(19) DANMARK

(10) **DK/EP 3326620 T3**

Patent- og Varemærkestyrelsen

(12) Oversættelse af europæisk patentskrift

(51) Int.Cl.: ***A 61 K 9/20 (2006.01)*** ***A 61 K 31/195 (2006.01)*** ***A 61 K 38/26 (2006.01)*** ***A 61 P 3/04 (2006.01)*** ***A 61 P 3/10 (2006.01)***

(45) Oversættelsen bekendtgjort den: **2020-05-25**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2020-03-04**

(86) Europæisk ansøgning nr.: **17204363.0**

(86) Europæisk indleveringsdag: **2011-12-16**

(87) Den europæiske ansøgnings publiceringsdag: **2018-05-30**

(30) Prioritet: **2010-12-16 EP 10195285** **2010-12-20 US 201061425087 P**

(62) Stamansøgningsnr: **11805824.7**

(84) Designerede stater: **AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR**

(73) Patenthaver: **Novo Nordisk A/S, Novo Allé, 2880 Bagsværd, Danmark**

(72) Opfinder: **BJERREGAARD, Simon, Novo Nordisk A/S, Novo Allé, 2880 Bagsværd, Danmark**
SAUERBERG, Per, Novo Nordisk A/S, Novo Allé, 2880 Bagsværd, Danmark
Seier, NIELSEN, Flemming, Novo Nordisk A/S, Novo Allé, 2880 Bagsværd, Danmark

(74) Fuldmægtig i Danmark: **Plougmann Vingtoft A/S, Strandvejen 70, 2900 Hellerup, Danmark**

(54) Benævnelse: **FASTE SAMMENSÆTNINGER OMFATTENDE EN GLP-1-AGONIST OG ET SALT AF N-(8-(2-HYDROXYBENZOYL)AMINO)CAPRYLSYRE**

(56) Fremdragne publikationer:
WO-A1-2010/020978
WO-A2-2010/092163
US-A1- 2005 148 497
BEGLINGER C ET AL: "Pharmacokinetics and Pharmacodynamic Effects of Oral GLP-1 and PYY3-36: A Proof-of-concept Study in Healthy Subjects", CLINICAL PHARMACOLOGY AND THERAPEUTICS, NATURE PUBLISHING GROUP, US, vol. 84, no. 4, 1 October 2008 (2008-10-01), pages 468-474, XP008149454, ISSN: 0009-9236, DOI: 10.1038/CLPT.2008.35 [retrieved on 2008-03-26]

Description

FIELD OF THE INVENTION

[0001] The present invention relates to solid compositions comprising a GLP-1 agonist and a salt of N-(8-(2-hydroxybenzoyl)amino)caprylic acid and their use in medicine.

BACKGROUND OF THE INVENTION

[0002] Human GLP-1 and analogues thereof have a low oral bioavailability. Exposure and bioavailability of human GLP-1 and analogues thereof is very low following oral administration. Human GLP-1 and analogues thereof can only be detected in plasma after oral administration if formulated with certain absorption enhancers in a specific amount. Steinert et al. (Am J Clin Nutr, Oct 2010; 92: 810 - 817) and Beglinger et al. (Clinical Pharmacology and therapeutics, Vol 84, no. 4, Oct 2008, p. 468-474) discloses oral administration of a tablet comprising GLP-1(7-36)amide and 150 and 200 mg sodium N-(8-(2-hydroxybenzoyl)amino)caprylate (SNAC), respectively. WO 2010/020978 dicloses an oral pharmaceutical composition comprising a protein and N-(8-[2-hydroxybenzoyl)amino)caprylate (SNAC). US2005/0148497 discloses oral pharmaceutical compositions comprising a GLP-1 compound and a different delivery agent. WO 2010/092163 describes an oral composition comprising DPP-4 inhibitor and optionally a further anti-diabetic agent.

[0003] There is still a need for an optimized pharmaceutical composition for oral administration of a GLP-1 agonist such as a GLP-1 agonist comprising a substituent.

SUMMARY OF THE INVENTION

[0004] The invention relates to a solid composition for oral administration comprising a GLP-1 agonist and a salt of N-(8-(2-hydroxybenzoyl)amino) caprylic acid, wherein said composition comprises at least 60 % of said salt of N-(8-(2-hydroxybenzoyl)amino) caprylic acid and wherein said GLP-1 agonist is semaglutide. In some embodiments the invention relates to a composition as defined herein for use in medicine.

DESCRIPTION OF THE INVENTION

[0005] The present invention relates to solid compositions of a GLP-1 agonist and salt of N-(8-(2-hydroxybenzoyl) amino)caprylic acid. Surprisingly, the present inventors have found that solid compositions comprising certain amounts of a salt of N-(8-(2-hydroxybenzoyl)amino)caprylic acid, such as SNAC, are optimal for oral administration of the GLP-1 agonist semaglutide. Accordingly, the compositions provide improved exposure and/or bioavailability of the GLP-1 agonist.

[0006] Generally, the term "bioavailability" as used herein refers to the fraction of an administered dose of an active pharmaceutical ingredient (API), such as a GLP-1 agonist as defined herein, which reaches the systemic circulation unchanged. By definition, when an API is administered intravenously, its bioavailability is 100%. However, when it is administered via other routes (such as orally), its bioavailability decreases (due to incomplete absorption and first-pass metabolism). Knowledge about bioavailability is important when calculating dosages for non-intravenous routes of administration.

[0007] Absolute oral bioavailability is calculated as the relative exposure of the API in systemic circulation following oral administration (estimated as the area under the plasma concentration versus time curve, or AUC) compared to the exposure of the API following intravenous administration.

GLP-1 agonist

[0008] The term "GLP-1 agonist" as used herein refers to a compound, which fully or partially activates the human GLP-1 receptor. The "GLP-1 agonist" can bind to a GLP-1 receptor, e.g., with an affinity constant (K_D) or activate the receptor with a potency (EC_{50}) of below 1 μM, e.g. below 100 nM as measured by methods known in the art (see e.g. WO 98/08871) and exhibits insulinotropic activity, where insulinotropic activity may be measured *in vivo* or *in vitro* assays known to those of ordinary skill in the art. For example, the GLP-1 agonist may be administered to an animal with increased blood glucose (e.g. obtained using an Intravenous Glucose Tolerance Test (IVGTT), a person skilled in the art will be able to determine a suitable glucose dosage and a suitable blood sampling regime, e.g. depending on the species of the animal, for the IVGTT) and the plasma insulin concentration measured over time.

[0009] A GLP-1 agonist can be a GLP-1 analogue, optionally comprising one substituent. The term "analogue" as used herein referring to a GLP-1 peptide (hereafter "peptide") means a peptide wherein at least one amino acid residue of the peptide has been substituted with another amino acid residue and/or wherein at least one amino acid residue has

been deleted from the peptide and/or wherein at least one amino acid residue has been added to the peptide and/or wherein at least one amino acid residue of the peptide has been modified. Such addition or deletion of amino acid residues may take place at the N-terminal of the peptide and/or at the C-terminal of the peptide. A simple nomenclature is used to describe the GLP-1 agonist, e.g., [Aib8] GLP-1(7-37) designates an analogue of GLP-1(7-37) wherein the naturally occurring Ala in position 8 has been substituted with Aib. The GLP-1 agonist can comprise a maximum of twelve, such as a maximum of 10, 8 or 6, amino acids which have been alterered, e.g., by substitution, deletion, insertion and/or modification, compared to e.g. GLP-1(7-37). The analogue can comprise up to 10 substitutions, deletions, additions and/or insertions, such as up to 9 substitutions, deletions, additions and/or insertions, up to 8 substitutions, deletions, additions and/or insertions, up to 7 substitutions, deletions, additions and/or insertions, up to 6 substitutions, deletions, additions and/or insertions, up to 5 substitutions, deletions, additions and/or insertions, up to 4 substitutions, deletions, additions and/or insertions or up to 3 substitutions, deletions, additions and/or insertions, compared to e.g. GLP-1(7-37) . Unless otherwise stated the GLP-1 comprises only L-amino acids.

