinide.

10 The oral pharmaceutical composition may be tablets, capsules, powders and granules, multi-particulate dosage forms and the likes. The multicompartiment dosage form may be bilayer tablets, capsule-in-capsule, tablet-in capsule and any other dosage form. The pharmaceutical compositions can be formulated by any techniques known to or appreciated by a person skilled in the art. In a specific
15 embodiment, pharmaceutical composition of present invention is prepared by direct compression method.

The oral pharmaceutical composition may further include optionally any one or a combination of one or more pharmaceutically acceptable excipients, such as but not limited to diluents, disintegrants, lubricating agents, binders, colorants,
20 pigments, stabilizers, preservatives, antioxidants and solubility enhancers. Diluent may be selected from microcrystalline cellulose, lactose, mannitol, modified starches, dibasic calcium phosphate, any other diluent or combination thereof. Disintegrant may be selected from cross-linked polyvinylpyrrolidone, sodium starch glycolate, any other disintegrant or combination thereof. Binder may be
25 selected from hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinyl pyrrolidone, any other binder or combination thereof. Lubricants may be selected

from calcium stearate, magnesium stearate, sodium stearyl fumarate, talc, any other lubricant or combination thereof.

Having described the invention with reference to the different embodiments of the invention, other embodiments will become apparent to one skilled in the art from
5 consideration of the specifications.

The innovation is further defined by reference to the following examples. It will be apparent to those skilled in the art that many modifications to the composition may be practiced without departing from the scope of this invention.

EXAMPLES

EXAMPLE – 1

5 Compositions:

Sr No	Ingredient	Quantity per tablet (mg)
1	Semaglutide	7
2	Sodium N-(8-(2-hydroxybenzoyl)amino)caprylate (SNAC)	150
3	Sodium caprate	450
4	Calcium carbonate	100
5	Sodium Starch Glycolate (SSG)	100
6	Magnesium stearate	20
	Total	827

Procedure :

1. All ingredients were weighed accurately.
- 10 2. SNAC, Sodium caprate, Calcium carbonate and SSG were mix in polybag for 3 min.
3. Semaglutide Powder added to above blend.
4. The above blend was passed through 40 mesh sieve.
5. The blend was lubricated using magnesium stearate for 3 min.
- 15 6. The Compression was performed using suitable punches.
7. The Tablets were packed in ALU-ALU blister.

Dissolution profile of the composition as per example 1 was performed in Phosphate Buffer with pH 6.8 and is as shown in fig 2.

A Single dose fasted state 3 way cross over biostudies were performed for the composition of example 1 versus Rybelsus (reference) tablet in human volunteers. Result are shown in figure 1. Results shows surprisingly higher plasma concentration for the composition of example 1 compare to reference product Rybelsus.

Formulation	Pilot study results (in healthy volunteers)
Rybelsus	AUC _{0-t} (ngxh/mL) values are 978.0±1239.6 AUC _{0-∞} (ngxh/mL) values are 1470.9±1822.5 C _{max} (ng/mL) values are 18.562±25.549 T _{max} (h) values are 1.44±0.72
T1 –(Ex-1)	AUC _{0-t} (ngxh/mL) values are 3438.7±4349.0 AUC _{0-∞} (ngxh/mL) values are 5007.6±6375.7 C _{max} (ng/mL) values are 54.944±67.907 T _{max} (h) values are 2.09±1.54

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EXAMPLE – 2

Sr No	Ingredient	Quantity per tablet (mg)
1	Semaglutide	7
2	Sodium N-(8-(2-hydroxybenzoyl)amino)caprylate (SNAC)	150
3	Sodium caprate	300
4	Calcium carbonate	80
5	Crospovidone	80

6	Magnesium stearate	10
	Total	627

Procedure – Composition was prepared with analogous procedure similar to example 1.

5 EXAMPLE – 3

Sr No	Ingredient	Quantity per tablet (mg)
1	Semaglutide	7
2	Sodium N-(8-(2-hydroxybenzoyl)amino)caprylate (SNAC)	100
3	Sodium caprate	250
4	Calcium carbonate	60
5	Sodium starch glycolate	50
6	Magnesium stearate	10
	Total	477

10 Procedure – Composition was prepared with analogous procedure similar to example 1.

COMPARATIVE EXAMPLE A

15 Composition

Sr No	Ingredient	Quantity per tablet (mg)
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Intragranular

1	Sodium caprate	450
2	Sodium Lauryl Sulphate (SLS)	10
3	Sodium starch glycolate (SSG)	150
4	Povidone	30
5	Semaglutide	7
6	Water	QS

Extragranular

6	Sodium starch glycolate (SSG)	100
7	Magnesium stearate	10
	Total	757

Procedure

1. All ingredients were weighed accurately.
- 5 2. Ingredients 1 to 5 were sifted in 40 # sieve.
3. The powder mixture was mixed in polybag for 5 min .
4. Approximately 3 mL water added drop wise to achieve granulation endpoint.
5. The resulting wet granules were dried in hot air oven for 10 hours at 45
- 10 degrees Celsius.
6. The dry granules were passed through 40 # sieve.
7. Mg stearate and sodium starch glycolate were added as extra granular part and mixed for 5 minutes.
8. The resulting blend was compressed using suitable punches.

