

Compositions and methods for delivering GLP-1 agonists (MetaboliX)**Field of the Invention**

- 5 [0001] The present invention relates to compositions comprising a biological active material. The present invention also relates to pharmaceutical compositions, dosage forms and methods for weight management.

Background

- 10 [0002] The following discussion of the background art is intended to facilitate an understanding of the present invention only. The discussion is not an acknowledgement or admission that any of the material referred to is or was part of the common general knowledge as at the priority date of the application.

[0003] *Semaglutide, Liraglutide and Dapagliflozin*

- 15 [0004] Semaglutide, liraglutide and dapagliflozin are drugs with long term weight loss effect. Both drugs cause more than 7.5% weight loss when taken separately and maintain the weight loss for 24 months and beyond. By combining both drugs into a single unit-dose it will have a synergistic weight loss effect of more than 15% weight loss capability. The doubling effect was due to their different pharmacology action. Dapagliflozin is a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist whereas semaglutide and liraglutide
20 are glucagon-like peptide 1 (GLP-1) agonists.

[0005] SGLT2 inhibits protein in the kidneys which is responsible for reabsorbing glucose back into the bloodstream. By blocking this protein, SGLT-2 inhibitors prevent glucose from being reabsorbed and instead promote its excretion in urine. This leads to a reduction in blood glucose levels and glucose calories.

- 25 [0006] GLP-1 agonist works by mimicking the effects of GLP-1, a hormone that is naturally produced in the body, mostly in the intestine. GLP-1 receptor agonists induce weight loss via the gastrointestinal tract-brain axis, with the primary action of increase in satiety. Also, GLP-1 decreases the secretion of acid in the stomach resulting in a delay of gastric emptying from the stomach, prolonging the sensation of fullness and a loss in
30 appetite.

- [0007] Semaglutide is designed to mimic the function of natural GLP-1 in the body. Natural or native GLP-1 has a very short half-life of around 1 to 2 min, is rapidly degraded by the enzyme dipeptidylpeptidase-4 (DPP-4), whereas the GLP-1 analogue, semaglutide, is resistant to DPP-4 degradation, increasing and prolonging its duration of action (half-life of 7
35 days) and reducing the drug administration frequency to once a week dosing.

[0008] GLP-1 (a hormone) is primarily produced in the intestine in the L-cells. The L-cells are enteroendocrine cells are open-type epithelial cells in contact directly with nutrients in the intestinal lumen. GLP-1 an incretin hormone, stimulates insulin secretion and inhibits glucagon secretion, playing an important role in regulating glucose metabolism and importantly appetite control (satiety via gut-brain axis).

[0009] Semaglutide acts on GLP-1 receptors in the intestines and other organs to stimulate insulin secretion, suppress glucagon release, slow down gastric emptying, reduce appetite, and regulate glucose homeostasis/metabolism, helping to improve glycaemic control, promote weight loss, and manage obesity.

10 [0010] Currently, semaglutide is available as a subcutaneous injection preparation approved for treatment of type 2 diabetes mellitus and obesity plus one oral tablet preparation approved for the treatment of type 2 diabetes mellitus. Semaglutide is less suitable for oral administration due to its very low oral bioavailability (less than 0.1%). The approved oral tablet semaglutide formulation has an oral bioavailability of 0.4 to 1% via stomach absorption. Semaglutide is also easily damaged by the stomach's gastric acid, digestive enzymes and intestinal mucosa barrier to absorption by passive diffusion against macromolecules penetration leading to poor absorption and low bioavailability.

20 [0011] There is a need in the art for improved compositions and methods for weight loss and weight management. It is an objective of the invention to overcome one or more problems foreshadowed by the prior art.

Summary of the Invention

25 [0012] In a first aspect, the invention broadly resides in a composition wherein said composition comprises at least one biologically active material selected from the group consisting of: a glucagon-like peptide 1 (GLP-1) agonist; and a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist.

[0013] In a preferred embodiment, the glucagon-like peptide 1 (GLP-1) agonist is selected from the group consisting of semaglutide; liraglutide; dulaglutide; exenatide; lixisenatide; and any combination thereof, and a pharmaceutically acceptable salt, analog, homolog or derivative thereof.

30 [0014] Preferably, the sodium glucose co-transporter-2 (SGLT-2) receptor antagonist is selected from the group consisting of dapagliflozin; empagliflozin; ertugliflozin; canagliflozin; bexagliflozin; and any combination thereof; and a pharmaceutically acceptable salt, analog, homolog or derivative thereof.

[0015] Preferably, the composition comprises two biologically active materials selected from the group consisting of: a glucagon-like peptide 1 (GLP-1) agonist; and a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist.

[0016] Preferably, the composition is a solid dosage form. Preferably, the composition is a rapidly disintegrating solid dosage form. Preferably, the composition is a wafer, tablet or capsule. Preferably, the composition is a wafer and is neutral pH protected against the acidic pH and enzymatic degradation in the stomach.

[0017] Preferably, the biologically active material is present in the composition at a concentration selected from the group consisting of: 0.01% (w/w); 0.1% (w/w); 1% (w/w); 2% (w/w); 3% (w/w); 4% (w/w); 5% (w/w); 6% (w/w); 7% (w/w); 8% (w/w); 9% (w/w); 10% (w/w); 11% (w/w); 12% (w/w); 13% (w/w); 14% (w/w); 15% (w/w); 16% (w/w); 17% (w/w); 18% (w/w); 19% (w/w); 20% (w/w); 21% (w/w); 22% (w/w); 23% (w/w); 24% (w/w); 25% (w/w); 26% (w/w); 27% (w/w); 28% (w/w); 29% (w/w); 30% (w/w); 31% (w/w); 32% (w/w); 33% (w/w); 34% (w/w); 35% (w/w); 36% (w/w); 37% (w/w); 38% (w/w); 39% (w/w); 40% (w/w); 41% (w/w); 42% (w/w); 43% (w/w); 44% (w/w); 45% (w/w); 46% (w/w); 47% (w/w); 48% (w/w); 49% (w/w); 50% (w/w); 0.2-95% (w/w); and 2-95% (w/w); 33-65% (w/w); 4-55% (w/w); 5-45% (w/w); 6-35% (w/w); 7-25% (w/w); 8-15% (w/w); and within 2 decimal points of each figure.

[0018] Preferably, the biologically active material is present in the composition at a quantity selected from the group consisting of: 1ng to 1000mg; 0.01ng to 100mg; 0.01mg; 0.02mg; 0.03mg; 0.04mg; 0.05mg; 0.06mg; 0.07mg; 0.08mg; 0.09mg; 0.10mg; 0.11mg; 0.12mg; 0.13mg; 0.14mg; 0.15mg; 0.16mg; 0.17mg; 0.18mg; 0.19mg; 0.20mg; 0.21mg; 0.22mg; 0.23mg; 0.24mg; 0.25mg; 0.26mg; 0.27mg; 0.28mg; 0.29mg; 0.30mg; 0.31mg; 0.32mg; 0.33mg; 0.34mg; 0.35mg; 0.36mg; 0.37mg; 0.38mg; 0.39mg; 0.40mg; 0.41mg; 0.42mg; 0.43mg; 0.44mg; 0.45mg; 0.46mg; 0.47mg; 0.48mg; 0.49mg; 0.50mg; 0.51mg; 0.52mg; 0.53mg; 0.54mg; 0.55mg; 0.56mg; 0.57mg; 0.58mg; 0.59mg; 0.60mg; 0.61mg; 0.62mg; 0.63mg; 0.64mg; 0.65mg; 0.66mg; 0.67mg; 0.68mg; 0.69mg; 0.70mg; 0.71mg; 0.72mg; 0.73mg; 0.74mg; 0.75mg; 0.76mg; 0.77mg; 0.78mg; 0.79mg; 0.80mg; 0.81mg; 0.82mg; 0.83mg; 0.84mg; 0.85mg; 0.86mg; 0.87mg; 0.88mg; 0.89mg; 0.90mg; 0.91mg; 0.92mg; 0.93mg; 0.94mg; 0.95mg; 0.96mg; 0.97mg; 0.98mg; 0.99mg; 1.00mg; 0.1mg; 0.2mg; 0.3mg; 0.4mg; 0.5mg; 0.6mg; 0.7mg; 0.8mg; 0.9mg; 1.0mg; 1mg; 2mg; 3mg; 4mg; 5mg; 6mg; 7mg; 8mg; 9mg; 10mg; 11mg; 12mg; 13mg; 14mg; 15mg; 16mg; 17mg; 18mg; 19mg; 20mg; 21mg; 22mg; 23mg; 24mg; 25mg; 26mg; 27mg; 28mg; 29mg; 30mg; 31mg; 32mg; 33mg; 34mg; 35mg; 36mg; 37mg; 38mg; 39mg; 40mg; 41mg; 42mg; 43mg; 44mg; 45mg; 46mg; 47mg; 48mg; 49mg; 50mg; 51mg; 52mg; 53mg; 54mg; 55mg; 56mg; 57mg;

58mg; 59mg; 60mg; 61mg; 62mg; 63mg; 64mg; 65mg; 66mg; 67mg; 68mg; 69mg; 70mg;
 71mg; 72mg; 73mg; 74mg; 75mg; 76mg; 77mg; 78mg; 79mg; 80mg; 81mg; 82mg; 83mg;
 84mg; 85mg; 86mg; 87mg; 88mg; 89mg; 90mg; 91mg; 92mg; 93mg; 94mg; 95mg; 96mg;
 97mg; 98mg; 99mg; 100mg; 101mg; 102mg; 103mg; 104mg; 105mg; 106mg; 107mg;
 5 108mg; 109mg; 110mg; 111mg; 112mg; 113mg; 114mg; 115mg; 116mg; 117mg; 118mg;
 119mg; 120mg; 121mg; 122mg; 123mg; 124mg; 125mg; 126mg; 127mg; 128mg; 129mg;
 130mg; 131mg; 132mg; 133mg; 134mg; 135mg; 136mg; 137mg; 138mg; 139mg; 140mg;
 141mg; 142mg; 143mg; 144mg; 145mg; 146mg; 147mg; 148mg; 149mg; 150mg; 151mg;
 152mg; 153mg; 154mg; 155mg; 156mg; 157mg; 158mg; 159mg; 160mg; 161mg; 162mg;
 10 163mg; 164mg; 165mg; 166mg; 167mg; 168mg; 169mg; 170mg; 171mg; 172mg; 173mg;
 174mg; 175mg; 176mg; 177mg; 178mg; 179mg; 180mg; 181mg; 182mg; 183mg; 184mg;
 185mg; 186mg; 187mg; 188mg; 189mg; 190mg; 191mg; 192mg; 193mg; 194mg; 195mg;
 196mg; 197mg; 198mg; 199mg; 200mg; 0.01mg to 1mg; 0.1mg to 1mg; 1 to 200mg; 1 to
 100mg; 1 to 50mg; 1 to 25mg; 1 to 15mg; 1 to 10mg; 10 to 100mg; 10 to 75mg; 10mg to
 15 50mg; and 10mg to 25mg.

[0019] Preferably, the biologically active material is present in the composition at a quantity selected from the group consisting of: 0.01mg; 0.1mg; 1mg; 2mg; 5mg; 10mg; 15mg; 20mg; 21mg; 0.25mg to 100mg; 1mg to 25mg; 1 mg to 50 mg; 1 mg to 30mg; 2 to 30mg; 5 mg to 15mg; 10mg to 20mg; and 10 to 50mg.

20 [0020] Preferably, the biologically active material is present in the composition at a quantity selected from the group consisting of: semaglutide 15mg; liraglutide 21mg; dulaglutide 10mg; exenatide 2mg; and lixisenatide 20mg.

[0021] Preferably, the biologically active material is present in the composition at a quantity selected from the group consisting of: dapagliflozin 10mg; empagliflozin 25mg; and
 25 ertugliflozin 5mg.

[0022] Preferably, the composition comprises one or more agents selected from the group consisting of: an entero-hepatic recycling agent; an absorption agent; a bile salt; a penetrant; a surfactant; an ionic water soluble post-disintegration viscosity agent; a mucolytic (mucus buster); a mucoadhesive; an adjuvant; a disintegration viscosity agent; a permeation
 30 enhancer; an absorption enhancer; and a entero-hepatic-biliary recirculation agent.

[0023] Preferably, the entero-hepatic recycling agent is selected from the group consisting of: glycodeoxycholate; glycocholate; taurocholate; glycolithocholate; glycohyocholate; tauroursodeoxycholate; taurohyodeoxycholate; and salts thereof.

- [0024] Preferably, the composition comprises a plurality of entero-hepatic recycling agents.
- [0025] Preferably, the entero-hepatic recycling agent is selected from the group consisting of: sodium glycodeoxycholate; and sodium deoxycholate.
- 5 [0026] Preferably, the concentration of the entero-hepatic recycling agent is selected from the group consisting of: 0.01%; 0.5%; 1%; 0.5%-10%; 0.5%; 1%-10%; 1%; 2%; 3%; 4%; 5%; 6%; 7%; 8%; 9%; 10%; and within 2 decimal points of each figure (w/w).
- [0027] Preferably, the entero-hepatic recycling agent(s) are bile salts and soy lecithin.
- [0028] Preferably, the entero-hepatic recycling agent(s) are permeation enhancers.
- 10 [0029] Preferably, the entero-hepatic recycling agent(s) open tight junctions in the sublingual/gastro-intestinal mucosa cells.
- [0030] Preferably, the entero-hepatic recycling agent(s) influence the integrity of tight junctions between epithelial cells and modulate these tight junctions, allowing for an increased in paracellular transport.
- 15 [0031] Preferably, the entero-hepatic recycling agent(s) improve/enhance the absorption of lipophilic compounds as they can interact with both lipophilic drugs and the lipids present in cell membranes
- [0032] Preferably, the entero-hepatic recycling agent(s) and the glucagon-like peptide 1 (GLP-1) agonist form a complex.
- 20 [0033] Preferably, the entero-hepatic recycling agent(s) and the glucagon-like peptide 1 (GLP-1) agonist form a complex which has a particle size less than 2000nm.
- [0034] Preferably, the entero-hepatic recycling agent(s) and the glucagon-like peptide 1 (GLP-1) agonist form a complex which is absorbed into the blood circulation and metabolised into the active glucagon-like peptide 1 (GLP-1) agonist improving the
- 25 bioavailability of the glucagon-like peptide 1 (GLP-1) agonist.
- [0035] Preferably, the ionic water soluble post-disintegration viscosity agent is selected from the group consisting of: carboxymethyl cellulose; anionic substituted cellulose or starch derivatives, such as salts of carboxymethyl celluloses (CMC), alginate and starch glycolates.
- [0036] Preferably, the ionic water soluble post-disintegration viscosity agent is
- 30 carboxymethyl cellulose.

- [0037] Preferably, the ionic water soluble post-disintegration viscosity agent is at a concentration selected from the group consisting of: 1%; 0.5%-10%; 0.5%; 1%-10%; 1%; 2%; 3%; 4%; 5%; 6%; 7%; 8%; 9%; 10%; and within 2 decimal points of each figure (w/w).
- [0038] Preferably, the disintegration viscosity agent is sodium alginate.
- 5 [0039] Preferably, the disintegration viscosity agent is at a concentration selected from the group consisting of: 1%; 0.5%-10%; 0.5%; 1%-10%; 1%; 2%; 3%; 4%; 5%; 6%; 7%; 8%; 9%; 10%; and within 2 decimal points of each figure (w/w).
- [0040] Preferably, the composition comprises a permeation enhancer. Preferably, the permeation enhancer is SNAC (salcaprozate sodium). Preferably, the permeation enhancer
- 10 is a non-ionic ester alkoxyate or an alkanolic acid ester alkoxyate. Examples of non-ionic ester alkoxyates are selected from the group consisting of: sorbitan fatty acid esters (Spans); polysorbates (Tweens). Preferably, the alkanolic acid ester alkoxyate is selected from the group consisting of: vitamin E ethoxylated derivatives; tocopherol succinate ethoxyate (TPGS); tocopherol; and ethoxylated phytosterol.
- 15 [0041] Preferably, the permeation enhancer is SNAC (salcaprozate sodium) and is surfactant-like structurally and has the ability to chaperone poorly-permeable macromolecules across plasma membranes via a transcellular mode of action and helps sublingual absorption of peptides.
- [0042] Preferably, the SNAC (salcaprozate sodium) and the glucagon-like peptide 1
- 20 (GLP-1) agonist form a complex. Preferably, the non-ionic ester alkoxyate (or alkanolic acid ester alkoxyate) and the glucagon-like peptide 1 (GLP-1) agonist form a complex.
- [0043] Preferably, the permeation enhancer is at a concentration selected from the group consisting of: 0%; 0.05%-10%; 0.5%; 1%-10%; 1%; 2%; 3%; 4%; 5%; 6%; 7%; 8%; 9%; 10%; 20%, 30%, 40%; and within 2 decimal points of each figure (w/w).
- 25 [0044] Preferably, the permeation enhancer is at a quantity selected from the group consisting of: 5mg; 10mg; 25mg; 30mg; 0.25mg to 100mg; 1mg to 25mg; 1 mg to 50 mg; 1 mg to 30mg; 2 to 30mg; 5 mg to 15mg; 10mg to 20mg; and 10 to 50mg.
- [0045] Preferably, the permeation enhancer protects the glucagon-like peptide 1 (GLP-1) agonist against the effects of pepsin (primary digestive enzymes in the stomach which
- 30 digest/convert protein and peptides to amino acids).
- [0046] Preferably, the composition comprises a glucagon-like peptide 1 (GLP-1) agonist-cholate-SNAC-sodium glucose co-transporter-2 (SGLT-2) receptor antagonist cluster or glucagon-like peptide 1 (GLP-1) agonist-cholate-non-ionic ester alkoxyate (or

alkanoic acid ester alkoxylate) (or alkanoic acid ester alkoxylate)-sodium glucose co-transporter-2 (SGLT-2) receptor antagonist cluster.

[0047] Preferably, the composition comprises a semaglutide-cholate-SNAC-dapagliflozin cluster or semaglutide-cholate-non-ionic ester alkoxylate (or alkanoic acid ester alkoxylate) (or alkanoic acid ester alkoxylate)-dapagliflozin cluster

[0048] Preferably, the composition is formulated to pH 5-7.5 to inhibit pepsin activity.

[0049] Preferably, the composition is formulated to pH 5-8.0 to inhibit pepsin activity.

[0050] Preferably, the entero-hepatic-biliary recirculation agent is soy lecithin.

[0051] Preferably, the entero-hepatic-biliary recirculation agent is soy lecithin.

10 [0052] Preferably, the entero-hepatic-biliary recirculation agent is at a concentration selected from the group consisting of: 0.05%-10%; 0.5%; 1%-10%; 1%; 2%; 3%; 4%; 5%; 6%; 7%; 8%; 9%; 10%; 20%, 30%, 40%; and within 2 decimal points of each figure (w/w).

[0053] Preferably, the entero-hepatic-biliary recirculation agent is at a quantity selected from the group consisting of: 5mg; 10mg; 25mg; 30mg; 0.25mg to 100mg; 1mg to 25mg; 15 mg to 50 mg; 1 mg to 30mg; 2 to 30mg; 5 mg to 15mg; 10mg to 20mg; and 10 to 50mg.

[0054] Preferably, the entero-hepatic-biliary recirculation agent provides absorption enhancement.

[0055] Preferably, the entero-hepatic-biliary recirculation agent provides absorption enhancement using factors selected from the group consisting of: a local alteration in the membrane structure and modification of its permeability; bioadhesion to the mucosa surfaces; and the lowering of the mucociliary clearance.

[0056] Preferably, the composition comprises a mucoadhesive polymer, with a mucolytic property to break the GI/oro-mucosal mucus layer/barrier for bioactive penetration.

25 [0057] Preferably, the composition comprises one or more agents selected from the group consisting of; sodium glycodeoxycholate; sodium deoxycholate; carboxymethyl cellulose; sodium alginate; SNAC (salcaprozate sodium); non-ionic ester alkoxylate (or alkanoic acid ester alkoxylate) (or alkanoic acid ester alkoxylate); and soy lecithin.

[0058] Preferably, the composition comprises one or more biologically active materials and agents selected from Table 1 or Table 2.

- [0059] Preferably, the composition has a pH selected from the group consisting of: between 5 to 6; between 4 to 7.5; between 6 to 7.5; between 7.0 – 7.5; and between 7.0 – 8.0.
- [0060] Preferably, the composition is a solid. Preferably, the composition is lyophilised.
- 5 [0061] Preferably, the particles of the composition have a size no greater than 2000 nm.
- [0062] Preferably, the particles of the composition have a nanoparticulate size.
- [0063] Preferably, the composition comprises further pharmaceutically acceptable additives and agents.
- 10 [0064] Preferably, the composition comprises a pharmaceutically acceptable buffering reagent.
- [0065] Preferably, the buffering reagent is selected from the group consisting of: salts of phosphates, carbonates, Tris; preferably combinations of phosphate salts; including sodium carbonate.
- 15 [0066] Preferably, the buffering reagent is present at a concentration selected from the group consisting of: 0.1-0.5%; 0.1%; 0.2%; 0.3%; 0.4%; 0.5%; and within 2 decimal points of each figure (w/w).
- [0067] Preferably, the wafers are buffered with a suitable buffer, most preferably a blend of mono- and di-alkaline salt phosphates, adjusted to afford a pH optimal for the stability of the chosen biological active, generally between 4 and 7.5.
- 20 [0068] Preferably, the wafers are buffered with a suitable buffer, most preferably a blend of mono- and di-alkaline salt phosphates, adjusted to afford a pH optimal for the stability of the chosen biological active, generally between 4 and 8.0.
- [0069] Preferably, the composition comprises a colouring agent.
- [0070] Preferably, the composition comprises a flavouring agent.
- 25 [0071] Preferably, the composition comprises a stability agent.
- [0072] Preferably, the stability agent is selected from the group consisting of: metal chelators such as EDTA, pharmaceutically acceptable surfactant including polysorbate 80.
- [0073] Preferably, the composition is a glucagon-like peptide 1 (GLP-1) agonist bile salt- lecithin complex.

[0074] Preferably, the composition is a glucagon-like peptide 1 (GLP-1) agonist bile salt- lecithin-SNAC (salcaprozate sodium) complex. Preferably, the composition is a glucagon-like peptide 1 (GLP-1) agonist bile salt- lecithin-non-ionic ester alkoxylate (or alkanolic acid ester alkoxylate) (or alkanolic acid ester alkoxylate) complex.

5 [0075] Preferably, the composition comprises a complex selected from the group consisting of: glucagon-like peptide 1 (GLP-1) agonist - bile salt - lecithin complex; glucagon-like peptide 1 (GLP-1) agonist - bile salt - lecithin - SNAC (salcaprozate sodium) complex; glucagon-like peptide 1 (GLP-1) agonist - entero-hepatic recycling agent(s) complex; glucagon-like peptide 1 (GLP-1) agonist - SNAC (salcaprozate sodium) complex; glucagon-like peptide 1 (GLP-1) agonist - entero-hepatic recycling agent(s) - SNAC (salcaprozate sodium) complex; a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - bile salt - lecithin complex; a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - bile salt - lecithin - SNAC (salcaprozate sodium) complex; a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - entero-hepatic recycling agent(s) complex; a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - SNAC (salcaprozate sodium) complex; a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - entero-hepatic recycling agent(s) - SNAC (salcaprozate sodium) complex; glucagon-like peptide 1 (GLP-1) agonist - a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - bile salt - lecithin complex; glucagon-like peptide 1 (GLP-1) agonist - a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - bile salt - lecithin - SNAC (salcaprozate sodium) complex; glucagon-like peptide 1 (GLP-1) agonist - a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - entero-hepatic recycling agent(s) complex; glucagon-like peptide 1 (GLP-1) agonist - a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - SNAC (salcaprozate sodium) complex; and glucagon-like peptide 1 (GLP-1) agonist - a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - entero-hepatic recycling agent(s) - SNAC (salcaprozate sodium) complex.

[0076] Preferably, the composition comprises a complex selected from the group consisting of: glucagon-like peptide 1 (GLP-1) agonist - bile salt - lecithin complex; glucagon-like peptide 1 (GLP-1) agonist - bile salt - lecithin - non-ionic ester alkoxylate (or alkanolic acid ester alkoxylate) (or alkanolic acid ester alkoxylate) complex; glucagon-like peptide 1 (GLP-1) agonist - entero-hepatic recycling agent(s) complex; glucagon-like peptide 1 (GLP-1) agonist - non-ionic ester alkoxylate (or alkanolic acid ester alkoxylate) (or alkanolic acid ester alkoxylate) complex; glucagon-like peptide 1 (GLP-1) agonist - entero-hepatic recycling agent(s) - non-ionic ester alkoxylate (or alkanolic acid ester alkoxylate) (or alkanolic acid ester alkoxylate) complex; a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - bile salt - lecithin complex; a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - bile

salt – lecithin - non-ionic ester alkoxylate (or alkanoic acid ester alkoxylate) (or alkanoic acid ester alkoxylate) complex; a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - entero-hepatic recycling agent(s) complex; a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - non-ionic ester alkoxylate (or alkanoic acid ester alkoxylate) (or alkanoic acid ester alkoxylate) complex; a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - entero-hepatic recycling agent(s) - non-ionic ester alkoxylate (or alkanoic acid ester alkoxylate) (or alkanoic acid ester alkoxylate) complex; glucagon-like peptide 1 (GLP-1) agonist - a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - bile salt - lecithin complex; glucagon-like peptide 1 (GLP-1) agonist - a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - bile salt – lecithin - non-ionic ester alkoxylate (or alkanoic acid ester alkoxylate) (or alkanoic acid ester alkoxylate) complex; glucagon-like peptide 1 (GLP-1) agonist - a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - entero-hepatic recycling agent(s) complex; glucagon-like peptide 1 (GLP-1) agonist - a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - non-ionic ester alkoxylate (or alkanoic acid ester alkoxylate) (or alkanoic acid ester alkoxylate) complex; and glucagon-like peptide 1 (GLP-1) agonist - a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - entero-hepatic recycling agent(s) - non-ionic ester alkoxylate (or alkanoic acid ester alkoxylate) (or alkanoic acid ester alkoxylate) complex.

[0077] Preferably, the composition disintegrates once placed in the oral cavity in a time period selected from the group consisting of: <10s; <20s; <30s; <40s; <50s; <60s; <70s; <80s; <90s; <100s; <110s; <120s (seconds).

[0078] Preferably, the composition disintegrates once placed in the oral cavity in a time period selected from the group consisting of: <10s; <20s; <30s; <40s; <50s; <60s; <70s; <80s; <90s; <100s; <110s; <120s; <130s; <140s; <150s; <160s; <170s; <180s; <190s; <200s; <210s; <220s; <230s; <240s; <250s; <260s; <270s; <280s; <290s; <300s; <310s; <320s; <330s; <340s; <350s; <360s; <370s; <380s; <390s; <400s; <410s; <420s; <430s; <440s; <450s; <460s; <470s; <480s; <490s; <500s; <510s; <520s; <530s; <540s; <550s; <560s; <570s; <580s; <590s; <600s; <610s; <620s; <630s; <640s; <650s; <660s; <670s; <680s; <690s; <700s; <710s; <720s; <730s; <740s; <750s; <760s; <770s; <780s; <790s; <800s; <810s; <820s; <830s; <840s; <850s; <860s; <870s; <880s; <890s; <900s; <900s; <930s; <960s; <990s; <1020s; <1050s; <1080s; <1110s; <1140s; <1170s; <1200s; <1230s; <1260s; <1290s; <1320s; <1350s; <1380s; <1410s; <1440s; <1470s; <1500s; <1530s; <1560s; <1590s; <1620s; <1650s; <1680s; <1710s; <1740s; <1770s; <1800s; <1830s; <1860s; <1890s; <1920s; <1950s; <1980s; <2010s; <2040s; <2070s; <2100s; <2130s; <2160s; <2190s; <2220s; <2250s; <2280s; <2310s; <2340s; <2370s; <2400s; <2430s; <2460s; <2490s; <2520s; <2550s; <2580s; <2610s; <2640s; <2670s; <2700s; <2730s;

<2760s; <2790s; <2820s; <2850s; <2880s; <2910s; <2940s; <2970s; <3000s; <3030s;
 <3060s; <3090s; <3120s; <3150s; <3180s; <3210s; <3240s; <3270s; <3300s; <3330s;
 <3360s; <3390s; <3420s; <3450s; <3480s; <3510s; <3540s; <3570s; <3600s; <3630s;
 <3660s; <3690s; <3720s; <3750s; <3780s; <3810s; <3840s; <3870s; <3900s; <3930s;
 5 <3960s; <3990s; <4020s; <4050s; <4080s; <4110s; <4140s; <4170s; <4200s; and <4230s
 (seconds).

[0079] Preferably, the composition disintegrates in the oral cavity without leaving a residue of said dosage form in the oral cavity that is detectable by a subject, thereby avoiding the urge for the subject to swallow the composition.

10 [0080] Preferably, the composition dissolves once placed in the oral cavity in a time period selected from the group consisting of: <10s; <20s; <30s; <40s; <50s; <60s; <70s; <80s; <90s; <100s; <110s; <120s; 180s, preferably 15-60s (seconds).

[0081] Preferably, the composition dissolves once placed in the oral cavity in a time period selected from the group consisting of: <10s; <20s; <30s; <40s; <50s; <60s; <70s;
 15 <80s; <90s; <100s; <110s; <120s; <130s; <140s; <150s; <160s; <170s; <180s; <190s; <200s; <210s; <220s; <230s; <240s; <250s; <260s; <270s; <280s; <290s; <300s; <310s; <320s; <330s; <340s; <350s; <360s; <370s; <380s; <390s; <400s; <410s; <420s; <430s; <440s; <450s; <460s; <470s; <480s; <490s; <500s; <510s; <520s; <530s; <540s; <550s; <560s; <570s; <580s; <590s; <600s; <610s; <620s; <630s; <640s; <650s; <660s; <670s;
 20 <680s; <690s; <700s; <710s; <720s; <730s; <740s; <750s; <760s; <770s; <780s; <790s; <800s; <810s; <820s; <830s; <840s; <850s; <860s; <870s; <880s; <890s; <900s; <900s; <930s; <960s; <990s; <1020s; <1050s; <1080s; <1110s; <1140s; <1170s; <1200s; <1230s; <1260s; <1290s; <1320s; <1350s; <1380s; <1410s; <1440s; <1470s; <1500s; <1530s; <1560s; <1590s; <1620s; <1650s; <1680s; <1710s; <1740s; <1770s; <1800s; <1830s;
 25 <1860s; <1890s; <1920s; <1950s; <1980s; <2010s; <2040s; <2070s; <2100s; <2130s; <2160s; <2190s; <2220s; <2250s; <2280s; <2310s; <2340s; <2370s; <2400s; <2430s; <2460s; <2490s; <2520s; <2550s; <2580s; <2610s; <2640s; <2670s; <2700s; <2730s; <2760s; <2790s; <2820s; <2850s; <2880s; <2910s; <2940s; <2970s; <3000s; <3030s; <3060s; <3090s; <3120s; <3150s; <3180s; <3210s; <3240s; <3270s; <3300s; <3330s;
 30 <3360s; <3390s; <3420s; <3450s; <3480s; <3510s; <3540s; <3570s; <3600s; <3630s; <3660s; <3690s; <3720s; <3750s; <3780s; <3810s; <3840s; <3870s; <3900s; <3930s; <3960s; <3990s; <4020s; <4050s; <4080s; <4110s; <4140s; <4170s; <4200s; and <4230s
 (seconds).

[0082] Preferably, the composition dissolves in the oral cavity without leaving a residue of said dosage form in the oral cavity that is detectable by a subject, thereby avoiding the urge for the subject to swallow the composition.

[0083] Preferably, water is removed from the combined agents by a freeze-drying process to a residual level of 0-10%, preferably 0-5%, most preferably 3-5%.

[0084] Preferably, the composition has a porosity profile selected from the group consisting of: the proportion of water removed by lyophilization is 65-75%; and the proportion of water removed by lyophilization is >60%.

[0085] Preferably, the composition has a patient weight loss property selected from the group consisting of: between 0.01% and 0.1% weight loss; between 0.01% and 1%; between 0.1% and 1%; between 0.01% and 0.1%; between 1 and 30%; between 5 and 25%; between 8 and 20%; 0.01%; 0.1%; 1%; 2%; 3%; 4%; 5%; 6%; 7%; 8%; 9%; 10%; 11%; 12%; 13%; 14%; 15%; 16%; 17%; 18%; 19%; 20%; 21%; 22%; 23%; 24%; 25%; 26%; 27%; 28%; 29%; 30% and within 2 decimal points of each figure.

[0086] Preferably, the composition has a residual moisture content after lyophilisation selected from the group consisting of: between: 0.01 and 20%; between 0.1 and 10%; between 1 and 5%; 0.01%; 0.02%; 0.03%; 0.04%; 0.05%; 0.06%; 0.07%; 0.08%; 0.09%; 0.10%; 0.01%; 0.02%; 0.03%; 0.04%; 0.05%; 0.06%; 0.07%; 0.08%; 0.09%; 0.10%; 1%; 2%; 3%; 4%; 5%; 6%; 7%; 8%; 9%; 10%; 11%; 12%; 13%; 14%; 15%; 16%; 17%; 18%; 19%; 20% and within 2 decimal points of each figure.

[0087] Preferably, the composition is stable for a time period selected from the group consisting of: 1 week; 2 weeks; 3 weeks; 4 weeks; 5 weeks; 6 weeks; 7 weeks; 8 weeks; 9 weeks; 10 weeks; 11 weeks; 12 weeks; 13 weeks; 14 weeks; 15 weeks; 16 weeks; 17 weeks; 18 weeks; 19 weeks; 20 weeks; 21 weeks; 22 weeks; 23 weeks; 24 weeks; 25 weeks; 26 weeks; 27 weeks; 28 weeks; 29 weeks; 30 weeks; 31 weeks; 32 weeks; 33 weeks; 34 weeks; 35 weeks; 36 weeks; 37 weeks; 38 weeks; 39 weeks; 40 weeks; 41 weeks; 42 weeks; 43 weeks; 44 weeks; 45 weeks; 46 weeks; 47 weeks; 48 weeks; 49 weeks; 50 weeks; 51 weeks; 52 weeks; 1 month; 2 months; 3 months; 4 months; 5 months; 6 months; 7 months; 8 months; 9 months; 10 months; 11 months; 12 months; 13 months; 14 months; 15 months; 16 months; 17 months; 18 months; 19 months; 20 months; 21 months; 22 months; 23 months; 24 months; 25 months; 26 months; 27 months; 28 months; 29 months; 30 months; 31 months; 32 months; 33 months; 34 months; 35 months; 36 months; 37 months; 38 months; 39 months; 40 months; 41 months; 42 months; 43 months; 44 months; 45 months; 46 months; 47 months; 48 months; 49 months; 50 months; 51 months;

52 months; 53 months; 54 months; 55 months; 56 months; 57 months; 58 months; 59 months; 60 months; 1 month to 12 months; 12 months to 24 months; 12 months to 36 months; 12 months to 48 months; 1 year to 2 years; 1 year to 3 years; and 1 year to 5 years. Preferably, the composition is stable as demonstrated by a potency assay run against a reference biological active material.

[0088] In another aspect, the invention is a pharmaceutical composition comprising the composition of the first aspect of the invention together with a pharmaceutical excipient or carrier.

[0089] In another aspect, the invention is a dosage form comprising the composition of the first aspect of the invention.

[0090] Preferably, the dosage form comprises the biologically active material at a dose selected from the group consisting of: 2mg; 5mg 10mg; 15mg; 20mg; 21mg; 0.25mg to 100mg; 1mg to 25mg; 1 mg to 50 mg; 1 mg to 30mg; 2 to 30mg; 5 mg to 15mg; 10mg to 20mg; and 10 to 50mg.

[0091] Preferably, the dosage form comprises the biologically active material at a dose selected from the group consisting of: semaglutide 15mg; liraglutide 21mg; dulaglutide 10mg; exenatide 2mg; and lixisenatide 20mg.

[0092] Preferably, the dosage form comprises the biologically active material at a dose selected from the group consisting of: dapagliflozin 10mg; empagliflozin 25mg; and ertugliflozin 5mg.

[0093] Preferably, the dosage form is solid. Preferably, the dosage form is freeze dried. Preferably, the dosage form is a wafer.

[0094] In another aspect, the invention is a method of treating or preventing or delaying a disease or disorder, said method comprising administering to a patient in need thereof a therapeutically effective amount of the dosage form of one aspect of the invention.

[0095] Preferably, the disease or disorder is selected from the group consisting of: appetite suppression; weight loss; weight management; obesity; type 2 diabetes, regulate blood sugar; lower the risk of heart attack, stroke, or death in patients with type 2 diabetes and heart or blood vessel disease; cardiovascular disease; Alzheimer's disease; nonalcoholic steatohepatitis (NASH).