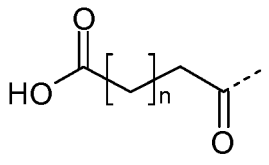
[0010] The term "GLP-1 analogue" or "analogue of GLP-1" as used herein refers to a peptide, or a compound, which is a variant of the human Glucagon-Like Peptide-1 (GLP-1(7-37)). GLP-1(7-37) has the sequence HAEGTFTSDV SSYLEGQAAKEFIAWLVKGRG (SEQ ID No: 1). The term "variant" refers to a compound which comprises one or more amino acid substitutions, deletions, additions and/or insertions.

[0011] The GLP-1 agonist can exhibit at least 60%, 65%, 70%, 80% or 90% sequence identity to GLP-1(7-37) over the entire length of GLP-1(7-37). As an example of a method for determination of sequence identity between two analogues the two peptides [Aib8]GLP-1(7-37) and GLP-1(7-37) are aligned. The sequence identity of [Aib8]GLP-1(7-37) relative to GLP-1(7-37) is given by the number of aligned identical residues minus the number of different residues divided by the total number of residues in GLP-1(7-37). Accordingly, in said example the sequence identity is (31-1)/31.

[0012] The C-terminal of the GLP-1 agonist can be an amide.

[0013] The GLP-1 agonist can be GLP-1(7-37) or GLP-1(7-36)amide. The GLP-1 agonist can be exendin-4, the sequence of which is HGEGTFITSDLSKQMEEEAVRLFIEWLK-NGGPSSGAPPPS (SEQ ID No: 2).

[0014] The GLP-1 agonist can comprise one substituent which is covalently attached to the peptide. The substituent can comprise a fatty acid or a fatty diacid. The substituent can comprise a C16, C18 or C20 fatty acid. The substituent can comprise a C16, C18 or C20 fatty diacid. The substituent can comprise formula (X)



(X),

wherein n is at least 13, such as n is 13, 14, 15, 16, 17, 18 or 19. The substituent can comprise formula (X), wherein n is in the range of 13 to 19, such as in the range of 13 to 17. The substituent can comprise formula (X), wherein n is 13, 15 or 17. The substituent comprises formula (X), wherein n is 13. The substituent can comprise formula (X), wherein n is 15. The substituent can comprise formula (X), wherein n is 17. The substituent can comprise one or more 8-amino-3,6-dioxaoctanoic acid (OEG), such as two OEG.

[0015] The substituent can be [2-(2-{2-[2-(2-{2-[(S)-4-carboxy-4-(17-carboxyheptadecanoylamino) butyrylamino]ethoxy}ethoxy)acetylamino] ethoxy}ethoxy)acetyl].

[0016] The substituent can be [2-(2-{2-[2-(2-{2-[(S)-4-carboxy-4-({trans-4-[(19-carboxynonadecanoylamino)methyl]cyclohexanecarbonyl} amino)butyrylamino]ethoxy}ethoxy)acetylamino]ethoxy}ethoxy)acetyl].

[0017] In the invention the GLP-1 agonist is semaglutide, also known as *N*-epsilon26-[2-(2-{2-[2-(2-{2-[(S)-4-carboxy-4-(17-carboxyheptadecanoylamino) butyrylamino]ethoxy}ethoxy)acetylamino]ethoxy}ethoxy)acetyl][Aib8,Arg34]GLP-1(7-37), which may be prepared as described in WO2006/097537, Example 4.

[0018] The composition may comprise the GLP-1 agonist or a pharmaceutically acceptable salt, amide, or ester thereof. The composition may comprise the GLP-1 agonist one or more pharmaceutically acceptable counter ions.

[0019] The dosage of GLP-1 may be in the range of 0.01 mg to 100 mg. The composition may comprise an amount of a GLP-1 agonist in the range of 0.1 to 40 mg or 1 to 20 mg. The composition may comprise an amount of a GLP-1 agonist in the range of 5 to 20 mg, such as in the range of 5 to 15 mg, such as 5 mg, such as 10 mg, such as 15 mg, such as 20 mg.

[0020] The composition may comprise an amount of a GLP-1 agonist in the range of 0.05 to 25 μmol, such as in the range of 0.5 to 2.5 μmol.

[0021] More GLP-1 agonist are mentioned in WO93/19175, WO96/29342, WO98/08871, WO99/43707, WO99/43706, WO99/43341, WO99/43708, WO2005/027978, WO2005/058954, WO2005/058958, WO2006/005667, WO2006/037810, WO2006/037811, WO2006/097537, WO2006/097538, WO2008/023050, WO2009/030738,

WO2009/030771 and WO2009/030774.

