

A PHARMACEUTICAL COMPOSITION OF GLP AGONIST FOR ORAL ADMINISTRATION

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 permeation enhancer, one or more mucoadhesive agent and one or more basifier. More preferably, permeation enhancer are medium chain fatty acid based permeation enhancers.

BACKGROUND OF INVENTION

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Peptides are large macromolecules mainly made up of amino acids (AAs) attached to each other. Peptides are the major therapeutic compounds used for the 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. However, majority of them has been unsuccessful largely due to susceptibility of peptide to gastrointestinal tract (GIT) enzymes and pH. 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 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 permeation enhancer, one or more mucoadhesive agent and one or more 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 for oral administration comprising

- a. a therapeutically effective amount of GLP receptor agonist or pharmaceutically acceptable salt or derivatives thereof,
- 5 b. one or more permeation enhancer,
- c. one or more mucoadhesive agent, and
- d. one or more basifier.

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

- 10 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,
- c. one or more mucoadhesive agent, and
- d. one or more basifier.

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

- a. therapeutically effective amount of semaglutide,
- b. one or more medium chain fatty acid based permeation enhancers,
- c. one or more mucoadhesive agent, and
- 20 d. one or more basifier.

In certain embodiments, medium chain fatty acid based permeation enhancers are medium chain fatty acid based permeation enhancers without aromatic functional group. In one embodiment, pharmaceutical composition comprises combination of sodium caprate and sodium caprylate.

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

- a. a therapeutically effective amount of semaglutide,
- b. sodium caprate or sodium caprylate or combinations thereof,
- 5 c. polyacrylate (Carbopol 934P), and
- d. calcium carbonate.

In an another embodiment, the pharmaceutical composition as per present invention is tablet and are prepared by direct compression method.

10 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
15 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.

20 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.

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 may be selected from one or more medium chain fatty acid based permeation enhancers with aromatic functional group, 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 8-(2-hydroxybenzamido) caprylate (Salcaprozate Sodium) is 25 mg to 200mg.

- 5 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 aromatic functional group may be in the range of 25mg to 800mg. In one
10 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 150 mg to 500 mg.

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BASIFIERS

- Basifier are compound that provide alkaline environment during and/or after dissolution of active ingredient. The basifiers may include but not limited to calcium carbonate, sodium carbonate, sodium bicarbonate, magnesium hydroxide,
20 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.

MUCOADHESIVE AGENT

- Mucoadhesion refers to the ability of a material to adhere to a biological surface. Mucoadhesive agents improves gastrointestinal retention through
25 facilitating bioadhesion of the pharmaceutical composition to the walls of the

gastrointestinal tract. Non limiting examples of mucoadhesive agent are polyacrylates (Carbopol), Chitosan and gums like alginates. The amount of mucoadhesive agent may be optimized based on extent of adhesion required. The amount of mucoadhesive agent may be within the range of 5 mg to 100 mg. More specifically, amount of mucoadhesive agent may be within the range of 20 mg to 60 mg. In a preferred embodiment, the mucoadhesive agent is polyacrylates commonly marketed under brand name of Carbopol. More specifically mucoadhesive agent is Carbopol 934P.

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.

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 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, 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 selected from hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinyl pyrrolidone, any other binder or combination thereof. Lubricants may be selected
5 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 consideration of the specifications.

- 10 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

Compositions:

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Sr No	Ingredient	Quantity per tablet (mg)
1	Semaglutide	7
2	Sodium caprylate	150
3	Sodium caprate	450
4	Calcium carbonate	100
5	Carbopol A934P	25
6	SSG	150
7	Magnesium stearate	20
	Total	902

Procedure :

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

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- A Single dose fasted state 3 way cross over biostudies were performed for the composition of example 1 versus Rybelsus (reference) 7mg tablet in human volunteers. Result are shown in figure 1. Results shows successful achievement of bioequivalence for the composition of example 1 compare to reference product
- 5 Rybelsus 7 mg.

Example – 2

Sr No	Ingredient	Quantity per tablet (mg)
1	Semaglutide	7
2	Sodium caprylate	150
3	Sodium caprate	250
4	Calcium carbonate	100
5	Carbopol A934P	15
6	Crospovidone	50
7	Magnesium stearate	10
	Total	582

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

Example – 3

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Sr No	Ingredient	Quantity per tablet (mg)
1	Semaglutide	7
2	Sodium caprylate	350
3	Sodium caprate	100

4	Calcium carbonate	80
5	Carbopol A934P	20
6	SSG	100
7	Magnesium stearate	10
	Total	667

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

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COMPARATIVE EXAMPLE A

Composition

Sr No	Ingredient	Quantity per tablet (mg)
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

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Procedure

1. All ingredients were weighed accurately.
2. Ingredients 1 to 5 were sifted in 40 # sieve.
3. The powder mixture was mixed in polybag for 5 min .
- 5 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 degrees Celsius.
6. The dry granules were passed through 40 # sieve.
- 10 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.

A Single dose fasted state 3 way cross over biostudies were performed for the
15 composition of comparative example A versus Rybelsus (reference) 7mg 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 tablets.

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CLAIMS

I/We claim

1. A pharmaceutical composition for oral administration comprising
 - a. a therapeutically effective amount of GLP receptor agonist or
5 pharmaceutically acceptable salt or derivatives thereof,
 - b. one or more permeation enhancer,
 - c. one or more mucoadhesive agent, and
 - d. one or more basifier.
2. The pharmaceutical composition as claimed in claim 1, wherein GLP
10 receptor agonist is semaglutide.
3. The pharmaceutical composition as claimed in claim 1, wherein one or more
permeation enhancer are medium chain fatty acid based permeation
enhancers.
4. The pharmaceutical composition as claimed in claim 3, wherein medium
15 chain fatty acid based permeation enhancers is salcaprozate sodium.
5. The pharmaceutical composition as claimed in claim 4, wherein
salcaprozate sodium is in the amount of 25 mg to 200mg.
6. The pharmaceutical composition as claimed in claim 3, wherein medium
chain fatty acid based permeation enhancers is sodium caprate or sodium
20 caprylate or combination thereof.
7. The pharmaceutical composition as claimed in claim 6, wherein sodium
caprate or sodium caprylate or combination thereof is in the amount of 25mg
to 800mg.
8. The pharmaceutical composition as claimed in claim 1, wherein said
25 mucoadhesive agent is polyacrylates.
9. The pharmaceutical composition as claimed in claim 1, wherein said
basifier is selected from group consisting of calcium carbonate, sodium

carbonate, sodium bicarbonate, magnesium hydroxide, and aluminium hydroxide or combination thereof.

10. The pharmaceutical composition as claimed in claim 1, wherein said composition is tablet.

5 11. The pharmaceutical composition as claimed in claim 1, wherein said tablet is prepared by direct compression method.

12. The pharmaceutical composition as claimed in claim 1, wherein said composition further comprises one or more additional active ingredient.

10 13. A pharmaceutical composition for oral administration comprising

- a. a therapeutically effective amount of semaglutide,
- b. sodium caprate or sodium caprylate or combinations thereof,
- c. polyacrylate (Carbopol 934P), and
- d. calcium carbonate.

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