[0096] In a preferred embodiment, the dosage form is administered to deliver a therapeutic effective amount of the biological active material.

[0097] In a preferred embodiment, the therapeutically effective amount is administered to the subject utilising a dosing regimen selected from the group consisting of: twice hourly; hourly; once every six hours; once every 8 hours; once every 12 hours; once daily; twice weekly; once weekly; once every 2 weeks; once every 6 weeks; once a month; once every 2
5 months; once every 3 months; once every 4 months; once every 5 months; once every 6 months; once yearly; and once.

[0098] Preferably, the dosage form delivers a therapeutic effective amount of the biologically active material.

[0099] Preferably, the therapeutically effective amount is an amount of biologically
10 active material selected from the group consisting of: between 0.001 to 100mg/kg; between 2 and 50mg/kg; between 5 and 40mg/kg; between 10 and 30mg/kg; between 20 and 25mg/kg; and 20mg/kg/day.

[0100] In a preferred embodiment, the therapeutically effective amount is an amount of biologically active material selected from the group consisting of: 2mg; 5mg 10mg; 15mg;
15 20mg; 21mg; 0.25mg to 100mg; 1mg to 25mg; 1 mg to 50 mg; 1 mg to 30mg; 2 to 30mg; 5 mg to 15mg; 10mg to 20mg; 10 to 50mg per dosage event.

[0101] Preferably, the therapeutically effective amount is an amount of biologically active material selected from the group consisting of: 2mg; 5mg 10mg; 15mg; 20mg; 21mg; 0.25mg to 100mg; 1mg to 25mg; 1 mg to 50 mg; 1 mg to 30mg; 2 to 30mg; 5 mg to 15mg;
20 10mg to 20mg; 10 to 50mg per day.

[0102] Preferably, the therapeutically effective amount is administered to the subject using a method selected from the group consisting of: orally; sublingually; buccally.

[0103] Preferably, the therapeutically effective amount is administered to the subject using a method selected from the group consisting of: beneath the tongue or buccally.

25 [0104] Preferably, detectable levels of the biologically active material enters the circulation system.

[0105] Preferably, the detectable levels of the biologically active material that enters the circulation system is selected from the group consisting of: less than 0.001%; less than 0.01%; less than 0.1%; less than 2%; less than 3%; less than 4%; less than 5%; less than
30 6%; less than 7%; less than 8%; less than 9%; less than 10%; less than 11%; less than 12%; less than 13%; less than 14%; less than 15%; less than 16%; less than 17%; less than 18%; less than 19%; less than 20%; less than 21%; less than 22%; less than 23%; less than 24%; less than 25%; less than 26%; less than 27%; less than 28%; less than 29%; less than

30%; less than 31%; less than 32%; less than 33%; less than 34%; less than 35%; less than 36%; less than 37%; less than 38%; less than 39%; less than 40%; less than 41%; less than 42%; less than 43%; less than 44%; less than 45%; less than 46%; less than 47%; less than 48%; less than 49%; less than 50%; less than 51%; less than 52%; less than 53%; less than 54%; less than 55%; less than 56%; less than 57%; less than 58%; less than 59%; less than 60%; less than 61%; less than 62%; less than 63%; less than 64%; less than 65%; less than 66%; less than 67%; less than 68%; less than 69%; less than 70%; less than 71%; less than 72%; less than 73%; less than 74%; and less than 75% (w/w%).

[00106] Preferably, said biologically active material is absorbed by diffusion directly into the systemic circulation.

[00107] Preferably, said biologically active material is sublingually absorbed rapidly.

[00108] Preferably, the drug form is delivered sublingually and more suitable for patients phobic to subcutaneous injection.

[00109] Preferably, the sublingual administered glucagon-like peptide 1 (GLP-1) agonist has multiple sites action, that is, initial rapid sublingual absorption, then, those glucagon-like peptide 1 (GLP-1) agonists not absorbed sublingually is swallowed into the stomach which then undergo stomach absorption and finally reaching the small intestine which then react locally in the intestinal and colon mucosa L-cells (enteroendocrine cells which produce and release hormones such as glucagon-like peptide-1 (GLP-1) and peptide YY (PYY)), a local intrinsic reaction for immediate satiety effect.

[00110] Preferably, the released GLP-1 stimulates pancreatic insulin, which helps regulate blood sugar levels and also inhibit glucagon secretion, slowing down gastric emptying, and promote a feeling of satiety or fullness (appetite suppression).

[00111] Preferably, the released PYY hormone produced by L-cells helps to reduce appetite, slow down gut motility, and modulate the absorption of nutrients from the intestines.

[00112] Preferably, the glucagon-like peptide 1 (GLP-1) agonist -bile salt-lecithin complex undergoes absorption in the small intestine and the absorbed complex undergoes liver first-pass metabolism and the free glucagon-like peptide 1 (GLP-1) agonist secrets back into the small intestine (entero-hepatic recirculation) actively attached onto the L-cells again releasing GLP-1 and PYY resulting in their pharmacological satiety effect, and wherein the parenteral administered semaglutide only has a systemic effect with minimal or no local intestinal/colon mucosa effect.

[00113] Preferably, currently oral semaglutide has very low oral bioavailability (0.8 to 1.4%) and may need up to 50 mg per dose to be effective, yet this sublingual semaglutide uses 3 times (15mg versus 50mg) less semaglutide due to its multiple sites of action.

5 [00114] Preferably, there is a correlation between semaglutide tablet erosion and semaglutide plasma exposure and wherein full tablet erosion at 1 hour resulted in very low plasma exposure of semaglutide, whereas less than 54 % tablet erosion resulted in high plasma exposure of semaglutide, hence the mandatory criteria of using less than 120mL of water during oral administration and wherein there is no problem with sublingual administration (no water needed for disintegration, fully disintegrated with saliva).

10 [00115] Preferably, the $t_{1/2}$ of the administered glucagon-like peptide 1 (GLP-1) agonist is selected from the group consisting of: between 15 and 20 min; between 20 and 25 min; between 25 and 30 min; between 30 and 35 min; between 35 and 40 min; between 40 and 45 min; between 45 and 50 min; between 30 and 60 min; between 1 and 2 hrs; between 2 and 3 hrs; between 3 and 4 hrs; between 4 and 5 hrs; between 5 and 6 hrs; between 6 and 12 hrs; between 12 and 24 hrs; between 1 and 2 days; between 2 and 3 days; between 3 and 4 days; between 4 and 5 days; between 5 and 6 days; between 6 and 7 days; between 6 and 7 days; between 1 and 2 weeks; between 2 and 3 weeks; between 3 and 4 weeks; between 1 and 2 months; between 2 and 3 months; between 3 and 4 months; between 4 and 5 months; between 5 and 6 months; between 6 and 12 months; and between 1 and 2 years.

[00116] In a preferred embodiment, the $t_{1/2}$ of the administered glucagon-like peptide 1 (GLP-1) agonist is selected from the group consisting of: between 30 and 40 min.

25 [00117] In a preferred embodiment, the $t_{1/2}$ of the administered glucagon-like peptide 1 (GLP-1) agonist is selected from the group consisting of: 33 min; 34 min; 35 min; 36 min; 38 min; between 30 and 40 min.

[00118] In a preferred embodiment, the $t_{1/2}$ of the administered semaglutide is selected from the group consisting of: 33 min; 34 min; 35 min; 36 min; 38 min; between 30 and 40 min.

30 [00119] In another aspect, the invention is a method of appetite suppression, weight loss and/or weight management, said method comprising administering to a patient in need thereof a therapeutically effective amount of the dosage form of one aspect of the invention.

[00120] Use of the composition of the first aspect of the invention in the manufacture of a medicament for the treatment or prevention of a disease or disorder.

[00121] In another aspect, the invention is a process of preparing the composition of the first aspect of the invention, said process comprising the steps of: (1) combining at least one matrix forming agent with a biological active material to form a mixture; and (2) freeze drying the mixture to form the solid dosage form.

5 [00122] In another aspect, the invention is a kit comprising the dosage form of one aspect of the invention together with instructions for its use.

[00123] In a preferred embodiment, the kit is directed to treating or preventing a disease or disorder selected from the group consisting of: appetite suppression; weight loss; weight management; obesity; type 2 diabetes, regulate blood sugar; lower the risk of heart attack, stroke, or death in patients with type 2 diabetes and heart or blood vessel disease; cardiovascular disease; Alzheimer's disease; nonalcoholic steatohepatitis (NASH).

[00124] Further features of the present invention are more fully described in the following description of several non-limiting embodiments thereof. This description is included solely for the purposes of exemplifying the present invention. It should not be understood as a restriction on the broad summary, disclosure or description of the invention as set out above.

Brief Description of the Drawings

[00125] Below is a brief description of each of the figures and drawings.

[00126] Figure 1 shows the pH dependence of semaglutide solubility.

[00127] Figure 2 shows the chemical structure of semaglutide.

20 [00128] Figure 3 shows the chemical structure of deoxycholate sodium.

[00129] Figure 4 shows the chemical structure of SNAC.

[00130] Figure 5 shows the chemical structure of dapagliflozin.

[00131] Figure 6 shows a schematic diagram of the semaglutide + cholate + SNAC + dapagliflozin cluster.

25 [00132] Figure 7 shows a schematic diagram of the process of semaglutide/dapagliflozin delivery via the gastrointestinal tract.

[00133] Figure 8 supplements Figure 7 and shows an expanded region of Figure 7, and, in particular, the entero-hepatic-biliary system.

[00134] Figure 9 shows a graph of the single dose pharmacokinetic study in Sprague-Dawley rats.

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Detailed Description of the Invention

[00135] For convenience, the following sections generally outline the various meanings of the terms used herein. Following this discussion, general aspects regarding compositions, use of medicaments and methods of the invention are discussed, followed by
5 specific examples demonstrating the properties of various embodiments of the invention and how they can be employed.

[00136] Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. The
10 invention includes all such variations and modifications. The invention also includes all of the steps, features, formulations and compounds referred to or indicated in the specification, individually or collectively and any and all combinations or any two or more of the steps or features.

[00137] Each document, reference, patent application or patent cited in this text is
15 expressly incorporated herein in their entirety by reference, which means that it should be read and considered by the reader as part of this text. That the document, reference, patent application or patent cited in this text is not repeated in this text is merely for reasons of conciseness. None of the cited material or the information contained in that material should, however, be understood to be common general knowledge.

[00138] Manufacturer's instructions, descriptions, product specifications, and product
20 sheets for any products mentioned herein or in any document incorporated by reference herein, are hereby incorporated herein by reference, and can be employed in the practice of the invention.

[00139] The invention described herein may include one or more ranges of values (e.g.,
25 size, concentration etc.). A range of values will be understood to include all values within the range, including the values defining the range, and values adjacent to the range that lead to the same or substantially the same outcome as the values immediately adjacent to that value which defines the boundary to the range.

[00140] The present invention is not to be limited in scope by any of the specific
30 embodiments described herein. These embodiments are intended for the purpose of exemplification only. Functionally equivalent products, formulations and methods are clearly within the scope of the invention as described herein.

1. DEFINITIONS –

[00141] The meaning of certain terms and phrases used in the specification, examples, and appended claims, are provided below. If there is an apparent discrepancy between the usage of a term in the art and its definition provided herein, the definition provided within the specification shall prevail.

- 5 [00142] Other than in the operating examples, or where otherwise indicated, all numbers expressing quantities of ingredients or reaction conditions used herein should be understood as modified in all instances by the term "about." The term "about" when used in connection with percentages can mean $\pm 1\%$.

- 10 [00143] The invention described herein may include one or more range of values (e.g., size, concentration etc.). A range of values will be understood to include all values within the range, including the values defining the range, and values adjacent to the range which lead to the same or substantially the same outcome as the values immediately adjacent to that value which defines the boundary to the range. For example, a person skilled in the field will understand that a 10% variation in upper or lower limits of a range can be totally appropriate and is encompassed by the invention. More particularly, the variation in upper or lower limits
15 of a range will be 5% or as is commonly recognised in the art, whichever is greater.

- [00144] In this application, the use of the singular also includes the plural unless specifically stated otherwise. In this application, the use of "or" means "and/or" unless stated otherwise. Furthermore, the use of the term "including", as well as other forms, such as
20 "includes" and "included", is not limiting. Also, terms such as "element" or "component" encompass both elements and components comprising one unit and elements and components that comprise more than one subunit unless specifically stated otherwise. Also, the use of the term "portion" can include part of a moiety or the entire moiety.

- [00145] Throughout this specification, unless the context requires otherwise, the word
25 "comprise" or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

- [00146] "Therapeutically effective amount" as used herein with respect to methods of treatment and in particular drug dosage, shall mean that dosage that provides the specific
30 pharmacological response for which the drug is administered in a significant number of subjects in need of such treatment. It is emphasized that "therapeutically effective amount," administered to a particular subject in a particular instance will not always be effective in treating the disorder, condition of diseases described herein, even though such dosage is deemed a "therapeutically effective amount" by those skilled in the art. It is to be further

understood that drug dosages are, in particular instances, measured as sublingual, oromucosal, or oral dosages, or with reference to drug levels as measured in blood. Amounts effective for such a use will depend on: the desired therapeutic effect; the potency of the biologically active material; the desired duration of treatment; the stage and severity of the disease being treated; the weight and general state of health of the patient; and the judgment of the prescribing physician. Treatment dosages need to be titrated to optimize safety and efficacy. One skilled in the art will appreciate that the appropriate dosage levels for treatment will thus vary depending, in part, upon the indication for which the active agent is being used, the route of administration, and the size (body weight, body surface or organ size) and condition (the age and general health) of the patient. Accordingly, the clinician may titrate the dosage and modify the route of administration to obtain the optimal therapeutic effect. A typical dosage may range from about 0.1 µg/kg to up to about 100 mg/kg or more, depending on the factors mentioned above. In other embodiments, the dosage may range from 0.1 µg/kg up to about 100 mg/kg; or 1 µg/kg up to about 100 mg/kg; or 5 µg/kg up to about 100 mg/kg.

[00147] The frequency of dosing will depend upon the pharmacokinetic parameters of the active agent and the formulation used. Typically, a clinician will administer the composition until a dosage is reached that achieves the desired effect. The composition may therefore be administered as a single dose, or as two or more doses (which may or may not contain the same amount of the desired molecule) over time, or as a continuous infusion via an implantation device or catheter. Further refinement of the appropriate dosage is routinely made by those of ordinary skill in the art and is within the ambit of tasks routinely performed by them. Appropriate dosages may be ascertained through use of appropriate dose-response data.

[00148] As used herein "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible.

[00149] As used herein the term "subject" generally includes mammals such as: humans; farm animals such as sheep, goats, pigs, cows, horses, llamas; companion animals such as dogs and cats; primates; birds, such as chickens, geese and ducks; fish; and reptiles. The subject is preferably human. In one embodiment, the human subject is an infant, child, or adolescent. In one embodiment, the human subject is a paediatric patient aged 21 or younger at the time of their diagnosis or treatment.

[00150] Other definitions for selected terms used herein may be found within the detailed description of the invention and apply throughout. Unless otherwise defined, all other

scientific and technical terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which the invention belongs.

[00151] Features of the invention will now be discussed with reference to the following non-limiting description and examples.

5 2. EMBODIMENTS

[00152] The inventors have developed a sublingual, oromucosal and oral deliverable semaglutide formulation. In one embodiment, by combining dapagliflozin and semaglutide with different pharmacological action, we have provided an improved weight loss effect.

10 [00153] The added advantage of sublingual, oromucosal and oral semaglutide is the targeted local pharmacological effect when taken orally making semaglutide more suitable for oral therapeutic use than subcutaneous injection. Most importantly, the sublingual, oromucosal and/or orally administered semaglutide has a double action, that is, to react locally sublingually and in the intestinal and colon mucosa (local effect) for immediate satiety effect as well as when absorbed into the blood stream have a systemic effect similar to
15 subcutaneous injection; a two prong pharmacological activities (local as well as parenteral effects unlike injection which only have parenteral effect and no local intestinal/colon mucosa effect).

[00154] Currently, semaglutide is available as a subcutaneous injection preparation approved for treatment of type 2 diabetes mellitus and obesity plus one oral tablet
20 preparation approved for the treatment of type 2 diabetes mellitus. Semaglutide is less suitable for oral administration due to its very low oral bioavailability (less than 0.1%). The approved oral tablet semaglutide formulation has an oral bioavailability of 0.4 to 1% via stomach absorption. Semaglutide is also easily damaged by the stomach's gastric acid, digestive enzymes and intestinal mucosa barrier to absorption by passive diffusion against
25 macromolecules penetration leading to poor absorption and low bioavailability.

[00155] Administration of a semaglutide wafer is a non-invasive procedure and is only taken once a day, is convenient with a better compliance instead of the invasive daily subcutaneous injection. Improving the absorption of semaglutide in the intestine/colon can be challenging since it is a peptide-based drug that can be susceptible to acid degradation.
30 Hence, we have invented a novel wafer which enhances the absorption of semaglutide, plus neutralising the hostile gastric environment and allowing some stomach absorption of semaglutide and transporting it onto the small intestine and colon where the absorption takes place. Our novel formulation techniques improve the water solubility (enhanced absorption via active uptake) and improves the stability of semaglutide, using nanoparticle

complexes, and vehicles that protect the drug from hostile acidic stomach and pepsin enzyme degradation.

[00156] This is the first semaglutide sublingual, oromucosal and/or oral wafer preparation and the first to have multiple pharmacological actions: (1) First, immediate sublingual
5 semaglutide absorption circulating into the brain satiety centre; (2) The unabsorbed sublingual semaglutide flows into the stomach via the physiological saliva flow and undergoes some stomach absorption, increasing the systemic blood concentration of semaglutide; (3) The remaining unabsorbed semaglutide in the stomach then flows into the small intestine, rapidly activates the nerve receptors in the intestinal epithelia cells, a local
10 reaction sending signal to the satiety centre located in the ventromedial hypothalamus in the brain; (4) The remaining semaglutide-bile salts-lecithin complexes are actively absorbed into the intestinal mucosa and metabolised to free semaglutide, lecithin and bile salts by the liver. The free semaglutide released into the small intestine (enterohepatic recirculation) then stimulate the L-cells to release native GLP-1 hormone (intrinsic effect) which also acts on the
15 satiety centre of the brain (hence a dual action by GLP-1 hormone and the GLP-1 analogue peptide semaglutide).

[00157] In one embodiment, the inventors have formulated a novel oral formulation of semaglutide (a GLP-1 analogue polypeptide) with the following advantages. Addition of permeation and absorption enhancers to improve the transport of semaglutide across the
20 intestinal epithelium. These substances can temporarily disrupt the integrity of the intestinal barrier, allowing for enhanced drug absorption. Absorption enhancers include surfactants, bile salts, and certain polymers, thereby improving bioavailability. The permeation absorption enhancers utilized in this oral formulation form a novel micellar, vesicular and polymer-based nano-particles therapeutic systems, a simple derivatization procedure,
25 turning into attractive building blocks for the oral delivery of semaglutide and other biologics with absorption-enhancing activity. Withstand the gastrointestinal impediments by preventing the peptide degradation in the acid stomach and effectively reach the small intestines maintaining its stability and potency, where semaglutide peptide can then exert its local effects in the small intestine and colon. Aid in the active transporter-mediated absorption of
30 semaglutide via the paracellular and transcellular cells absorption as well as via the tight-junction mucosa cells. Binding of semaglutide to the nuclear-receptors present in the intestinal mucosal cell surfaces which then activate transcriptional networks, which then effect the expression of a number of target genes, including those for membrane transport proteins improving the bioavailability of semaglutide. Create micellar solubilization with
35 nanoparticles below 200nm influencing and improving the semaglutide and the easy transport across the intestinal mucosa membranes. The absorption enhancer-semaglutide is

ion-pairing and the formed complexes may have either higher or lower polarity compared to the drug molecule itself, which changes its physicochemical and pharmacokinetic properties. The further incorporation of enzyme inhibitors as well as a mucoadhesive polymer in the oral dosage forms is also further contributed to an improvement of an oral bioavailable active
5 form of polypeptide semaglutide macromolecular drugs, with effective protection and absorption enhancement properties.

Composition

[00158] The composition of the present invention comprises at least one matrix forming agent. In the freeze-dried systems of the prior art, gelatin is the most commonly used carrier
10 or structure forming agent due to its wall-forming ability. Gelatin is an ionic water soluble polymer, and as such, when mixed with active pharmaceutical ingredients in water; the increasing viscosity of the solution over time may cause a decreasing solubility of poorly soluble drugs in the mixture, and lead to a suspension of the drug in gelatin matrix. This can cause phase separation to occur; and the drug in amorphous or crystalline forms may not be
15 homogeneously dispersed in the matrix, which will eventually affect the dissolution and absorption of the final product.

[00159] Applicant has found that other polymer materials suitable for forming a matrix may be selected for specific application in the field of drug delivery, especially for site-specific drug delivery system such as in the oral cavity. Matrix forming agents of the present
20 invention may be selected from the group consisting of: non-mammalian gelatin, dextrin, soy protein, wheat protein, psyllium seed protein, acacia gum, guar gum, agar gum, xanthin gum, polysaccharides; alginates; sodium carboxymethylcellulose; carrageenans; dextrans; pectins; sugars; amino acids; starch; modified starches; carboxymethylcellulose; hydroxypropylmethylcellulose; hydroxypropyl cellulose and methyl cellulose inorganic salts;
25 synthetic polymers; amylopectin, polypeptide/protein or poly-saccharide complexes. Examples of at least one matrix forming agent that are carbohydrates include mannitol, dextrose, lactose, galactose, sorbitol and trehalose and cyclodextrin. Examples of matrix forming agents that are inorganic salts may be selected from the group consisting of: sodium phosphate, sodium chloride and aluminium silicates. The at least one matrix forming agent
30 may also be an amino acid. Examples of suitable amino acids include glycine, L-alanine, L-aspartic acid, L-glutamic acid, L-hydroxyproline, L-isoleucine, L-leucine and L-phenylalanine.

[00160] In a highly preferred embodiment, at least one matrix forming agent is sodium carboxymethylcellulose. When at least one matrix forming agent is sodium carboxymethyl cellulose, the polymer is present in a concentration of from about 0.1% to about 19% by dry
35 weight of the solid dosage form. In a preferred embodiment the sodium

carboxymethylcellulose is present in an amount of about 0.1% to about 15% by dry weight of the dosage form. In a highly preferred embodiment of the present invention, the sodium carboxymethyl cellulose is present in an amount of about 0.1 % to about 1.0% by dry weight of the solid dosage form. In another embodiment of the present invention, the dissolving dosage form comprises amylopectin as at least one matrix forming agent. Amylopectin is capable of increasing the release of the biologically active material by promoting formulation disintegration. Amylopectin may be present in the dosage form at a concentration about 2% up to no greater than 20% by dry weight of the solid dosage form. In a highly preferred form of the present invention, amylopectin is present in an amount of about 2% to about 17% dry weight of the dosage form.

[00161] To achieve dissolution of drugs, low MW diluents may be added as at least one matrix forming material. Diluents include microcrystalline cellulose (e.g., Avicel PH 101® and Avicel PH 102®), lactose, starch and sorbitol. These diluents may be present in the dosage form either alone or as a mixture in different ratios, and may be about 1% to about 80%, preferably about 2% to about 50%, either individually or cumulatively. In one embodiment of the present invention, the dissolving dosage form comprises microcrystalline cellulose as the at least one matrix forming agent. Microcrystalline cellulose may act as a filler and binder in the dosage form of the present invention. Microcrystalline cellulose has the ability to compact with minimum compression pressures, and results in a hard, stable and dissolving dosage form. Due to its large surface area and high internal porosity, microcrystalline cellulose is able to absorb and retain large amounts of water, which is desirable in the dosage form of the invention. When the solid dosage form of the present invention comprises microcrystalline cellulose, it is present in an amount of about 1% to about 10%, and preferably from about 1% to about 8% by dry weight of the dosage form. The effectiveness of the dissolving dosage form of the present invention relies on the drug dissolving in a small volume of fluid, such as in the oral cavity, prior to absorption into the systemic circulation. Therefore, the rate of dissolution of the dosage form is important. In a preferred embodiment of the present invention, the dosage form comprises a super-disintegrant as at least one matrix forming material.

[00162] In a highly preferred embodiment, the dissolving dosage form of the present invention comprises glycine. Glycine is an amino acid with excellent wetting properties and is suitable for the dissolving formulation. Low amounts of glycine may be used in the formulation of the present invention to control the dissolution rate of the dosage form. Furthermore, glycine may also be used as an anti-collapsing agent, which maintains the dosage form from shrinking either during the manufacture process or after packing. In one embodiment, the dosage form of the present invention comprises from about 0.5% to about

5% dry weight of the dosage form. According to another embodiment of the invention, the solid dosage form may include a matrix forming agent such as mannitol. Mannitol is a component that may aid in the crystalline structure and impart hardness of the dosage form. When mannitol is present in the dosage form, it occurs in a concentration of from about 5%
5 to about 80%, and preferably from about 10% to about 60% by dry weight of the dosage form.

[00163] In addition, the dissolving dosage form of the present invention may include lubricants, such as polyethylene glycol (PEG) 1000, 1500, 2000, 4000 and 6000, sodium lauryl sulphate, fats or oils. One advantage of the use of these lubricants is to aid in the
10 removal of the dosage form from the mould. These lubricants may be present in the dosage form either alone or as a mixture in different ratios, and may be between 0.05% to 5%, preferable between 0.1% and 2%, preferable about 1.5%, either individually or cumulatively. In one embodiment, the composition includes between 0.05% to 5% polyethylene glycol 1500, preferably between 0.1% and 2% by dry weight of the dosage form, or as mixtures of
15 the various glycols. The invention extends, in another aspect thereof, to improve sublingual absorption of weak base compounds, the composition comprising a solid buffer reagent that affords to produce a saliva pH of 4-6 when dissolved in oral cavity. Increasing the pH of the solution of a weak base compound can increase the ratio of unionized to ionized, which will lead to enhanced sublingual absorption. The solid buffer reagent include sodium dihydrogen
20 phosphate dihydrate, sodium hydrogen phosphate, sodium hydrogen carbonate and sodium carbonate, which may be present in the dosage form either alone or as a mixture in different ratios in a concentration of about 0.01% to about 10% by weight of the composition. Preferably, the buffer reagent is sodium carbonate, which may be present in a concentration of about 0.01% to about 10% by weight of the composition, preferably between 0.1% to 1%,
25 most preferably about 0.3%.

[00164] When mannitol is present in the dosage form, it occurs in a concentration of from about 5% to about 80%, and preferably from about 10% to about 60% by dry weight of the dosage form.

[00165] The composition may, in certain embodiments, include an absorption enhancer.
30 The absorption enhancer may be a polysaccharide and may be positively charged. Preferably, the absorption enhancer is β -cyclodextrin or its derivatives. The β -cyclodextrin or derivative may be present in a concentration of from about 0.01% to about 10% by dry weight of the dosage form, preferably between 0.2% to 2%, and most preferably about 1 %. The solid dosage form of the present invention may comprise flocculating agents to maintain
35 disbursement of the biologically active material evenly dispersed in the matrix during the

manufacture process. The flocculating agent may be gums. Preferably, the gum is xanthan gum. The xanthan gum may be present in a concentration of about 0.01% to about 10% by dry weight of the composition, preferably from about 0.2% to 2%, and most preferably about 1%.

5 [00166] To aid dissolution of the biologically active material into the aqueous environment, a surfactant may be added to the solution as a wetting agent. Suitable surfactants include anionic detergents such as sodium lauryl sulfate, dioctyl sodium sulfosuccinate and dioctyl sodium sulfonate. Cationic detergents may be used and include benzalkonium chloride or benzethonium chloride. The list of possible non-ionic detergents
10 includes laurmacrogol 400, polyoxyl 40 stearate, polyoxyethylene hydrogenated castor oil 10, 50 and 60, glycerol monostearate, Polysorbate 40, 60, 65 and 80, sucrose fatty acid ester, methyl cellulose and carboxymethyl cellulose. These surfactants may be present in the dosage form either alone or as a mixture in different ratios. Additives which potentially enhance uptake of the compounds are fatty acids such as oleic acid, linoleic acid and
15 linolenic acid.

[00167] In order to enhance the aesthetic and taste appeal of the dissolving dosage form to the subject, the dosage form may also contain colouring agents, such as FD & C dyes Blue No. 2 and Red No. 40; flavoring agents, such as orange, mixed berry, cherry, peppermint, raspberry and caramel; and/or sweeteners such as aspartame, stevia,
20 sucralose and saccharin.

[00168] The solid dosage form of the present invention is suitable for oral administration to a subject. As discussed above, the dosage form comprises biologically active material. The biologically active material is therefore delivered to the subject via the oral cavity mucosa and into the systemic blood system within a relatively short period of time. In a
25 preferred embodiment, an effective plasma concentration of the biologically active material is reached within a period of no more than two hours, preferably within 30 minutes, and most preferably within 10 minutes.

[00169] Furthermore, an advantage of the present invention is that the solid dosage form completely dissolves within 2 seconds to 60 seconds, preferably 2 seconds to 30 seconds,
30 and most preferably within 2 seconds to 10 seconds after administration of the dosage form. In a highly preferred embodiment of the present invention, there is no residue remaining of the dosage form of the present invention after administration that is detectable by the patient. As such, the subject has no urge to swallow the dosage form.

[00170] The subject receiving the dissolving dosage form of the present invention may be an animal or human being. When the subject is a human being, it may be an adult or a child, including elderly adults and infants. In particular, the subject is a subject that is unable to or has difficulties in swallowing.

5 [00171] The solid dosage form may comprise sodium carboxymethylcellulose as a formulation aide in low levels. When the amount of sodium carboxymethylcellulose is between about 0.1% and 15% by dry weight of the dosage form, the wafer releases the active agent, without leaving a residue in the oral cavity. In addition, the use of gelatin was avoided by the inventors, and therefore prevents the unwanted residue left in the oral cavity
10 after administration. The addition of lactose and or mannitol was also found to be advantageous in the dosage formulation of the present invention.

[00172] Thus, in one embodiment, the present invention provides a solid dosage form adapted for the release of biologically active material in the oral cavity wherein the dosage form comprises: (i) biologically active material and (ii) at least one matrix forming agent,
15 wherein the dosage form substantially dissolves in the oral cavity, wherein the dosage form comprises 0.1-0.3% sodium carbonate, 0.1-4% sodium carboxymethylcellulose, 0.1-10% PEG 1500, 1-4%% glycine, 1-10%% microcrystalline cellulose; 2-17% amylopectin, 10-30% lactose and 30-50% mannitol as a dry weight of the solid dosage form, and which does not result in substantial detectable levels of residue left over in the oral cavity of the patient.

20 Pharmaceutical Compositions

[00173] The present invention also provides a pharmaceutical composition comprising the composition of the invention together with a pharmaceutically acceptable carrier.

[00174] Therapeutic compositions are within the scope of the present invention. Preferably the compositions are combined with a pharmaceutically acceptable carrier or
25 diluent to produce a pharmaceutical composition (which may be for human or animal use). Suitable carriers and diluents include isotonic saline solutions, for example phosphate-buffered saline. As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for
30 pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions. See, e.g., Remington's Pharmaceutical Sciences, 2th Ed. (1995, Mack Publishing Co., Easton, Pa.) which is herein incorporated by reference.

[00175] The pharmaceutical composition can contain formulation materials for modifying, maintaining or preserving, for example, the pH, osmolarity, viscosity, clarity, colour, isotonicity, odour, sterility, stability, rate of dissolution or release, adsorption or penetration of the composition. Suitable formulation materials include, but are not limited to, amino acids (such as glycine, glutamine, asparagine, arginine or lysine); antimicrobials; antioxidants (such as ascorbic acid, sodium sulphite or sodium hydrogen-sulphite, Vitamin E, Vitamin E phosphate – lipid soluble vitamins, nano emulsions); buffers (such as borate, bicarbonate, tris-HCl, citrates, phosphates or other organic acids); bulking agents (such as mannitol or glycine); chelating agents (such as ethylenediamine tetraacetic acid (EDTA)); complexing agents (such as caffeine, polyvinylpyrrolidone, beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin), fillers; monosaccharides, disaccharides; and other carbohydrates (such as glucose, mannose, or dextrans); proteins (such as serum albumin, gelatin or immunoglobulins); colouring, flavouring (natural and natural derived products) and diluting agents; emulsifying agents; hydrophilic polymers (such as polyvinylpyrrolidone); low molecular weight polypeptides; salt-forming counterions (such as sodium); preservatives (such as benzalkonium chloride, benzoic acid, salicylic acid, thimerosal, phenethyl alcohol, methylparaben, propylparaben, chlorhexidine, sorbic acid or hydrogen peroxide); solvents (such as glycerin, propylene glycol or polyethylene glycol); sugar alcohols – and artificial sweeteners (such as mannitol or sorbitol); suspending agents; surfactants or wetting agents (such as pluronics, PEG, sorbitan esters, polysorbates such as polysorbate 20, polysorbate 80, triton, tromethamine, lecithin, cholesterol, tyloxapol); stability enhancing agents (sucrose or sorbitol); tonicity enhancing agents (such as alkali metal halides, preferably sodium or potassium chloride), delivery vehicles, diluents, excipients and/or pharmaceutical adjuvants.

[00176] The optimal pharmaceutical composition will be determined by one skilled in the art depending upon, for example, the intended route of administration, delivery format, and desired dosage. Such compositions may influence the physical state, stability, rate of in vivo release, and rate of in vivo clearance of the composition of the invention. The preferred form of the pharmaceutical composition depends on the intended mode of administration and therapeutic application.

[00177] The primary vehicle or carrier in a pharmaceutical composition is aqueous and non-aqueous in nature. For example, a suitable vehicle or carrier may be water for injection, physiological saline solution, possibly supplemented with other materials. Neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. Other exemplary pharmaceutical compositions comprise tris buffer of about pH 7.0-8.5, or acetate buffer of about pH 4.0-5.5, which may further include sorbitol or a suitable substitute thereof. In one embodiment of the present invention, pharmaceutical compositions may be prepared for

storage by mixing the selected composition having the desired degree of purity with optional formulation agents in the form of an aqueous solution and non-aqueous.

[00178] The formulation components are present in concentrations that are acceptable to the site of administration. For example, buffers are used to maintain the composition at
5 physiological pH or at a slightly lower pH, typically within a pH range of from about 5 (4.5) to about 8

[00179] Additional pharmaceutical compositions will be evident to those skilled in the art, including formulations of the invention in sustained- or controlled-delivery formulations. Techniques for formulating a variety of other sustained- or controlled-delivery means, such
10 as liposome carriers, bio-erodible microparticles or porous beads and depot injections, are also known to those skilled in the art. Additional examples of sustained-sustained-release preparations include semipermeable polymer matrices in the form of shaped articles, for example, films, or microcapsules. Sustained release matrices may include polyesters, hydrogels, polylactides, copolymers of L-glutamic acid and gamma ethyl-L-glutamate,
15 ethylene vinyl acetate or poly-D(-)-3-hydroxybutyric acid. Sustained-release compositions may also include liposomes, which can be prepared by any of several methods known in the art.

[00180] The pharmaceutical composition to be used for in vivo administration typically must be sterile. This may be accomplished by filtration through sterile filtration membranes.
20 In addition, the compositions generally are placed into a container having a sterile access port. Once the pharmaceutical composition has been formulated, it may be stored in sterile vials as a solution.

[00181] In yet a further preferred embodiment, the composition retains its effective biological activity for a period selected from the group consisting of; greater than 24 hours; greater than 36 hours; and greater than 48 hours. Preferably, the composition is stable for
25 periods selected from the group consisting of: 6 months, 1 year and 2 years. In one example, the composition is stable at temperatures selected from the group consisting of: -4°C, 4°C, 18°C and 25°C.