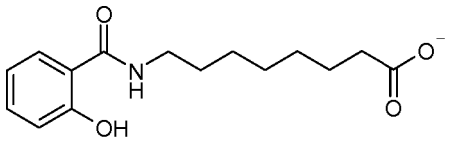
[0022] Other GLP-1 agonists are N-epsilon37{2-[2-(2-{2-[2-((R)-3-carboxy-3-{[1-(19-carboxynonadecanoyl) piperidine-4-carbonyl]amino}propionylamino)ethoxy]ethoxy}acetylamino)ethoxy]ethoxy}acetyl [desaminoHis7,Glu22,Arg26, Arg34,Lys37]GLP-1(7-37)amide; N-epsilon26{2-[2-(2-{2-[2-((R)-3-carboxy-3-{[1-(19-carboxynonadecanoyl)piperidine-4-carbonyl]amino}propionylamino)ethoxy]ethoxy}acetylamino)ethoxy]ethoxy}acetyl [desaminoHis7, Arg34] GLP-1-(7-37); N-epsilon37{2-[2-(2-{2-[2-((S)-3-carboxy-3-{[1-(19-carboxynonadecanoyl)piperidine-4-carbonyl]amino}propionylamino)ethoxy]ethoxy}acetylamino)ethoxy]ethoxy}acetyl[Aib8,Glu22,Arg26,Arg34,Lys37]GLP-1-(7-37)amide; N-epsilon37-[2-(2-[2-(2-[2-(2-((R)-3-[1-(17-carboxyheptadecanoyl)piperidin-4-ylcarbonylamino]3-carboxypropionylamino) ethoxy)ethoxy]acetylamino)ethoxy] ethoxy)acetyl][,DesaminoHis7, Glu22 Arg26, Arg 34, Phe(m-CF3)28]GLP-1-(7-37) amide; N-epsilon26-[(S)-4-carboxy-4-({trans-4-[(19-carboxynonadecanoylamino)methyl]cyclohexanecarbonyl}amino) butyryl][Aib8,Arg34]GLP-1-(7-37); N-epsilon26-{4-[(S)-4-carboxy-4-({trans-4-[(19-carboxynonadecanoylamino)methyl]cyclohexanecarbonyl} amino)butyrylamino]butyryl}[Aib8,Arg34]GLP-1-(7-37); N-epsilon26-[2-(2-{2-[(S)-4-carboxy-4-({trans-4-[(19-carboxynonadecanoylamino)methyl]cyclohexanecarbonyl}amino)butyrylamino]ethoxy}ethoxy) acetyl][Aib8,Arg34]GLP-1-(7-37); N-epsilon26-[2-(2-{2-[2-(2-{2-[(S)-4-carboxy-4-({trans-4-[(19-carboxy-nonadecanoylamino)methyl] cyclohexanecarbonyl}amino)butyrylamino]ethoxy}ethoxy)acetylamino]ethoxy}ethoxy) acetyl][Aib8,Arg34]GLP-1-(7-37)amide; N-epsilon37-[2-(2-{2-[2-(2-{2-[(S)-4-carboxy-4-({trans-4-[(19-carboxy-nonadecanoylamino)methyl]cyclohexanecarbonyl}amino)butyrylamino]ethoxy}ethoxy)acetylamino]ethoxy}ethoxy)acetyl][Aib8, Glu22,Arg26, Arg34,Lys37]GLP-1-(7-37)amide; N-epsilon37-[2-(2-{2-[2-(2-{2-[(S)-4-carboxy-4-({trans-4-[(19-carboxy-nonadecanoylamino)methyl]cyclohexanecarbonyl}amino)butyrylamino]ethoxy}ethoxy)acetylamino]ethoxy}ethoxy) acetyl][DesaminoHis7,Glu22, Arg26,Arg34,Lys37]GLP-1-(7-37)amide; N-epsilon37-[2-(2-{2-[2-(2-{2-[(S)-4-carboxy-4-({4-[(trans-19-carboxy-nonadecanoylamino)methyl]cyclohexanecarbonyl}amino) butyrylamino]ethoxy}ethoxy) acetylamino]ethoxy}ethoxy)acetyl][DesaminoHis7,Arg26,Arg34,Lys37]GLP-1-(7-37)amide; N-epsilon37-[2-(2-{2-[2-(2-{2-[(S)-4-carboxy-4-({trans-4-[(19-carboxy-nonadecanoylamino)methyl]cyclohexanecarbonyl}amino) butyrylamino]ethoxy}ethoxy)acetylamino]ethoxy}ethoxy)acetyl][DesaminoHis7,Glu22,Arg26,Arg 34, Lys37]GLP-1-(7-37); N-epsilon26[2-(2-{2-[2-(2-{2-[(S)-4-carboxy-4-({4-[(19-carboxy-nonadecanoylamino)methyl]cyclohexanecarbonyl}amino)butyrylamino] ethoxy}ethoxy) acetylamino]ethoxy}ethoxy)acetyl[Aib8, Lys 26]GLP-1 (7-37) amide; N-epsilon26 [2-(2-[2-(2-[2-(2-((S)-2-[trans-4-((9-carboxynonadecanoylamino]methyl) cyclohexylcarbonylamino]-4-carboxybutanoylamino)ethoxy)ethoxy]acetylamino) ethoxy]ethoxy)acetyl][Aib8, Lys26] GLP-1 (7-37)amide; N-epsilon37-[2-(2-{2-[2-(2-{2-[(S)-4-carboxy-4-({trans-4-[(19-carboxy-nonadecanoylamino)methyl]cyclohexanecarbonyl}amino)butyrylamino]ethoxy}ethoxy)acetylamino]ethoxy}ethoxy)acetyl] [DesaminoHis7,Arg26,Arg34,Lys37]GLP-1-(7-37); N-epsilon37-[2-(2-{2-[2-(2-{2-[(S)-4-carboxy-4-({trans-4-[(19-carboxy-nonadecanoylamino)methyl]cyclohexanecarbonyl}amino)butyrylamino]ethoxy}ethoxy)acetylamino]ethoxy}ethoxy)acetyl][DesaminoHis7,Glu2 2,Arg26, Glu30,Arg34,Lys37]GLP-1-(7-37); N-epsilon26-[2-(2-{2-[(S)-4-carboxy-4-((S)-4-carboxy-4-{4-[4-(16-(1H-tetrazol-5-yl) -hexadecanoylsulfamoyl)butyrylamino]-butyrylamino}butyrylamino)butyrylamino]ethoxy}ethoxy)acetyl][Aib8, Arg34]GLP-1-(7-37); N-epsilon26-[2-(2-{2-[(S)-4-carboxy-4-((S)-4-carboxy-4-{12-[4-(16-(1H-tetrazol-5-yl)hexadecanoyl-sulfamoyl)butyrylamino]dodecanoylamino}butyrylamino)butyrylamino]ethoxy}ethoxy)acetyl][Aib8,Arg34]GLP-1-(7-37); N-epsilon26-[2-(2-{2-[(S)-4-carboxy-4-((S)-4-carboxy-4-{6-[4-(16-(1H-tetrazol-5-yl)hexadecanoyl-sulfamoyl) butyrylamino]hexanoylamino} butyrylamino)butyrylamino]ethoxy}ethoxy) acetyl][Aib8,Arg34]GLP-1-(7-37); N-epsilon26-[2-(2-{2-[(S)-4-carboxy-4-((S)-4-carboxy-4-{4-[4-(16-(1H-tetrazol-5-yl)hexadecanoylsulfamoyl)butyrylamino]butyrylamino}butyrylamino)butyrylamino]ethoxy}ethoxy)acetyl][Aib8,Arg34]GLP-1-(7-34); N-epsilon26-[2-(2-{2-[(S)-4-carboxy-4-((S)-4-carboxy-4-{12-[4-(16-(1H-tetrazol-5-yl)hexadecanoylsulfamoyl)butyrylamino]-dodecanoylamino}butyrylamino) butyrylamino]ethoxy}ethoxy)acetyl][Aib8,Arg34]GLP-1-(7-34); N-epsilon26-[2-(2-{2-[(S)-4-carboxy-4-((S)-4-carboxy-4-{6-[4-(16-(1H-tetrazol-5-yl)hexadecanoylsulfamoyl)butyryla-mino]hexanoylamino}butyrylamino)butyrylamino]ethoxy}ethoxy)acetyl] [Aib8,Arg34]GLP-1-(7-34); N-epsilon26-[2-(2-{2-[(S)-4-carboxy-4-((S)-4-carboxy-4-{12-[4-(16-(1H-tetrazol-5-yl)hexadecanoyl-sulfamoyl)butyrylamino]dodecanoylamino} butyrylamino)butyrylamino]ethoxy}ethoxy)acetyl][Aib8,Arg34]GLP-1-(7-35); N-epsilon26-[2-(2-{2-[(S)-4-carboxy-4-((S)-4-carboxy-4-{6-[4-(16-(1H-tetrazol-5-yl)hexadecanoylsulfamoyl)butyrylamino]hexanoylamino}butyrylamino)butyrylamino] ethoxy}ethoxy)acetyl][Aib8,Arg34]GLP-1-(7-35); N-epsilon26-[2-(2-{2-[(S)-4-carboxy-4-((S)-4-carboxy-4-{6-[4-(16-(1H-tetrazol-5-yl)hexadecanoylsulfamoyl)butyrylamino] hexanoylamino}butyrylamino)butyrylamino]ethoxy}ethoxy) acetyl][Aib8,Arg34]GLP-1-(7-36)amide; N-epsilon26-[2-(2-{2-[(S)-4-carboxy-4-((S)-4-carboxy-4-{6-[4-(16-(1H-tetrazol-5-yl)hexadecanoylsulfamoyl) butyrylamino]hexanoylamino}butyrylamino) butyrylamino]ethoxy}ethoxy)acetyl][Aib8, Arg34]GLP-1-(7-35); N-epsilon26-[2-(2-{2-[(S)-4-carboxy-4-((S)-4-carboxy-4-{12-[4-(16-(1H-tetrazol-5-yl)hexadecanoyl-sulfamoyl)butyrylamino]dodecanoylamino}butyryl-amino)butyrylamino]ethoxy} ethoxy)acetyl][Aib8,Lys33, Arg34]GLP-1-(7-34); N-epsilon26-[2-(2-{2-[(S)-4-carboxy-4-((S)-4-carboxy-4-{12-[4-(16-(1H-tetrazol-5-yl)hexadecanoylsulfamoyl)butyrylamino] dodecanoylamino}butyrylamino)butyrylamino]ethoxy}ethoxy)acetyl][Aib8,Arg34]GLP-1-(7-36)amide; N-epsilon26-[2-(2-{2-[2-(2-{2-[2-(2-{2-[2-(2-{2-[2-(2-{2-[2-(2-{2-[(S)-4-carboxy-4-((S)-4-carboxy-4-{12-[4-(16-(1H-tetrazol-5-yl)hexadecanoylsulfamoyl)butyrylamino]dodecanoylamino}butyrylamino)butyrylamino]ethoxy}ethoxy)acetylami-no]ethoxy}ethoxy)acetylamino]ethoxy}ethoxy)acetylamino]ethoxy}ethoxy)acetylami-