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A Single dose fasted state 3 way cross over biostudies were performed for the composition of comparative example A versus Rybelsus (reference) tablet in human

volunteers. Result are shown in figure 3. Results shows very low plasma concentration for the composition of comparative example A compare to reference product Rybelsus 7 mg.

CLAIMS

I/We Claim

1. A pharmaceutical composition for oral administration comprising
 - a. a therapeutically effective amount of GLP receptor agonist or pharmaceutically acceptable salt or derivatives thereof,
 - b. one or more medium chain fatty acid based permeation enhancers with aromatic functional group, and
 - c. one or more medium chain fatty acid based permeation enhancers without aromatic functional group.
2. The pharmaceutical composition as claimed in claim 1, wherein GLP receptor agonist is semaglutide.
3. The pharmaceutical composition as claimed in claim 1, wherein medium chain fatty acid based permeation enhancers with aromatic functional group is in amount of 25 mg to 200mg.
4. The pharmaceutical composition as claimed in claim 1, wherein medium chain fatty acid based permeation enhancers with aromatic functional group is salcaprozate sodium.
5. The pharmaceutical composition as claimed in claim 1, wherein medium chain fatty acid based permeation enhancers without aromatic functional group is selected from group consisting of sodium caprate or sodium caprylate or combinations thereof.
6. The pharmaceutical composition as claimed in claim 5, wherein sodium caprate or sodium caprylate or combinations thereof is in an amount of 200mg to 500mg.
7. The pharmaceutical composition as claimed in claim 1, wherein said composition does not contains binder.
8. The pharmaceutical composition as claimed in claim 1, wherein said pharmaceutical composition is tablet.

9. The pharmaceutical composition as claimed in claim 8, wherein said tablet is prepared by direct compression method.
10. The pharmaceutical composition as claimed in claim 1, wherein said composition further comprises one or more additional active ingredient.
- 5 11. The pharmaceutical composition as claimed in claim 1, wherein AUC_{0-4} (ngxh/mL) for said pharmaceutical composition is 1.5 times or more compare to AUC_{0-4} (ngxh/mL) for reference product Rybelsus in single dose fasted study in human volunteers.
- 10 12. The pharmaceutical composition as claimed in claim 1, wherein C_{max} (ng/mL) for said pharmaceutical composition is 1.5 times or more compare to C_{max} (ng/mL) for reference product Rybelsus in single dose fasted study in human volunteers.
- 15 13. A pharmaceutical composition for oral administration comprising
 - a. a therapeutically effective amount of GLP receptor agonist or pharmaceutically acceptable salt or derivatives thereof,
 - b. one or more medium chain fatty acid based permeation enhancers with aromatic functional group,
 - c. one or more medium chain fatty acid based permeation enhancers without aromatic functional group, and
 - 20 d. one or more basifier.
14. The pharmaceutical composition as claimed in claim 13, wherein GLP receptor agonist is semaglutide.
15. The pharmaceutical composition as claimed in claim 13, wherein medium chain fatty acid based permeation enhancers with aromatic functional group is in amount of 25 mg to 200mg.
- 25 16. The pharmaceutical composition as claimed in claim 13, wherein medium chain fatty acid based permeation enhancers with aromatic functional group is salcaprozate sodium.

17. The pharmaceutical composition as claimed in claim 13, wherein medium chain fatty acid based permeation enhancers without aromatic functional group is selected from group consisting of sodium caprate or sodium caprylate or combinations thereof.
- 5 18. The pharmaceutical composition as claimed in claim 17, wherein sodium caprate or sodium caprylate or combinations thereof is in an amount of 200mg to 500mg.
19. The pharmaceutical composition as claimed in claim 13, wherein said composition does not contains binder.
- 10 20. The pharmaceutical composition as claimed in claim 13, wherein said pharmaceutical composition is tablet.
21. The pharmaceutical composition as claimed in claim 20, wherein said tablet is prepared by direct compression method.
22. The pharmaceutical composition as claimed in claim 13, wherein basifier is calcium carbonate.
- 15 23. The pharmaceutical composition as claimed in claim 13, wherein AUC_{0-t} (ngxh/mL) for said pharmaceutical composition is 1.5 times or more compare to AUC_{0-t} (ngxh/mL) for reference product Rybelsus in single dose fasted study in human volunteers.
- 20 24. The pharmaceutical composition as claimed in claim 13, wherein C_{max} (ng/mL) for said pharmaceutical composition is 1.5 times or more compare to C_{max} (ng/mL) for reference product Rybelsus in single dose fasted study in human volunteers.
- 25 25. A pharmaceutical composition for oral administration comprising
 - a. a therapeutically effective amount of semaglutide,
 - b. 25 mg to 200mg of salcaprozate sodium, and
 - c. 200mg to 500mg of sodium caprate or sodium caprylate or combinations thereof.
26. A pharmaceutical composition for oral administration comprising

- a. a therapeutically effective amount of semaglutide,
- b. salcaprozate sodium,
- c. sodium caprate or sodium caprylate or combinations thereof, and
- d. calcium carbonate.