[00182] As discussed above, the medicaments of the present invention may include one
30 or more pharmaceutically acceptable carriers. The use of such media and agents for the manufacture of medicaments is well known in the art. Except insofar as any conventional media or agent is incompatible with the pharmaceutically acceptable material, use thereof in the manufacture of a pharmaceutical composition according to the invention is

contemplated. Pharmaceutical acceptable carriers according to the invention may include one or more of the following examples:

- [00183] (1) surfactants and polymers, including, however not limited to polyethylene glycol (PEG), polyvinylpyrrolidone, polyvinylalcohol, crospovidone, polyvinylpyrrolidone-
5 polyvinylacrylate copolymer, cellulose derivatives, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, carboxymethylethyl cellulose, hydroxypropylmethyl cellulose phthalate, polyacrylates and polymethacrylates, urea, sugars, polyols, and their polymers, emulsifiers, sugar gum, starch, organic acids and their salts, vinyl pyrrolidone and vinyl acetate; and/or
- 10 [00184] (2) binding agents such as various celluloses and cross-linked polyvinylpyrrolidone, microcrystalline cellulose; and/or (3) filling agents such as lactose monohydrate, lactose anhydrous, microcrystalline cellulose and various starches; and/or
- [00185] (4) lubricating agents such as agents that act on the increased ability of the dosage form to be ejected from the packaging cavity, and/or
- 15 [00186] (5) sweeteners such as any natural or artificial sweetener including sucrose, xylitol, sodium saccharin, cyclamate, aspartame, and acesulfame K; and/or
- [00187] (6) flavouring agents; and/or
- [00188] (7) preservatives such as potassium sorbate, methylparaben, propylparaben, benzoic acid and its salts, other esters of parahydroxybenzoic acid such as butylparaben,
20 alcohols such as ethyl or benzyl alcohol, phenolic chemicals such as phenol, or quarternary compounds such as benzalkonium chloride; and/or
- [00189] (8) buffers; and/or
- [00190] (9) diluents such as pharmaceutically acceptable inert fillers, such as microcrystalline cellulose, lactose, dibasic calcium phosphate, saccharides, and/or mixtures
25 of any of the foregoing; and/or
- [00191] (10) wetting agents such as corn starch, potato starch, maize starch, and modified starches, croscarmellose sodium, crospovidone, sodium starch glycolate, and mixtures thereof; and/or
- [00192] (11) disintegrants; and/or
- 30 [00193] (12) effervescent agents such as effervescent couples such as an organic acid (e.g., citric, tartaric, malic, fumaric, adipic, succinic, and alginic acids and anhydrides and acid salts), or a carbonate (e.g. sodium carbonate, potassium carbonate, magnesium

carbonate, sodium glycine carbonate, L-lysine carbonate, and arginine carbonate) or bicarbonate (e.g. sodium bicarbonate or potassium bicarbonate);

[00194] Permeation enhancer; entero-hepatic recycling agent, mucolytic; mucoadhesive, entero-hepatic-biliary recirculation agent such as sodium glycodeoxycholate, sodium deoxycholate, carboxymethyl cellulose, sodium alginate, SNAC (salcaprozate sodium), non-
5 ionic ester alkoxylate (or alkanolic acid ester alkoxylate), soy lecithin etc. and other pharmaceutically acceptable excipients; and/or

[00195] (13) other pharmaceutically acceptable excipients.

[00196] Medicaments of the invention suitable for use in animals and in particular in
10 human beings typically must be sterile and stable under the conditions of manufacture and storage. The medicaments of the invention comprising biologically active material can be formulated as a solid, a liposome, or other ordered structures suitable to high drug concentration adapted for oral delivery.

[00197] In another embodiment, the biologically active material may be combined into a
15 medicament with another biologically active material, or even the same biologically active material.

[00198] Medicaments of the invention can be orally, sublingually or oromucosally administered to a subject. Solid dosage forms for oral administration include wafers, but also tablets and capsules. Further, incorporating any of the normally employed excipients, such
20 as those previously listed, and generally 0.1% to 95% of the biologically active material, and more preferably at a concentration of 0.1% to 75% will form a pharmaceutically acceptable non-toxic oral administration.

Dosage Form

[00199] Dosage forms are within the scope of the invention. In a preferred embodiment,
25 the invention provides a dosage form comprising the composition as described in the first aspect of this invention.

[00200] In a further embodiment, the dosage form is a wafer.

[00201] Preferably, the dosage form is stored in a sealed and sterile container.

Method for treating or preventing

[00202] The invention also provides a method of treating a condition, disease or disorder,
30 said method comprising administering to a patient in need thereof a therapeutically effective amount of the dosage form of the invention.

[00203] In a further preferred embodiment, the dosage form is administered at an amount to at least partially treat the disorder, disease or condition.

[00204] In a further preferred embodiment, the therapeutically effective amount is an amount of biologically active material selected from the group consisting of: between 0.001 to 100mg/kg/day; between 1 to 100mg/kg/day; between 2 and 50mg/kg/day; between 5 and 40mg/kg/day; between 10 and 30mg/kg/day; between 20 and 25mg/kg/day; and 20mg/kg/day. Preferably, the therapeutically effective amount is an amount of biologically active material vis selected from the group consisting of: 0.1mg/day; 5mg/day; 10mg/day; 15mg/day; 40mg/day; 400mg/day; 600mg/day; 800mg/day; 1280mg/day; 1500mg/day.

10 [00205] In a further preferred embodiment, therapeutically effective amount is an amount of biologically active material selected from the group consisting of: between 0.01 to 100mg/kg/day; between 1 to 100mg/kg/day; between 2 and 50mg/kg/day; between 5 and 40mg/kg/day; between 10 and 30mg/kg/day; between 20 and 25mg/kg/day; and 20mg/kg/day. Preferably, the therapeutically effective amount is an amount of biologically
15 active material vis selected from the group consisting of: 10mg/day; 15mg/day; 40mg/day; 400mg/day; 600mg/day; 800mg/day; 1280mg/day; 1500mg/day.

[00206] In a further preferred embodiment, T_{max} occurs between 0.01 and 336 hours; 1 and 4 hours.

[00207] In a further preferred embodiment, T_{1/2} occurs between 0.11 and 12 hours;
20 0.01 and 12 hours; 1.1 and 2.4 hours.

[00208] In a further preferred embodiment, the therapeutically effective amount is administered to the subject to treat the disorder.

[00209] Preferably the therapeutically effective amount is administered to the subject utilising a dosing regimen selected from the group consisting of: twice hourly; hourly; once
25 every six hours; once every 8 hours; once every 12 hours; once daily; twice weekly; once weekly; once every 2 weeks; once every 6 weeks; once a month; every 2 months; every 3 months; once every 6 months; and once yearly.

[00210] Preferably the therapeutically effective amount is administered to the subject using a method selected from the group consisting of: sublingually.

30 [00211] A subject that can be treated with the invention will include humans as well as other mammals and animals.

[00212] In a further preferred embodiment, the method comprises administering to a patient in need thereof a therapeutically effective amount of the dosage form of the invention

together with an additional active ingredient. In a preferred form, the additional active ingredient is administered using a dosing regimen selected from the group consisting of: at the same time as administering the dosing form of the invention; before administering the dosing form of the invention; after administering the dosing form of the invention; concurrently with administering the dosing form of the invention; sequentially before administering the dosing form of the invention; and sequentially after administering the dosing form of the invention.

[00213] Preferably, the additional active ingredient is selected from the group consisting of: a amino acid; a bipeptide; a tripeptide; a polypeptide; an antibody; a small chemical entity.

Use of a composition in the manufacture of a medicament

[00214] Uses are within the scope of this invention. The invention also provides a use of the composition of the first aspect of the invention in the manufacture of a medicament for the treatment of a condition, disease or disorder.

Kit

[00215] The invention also provides a kit comprising the dosage form of one aspect of the invention together with instructions for its use.

Device

[00216] Devices are within the scope of the invention. In a preferred embodiment, the invention provides a device, wherein the device comprises: (1) the composition as described in the first aspect of this invention; and (2) an applicator.

Method for stabilising

[00217] Methods for stabilizing the composition are within the scope of the invention.

[00218] In a further preferred embodiment, the said method protects the composition against degradation.

[00219] In yet a further preferred embodiment, the composition retains its effective biological activity for a period selected from the group consisting of; greater than 24 hours; greater than 36 hours; greater than 48 hours; greater than 168 hours.

[00220] The addition of approved pharmaceutical excipients to stabilise the composition is preferred from a safety standpoint, as the simpler methodology is likely to produce a less variable outcome and the choice of excipient can be limited to those with Generally Regarded as Safe (GRAS) status. Excipients for the stabilisation of protein solutions can be

classified into four broad categories: salts, sugars, polymers or protein/amino acids, based on their chemical properties and mechanism of action. Salts (e.g., chlorides, nitrates) stabilise the tertiary structure of proteins by shielding charges through ionic interactions. Sugars (e.g., glycerol, sorbitol, fructose, trehalose) increase the surface tension and viscosity of the solution to prevent protein aggregation. Similarly, polymers (e.g. polyethylene glycol, cellulose derivatives) stabilise the protein tertiary structure by increasing the viscosity of the solution to prevent protein aggregation and intra- and inter-molecular electrostatic interactions between amino acids in the protein. Proteins (e.g. human serum albumin) are able to stabilise the structure of other proteins through ionic, electrostatic and hydrophobic interactions. Similarly, small amino acids with no net charge, such as alanine and glycine, stabilise proteins through the formation of weak electrostatic interactions.

[00221] As discussed above, the medicaments of the present invention may include one or more pharmaceutically acceptable carriers. The use of such media and agents for the manufacture of medicaments is well known in the art. Except insofar as any conventional media or agent is incompatible with the pharmaceutically acceptable material, use thereof in the manufacture of a pharmaceutical composition according to the invention is contemplated. Pharmaceutical acceptable carriers according to the invention may include one or more of the following examples:

- a. surfactants and polymers, including, however not limited to polyethylene glycol (PEG), polyvinylpyrrolidone, polyvinylalcohol, crospovidone, polyvinylpyrrolidone-polyvinylacrylate copolymer, cellulose derivatives, HPMC, hydroxypropyl cellulose, carboxymethylethyl cellulose, hydroxypropylmethyl cellulose phthalate, polyacrylates and polymethacrylates, urea, sugars, polyols, and their polymers, emulsifiers, sugar gum, starch, organic acids and their salts, vinyl pyrrolidone and vinyl acetate; and/or
- b. binding agents such as various celluloses and cross-linked polyvinylpyrrolidone, microcrystalline cellulose; and/or (3) filling agents such as lactose monohydrate, lactose anhydrous, microcrystalline cellulose and various starches; and/or
- c. filling agents such as lactose monohydrate, lactose anhydrous, mannitol, microcrystalline cellulose and various starches; and/or
- d. lubricating agents such as agents that act on the increased ability of the dosage form to be ejected from the packaging cavity, and/or
- e. sweeteners such as any natural or artificial sweetener including sucrose, xylitol, sodium saccharin, cyclamate, aspartame, and acesulfame K; and/or

- 5 f. flavouring agents; and/or
- g. preservatives such as potassium sorbate, methylparaben, propylparaben, benzoic acid and its salts, other esters of parahydroxybenzoic acid such as butylparaben, alcohols such as ethyl or benzyl alcohol, phenolic chemicals such as phenol, or
- 10 quaternary compounds such as benzalkonium chloride; and/or
- h. buffers; and/or
- i. diluents such as pharmaceutically acceptable inert fillers, such as microcrystalline cellulose, lactose, dibasic calcium phosphate, saccharides, and/or mixtures of any of the foregoing; and/or
- 15 j. absorption enhancer such as glyceryl trinitrate;
- k. add penetrants, permeation enhancer; entero-hepatic recycling agent, mucolytic; mucoadhesive, entero-hepatic-biliary recirculation agent such as sodium glycodeoxycholate, sodium deoxycholate, carboxymethyl cellulose, sodium alginate, SNAC (salcaprozate sodium), non-ionic ester alkoxylate (or alkanolic acid ester alkoxylate), soy lecithin Sodium glycodeoxycholate; and/or
- 20 l. other pharmaceutically acceptable excipients.

[00222] Medicaments of the invention suitable for use in animals and in particular in human beings typically must be sterile and stable under the conditions of manufacture and storage.

20 [00223] Methods to produce

[00224] According to a further aspect of the present invention, there is provided a method to produce the dosage form of the present invention comprising the steps of combining at least one matrix forming agent with a biological active material to form a mixture and then freeze drying the mixture to form the solid dosage form. In a preferred embodiment of the

25 present invention, the mixture is measured (by weight or volume) into a preformed plastic or aluminium blister mould (individual dose). The blister mould is placed into a freeze dryer for 24 hours and the resultant solid dosage form (wafer) is then sealed with aluminium or plastics foil to prevent moisture absorption.

[00225] In one embodiment of the present invention, the method may require that the pH

30 of the mixture is adjusted to a pH within the range of between 3.0 and 10.0, preferably between 6.4 and 7.8. If required, the pH may be adjusted by using an acid, such as hydrochloric acid, phosphoric acid or citric acid; or a basic compound such as sodium

hydroxide, sodium dihydrogen phosphate dehydrate, sodium hydrogen phosphate, sodium hydrogen carbonate, tris hydrochloride and sodium carbonate.

[00226] In another embodiment, the method may include the step of using a solvent, such as water. If water is used as a solvent, it is preferable to be removed by freeze drying

5 [00227] The invention also provides a composition, methods and processes as described by the foregoing examples.

[00228] The present invention will now be described with reference to the following non-limiting Examples. The description of the Examples is in no way limiting on the preceding paragraphs of this specification, however, is provided for exemplification of the methods and
10 compositions of the invention.

Examples

[00229] It will be apparent to persons skilled in the pharmaceutical arts that numerous enhancements and modifications can be made to the above-described processes without departing from the basic inventive concepts. For example, in some applications the
15 biologically active material may be pretreated and supplied to the process in the pretreated form. All such modifications and enhancements are considered to be within the scope of the present invention, the nature of which is to be determined from the foregoing description and the appended claims. Furthermore, the following Examples are provided for illustrative purposes only, and are not intended to limit the scope of the processes or compositions of
20 the invention.

A EXAMPLE 1 – PREPARATION OF PREFERRED COMPOSITION

A.1 AIM

[00230] The objective is to improve the solubility and bioavailability of the GLP-1 active
25 (<1% for semaglutide) and the solubility of the SGLT-2 active (dapagliflozin is soluble to 1mg/mL in water) with the aim of reducing the dosage levels of one or both of these actives and therefore leading to a reduced side effect profile (side effects may include belching; bloating; excess air or gas in the stomach or intestines; gaseous stomach pain; heartburn; passing gas; recurrent fever; stomach discomfort or pain; sick feeling; feeling thirsty;
30 confused; unusually tired; breathing more deeply or faster). The improved solubility and permeability using surfactants and other excipients “pushes” GLP-1 agonist as well as SGLT-2 antagonists into Class 1 drugs hence increases mucosal absorption. Class I drugs

(Biopharmaceutical Classification System or BCS) are generally expected to undergo mucosal absorption more efficiently because they have both high solubility and high permeability. The mucosal surfaces, such as those in the gastrointestinal tract, allow for absorption of substances, and drugs in Class I have characteristics that favor this process with the aim of reducing the dosage.

A.2 MATERIALS AND METHODS

[00231] The inventors combined a number of molecular properties in a novel manner to deliver molecules of the flozin family of sodium glucose co-transporter-2 (SGLT-2) antagonist (dapagliflozin, empagliflozin, ertugliflozin, canagliflozin, bexagliflozin and/or glutide or natide family of glucogen-like peptide 1 (GLP-1) (semaglutide, liraglutide, dulaglutide, exenatide, lixisenatide) agonists, individually or in combination, both sublingually into the mucosal bloodstream. As a consequence of the unique protective features described in further details below, these agonists can also be delivered through the absorption in the stomach and intestinal tract.

[00232] By way of a background, semaglutide is a moderate MW polypeptide derivative (MW 4113) that has pH-dependent solubility, and several polar and non-polar regions. Above pH 7, semaglutide is moderately water soluble, up to 20mg/mL, and poorly soluble below pH7. See Figure 1 from Chen et al., Design and Development of a New Glucagon-Like Peptide-1 Receptor Agonist to Obtain High Oral Bioavailability. *Pharmaceutical Research* (2022) 39:1891–1906) and also Figure 2 for the chemical structure of semaglutide. Developing a protective mechanism against the pH of the surrounding aqueous medium to allow multiple points of absorption orally (pH 5-6), gastrically (pH 1-3) and intestinally (pH 7) would therefore be highly advantageous.

[00233] The inventors have proposed to use a combination of members of the cholate family, such as deoxycholate and taurodeoxycholate permeation enhancers, and SNAC (sodium salcaprozate, sodium N-[8-(2-hydroxybenzoyl)amino] caprylate) transport/permeation enhancer or non-ionic ester alkoxylate (or alkanoic acid ester alkoxylate) to bind to semaglutide to form a protective barrier to pH changes, to enhance solubility to minimise pepsin enzyme degradation of GLP-1 drugs in the stomach and enhance mucosal absorption at several points in oral-gastrointestinal tract.

[00234] Both the cholates (see Figure 3) and SNAC (see Figure 4) are also surfactant-like, with carboxylate polar heads and non-polar tails. Semaglutide has numerous amine and arginine sites (five) that would be positively charged at pH<8, and capable of binding many negatively charged cholate and SNAC molecules, to form a protective coating that bristles

with non-polar tails around each semaglutide molecule to prevent peptidolysis and pH change effects (peptide protection hypothesis). They may form individual molecular particles, or agglomerates.

5 [00235] Dapagliflozin is an interesting molecule in that it is itself surfactant-like, with a polar headgroup sugar and a non-polar tail (Figure 5). It cannot bind ionically to the cholates (see Figure 3) or SNAC (see Figure 4), since there are no ionizable atoms, or to semaglutide. However, it potentially acts as a non-ionic surfactant and help to stabilize the semaglutide particles. The dapagliflozin may interleave with the cholate tails and stabilize them so that can point out into the water phase.

10 [00236] When dapagliflozin, semaglutide, cholates and SNAC are combined in water and nanosized, in addition to phosphatidyl choline surfactant, semaglutide+cholate+SNAC ionically bonded nanoparticles will form, with outward-pointing non-polar tails stabilized with the non-ionic dapagliflozin "surfactant" (and dispersion aide phosphatidyl choline), a four in one particle combo (see Figure 6). These nanoparticles will have a particle size (by volume and number) below 2000nm. Dapagliflozin is poorly water soluble (1mg/mL) and this
15 combination will provide greater solubility in water, and enhance mucosal absorption.

[00237] The formulations are freeze dried and prepared in the form of a wafer for sublingual delivery.

20 [00238] The present invention will now be described with reference to the following non-limiting Examples. The description of the Examples is in no way limiting on the preceding paragraphs of this specification, however is provided for exemplification of the methods and compositions of the invention.

B EXAMPLE 2 – PREFERRED DOSES AND CONCENTRATION RANGES

25 [00239] A formulation of the present invention, in the form of a solid dosage form (wafer), was prepared in accordance with the method and ingredients below and as set out below in Table 1.

30 [00240] Wafers of the invention were prepared using the following methods. Sodium carboxymethylcellulose and sodium alginate were added in a portion of purified water by mixing thoroughly with a stirrer. The mixture was then heated to 50°C for ten minutes to allow dissolution of the polymers. Once the solution cooled down to room temperature, sodium glycodeoxycholate, sodium deoxycholate, carboxymethyl cellulose, sodium alginate, SNAC (salcaprozate sodium), soy lecithin lactose, mannitol, polyethylene glycol 2000, glycine, microcrystalline cellulose were added individually, under stirring to obtain a

homogenously solution. This solution was then homogenized into nanoparticles. The viscosity of the solution and particle sizes were measured at 25° C using a Brookfield Digital Viscometer (Brookfield Engineering Laboratories Inc., MA, USA) and Malvern Laser PSD Mastersizer 2000 respectively.

5 [00241] Wafers of the invention were freeze dried using the following methods. The resulting mixture was transferred by pipette and accurately weighed into pre-formed blister packs, and then transferred into a freezer (-30° C) for approximately 24 hours. After freezing, the sample was freeze-dried (DYNA-VAC, Australia) for 24 hours using standard methods known in the art. The prepared sample was stored in desiccator over silica gel at a room
10 temperature.

[00242] Uniformity of Weight: The uniformity of the weight of the fast-dissolving dosage wafer form was tested in accordance with the British Pharmacopoeia (BP) 2009 test. Twenty wafers from each of the formulations listed in Table 1 + 2 were individually weighed, and the average weight and relative standard was calculated. All the prepared wafers from different
15 formulations were within the accepted weight variation from between 0.25 to 2%.

[00243] The strength of the fast-dissolving solid dosage wafer forms, i.e. their ability to be reduced from a solid substance into smaller pieces was measured. The test was conducted according to BP 2009 method (i.e. friability of uncoated tablets), using the Erweka friability tester (Germany). A sample of 20 wafers was weighed accurately and placed in the
20 apparatus. A rotation time of four minutes at 25 rpm was used. Wafers were removed and reweighed and the percent-age weight loss was calculated. It was found that the weight loss of the 20 wafers ranged from 8 to 20%. Although this weight loss does not comply with the BP 2009 standard of about 1 % weight loss for compressed tablets, there is no such standard for wafers in either the BP or USP monograph.

25 [00244] Moisture Analysis: The moisture content of the wafers was analysed after lyophilisation using the 870 Karl Fisher Titrino Plus (Metrohm Ag, Germany). The results show that the residual moisture content varied between 1 % to 5% for different formulations.

[00245] Various batches of the solid dosage wafer form were then prepared based on the formulation shown in Table 1 and Table 2

30 B.1 RESULTS

[00246] Suitable compositions can be prepared according to TABLE 1 and TABLE 2.

[00247] TABLE 1 - Preferred dose and concentration ranges

CHEMICAL NAME	FAMILY OR CLASS	PREFERRED DOSE AND CONCENTRATIONS RANGES	MORE PREFERRED DOSE AND CONCENTRATIONS RANGES
<i>FORMULATION</i> Semaglutide, (alternatively, liraglutide; dulaglutide; exenatide; and lixisenatide).	GLP-1 agonist	Concentration: 0.001%; 0.1%; 1% (w/w); 2% (w/w); 3% (w/w); 4% (w/w); 5% (w/w); 6% (w/w); 7% (w/w); 8% (w/w); 9% (w/w); 10% (w/w); 11% (w/w); 12% (w/w); 13% (w/w); 14% (w/w); 15% (w/w); 16% (w/w); 17% (w/w); 18% (w/w); 19% (w/w); 20% (w/w); 21% (w/w); 22% (w/w); 23% (w/w); 24% (w/w); 25% (w/w); 26% (w/w); 27% (w/w); 28% (w/w); 29% (w/w); 30% (w/w); 31% (w/w); 32% (w/w); 33% (w/w); 34% (w/w); 35% (w/w); 36% (w/w); 37% (w/w); 38% (w/w); 39% (w/w); 40% (w/w); 41% (w/w); 42% (w/w); 43% (w/w); 44% (w/w); 45% (w/w); 46% (w/w); 47% (w/w); 48% (w/w); 49% (w/w); 50% (w/w); and 2.95% (w/w); 3-65% (w/w); 4-55% (w/w); 5-45% (w/w); 5-35% (w/w); 7-25% (w/w); 8-15% (w/w); and within 2 decimal points of each figure. A suitable dose could include: 0.01mg; 0.1mg; 1mg; 2mg; 5mg; 10mg; 15mg; 20mg; 21mg; 0.25mg to 100mg; 1mg to 25mg; 1mg to 50 mg; 1 mg to 30mg; 2 to 30mg; 5 mg to 15mg; 10mg to 20mg; 10 to 50mg. A suitable dose could also include: 0.01mg; 0.02mg; 0.03mg; 0.04mg; 0.05mg; 0.06mg; 0.07mg; 0.08mg; 0.09mg; 0.10mg; 0.11mg; 0.12mg; 0.13mg; 0.14mg; 0.15mg; 0.16mg; 0.17mg; 0.18mg; 0.19mg; 0.20mg; 0.21mg; 0.22mg; 0.23mg; 0.24mg; 0.25mg; 0.26mg; 0.27mg; 0.28mg; 0.29mg; 0.30mg; 0.31mg; 0.32mg; 0.33mg; 0.34mg; 0.35mg; 0.36mg; 0.37mg; 0.38mg; 0.39mg; 0.40mg; 0.41mg; 0.42mg; 0.43mg; 0.44mg; 0.45mg; 0.46mg; 0.47mg; 0.48mg; 0.49mg; 0.50mg; 0.51mg; 0.52mg; 0.53mg; 0.54mg; 0.55mg; 0.56mg; 0.57mg; 0.58mg; 0.59mg; 0.60mg; 0.61mg; 0.62mg; 0.63mg; 0.64mg; 0.65mg; 0.66mg; 0.67mg; 0.68mg; 0.69mg; 0.70mg; 0.71mg; 0.72mg; 0.73mg; 0.74mg; 0.75mg; 0.76mg; 0.77mg; 0.78mg; 0.79mg; 0.80mg; 0.81mg; 0.82mg; 0.83mg; 0.84mg; 0.85mg; 0.86mg; 0.87mg; 0.88mg; 0.89mg; 0.90mg; 0.91mg; 0.92mg; 0.93mg; 0.94mg; 0.95mg; 0.96mg; 0.97mg; 0.98mg; 0.99mg; 1.00mg; 0.1mg; 0.2mg; 0.3mg; 0.4mg; 0.5mg; 0.6mg; 0.7mg; 0.8mg; 0.9mg; 1.0mg; 1mg; 2mg; 3mg; 4mg; 5mg; 6mg; 7mg; 8mg; 9mg; 10mg; 11mg; 12mg; 13mg; 14mg; 15mg; 16mg; 17mg; 18mg; 19mg; 20mg; 21mg; 22mg; 23mg; 24mg; 25mg; 26mg; 27mg; 28mg; 29mg; 30mg; 31mg; 32mg; 33mg; 34mg; 35mg; 36mg; 37mg; 38mg; 39mg; 40mg; 41mg; 42mg; 43mg; 44mg; 45mg; 46mg; 47mg; 48mg; 49mg; 50mg; 51mg; 52mg; 53mg; 54mg; 55mg; 56mg; 57mg; 58mg; 59mg; 60mg; 61mg; 62mg; 63mg; 64mg; 65mg; 66mg; 67mg; 68mg; 69mg; 70mg; 71mg; 72mg; 73mg; 74mg; 75mg; 76mg; 77mg; 78mg; 79mg; 80mg; 81mg; 82mg; 83mg; 84mg; 85mg; 86mg; 87mg; 88mg; 89mg; 90mg; 91mg; 92mg; 93mg; 94mg; 95mg; 96mg; 97mg; 98mg; 99mg; 100mg; 101mg; 102mg; 103mg; 104mg; 105mg; 106mg; 107mg; 108mg; 109mg; 110mg; 111mg; 112mg; 113mg; 114mg; 115mg; 116mg; 117mg; 118mg; 119mg; 120mg; 121mg; 122mg; 123mg; 124mg; 125mg; 126mg; 127mg; 128mg; 129mg; 130mg; 131mg; 132mg; 133mg; 134mg; 135mg; 136mg; 137mg; 138mg; 139mg.	Semaglutide 3mg, 7mg, 14mg, 15mg, or 21mg; (Alternatively, liraglutide 0.6mg, 1.2mg, 1.8mg, 2.4 mg, 3.0mg, or 15mg; dulaglutide 10mg; exenatide 2mg; and lixisenatide 20mg)

		140mg; 141mg; 142mg; 143mg; 144mg; 145mg; 146mg; 147mg; 148mg; 149mg; 150mg; 151mg; 152mg; 153mg; 154mg; 155mg; 156mg; 157mg; 158mg; 159mg; 160mg; 161mg; 162mg; 163mg; 164mg; 165mg; 166mg; 167mg; 168mg; 169mg; 170mg; 171mg; 172mg; 173mg; 174mg; 175mg; 176mg; 177mg; 178mg; 179mg; 180mg; 181mg; 182mg; 183mg; 184mg; 185mg; 186mg; 187mg; 188mg; 189mg; 190mg; 191mg; 192mg; 193mg; 194mg; 195mg; 196mg; 197mg; 198mg; 199mg; 200mg; 0.01mg to 1mg; 0.1mg to 1mg; 1 to 200mg; 1 to 100mg; 1 to 50mg; 1 to 25mg; 1 to 15mg; 1 to 10mg; 10 to 100mg; 10 to 75mg; 10mg to 50mg; 10mg to 25mg.	
Dapagliflozin, (alternatively, empagliflozin; and ertugliflozin)	SGLT-2 antagonist	Concentration: 1% (w/w); 2% (w/w); 3% (w/w); 4% (w/w); 5% (w/w); 6% (w/w); 7% (w/w); 8% (w/w); 9% (w/w); 10% (w/w); 11% (w/w); 12% (w/w); 13% (w/w); 14% (w/w); 15% (w/w); 16% (w/w); 17% (w/w); 18% (w/w); 19% (w/w); 20% (w/w); 21% (w/w); 22% (w/w); 23% (w/w); 24% (w/w); 25% (w/w); 26% (w/w); 27% (w/w); 28% (w/w); 29% (w/w); 30% (w/w); 31% (w/w); 32% (w/w); 33% (w/w); 34% (w/w); 35% (w/w); 36% (w/w); 37% (w/w); 38% (w/w); 39% (w/w); 40% (w/w); 41% (w/w); 42% (w/w); 43% (w/w); 44% (w/w); 45% (w/w); 46% (w/w); 47% (w/w); 48% (w/w); 49% (w/w); 50% (w/w); and 2-95% (w/w); 3-55% (w/w); 4-55% (w/w); 5-45% (w/w); 6-35% (w/w); 7-25% (w/w); 8-15% (w/w); and within 2 decimal points of each figure. A suitable dose could include: 2mg; 5mg; 10mg; 15mg; 20mg; 21mg; 0.25mg to 100mg; 1mg to 25mg; 1 mg to 50 mg; 1 mg to 30mg; 2 to 30mg; 5 mg to 15mg; 10mg to 20mg; 10 to 50mg. A suitable dose could also include: 1mg to 1000mg; 0.01mg to 100mg; 0.01mg; 0.02mg; 0.03mg; 0.04mg; 0.05mg; 0.06mg; 0.07mg; 0.08mg; 0.09mg; 0.10mg; 0.11mg; 0.12mg; 0.13mg; 0.14mg; 0.15mg; 0.16mg; 0.17mg; 0.18mg; 0.19mg; 0.20mg; 0.21mg; 0.22mg; 0.23mg; 0.24mg; 0.25mg; 0.26mg; 0.27mg; 0.28mg; 0.29mg; 0.30mg; 0.31mg; 0.32mg; 0.33mg; 0.34mg; 0.35mg; 0.36mg; 0.37mg; 0.38mg; 0.39mg; 0.40mg; 0.41mg; 0.42mg; 0.43mg; 0.44mg; 0.45mg; 0.46mg; 0.47mg; 0.48mg; 0.49mg; 0.50mg; 0.51mg; 0.52mg; 0.53mg; 0.54mg; 0.55mg; 0.56mg; 0.57mg; 0.58mg; 0.59mg; 0.60mg; 0.61mg; 0.62mg; 0.63mg; 0.64mg; 0.65mg; 0.66mg; 0.67mg; 0.68mg; 0.69mg; 0.70mg; 0.71mg; 0.72mg; 0.73mg; 0.74mg; 0.75mg; 0.76mg; 0.77mg; 0.78mg; 0.79mg; 0.80mg; 0.81mg; 0.82mg; 0.83mg; 0.84mg; 0.85mg; 0.86mg; 0.87mg; 0.88mg; 0.89mg; 0.90mg; 0.91mg; 0.92mg; 0.93mg; 0.94mg; 0.95mg; 0.96mg; 0.97mg; 0.98mg; 0.99mg; 1.00mg; 0.1mg; 0.2mg; 0.3mg; 0.4mg; 0.5mg; 0.6mg; 0.7mg; 0.8mg; 0.9mg; 1.0mg; 1mg; 2mg; 3mg; 4mg; 5mg; 6mg; 7mg; 8mg; 9mg; 10mg; 11mg; 12mg; 13mg; 14mg; 15mg; 16mg; 17mg; 18mg; 19mg; 20mg; 21mg; 22mg; 23mg; 24mg; 25mg; 26mg; 27mg; 28mg; 29mg; 30mg; 31mg; 32mg; 33mg; 34mg; 35mg; 36mg; 37mg; 38mg; 39mg; 40mg; 41mg; 42mg; 43mg; 44mg; 45mg; 46mg; 47mg; 48mg; 49mg; 50mg; 51mg; 52mg; 53mg; 54mg; 55mg; 56mg; 57mg; 58mg; 59mg; 60mg; 61mg; 62mg; 63mg; 64mg; 65mg; 66mg; 67mg; 68mg; 69mg; 70mg; 71mg; 72mg; 73mg; 74mg; 75mg; 76mg; 77mg; 78mg; 79mg; 80mg; 81mg; 82mg; 83mg; 84mg; 85mg; 86mg; 87mg; 88mg; 89mg; 90mg; 91mg; 92mg; 93mg; 94mg; 95mg; 96mg; 97mg; 98mg; 99mg; 100mg; 101mg; 102mg; 103mg; 104mg; 105mg; 106mg; 107mg; 108mg; 109mg; 110mg; 111mg; 112mg; 113mg; 114mg; 115mg; 116mg; 117mg; 118mg; 119mg; 120mg; 121mg; 122mg; 123mg; 124mg; 125mg; 126mg; 127mg; 128mg; 129mg; 130mg; 131mg; 132mg; 133mg; 134mg; 135mg; 136mg; 137mg; 138mg; 139mg; 140mg; 141mg; 142mg; 143mg; 144mg; 145mg; 146mg; 147mg; 148mg; 149mg; 150mg; 151mg; 152mg; 153mg; 154mg; 155mg; 156mg; 157mg; 158mg; 159mg; 160mg; 161mg; 162mg; 163mg; 164mg; 165mg; 166mg; 167mg; 168mg; 169mg; 170mg; 171mg; 172mg; 173mg; 174mg; 175mg; 176mg; 177mg; 178mg; 179mg; 180mg; 181mg; 182mg; 183mg; 184mg; 185mg; 186mg; 187mg; 188mg; 189mg; 190mg; 191mg; 192mg; 193mg; 194mg; 195mg; 196mg; 197mg; 198mg; 199mg; 200mg;	Dapagliflozin 10mg, (Alternatively, empagliflozin 25mg; and ertugliflozin 5mg, canagliflozin 200mg, bexagliflozin 20mg)

Sodium glycodeoxycholate.	Permeation enhancer; entero-hepatic recycling agent.	0.01mg to 1mg; 0.1mg to 1mg; 1 to 200mg; 1 to 100mg; 1 to 50mg; 1 to 25mg; 1 to 10mg; 10 to 100mg; 10 to 75mg; 10mg to 50mg; 10mg to 25mg.	0.5% and within 2 decimal points (w/w).
Sodium deoxycholate.	Permeation enhancer; entero-hepatic recycling agent.	Concentration: 0.01%; 0.1%; 0.5%; 1%; 0.5%-10%; 0.5%; 1%-10%; 1%; 2%; 3%; 4%; 5%; 6%; 7%; 8%; 9%; 10%; and within 2 decimal points of each figure (w/w).	0.5% and within 2 decimal points (w/w).
Carboxymethyl cellulose.	Mucolytic; mucoadhesive.	Concentration: 0.5%; 1%; 0.5%-10%; 0.5%; 1%-10%; 1%; 2%; 3%; 4%; 5%; 6%; 7%; 8%; 9%; 10%; and within 2 decimal points of each figure (w/w).	1.0% and within 2 decimal points (w/w).
Sodium alginate.	Mucolytic; mucoadhesive.	Concentration: 1%; 0.5%-10%; 0.5%; 1%-10%; 1%; 2%; 3%; 4%; 5%; 6%; 7%; 8%; 9%; 10%; and within 2 decimal points of each figure (w/w).	1.0% and within 2 decimal points (w/w).
SNAC (salcaprozate sodium); or non-ionic ester alkoxylate (or alkanolic acid ester alkoxylate)	Permeation enhancer.	Concentration: 0%-10%; 0.5%; 1%-10%; 1%; 2%; 3%; 4%; 5%; 6%; 7%; 8%; 9%; 10%; 20%; 30%; 40%; and within 2 decimal points of each figure (w/w). A suitable dose could include: 5mg; 10mg; 25mg; 30mg; 0.25mg to 100mg; 1mg to 25mg; 1 mg to 50 mg; 1 mg to 30mg; 2 to 30mg; 5 mg to 15mg; 10mg to 20mg; 10 to 50mg.	30mg
Soy lecithin.	Entero-hepatic-biliary recirculation agent.	Concentration: 0.05%-10%; 0.5%; 1%-10%; 1%; 2%; 3%; 4%; 5%; 6%; 7%; 8%; 9%; 10%; 20%; 30%; 40%; and within 2 decimal points of each figure (w/w). A suitable dose could include: 5mg; 10mg; 25mg; 30mg; 0.25mg to 100mg; 1mg to 25mg; 1 mg to 50 mg; 1 mg to 30mg; 2 to 30mg; 5 mg to 15mg; 10mg to 20mg; 10 to 50mg.	10mg
Glycine	Excipients, GLP-1 peptide stabiliser	0.37%	2mg
Lactose	Disintegrant	0.74%	5mg
Polyethylene glycol 2000	Binder	1%	1mg
Amylepectin	Matrix Scaffold	4%	10mg
Microcrystalline cellulose	Super-disintegrant	1%	0.5mg
Form		Solid freeze dried	
pH		Between pH 6.0 and 7.5. Between pH 6.0 and 8.0	
Particle Size		Less than 200nm.	Less than 0.2 micron
Complexes		Preferred embodiments include: glucagon-like peptide 1 (GLP-1) agonist - bile salt - lecithin complex; glucagon-like peptide 1 (GLP-1) agonist - bile salt - lecithin - SNAC (salcaprozate sodium) complex; glucagon-like peptide 1 (GLP-1) agonist - entero-hepatic recycling agent(s) complex; glucagon-like peptide 1 (GLP-1) agonist - SNAC (salcaprozate sodium) complex; glucagon-like peptide 1 (GLP-1) agonist - entero-hepatic recycling agent(s) - SNAC (salcaprozate sodium) complex; a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - bile salt - lecithin complex; a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - bile salt - lecithin - SNAC	