no]ethoxy}ethoxy)acetylamino]ethoxy}ethoxy)acetyl][Aib8,Lys26,Arg34]GLP-1-(7-36)amide; N-epsilon37-[2-(2-{2-[(S)-4-carboxy-4-((S)-4-carboxy-4-{12-[4-(16-(1H-tetrazol-5-yl)hexadecanoylsulfamoyl)butyrylamino] dodecanoylamino}butyrylamino) butyrylamino]ethoxy}ethoxy)acetyl][Aib8,Glu22,Arg26,Arg34,Lys37]GLP-1-(7-37)amide; N-epsilon37-[2-(2-{2-[(S)-4-carboxy-4-((S)-4-carboxy-4-{12-[4-(16-(1H-tetrazol-5-yl)hexadecanoylsulfamoyl)butyrylamino]dodecanoylamino}butyrylamino)butyrylamino]ethoxy}ethoxy)acetyl][DesaminoHis7,Glu22,Arg26,Arg34, Lys37]GLP-1-(7-37)amide; N-epsilon37{2-[2-(2-{2-[2-((R)-3-carboxy-3-{[1-(19-carboxy-nonadecanoyl)piperidine-4-carbonyl]amino}propionylamino)ethoxy]ethoxy}acetylamino)ethoxy]ethoxy}acetyl[desaminoHis7,Glu22,Arg26,Arg34, Lys37]GLP-1(7-37)amide; N-epsilon37{2-[2-(2-{2-[2-((S)-3-carboxy-3-{[1-(19-carboxynonadecanoyl)piperidine-4-carbonyl]amino}propionylamino)ethoxy]ethoxy}acetylamino)ethoxy]ethoxy}acetyl [Aib8,Glu22, Arg26,Arg34, Lys37]GLP-1-(7-37)amide; N-epsilon37-[2-(2-[2-(2-[2-(2-((R)-3-[1-(17-carboxyhepta-decanoyl)piperidin-4-ylcarbonylamino]3-carboxy-propionylamino)ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl] [DesaminoHis7, Glu22,Arg26, Arg34,Phe(m-CF3)28] GLP-1-(7-37)amide; N-epsilon37-[2-(2-{2-[2-(2-{2-[(S)-4-carboxy-4-({trans-4-[(19-carboxynonadecanoylamino)methyl]cyclohexanecarbonyl}amino)butyrylamino]ethoxy}ethoxy)acetylamino]ethoxy}ethoxy)acetyl] [Aib8,Glu22, Arg26,Arg34,Lys37]GLP-1-(7-37)amide; N-epsilon37-[2-(2-{2-[2-(2-{2-[(S)-4-carboxy-4-({trans-4-[(19-carboxy-nonadecanoylamino)methyl]cyclohexanecarbonyl}amino)butyrylamino]ethoxy}ethoxy)acetylamino]ethoxy}ethoxy)acetyl] [DesaminoHis7,Glu22,Arg26,Arg34,Lys37]GLP-1-(7-37)amide; N-epsilon37-[2-(2-{2-[2-(2-{2-[(S)-4-carboxy-4-({trans-4-[(19-carboxy-nonadecanoylamino)methyl]cyclohexanecarbonyl}amino)butyrylamino]ethoxy}ethoxy)acetylamino]ethoxy}ethoxy)acetyl] [DesaminoHis7,Glu22,Arg26,Arg34, Lys37]GLP-1-(7-37); N-epsilon37-[2-(2-{2-[2-(2-{2-[(S)-4-carboxy-4-({trans-4-[(19-carboxynonadecanoylamino)methyl]cyclohexanecarbonyl}amino)butyrylamino]ethoxy}ethoxy)acetylamino]ethoxy}ethoxy)acetyl] [DesaminoHis7,Glu22,Arg26,Glu30,Arg34, Lys37]GLP-1-(7-37); N-epsilon37-[2-(2-{2-[(S)-4-carboxy-4-((S)-4-carboxy-4-{12-[4-(16-(1H-tetrazol-5-yl)hexadecanoylsulfamoyl)butyrylamino]dodecanoylamino}butyrylamino)butyrylamino]ethoxy}ethoxy)acetyl][Aib8,Glu22,Arg26,Arg34,Lys37]GLP-1-(7-37)amide; N-epsilon37-[2-(2-{2-[(S)-4-carboxy-4-((S)-4-carboxy-4-{12-[4-(16-(1H-tetrazol-5-yl)hexadecanoylsulfamoyl)butyrylamino]dodecanoylamino}butyrylamino)butyrylamino] ethoxy}ethoxy)acetyl] [DesaminoHis7,Glu22,Arg26, Arg34,Lys37]GLP-1-(7-37)amide; N-epsilon37-(3-((2-(2-(2-(2-(2-Hexadecyloxyethoxy)ethoxy)ethoxy)ethoxy)ethoxy)) propionyl)[DesaminoHis7,Glu22,Arg26,Arg34,Lys37]GLP-1(7-37)-amide; N-epsilon37-{2-(2-(2-(2-[2-(2-(4-(hexadecanoylamino)-4-carboxybutyryl-amino)ethoxy)ethoxy]acetyl)ethoxy)ethoxy)acetyl)}-[desaminoHis7,Glu22,Arg26, Glu30,Arg34,Lys37]GLP-1-(7-37)amide; N-epsilon37-{2-(2-(2-(2-[2-(2-(4-(hexadecanoylamino)-4-carboxy-butyrylamino)ethoxy)ethoxy]acetyl)ethoxy)ethoxy)acetyl)}-[desaminoHis7,Glu22, Arg26, Arg34,Lys37]GLP-1-(7-37)amide; N-epsilon37-(2-(2-(2-(2-(2-(2-(2-(2-(octadecanoyl-amino)ethoxy)ethoxy)acetylamino)ethoxy)ethoxy)acetylamino) ethoxy)ethoxy)acetyl)[desaminoHis7,Glu22,Arg26,Arg34,Lys37] GLP-1 (7-37)amide; N-epsilon37-[4-(16-(1H-Tetrazol-5-yl)hexadecanoylsulfamoyl) butyryl] [DesaminoHis7,Glu22,Arg26, Arg34, Lys37]GLP-1-(7-37)amide; N-epsilon37-[2-(2-{2-[2-(2-{2-[(S)-4-carboxy-4-(19-carboxynonadecanoylamino)butyrylamino]ethoxy}ethoxy)acetylamino]ethoxy}ethoxy)acetyl] [DesaminoHis7,Glu22,Arg26, Arg34,Lys37]GLP-1-(7-37); N-epsilon37-(2-{2-[2-((S)-4-carboxy-4-{(S)-4-carboxy-4-[(S)-4-carboxy-4-(19-carboxy-nonadecanoylamino)butyrylamino]butyrylamino} butyrylamino) ethoxy]ethoxy} acetyl)[DesaminoHis7,Glu22,Arg26,Arg34,Lys37]GLP-1-(7-37); N-epsilon37-{2-[2-(2-{(S)-4-[(S)-4-(12-{4-[16-(2-tert-Butyl-2H-tetrazol-5-yl)-hexadecanoylsulfamoyl]butyrylamino}dodecanoylamino)-4-carboxybutyrylamino]-4-carboxybutyrylamino} ethoxy)ethoxy]acetyl}[DesaminoHis7,Glu22,Arg26,Arg34,Lys37] GLP-1 (7-37); N-epsilon37-[2-(2-{2-[2-(2-{2-[(S)-4-carboxy-4-(17-carboxy-heptadecanoylamino)-butyrylamino]-ethoxy}-ethoxy) -acetylamino]-ethoxy}-ethoxy)-acetyl] [Aib8,Glu22, Arg26,Arg34,Lys37]GLP-1-(7-37); N-alpha37-[2-(2-{2-[2-(2-{2-[(S)-4-carboxy-4-(17-carboxy-heptadecanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetylamino]-ethoxy}-ethoxy)-acetyl] [Aib8,Glu22,Arg26,Arg34,epsilon-Lys37]GLP-1-(7-37)peptide; N-epsilon37-[2-(2-{2-[2-(2-{2-[(S)-4-carboxy-4-(17-carboxy-heptadecanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetylamino]-ethoxy}-ethoxy)-acetyl] [desaminoHis7,Glu22, Arg26,Arg34,Lys37] GLP-1-(7-37); N-epsilon36-[2-(2-{2-[2-(2-{2-[(S)-4-carboxy-4-(15-carboxy-pentadecanoylamino) -butyrylamino]-ethoxy}-ethoxy)-acetylamino]-ethoxy}-ethoxy)-acetyl] [desaminoHis7, Glu22,Arg26,Glu30,Arg34,Lys36] GLP-1-(7-37)-Glu-Lys peptide; N-epsilon37-[2-(2-{2-[2-(2-{2-[(S)-4-carboxy-4-({trans-4-[(19-carboxynonadecanoylamino)methyl]cyclohexanecarbonyl}amino)butyrylamino]ethoxy}ethoxy)acetylamino]ethoxy}ethoxy)acetyl][Aib8,Glu22, Arg26,Arg34,Lys37]GLP-1-(7-37); N-epsilon37-[2-(2-{2-[2-(2-{2-[(S)-4-carboxy-4-(17-carboxy-heptadecanoylamino) -butyrylamino]-ethoxy}-ethoxy)-acetylamino]-ethoxy}-ethoxy)-acetyl]-[Aib8,Glu22, Arg26,Arg34,Aib35,Lys37]GLP-1-(7-37); N-epsilon37-[(S)-4-carboxy-4-(2-{2-[2-(2-{2-[2-(17-carboxyheptadecanoylamino) ethoxy] ethoxy} acetylamino) ethoxy]ethoxy}acetylamino)butyryl] [Aib8,Glu22,Arg26,34,Lys37] GLP-1 (7-37); N-epsilon37-[2-(2-[2-(2-[2-(2-[4-(17-carboxyheptadecanoylamino)-4(S)-carboxybutyry-lamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl] [ImPr7, Glu22, Arg26,34,Lys37], GLP-1-(7-37); N-epsilon26-{2-[2-(2-{2-[2-(2-{(S)-4-carboxy-4-[10-(4-carboxyphenoxy)decanoylamino]butyrylamino}ethoxy)ethoxy]acetylamino}ethoxy) ethoxy]acetyl}, N-epsilon37-{2-[2-(2-{2-[2-(2-{(S)-4-carboxy-4-[10-(4-carboxy-phenoxy)decanoylamino]butyrylamino}ethoxy)ethoxy]acetylamino}ethoxy)ethoxy]acetyl}-[Aib8, Arg34,Lys37]GLP-1(7-37)-OH; N-epsilon26 (17-carboxyheptadecanoyl)-[Aib8,Arg34]GLP-1-(7-37)-peptide; N-epsilon26-(19-carboxynonadecanoyl)-[Aib8,Arg34]GLP-1-(7-37); N-epsilon26-(4-{[N-(2-carboxyethyl)-N-(15-carboxypentadecanoyl)amino]methyl}benzoyl[Arg34]GLP-1-(7-37); N-epsilon26-[2-(2-[2-(2-[2-(2-[4-(17-carboxyheptade-

canoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy] acetylamino) ethoxy]ethoxy)acetyl][Aib8,Arg34]GLP-1-(7-37); N-epsilon26-[2-(2-[2-(2-[2-(2-[4-(19-carboxynonadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy] acetylamino)ethoxy]ethoxy)acetyl][Aib8,Arg34]GLP-1-(7-37); N-epsilon26-[2-(2-[2-(2-[2-(2-[4-(17-carboxyheptadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy] acetylamino)ethoxy]ethoxy)acetyl][3-(4-Imidazolyl)Propionyl7,Arg34]GLP-1-(7-37); N-epsilon26-[2-(2-[2-(2-[2-(2-[4-(17-carboxyheptadecanoylamino)-(carboxymethylamino)acetylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Aib8,Arg34]GLP-1-(7-37); N-epsilon26-[2-(2-[2-(2-[2-(2-[4-(17-carboxyheptadecanoylamino)-3(S)-Sulfopropionylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Aib8,Arg34]GLP-1-(7-37); N-epsilon26-[2-(2-[2-(2-[2-(2-[4-(17-carboxyheptadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Gly8,Arg34]GLP-1-(7-37); N-epsilon26-[2-(2-[2-(2-[2-(2-[4-(17-carboxyheptadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Aib8,Arg34]GLP-1-(7-37)-amide; N-epsilon26-[2-(2-[2-(2-[2-(2-[4-(17-carboxyheptadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl] [Aib8,Arg34,Pro37]GLP-1-(7-37)amide; Aib8,Lys26(N-epsilon26-{2-(2-(2-(2-[2-(2-(4-(pentadecanoylamino)-4-carboxybutyrylamino)ethoxy)ethoxy]acetyl)ethoxy) ethoxy) acetyl)}), Arg34)GLP-1H(7-37)-OH; N-epsilon26-[2-(2-[2-(2-[2-(2-[4-{[N-(2-carboxyethyl)-N-(17-carboxyheptadecanoyl) amino]methyl}benzoyl)amino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Aib8,Arg34]GLP-1(7-37); N-alpha7-formyl, N-epsilon26-[2-(2-[2-(2-[2-(2-[4-(17-carboxyheptadecanoyl-amino)-4(S)-carboxy-butyrylamino]ethoxy) ethoxy]acetylamino)ethoxy]ethoxy)acetyl] [Arg34]GLP-1-(7-37); N-epsilon2626-[2-(2-[2-(2-[2-(2-[4-(17-carboxyheptadecanoylamino)-4(S)-carboxy-butyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Aib8, Glu22, Arg34]GLP-1-(7-37); N-epsilon26{3-[2-(2-{2-[2-(2-{2-[2-(2-[4-(15-(N-((S)-1,3-dicarboxypropyl) carbamoyl)pentadecanoylamino)-(S) -4-carboxybutyrylamino] ethoxy)ethoxy] ethoxy}ethoxy)ethoxy]ethoxy}ethoxy)ethoxy]propionyl} [Aib8,Arg34]GLP-1-(7-37); N-epsilon26-[2-(2-[2-(2-[2-(2-[4-{[N-(2-carboxyethyl)-N-(17-carboxy-heptadecanoyl)amino]methyl}benzoyl) amino](4(S)-carboxybutyryl-amino)ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Aib8,Arg34] GLP-1(7-37); N-epsilon26-{(S)-4-carboxy-4-((S)-4-carboxy-4-((S)-4-carboxy-4-((S)-4-carboxy-4-(19-carboxy-nonadecanoylamino)butyrylamino)butyrylamino)butyrylamino)butyrylamino}[Aib8,Arg34]GLP-1-(7-37); N-epsilon26-4-(17-carboxyheptadecanoyl-amino)-4(S)-carboxybutyryl-[Aib8,Arg34]GLP-1-(7-37); N-epsilon26-{3-[2-(2-{2-[2-(2-{2-[2-(2-[4-(17-carboxyheptadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]ethoxy}ethoxy)ethoxy]ethoxy}ethoxy)ethoxy]propionyl}[Aib8,Arg34]GLP-1-(7-37); N-epsilon26-{2-(2-(2-(2-[2-(2-(4-(17-carboxyheptadecanoylamino)-4-carboxybutyrylamino)ethoxy)ethoxy]acetyl)ethoxy)ethoxy)acetyl)}-[Aib8,22,27,30,35,Arg34,Pro37, Lys26] GLP-1 (7-37)amide; N-epsilon26-[2-(2-[2-[4-(21-carboxyuneicosanoylamino)-4(S)-carboxybutyrylamino]ethoxy]ethoxy)acetyl][Aib8, Arg34]GLP-1-(7-37); and N-epsilon26-[2-(2-[2-(2-[2-(2-[4-(21-carboxyuneicosanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Aib8,Arg34]GLP-1-(7-37).

Delivery agent: salt of N-(8-(2-hydroxybenzoyl)amino)caprylic acid

[0023] The delivery agent used in the present invention is a salt of N-(8-(2-hydroxybenzoyl)amino)caprylic acid. The structural formula of N-(8-(2-hydroxybenzoyl)amino)caprylate is shown in formula (I).



(I)

[0024] The salt of N-(8-(2-hydroxybenzoyl)amino)caprylic acid may comprise one monovalent cation, two monovalent cations or one divalent cation. The salt of N-(8-(2-hydroxybenzoyl)amino)caprylic acid may be selected from the group consisting of the sodium salt, potassium salt and calcium salt of of N-(8-(2-hydroxybenzoyl)amino)caprylic acid.

[0025] Salts of N-(8-(2-hydroxybenzoyl)amino)caprylate may be prepared using the method described in e.g. WO96/030036, WO00/046182, WO01/092206 or WO2008/028859.

[0026] The salt of N-(8-(2-hydroxybenzoyl)amino)caprylic acid may be crystalline and/or amorphous. The delivery agent may comprise the anhydrate, monohydrate, dihydrate, trihydrate, a solvate or one third of a hydrate of the salt of N-(8-(2-hydroxybenzoyl)amino) caprylic acid as well as combinations thereof. The delivery agent may be a salt of N-(8-(2-hydroxybenzoyl)amino)caprylic acid as described in WO2007/121318.

[0027] The delivery agent may be sodium N-(8-(2-hydroxybenzoyl)amino)caprylate (referred to as "SNAC" herein), also known as sodium 8-(salicyloylamino) octanoate.