		(sacaprozate sodium) complex; a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - entero-hepatic recycling agent(s) complex; a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - SNAC (sacaprozate sodium) complex; a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - entero-hepatic recycling agent(s) - SNAC (sacaprozate sodium) complex; glucagon-like peptide 1 (GLP-1) agonist - a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - bile salt - lecithin complex; glucagon-like peptide 1 (GLP-1) agonist - a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - bile salt - lecithin - SNAC (sacaprozate sodium) complex; glucagon-like peptide 1 (GLP-1) agonist - a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - entero-hepatic recycling agent(s) complex; glucagon-like peptide 1 (GLP-1) agonist - a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - SNAC (sacaprozate sodium) complex; and/or glucagon-like peptide 1 (GLP-1) agonist - a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - entero-hepatic recycling agent(s) - SNAC (sacaprozate sodium) complex. Preferred embodiments also include: glucagon-like peptide 1 (GLP-1) agonist - bile salt - lecithin complex; glucagon-like peptide 1 (GLP-1) agonist - bile salt - lecithin - non-ionic ester alkoxylate (or alkanolic acid ester alkoxylate) complex; glucagon-like peptide 1 (GLP-1) agonist - entero-hepatic recycling agent(s) complex; glucagon-like peptide 1 (GLP-1) agonist - non-ionic ester alkoxylate (or alkanolic acid ester alkoxylate) complex; glucagon-like peptide 1 (GLP-1) agonist - entero-hepatic recycling agent(s) - non-ionic ester alkoxylate (or alkanolic acid ester alkoxylate) complex; a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - bile salt - lecithin complex; a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - bile salt - lecithin - non-ionic ester alkoxylate (or alkanolic acid ester alkoxylate) complex; a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - entero-hepatic recycling agent(s) complex; a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - non-ionic ester alkoxylate (or alkanolic acid ester alkoxylate) complex; a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - entero-hepatic recycling agent(s) - non-ionic ester alkoxylate (or alkanolic acid ester alkoxylate) complex; a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - entero-hepatic recycling agent(s) - non-ionic ester alkoxylate (or alkanolic acid ester alkoxylate) complex; glucagon-like peptide 1 (GLP-1) agonist - a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - bile salt - lecithin complex; glucagon-like peptide 1 (GLP-1) agonist - a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - entero-hepatic recycling agent(s) complex; glucagon-like peptide 1 (GLP-1) agonist - a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - non-ionic ester alkoxylate (or alkanolic acid ester alkoxylate) complex; and/or
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		glucagon-like peptide 1 (GLP-1) agonist - a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - entero-hepatic recycling agent(s) - non ionic ester alkoxylate (or alkanolic acid ester alkoxylate) complex.	
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[00248]

TABLE 2 – Alternative preferred dose and concentration ranges

CHEMICAL NAME	FAMILY OR CLASS	PREFERRED DOSE AND CONCENTRATIONS RANGES	MORE PREFERRED DOSE AND CONCENTRATIONS RANGES
FORMULATION			
Liraglutide (alternatively, semaglutide; dulaglutide; exenatide; and lixisenatide).	GLP-1 agonist	Concentration: 0.01%; 0.1%; 1% (w/w); 2% (w/w); 3% (w/w); 4% (w/w); 5% (w/w); 6% (w/w); 7% (w/w); 8% (w/w); 9% (w/w); 10% (w/w); 11% (w/w); 12% (w/w); 13% (w/w); 14% (w/w); 15% (w/w); 16% (w/w); 17% (w/w); 18% (w/w); 19% (w/w); 20% (w/w); 21% (w/w); 22% (w/w); 23% (w/w); 24% (w/w); 25% (w/w); 26% (w/w); 27% (w/w); 28% (w/w); 29% (w/w); 30% (w/w); 31% (w/w); 32% (w/w); 33% (w/w); 34% (w/w); 35% (w/w); 36% (w/w); 37% (w/w); 38% (w/w); 39% (w/w); 40% (w/w); 41% (w/w); 42% (w/w); 43% (w/w); 44% (w/w); 45% (w/w); 46% (w/w); 47% (w/w); 48% (w/w); 49% (w/w); 50% (w/w); and 2-95% (w/w); 3-65% (w/w); 4-55% (w/w); 5-45% (w/w); 6-35% (w/w); 7-25% (w/w); 8-15% (w/w); and within 2 decimal points of each figure. A suitable dose could include: 0.01mg; 0.1 mg; 1mg; 2mg; 5mg; 10mg; 15mg; 20mg; 21mg; 0.25mg to 100mg; 1mg to 25mg; 1mg to 50 mg; 1 mg to 30mg; 2 to 30mg; 5 mg to 15mg; 10mg to 20mg; 10 to 50mg. A suitable dose could also include: 0.01 mg; 0.02mg; 0.03mg; 0.04mg; 0.05mg; 0.06mg; 0.07mg; 0.08mg; 0.09mg; 0.10mg; 0.11mg; 0.12mg; 0.13mg; 0.14mg; 0.15mg; 0.16mg; 0.17mg; 0.18mg; 0.19mg; 0.20mg; 0.21mg; 0.22mg; 0.23mg; 0.24mg; 0.25mg; 0.26mg; 0.27mg; 0.28mg; 0.29mg; 0.30mg; 0.31mg; 0.32mg; 0.33mg; 0.34mg; 0.35mg; 0.36mg; 0.37mg; 0.38mg; 0.39mg; 0.40mg; 0.41mg; 0.42mg; 0.43mg; 0.44mg; 0.45mg; 0.46mg; 0.47mg; 0.48mg; 0.49mg; 0.50mg; 0.51mg; 0.52mg; 0.53mg; 0.54mg; 0.55mg; 0.56mg; 0.57mg; 0.58mg; 0.59mg; 0.60mg; 0.61mg; 0.62mg; 0.63mg; 0.64mg; 0.65mg; 0.66mg; 0.67mg; 0.68mg; 0.69mg; 0.70mg; 0.71mg; 0.72mg; 0.73mg; 0.74mg; 0.75mg; 0.76mg; 0.77mg; 0.78mg; 0.79mg; 0.80mg; 0.81mg; 0.82mg; 0.83mg; 0.84mg; 0.85mg; 0.86mg; 0.87mg; 0.88mg; 0.89mg; 0.90mg; 0.91mg; 0.92mg; 0.93mg; 0.94mg; 0.95mg; 0.96mg; 0.97mg; 0.98mg; 0.99mg; 1.00mg; 0.1mg; 0.2mg; 0.3mg; 0.4mg; 0.5mg; 0.6mg; 0.7mg; 0.8mg; 0.9mg; 1.0mg; 1mg; 2mg; 3mg; 4mg; 5mg; 6mg; 7mg; 8mg; 9mg; 10mg; 11mg; 12mg; 13mg; 14mg; 15mg; 16mg; 17mg; 18mg; 19mg; 20mg; 21mg; 22mg; 23mg; 24mg; 25mg; 26mg; 27mg; 28mg; 29mg; 30mg; 31mg; 32mg; 33mg; 34mg; 35mg; 36mg; 37mg; 38mg; 39mg; 40mg; 41mg; 42mg; 43mg; 44mg; 45mg; 46mg; 47mg; 48mg; 49mg; 50mg; 51mg; 52mg; 53mg; 54mg; 55mg; 56mg; 57mg; 58mg; 59mg; 60mg; 61mg; 62mg; 63mg; 64mg; 65mg; 66mg; 67mg; 68mg; 69mg; 70mg; 71mg; 72mg; 73mg; 74mg; 75mg; 76mg; 77mg; 78mg; 79mg; 80mg; 81mg; 82mg; 83mg; 84mg; 85mg; 86mg; 87mg; 88mg; 89mg; 90mg; 91mg; 92mg; 93mg; 94mg; 95mg; 96mg; 97mg; 98mg; 99mg; 100mg; 101mg; 102mg; 103mg; 104mg; 105mg; 106mg; 107mg; 108mg; 109mg; 110mg; 111mg; 112mg; 113mg; 114mg; 115mg; 116mg; 117mg; 118mg; 119mg; 120mg; 121mg; 122mg; 123mg; 124mg; 125mg; 126mg; 127mg; 128mg; 129mg; 130mg; 131mg; 132mg; 133mg; 134mg; 135mg; 136mg; 137mg; 138mg; 139mg; 140mg; 141mg; 142mg; 143mg; 144mg; 145mg;	Liraglutide 0.6mg, 1.2mg, 1.8mg, 2.4 mg, 3.0mg, or 15mg. (Alternatively, semaglutide 3mg, 7mg, 14mg, 15mg, or 21mg; dulaglutide 10mg; exenatide 2mg; and lixisenatide 20mg)

Dapagliflozin, (alternatively, empagliflozin, and ertugliflozin)	SGLT-2 antagonist	146mg; 147mg; 148mg; 149mg; 150mg; 151mg; 152mg; 153mg; 154mg; 155mg; 156mg; 157mg; 158mg; 159mg; 160mg; 161mg; 162mg; 163mg; 164mg; 165mg; 166mg; 167mg; 168mg; 169mg; 170mg; 171mg; 172mg; 173mg; 174mg; 175mg; 176mg; 177mg; 178mg; 179mg; 180mg; 181mg; 182mg; 183mg; 184mg; 185mg; 186mg; 187mg; 188mg; 189mg; 190mg; 191mg; 192mg; 193mg; 194mg; 195mg; 196mg; 197mg; 198mg; 199mg; 200mg; 0.01mg to 1mg; 0.1mg to 1mg; 1 to 200mg; 1 to 100mg; 1 to 25mg; 1 to 15mg; 1 to 10mg; 10 to 100mg; 10 to 75mg; 10mg to 50mg; 10mg to 25mg. Concentration: 1% (w/w); 2% (w/w); 3% (w/w); 4% (w/w); 5% (w/w); 6% (w/w); 7% (w/w); 8% (w/w); 9% (w/w); 10% (w/w); 11% (w/w); 12% (w/w); 13% (w/w); 14% (w/w); 15% (w/w); 16% (w/w); 17% (w/w); 18% (w/w); 19% (w/w); 20% (w/w); 21% (w/w); 22% (w/w); 23% (w/w); 24% (w/w); 25% (w/w); 26% (w/w); 27% (w/w); 28% (w/w); 29% (w/w); 30% (w/w); 31% (w/w); 32% (w/w); 33% (w/w); 34% (w/w); 35% (w/w); 36% (w/w); 37% (w/w); 38% (w/w); 39% (w/w); 40% (w/w); 41% (w/w); 42% (w/w); 43% (w/w); 44% (w/w); 45% (w/w); 46% (w/w); 47% (w/w); 48% (w/w); 49% (w/w); 50% (w/w); and 2-95% (w/w); 3-65% (w/w); 4-55% (w/w); 5-45% (w/w); 6-35% (w/w); 7-25% (w/w); 8-15% (w/w); and within 2 decimal points of each figure. A suitable dose could include: 2mg; 5mg; 10mg; 15mg; 20mg; 21mg; 0.25mg to 100mg; 1mg to 25mg; 1 mg to 50 mg, 1 mg to 30mg; 2 to 30mg; 5 mg to 15mg; 10mg to 20mg; 10 to 50mg. A suitable dose could also include: 1mg to 1000mg; 0.01mg to 100mg; 0.01mg; 0.02mg; 0.03mg; 0.04mg; 0.05mg; 0.06mg; 0.07mg; 0.08mg; 0.09mg; 0.10mg; 0.11mg; 0.12mg; 0.13mg; 0.14mg; 0.15mg; 0.16mg; 0.17mg; 0.18mg; 0.19mg; 0.20mg; 0.21mg; 0.22mg; 0.23mg; 0.24mg; 0.25mg; 0.26mg; 0.27mg; 0.28mg; 0.29mg; 0.30mg; 0.31mg; 0.32mg; 0.33mg; 0.34mg; 0.35mg; 0.36mg; 0.37mg; 0.38mg; 0.39mg; 0.40mg; 0.41mg; 0.42mg; 0.43mg; 0.44mg; 0.45mg; 0.46mg; 0.47mg; 0.48mg; 0.49mg; 0.50mg; 0.51mg; 0.52mg; 0.53mg; 0.54mg; 0.55mg; 0.56mg; 0.57mg; 0.58mg; 0.59mg; 0.60mg; 0.61mg; 0.62mg; 0.63mg; 0.64mg; 0.65mg; 0.66mg; 0.67mg; 0.68mg; 0.69mg; 0.70mg; 0.71mg; 0.72mg; 0.73mg; 0.74mg; 0.75mg; 0.76mg; 0.77mg; 0.78mg; 0.79mg; 0.80mg; 0.81mg; 0.82mg; 0.83mg; 0.84mg; 0.85mg; 0.86mg; 0.87mg; 0.88mg; 0.89mg; 0.90mg; 0.91mg; 0.92mg; 0.93mg; 0.94mg; 0.95mg; 0.96mg; 0.97mg; 0.98mg; 0.99mg; 1.00mg; 0.1mg; 0.2mg; 0.3mg; 0.4mg; 0.5mg; 0.6mg; 0.7mg; 0.8mg; 0.9mg; 1.0mg; 1mg; 2mg; 3mg; 4mg; 5mg; 6mg; 7mg; 8mg; 9mg; 10mg; 11mg; 12mg; 13mg; 14mg; 15mg; 16mg; 17mg; 18mg; 19mg; 20mg; 21mg; 22mg; 23mg; 24mg; 25mg; 26mg; 27mg; 28mg; 29mg; 30mg; 31mg; 32mg; 33mg; 34mg; 35mg; 36mg; 37mg; 38mg; 39mg; 40mg; 41mg; 42mg; 43mg; 44mg; 45mg; 46mg; 47mg; 48mg; 49mg; 50mg; 51mg; 52mg; 53mg; 54mg; 55mg; 56mg; 57mg; 58mg; 59mg; 60mg; 61mg; 62mg; 63mg; 64mg; 65mg; 66mg; 67mg; 68mg; 69mg; 70mg; 71mg; 72mg; 73mg; 74mg; 75mg; 76mg; 77mg; 78mg; 79mg; 80mg; 81mg; 82mg; 83mg; 84mg; 85mg; 86mg; 87mg; 88mg; 89mg; 90mg; 91mg; 92mg; 93mg; 94mg; 95mg; 96mg; 97mg; 98mg; 99mg; 100mg; 101mg; 102mg; 103mg; 104mg; 105mg; 106mg; 107mg; 108mg; 109mg; 110mg; 111mg; 112mg; 113mg; 114mg; 115mg; 116mg; 117mg; 118mg; 119mg; 120mg; 121mg; 122mg; 123mg; 124mg; 125mg; 126mg; 127mg; 128mg; 129mg; 130mg; 131mg; 132mg; 133mg; 134mg; 135mg; 136mg; 137mg; 138mg; 139mg; 140mg; 141mg; 142mg; 143mg; 144mg; 145mg; 146mg; 147mg; 148mg; 149mg; 150mg; 151mg; 152mg; 153mg; 154mg; 155mg; 156mg; 157mg; 158mg; 159mg; 160mg; 161mg; 162mg; 163mg; 164mg; 165mg; 166mg; 167mg; 168mg; 169mg; 170mg; 171mg; 172mg; 173mg; 174mg; 175mg; 176mg; 177mg; 178mg; 179mg; 180mg; 181mg; 182mg; 183mg; 184mg; 185mg; 186mg; 187mg; 188mg; 189mg; 190mg; 191mg; 192mg; 193mg; 194mg; 195mg; 196mg; 197mg; 198mg; 199mg; 200mg; 0.01mg to 1mg; 0.1mg to 1mg; 1 to 200mg; 1 to 100mg; 1 to 50mg; 1 to 25mg; 1 to 15mg; 1 to 10mg; 10 to 100mg; 10 to 75mg; 10mg to 50mg; 10mg to 25mg.	Dapagliflozin 10mg. (Alternatively, empagliflozin 25mg; and ertugliflozin 5mg, canagliflozin 200mg, bexagliflozin 20mg)
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Sodium glycodeoxycholate.	Permeation enhancer; entero-hepatic recycling agent.	25mg.	Concentration: 0.5%, 1%, 0.5%-10%; 0.5%, 1%-10%; 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%; and within 2 decimal points of each figure (w/w).	0.5% and within 2 decimal points (w/w).
Sodium deoxycholate.	Permeation enhancer; entero-hepatic recycling agent.		Concentration: 0.5%, 1%, 0.5%-10%; 0.5%, 1%-10%; 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%; and within 2 decimal points of each figure (w/w).	1.0% and within 2 decimal points (w/w).
Carboxymethyl cellulose.	Mucolytic; Mucoadhesive.		Concentration: 1%, 0.5%-10%; 0.5%, 1%-10%; 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%; and within 2 decimal points of each figure (w/w).	1.0% and within 2 decimal points (w/w).
Sodium alginate.	Mucolytic; Mucoadhesive.		Concentration: 1%, 0.5%-10%; 0.5%, 1%-10%; 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%; and within 2 decimal points of each figure (w/w).	1.0% and within 2 decimal points (w/w).
SNAC (saccharoprote sodium); or a non-ionic ester alkoxide (or alkanolic acid ester alkoxide).	Permeation enhancer.		Concentration: 0.05%-10%; 0.5%, 1%-10%; 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%; 20%, 30%, 40%; and within 2 decimal points of each figure (w/w). A suitable dose could include: 5mg; 10mg; 25mg; 30mg; 0.25mg to 100mg; 1mg to 25mg; 1mg to 50mg; 1mg to 30mg; 2 to 30mg; 5mg to 15mg; 10mg to 20mg; 10 to 50mg.	30mg
Soy lecithin.	Entero-hepatic-biliary recirculation agent.		Concentration: 0.05%-10%; 0.5%, 1%-10%; 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%; 20%, 30%, 40%; and within 2 decimal points of each figure (w/w). A suitable dose could include: 5mg; 10mg; 25mg; 30mg; 0.25mg to 100mg; 1mg to 25mg; 1mg to 50mg; 1mg to 30mg; 2 to 30mg; 5mg to 15mg; 10mg to 20mg; 10 to 50mg.	10mg
Glycine	Excipients, GLP-1 peptide stabiliser	0.37%		2mg
Lactose	Disintegrant	0.74%		5mg
Polyethylene glycol 2000	Binder	1%		1mg
Amylonectin	Matrix Scaffold	4%		10mg
Microcrystalline cellulose	Super-disintegrant	1%		0.5mg
Form		Solid freeze dried.		
pH		Between pH 6.0 and 7.5. Between pH 6.0 and 8.0.		
Particle Size		Less than 2000nm.		Less than 0.2 micron
Complexes		Preferred embodiments include: glucagon-like peptide 1 (GLP-1) agonist - bile salt - lecithin complex; glucagon-like peptide 1 (GLP-1) agonist - bile salt - SNAC (saccharoprote sodium) complex; glucagon-like peptide 1 (GLP-1) agonist - entero-hepatic recycling agent(s) complex; glucagon-like peptide 1 (GLP-1) agonist - SNAC (saccharoprote sodium) complex; glucagon-like peptide 1 (GLP-1) agonist - entero-hepatic recycling agent(s) - SNAC (saccharoprote sodium)		

		complex; a sodium glucose co transporter-2 (SGLT-2) receptor antagonist - bile salt - lecithin complex; a sodium glucose co transporter-2 (SGLT-2) receptor antagonist - bile salt – lecithin - SNAC (salcaprozate sodium) complex; a sodium glucose co transporter-2 (SGLT-2) receptor antagonist - entero-hepatic recycling agent(s) complex; a sodium glucose co transporter-2 (SGLT-2) receptor antagonist - SNAC (salcaprozate sodium) complex; a sodium glucose co transporter-2 (SGLT-2) receptor antagonist - entero-hepatic recycling agent(s) - SNAC (salcaprozate sodium) complex; glucagon-like peptide 1 (GLP-1) agonist - a sodium glucose co transporter-2 (SGLT-2) receptor antagonist - bile salt - lecithin complex; glucagon-like peptide 1 (GLP-1) agonist - a sodium glucose co transporter-2 (SGLT-2) receptor antagonist - bile salt – lecithin - SNAC (salcaprozate sodium) complex; glucagon-like peptide 1 (GLP-1) agonist - a sodium glucose co transporter-2 (SGLT-2) receptor antagonist - entero-hepatic recycling agent(s) complex; glucagon-like peptide 1 (GLP-1) agonist - a sodium glucose co transporter-2 (SGLT-2) receptor antagonist - SNAC (salcaprozate sodium) complex; and/or glucagon-like peptide 1 (GLP-1) agonist - a sodium glucose co transporter-2 (SGLT-2) receptor antagonist - entero-hepatic recycling agent(s) - SNAC (salcaprozate sodium) complex. Preferred embodiments also include: glucagon-like peptide 1 (GLP-1) agonist - bile salt - lecithin complex; glucagon like peptide 1 (GLP-1) agonist - bile salt – lecithin - non ionic ester alkoxylate (or alkanolic acid ester alkoxylate) complex; glucagon-like peptide 1 (GLP-1) agonist - entero-hepatic recycling agent(s) complex; glucagon-like peptide 1 (GLP-1) agonist - non-ionic ester alkoxylate (or alkanolic acid ester alkoxylate) complex; glucagon-like peptide 1 (GLP-1) agonist - entero-hepatic recycling agent(s) - non-ionic ester alkoxylate (or alkanolic acid ester alkoxylate) complex; a sodium glucose co transporter-2 (SGLT-2) receptor antagonist - bile salt - lecithin complex; (or alkanolic acid ester alkoxylate) complex; a sodium glucose co transporter-2 (SGLT-2) receptor antagonist - entero-hepatic recycling agent(s) complex; a sodium glucose co transporter-2 (SGLT-2) receptor antagonist - non-ionic ester alkoxylate (or alkanolic acid ester alkoxylate) complex; a sodium glucose co transporter-2 (SGLT-2) receptor antagonist - entero-hepatic recycling agent(s) - non-ionic ester alkoxylate (or alkanolic acid ester alkoxylate) complex; glucagon-like peptide 1 (GLP-1) agonist - a sodium glucose co transporter-2 (SGLT-2) receptor antagonist - bile salt - lecithin complex; glucagon-like peptide 1 (GLP-1) agonist - a sodium glucose co transporter-2 (SGLT-2) receptor antagonist - bile salt – lecithin - non-ionic ester alkoxylate (or alkanolic acid ester alkoxylate) complex; glucagon-like peptide 1 (GLP-1) agonist - a sodium glucose co transporter-2 (SGLT-2) receptor antagonist - entero-hepatic recycling agent(s) complex; glucagon-like peptide 1 (GLP-1) agonist - a sodium glucose co transporter-2 (SGLT-2) receptor antagonist - non-ionic ester alkoxylate (or alkanolic acid ester alkoxylate) complex; and/or
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			glucagon-like peptide 1 (GLP-1) agonist - a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - entero-hepatic recycling agent(s) - non-ionic ester alkoxylate (or alkanolic acid ester alkoxylate) complex.
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[00249] Another preferred proposed formula sublingual semaglutide with dapagliflozin (per wafer) is also presented in TABLE 3 and TABLE 4.

TABLE 3: One preferred proposed formula sublingual semaglutide with dapagliflozin (per wafer):

Ingredients	Quantity
Dapagliflozin (SGLT-2 antagonist)	10 mg
Semaglutide (GLP-1 agonist)	15 mg
Sodium glycodeoxycholate (permeation enhancers, entero-hepatic recirculation)	1 mg
Sodium dexycholeate (permeation enhancer, entero-hepatic recirculation)	2 mg
SNAC (permeation enhancers)	30 mg
CMC (carboxymethyl cellulose) (mucolytic, mucoadhesive)	3 mg
Sodium alginate (mucolytic, mucoadhesive)	3 mg
Soy lecithin (entero-hepatic-biliary recirculation)	10 mg
WaferlogiX carrier	QS

TABLE 4: Another preferred proposed formula sublingual semaglutide with dapagliflozin (per tablet or capsule):

Ingredients	Quantity
Dapagliflozin (SGLT-2 antagonist)	10 mg
Semaglutide (GLP-1 agonist)	21 mg
Sodium glycodeoxycholate (permeation enhancers, entero-hepatic recirculation)	0.5%
Sodium dexycholeate (permeation enhancer, entero-hepatic recirculation)	1%
polyethylene glycol 1500	0.5%
CMC (carboxymethyl cellulose) (mucolytic, mucoadhesive)	1%
Croscarmellose sodium	150mg
Silica	10mg
Magnesium stearate	5mg

- 10 [00250] A schematic diagram of the process of semaglutide/dapagliflozin delivery via the gastrointestinal track is presented in Figure 7.

C EXAMPLE 3 – SINGLE DOSE PHARMACOKINETIC STUDY OF LIRAGLUTIDE FOLLOWING SUBLINGUAL, INTRAVENOUS AND SUBCUTANEOUS ROUTE OF ADMINISTRATION IN MALE SPRAGUE DAWLEY RAT.

- 15 [00251] **STUDY AIM**

[00252] To determine the pharmacokinetics of liraglutide following sublingual (formulations of the invention), intravenous and subcutaneous route of administration in male Sprague Dawley Rat.

[00253] **MATERIALS**[00254] **TABLE 5: Liraglutide wafer formulation A**

Test item name	Liraglutide wafer formulation A
Appearance	Appearance: white
Correction factor	Correction factor: 1
Storage Conditions	Refrigerate or store below 25 Deg C

[00255] **TABLE 6: Liraglutide wafer formulation B**

Test item name	Liraglutide wafer formulation B
Appearance	Appearance: white
Correction factor	Correction factor: 1
Storage Conditions	Refrigerate or store below 25 Deg C

5

[00256] **Test System**

- [00257] Species: Rat. Strain: Sprague Dawley. Sex: Male; Rationale: Sprague Dawley rat is commonly used rodent species in the pharmacokinetic evaluation of drugs and acceptable to the regulatory authorities; Source of animals: Hylasco Biotechnology (India) Pvt. Ltd., Hyderabad; Total number of animals: 24 Rats (6 rats/group); Age/ Body Weight at study initiation: 7-10 weeks, 250-350 g; Veterinary Examination: Prior to the final assignment to the study, animals will be subjected to complete veterinary health examination to ensure that the selected animals are in a good state of health; Animal Identification: Animals will be uniquely identified by individual tail marking with a permanent marker along with cage card.
- 15 [00258] Acclimatization: On receipt from supplier, the animals will be examined for any external signs of ill health and aberrant behavior prior to acceptance. After health examination, animals will be quarantined for one week under test conditions and then acclimatized for a minimum of 5 days in study room. Only animals without any visible signs of illness will be used for the study.
- 20 [00259] Animal catheterization: Under Ketamine and Xylazine anesthesia, all animals will be cannulated in right external jugular vein. Rats will be surgically implanted with a catheter (jugular vein, Polyethylene-50 tubing attached to Polyurethane-40 catheter) for blood collection. Rats will be allowed to recover for minimum of 48 h after cannulation, before inclusion in study and drug administration. General animal health and cannula patency will
- 25 be confirmed prior to dose administration.

[00260] **METHODS**

[00261] **Husbandry**

[00262] Housing Conditions: Standard laboratory conditions, temperature will be maintained between $22\pm 3^{\circ}\text{C}$ and relative humidity between 30–70 % under a 12 h light/dark cycle. Air changes of 12-15 times per hour via a centrally placed air intake and peripheral ventilators will be maintained.

[00263] Accommodation: Each animal will be placed in individual polycarbonate cage with stainless steel grill top with facilities for feed and water bottle and bedding of clean corn cob.

[00264] Feed: Hypro pelleted rodent feed manufactured by Krishna valley Agrotech LLP, Sangli, Maharashtra (India) diet source, was provided ad libitum. Sublingual group rats will be fasted overnight. No feed will be provided. Subcutaneous and IV group rats will be free access to feed.

[00265] Water: Deep bore-well water passed through activated charcoal filter and exposed to UV rays in Aquaguard on-line water filter-cum-purifier manufactured by Eureka Forbes Ltd., Mumbai - 400 001, India., will be provided ad libitum in polycarbonate bottles with stainless steel sipper tubes. All rats will have access to water ad libitum.

[00266] Animal handling: Experiment will be carried out by qualified & trained scientific personnel (trained in animal handling, drug administration and experimentation).

[00267] Body weight: On the day of dosing.

[00268] Clinical signs: Animals will be observed for any apparent clinical signs of ill-health and toxicity during study duration.

25 [00269] **Dose Formulation Preparation**

[00270] The dose formulation will be prepared freshly on the day of dosing.

[00271] **TABLE 7: Group Allocation and Treatment**

Group	Treatment (Dose)	Animal ID	Formulation strength	ROA
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1	Liraglutide wafer formulation A. 10-30mg/Kg	1 to 6	(see Table below)	Sublingual
2	Liraglutide wafer formulation B. 10-30mg/Kg	7 to 12	(see Table below)	Sublingual
3	VICTOZA (30nmol/kg) 0.12-0.36mg/Kg	13 to 18	6mg/mL	SC
4	VICTOZA (30nmol/kg) 0.12-0.36mg/Kg	19 to 24	6mg/mL	IV

[00272] Note: Permanent IDs of Rat used in this study will be captured in the final report.

[00273] **TABLE 8: Formulations**

Group	Treatment (Dose)	Formulation composition
1	Liraglutide wafer formulation A.	(see Table below)
2	Liraglutide wafer formulation B.	(see Table below)
3	VICTOZA (30nmol/kg)	Victoza® contains liraglutide 6 mg/mL as the active ingredient. And the following inactive ingredients: • dibasic sodium phosphate dihydrate • propylene glycol • phenol • hydrochloric acid • sodium hydroxide • water for injection
4	VICTOZA (30nmol/kg)	Victoza® contains liraglutide 6 mg/mL as the active ingredient. And the following inactive ingredients: • dibasic sodium phosphate dihydrate • propylene glycol • phenol • hydrochloric acid • sodium hydroxide • water for injection

5 [00274] **TABLE 9: Formulations A and B**

#	FORMULATION INGREDIENT	FORMULATION A (MG/WAFER)	FORMULATION B (MG/WAFER))
1	Liraglutide	2.5mg to 50mg	2.5mg to 50mg
2	CMC	0.7	0.7
3	Sodium alginate	0.7	0.7
4	Mannitol	50.8	50.8
5	Lactose monohydrate	39.2	39.2
6	Amylogum CLS	31.2	31.2

7	Glycine	4.4	4.4
8	PEG 1500	2.2	2.2
9	MCC	4.3	4.3
10	d- α -tocopheryl polyethylene glycol succinate (TPGS) (penetrant/surfactant/permeation enhancer)	0.1% to 20%	0.1% to 20%
11	Sodium deoxycholate (penetrant/surfactant)	0.1% to 20%	0.1% to 20%
12	pH observed 8 (Sodium dihydrogen phosphate dihydrate buffer pH 8.0)	QS	QS
13	Sucralose	9.0	9.0
14	Peppermint flavour Sensient	1.0	1.0

[00275] The range values for selecting values for Formulation A and B above include:

[00276] *Liraglutide - 2.5mg to 50 mg per wafer, including:* 2.4mg; 2.5mg; 2.6mg; 2.7mg; 2.8mg; 2.9mg; 3.0mg; 3.1mg; 3.2mg; 3.3mg; 3.4mg; 3.5mg; 3.6mg; 3.7mg; 3.8mg; 3.9mg; 4.0mg; 4.1mg; 4.2mg; 4.3mg; 4.4mg; 4.5mg; 4.6mg; 4.7mg; 4.8mg; 4.9mg; 5.0mg; 5.1mg; 5.2mg; 5.3mg; 5.4mg; 5.5mg; 5.6mg; 5.7mg; 5.8mg; 5.9mg; 6.0mg; 6.1mg; 6.2mg; 6.3mg; 6.4mg; 6.5mg; 6.6mg; 6.7mg; 6.8mg; 6.9mg; 7.0mg; 7.1mg; 7.2mg; 7.3mg; 7.4mg; 7.5mg; 7.6mg; 7.7mg; 7.8mg; 7.9mg; 8.0mg; 8.1mg; 8.2mg; 8.3mg; 8.4mg; 8.5mg; 8.6mg; 8.7mg; 8.8mg; 8.9mg; 9.0mg; 9.1mg; 9.2mg; 9.3mg; 9.4mg; 9.5mg; 9.6mg; 9.7mg; 9.8mg; 9.9mg; 10.0mg; 10.1mg; 10.2mg; 10.3mg; 10.4mg; 10.5mg; 10.6mg; 10.7mg; 10.8mg; 10.9mg; 11.0mg; 11.1mg; 11.2mg; 11.3mg; 11.4mg; 11.5mg; 11.6mg; 11.7mg; 11.8mg; 11.9mg; 12.0mg; 12.1mg; 12.2mg; 12.3mg; 12.4mg; 12.5mg; 12.6mg; 12.7mg; 12.8mg; 12.9mg; 13.0mg; 13.1mg; 13.2mg; 13.3mg; 13.4mg; 13.5mg; 13.6mg; 13.7mg; 13.8mg; 13.9mg; 14.0mg; 14.1mg; 14.2mg; 14.3mg; 14.4mg; 14.5mg; 14.6mg; 14.7mg; 14.8mg; 14.9mg; 15.0mg; 15.1mg; 15.2mg; 15.3mg; 15.4mg; 15.5mg; 15.6mg; 15.7mg; 15.8mg; 15.9mg; 16.0mg; 16.1mg; 16.2mg; 16.3mg; 16.4mg; 16.5mg; 16.6mg; 16.7mg; 16.8mg; 16.9mg; 17.0mg; 17.1mg; 17.2mg; 17.3mg; 17.4mg; 17.5mg; 17.6mg; 17.7mg; 17.8mg; 17.9mg; 18.0mg; 18.1mg; 18.2mg; 18.3mg; 18.4mg; 18.5mg; 18.6mg; 18.7mg; 18.8mg; 18.9mg; 19.0mg; 19.1mg; 19.2mg; 19.3mg; 19.4mg; 19.5mg; 19.6mg; 19.7mg; 19.8mg; 19.9mg; 20.0mg; 20.1mg; 20.2mg; 20.3mg; 20.4mg; 20.5mg; 20.6mg; 20.7mg; 20.8mg; 20.9mg; 21.0mg; 21.1mg; 21.2mg; 21.3mg;