[0028] The amount of the salt of N-(8-(2-hydroxybenzoyl) amino)caprylic acid in the composition may be at least 0.6 mmol, such as selected from the group consisting of at least 0.65 mmol, at least 0.7 mmol, at least 0.75 mmol, at least 0.8 mmol, at least 0.8 mmol, at least 0.9 mmol, at least 0.95 mmol and at least 1 mmol. The amount of the salt of N-(8-(2-hydroxybenzoyl) amino)caprylic acid in the composition may be in the range of 0.6-2.1 mmol or 0.6-1.9 mmol. In some

embodiments the amount of the salt of N-(8-(2-hydroxybenzoyl) amino)caprylic acid in the composition is in the range of 0.7-1.7 mmol or 0.8-1.3 mmol. The amount of the salt of N-(8-(2-hydroxybenzoyl)amino)caprylic acid in the composition may be up to 2.1 mmol, such as selected from the group consisting of up to 2.1 mmol, up to 2 mmol, up to 1.9 mmol, up to 1.8 mmol, up to 1.7 mmol, up to 1.6 mmol, up to 1.5 mmol, up to 1.4 mmol, up to 1.3 mmol, up to 1.2 mmol and up to 1.1 mmol. The amount of the salt of N-(8-(2-hydroxybenzoyl)amino)caprylic acid may be 1 mmol, such as 1.08 mmol.

[0029] The amount of SNAC in the composition may be at least 175 mg, such as an amount selected from the group consisting of at least 200 mg, at least 210 mg, at least 220 mg, at least 230 mg, at least 240 mg, at least 250 mg, at least 260 mg, at least 270 mg and at least 280 mg. The amount of SNAC in the composition may be in the range of 175-575 mg, such as 200-500 mg or 250-400 mg. The amount of SNAC in the composition may be up to 575 mg, such as an amount selected from the group consisting of up to 550 mg, up to 525 mg, up to 500 mg, up to 475 mg, up to 450 mg, up to 425 mg, up to 400 mg, up to 375 mg, up to 350 mg and up to 325 mg. The amount of SNAC in the composition may be 300 mg.

[0030] The molar ratio between GLP-1 agonist and delivery agent in the composition may be less than 10, such as less than 5 or less than 1.

Composition

[0031] The composition of the present invention is a solid composition and is administered by the oral route.

[0032] The composition may comprise at least one pharmaceutically acceptable excipient. The term **"excipient"** as used herein broadly refers to any component other than the active therapeutic ingredient(s). The excipient may be an inert substance, an inactive substance, and/or a not medicinally active substance. The excipient may serve various purposes, e.g. as a carrier, vehicle, filler, binder, lubricant, glidant, disintegrant, flow control agents, crystallization retarders, solubilizers, stabilizer, colouring agent, flavouring agent, surfactant, emulsifier and/or to improve administration, and/or absorption of the active substance. A person skilled in the art may select one or more of the aforementioned excipients with respect to the particular desired properties of the solid oral dosage form by routine experimentation and without any undue burden. The amount of each excipient used may vary within ranges conventional in the art. Techniques and excipients which may be used to formulate oral dosage forms are described in Handbook of Pharmaceutical Excipients, 6th edition, Rowe et al., Eds., American Pharmaceuticals Association and the Pharmaceutical Press, publications department of the Royal Pharmaceutical Society of Great Britain (2009); and Remington: the Science and Practice of Pharmacy, 21th edition, Gennaro, Ed., Lippincott Williams & Wilkins (2005). The excipients may be selected from binders, such as polyvinyl pyrrolidone (povidone), etc.; **fillers** such as cellulose powder, microcrystalline cellulose, cellulose derivatives like hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxy-propylmethylcellulose, dibasic calcium phosphate, corn starch, pregelatinized starch, etc.; **lubricants** and/or **glidants** such as stearic acid, magnesium stearate, sodium stearylfumarate, glycerol tribehenate, etc.; **flow control agents** such as colloidal silica, talc, etc.; **crystallization retarders** such as Povidone, etc.; **solubilizers** such as Pluronic, Povidone, etc.; **colouring agents,** including dyes and pigments such as Iron Oxide Red or Yellow, titanium dioxide, talc, etc.; **pH control agents** such as citric acid, tartaric acid, fumaric acid, sodium citrate, dibasic calcium phosphate, dibasic sodium phosphate, etc.; **surfactants** and **emulsifiers** such as Pluronic, polyethylene glycols, sodium carboxymethyl cellulose, polyethoxylated and hydrogenated castor oil, etc.; and mixtures of two or more of these excipients and/or adjuvants.

[0033] The composition may comprise at least 60% (w/w) delivery agent, less than 10% (w/w) binder, 5-40% (w/w) filler, and less than 10% (w/w) lubricant or glidant.

[0034] The composition may comprise at least 60% (w/w), such as at least 70% (w/w) or at least 75% (w/w), delivery agent.

[0035] The composition may comprise 0.1-10% (w/w), such as 0.2-4% (w/w) or 0.5-3% (w/w), of binder. The composition may comprise 1% (w/w) or 2% (w/w) of binder. The composition may comprise a **binder,** such as povidone; starches; celluloses and derivatives thereof, such as microcrystalline cellulose, e.g., AVICEL PH from FMC (Philadelphia, PA), hydroxypropyl cellulose hydroxylethyl cellulose and hydroxylpropylmethyl cellulose METHOCEL from Dow Chemical Corp. (Midland, MI); sucrose; dextrose; corn syrup; polysaccharides; and gelatin. The **binder** may be selected from the group consisting of dry binders and/or wet granulation binders. Suitable dry binders are, e.g., cellulose powder and microcrystalline cellulose, such as Avicel PH 102 and Avicel PH 200. The composition may comprise avicel, such as avicel PH 102. Suitable binders for wet granulation or dry granulation are corn starch, polyvinyl pyrrolidone (povidon), vinylpyrrolidone-vinylacetate copolymer (copovidone) and cellulose derivatives like hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxylpropylmethylcellulose. The composition maycomprise povidone.

[0036] The composition may comprise 5-40% (w/w), such as 10-30% (w/w) or 5-25% (w/w), of filler. The composition may comprise 10.9% (w/w) or 18%(w/w) of filler, or comprise 19.5% (w/w) or 20.5 (w/w) of filler. The **filler** may be selected from lactose, mannitol, erythritol, sucrose, sorbitol, calcium phosphate, such as calciumhydrogen phosphate, microcrystalline cellulose, powdered cellulose, confectioner's sugar, compressible sugar, dextrates, dextrin and dextrose. The composition may comprise microcrystalline cellulose, such as Avicel PH 102 or Avicel PH 200.

[0037] The composition may comprise 0.1-10% (w/w) or 0.5-5% (w/w), such as 1-3.5% (w/w) or 1% (w/w), of lubricant and/or a glidant. The composition may comprise a **lubricant** and/or a **glidant,** such as talc, magnesium stearate, calcium stearate, zinc stearate, glyceryl behenate, polyethylene oxide polymers, sodium lauryl sulfate, magnesium lauryl sulfate, sodium oleate, sodium stearyl fumarate, stearic acid, hydrogenated vegetable oils, silicon dioxide and/or polyethylene glycol. The composition may comprise magnesium stearate.

[0038] The composition may comprise a disintegrant, such as sodium starch glycolate, polacrilin potassium, sodium starch glycolate, crospovidon, croscarmellose, sodium carboxymethylcellulose or dried corn starch.

[0039] The composition may comprise one or more **surfactants,** for example a surfactant, at least one surfactant, or two different surfactants. The term "surfactant" refers to any molecules or ions that are comprised of a water-soluble (hydrophilic) part, and a fatsoluble (lipophilic) part. The surfactant may e.g. be selected from the group consisting of anionic surfactants, cationic surfactants, nonionic surfactants, and/or zwitterionic surfactants.

[0040] Still further, the composition may be formulated as is known in the art of oral formulations of insulinotropic compounds, e.g. using any one or more of the formulations described in WO 2008/145728.

[0041] A composition may also be used in the formulation of site specific, controlled, sustained, protracted, prolonged, delayed, pulsatile, retarded, and/or slow release drug delivery systems.

[0042] The composition of the invention may be prepared as is known in the art.

[0043] The composition may be administered in several dosage forms, for example as a tablet; a coated tablet; a chewing gum; a capsule such as hard or soft gelatine capsules or a powder. The composition may further be compounded in a drug carrier or drug delivery system, e.g. in order to improve stability and/or solubility or further improve bioavailability. The composition may be a freeze-dried or spray-dried composition.

[0044] The composition may be in the form of a tablet. The weight of the tablet may be in the range of 175 mg to 1000 mg, such as in the range of 175-250 mg, 300-500 mg or 500-900 mg, or such as about 200 mg, about 400 mg or about 700 mg. The weight of the tablet may be in the range of 200 mg to 1000 mg, such as in the range of 500-700 mg or 600-1000 mg, or such as about 200 mg, about 400 mg, about 600 mg or about 800 mg.

[0045] The composition may be granulated prior to being compacted. The composition may comprise an intragranular part and an extragranular part, wherein the intragranular part has been granulated and the extragranular part has been added after granulation. The intragranular part may comprise the GLP-1 agonist, the delivery agent and a binder. The intragranular part may comprise povidone. The extragranular part may comprise a filler, a lubricant and/or a glidant. The extragranular part may comprise microcrystalline cellulose, such as avicel, e.g. avicel PH120 or avicel PH200. The extragranular part may comprise magnesium stearate.

[0046] To prepare a dry **blend** of tabletting material, the various components are weighed, optionally delumped and then combined. The mixing of the components may be carried out until a homogeneous blend is obtained.

[0047] If granules are to be used in the tabletting material, granules may be produced in a manner known to a person skilled in the art, for example using **wet granulation** methods known for the production of "built-up" granules or "broken-down" granules. Methods for the formation of **built-up granules** may operate continuously and comprise, for example simultaneously spraying the granulation mass with granulation solution and drying, for example in a drum granulator, in pan granulators, on disc granulators, in a fluidized bed, by spray-drying or spray-solidifying, or operate discontinuously, for example in a fluidized bed, in a rotary fluid bed, in a batch mixer, such as a high shear mixer or a low shear mixer, or in a spray-drying drum. Methods for the production of **broken-down granules,** which may be carried out discontinuously and in which the granulation mass first forms a wet aggregate with the granulation solution, which is subsequently comminuted or by other means formed into granules of the desired size and the granules may then be dried. Suitable equipment for the granulation step are planetary mixers, low shear mixers, high shear mixers, extruders and spheronizers, such as an apparatus from the companies Loedige, Glatt, Diosna, Fielder, Collette, Aeschbach, Alexanderwerk, Ytron, Wyss & Probst, Werner & Pfleiderer, HKD, Loser, Fuji, Nica, Caleva and Gabler. Granules may be also formed by **dry granulation** techniques in which the pharmaceutically active agent is compressed with the excipients to form relatively large moldings, for example slugs or ribbons, which are comminuted by grinding, and the ground material serves as the tabletting material to be later compacted. Suitable equipment for dry granulation is roller compaction equipment from Gerteis, such as Gerteis MINI-PACTOR.

[0048] To **compact** the tabletting material into a solid oral dosage form, for example a tablet, a tablet press may be used. In a tabletting press, the tabletting material is filled (e.g. force fed or gravity fed) into a die cavity. The tabletting material is then compacted by a punch with pressure. Subsequently, the resulting compact, or tablet is ejected from the tabletting press. The above mentioned compaction process is subsequently referred to herein as the "compaction process". Suitable **tablet presses** include, but are not limited to, rotary tablet presses and eccentric tablet presses. Examples of tablet presses include, but are not limited to, the Fette 102i (Fette GmbH), the Korsch XL100, the Korsch PH 106 rotary tablet press (Korsch AG, Germany), the Korsch EK-O eccentric tabletting press (Korsch AG, Germany) and the Manesty F-Press (Manesty Machines Ltd., United Kingdom).

[0049] The method of preparation of the tablet may comprise a) wet granulation of a mixture comprising the GLP-1 agonist, the delivery agent and a binder; b) optionally drying the wet granulate; c) blending of the dried wet granulates

with at least a filler and at least a lubricant or a glidant, and then d) compression of the blend into tablets. The granulation may be a wet granulation or a dry granulation.

[0050] *Disintegration time:* The disintegration time of the tablet may be in the range of 7 minutes to 15 minutes, such as in the range of 8 minutes to 13 minutes. Disintegration time may be determined using a Pharma Test PTZ AUTO disintegration test apparatus. The disintegration apparatus consists of a basket rack holding 2 x 6 plastic tubes, open at the top and bottom, the bottom of the tube is covered by a screen. Tablets are placed in the tubes and on top of the tablets are placed discs for automated disintegration detection. The basket is immersed in 800 ml purified water maintained at 37°C, in a 1L beaker. Time for complete disintegration is measured. Furthermore, tablets may be observed visually for surface eroding behaviour during the disintegration test.

[0051] The tablet of the invention may **co-releases** the active ingredients and the delivery agent by surface erosion; hence, the tablets becomes smaller and smaller with time by dissolution primarily from the surface from non-disintegrated tablets. *Concurrent release:* The compositions may show concurrent release of the GLP-1 agonist and the delivery agent from the surface of the tablet. This can be tested by visual inspection during the disintegration test; the tablets do not have concurrent release of the GLP-1 agonist and the delivery agent from the surface of the tablet if the tablet breaks into smaller parts during the first 8 minutes of the disintegration test.

[0052] *Dissolution test:* Another test for concurrent release of the GLP-1 agonist and the delivery agent is the dissolution test. Here, the rate of appearance (in percentage) of the GLP-1 agonist and the delivery agent is measured. The dissolution test may be carried out as described in the following: Dissolution is performed on a Varian 705 DS. The analysis is based on the pharmacopeia method Ph Eur 2.9.3, Apparatus 2 (Paddle apparatus). 100 ml mini vessel with mini-paddles is used, and paddle speed is 75 rpm. After 120 minutes, the paddle speed is changed to 250 rpm. The dissolution medium used for the dissolution test is 100 ml of 200 mM KH2PO4 (containing 0.07% Tween 80 to avoid the GLP-1 agonist from sticking to the wall of the bath and to the paddle), with pH 6.8. Samples are taken after 5, 15, 30, 45, 60, 120 and 135 minutes. The volume of the sample is 2 ml, and the sample is taken with a disposable syringe. After each sample is taken, the same volume (2 ml) of the dissolution medium is added to the bath, in order to keep the total volume of 100 ml constant. The sample is pressed through a 0.22 μm Millex®-GV filter. Finally, the samples are analysed for concentration of the GLP-1 agonist and for concentration of the delivery agent by UPLC.

[0053] *Hardness test:* The hardness of the tablets is measured with a Pharma Test (33AA02), which measures the force required to disrupt the tablet, and the test is based on the pharmacopeia method Ph Eur 2.9.8.

[0054] The treatment with a composition according to the present invention may also be combined with one or more additional pharmacologically active substances, e.g. selected from antidiabetic agents, antiobesity agents, appetite regulating agents, antihypertensive agents, agents for the treatment and/or prevention of complications resulting from or associated with diabetes and agents for the treatment and/or prevention of complications and disorders resulting from or associated with obesity. Examples of these pharmacologically active substances are: Insulin, sulphonylureas, biguanides, meglitinides, glucosidase inhibitors, glucagon antagonists, DPP-IV (dipeptidyl peptidase-IV) inhibitors, inhibitors of hepatic enzymes involved in stimulation of gluconeogenesis and/or glycogenolysis, glucose uptake modulators, compounds modifying the lipid metabolism such as antihyperlipidemic agents as HMG CoA inhibitors (statins), Gastric Inhibitory Polypeptides (GIP analogs), compounds lowering food intake, RXR agonists and agents acting on the ATP-dependent potassium channel of the β-cells; Cholestyramine, colestipol, clofibrate, gemfibrozil, lovastatin, pravastatin, simvastatin, probucol, dextrothyroxine, neteglinide, repaglinide; β-blockers such as alprenolol, atenolol, timolol, pindolol, propranolol and metoprolol, ACE (angiotensin converting enzyme) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, alatriopril, quinapril and ramipril, calcium channel blockers such as nifedipine, felodipine, nicardipine, isradipine, nimodipine, diltiazem and verapamil, and α-blockers such as doxazosin, urapidil, prazosin and terazosin; CART (cocaine amphetamine regulated transcript) agonists, NPY (neuropeptide Y) antagonists, PYY agonists, Y2 receptor agonists, Y4 receptor agonits, mixed Y2/Y4 receptor agonists, MC4 (melanocortin 4) agonists, orexin antagonists, TNF (tumor necrosis factor) agonists, CRF (corticotropin releasing factor) agonists, CRF BP (corticotropin releasing factor binding protein) antagonists, urocortin agonists, β3 agonists, oxyntomodulin and analogues, MSH (melanocyte-stimulating hormone) agonists, MCH (melanocyte-concentrating hormone) antagonists, CCK (cholecystokinin) agonists, serotonin re-uptake inhibitors, serotonin and noradrenaline re-uptake inhibitors, mixed serotonin and noradrenergic compounds, 5HT (serotonin) agonists, bombesin agonists, galanin antagonists, growth hormone, growth hormone releasing compounds, TRH (thyreotropin releasing hormone) agonists, UCP 2 or 3 (uncoupling protein 2 or 3) modulators, leptin agonists, DA agonists (bromocriptin, doprexin), lipase/amylase inhibitors, RXR (retinoid X receptor) modulators, TR β agonists; histamine H3 antagonists, Gastric Inhibitory Polypeptide agonists or antagonists (GIP analogs), gastrin and gastrin analogs.