- 21.4mg; 21.5mg; 21.6mg; 21.7mg; 21.8mg; 21.9mg; 22.0mg; 22.1mg; 22.2mg; 22.3mg;
22.4mg; 22.5mg; 22.6mg; 22.7mg; 22.8mg; 22.9mg; 23.0mg; 23.1mg; 23.2mg; 23.3mg;
23.4mg; 23.5mg; 23.6mg; 23.7mg; 23.8mg; 23.9mg; 24.0mg; 24.1mg; 24.2mg; 24.3mg;
24.4mg; 24.5mg; 24.6mg; 24.7mg; 24.8mg; 24.9mg; 25.0mg; 25.1mg; 25.2mg; 25.3mg;
- 5 25.4mg; 25.5mg; 25.6mg; 25.7mg; 25.8mg; 25.9mg; 26.0mg; 26.1mg; 26.2mg; 26.3mg;
26.4mg; 26.5mg; 26.6mg; 26.7mg; 26.8mg; 26.9mg; 27.0mg; 27.1mg; 27.2mg; 27.3mg;
27.4mg; 27.5mg; 27.6mg; 27.7mg; 27.8mg; 27.9mg; 28.0mg; 28.1mg; 28.2mg; 28.3mg;
28.4mg; 28.5mg; 28.6mg; 28.7mg; 28.8mg; 28.9mg; 29.0mg; 29.1mg; 29.2mg; 29.3mg;
29.4mg; 29.5mg; 29.6mg; 29.7mg; 29.8mg; 29.9mg; 30.0mg; 30.1mg; 30.2mg; 30.3mg;
- 10 30.4mg; 30.5mg; 30.6mg; 30.7mg; 30.8mg; 30.9mg; 31.0mg; 31.1mg; 31.2mg; 31.3mg;
31.4mg; 31.5mg; 31.6mg; 31.7mg; 31.8mg; 31.9mg; 32.0mg; 32.1mg; 32.2mg; 32.3mg;
32.4mg; 32.5mg; 32.6mg; 32.7mg; 32.8mg; 32.9mg; 33.0mg; 33.1mg; 33.2mg; 33.3mg;
33.4mg; 33.5mg; 33.6mg; 33.7mg; 33.8mg; 33.9mg; 34.0mg; 34.1mg; 34.2mg; 34.3mg;
34.4mg; 34.5mg; 34.6mg; 34.7mg; 34.8mg; 34.9mg; 35.0mg; 35.1mg; 35.2mg; 35.3mg;
- 15 35.4mg; 35.5mg; 35.6mg; 35.7mg; 35.8mg; 35.9mg; 36.0mg; 36.1mg; 36.2mg; 36.3mg;
36.4mg; 36.5mg; 36.6mg; 36.7mg; 36.8mg; 36.9mg; 37.0mg; 37.1mg; 37.2mg; 37.3mg;
37.4mg; 37.5mg; 37.6mg; 37.7mg; 37.8mg; 37.9mg; 38.0mg; 38.1mg; 38.2mg; 38.3mg;
38.4mg; 38.5mg; 38.6mg; 38.7mg; 38.8mg; 38.9mg; 39.0mg; 39.1mg; 39.2mg; 39.3mg;
39.4mg; 39.5mg; 39.6mg; 39.7mg; 39.8mg; 39.9mg; 40.0mg; 40.1mg; 40.2mg; 40.3mg;
- 20 40.4mg; 40.5mg; 40.6mg; 40.7mg; 40.8mg; 40.9mg; 41.0mg; 41.1mg; 41.2mg; 41.3mg;
41.4mg; 41.5mg; 41.6mg; 41.7mg; 41.8mg; 41.9mg; 42.0mg; 42.1mg; 42.2mg; 42.3mg;
42.4mg; 42.5mg; 42.6mg; 42.7mg; 42.8mg; 42.9mg; 43.0mg; 43.1mg; 43.2mg; 43.3mg;
43.4mg; 43.5mg; 43.6mg; 43.7mg; 43.8mg; 43.9mg; 44.0mg; 44.1mg; 44.2mg; 44.3mg;
44.4mg; 44.5mg; 44.6mg; 44.7mg; 44.8mg; 44.9mg; 45.0mg; 45.1mg; 45.2mg; 45.3mg;
- 25 45.4mg; 45.5mg; 45.6mg; 45.7mg; 45.8mg; 45.9mg; 46.0mg; 46.1mg; 46.2mg; 46.3mg;
46.4mg; 46.5mg; 46.6mg; 46.7mg; 46.8mg; 46.9mg; 47.0mg; 47.1mg; 47.2mg; 47.3mg;
47.4mg; 47.5mg; 47.6mg; 47.7mg; 47.8mg; 47.9mg; 48.0mg; 48.1mg; 48.2mg; 48.3mg;
48.4mg; 48.5mg; 48.6mg; 48.7mg; 48.8mg; 48.9mg; 49.0mg; 49.1mg; 49.2mg; 49.3mg;
49.4mg; 49.5mg; 49.6mg; 49.7mg; 49.8mg; 49.9mg; 50.0mg.
- 30 [00277] *TPGS (d- α -tocopheryl polyethylene glycol succinate) penetrant/surfactant 0.1%
to 20%, including:* 0.1%; 0.2%; 0.3%; 0.4%; 0.5%; 0.6%; 0.7%; 0.8%; 0.9%; 1.0%; 1.1%;
1.2%; 1.3%; 1.4%; 1.5%; 1.6%; 1.7%; 1.8%; 1.9%; 2.0%; 2.1%; 2.2%; 2.3%; 2.4%; 2.5%;
2.6%; 2.7%; 2.8%; 2.9%; 3.0%; 3.1%; 3.2%; 3.3%; 3.4%; 3.5%; 3.6%; 3.7%; 3.8%; 3.9%;
4.0%; 4.1%; 4.2%; 4.3%; 4.4%; 4.5%; 4.6%; 4.7%; 4.8%; 4.9%; 5.0%; 5.1%; 5.2%; 5.3%;
- 35 5.4%; 5.5%; 5.6%; 5.7%; 5.8%; 5.9%; 6.0%; 6.1%; 6.2%; 6.3%; 6.4%; 6.5%; 6.6%; 6.7%;
6.8%; 6.9%; 7.0%; 7.1%; 7.2%; 7.3%; 7.4%; 7.5%; 7.6%; 7.7%; 7.8%; 7.9%; 8.0%; 8.1%;

8.2%; 8.3%; 8.4%; 8.5%; 8.6%; 8.7%; 8.8%; 8.9%; 9.0%; 9.1%; 9.2%; 9.3%; 9.4%; 9.5%;
9.6%; 9.7%; 9.8%; 9.9%; 10.0%; 10.1%; 10.2%; 10.3%; 10.4%; 10.5%; 10.6%; 10.7%;
10.8%; 10.9%; 11.0%; 11.1%; 11.2%; 11.3%; 11.4%; 11.5%; 11.6%; 11.7%; 11.8%; 11.9%;
12.0%; 12.1%; 12.2%; 12.3%; 12.4%; 12.5%; 12.6%; 12.7%; 12.8%; 12.9%; 13.0%; 13.1%;
5 13.2%; 13.3%; 13.4%; 13.5%; 13.6%; 13.7%; 13.8%; 13.9%; 14.0%; 14.1%; 14.2%; 14.3%;
14.4%; 14.5%; 14.6%; 14.7%; 14.8%; 14.9%; 15.0%; 15.1%; 15.2%; 15.3%; 15.4%; 15.5%;
15.6%; 15.7%; 15.8%; 15.9%; 16.0%; 16.1%; 16.2%; 16.3%; 16.4%; 16.5%; 16.6%; 16.7%;
16.8%; 16.9%; 17.0%; 17.1%; 17.2%; 17.3%; 17.4%; 17.5%; 17.6%; 17.7%; 17.8%; 17.9%;
18.0%; 18.1%; 18.2%; 18.3%; 18.4%; 18.5%; 18.6%; 18.7%; 18.8%; 18.9%; 19.0%; 19.1%;
10 19.2%; 19.3%; 19.4%; 19.5%; 19.6%; 19.7%; 19.8%; 19.9%; and 20.0%.

[00278] *Sodium deoxycholate - 0.1% to 20%, including:* 0.1%; 0.2%; 0.3%; 0.4%; 0.5%;
0.6%; 0.7%; 0.8%; 0.9%; 1.0%; 1.1%; 1.2%; 1.3%; 1.4%; 1.5%; 1.6%; 1.7%; 1.8%; 1.9%;
2.0%; 2.1%; 2.2%; 2.3%; 2.4%; 2.5%; 2.6%; 2.7%; 2.8%; 2.9%; 3.0%; 3.1%; 3.2%; 3.3%;
3.4%; 3.5%; 3.6%; 3.7%; 3.8%; 3.9%; 4.0%; 4.1%; 4.2%; 4.3%; 4.4%; 4.5%; 4.6%; 4.7%;
15 4.8%; 4.9%; 5.0%; 5.1%; 5.2%; 5.3%; 5.4%; 5.5%; 5.6%; 5.7%; 5.8%; 5.9%; 6.0%; 6.1%;
6.2%; 6.3%; 6.4%; 6.5%; 6.6%; 6.7%; 6.8%; 6.9%; 7.0%; 7.1%; 7.2%; 7.3%; 7.4%; 7.5%;
7.6%; 7.7%; 7.8%; 7.9%; 8.0%; 8.1%; 8.2%; 8.3%; 8.4%; 8.5%; 8.6%; 8.7%; 8.8%; 8.9%;
9.0%; 9.1%; 9.2%; 9.3%; 9.4%; 9.5%; 9.6%; 9.7%; 9.8%; 9.9%; 10.0%; 10.1%; 10.2%;
10.3%; 10.4%; 10.5%; 10.6%; 10.7%; 10.8%; 10.9%; 11.0%; 11.1%; 11.2%; 11.3%; 11.4%;
20 11.5%; 11.6%; 11.7%; 11.8%; 11.9%; 12.0%; 12.1%; 12.2%; 12.3%; 12.4%; 12.5%; 12.6%;
12.7%; 12.8%; 12.9%; 13.0%; 13.1%; 13.2%; 13.3%; 13.4%; 13.5%; 13.6%; 13.7%; 13.8%;
13.9%; 14.0%; 14.1%; 14.2%; 14.3%; 14.4%; 14.5%; 14.6%; 14.7%; 14.8%; 14.9%; 15.0%;
15.1%; 15.2%; 15.3%; 15.4%; 15.5%; 15.6%; 15.7%; 15.8%; 15.9%; 16.0%; 16.1%; 16.2%;
16.3%; 16.4%; 16.5%; 16.6%; 16.7%; 16.8%; 16.9%; 17.0%; 17.1%; 17.2%; 17.3%; 17.4%;
25 17.5%; 17.6%; 17.7%; 17.8%; 17.9%; 18.0%; 18.1%; 18.2%; 18.3%; 18.4%; 18.5%; 18.6%;
18.7%; 18.8%; 18.9%; 19.0%; 19.1%; 19.2%; 19.3%; 19.4%; 19.5%; 19.6%; 19.7%; 19.8%;
19.9%; and 20.0%.

[00279] **Dose administration**

[00280] Group 1 & 2 Rat, wafer will be placed in moist sublingual cavity. Wafers will be
30 crushed and weighed on an accurate balance and placed in the sublingual space under
isoflurane anesthesia for 4-5 min followed by up to 1-2 drops of water to assist in
disintegration (use minimal amount required to disintegrate wafers).

[00281] Note: The sublingual mucosa moistness will be ensured prior to administering
the SL wafer by administering a small quantity of water into the SL space, just prior to
35 anesthesia.

- [00282] Group 3 rats will be administered subcutaneously on the dorsal side towards Cranial.
- [00283] Group 4 rats will be administered intravenously through lateral tail vein.
- 5 [00284] **Blood Collection and storage of samples.**
- [00285] Site of blood collection: Jugular vein via cannulation.
- [00286] Anticoagulant: K₂EDTA (20 µL of 200 mM solution per 1 mL of blood).
- [00287] Blood collection time points: 0 (pre-dose), 0.083 h, 0.25 h, 0.5 h, 1 h, 2 h, 4h, 8 h and 24 h post dose (Total 9 time points/rat).
- 10 [00288] Volume of blood collected: ~0.2 mL at each time points from each rat.
- [00289] Blood sampling procedure: Serial sampling.
- [00290] Blood centrifugation time: 4000 rpm for 10 minutes at 4 °C.
- [00291] Matrix: Plasma.
- [00292] Matrix storage: -70 ± 10 °C until analysis.
- 15 [00293] Matrix labelling details: Study number, Group, Animal ID, and Time point.
- [00294] Note: Blood samples will be kept on wet ice until centrifugation. Centrifugation will be done within 30 minutes of collection and plasma will be checked for hemolysis. If samples are hemolyzed, another sample will be taken as soon as possible. Prepared dose formulation will be discarded after the completion of in-life phase. On completion of the last
- 20 blood sampling, animals will be sacrificed, and carcasses discarded.
- [00295] **Bioanalysis**
- [00296] Matrix: Plasma.
- [00297] Analyte: Liraglutide.
- 25 [00298] Bioanalysis will be performed by fit-for-purpose analytical method using LC-MS/MS.
- [00299] Upon finalization of study report, remaining biological study samples will be discarded.

[00300] **Pharmacokinetic data analysis and evaluation**

[00301] Pharmacokinetic Software: Phoenix[®] Software, version 8.3, USA.

[00302] Pharmacokinetic Parameters: C_0 , C_{max} , T_{max} , AUC_{0-t} , $AUC_{0-\infty}$, K_{el} , $T_{1/2}$, V_d , V_d/F ,
5 Cl , Cl/F and MRT_{last} .

[00303] **RESULTS**

[00304] The study is to determine the relative bioavailability of two formulations of a
sublingual lyophilised liraglutide wafer compared to subcutaneous injection of liraglutide
(Victoza) in rats. We expect the relative bioavailability to be in the range of 2-50%. In
10 addition, we expect to see more rapid absorption into plasma following administration with
the sublingual wafer compared to subcutaneous injection.

[00305] **DISCUSSION**

[00306] These results would represent to our knowledge the first data available on the
relative bioavailability of sublingual administration of liraglutide. Obtaining systemic
15 absorption of liraglutide via sublingual administration with this novel wafer creates the
potential for a non-injectable formulation of liraglutide. At present, liraglutide is only available
as an injectable product. Such a product would be non-invasive, easier to use, convenient
and improve patient compliance.

20 **D EXAMPLE 4 – SINGLE DOSE PHARMACOKINETIC STUDY OF SEMAGLUTIDE
FOLLOWING ORAL AND SUBLINGUAL ROUTE OF ADMINISTRATION IN MALE
C57BL/6 MICE.**

[00307] **STUDY AIM**

[00308] The goal of this study was to determine the pharmacokinetics of semaglutide
25 following oral and sublingual route of administration in male C57BL/6 mice.

[00309] **MATERIALS AND METHODS**

[00310] This study was performed in overnight fasted male C57BL/6 mice. Rybelsus[®]
Semaglutide, 14 mg Tablets (Batch No.: PS6LE23) and Semaglutide B-14 mg Freeze-dried
oral disintegrating Tablets (wafers) (Batch No.: B240836), were test items used in this study.
30 Dose formulations were prepared freshly on the day of dosing. 0.5% of methyl cellulose in

Milli Q water were used as the vehicle. See Tables 33 to 35 for further information on the formulations.

[00311] **TABLE 10: Group allocation and treatment**

Group	Treatment (Dose)	Animal ID	Dose Volume	Formulation strength	ROA
1	Semaglutide Table (10 mg/kg)	1 to 9	10 mL/kg	1 mg/mL of semaglutide (Crushed tablet in 14 mL)	Oral
2	Semaglutide Wafer (10 mg/kg)	10 to 18	4 mg wafer per mouse	13.32 mg of semaglutide in 200 mg of water	Sublingual

5 [00312] Note: Permanent Id's of mice used in this study were Mj1824 to Mj1841

[00313] Blood samples were collected through retro orbital sinus puncture at 0 (pre-dose), 5 mins, 15 mins, 30 mins, 45 mins, 60 mins, 90 mins, 120 mins, 240 mins and 480 mins post dose (Total 10 time point) At each time points, ~0.2 mL of blood was withdrawn and transferred into pre-labeled microcentrifuge tubes containing 20 µL per mL of blood of 10 200 mM K₂EDTA solution as anticoagulant. Blood samples were kept on wet ice and were centrifuged immediately at 4000 rpm for 10 min at 4 °C. Plasma was separated after centrifugation. Plasma samples were transferred into pre-labeled (Animal ID No., Time point, Study No., Matrix and Group) tubes. All plasma samples were stored at -70 ± 10 °C until bioanalysis.

15 [00314] Bioanalysis was performed using fit-for-purpose LC-MS/MS method for the quantification of Semaglutide in plasma samples.

[00315] The plasma pharmacokinetic parameters of semaglutide were determined from mean concentration time curves obtained following a single oral and sublingual route of administration in male C57BL/6 mice. Values are expressed as Mean ± SD and n=3 20 mice/time point/group.

[00316] Plasma pharmacokinetic parameters were calculated using standard non-compartmental analysis (Phoenix® software, version 8.3, Certara Corporation, Mountain View, California 94040/USA) using linear trapezoidal method with linear interpolation.

[00317] **RESULTS AND DISCUSSION**

25 [00318] No clinical signs, mortality or morbidity was observed in treated group animals at the doses tested.

[00319] The plasma pharmacokinetic parameters semaglutide were determined from mean concentration time curves obtained following a single oral and sublingual route of administration in male C57BL/6 mice. Values are expressed as Mean $\pm$ SD and n=3 mice/time point/group

5 [00320] In Group 1 (semaglutide tablet 10 mg/kg, oral ROA to Male C57BL/6 mice), time to reach peak plasma concentration (T_{max}) of mean was 45 min and peak plasma concentration (C_{max}) of 54.4 ng/mL. The mean exposure, AUC_{last} was found to be 72 ng*h/mL.

10 [00321] In Group 2 (semaglutide wafer 10 mg/kg, sublingual ROA to Male C57BL/6 mice), time to reach peak plasma concentration (T_{max}) of mean was 30 min and peak plasma concentration (C_{max}) of 720 ng/mL. The mean exposure, AUC_{last} was found to be 794 ng*h/mL.

[00322] **TABLE 11: Arithmetic Mean plasma pharmacokinetic parameters of Semaglutide following single oral and sublingual route of administration to male C57BL/6 mice.**

PK Parameters	Group 1: Semaglutide Tablet/ 10 mg/kg/ Oral	Group 2: Semaglutide Wafer/ 10 mg/kg/ sublingual
C_{max} (ng/mL)	54.4	720
T_{max} (min)	45	30
AUC_{last} (ng*h/mL)	72	794
AUC_{inf_obs} (ng*h/mL)	169*	NC
K_{el} (1/h)	0.0939*	NC
$T_{1/2}$ (h)	7.38*	NC
Cl/F_{obs} (mL/min/kg)	987*	NC
Vz/F_{obs} (L/kg)	630*	NC
MRT_{last} (h)	2.9	3.46

[00323] Note: NC: Not Calculated due to insufficient elimination phase; *: represents value should not be considered as % AUC_{exp} >30%.

[00324] **TABLE 12: Arithmetic Mean plasma concentration time profile of Semaglutide following single Oral and Sublingual route of administration to male C57BL/6 mice.**

Time Points (mins)	Group 1: Semaglutide Tablet/ 10 mg/kg/ Oral		Group 2: Semaglutide Wafer/ 10 mg/kg/ sublingual	
	Mean (ng/mL)	SD (ng/mL)	Mean (ng/mL)	SD (ng/mL)
0	0	0	0	0
5	31.9	14.9	44	65
15	10.4	13.1	8.8	9.95
30	33.8	33.3	720	282
45	54.4	57.2	47.7	39.8
60	11.6	10.2	0.91	1.58
90	19.8	19.9	631	183
120	6.67	11.5	5.77	9.99
240	1.02	1.76	1	1.73
480	9.1	15.8	134	158

5 [00325] **TABLE 13: Individual plasma concentrations of Semaglutide tablet following single Oral route of administration to male C57BL/6 mice (G1: 10 mg/kg)**

Group: Treatment / Dose / ROA	Time (min) / Animal Id	Plasma Concentrations (ng/mL)									
		0	5	15	30	45	60	90	120	240	480
Group 1: Semaglutide Tablet/ 10 mg/kg/ Oral	1	0			25.7			19.6			0
	2	0			5.4			0			0
	3	0			70.4			39.8			27.3
	4		16.9			0			0		
	5		46.6			114			0		
	6		32.3			49.2			20		
	7			6.02			15.7			0	
	8			25.1			19			3.05	
	9			0			0			0	
	Mean	0	31.9	10.4	33.8	54.4	11.6	19.8	6.67	1.02	9.1

	SD	0	14.9	13.1	33.3	57.2	10.2	19.9	11.5	1.76	15.8
	%CV	NA	46.5	126	98.3	105	87.8	101	173	173	173

[00326] **TABLE 14: Individual plasma concentrations of Semaglutide following single Sublingual wafer route of administration to male C57BL/6 mice (G2: 10 mg/kg)**

Group: Treatment / Dose / ROA	Time (min) / Animal Id	Plasma Concentrations (ng/mL)									
		0	5	15	30	45	60	90	120	240	480
Group 2: Semaglutide Wafer/ 10 mg/kg/ sublingual	10	0			681			689			3.17
	11	0			460			426			309
	12	0			1020			779			90.1
	13		3.99			6.17			0		
	14		119			51.6			0		
	15		9.09			85.4			17.3		
	16			6.8			0			0	
	17			0			0			0	
	18			19.6			2.73			3	
	Mean	0	44	8.8	720	47.7	0.91	631	5.77	1	134
	SD	0	65	9.95	282	39.8	1.58	183	9.99	1.73	158
	%CV	NA	148	113	39.2	83.3	173	29.1	173	173	118

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E EXAMPLE 5 – SINGLE DOSE PHARMACOKINETIC STUDY OF SEMAGLUTIDE FOLLOWING SUBLINGUAL AND ORAL ROUTE OF ADMINISTRATION IN MALE SPRAGUE DAWLEY RAT.

[00327] STUDY AIM

- 10 [00328] The goal of this study was to determine the pharmacokinetics of semaglutide following oral and sublingual route of administration in male Sprague Dawley rats.

[00329] MATERIALS AND METHODS

- 15 [00330] This study was performed in overnight fasted male SD Rats. Rybelsus® Semaglutide, 14 mg Tablets (Batch No.: PS6LE23) and Semaglutide B-14 mg Freeze-dried oral disintegrating Tablets (wafers) (Batch No.: B240836), were test items used in this study. Dose formulations were prepared freshly on the day of dosing. 0.5% of methyl cellulose in Milli Q water were used as the vehicle. See Tables 33 to 35 for further information on the formulations.

[00331] **TABLE 15: Group allocation and treatment**

Group	Treatment (Dose)	Animal ID	Dose Volume	Formulation strength	ROA
1	Semaglutide Wafer (10 mg/kg)	1 to 6	50 mg wafer per rat	13.32 mg of semaglutide in 200 mg of wafer	Sublingual
2	Semaglutide Tablet (10 mg/kg)	7 to 12	10 mL/kg	1 mg/mL of semaglutide (Crushed tablet in 14 mL)	Oral

[00332] Note: Permanent Id's of Rat used in this study were Rja8167 to Rja8178.

[00333] Blood samples were collected through retro orbital plexus puncture at 0 (pre-dose), 5 mins, 15 mins, 30 mins, 60 mins, 90 mins, 120 mins, 240 mins and 480 mins post dose (Total 9 time points / rat) At each time points, ~0.2 mL of blood was withdrawn and transferred into pre-labeled microcentrifuge tubes containing 20 μ L per mL of blood of 200 mM K₂EDTA solution as anticoagulant. Blood samples were kept on wet ice and were centrifuged immediately at 4000 rpm for 10 min at 4 °C. Plasma was separated after centrifugation. Plasma samples were transferred into pre-labeled (Animal ID No., Time point, Study No., Matrix and Group) tubes. All plasma samples were stored at -70 $\pm$ 10 °C until bioanalysis.

[00334] Bioanalysis was performed using fit-for-purpose LC-MS/MS method for the quantification of semaglutide in plasma samples.

[00335] The plasma pharmacokinetic parameters of semaglutide were determined from mean concentration time curves obtained following a single sublingual and oral route of administration in male SD rats. Values are expressed as Mean $\pm$ SD and n=6 rat/time point/group.

[00336] Plasma pharmacokinetic parameters were calculated using standard non-compartmental analysis (Phoenix[®] software, version 8.3, Certara Corporation, Mountain View, California 94040/USA) using linear trapezoidal method with linear interpolation.

[00337] **RESULTS AND DISCUSSION**

[00338] No clinical signs, mortality or morbidity was observed in treated group animals at the doses tested.

[00339] The plasma pharmacokinetic parameters Semaglutide were determined from mean concentration time curves obtained following a single sublingual and oral route of

administration in male Sprague Dawley rat. Values are expressed as Mean $\pm$ SD and n=6 Rat/time point/group.

[00340] In Group 1 (Semaglutide wafer 10 mg/kg, Sublingual ROA to Male SD rat) time to reach peak plasma concentration (T_{max}) of mean was 120 min and peak plasma concentration (C_{max}) of 2250 ± 2210 ng/mL. The mean exposure, AUC_{last} and MRT_{last} was found to be 11000 ± 9640 ng*h/mL and 3.64 ± 0.529 h.

[00341] In Group 2 (Semaglutide tablet 10 mg/kg, oral ROA to Male SD rat), time to reach peak plasma concentration (T_{max}) of mean was 30 min and peak plasma concentration (C_{max}) of 168 ± 244 ng/mL. The mean exposure, AUC_{last} and MRT_{last} was found to be 553 ± 782 ng*h/mL and 2.75 ± 0.999 h.

[00342] **TABLE 16: Arithmetic Mean plasma pharmacokinetic parameters of Semaglutide following single sublingual and oral route of administration to male Sprague Dawley rat.**

PK Parameters	Group 1: Semaglutide Wafer/ 10 mg/kg/ Sublingual	Group 2: Semaglutide Tablet/ 10 mg/kg/ Oral
C_{max} (ng/mL)	2250 ± 2210	168 ± 244
T_{max} (min)	120 (30-480)	30 (15-30)
AUC_{last} (ng*h/mL)	11000 ± 9640	553 ± 782
MRT_{last} (h)	3.64 ± 0.529	2.75 ± 0.999

15 [00343] **TABLE 17: Individual plasma pharmacokinetic parameters of Semaglutide wafer following single sublingual route of administration to male Sprague Dawley rat (G1: 10 mg/kg).**

Group: Treatment / Dose / ROA	Animal Id	PK Parameters			
		C_{max} (ng/mL)	T_{max} (min)	AUC_{last} (ng*h/mL)	MRT_{last} (h)
Group 1: Semaglutide wafer/ 10 mg/kg/	Rat 1	159	30	469	3.19
	Rat 2	285	120	886	3.44
	Rat 3	1660	90	11200	4.3
	Rat 4	1430	480	9930	4.34

sublingual	Rat 5	5290	240	24700	3.24
	Rat 6	4680	120	18900	3.35
	Mean	2250	180	11000	3.64
	SD	2210	162	9640	0.529
	CV%	98.2	90.1	87.5	14.5

[00344] **TABLE 18: Individual plasma pharmacokinetic parameters of Semaglutide tablet following single oral route of administration to male Sprague Dawley rat (G2: 10 mg/kg).**

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Group: Treatment / Dose / ROA	Animal Id	PK Parameters			
		C _{max} (ng/mL)	T _{max} (min)	AUC _{last} (ng*h/mL)	MRT _{last} (h)
Group 1: Semaglutide Tablet/ 10 mg/kg/ Oral	Rat 7	74.8	15	246	2.99
	Rat 8	649	15	2080	3.16
	Rat 9	188	30	670	3.1
	Rat 10	65.7	30	243	3.23
	Rat 11	19.7	15	67.1	3.3
	Rat 12	9.7	15	11.9	0.724
	Mean	168	20	553	2.75
	SD	244	7.75	782	0.999
	CV%	145	38.7	141	36.3

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[00345] **TABLE 19: Arithmetic Mean plasma concentration time profile of Semaglutide following single Sublingual and oral route of administration to Sprague Dawley rat.**

Time Points (mins)	Group 1: Semaglutide wafer/ 10 mg/kg/ sublingual		Group 2: Semaglutide Tablet/ 10 mg/kg/ oral	
	Mean (ng/mL)	SD (ng/mL)	Mean (ng/mL)	SD (ng/mL)
0	0	0	0	0

5	167	169	65.3	79.3
15	270	252	152	248
30	637	574	150	211
60	655	711	99.6	129
90	1340	1420	85.1	104
120	1960	1960	80.4	105
240	2100	2190	60.8	95.4
480	530	710	40.7	54.6

[00346] **TABLE 20: Individual plasma concentrations of Semaglutide wafer following single sublingual route of administration to male Sprague Dawley rats (G1: 10 mg/kg)**

Group: Treatment / Dose / ROA	Time (min) / Animal Id	Plasma Concentrations (ng/mL)								
		0	5	15	30	60	90	120	240	480
Group 1: Semaglutide wafer/ 10 mg/kg/ sublingual	Rat 1	0	15.1	116	159	54.8	84.2	69.4	51.6	36.2
	Rat 2	0	10.5	18.2	27.4	25.9	27900*	285	102	58.9
	Rat 3	0	219	399	757	932	1660	1390	1610	1460
	Rat 4	0	291	436	778	1200	1400	1210	1280	1430
	Rat 5	0	418	627	1630	1670	3510	4100	5290	161
	Rat 6	0	50.9	26.7	472	46.2	52.6	4680	4260	35.1
	Mean	0	167	270	637	655	1340	1960	2100	530
	SD	0	169	252	574	711	1420	1960	2190	710
	%CV	NA	101	93.2	90.1	109	106	100	104	134

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[00347] **TABLE 21: Individual plasma concentrations of Semaglutide tablet following single oral route of administration to male Sprague Dawley rats (G2: 10 mg/kg)**

Group: Treatment / Dose / ROA	Time (min) / Animal Id	Plasma Concentrations (ng/mL)								
		0	5	15	30	60	90	120	240	480
Group 2: Semaglutide tablet/ 10 mg/kg/ oral	Rat 7	0	50.6	74.8	65.3	54	38.3	39.6	22.3	18.6
	Rat 8	0	216	649	560	350	275	281	250	146
	Rat 9	0	83.5	133	188	123	134	108	65.1	51.3
	Rat 10	0	26.5	28.4	65.7	49.6	44.5	44.6	20.8	22.1

	Rat 11	0	8.48	19.7	13.3	12.7	12.7	9.29	6.86	6.01
	Rat 12	0	6.58	9.7	9.37	8	6.05	0	0	0
	Mean	0	65.3	152	150	99.6	85.1	80.4	60.8	40.7
	SD	0	79.3	248	211	129	104	105	95.4	54.6
	%CV	NA	121	162	140	130	122	131	157	134

**F EXAMPLE 6 – SINGLE DOSE PHARMACOKINETIC STUDY OF SEMAGLUTIDE
FOLLOWING SUBLINGUAL AND SUBCUTANEOUS ROUTE OF ADMINISTRATION
IN MALE SPRAGUE DAWLEY RAT.**

[00348] STUDY AIM

[00349] The goal of this study was to determine the pharmacokinetics of semaglutide following Sublingual and subcutaneous route of administration in male Sprague Dawley rats.

[00350] MATERIALS AND METHODS

10 [00351] This study was performed in overnight fasted animals in sublingual group and non-fasted in subcutaneous group with Male SD rats. OZEMPIC® semaglutide injection 1.34mg (Batch No.: PP5K651) and semaglutide B-14 mg Freeze-dried oral disintegrating Tablets (wafers) (Batch No.: B240847 and B240846), were test items used in this study. Dose formulations were prepared freshly on the day of dosing. 0.9% Normal saline was used as diluent. See Tables 33 to 35 for further information on the formulations.

[00352] TABLE 22: Group allocation and treatment

Group	Treatment (Dose)	Animal ID	Dose Volume	Formulation strength	ROA
1	OZEMPIC® Semaglutide injection 1.34mg (30 nmol/kg)	1 to 6	1 mL/kg	0.12 mg/mL	SC
2	Semaglutide Wafer (B. No: B240847) (~10 mg/kg)	7 to 12	50 mg wafer per rat	13.32 mg of Semaglutide in 200 mg of wafer	Sublingual
3	Semaglutide Wafer (B. No: B240846) (~10 mg/kg)	13 to 18	50 mg wafer per rat	13.32 mg of Semaglutide in 200 mg of wafer	Sublingual

[00353] Note: Permanent Id's of Rat used in this study were Rja8206 to Rja8223

- [00354] Blood samples were collected through jugular vein cannulation at 0 (pre-dose), 5 mins, 15 mins, 30 mins, 60 mins, 90 mins, 120 mins, 240 mins and 480 mins post dose (Total 9 time points / rat) At each time points, ~0.2 mL of blood was withdrawn and transferred into pre-labelled microcentrifuge tubes containing 20 μ L per mL of blood of 200 mM K_2EDTA solution as anticoagulant. Blood samples were kept on wet ice and were centrifuged immediately at 4000 rpm for 10 min at 4 °C. Plasma was separated after centrifugation. Plasma samples were transferred into pre-labelled (Animal ID No., Time point, Study No., Matrix and Group) tubes. All plasma samples were stored at -70 ± 10 °C until bioanalysis.
- 5
- [00355] Bioanalysis was performed using fit-for-purpose LC-MS/MS method for the quantification of Semaglutide in plasma samples.
- 10
- [00356] The plasma pharmacokinetic parameters of Semaglutide were determined from mean concentration time curves obtained following a single subcutaneous and sublingual route of administration in male SD rats. Values are expressed as Mean $\pm$ SD and n=6 rat/time point/group.
- 15
- [00357] Plasma pharmacokinetic parameters were calculated using standard non-compartmental analysis (Phoenix® software, version 8.3, Certara Corporation, Mountain View, California 94040/USA) using linear trapezoidal method with linear interpolation.
- [00358] **RESULTS AND DISCUSSION**
- 20
- [00359] No clinical signs, mortality or morbidity was observed in treated group animals at the doses tested.
- [00360] The plasma pharmacokinetic parameters Semaglutide were determined from mean concentration time curves obtained following a single sublingual and subcutaneous route of administration in male Sprague Dawley rat. Values are expressed as Mean $\pm$ SD and n=6 Rat/time point/group.
- 25
- [00361] In Group 1 (OZEMPIC® Semaglutide injection 1.34mg, 30nmol/kg, Subcutaneous ROA to Male SD rat) time to reach peak plasma concentration (T_{max}) of mean was 480 min and peak plasma concentration (C_{max}) of 586 ± 255 ng/mL. The mean exposure, AUC_{last} and MRT_{last} was found to be 3430 ± 98 ng*h/mL and 4.68 ± 0.222 h.
- 30
- [00362] In Group 2 (Semaglutide Wafer (B.No.: B240847), 10 mg/kg, Sublingual ROA to Male SD rat), time to reach peak plasma concentration (T_{max}) of mean was 60 min and peak plasma concentration (C_{max}) of 972 ± 1690 ng/mL. The mean exposure, AUC_{last} and MRT_{last} was found to be 5060 ± 9830 ng*h/mL and 2.9 ± 1.67 h.

[00363] In Group 3 (Semaglutide Wafer (B.No.: B240846), 10 mg/kg, Sublingual ROA to Male SD rat), time to reach peak plasma concentration (T_{max}) of mean was 90 min and peak plasma concentration (C_{max}) of 292 ± 160 ng/mL. The mean exposure, AUC_{last} and MRT_{last} was found to be 1200 ± 822 ng*h/mL and 3.28 ± 0.945 h.

- 5 [00364] **TABLE 23: Arithmetic Mean plasma pharmacokinetic parameters of Semaglutide following single sublingual and subcutaneous route of administration to male Sprague Dawley rat.**

PK Parameters	Group 1: OZEMPIC® semaglutide injection 1.34 mg/ 30 nmol /kg / Subcutaneous	Group 2: Semaglutide Wafer (B.No.: B240847) / 10 mg/kg/ Sublingual	Group 3: Semaglutide Wafer (B.No.: B240843) / 10 mg/kg/ Sublingual
C_{max} (ng/mL)	586 ± 255	972 ± 1690	292 ± 160
T_{max} (min)	480 (240 - 480)	60 (5 - 480)	90 (30 - 120)
AUC_{last} (ng*h/mL)	3430 ± 98	5060 ± 9830	1200 ± 822
MRT_{last} (h)	4.68 ± 0.222	2.9 ± 1.67	3.28 ± 0.945

- 10 [00365] **TABLE 24: Individual plasma pharmacokinetic parameters of OZEMPIC® semaglutide injection 1.34 mg following single subcutaneous route of administration to male Sprague Dawley rat (G1: 30 nmol /kg).**

Group: Treatment / Dose / ROA	Animal Id	PK Parameters			
		C_{max} (ng/mL)	T_{max} (min)	AUC_{last} (ng*h/mL)	MRT_{last} (h)
Group 1: OZEMPIC® semaglutide injection 1.34 mg/ 30 nmol /kg / Subcutaneous	Rat 1	486	480	2960	4.78
	Rat 2	456	240	2700	4.34
	Rat 3	584	480	3540	4.59
	Rat 4	281	480	1640	4.75
	Rat 5	681	480	3500	5.01
	Rat 6	1030	480	6230	4.66
	Mean	586	440	3430	4.68
	SD	255	98	1540	0.222
	CV%	43.6	22.3	44.8	4.74

[00366] **TABLE 25: Individual plasma pharmacokinetic parameters of Semaglutide wafer (B.No.: B240847) following single sublingual route of administration to male Sprague Dawley rat (G2: 10 mg/kg).**

Group: Treatment / Dose / ROA	Animal Id	PK Parameters			
		C _{max} (ng/mL)	T _{max} (min)	AUC _{last} (ng*h/mL)	MRT _{last} (h)
Group 2: Semaglutide Wafer (B.No.: B240847) / 10 mg/kg/ Sublingual	Rat 7	132	90	513	2.88
	Rat 8	3980	480	22600	4.99
	Rat 9	256	5	47.1	0.322
	Rat 10	395	60	1670	3.06
	Rat 12	97.1	60	445	3.25
	Mean	972	139	5060	2.9
	SD	1690	193	9830	1.67
	CV%	173	139	194	57.6

[00367] Note: Rat 11 considered as outlier due to anomalous behaviour within group.

[00368] **TABLE 26: Individual plasma pharmacokinetic parameters of Semaglutide wafer (B.No.: B240846) following single sublingual route of administration to male Sprague Dawley rat (G3: 10 mg/kg).**

Group: Treatment / Dose / ROA	Animal Id	PK Parameters			
		C _{max} (ng/mL)	T _{max} (min)	AUC _{last} (ng*h/mL)	MRT _{last} (h)
Group 3: Semaglutide Wafer (B.No.: B240846) / 10 mg/kg/ Sublingual	Rat 13	346	90	1790	3.6
	Rat 14	261	120	1370	4.11
	Rat 15	534	90	386	1.45
	Rat 16	75.9	30	388	3.42
	Rat 17	174	60	821	3.23
	Rat 18	361	90	2440	3.85
	Mean	292	80	1200	3.28
	SD	160	31	822	0.945

	CV%	54.8	38.7	68.5	28.9
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[00369] **TABLE 27: Arithmetic Mean plasma concentration time profile of Semaglutide following single Subcutaneous and sublingual route of administration to Sprague Dawley rat.**

Time Points (mins)	Group 1: OZEMPIC® semaglutide injection 1.34 mg/ 30 nmol /kg / Subcutaneous		Group 2: Semaglutide Wafer (B.No.: B240847) / 10 mg/kg/ Sublingual		Group 3: Semaglutide Wafer (B.No.: B240846) / 10 mg/kg/ Sublingual	
	Mean (ng/mL)	SD (ng/mL)	Mean (ng/mL)	SD (ng/mL)	Mean (ng/mL)	SD (ng/mL)
0	0	0	0	0	0	0
5	14.2	10.6	111	94.2	102	42.7
15	66	41	78.8	69.1	73.9	43.4
30	178	137	235	265	129	101
60	283	172	353	463	154	116
90	409	204	432	649	250	196
120	371	157	467	818	189	128
240	470	198	770	1550	161	129
480	564	275	826	1760	103	91

[00370] **TABLE 28: Individual plasma concentrations of OZEMPIC® semaglutide injection 1.34 mg following single subcutaneous route of administration to male Sprague Dawley rat (G1: 30 nmol /kg).**

Group: Treatment / Dose / ROA	Time (min) / Animal Id	Plasma Concentrations (ng/mL)								
		0	5	15	30	60	90	120	240	480
Group 1: OZEMPIC® semaglutide injection 1.34 mg/ 30 nmol /kg / Subcutaneous	Rat 1	0	11.5	39.3	103	203	265	313	438	486
	Rat 2	0	0	38.9	94.6	181	404	285	456	319
	Rat 3	0	28.8	112	248	338	511	409	439	584
	Rat 4	0	7.1	27.3	62.7	145	161	198	217	281
	Rat 5	0	14	55.5	132	223	365	365	442	681

	Rat 6	0	23.8	123	425	609	746	656	828	1030
	Mean	0	14.2	66	178	283	409	371	470	564
	SD	0	10.6	41	137	172	204	157	198	275
	%CV	NA	74.8	62.2	77.2	60.9	49.9	42.3	42	48.8

[00371] **TABLE 29: Individual plasma concentrations of Semaglutide wafer (B.No.: B240847) following single sublingual route of administration to male Sprague Dawley rat (G2: 10 mg/kg).**

Group: Treatment / Dose / ROA	Time (min) / Animal Id	Plasma Concentrations (ng/mL)								
		0	5	15	30	60	90	120	240	480
Group 2: Semaglutide Wafer (B.No.: B240847) / 10 mg/kg/ Sublingual	Rat 7	0	31.8	91.8	109	124	132	76.4	58.6	25
	Rat 8	0	103	81.8	663	1140	1570	1920	3540	3980
	Rat 9	0	256	8.13	14.7	10.2	11.3	0	0	0
	Rat 10	0	138	185	319	395	357	263	199	95
	Rat 11	0*	12.8*	7.13*	8.14*	7.53*	9.8*	7.32*	0*	0*
	Rat 12	0	24.9	27.5	70.1	97.1	87.5	76.5	54	29.9
	Mean	0	111	78.8	235	353	432	467	770	826
	SD	0	94.2	69.1	265	463	649	818	1550	1760
	%CV	NA	85.1	87.6	113	131	150	175	201	214

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[00372] Note: NA: Not Applicable & Rat 11 considered as outlier due to anomalous behaviour within group.

[00373] **TABLE 30: Individual plasma concentrations of Semaglutide wafer (B.No.: B240846) following single sublingual route of administration to male Sprague Dawley rat (G3: 10 mg/kg).**

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Group: Treatment / Dose / ROA	Time (min) / Animal Id	Plasma Concentrations (ng/mL)								
		0	5	15	30	60	90	120	240	480
Group 3: Semaglutide Wafer (B.No.: B240846) / 10 mg/kg/ Sublingual	Rat 13	0	150	115	198	296	346	279	229	160
	Rat 14	0	83.2	13.6	93.7	45	37.1	261	229	136
	Rat 15	0	140	43.5	32.6	66.8	534	28	11.8	0
	Rat 16	0	58.1	52.9	75.9	55.3	60.9	55.7	51.2	30.2
	Rat 17	0	52.8	98.3	71	174	158	166	94.9	54.4
	Rat 18	0	128	120	300	286	361	344	350	240
	Mean	0	102	73.9	129	154	250	189	161	103
	SD	0	42.7	43.4	101	116	196	128	129	91
	%CV	NA	41.9	58.7	78.4	75.4	78.5	67.6	80.3	87.9

**G EXAMPLE 7 – SINGLE DOSE PHARMACOKINETIC STUDY OF COMBINATION
LIRAGLUTIDE/DAPAGLIFLOZIN SUBLINGUAL WAFER IN MALE SPRAGUE
DAWLEY RATS.**

5 [00374] **STUDY AIM**

[00375] To determine the pharmacokinetics of a combination Liraglutide and Dapagliflozin sublingual wafer in male Sprague Dawley Rat.

[00376] **MATERIALS AND METHODS**

[00377] *Test System*

- 10 [00378] Species: Rat; Strain: Sprague Dawley; Sex: Male; Rationale: Sprague Dawley rat is commonly used rodent species in the pharmacokinetic evaluation of drugs and acceptable to the regulatory authorities; Total number of animals: 18 Rats (6 rats/group); Age/ Body Weight at study initiation: 7-10 weeks, 250- 350 g; Veterinary Examination: Prior to the final assignment to the study, animals will be subjected to complete veterinary health examination
- 15 to ensure that the selected animals are in a good state of health; Animal Identification: Animals will be uniquely identified by individual tail marking with a permanent marker along with cage card; Acclimatization: On receipt from supplier, the animals will be examined for any external signs of ill health and aberrant behavior prior to acceptance. After health examination, animals will be quarantined for one week under test conditions and then
- 20 acclimatized for a minimum of 5 days in study room. Only animals without any visible signs of illness will be used for the study; Animal catheterization: Under Ketamine and Xylazine anesthesia, all animals will be cannulated in right external jugular vein. Rats will be surgically implanted with a catheter (jugular vein, Polyethylene-50 tubing attached to Polyurethane-40 catheter) for blood collection. Rats will be allowed to recover for minimum of 48 h after
- 25 cannulation, before inclusion in study and drug administration. General animal health and cannula patency will be confirmed prior to dose administration.

[00379] *Husbandry*

- [00380] Housing Conditions: Standard laboratory conditions, temperature will be maintained between 22±3°C and relative humidity between 30–70 % under a 12 h light/dark
- 30 cycle. Air changes of 12-15 times per hour via a centrally placed air intake and peripheral ventilators will be maintained. Accommodation: Each animal will be placed in individual polycarbonate cage with stainless steel grill top with facilities for feed and water bottle and bedding of clean corn cob. Feed: Hypro pelleted rodent feed will be provided ad libitum. All

- group rats will be fasted overnight. No feed will be provided. Water: Deep bore-well water passed through activated charcoal filter and exposed to UV rays in Aquaguard on-line water filter-cum-purifier will be provided ad libitum in polycarbonate bottles with stainless steel sipper tubes. All rats will have access to water ad libitum. Animal handling: Experiment will
- 5 be carried out by qualified & trained scientific personnel (trained in animal handling, drug administration and experimentation). Body weight: On the day of dosing. Clinical signs: Animals will be observed for any apparent clinical signs of ill-health and toxicity during study duration.

[00381] *Dose Formulation Preparation*

- 10 [00382] The dose formulation will be prepared freshly on the day of dosing.

[00383] **TABLE 31: Group Allocation and Treatment**

Group	Treatment	Animal ID	Formulation strength	ROA
1	Liraglutide/ Dapagliflozin wafer	1 to 6	Liraglutide 15mg/Dapagliflozin 10mg	Sublingual
2	Liraglutide injection (Victoza); Dapagliflozin tablet (Fariga)	7 to 12	Liraglutide 1.8mg injection	SC & Oral
3	Dapagliflozin wafer	13 to 18	Dapagliflozin 10mg tablet	Sublingual

- [00384] Note: See Tables 33 to 35 for further information on the formulations. Liraglutide SL wafer and Liraglutide SC injection only rat pK data are being generated in another study.
- 15 These data will be used for comparison to data generated in this study.

[00385] *Dose administration*

[00386] Wafers will be crushed and weighed on an accurate balance and placed in the sublingual space under isoflurane anesthesia for 4-5 min followed by up to 1-2 drops of water to assist in disintegration (use minimal amount required to disintegrate wafers).

- 20 [00387] Note: The sublingual mucosa moistness will be ensured prior to administering the SL wafer by administering a small quantity of water into the SL space, just prior to anesthesia.

[00388] Subcutaneous administration will be on the dorsal side towards Cranial.

[00389] *Blood collection and storage of samples*

[00390] Site of blood collection: Jugular vein via cannulation; Anticoagulant: K2EDTA (20 µL of 200 mM solution per 1 mL of blood); Blood collection time points: 0 (pre-dose), 0.083 h, 0.25 h, 0.5 h, 1 h, 2 h, 4h, 8 h and 24 h post dose (Total 9 time points/rat); Volume of blood collected: ~0.2 mL at each time points from each rat; Blood sampling procedure: Serial sampling

[00391] Blood centrifugation time: 4000 rpm for 10 minutes at 4 °C; Matrix: Plasma; Matrix storage: -70 ± 10 °C until analysis; Matrix labeling details: Study number, Group, Animal ID, and Time point; Note: 1. Blood samples will be kept on wet ice until centrifugation. Centrifugation will be done within 30 minutes of collection and plasma will be checked for hemolysis. If samples are hemolyzed, another sample will be taken as soon as possible. 2. Prepared dose formulation will be discarded after the completion of in-life phase. 3. On completion of the last blood sampling, animals will be sacrificed, and carcasses discarded.

[00392] *Bioanalysis*

15 [00393] Matrix: Plasma. Analyte: Liraglutide and Dapagliflozin. Bioanalysis will be performed by fit-for-purpose analytical method using LC-MS/MS. Upon finalization of study report, remaining biological study samples will be discarded.

[00394] *Pharmacokinetic data and analysis and evaluation*

[00395] Pharmacokinetic Software: Phoenix® Software, version 8.3, USA.

20 [00396] Pharmacokinetic Parameters: C₀, C_{max}, T_{max}, AUC_{0-t}, AUC_{0-∞}, K_{el}, T_{1/2}, V_d, V_d/F, Cl, Cl/F and MRT_{last}.

[00397] **RESULTS**

25 [00398] The study is to determine the relative bioavailability of a novel formulation of a sublingual lyophilised combination product containing liraglutide and dapagliflozin compared to administering both liraglutide injection subcutaneously and dapagliflozin tablets orally, as well as dapagliflozin in a sublingual wafer. We expect the relative bioavailability to be in the range of 2-50% for liraglutide and 70-95% for dapagliflozin. In addition, we expect to see more rapid absorption into plasma following administration with the sublingual wafer compared to subcutaneous injection.

30 [00399] **DISCUSSION**

[00400] These results represent the first data available on the relative bioavailability of sublingual administration of liraglutide and dapagliflozin. Obtaining systemic absorption of

liraglutide via sublingual administration with this novel wafer creates the potential for a non-injectable formulation of liraglutide. At present, liraglutide is only available as an injectable product. Although Dapagliflozin is available as an oral tablet today, there is no combination product of both liraglutide and dapagliflozin. These combination of these two drug classes is
5 expected to have greater efficacy than either product alone due to the complementary mechanisms of action. Such a product would be non-invasive, easier to use, convenient and improve patient compliance.

10 **H EXAMPLE 8 – SINGLE DOSE PHARMACOKINETIC STUDY OF COMBINATION
SEMAGLUTIDE/DAPAGLIFLOZIN SUBLINGUAL WAFER IN MALE SPRAGUE
DAWLEY RATS.**

[00401] **STUDY AIM**

[00402] To determine the pharmacokinetics of a combination Semaglutide and Dapagliflozin sublingual wafer in male Sprague Dawley Rat.

15 [00403] **MATERIALS AND METHODS**

[00404] *Test System*

[00405] Species: Rat; Strain: Sprague Dawley; Sex: Male; Rationale: Sprague Dawley rat is commonly used rodent species in the pharmacokinetic evaluation of drugs and acceptable to the regulatory authorities; Total number of animals: 18 Rats (6 rats/group); Age/ Body
20 Weight at study initiation: 7-10 weeks, 250- 350 g; Veterinary Examination: Prior to the final assignment to the study, animals will be subjected to complete veterinary health examination to ensure that the selected animals are in a good state of health; Animal Identification: Animals will be uniquely identified by individual tail marking with a permanent marker along with cage card; Acclimatization: On receipt from supplier, the animals will be examined for
25 any external signs of ill health and aberrant behavior prior to acceptance. After health examination, animals will be quarantined for one week under test conditions and then acclimatized for a minimum of 5 days in study room. Only animals without any visible signs of illness will be used for the study; Animal catheterization: Under Ketamine and Xylazine anesthesia, all animals will be cannulated in right external jugular vein. Rats will be surgically
30 implanted with a catheter (jugular vein, Polyethylene-50 tubing attached to Polyurethane-40 catheter) for blood collection. Rats will be allowed to recover for minimum of 48 h after cannulation, before inclusion in study and drug administration. General animal health and cannula patency will be confirmed prior to dose administration.

[00406] Husbandry

[00407] Housing Conditions: Standard laboratory conditions, temperature will be maintained between 22±3°C and relative humidity between 30–70 % under a 12 h light/dark cycle. Air changes of 12-15 times per hour via a centrally placed air intake and peripheral ventilators will be maintained. Accommodation: Each animal will be placed in individual polycarbonate cage with stainless steel grill top with facilities for feed and water bottle and bedding of clean corn cob. Feed: Hypro pelleted rodent feed will be provided ad libitum. All group rats will be fasted overnight. No feed will be provided. Water: Deep bore-well water passed through activated charcoal filter and exposed to UV rays in Aquaguard on-line water filter-cum-purifier will be provided ad libitum in polycarbonate bottles with stainless steel sipper tubes. All rats will have access to water ad libitum. Animal handling: Experiment will be carried out by qualified & trained scientific personnel (trained in animal handling, drug administration and experimentation). Body weight: On the day of dosing. Clinical signs: Animals will be observed for any apparent clinical signs of ill-health and toxicity during study duration.

[00408] Dose Formulation Preparation

[00409] The dose formulation will be prepared freshly on the day of dosing.

[00410] TABLE 31: Group Allocation and Treatment

Group	Treatment	Animal ID	Formulation strength	ROA
1	Semaglutide/ Dapagliflozin wafer	1 to 6	Semaglutide 14mg/Dapagliflozin 10mg	Sublingual
2	Semaglutide injection 1.34mg (Ozempic); Dapagliflozin tablet (Fariga)	7 to 12	Semaglutide injection 1.34mg	SC & Oral
2	Liraglutide injection (Victoza); Dapagliflozin tablet (Fariga)	13 to 18	Liraglutide 1.8mg injection / Dapagliflozin 10mg	SC & Oral
3	Dapagliflozin wafer	19 to 24	Dapagliflozin 10mg tablet	Sublingual

[00411] Note: See Tables 33 to 35 for further information on the formulations. Semaglutide SL wafer and Semaglutide SC injection only rat pK data are being generated in another study. These data will be used for comparison to data generated in this study.

[00412] Dose administration

[00413] Wafers will be crushed and weighed on an accurate balance and placed in the sublingual space under isoflurane anesthesia for 4-5 min followed by up to 1-2 drops of water to assist in disintegration (use minimal amount required to disintegrate wafers).

[00414] Note: The sublingual mucosa moistness will be ensured prior to administering the SL wafer by administering a small quantity of water into the SL space, just prior to anesthesia.

[00415] Subcutaneous administration will be on the dorsal side towards Cranial.

[00416] *Blood collection and storage of samples*

[00417] Site of blood collection: Jugular vein via cannulation; Anticoagulant: K2EDTA (20 μ L of 200 mM solution per 1 mL of blood); Blood collection time points: 0 (pre-dose), 0.083 h, 0.25 h, 0.5 h, 1 h, 2 h, 4h, 8 h and 24 h post dose (Total 9 time points/rat); Volume of blood collected: ~0.2 mL at each time points from each rat; Blood sampling procedure: Serial sampling

[00418] Blood centrifugation time: 4000 rpm for 10 minutes at 4 °C; Matrix: Plasma; Matrix storage: -70 $\pm$ 10 °C until analysis; Matrix labeling details: Study number, Group, Animal ID, and Time point; Note: 1. Blood samples will be kept on wet ice until centrifugation. Centrifugation will be done within 30 minutes of collection and plasma will be checked for hemolysis. If samples are hemolyzed, another sample will be taken as soon as possible. 2. Prepared dose formulation will be discarded after the completion of in-life phase. 3. On completion of the last blood sampling, animals will be sacrificed, and carcasses discarded.

[00419] *Bioanalysis*

[00420] Matrix: Plasma. Analyte: Semaglutide and Dapagliflozin. Bioanalysis will be performed by fit-for-purpose analytical method using LC-MS/MS. Upon finalization of study report, remaining biological study samples will be discarded.

[00421] *Pharmacokinetic data and analysis and evaluation*

[00422] Pharmacokinetic Software: Phoenix® Software, version 8.3, USA.

[00423] Pharmacokinetic Parameters: C₀, C_{max}, T_{max}, AUC_{0-t}, AUC_{0-∞}, K_{el}, T_{1/2}, V_d, V_d/F, Cl, Cl/F and MRT_{last}.

[00424] **RESULTS**

[00425] The study is to determine the relative bioavailability of a novel formulation of a sublingual lyophilised combination product containing semaglutide and dapagliflozin compared to administering both semaglutide and dapagliflozin tablets orally. We expect the relative bioavailability to be in the range of 70-95% for dapagliflozin. We expect the relative bioavailability of semaglutide with the sublingual wafer to be approximately 20 times that of oral semaglutide (Rybelsus®) based on previous pharmacokinetic data in rats. In addition, we expect to see more rapid absorption into plasma following administration with the sublingual wafer compared to oral tables.

[00426] **DISCUSSION**

10 [00427] These results represent the first data available on the relative bioavailability of sublingual administration of semaglutide and dapagliflozin. Obtaining systemic absorption of semaglutide via sublingual administration with this novel wafer creates the potential for a more effective non-injectable formulation of semaglutide than the existing oral tablet, Rybelsus®. Although Dapagliflozin is available as an oral tablet today, there is no combination product of both semaglutide and dapagliflozin. These combination of these two drug classes is expected to have greater efficacy than either product alone due to the complementary mechanisms of action. Such a product would be non-invasive, easier to use, convenient and improve patient compliance.

20 **I EXAMPLE 9 – SINGLE DOSE PHARMACOKINETIC STUDY OF SEMAGLUTIDE
SUBLINGUAL WAFER IN MALE SPRAGUE DAWLEY RATS.**

[00428] **STUDY AIM**

[00429] To determine the pharmacokinetics of Semaglutide sublingual wafer in male Sprague Dawley Rat.

25 [00430] **MATERIALS AND METHODS**

[00431] A further study was conducted using the methods described above and standard methods described in the art.

[00432] It was a single-dose pK study in Sprague-Dawley rats (n=30, 7-10 weeks old, weighing 300-350g). Animals were anaesthetised during sublingual administration for ~3 minutes. Venous blood samples were obtained over 8-hour period. Plasma samples were analysed by LC-MS/MS.

[00433] The treatment arms were as follows:

- [00434] SL Wafer Formulation A, 10mg/kg (n=6)
- [00435] SL Wafer Formulation B, 10mg/kg (n=6)
- [00436] SL Wafer Formulation C, 10mg/kg (n=6)
- [00437] PO Rybelsus® tablet, 10mg/kg (n=6)
- 5 [00438] S/C Ozempic®, 0.12mg/kg (n=6)
- [00439] See Tables 33 to 35 for further information on the formulations.

[00440] **RESULTS**

[00441] The results are presented in Figure 9. Formulation A administration resulted in ~20x higher bioavailability and lower variability (CV 87% v 141%) than Rybelsus® oral tablet
10 in Sprague-Dawley rats. See Tables 33 to 35 for further information on the formulations.

[00442] **TABLE 32: Pharmacokinetic results**

Drug	Route	Dose (mg/Kg)	T _{max} (mins)	C _{max} (ng/mL)	AUC ₀₋₈ (ng•h/mL)	Relative Bioavailability (PO)	Relative Bioavailability (SC)
Rybelsus®	Oral	10	20	168	553	100%	0.2%
iXB 401 Formulation A	Sublingual	10	240	2,250	11,000	1989%	4.0%
iXB 401 Formulation B	Sublingual	10	139	972	5,060	915%	1.8%
iXB 401 Formulation C	Sublingual	10	90	292	1,200	217%	0.4%
Ozempic®	Subcutaneous	0.12	440	586	3,430	50,264%	100%

[00443] **DISCUSSION**

[00444] These results demonstrate superior pharmacokinetics of all three formulations of
15 a novel sublingual semaglutide wafer (see Table 32). The sublingual formulation A demonstrated to most superior pharmacokinetic profile with a bioavailability of approximately 20 times that of oral semaglutide tablet, Rybelsus® in Sprague-Dawley rats. Compared to subcutaneous injection, the relative bioavailability of this sublingual formulation was approximately 4%. These results show the potential for a more effective non-invasive
20 formulation of semaglutide compared to Rybelsus®. This could result in the use of a lower dosage whilst maintaining efficacy and with the potential for a lower side effect profile.

J EXAMPLE 10 – FORMULATIONS USED IN EXAMPLES.**[00445] FORMULATIONS**

[00446] Please see Tables 33 to 36 below for the formulations used in the studies described above.

5 [00447] TABLE 33: Semaglutide formula A, B, C

14mg Semaglutide				
ITEM NO.	RAW MATERIAL	Formula A B240846	Formula B B240847	Formula C B240836
1	semaglutide	14.0	14.0	14.0
2	Sodium phosphate buffer pH 9			
3	CMC	1.0	1.0	0.7
4	Sodium alginate	1.0	1.0	0.7
5	Mannitol	52.0	52.9	50.8
6	Lactose monohydrate	40.0	40.7	39.1
7	Amylogum CLS	32.0	32.5	31.2
8	Glycine	4.5	4.6	4.4
9	PEG 1500	2.2	2.3	2.2
10	MCC	4.4	4.5	4.3
11	SNAC	See range.	See range.	See range.
12	Soy lecithin	See range.	See range.	See range.
13	Sodium deoxycholate	See range.	See range.	See range.
14	pH observed 7.72	0.0	0.0	0.0
15	Phosphate Buffer to adjust (final)			

16	Sucralose	9.0	9.2	9.0
17	Peppermint flavour Sensient	1.0	1.0	1.0

[00448] The range values are: 1. semaglutide 2mg to 50 mg per wafer; 2. SNAC value 0.1% to 80%; 3. Sodium deoxycholate 0.1% to 20%; 4. Soy lecithin 0% to 30%; and 5. pH buffer from pH 5 to 9 using either TRIS or phosphate buffer.

5 [00449] **TABLE 34: Liraglutide/Dapagliflozin and Dapagliflozin formulation**

		10mg Liraglutide-10mg dapagliflozin wafer	10mg Dapagliflozin wafer
ITEM NO.	RAW MATERIAL	WAFER CONT. (mg/wafer)	
1	Liraglutide	See range.	See range.
2	Sodium dihydrogen phosphate dihydrate buffer pH 8.0		
3	CMC	1.7	1.7
4	Sodium alginate	1.7	1.7
5	Mannitol	127.0	127.0
6	Lactose monohydrate	98.0	98.0
7	Amylogum CLS	78.0	78.0
8	Glycine	11.0	11.0
9	PEG 1500	5.5	5.5
10	MCC	10.7	10.7
11	d- α -tocopheryl polyethylene glycol succinate (TPGS)	See range.	See range.
12	Dapagliflozin proprandirol monohydrate	12.3	12.3

13	Sodium deoxycholate	See range.	See range.
14	pH observed 8	0.0	0.0
15	Sodium dihydrogen phosphate dihydrate buffer pH 8.0		
16	Sucralose	22.5	22.5
17	Peppermint flavour Sensient	2.5	2.5

[00450] The range values are: 1. Liraglutide 2.5mg to 50 mg per wafer; 2. Dapagliflozin 2.5 to 30 mg; 3. TPGS (d- α -tocopheryl polyethylene glycol succinate) penetrant/surfactant 0.1%; to 20%; 4. Sodium deoxycholate 0.1% to 20%.

5 [00451] **TABLE 35: Semaglutide dapagliflozin formulation**

14mg Semaglutide- 10mg Dapagliflozin		
ITEM NO.	RAW MATERIAL	Formula
1	Semaglutide	See range.
2	Sodium phosphate buffer pH 9	
3	CMC	1.0
4	Sodium alginate	1.0
5	Mannitol	52.0
6	Lactose monohydrate	40.0
7	Amylogum CLS	32.0
8	Glycine	4.5
9	PEG 1500	2.2
10	MCC	4.4
11	SNAC	See range.

12	Soy lecithin	See range.
13	Sodium deoxycholate	See range.
14	pH observed 7.72	0.0
15	Dapagliflozin proprandiol monohydrate	12.3
16	Sucralose	9.0
17	Peppermint flavour Sensient	1.0

[00452] The range values are: 1. Semaglutide 2mg to 50 mg per wafer; 2. Dapagliflozin 2.5 to 30 mg; 3. SNAC 0.1% to 20%; 4. Soy lecithin 0% to 30%; and 5. Sodium deoxycholate 0.1% to 20%.

5 [00453] THE PREFERRED RANGES AND VALUES IN THE FORMULATIONS PRESENTED IN TABLES 33, 34 AND 35 ARE AS FOLLOWS.

[00454] *Semaglutide - 2.5mg to 50 mg per wafer, including:* 2.4mg; 2.5mg; 2.6mg; 2.7mg; 2.8mg; 2.9mg; 3.0mg; 3.1mg; 3.2mg; 3.3mg; 3.4mg; 3.5mg; 3.6mg; 3.7mg; 3.8mg; 3.9mg; 4.0mg; 4.1mg; 4.2mg; 4.3mg; 4.4mg; 4.5mg; 4.6mg; 4.7mg; 4.8mg; 4.9mg; 5.0mg; 5.1mg; 5.2mg; 5.3mg; 5.4mg; 5.5mg; 5.6mg; 5.7mg; 5.8mg; 5.9mg; 6.0mg; 6.1mg; 6.2mg; 6.3mg; 6.4mg; 6.5mg; 6.6mg; 6.7mg; 6.8mg; 6.9mg; 7.0mg; 7.1mg; 7.2mg; 7.3mg; 7.4mg; 7.5mg; 7.6mg; 7.7mg; 7.8mg; 7.9mg; 8.0mg; 8.1mg; 8.2mg; 8.3mg; 8.4mg; 8.5mg; 8.6mg; 8.7mg; 8.8mg; 8.9mg; 9.0mg; 9.1mg; 9.2mg; 9.3mg; 9.4mg; 9.5mg; 9.6mg; 9.7mg; 9.8mg; 9.9mg; 10.0mg; 10.1mg; 10.2mg; 10.3mg; 10.4mg; 10.5mg; 10.6mg; 10.7mg; 10.8mg; 10.9mg; 11.0mg; 11.1mg; 11.2mg; 11.3mg; 11.4mg; 11.5mg; 11.6mg; 11.7mg; 11.8mg; 11.9mg; 12.0mg; 12.1mg; 12.2mg; 12.3mg; 12.4mg; 12.5mg; 12.6mg; 12.7mg; 12.8mg; 12.9mg; 13.0mg; 13.1mg; 13.2mg; 13.3mg; 13.4mg; 13.5mg; 13.6mg; 13.7mg; 13.8mg; 13.9mg; 14.0mg; 14.1mg; 14.2mg; 14.3mg; 14.4mg; 14.5mg; 14.6mg; 14.7mg; 14.8mg; 14.9mg; 15.0mg; 15.1mg; 15.2mg; 15.3mg; 15.4mg; 15.5mg; 15.6mg; 15.7mg; 15.8mg; 15.9mg; 16.0mg; 16.1mg; 16.2mg; 16.3mg; 16.4mg; 16.5mg; 16.6mg; 16.7mg; 16.8mg; 16.9mg; 17.0mg; 17.1mg; 17.2mg; 17.3mg; 17.4mg; 17.5mg; 17.6mg; 17.7mg; 17.8mg; 17.9mg; 18.0mg; 18.1mg; 18.2mg; 18.3mg; 18.4mg; 18.5mg; 18.6mg; 18.7mg; 18.8mg; 18.9mg; 19.0mg; 19.1mg; 19.2mg; 19.3mg; 19.4mg; 19.5mg; 19.6mg; 19.7mg; 19.8mg; 19.9mg; 20.0mg; 20.1mg; 20.2mg; 20.3mg; 20.4mg; 20.5mg; 20.6mg; 20.7mg; 20.8mg; 20.9mg; 21.0mg; 21.1mg; 21.2mg; 21.3mg;

- 21.4mg; 21.5mg; 21.6mg; 21.7mg; 21.8mg; 21.9mg; 22.0mg; 22.1mg; 22.2mg; 22.3mg;
 22.4mg; 22.5mg; 22.6mg; 22.7mg; 22.8mg; 22.9mg; 23.0mg; 23.1mg; 23.2mg; 23.3mg;
 23.4mg; 23.5mg; 23.6mg; 23.7mg; 23.8mg; 23.9mg; 24.0mg; 24.1mg; 24.2mg; 24.3mg;
 24.4mg; 24.5mg; 24.6mg; 24.7mg; 24.8mg; 24.9mg; 25.0mg; 25.1mg; 25.2mg; 25.3mg;
 5 25.4mg; 25.5mg; 25.6mg; 25.7mg; 25.8mg; 25.9mg; 26.0mg; 26.1mg; 26.2mg; 26.3mg;
 26.4mg; 26.5mg; 26.6mg; 26.7mg; 26.8mg; 26.9mg; 27.0mg; 27.1mg; 27.2mg; 27.3mg;
 27.4mg; 27.5mg; 27.6mg; 27.7mg; 27.8mg; 27.9mg; 28.0mg; 28.1mg; 28.2mg; 28.3mg;
 28.4mg; 28.5mg; 28.6mg; 28.7mg; 28.8mg; 28.9mg; 29.0mg; 29.1mg; 29.2mg; 29.3mg;
 29.4mg; 29.5mg; 29.6mg; 29.7mg; 29.8mg; 29.9mg; 30.0mg; 30.1mg; 30.2mg; 30.3mg;
 10 30.4mg; 30.5mg; 30.6mg; 30.7mg; 30.8mg; 30.9mg; 31.0mg; 31.1mg; 31.2mg; 31.3mg;
 31.4mg; 31.5mg; 31.6mg; 31.7mg; 31.8mg; 31.9mg; 32.0mg; 32.1mg; 32.2mg; 32.3mg;
 32.4mg; 32.5mg; 32.6mg; 32.7mg; 32.8mg; 32.9mg; 33.0mg; 33.1mg; 33.2mg; 33.3mg;
 33.4mg; 33.5mg; 33.6mg; 33.7mg; 33.8mg; 33.9mg; 34.0mg; 34.1mg; 34.2mg; 34.3mg;
 34.4mg; 34.5mg; 34.6mg; 34.7mg; 34.8mg; 34.9mg; 35.0mg; 35.1mg; 35.2mg; 35.3mg;
 15 35.4mg; 35.5mg; 35.6mg; 35.7mg; 35.8mg; 35.9mg; 36.0mg; 36.1mg; 36.2mg; 36.3mg;
 36.4mg; 36.5mg; 36.6mg; 36.7mg; 36.8mg; 36.9mg; 37.0mg; 37.1mg; 37.2mg; 37.3mg;
 37.4mg; 37.5mg; 37.6mg; 37.7mg; 37.8mg; 37.9mg; 38.0mg; 38.1mg; 38.2mg; 38.3mg;
 38.4mg; 38.5mg; 38.6mg; 38.7mg; 38.8mg; 38.9mg; 39.0mg; 39.1mg; 39.2mg; 39.3mg;
 39.4mg; 39.5mg; 39.6mg; 39.7mg; 39.8mg; 39.9mg; 40.0mg; 40.1mg; 40.2mg; 40.3mg;
 20 40.4mg; 40.5mg; 40.6mg; 40.7mg; 40.8mg; 40.9mg; 41.0mg; 41.1mg; 41.2mg; 41.3mg;
 41.4mg; 41.5mg; 41.6mg; 41.7mg; 41.8mg; 41.9mg; 42.0mg; 42.1mg; 42.2mg; 42.3mg;
 42.4mg; 42.5mg; 42.6mg; 42.7mg; 42.8mg; 42.9mg; 43.0mg; 43.1mg; 43.2mg; 43.3mg;
 43.4mg; 43.5mg; 43.6mg; 43.7mg; 43.8mg; 43.9mg; 44.0mg; 44.1mg; 44.2mg; 44.3mg;
 44.4mg; 44.5mg; 44.6mg; 44.7mg; 44.8mg; 44.9mg; 45.0mg; 45.1mg; 45.2mg; 45.3mg;
 25 45.4mg; 45.5mg; 45.6mg; 45.7mg; 45.8mg; 45.9mg; 46.0mg; 46.1mg; 46.2mg; 46.3mg;
 46.4mg; 46.5mg; 46.6mg; 46.7mg; 46.8mg; 46.9mg; 47.0mg; 47.1mg; 47.2mg; 47.3mg;
 47.4mg; 47.5mg; 47.6mg; 47.7mg; 47.8mg; 47.9mg; 48.0mg; 48.1mg; 48.2mg; 48.3mg;
 48.4mg; 48.5mg; 48.6mg; 48.7mg; 48.8mg; 48.9mg; 49.0mg; 49.1mg; 49.2mg; 49.3mg;
 49.4mg; 49.5mg; 49.6mg; 49.7mg; 49.8mg; 49.9mg; and 50.0mg.
- 30 [00455] *Dapagliflozin* - 2.5mg to 30 mg per wafer, including: 2.4mg; 2.5mg; 2.6mg;
 2.7mg; 2.8mg; 2.9mg; 3.0mg; 3.1mg; 3.2mg; 3.3mg;
 3.4mg; 3.5mg; 3.6mg; 3.7mg; 3.8mg; 3.9mg; 4.0mg; 4.1mg; 4.2mg; 4.3mg;
 4.4mg; 4.5mg; 4.6mg; 4.7mg; 4.8mg; 4.9mg; 5.0mg; 5.1mg; 5.2mg; 5.3mg;
 5.4mg; 5.5mg; 5.6mg; 5.7mg; 5.8mg; 5.9mg; 6.0mg; 6.1mg; 6.2mg; 6.3mg;
 35 6.4mg; 6.5mg; 6.6mg; 6.7mg; 6.8mg; 6.9mg; 7.0mg; 7.1mg; 7.2mg; 7.3mg;
 7.4mg; 7.5mg; 7.6mg; 7.7mg; 7.8mg; 7.9mg; 8.0mg; 8.1mg; 8.2mg; 8.3mg;

	8.4mg;	8.5mg;	8.6mg;	8.7mg;	8.8mg;	8.9mg;	9.0mg;	9.1mg;	9.2mg;	9.3mg;
	9.4mg;	9.5mg;	9.6mg;	9.7mg;	9.8mg;	9.9mg;	10.0mg;	10.1mg;	10.2mg;	10.3mg;
	10.4mg;	10.5mg;	10.6mg;	10.7mg;	10.8mg;	10.9mg;	11.0mg;	11.1mg;	11.2mg;	11.3mg;
	11.4mg;	11.5mg;	11.6mg;	11.7mg;	11.8mg;	11.9mg;	12.0mg;	12.1mg;	12.2mg;	12.3mg;
5	12.4mg;	12.5mg;	12.6mg;	12.7mg;	12.8mg;	12.9mg;	13.0mg;	13.1mg;	13.2mg;	13.3mg;
	13.4mg;	13.5mg;	13.6mg;	13.7mg;	13.8mg;	13.9mg;	14.0mg;	14.1mg;	14.2mg;	14.3mg;
	14.4mg;	14.5mg;	14.6mg;	14.7mg;	14.8mg;	14.9mg;	15.0mg;	15.1mg;	15.2mg;	15.3mg;
	15.4mg;	15.5mg;	15.6mg;	15.7mg;	15.8mg;	15.9mg;	16.0mg;	16.1mg;	16.2mg;	16.3mg;
	16.4mg;	16.5mg;	16.6mg;	16.7mg;	16.8mg;	16.9mg;	17.0mg;	17.1mg;	17.2mg;	17.3mg;
10	17.4mg;	17.5mg;	17.6mg;	17.7mg;	17.8mg;	17.9mg;	18.0mg;	18.1mg;	18.2mg;	18.3mg;
	18.4mg;	18.5mg;	18.6mg;	18.7mg;	18.8mg;	18.9mg;	19.0mg;	19.1mg;	19.2mg;	19.3mg;
	19.4mg;	19.5mg;	19.6mg;	19.7mg;	19.8mg;	19.9mg;	20.0mg;	20.1mg;	20.2mg;	20.3mg;
	20.4mg;	20.5mg;	20.6mg;	20.7mg;	20.8mg;	20.9mg;	21.0mg;	21.1mg;	21.2mg;	21.3mg;
	21.4mg;	21.5mg;	21.6mg;	21.7mg;	21.8mg;	21.9mg;	22.0mg;	22.1mg;	22.2mg;	22.3mg;
15	22.4mg;	22.5mg;	22.6mg;	22.7mg;	22.8mg;	22.9mg;	23.0mg;	23.1mg;	23.2mg;	23.3mg;
	23.4mg;	23.5mg;	23.6mg;	23.7mg;	23.8mg;	23.9mg;	24.0mg;	24.1mg;	24.2mg;	24.3mg;
	24.4mg;	24.5mg;	24.6mg;	24.7mg;	24.8mg;	24.9mg;	25.0mg;	25.1mg;	25.2mg;	25.3mg;
	25.4mg;	25.5mg;	25.6mg;	25.7mg;	25.8mg;	25.9mg;	26.0mg;	26.1mg;	26.2mg;	26.3mg;
	26.4mg;	26.5mg;	26.6mg;	26.7mg;	26.8mg;	26.9mg;	27.0mg;	27.1mg;	27.2mg;	27.3mg;
20	27.4mg;	27.5mg;	27.6mg;	27.7mg;	27.8mg;	27.9mg;	28.0mg;	28.1mg;	28.2mg;	28.3mg;
	28.4mg;	28.5mg;	28.6mg;	28.7mg;	28.8mg;	28.9mg;	29.0mg;	29.1mg;	29.2mg;	29.3mg;
	29.4mg;	29.5mg;	29.6mg;	29.7mg;	29.8mg;	29.9mg;	and 30.0mg.			
	[00456] <i>Liraglutide - 2.5mg to 50 mg per wafer, including:</i> 2.4mg; 2.5mg; 2.6mg; 2.7mg;									
	2.8mg;	2.9mg;	3.0mg;	3.1mg;	3.2mg;	3.3mg;				
25	3.4mg;	3.5mg;	3.6mg;	3.7mg;	3.8mg;	3.9mg;	4.0mg;	4.1mg;	4.2mg;	4.3mg;
	4.4mg;	4.5mg;	4.6mg;	4.7mg;	4.8mg;	4.9mg;	5.0mg;	5.1mg;	5.2mg;	5.3mg;
	5.4mg;	5.5mg;	5.6mg;	5.7mg;	5.8mg;	5.9mg;	6.0mg;	6.1mg;	6.2mg;	6.3mg;
	6.4mg;	6.5mg;	6.6mg;	6.7mg;	6.8mg;	6.9mg;	7.0mg;	7.1mg;	7.2mg;	7.3mg;
	7.4mg;	7.5mg;	7.6mg;	7.7mg;	7.8mg;	7.9mg;	8.0mg;	8.1mg;	8.2mg;	8.3mg;
30	8.4mg;	8.5mg;	8.6mg;	8.7mg;	8.8mg;	8.9mg;	9.0mg;	9.1mg;	9.2mg;	9.3mg;
	9.4mg;	9.5mg;	9.6mg;	9.7mg;	9.8mg;	9.9mg;	10.0mg;	10.1mg;	10.2mg;	10.3mg;
	10.4mg;	10.5mg;	10.6mg;	10.7mg;	10.8mg;	10.9mg;	11.0mg;	11.1mg;	11.2mg;	11.3mg;
	11.4mg;	11.5mg;	11.6mg;	11.7mg;	11.8mg;	11.9mg;	12.0mg;	12.1mg;	12.2mg;	12.3mg;
	12.4mg;	12.5mg;	12.6mg;	12.7mg;	12.8mg;	12.9mg;	13.0mg;	13.1mg;	13.2mg;	13.3mg;
35	13.4mg;	13.5mg;	13.6mg;	13.7mg;	13.8mg;	13.9mg;	14.0mg;	14.1mg;	14.2mg;	14.3mg;
	14.4mg;	14.5mg;	14.6mg;	14.7mg;	14.8mg;	14.9mg;	15.0mg;	15.1mg;	15.2mg;	15.3mg;

15.4mg; 15.5mg; 15.6mg; 15.7mg; 15.8mg; 15.9mg; 16.0mg; 16.1mg; 16.2mg; 16.3mg;
16.4mg; 16.5mg; 16.6mg; 16.7mg; 16.8mg; 16.9mg; 17.0mg; 17.1mg; 17.2mg; 17.3mg;
17.4mg; 17.5mg; 17.6mg; 17.7mg; 17.8mg; 17.9mg; 18.0mg; 18.1mg; 18.2mg; 18.3mg;
18.4mg; 18.5mg; 18.6mg; 18.7mg; 18.8mg; 18.9mg; 19.0mg; 19.1mg; 19.2mg; 19.3mg;
5 19.4mg; 19.5mg; 19.6mg; 19.7mg; 19.8mg; 19.9mg; 20.0mg; 20.1mg; 20.2mg; 20.3mg;
20.4mg; 20.5mg; 20.6mg; 20.7mg; 20.8mg; 20.9mg; 21.0mg; 21.1mg; 21.2mg; 21.3mg;
21.4mg; 21.5mg; 21.6mg; 21.7mg; 21.8mg; 21.9mg; 22.0mg; 22.1mg; 22.2mg; 22.3mg;
22.4mg; 22.5mg; 22.6mg; 22.7mg; 22.8mg; 22.9mg; 23.0mg; 23.1mg; 23.2mg; 23.3mg;
23.4mg; 23.5mg; 23.6mg; 23.7mg; 23.8mg; 23.9mg; 24.0mg; 24.1mg; 24.2mg; 24.3mg;
10 24.4mg; 24.5mg; 24.6mg; 24.7mg; 24.8mg; 24.9mg; 25.0mg; 25.1mg; 25.2mg; 25.3mg;
25.4mg; 25.5mg; 25.6mg; 25.7mg; 25.8mg; 25.9mg; 26.0mg; 26.1mg; 26.2mg; 26.3mg;
26.4mg; 26.5mg; 26.6mg; 26.7mg; 26.8mg; 26.9mg; 27.0mg; 27.1mg; 27.2mg; 27.3mg;
27.4mg; 27.5mg; 27.6mg; 27.7mg; 27.8mg; 27.9mg; 28.0mg; 28.1mg; 28.2mg; 28.3mg;
28.4mg; 28.5mg; 28.6mg; 28.7mg; 28.8mg; 28.9mg; 29.0mg; 29.1mg; 29.2mg; 29.3mg;
15 29.4mg; 29.5mg; 29.6mg; 29.7mg; 29.8mg; 29.9mg; 30.0mg; 30.1mg; 30.2mg; 30.3mg;
30.4mg; 30.5mg; 30.6mg; 30.7mg; 30.8mg; 30.9mg; 31.0mg; 31.1mg; 31.2mg; 31.3mg;
31.4mg; 31.5mg; 31.6mg; 31.7mg; 31.8mg; 31.9mg; 32.0mg; 32.1mg; 32.2mg; 32.3mg;
32.4mg; 32.5mg; 32.6mg; 32.7mg; 32.8mg; 32.9mg; 33.0mg; 33.1mg; 33.2mg; 33.3mg;
33.4mg; 33.5mg; 33.6mg; 33.7mg; 33.8mg; 33.9mg; 34.0mg; 34.1mg; 34.2mg; 34.3mg;
20 34.4mg; 34.5mg; 34.6mg; 34.7mg; 34.8mg; 34.9mg; 35.0mg; 35.1mg; 35.2mg; 35.3mg;
35.4mg; 35.5mg; 35.6mg; 35.7mg; 35.8mg; 35.9mg; 36.0mg; 36.1mg; 36.2mg; 36.3mg;
36.4mg; 36.5mg; 36.6mg; 36.7mg; 36.8mg; 36.9mg; 37.0mg; 37.1mg; 37.2mg; 37.3mg;
37.4mg; 37.5mg; 37.6mg; 37.7mg; 37.8mg; 37.9mg; 38.0mg; 38.1mg; 38.2mg; 38.3mg;
38.4mg; 38.5mg; 38.6mg; 38.7mg; 38.8mg; 38.9mg; 39.0mg; 39.1mg; 39.2mg; 39.3mg;
25 39.4mg; 39.5mg; 39.6mg; 39.7mg; 39.8mg; 39.9mg; 40.0mg; 40.1mg; 40.2mg; 40.3mg;
40.4mg; 40.5mg; 40.6mg; 40.7mg; 40.8mg; 40.9mg; 41.0mg; 41.1mg; 41.2mg; 41.3mg;
41.4mg; 41.5mg; 41.6mg; 41.7mg; 41.8mg; 41.9mg; 42.0mg; 42.1mg; 42.2mg; 42.3mg;
42.4mg; 42.5mg; 42.6mg; 42.7mg; 42.8mg; 42.9mg; 43.0mg; 43.1mg; 43.2mg; 43.3mg;
43.4mg; 43.5mg; 43.6mg; 43.7mg; 43.8mg; 43.9mg; 44.0mg; 44.1mg; 44.2mg; 44.3mg;
30 44.4mg; 44.5mg; 44.6mg; 44.7mg; 44.8mg; 44.9mg; 45.0mg; 45.1mg; 45.2mg; 45.3mg;
45.4mg; 45.5mg; 45.6mg; 45.7mg; 45.8mg; 45.9mg; 46.0mg; 46.1mg; 46.2mg; 46.3mg;
46.4mg; 46.5mg; 46.6mg; 46.7mg; 46.8mg; 46.9mg; 47.0mg; 47.1mg; 47.2mg; 47.3mg;
47.4mg; 47.5mg; 47.6mg; 47.7mg; 47.8mg; 47.9mg; 48.0mg; 48.1mg; 48.2mg; 48.3mg;
48.4mg; 48.5mg; 48.6mg; 48.7mg; 48.8mg; 48.9mg; 49.0mg; 49.1mg; 49.2mg; 49.3mg;
35 49.4mg; 49.5mg; 49.6mg; 49.7mg; 49.8mg; 49.9mg; and 50.0mg.

[00457] *Soy lecithin - 0% to 30% including:* 0.1%; 0.2%; 0.3%; 0.4%; 0.5%; 0.6%; 0.7%; 0.8%; 0.9%; 1.0%; 1.1%; 1.2%; 1.3%; 1.4%; 1.5%; 1.6%; 1.7%; 1.8%; 1.9%; 2.0%; 2.1%; 2.2%; 2.3%; 2.4%; 2.5%; 2.6%; 2.7%; 2.8%; 2.9%; 3.0%; 3.1%; 3.2%; 3.3%; 3.4%; 3.5%; 3.6%; 3.7%; 3.8%; 3.9%; 4.0%; 4.1%; 4.2%; 4.3%; 4.4%; 4.5%; 4.6%; 4.7%; 4.8%; 4.9%; 5.0%; 5.1%; 5.2%; 5.3%; 5.4%; 5.5%; 5.6%; 5.7%; 5.8%; 5.9%; 6.0%; 6.1%; 6.2%; 6.3%; 6.4%; 6.5%; 6.6%; 6.7%; 6.8%; 6.9%; 7.0%; 7.1%; 7.2%; 7.3%; 7.4%; 7.5%; 7.6%; 7.7%; 7.8%; 7.9%; 8.0%; 8.1%; 8.2%; 8.3%; 8.4%; 8.5%; 8.6%; 8.7%; 8.8%; 8.9%; 9.0%; 9.1%; 9.2%; 9.3%; 9.4%; 9.5%; 9.6%; 9.7%; 9.8%; 9.9%; 10.0%; 10.1%; 10.2%; 10.3%; 10.4%; 10.5%; 10.6%; 10.7%; 10.8%; 10.9%; 11.0%; 11.1%; 11.2%; 11.3%; 11.4%; 11.5%; 11.6%; 11.7%; 11.8%; 11.9%; 12.0%; 12.1%; 12.2%; 12.3%; 12.4%; 12.5%; 12.6%; 12.7%; 12.8%; 12.9%; 13.0%; 13.1%; 13.2%; 13.3%; 13.4%; 13.5%; 13.6%; 13.7%; 13.8%; 13.9%; 14.0%; 14.1%; 14.2%; 14.3%; 14.4%; 14.5%; 14.6%; 14.7%; 14.8%; 14.9%; 15.0%; 15.1%; 15.2%; 15.3%; 15.4%; 15.5%; 15.6%; 15.7%; 15.8%; 15.9%; 16.0%; 16.1%; 16.2%; 16.3%; 16.4%; 16.5%; 16.6%; 16.7%; 16.8%; 16.9%; 17.0%; 17.1%; 17.2%; 17.3%; 17.4%; 17.5%; 17.6%; 17.7%; 17.8%; 17.9%; 18.0%; 18.1%; 18.2%; 18.3%; 18.4%; 18.5%; 18.6%; 18.7%; 18.8%; 18.9%; 19.0%; 19.1%; 19.2%; 19.3%; 19.4%; 19.5%; 19.6%; 19.7%; 19.8%; 19.9%; and 20.0%; 20.1%; 20.2%; 20.3%; 20.4%; 20.5%; 20.6%; 20.7%; 20.8%; 20.9%; 21.0%; 21.1%; 21.2%; 21.3%; 21.4%; 21.5%; 21.6%; 21.7%; 21.8%; 21.9%; 22.0%; 22.1%; 22.2%; 22.3%; 22.4%; 22.5%; 22.6%; 22.7%; 22.8%; 22.9%; 23.0%; 23.1%; 23.2%; 23.3%; 23.4%; 23.5%; 23.6%; 23.7%; 23.8%; 23.9%; 24.0%; 24.1%; 24.2%; 24.3%; 24.4%; 24.5%; 24.6%; 24.7%; 24.8%; 24.9%; 25.0%; 25.1%; 25.2%; 25.3%; 25.4%; 25.5%; 25.6%; 25.7%; 25.8%; 25.9%; 26.0%; 26.1%; 26.2%; 26.3%; 26.4%; 26.5%; 26.6%; 26.7%; 26.8%; 26.9%; 27.0%; 27.1%; 27.2%; 27.3%; 27.4%; 27.5%; 27.6%; 27.7%; 27.8%; 27.9%; 28.0%; 28.1%; 28.2%; 28.3%; 28.4%; 28.5%; 28.6%; 28.7%; 28.8%; 28.9%; 29.0%; 29.1%; 29.2%; 29.3%; 29.4%; 29.5%; 29.6%; 29.7%; 29.8%; 29.9%; and 30.0%.

[00458] *Sodium deoxycholate - 0.1% to 20%, including:* 0.1%; 0.2%; 0.3%; 0.4%; 0.5%; 0.6%; 0.7%; 0.8%; 0.9%; 1.0%; 1.1%; 1.2%; 1.3%; 1.4%; 1.5%; 1.6%; 1.7%; 1.8%; 1.9%; 2.0%; 2.1%; 2.2%; 2.3%; 2.4%; 2.5%; 2.6%; 2.7%; 2.8%; 2.9%; 3.0%; 3.1%; 3.2%; 3.3%; 3.4%; 3.5%; 3.6%; 3.7%; 3.8%; 3.9%; 4.0%; 4.1%; 4.2%; 4.3%; 4.4%; 4.5%; 4.6%; 4.7%; 4.8%; 4.9%; 5.0%; 5.1%; 5.2%; 5.3%; 5.4%; 5.5%; 5.6%; 5.7%; 5.8%; 5.9%; 6.0%; 6.1%; 6.2%; 6.3%; 6.4%; 6.5%; 6.6%; 6.7%; 6.8%; 6.9%; 7.0%; 7.1%; 7.2%; 7.3%; 7.4%; 7.5%; 7.6%; 7.7%; 7.8%; 7.9%; 8.0%; 8.1%; 8.2%; 8.3%; 8.4%; 8.5%; 8.6%; 8.7%; 8.8%; 8.9%; 9.0%; 9.1%; 9.2%; 9.3%; 9.4%; 9.5%; 9.6%; 9.7%; 9.8%; 9.9%; 10.0%; 10.1%; 10.2%; 10.3%; 10.4%; 10.5%; 10.6%; 10.7%; 10.8%; 10.9%; 11.0%; 11.1%; 11.2%; 11.3%; 11.4%; 11.5%; 11.6%; 11.7%; 11.8%; 11.9%; 12.0%; 12.1%; 12.2%; 12.3%; 12.4%; 12.5%; 12.6%;

12.7%; 12.8%; 12.9%; 13.0%; 13.1%; 13.2%; 13.3%; 13.4%; 13.5%; 13.6%; 13.7%; 13.8%;
13.9%; 14.0%; 14.1%; 14.2%; 14.3%; 14.4%; 14.5%; 14.6%; 14.7%; 14.8%; 14.9%; 15.0%;
15.1%; 15.2%; 15.3%; 15.4%; 15.5%; 15.6%; 15.7%; 15.8%; 15.9%; 16.0%; 16.1%; 16.2%;
16.3%; 16.4%; 16.5%; 16.6%; 16.7%; 16.8%; 16.9%; 17.0%; 17.1%; 17.2%; 17.3%; 17.4%;
5 17.5%; 17.6%; 17.7%; 17.8%; 17.9%; 18.0%; 18.1%; 18.2%; 18.3%; 18.4%; 18.5%; 18.6%;
18.7%; 18.8%; 18.9%; 19.0%; 19.1%; 19.2%; 19.3%; 19.4%; 19.5%; 19.6%; 19.7%; 19.8%;
19.9%; and 20.0%.

[00459] *TPGS (d- α -tocopheryl polyethylene glycol succinate) penetrant/surfactant - 0.1%
to 20%, including:* 0.1%; 0.2%; 0.3%; 0.4%; 0.5%; 0.6%; 0.7%; 0.8%; 0.9%; 1.0%; 1.1%;
10 1.2%; 1.3%; 1.4%; 1.5%; 1.6%; 1.7%; 1.8%; 1.9%; 2.0%; 2.1%; 2.2%; 2.3%; 2.4%; 2.5%;
2.6%; 2.7%; 2.8%; 2.9%; 3.0%; 3.1%; 3.2%; 3.3%; 3.4%; 3.5%; 3.6%; 3.7%; 3.8%; 3.9%;
4.0%; 4.1%; 4.2%; 4.3%; 4.4%; 4.5%; 4.6%; 4.7%; 4.8%; 4.9%; 5.0%; 5.1%; 5.2%; 5.3%;
5.4%; 5.5%; 5.6%; 5.7%; 5.8%; 5.9%; 6.0%; 6.1%; 6.2%; 6.3%; 6.4%; 6.5%; 6.6%; 6.7%;
6.8%; 6.9%; 7.0%; 7.1%; 7.2%; 7.3%; 7.4%; 7.5%; 7.6%; 7.7%; 7.8%; 7.9%; 8.0%; 8.1%;
15 8.2%; 8.3%; 8.4%; 8.5%; 8.6%; 8.7%; 8.8%; 8.9%; 9.0%; 9.1%; 9.2%; 9.3%; 9.4%; 9.5%;
9.6%; 9.7%; 9.8%; 9.9%; 10.0%; 10.1%; 10.2%; 10.3%; 10.4%; 10.5%; 10.6%; 10.7%;
10.8%; 10.9%; 11.0%; 11.1%; 11.2%; 11.3%; 11.4%; 11.5%; 11.6%; 11.7%; 11.8%; 11.9%;
12.0%; 12.1%; 12.2%; 12.3%; 12.4%; 12.5%; 12.6%; 12.7%; 12.8%; 12.9%; 13.0%; 13.1%;
13.2%; 13.3%; 13.4%; 13.5%; 13.6%; 13.7%; 13.8%; 13.9%; 14.0%; 14.1%; 14.2%; 14.3%;
20 14.4%; 14.5%; 14.6%; 14.7%; 14.8%; 14.9%; 15.0%; 15.1%; 15.2%; 15.3%; 15.4%; 15.5%;
15.6%; 15.7%; 15.8%; 15.9%; 16.0%; 16.1%; 16.2%; 16.3%; 16.4%; 16.5%; 16.6%; 16.7%;
16.8%; 16.9%; 17.0%; 17.1%; 17.2%; 17.3%; 17.4%; 17.5%; 17.6%; 17.7%; 17.8%; 17.9%;
18.0%; 18.1%; 18.2%; 18.3%; 18.4%; 18.5%; 18.6%; 18.7%; 18.8%; 18.9%; 19.0%; 19.1%;
19.2%; 19.3%; 19.4%; 19.5%; 19.6%; 19.7%; 19.8%; 19.9%; and 20.0%.

25 [00460] *SNAC - 0.1% to 80% including:* 0.1%; 0.2%; 0.3%; 0.4%; 0.5%; 0.6%; 0.7%;
0.8%; 0.9%; 1.0%; 1.1%; 1.2%; 1.3%; 1.4%; 1.5%; 1.6%; 1.7%; 1.8%; 1.9%; 2.0%; 2.1%;
2.2%; 2.3%; 2.4%; 2.5%; 2.6%; 2.7%; 2.8%; 2.9%; 3.0%; 3.1%; 3.2%; 3.3%; 3.4%; 3.5%;
3.6%; 3.7%; 3.8%; 3.9%; 4.0%; 4.1%; 4.2%; 4.3%; 4.4%; 4.5%; 4.6%; 4.7%; 4.8%; 4.9%;
5.0%; 5.1%; 5.2%; 5.3%; 5.4%; 5.5%; 5.6%; 5.7%; 5.8%; 5.9%; 6.0%; 6.1%; 6.2%; 6.3%;
30 6.4%; 6.5%; 6.6%; 6.7%; 6.8%; 6.9%; 7.0%; 7.1%; 7.2%; 7.3%; 7.4%; 7.5%; 7.6%; 7.7%;
7.8%; 7.9%; 8.0%; 8.1%; 8.2%; 8.3%; 8.4%; 8.5%; 8.6%; 8.7%; 8.8%; 8.9%; 9.0%; 9.1%;
9.2%; 9.3%; 9.4%; 9.5%; 9.6%; 9.7%; 9.8%; 9.9%; 10.0%; 10.1%; 10.2%; 10.3%; 10.4%;
10.5%; 10.6%; 10.7%; 10.8%; 10.9%; 11.0%; 11.1%; 11.2%; 11.3%; 11.4%; 11.5%; 11.6%;
11.7%; 11.8%; 11.9%; 12.0%; 12.1%; 12.2%; 12.3%; 12.4%; 12.5%; 12.6%; 12.7%; 12.8%;
35 12.9%; 13.0%; 13.1%; 13.2%; 13.3%; 13.4%; 13.5%; 13.6%; 13.7%; 13.8%; 13.9%; 14.0%;
14.1%; 14.2%; 14.3%; 14.4%; 14.5%; 14.6%; 14.7%; 14.8%; 14.9%; 15.0%; 15.1%; 15.2%;

	15.3%; 15.4%; 15.5%; 15.6%; 15.7%; 15.8%; 15.9%; 16.0%; 16.1%; 16.2%; 16.3%; 16.4%;
	16.5%; 16.6%; 16.7%; 16.8%; 16.9%; 17.0%; 17.1%; 17.2%; 17.3%; 17.4%; 17.5%; 17.6%;
	17.7%; 17.8%; 17.9%; 18.0%; 18.1%; 18.2%; 18.3%; 18.4%; 18.5%; 18.6%; 18.7%; 18.8%;
	18.9%; 19.0%; 19.1%; 19.2%; 19.3%; 19.4%; 19.5%; 19.6%; 19.7%; 19.8%; 19.9%; 20.0%;
5	20.1%; 20.2%; 20.3%; 20.4%; 20.5%; 20.6%; 20.7%; 20.8%; 20.9%; 21.0%;
	21.1%; 21.2%; 21.3%; 21.4%; 21.5%; 21.6%; 21.7%; 21.8%; 21.9%; 22.0%;
	22.1%; 22.2%; 22.3%; 22.4%; 22.5%; 22.6%; 22.7%; 22.8%; 22.9%; 23.0%;
	23.1%; 23.2%; 23.3%; 23.4%; 23.5%; 23.6%; 23.7%; 23.8%; 23.9%; 24.0%;
	24.1%; 24.2%; 24.3%; 24.4%; 24.5%; 24.6%; 24.7%; 24.8%; 24.9%; 25.0%;
10	25.1%; 25.2%; 25.3%; 25.4%; 25.5%; 25.6%; 25.7%; 25.8%; 25.9%; 26.0%;
	26.1%; 26.2%; 26.3%; 26.4%; 26.5%; 26.6%; 26.7%; 26.8%; 26.9%; 27.0%;
	27.1%; 27.2%; 27.3%; 27.4%; 27.5%; 27.6%; 27.7%; 27.8%; 27.9%; 28.0%;
	28.1%; 28.2%; 28.3%; 28.4%; 28.5%; 28.6%; 28.7%; 28.8%; 28.9%; 29.0%;
	29.1%; 29.2%; 29.3%; 29.4%; 29.5%; 29.6%; 29.7%; 29.8%; 29.9%; 30.0%;
15	30.1%; 30.2%; 30.3%; 30.4%; 30.5%; 30.6%; 30.7%; 30.8%; 30.9%; 31.0%;
	31.1%; 31.2%; 31.3%; 31.4%; 31.5%; 31.6%; 31.7%; 31.8%; 31.9%; 32.0%;
	32.1%; 32.2%; 32.3%; 32.4%; 32.5%; 32.6%; 32.7%; 32.8%; 32.9%; 33.0%;
	33.1%; 33.2%; 33.3%; 33.4%; 33.5%; 33.6%; 33.7%; 33.8%; 33.9%; 34.0%;
	34.1%; 34.2%; 34.3%; 34.4%; 34.5%; 34.6%; 34.7%; 34.8%; 34.9%; 35.0%;
20	35.1%; 35.2%; 35.3%; 35.4%; 35.5%; 35.6%; 35.7%; 35.8%; 35.9%; 36.0%;
	36.1%; 36.2%; 36.3%; 36.4%; 36.5%; 36.6%; 36.7%; 36.8%; 36.9%; 37.0%;
	37.1%; 37.2%; 37.3%; 37.4%; 37.5%; 37.6%; 37.7%; 37.8%; 37.9%; 38.0%;
	38.1%; 38.2%; 38.3%; 38.4%; 38.5%; 38.6%; 38.7%; 38.8%; 38.9%; 39.0%;
	39.1%; 39.2%; 39.3%; 39.4%; 39.5%; 39.6%; 39.7%; 39.8%; 39.9%; 40.0%;
25	40.1%; 40.2%; 40.3%; 40.4%; 40.5%; 40.6%; 40.7%; 40.8%; 40.9%; 41.0%;
	41.1%; 41.2%; 41.3%; 41.4%; 41.5%; 41.6%; 41.7%; 41.8%; 41.9%; 42.0%;
	42.1%; 42.2%; 42.3%; 42.4%; 42.5%; 42.6%; 42.7%; 42.8%; 42.9%; 43.0%;
	43.1%; 43.2%; 43.3%; 43.4%; 43.5%; 43.6%; 43.7%; 43.8%; 43.9%; 44.0%;
	44.1%; 44.2%; 44.3%; 44.4%; 44.5%; 44.6%; 44.7%; 44.8%; 44.9%; 45.0%;
30	45.1%; 45.2%; 45.3%; 45.4%; 45.5%; 45.6%; 45.7%; 45.8%; 45.9%; 46.0%;
	46.1%; 46.2%; 46.3%; 46.4%; 46.5%; 46.6%; 46.7%; 46.8%; 46.9%; 47.0%;
	47.1%; 47.2%; 47.3%; 47.4%; 47.5%; 47.6%; 47.7%; 47.8%; 47.9%; 48.0%;
	48.1%; 48.2%; 48.3%; 48.4%; 48.5%; 48.6%; 48.7%; 48.8%; 48.9%; 49.0%;
	49.1%; 49.2%; 49.3%; 49.4%; 49.5%; 49.6%; 49.7%; 49.8%; 49.9%; 50.0%;
35	50.1%; 50.2%; 50.3%; 50.4%; 50.5%; 50.6%; 50.7%; 50.8%; 50.9%; 51.0%;
	51.1%; 51.2%; 51.3%; 51.4%; 51.5%; 51.6%; 51.7%; 51.8%; 51.9%; 52.0%;
	52.1%; 52.2%; 52.3%; 52.4%; 52.5%; 52.6%; 52.7%; 52.8%; 52.9%; 53.0%;

	53.1%;	53.2%;	53.3%;	53.4%;	53.5%;	53.6%;	53.7%;	53.8%;	53.9%;	54.0%;
	54.1%;	54.2%;	54.3%;	54.4%;	54.5%;	54.6%;	54.7%;	54.8%;	54.9%;	55.0%;
	55.1%;	55.2%;	55.3%;	55.4%;	55.5%;	55.6%;	55.7%;	55.8%;	55.9%;	56.0%;
	56.1%;	56.2%;	56.3%;	56.4%;	56.5%;	56.6%;	56.7%;	56.8%;	56.9%;	57.0%;
5	57.1%;	57.2%;	57.3%;	57.4%;	57.5%;	57.6%;	57.7%;	57.8%;	57.9%;	58.0%;
	58.1%;	58.2%;	58.3%;	58.4%;	58.5%;	58.6%;	58.7%;	58.8%;	58.9%;	59.0%;
	59.1%;	59.2%;	59.3%;	59.4%;	59.5%;	59.6%;	59.7%;	59.8%;	59.9%;	60.0%;
	60.1%;	60.2%;	60.3%;	60.4%;	60.5%;	60.6%;	60.7%;	60.8%;	60.9%;	61.0%;
	61.1%;	61.2%;	61.3%;	61.4%;	61.5%;	61.6%;	61.7%;	61.8%;	61.9%;	62.0%;
10	62.1%;	62.2%;	62.3%;	62.4%;	62.5%;	62.6%;	62.7%;	62.8%;	62.9%;	63.0%;
	63.1%;	63.2%;	63.3%;	63.4%;	63.5%;	63.6%;	63.7%;	63.8%;	63.9%;	64.0%;
	64.1%;	64.2%;	64.3%;	64.4%;	64.5%;	64.6%;	64.7%;	64.8%;	64.9%;	65.0%;
	65.1%;	65.2%;	65.3%;	65.4%;	65.5%;	65.6%;	65.7%;	65.8%;	65.9%;	66.0%;
	66.1%;	66.2%;	66.3%;	66.4%;	66.5%;	66.6%;	66.7%;	66.8%;	66.9%;	67.0%;
15	67.1%;	67.2%;	67.3%;	67.4%;	67.5%;	67.6%;	67.7%;	67.8%;	67.9%;	68.0%;
	68.1%;	68.2%;	68.3%;	68.4%;	68.5%;	68.6%;	68.7%;	68.8%;	68.9%;	69.0%;
	69.1%;	69.2%;	69.3%;	69.4%;	69.5%;	69.6%;	69.7%;	69.8%;	69.9%;	70.0%;
	70.1%;	70.2%;	70.3%;	70.4%;	70.5%;	70.6%;	70.7%;	70.8%;	70.9%;	71.0%;
	71.1%;	71.2%;	71.3%;	71.4%;	71.5%;	71.6%;	71.7%;	71.8%;	71.9%;	72.0%;
20	72.1%;	72.2%;	72.3%;	72.4%;	72.5%;	72.6%;	72.7%;	72.8%;	72.9%;	73.0%;
	73.1%;	73.2%;	73.3%;	73.4%;	73.5%;	73.6%;	73.7%;	73.8%;	73.9%;	74.0%;
	74.1%;	74.2%;	74.3%;	74.4%;	74.5%;	74.6%;	74.7%;	74.8%;	74.9%;	75.0%;
	75.1%;	75.2%;	75.3%;	75.4%;	75.5%;	75.6%;	75.7%;	75.8%;	75.9%;	76.0%;
	76.1%;	76.2%;	76.3%;	76.4%;	76.5%;	76.6%;	76.7%;	76.8%;	76.9%;	77.0%;
25	77.1%;	77.2%;	77.3%;	77.4%;	77.5%;	77.6%;	77.7%;	77.8%;	77.9%;	78.0%;
	78.1%;	78.2%;	78.3%;	78.4%;	78.5%;	78.6%;	78.7%;	78.8%;	78.9%;	79.0%;
	79.1%;	79.2%;	79.3%;	79.4%;	79.5%;	79.6%;	79.7%;	79.8%;	79.9%;	and 80.0%.

CLAIMS

1. A composition wherein said composition comprises at least one biologically active material selected from the group consisting of: a glucagon-like peptide 1 (GLP-1) agonist; and a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist.
5
2. The composition of claim 1, wherein the glucagon-like peptide 1 (GLP-1) agonist is selected from the group consisting of semaglutide; liraglutide; dulaglutide; exenatide; lixisenatide; and a pharmaceutically acceptable salt, analog, homolog or derivative thereof.
- 10 3. The composition of any one of the above claims, wherein the sodium glucose co-transporter-2 (SGLT-2) receptor antagonist is selected from the group consisting of dapagliflozin; empagliflozin; ertugliflozin; canagliflozin; bexagliflozin; and a pharmaceutically acceptable salt, analog, homolog or derivative thereof.
- 15 4. The composition of any one of the above claims, wherein the composition comprises two biologically active materials selected from the group consisting of: a glucagon-like peptide 1 (GLP-1) agonist; and a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist.
5. The composition of any one of the above claims, wherein the composition is a solid dosage form.
- 20 6. The composition of any one of the above claims, wherein the composition is a rapidly disintegrating solid dosage form.
7. The composition of any one of the above claims, wherein the composition is a wafer, tablet or capsule.
- 25 8. The composition of any one of the above claims, wherein the composition is a wafer and is neutral pH protected against the acidic pH and enzymatic degradation in the stomach.
9. The composition of any one of the above claims, wherein the biologically active material is present in the composition at a concentration selected from the group consisting of: 0.01% (w/w); 0.1% (w/w); 1% (w/w); 2% (w/w); 3% (w/w); 4% (w/w); 5% (w/w); 6% (w/w); 7% (w/w); 8% (w/w); 9% (w/w); 10% (w/w); 11% (w/w); 12% (w/w); 13% (w/w); 14% (w/w); 15% (w/w); 16% (w/w); 17% (w/w); 18% (w/w); 19% (w/w); 20% (w/w); 21% (w/w); 22% (w/w); 23% (w/w); 24% (w/w); 25% (w/w); 26% (w/w);
30

- 27% (w/w); 28% (w/w); 29% (w/w); 30% (w/w); 31% (w/w); 32% (w/w); 33% (w/w); 34% (w/w); 35% (w/w); 36% (w/w); 37% (w/w); 38% (w/w); 39% (w/w); 40% (w/w); 41% (w/w); 42% (w/w); 43% (w/w); 44% (w/w); 45% (w/w); 46% (w/w); 47% (w/w); 48% (w/w); 49% (w/w); 50% (w/w); 0.2-95% (w/w); and 2-95% (w/w); 33-65% (w/w); 4-55% (w/w); 5-45% (w/w); 6-35% (w/w); 7-25% (w/w); 8-15% (w/w); and within 2 decimal points of each figure.
- 5
10. The composition of any one of the above claims, wherein the biologically active material is present in the composition at a quantity selected from the group consisting of:
- 10 0.01mg; 0.02mg; 0.03mg; 0.04mg; 0.05mg; 0.06mg; 0.07mg; 0.08mg; 0.09mg; 0.10mg; 0.11mg; 0.12mg; 0.13mg; 0.14mg; 0.15mg; 0.16mg; 0.17mg; 0.18mg; 0.19mg; 0.20mg; 0.21mg; 0.22mg; 0.23mg; 0.24mg; 0.25mg; 0.26mg; 0.27mg; 0.28mg; 0.29mg; 0.30mg; 0.31mg; 0.32mg; 0.33mg; 0.34mg; 0.35mg; 0.36mg; 0.37mg; 0.38mg; 0.39mg; 0.40mg; 0.41mg; 0.42mg; 0.43mg; 0.44mg; 0.45mg; 0.46mg; 0.47mg; 0.48mg; 0.49mg; 0.50mg;
- 15 0.51mg; 0.52mg; 0.53mg; 0.54mg; 0.55mg; 0.56mg; 0.57mg; 0.58mg; 0.59mg; 0.60mg; 0.61mg; 0.62mg; 0.63mg; 0.64mg; 0.65mg; 0.66mg; 0.67mg; 0.68mg; 0.69mg; 0.70mg; 0.71mg; 0.72mg; 0.73mg; 0.74mg; 0.75mg; 0.76mg; 0.77mg; 0.78mg; 0.79mg; 0.80mg; 0.81mg; 0.82mg; 0.83mg; 0.84mg; 0.85mg; 0.86mg; 0.87mg; 0.88mg; 0.89mg; 0.90mg; 0.91mg; 0.92mg; 0.93mg; 0.94mg; 0.95mg;
- 20 0.96mg; 0.97mg; 0.98mg; 0.99mg; 1.00mg; 1mg; 2mg; 3mg; 4mg; 5mg; 6mg; 7mg; 8mg; 9mg; 10mg; 11mg; 12mg; 13mg; 14mg; 15mg; 16mg; 17mg; 18mg; 19mg; 20mg; 21mg; 22mg; 23mg; 24mg; 25mg; 26mg; 27mg; 28mg; 29mg; 30mg; 31mg; 32mg; 33mg; 34mg; 35mg; 36mg; 37mg; 38mg; 39mg; 40mg; 41mg; 42mg; 43mg; 44mg;
- 25 45mg; 46mg; 47mg; 48mg; 49mg; 50mg; 51mg; 52mg; 53mg; 54mg; 55mg; 56mg; 57mg; 58mg; 59mg; 60mg; 61mg; 62mg; 63mg; 64mg; 65mg; 66mg; 67mg; 68mg; 69mg; 70mg; 71mg; 72mg; 73mg; 74mg; 75mg; 76mg; 77mg; 78mg; 79mg; 80mg; 81mg; 82mg; 83mg; 84mg; 85mg; 86mg; 87mg; 88mg; 89mg; 90mg; 91mg; 92mg; 93mg; 94mg; 95mg; 96mg; 97mg; 98mg; 99mg; 100mg; 101mg; 102mg; 103mg;
- 30 104mg; 105mg; 106mg; 107mg; 108mg; 109mg; 110mg; 111mg; 112mg; 113mg; 114mg; 115mg; 116mg; 117mg; 118mg; 119mg; 120mg; 121mg; 122mg; 123mg; 124mg; 125mg; 126mg; 127mg; 128mg; 129mg; 130mg; 131mg; 132mg; 133mg; 134mg; 135mg; 136mg; 137mg; 138mg; 139mg; 140mg; 141mg; 142mg; 143mg; 144mg; 145mg; 146mg; 147mg; 148mg; 149mg; 150mg; 151mg; 152mg; 153mg;
- 35 154mg; 155mg; 156mg; 157mg; 158mg; 159mg; 160mg; 161mg; 162mg; 163mg; 164mg; 165mg; 166mg; 167mg; 168mg; 169mg; 170mg; 171mg; 172mg; 173mg;

- 174mg; 175mg; 176mg; 177mg; 178mg; 179mg; 180mg; 181mg; 182mg; 183mg;
184mg; 185mg; 186mg; 187mg; 188mg; 189mg; 190mg; 191mg; 192mg; 193mg;
194mg; 195mg; 196mg; 197mg; 198mg; 199mg; 200mg; 0.01mg to 1mg; 0.1mg to
1mg; 1 to 200mg; 1 to 100mg; 1 to 50mg; 1 to 25mg; 1 to 15mg; 1 to 10mg; 10 to
5 100mg; 10 to 75mg; 10mg to 50mg; and 10mg to 25mg.
11. The composition of any one of the above claims, wherein the biologically active
material is present in the composition at a quantity selected from the group consisting
of: 0.01mg; 0.1mg; 1mg; 2mg; 5mg; 10mg; 15mg; 20mg; 21mg; 0.25mg to 100mg;
1mg to 25mg; 1 mg to 50 mg; 1 mg to 30mg; 2 to 30mg; 5 mg to 15mg; 10mg to 20mg;
10 and 10 to 50mg.
12. The composition of any one of the above claims, wherein the biologically active
material is present in the composition at a quantity selected from the group consisting
of: semaglutide 15mg; liraglutide 21mg; dulaglutide 10mg; exenatide 2mg; and
lixisenatide 20mg.
- 15 13. The composition of any one of the above claims, wherein the biologically active
material is present in the composition at a quantity selected from the group consisting
of: dapagliflozin 10mg; empagliflozin 25mg; and ertugliflozin 5mg.
14. The composition of any one of the above claims, wherein the composition comprises
one or more agents selected from the group consisting of: an entero-hepatic recycling
20 agent; an absorption agent; a bile salt; a penetrant; a surfactant; an ionic water soluble
post-disintegration viscosity agent; a mucolytic (mucus buster); a mucoadhesive; an
adjuvant; a disintegration viscosity agent; a permeation enhancer; an absorption
enhancer; and a entero-hepatic-biliary recirculation agent.
15. The composition of any one of the above claims, wherein the entero-hepatic recycling
25 agent is selected from the group consisting of: glycodeoxycholate; glycocholate;
taurocholate; glycolithocholate; glycohyocholate; tauroursodeoxycholate;
taurohyodeoxycholate; and salts thereof.
16. The composition of any one of the above claims, wherein the composition comprises a
plurality of entero-hepatic recycling agents.
- 30 17. The composition of any one of the above claims, wherein the entero-hepatic recycling
agent is selected from the group consisting of: sodium glycodeoxycholate; and sodium
deoxycholate.

18. The composition of any one of the above claims, wherein the concentration of the entero-hepatic recycling agent is selected from the group consisting of: 0.01%; 0.5%; 1%; 0.5%-10%; 0.5%; 1%-10%; 1%; 2%; 3%; 4%; 5%; 6%; 7%; 8%; 9%; 10%; and within 2 decimal points of each figure (w/w).
- 5 19. The composition of any one of the above claims, wherein the entero-hepatic recycling agent(s) are bile salts and soy lecithin.
20. The composition of any one of the above claims, wherein the entero-hepatic recycling agent(s) are permeation enhancers.
- 10 21. The composition of any one of the above claims, wherein the entero-hepatic recycling agent(s) open tight junctions in the sublingual/gastro-intestinal mucosa cells.
22. The composition of any one of the above claims, wherein the entero-hepatic recycling agent(s) influence the integrity of tight junctions between epithelial cells and modulate these tight junctions, allowing for an increased in paracellular transport.
- 15 23. The composition of any one of the above claims, wherein the entero-hepatic recycling agent(s) improve/enhance the absorption of lipophilic compounds as they can interact with both lipophilic drugs and the lipids present in cell membranes
24. The composition of any one of the above claims, wherein the entero-hepatic recycling agent(s) and the glucagon-like peptide 1 (GLP-1) agonist form a complex.
- 20 25. The composition of any one of the above claims, wherein the entero-hepatic recycling agent(s) and the glucagon-like peptide 1 (GLP-1) agonist form a complex which has a particle size less than 2000nm.
- 25 26. The composition of any one of the above claims, wherein the entero-hepatic recycling agent(s) and the glucagon-like peptide 1 (GLP-1) agonist form a complex which is absorbed into the blood circulation and metabolised into the active glucagon-like peptide 1 (GLP-1) agonist improving the bioavailability of the glucagon-like peptide 1 (GLP-1) agonist.
- 30 27. The composition of any one of the above claims, wherein the ionic water soluble post-disintegration viscosity agent is selected from the group consisting of: carboxymethyl cellulose; anionic substituted cellulose or starch derivatives, such as salts of carboxymethyl celluloses (CMC), alginate and starch glycolates.
28. The composition of any one of the above claims, wherein the ionic water soluble post-disintegration viscosity agent is carboxymethyl cellulose.

29. The composition of any one of the above claims, wherein the ionic water soluble post-disintegration viscosity agent is at a concentration selected from the group consisting of: 1%; 0.5%-10%; 0.5%; 1%-10%; 1%; 2%; 3%; 4%; 5%; 6%; 7%; 8%; 9%; 10%; and within 2 decimal points of each figure (w/w).
- 5 30. The composition of any one of the above claims, wherein the disintegration viscosity agent is sodium alginate.
31. The composition of any one of the above claims, wherein the disintegration viscosity agent is at a concentration selected from the group consisting of: 1%; 0.5%-10%; 0.5%; 1%-10%; 1%; 2%; 3%; 4%; 5%; 6%; 7%; 8%; 9%; 10%; and within 2 decimal points of each figure (w/w).
- 10 32. The composition of any one of the above claims, wherein the permeation enhancer is SNAC (salcaprozate sodium) or a non-ionic ester alkoxylate (or alkanolic acid ester alkoxylate).
33. The composition of any one of the above claims, wherein the permeation enhancer is SNAC (salcaprozate sodium) and is surfactant-like structurally and has the ability to chaperone poorly-permeable macromolecules across plasma membranes via a transcellular mode of action and helps sublingual absorption of peptides.
- 15 34. The composition of any one of the above claims, wherein the SNAC (salcaprozate sodium) and the glucagon-like peptide 1 (GLP-1) agonist form a complex; or wherein the non-ionic ester alkoxylate (or alkanolic acid ester alkoxylate) and the glucagon-like peptide 1 (GLP-1) form a complex.
- 20 35. The composition of any one of the above claims, wherein the permeation enhancer is at a concentration selected from the group consisting of: 0%; 0.05%-10%; 0.5%; 1%-10%; 1%; 2%; 3%; 4%; 5%; 6%; 7%; 8%; 9%; 10%; 20%, 30%, 40%; and within 2 decimal points of each figure (w/w).
- 25 36. The composition of any one of the above claims, wherein the permeation enhancer is at a quantity selected from the group consisting of: 0mg; 5mg; 10mg; 25mg; 30mg; 0.25mg to 100mg; 1mg to 25mg; 1 mg to 50 mg; 1 mg to 30mg; 2 to 30mg; 5 mg to 15mg; 10mg to 20mg; and 10 to 50mg.
- 30 37. The composition of any one of the above claims, wherein the permeation enhancer protects the glucagon-like peptide 1 (GLP-1) agonist against the effects of pepsin (primary digestive enzymes in the stomach which digest/convert protein and peptides to amino acids).

38. The composition of any one of the above claims, wherein the composition comprises a glucagon-like peptide 1 (GLP-1) agonist-cholate- non-ionic ester alkoxylate (or alkanolic acid ester alkoxylate)s-sodium glucose co-transporter-2 (SGLT-2) receptor antagonist cluster or glucagon-like peptide 1 (GLP-1) agonist-cholate-non-ionic ester alkoxylate (or alkanolic acid ester alkoxylate)-sodium glucose co-transporter-2 (SGLT-2) receptor antagonist cluster.
39. The composition of any one of the above claims, wherein the composition comprises a semaglutide-cholate-SNAC-dapagliflozin cluster or semaglutide-cholate-non-ionic ester alkoxylate (or alkanolic acid ester alkoxylate)-dapagliflozin cluster
40. The composition of any one of the above claims, wherein the composition is formulated to pH 5-8.0 to inhibit pepsin activity.
41. The composition of any one of the above claims, wherein the entero-hepatic-biliary recirculation agent is soy lecithin.
42. The composition of any one of the above claims, wherein the permeation enhancer is SNAC or non-ionic ester alkoxylate (or alkanolic acid ester alkoxylate).
43. The composition of any one of the above claims, wherein the entero-hepatic-biliary recirculation agent is at a concentration selected from the group consisting of: 0.05%-10%; 0.5%; 1%-10%; 1%; 2%; 3%; 4%; 5%; 6%; 7%; 8%; 9%; 10%; 20%, 30%, 40%; and within 2 decimal points of each figure (w/w).
44. The composition of any one of the above claims, wherein the entero-hepatic-biliary recirculation agent is at a quantity selected from the group consisting of: 5mg; 10mg; 25mg; 30mg; 0.25mg to 100mg; 1mg to 25mg; 1 mg to 50 mg; 1 mg to 30mg; 2 to 30mg; 5 mg to 15mg; 10mg to 20mg; and 10 to 50mg.
45. The composition of any one of the above claims, wherein the entero-hepatic-biliary recirculation agent provides absorption enhancement.
46. The composition of any one of the above claims, wherein the entero-hepatic-biliary recirculation agent provides absorption enhancement using factors selected from the group consisting of: a local alteration in the membrane structure and modification of its permeability; bioadhesion to the mucosa surfaces; and the lowering of the mucociliary clearance.

47. The composition of any one of the above claims, wherein the composition comprises a mucoadhesive polymer, with a mucolytic property to break the GI/oro-mucosal mucus layer/barrier for bioactive penetration.
- 5 48. The composition of any one of the above claims, wherein the composition comprises one or more agents selected from the group consisting of; sodium glycodeoxycholate; sodium deoxycholate; carboxymethyl cellulose; sodium alginate; SNAC (salcaprozate sodium); a non-ionic ester alkoxylate (or alkanoic acid ester alkoxylate); and soy lecithin.
- 10 49. The composition of any one of the above claims, wherein the composition comprises one or more biologically active materials and agents selected from Table 1 or Table 2.
50. The composition of any one of the above claims, wherein the composition has a pH selected from the group consisting of: between 5 to 6; between 4 to 7.5; between 6 to 7.5; between 7.0 – 7.5; and between 7.0 – 8.0.
51. The composition of any one of the above claims, wherein the composition is a solid.
- 15 52. The composition of any one of the above claims, wherein the composition is lyophilised.
53. The composition of any one of the above claims, wherein the particles of the composition have a size no greater than 2000 nm.
- 20 54. The composition of any one of the above claims, wherein the particles of the composition have a nanoparticulate size.
55. The composition of any one of the above claims, wherein the composition comprises further pharmaceutically acceptable additives and agents.
56. The composition of any one of the above claims, wherein the composition comprises a pharmaceutically acceptable buffering reagent.
- 25 57. The composition of any one of the above claims, wherein the buffering reagent is selected from the group consisting of: salts of phosphates, carbonates, Tris; preferably combinations of phosphate salts; including sodium carbonate.
- 30 58. The composition of any one of the above claims, wherein the buffering reagent is present at a concentration selected from the group consisting of: 0.1-0.5%; 0.1%; 0.2%; 0.3%; 0.4%; 0.5%; and within 2 decimal points of each figure (w/w).

59. The composition of any one of the above claims, wherein the wafers are buffered with a suitable buffer, most preferably a blend of mono- and di-alkaline salt phosphates, adjusted to afford a pH optimal for the stability of the chosen biological active, generally between 4 and 8.0.
- 5 60. The composition of any one of the above claims, wherein the composition comprises a colouring agent.
61. The composition of any one of the above claims, wherein the composition comprises a flavouring agent.
62. The composition of any one of the above claims, wherein the composition comprises a
10 stability agent.
63. The composition of any one of the above claims, wherein the stability agent is selected from the group consisting of: metal chelators such as EDTA, pharmaceutically acceptable surfactant including polysorbate 80.
64. The composition of any one of the above claims, wherein the composition is a
15 glucagon-like peptide 1 (GLP-1) agonist bile salt-lecithin complex.
65. The composition of any one of the above claims, wherein the composition is a glucagon-like peptide 1 (GLP-1) agonist bile salt-lecithin-SNAC (salcaprozate sodium) complex or glucagon-like peptide 1 (GLP-1) agonist bile salt-lecithin-non-ionic ester alkoxylate (or alkanolic acid ester alkoxylate)- complex
- 20 66. The composition of any one of the above claims, wherein the composition comprises a complex selected from the group consisting of: glucagon-like peptide 1 (GLP-1) agonist - bile salt - lecithin - non-ionic ester alkoxylate (or alkanolic acid ester alkoxylate) complex; glucagon-like peptide 1 (GLP-1) agonist - bile salt - lecithin -
25 SNAC (salcaprozate sodium) complex; glucagon-like peptide 1 (GLP-1) agonist - entero-hepatic recycling agent(s) - non-ionic ester alkoxylate (or alkanolic acid ester alkoxylate) complex; glucagon-like peptide 1 (GLP-1) agonist - SNAC (salcaprozate sodium) complex; glucagon-like peptide 1 (GLP-1) agonist - entero-hepatic recycling agent(s) - SNAC (salcaprozate sodium) complex; a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - bile salt - lecithin - non-ionic ester alkoxylate (or
30 alkanolic acid ester alkoxylate) complex; a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - bile salt - lecithin - SNAC (salcaprozate sodium) complex; a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - entero-hepatic recycling agent(s) - non-ionic ester alkoxylate (or alkanolic acid ester alkoxylate) complex; a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - SNAC

- (salsaprozate sodium) complex; a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - entero-hepatic recycling agent(s) - SNAC (salsaprozate sodium) complex; glucagon-like peptide 1 (GLP-1) agonist - a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - bile salt – lecithin - non-ionic ester alkoxylate (or alkanoic acid ester alkoxylate) complex; glucagon-like peptide 1 (GLP-1) agonist - a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - bile salt – lecithin - SNAC (salsaprozate sodium) complex; glucagon-like peptide 1 (GLP-1) agonist - a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - entero-hepatic recycling agent(s) - non-ionic ester alkoxylate (or alkanoic acid ester alkoxylate) complex; glucagon-like peptide 1 (GLP-1) agonist - a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - SNAC (salsaprozate sodium) complex; and glucagon-like peptide 1 (GLP-1) agonist - a sodium glucose co-transporter-2 (SGLT-2) receptor antagonist - entero-hepatic recycling agent(s) - SNAC (salsaprozate sodium) complex.
67. The composition of any one of the above claims, wherein the composition disintegrates once placed in the oral cavity in a time period selected from the group consisting of: <10s; <20s; <30s; <40s; <50s; <60s; <70s; <80s; <90s; <100s; <110s; <120s (seconds).
68. The composition of any one of the above claims, wherein the composition disintegrates once placed in the oral cavity in a time period selected from the group consisting of: <10s; <20s; <30s; <40s; <50s; <60s; <70s; <80s; <90s; <100s; <110s; <120s; <130s; <140s; <150s; <160s; <170s; <180s; <190s; <200s; <210s; <220s; <230s; <240s; <250s; <260s; <270s; <280s; <290s; <300s; <310s; <320s; <330s; <340s; <350s; <360s; <370s; <380s; <390s; <400s; <410s; <420s; <430s; <440s; <450s; <460s; <470s; <480s; <490s; <500s; <510s; <520s; <530s; <540s; <550s; <560s; <570s; <580s; <590s; <600s; <610s; <620s; <630s; <640s; <650s; <660s; <670s; <680s; <690s; <700s; <710s; <720s; <730s; <740s; <750s; <760s; <770s; <780s; <790s; <800s; <810s; <820s; <830s; <840s; <850s; <860s; <870s; <880s; <890s; <900s; <900s; <930s; <960s; <990s; <1020s; <1050s; <1080s; <1110s; <1140s; <1170s; <1200s; <1230s; <1260s; <1290s; <1320s; <1350s; <1380s; <1410s; <1440s; <1470s; <1500s; <1530s; <1560s; <1590s; <1620s; <1650s; <1680s; <1710s; <1740s; <1770s; <1800s; <1830s; <1860s; <1890s; <1920s; <1950s; <1980s; <2010s; <2040s; <2070s; <2100s; <2130s; <2160s; <2190s; <2220s; <2250s; <2280s; <2310s; <2340s; <2370s; <2400s; <2430s; <2460s; <2490s; <2520s; <2550s; <2580s; <2610s; <2640s; <2670s; <2700s; <2730s; <2760s; <2790s; <2820s; <2850s; <2880s; <2910s; <2940s; <2970s; <3000s; <3030s; <3060s; <3090s; <3120s; <3150s; <3180s; <3210s; <3240s; <3270s; <3300s; <3330s; <3360s; <3390s; <3420s; <3450s; <3480s; <3510s;

<3540s; <3570s; <3600s; <3630s; <3660s; <3690s; <3720s; <3750s; <3780s; <3810s;
<3840s; <3870s; <3900s; <3930s; <3960s; <3990s; <4020s; <4050s; <4080s; <4110s;
<4140s; <4170s; <4200s; and <4230s (seconds).

- 5 69. The composition of any one of the above claims, wherein the composition disintegrates in the oral cavity without leaving a residue of said dosage form in the oral cavity that is detectable by a subject, thereby avoiding the urge for the subject to swallow the composition.
- 10 70. The composition of any one of the above claims, wherein the composition dissolves once placed in the oral cavity in a time period selected from the group consisting of: <10s; <20s; <30s; <40s; <50s; <60s; <70s; <80s; <90s; <100s; <110s; <120s; 180s, preferably 15-60s (seconds).
- 15 71. The composition of any one of the above claims, wherein the composition dissolves once placed in the oral cavity in a time period selected from the group consisting of: <10s; <20s; <30s; <40s; <50s; <60s; <70s; <80s; <90s; <100s; <110s; <120s; <130s; <140s; <150s; <160s; <170s; <180s; <190s; <200s; <210s; <220s; <230s; <240s; <250s; <260s; <270s; <280s; <290s; <300s; <310s; <320s; <330s; <340s; <350s; <360s; <370s; <380s; <390s; <400s; <410s; <420s; <430s; <440s; <450s; <460s; <470s; <480s; <490s; <500s; <510s; <520s; <530s; <540s; <550s; <560s; <570s; <580s; <590s; <600s; <610s; <620s; <630s; <640s; <650s; <660s; <670s; <680s; <690s; <700s; <710s; <720s; <730s; <740s; <750s; <760s; <770s; <780s; <790s; <800s; <810s; <820s; <830s; <840s; <850s; <860s; <870s; <880s; <890s; <900s; <900s; <930s; <960s; <990s; <1020s; <1050s; <1080s; <1110s; <1140s; <1170s; <1200s; <1230s; <1260s; <1290s; <1320s; <1350s; <1380s; <1410s; <1440s; <1470s; <1500s; <1530s; <1560s; <1590s; <1620s; <1650s; <1680s; <1710s; <1740s; <1770s; <1800s; <1830s; <1860s; <1890s; <1920s; <1950s; <1980s; <2010s; <2040s; <2070s; <2100s; <2130s; <2160s; <2190s; <2220s; <2250s; <2280s; <2310s; <2340s; <2370s; <2400s; <2430s; <2460s; <2490s; <2520s; <2550s; <2580s; <2610s; <2640s; <2670s; <2700s; <2730s; <2760s; <2790s; <2820s; <2850s; <2880s; <2910s; <2940s; <2970s; <3000s; <3030s; <3060s; <3090s; <3120s; <3150s; <3180s; <3210s; <3240s; <3270s; <3300s; <3330s; <3360s; <3390s; <3420s; <3450s; <3480s; <3510s; <3540s; <3570s; <3600s; <3630s; <3660s; <3690s; <3720s; <3750s; <3780s; <3810s; <3840s; <3870s; <3900s; <3930s; <3960s; <3990s; <4020s; <4050s; <4080s; <4110s; <4140s; <4170s; <4200s; and <4230s (seconds).
- 20 72. The composition of any one of the above claims, wherein the composition dissolves in the oral cavity without leaving a residue of said dosage form in the oral cavity that is
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detectable by a subject, thereby avoiding the urge for the subject to swallow the composition.

73. The composition of any one of the above claims, wherein water is removed from the combined agents by a freeze-drying process to a residual level of 0-10%, preferably 0-5%, most preferably 3-5%.
74. The composition of any one of the above claims, wherein the composition has a porosity profile selected from the group consisting of: the proportion of water removed by lyophilization is 65-75%; and the proportion of water removed by lyophilization is >60%.
75. The composition of any one of the above claims, wherein the composition has undergoing weight loss selected from the group consisting of: between 0.01% and 0.1%; between 0.01% and 1%; between 0.1% and 1%; between 0.01% and 0.1%; between 1 and 30%; between 5 and 25%; between 8 and 20%; 0.01%; 0.1%; 1%; 2%; 3%; 4%; 5%; 6%; 7%; 8%; 9%; 10%; 11%; 12%; 13%; 14%; 15%; 16%; 17%; 18%; 19%; 20%; 21%; 22%; 23%; 24%; 25%; 26%; 27%; 28%; 29%; 30% and within 2 decimal points of each figure.
76. The composition of any one of the above claims, wherein the composition has a residual moisture content after lyophilisation selected from the group consisting of: between: 0.01 and 20%; between 0.1 and 10%; between 1 and 5%; 0.01%; 0.02%; 0.03%; 0.04%; 0.05%; 0.06%; 0.07%; 0.08%; 0.09%; 0.10%; 0.01%; 0.02%; 0.03%; 0.04%; 0.05%; 0.06%; 0.07%; 0.08%; 0.09%; 0.10%; 1%; 2%; 3%; 4%; 5%; 6%; 7%; 8%; 9%; 10%; 11%; 12%; 13%; 14%; 15%; 16%; 17%; 18%; 19%; 20% and within 2 decimal points of each figure.
77. The composition of any one of the above claims, wherein the composition is stable for a time period selected from the group consisting of: 1 week; 2 weeks; 3 weeks; 4 weeks; 5 weeks; 6 weeks; 7 weeks; 8 weeks; 9 weeks; 10 weeks; 11 weeks; 12 weeks; 13 weeks; 14 weeks; 15 weeks; 16 weeks; 17 weeks; 18 weeks; 19 weeks; 20 weeks; 21 weeks; 22 weeks; 23 weeks; 24 weeks; 25 weeks; 26 weeks; 27 weeks; 28 weeks; 29 weeks; 30 weeks; 31 weeks; 32 weeks; 33 weeks; 34 weeks; 35 weeks; 36 weeks; 37 weeks; 38 weeks; 39 weeks; 40 weeks; 41 weeks; 42 weeks; 43 weeks; 44 weeks; 45 weeks; 46 weeks; 47 weeks; 48 weeks; 49 weeks; 50 weeks; 51 weeks; 52 weeks; 1 month; 2 months; 3 months; 4 months; 5 months; 6 months; 7 months; 8 months; 9 months; 10 months; 11 months; 12 months; 13 months; 14 months; 15 months; 16 months; 17 months; 18 months; 19 months; 20 months; 21 months; 22

- months; 23 months; 24 months; 25 months; 26 months; 27 months; 28 months; 29 months; 30 months; 31 months; 32 months; 33 months; 34 months; 35 months; 36 months; 37 months; 38 months; 39 months; 40 months; 41 months; 42 months; 43 months; 44 months; 45 months; 46 months; 47 months; 48 months; 49 months; 50 months; 51 months; 52 months; 53 months; 54 months; 55 months; 56 months; 57 months; 58 months; 59 months; 60 months; 1 month to 12 months; 12 months to 24 months; 12 months to 36 months; 12 months to 48 months; 1 year to 2 years; 1 year to 3 years; and 1 year to 5 years. The composition of any one of the above claims, wherein the composition is stable as demonstrated by a potency assay run against a reference biological active material.
78. A pharmaceutical composition comprising the composition of any one of claims 1 to 77 together with a pharmaceutical excipient or carrier.
79. A dosage form comprising the composition of any one of claims 1 to 77 .
80. The dosage form of claim 79, wherein the dosage form comprises the biologically active material at a dose selected from the group consisting of: 2mg; 5mg 10mg; 15mg; 20mg; 21mg; 0.25mg to 100mg; 1mg to 25mg; 1 mg to 50 mg; 1 mg to 30mg; 2 to 30mg; 5 mg to 15mg; 10mg to 20mg; and 10 to 50mg.
81. The dosage form of any one of claims 79 to 80, wherein the dosage form comprises the biologically active material at a dose selected from the group consisting of: semaglutide 15mg; liraglutide 21mg; dulaglutide 10mg; exenatide 2mg; and lixisenatide 20mg.
82. The dosage form of any one of claims 79 to 81, wherein the dosage form comprises the biologically active material at a dose selected from the group consisting of: dapagliflozin 10mg; empagliflozin 25mg; and ertugliflozin 5mg.
83. The dosage form of any one of claims 79 to 82, wherein the dosage form is solid.
84. The dosage form of any one of claims 79 to 83, wherein the dosage form is freeze dried.
85. The dosage form of any one of claims 79 to 84, wherein the dosage form is a wafer.
86. A method of treating or preventing or delaying a disease or disorder, said method comprising administering to a patient in need thereof a therapeutically effective amount of the dosage form of claims 79 to 85.

87. The method of claim 86, wherein the disease or disorder is selected from the group consisting of: appetite suppression; weight loss; weight management; obesity; type 2 diabetes, regulate blood sugar; lower the risk of heart attack, stroke, or death in patients with type 2 diabetes and heart or blood vessel disease; cardiovascular disease; Alzheimer's disease; nonalcoholic steatohepatitis (NASH).
88. The method of any one of claims 86 to 87, wherein the dosage form is administered to deliver a therapeutic effective amount of the biological active material.
89. The method of any one of claims 86 to 88, wherein the therapeutically effective amount is administered to the subject utilising a dosing regimen selected from the group consisting of: twice hourly; hourly; once every six hours; once every 8 hours; once every 12 hours; once daily; twice weekly; once weekly; once every 2 weeks; once every 6 weeks; once a month; once every 2 months; once every 3 months; once every 4 months; once every 5 months; once every 6 months; once yearly; and once.
90. The method of any one of claims 86 to 89, wherein the dosage form delivers a therapeutic effective amount of the biologically active material.
91. The method of any one of claims 86 to 90, wherein the therapeutically effective amount is an amount of biologically active material selected from the group consisting of: between 0.001 to 100mg/kg; between 2 and 50mg/kg; between 5 and 40mg/kg; between 10 and 30mg/kg; between 20 and 25mg/kg; and 20mg/kg/day.
92. The method of any one of claims 86 to 91, wherein the therapeutically effective amount is an amount of biologically active material selected from the group consisting of: 2mg; 5mg 10mg; 15mg; 20mg; 21mg; 0.25mg to 100mg; 1mg to 25mg; 1 mg to 50 mg; 1 mg to 30mg; 2 to 30mg; 5 mg to 15mg; 10mg to 20mg; 10 to 50mg per dosage event.
93. The method of any one of claims 86 to 92, wherein the therapeutically effective amount is an amount of biologically active material selected from the group consisting of: 2mg; 5mg 10mg; 15mg; 20mg; 21mg; 0.25mg to 100mg; 1mg to 25mg; 1 mg to 50 mg; 1 mg to 30mg; 2 to 30mg; 5 mg to 15mg; 10mg to 20mg; 10 to 50mg per day.
94. The method of any one of claims 86 to 93, wherein the therapeutically effective amount is administered to the subject using a method selected from the group consisting of: orally; sublingually; buccally.

95. The method of any one of claims 86 to 94, wherein the therapeutically effective amount is administered to the subject using a method selected from the group consisting of: beneath the tongue or buccally.
- 5 96. The method of any one of claims 86 to 95, wherein detectable levels of the biologically active material enters the circulation system.
- 10 97. The method of any one of claims 86 to 96, wherein the detectable levels of the biologically active material that enters the circulation system is selected from the group consisting of: less than 0.001%; less than 0.01%; less than 0.1%; less than 2%; less than 3%; less than 4%; less than 5%; less than 6%; less than 7%; less than 8%; less than 9%; less than 10%; less than 11%; less than 12%; less than 13%; less than 14%; less than 15%; less than 16%; less than 17%; less than 18%; less than 19%; less than 20%; less than 21%; less than 22%; less than 23%; less than 24%; less than 25%; less than 26%; less than 27%; less than 28%; less than 29%; less than 30%; less than 31%; less than 32%; less than 33%; less than 34%; less than 35%; less than 36%; less than 37%; less than 38%; less than 39%; less than 40%; less than 41%; less than 42%; less than 43%; less than 44%; less than 45%; less than 46%; less than 47%; less than 48%; less than 49%; less than 50%; less than 51%; less than 52%; less than 53%; less than 54%; less than 55%; less than 56%; less than 57%; less than 58%; less than 59%; less than 60%; less than 61%; less than 62%; less than 63%; less than 64%; less than 65%; less than 66%; less than 67%; less than 68%; less than 69%; less than 70%; less than 71%; less than 72%; less than 73%; less than 74%; and less than 75% (w/w%).
- 15 20 25 98. The method of any one of claims 86 to 97, wherein said biologically active material is absorbed by diffusion directly into the systemic circulation.
99. The method of any one of claims 86 to 98, wherein said biologically active material is sublingually absorbed rapidly.
100. The method of any one of claims 86 to 99, wherein the drug form is delivered sublingually and more suitable for patients phobic to subcutaneous injection.
- 30 101. The method of any one of claims 86 to 100, wherein the sublingual administered glucagon-like peptide 1 (GLP-1) agonist has multiple sites action, that is, initial rapid sublingual absorption, then, those glucagon-like peptide 1 (GLP-1) agonists not absorbed sublingually is swallowed into the stomach which then undergo stomach absorption and finally reaching the small intestine which then react locally in the intestinal and colon mucosa L-cells (enteroendocrine cells which produce and release

hormones such as glucagon-like peptide-1 (GLP-1) and peptide YY (PYY)), a local intrinsic reaction for immediate satiety effect.

- 5 102. The method of any one of claims 86 to 101, wherein the released GLP-1 stimulates pancreatic insulin, which helps regulate blood sugar levels and also inhibit glucagon secretion, slowing down gastric emptying, and promote a feeling of satiety or fullness (appetite suppression).
103. The method of any one of claims 86 to 102, wherein the released PYY hormone produced by L-cells helps to reduce appetite, slow down gut motility, and modulate the absorption of nutrients from the intestines.
- 10 104. The method of any one of claims 86 to 103, wherein the glucagon-like peptide 1 (GLP-1) agonist -bile salt-lecithin complex undergoes absorption in the small intestine and the absorbed complex undergoes liver first-pass metabolism and the free glucagon-like peptide 1 (GLP-1) agonist secretes back into the small intestine (entero-hepatic recirculation) actively attached onto the L-cells again releasing GLP-1 and PYY
15 resulting in their pharmacological satiety effect, and wherein the parenteral administered semaglutide only has a systemic effect with minimal or no local intestinal/colon mucosa effect.
105. The method of any one of claims 86 to 104, wherein currently oral semaglutide has very low oral bioavailability (0.8 to 1.4%) and may need up to 50 mg per dose to be
20 effective, yet this sublingual semaglutide uses 3 times (15mg versus 50mg) less semaglutide due to its multiple sites of action.
106. The method of any one of claims 86 to 105, wherein there is a correlation between semaglutide tablet erosion and semaglutide plasma exposure and wherein full tablet erosion at 1 hour resulted in very low plasma exposure of semaglutide, whereas less
25 than 54 % tablet erosion resulted in high plasma exposure of semaglutide, hence the mandatory criteria of using less than 120mL of water during oral administration and wherein there is no problem with sublingual administration (no water needed for disintegration, fully disintegrated with saliva).
107. The method of any one of claims 86 to 106, wherein the $t_{1/2}$ of the administered glucagon-like peptide 1 (GLP-1) agonist is selected from the group consisting of:
30 between 15 and 20 min; between 20 and 25 min; between 25 and 30 min; between 30 and 35 min; between 35 and 40 min; between 40 and 45 min; between 45 and 50 min; between 30 and 60 min; between 1 and 2 hrs; between 2 and 3 hrs; between 3 and 4 hrs; between 4 and 5 hrs; between 5 and 6 hrs; between 6 and 12 hrs; between 12

- and 24 hrs; between 1 and 2 days; between 2 and 3 days; between 3 and 4 days; between 4 and 5 days; between 5 and 6 days; between 6 and 7 days; between 6 and 7 days; between 1 and 2 weeks; between 2 and 3 weeks; between 3 and 4 weeks; between 1 and 2 months; between 2 and 3 months; between 3 and 4 months; between 4 and 5 months; between 5 and 6 months; between 6 and 12 months; and between 1 and 2 years.
- 5 108. The method of any one of claims 86 to 107, wherein the $t_{1/2}$ of the administered glucagon-like peptide 1 (GLP-1) agonist is selected from the group consisting of: between 30 and 40 min.
- 10 109. The method of any one of claims 86 to 108, wherein the $t_{1/2}$ of the administered glucagon-like peptide 1 (GLP-1) agonist is selected from the group consisting of: 33 min; 34 min; 35 min; 36 min; 38 min; between 30 and 40 min.
- 15 110. The method of any one of claims 86 to 109, wherein the $t_{1/2}$ of the administered semaglutide is selected from the group consisting of: 33 min; 34 min; 35 min; 36 min; 38 min; between 30 and 40 min.
111. A method of appetite suppression, weight loss and/or weight management, said method comprising administering to a patient in need thereof a therapeutically effective amount of the dosage form of claims 79 to 85.
- 20 112. Use of the composition of claims 1 to 77 in the manufacture of a medicament for the treatment or prevention of a disease or disorder.
113. A process of preparing the composition of claims 1 to 77, said process comprising the steps of: (1) combining at least one matrix forming agent with a biological active material to form a mixture; and (2) freeze drying the mixture to form the solid dosage form.
- 25 114. A kit comprising the dosage form of claims 79 to 85 together with instructions for its use.
- 30 115. The kit of claim 114, wherein the kit is directed to treating or preventing a disease or disorder selected from the group consisting of: appetite suppression; weight loss; weight management; obesity; type 2 diabetes, regulate blood sugar; lower the risk of heart attack, stroke, or death in patients with type 2 diabetes and heart or blood vessel disease; cardiovascular disease; Alzheimer's disease; nonalcoholic steatohepatitis (NASH).