Pharmaceutical Indications

[0055] The present invention also relates to a composition of the invention for use as a medicament. In particular, the composition of the invention may be used for the following medical treatments, all preferably relating one way or the

other to diabetes:

(i) prevention and/or treatment of all forms of diabetes, such as hyperglycemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, non-insulin dependent diabetes, MODY (maturity onset diabetes of the young), gestational diabetes, and/or for reduction of HbA1C;
(ii) delaying or preventing diabetic disease progression, such as progression in type 2 diabetes, delaying the progression of impaired glucose tolerance (IGT) to insulin requiring type 2 diabetes, and/or delaying the progression of non-insulin requiring type 2 diabetes to insulin requiring type 2 diabetes;
(iii) improving β-cell function, such as decreasing β-cell apoptosis, increasing β-cell function and/or β-cell mass, and/or for restoring glucose sensitivity to β-cells;
(iv) prevention and/or treatment of cognitive disorders;
(v) prevention and/or treatment of eating disorders, such as obesity, e.g. by decreasing food intake, reducing body weight, suppressing appetite, inducing satiety; treating or preventing binge eating disorder, bulimia nervosa, and/or obesity induced by administration of an antipsychotic or a steroid; reduction of gastric motility; and/or delaying gastric emptying;
(vi) prevention and/or treatment of diabetic complications, such as neuropathy, including peripheral neuropathy; nephropathy; or retinopathy;
(vii) improving lipid parameters, such as prevention and/or treatment of dyslipidemia, lowering total serum lipids; lowering HDL; lowering small, dense LDL; lowering VLDL: lowering triglycerides; lowering cholesterol; increasing HDL; lowering plasma levels of lipoprotein a (Lp(a)) in a human; inhibiting generation of apolipoprotein a (apo(a)) in vitro and/or in vivo;
(iix) prevention and/or treatment of cardiovascular diseases, such as syndrome X; atherosclerosis; myocardial infarction; coronary heart disease; stroke, cerebral ischemia; an early cardiac or early cardiovascular disease, such as left ventricular hypertrophy; coronary artery disease; essential hypertension; acute hypertensive emergency; cardiomyopathy; heart insufficiency; exercise tolerance; chronic heart failure; arrhythmia; cardiac dysrhythmia; syncopy; atheroschlerosis; mild chronic heart failure; angina pectoris; cardiac bypass reocclusion; intermittent claudication (atheroschlerosis oblitterens); diastolic dysfunction; and/or systolic dysfunction;
(ix) prevention and/or treatment of gastrointestinal diseases, such as inflammatory bowel syndrome; small bowel syndrome, or Crohn's disease; dyspepsia; and/or gastric ulcers;
(x) prevention and/or treatment of critical illness, such as treatment of a critically ill patient, a critical illness polynephropathy (CIPNP) patient, and/or a potential CIPNP patient; prevention of critical illness or development of CIPNP; prevention, treatment and/or cure of systemic inflammatory response syndrome (SIRS) in a patient; and/or for the prevention or reduction of the likelihood of a patient suffering from bacteraemia, septicaemia, and/or septic shock during hospitalisation; and/or
(xi) prevention and/or treatment of polycystic ovary syndrome (PCOS).

[0056] In a particular embodiment, the indication is selected from the group consisting of (i)-(iii) and (v)-(iix), such as indications (i), (ii), and/or (iii); or indication (v), indication (vi), indication (vii), and/or indication (iix). In another particular embodiment, the indication is (i). In a further particular embodiment the indication is (v). In a still further particular embodiment the indication is (iix). The indications may be type 2 diabetes and/or obesity.

EXAMPLES

EXAMPLE 1

[0057] The objective of the present study was to evaluate the oral bioavailability in beagle dogs of a series of compositions comprising semaglutide and SNAC.

Method

Animals, Dosing and Blood Sampling

[0058] Twenty four male and 24 female beagle dogs, weighing 6-11 kg during the study period were included in the study. The dogs were dosed in fasting state. The compositions were administered by a single oral dosing to the dogs in groups of 4 male and 4 females. Blood samples were taken at the following time points: predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 24, 48, 72, 96, 120, 144, 192 and 240 hours post dosing.

[0059] The i.v. solution (20 nmol/mL in a pH 7.4 solution comprising 0.1 mg/ml Tween 20, 5.5 mg/ml Phenol, 1.42 mg/ml Na2HPO4 and 14 mg/ml Propylene Glycol) was dosed in a dose volume of 0.1 mL/kg in the same dog colony in

one dosing group (n=8). Blood samples were taken at the following time points: predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 24, 48, 72, 96, 120, 144, 192 and 240 hours post dosing.

Preparation of Plasma

[0060] All blood samples were collected into test tubes containing EDTA for stabilisation and kept on ice until centrifugation. Plasma was separated from whole blood by centrifugation and the plasma was stored at -20°C or lower until analysis.

Analysis of Plasma Samples

[0061] The plasma was analyzed for semaglutide using a Luminescence Oxygen Channeling Immunoassay (LOCI). The LOCI assay employs donor beads coated with streptavidin and acceptor beads conjugated with a monoclonal antibody binding to a midmolecular region of semaglutide. The other monoclonal antibody, specific for an N-terminal epitope, was biotinylated. In the assay the three reactants were combined with the semaglutide which form a two-sited immuno-complex. Illumination of the complex releases singlet oxygen atoms from the donor beads which channels into the acceptor beads and trigger chemiluminescence which was measured in the EnVision plate reader. The amount of light was proportional to the concentration of semaglutide and the lower limit of quantification (LLOQ) in plasma was 100 pM.

Analysis of Compositions

[0062] The amount of semaglutide and SNAC in the composition were assayed using a reversed-phase HPLC method, with UV detection at 230 nm, a linear gradient of mobile phases made up of deionised H2O:trifluoroacetic acid (TFA) (1000:1) (v/v) (A), and acetonitrile:TFA (1000:1) (v/v) (B).

Pharmacokinetic Calculations

[0063] Semaglutide plasma concentration data were subjected to non-compartmental pharmacokinetic analysis using the PC based software WinNonlin, v. 5.2 (Pharsight, Mountain View, CA. 94041, USA). For each individual dog the maximum plasma concentration (C_{max}) and time for maximum plasma concentration (t_{max}) were read from the plasma concentration time curves. The following pharmacokinetic parameters were estimated: Area Under the Curve to infinity (AUCinf.), and AUCinf./Dose (AUCinf./D). Bioavailability (F) was calculated as the fraction absorbed (in %) based on the dose normalised AUC (AUCinf./D) following oral and intravenous administration. Summary statistics of pharmacokinetic results were presented as arithmetic mean with calculated standard deviation, also for T_{max} and plasma half life.

Preparation of compositions

[0064] Tablets with different amounts of SNAC (150, 300 and 600 mg) and semaglutide (5, 10, 15 and 20 mg) were prepared. The composition of the tablets is shown in Table 1.

Table 1. Tablet composition expressed as "per tablet"

Composition	A	B	C	D	E	F
Semaglutide (mg)	10	10	10	5	15	20
SNAC (mg)	150	300	600	300	300	300
Povidone (mg)	2	4	7	3.5	4	4

(continued)

Composition		A	B	C	D	E	F
Extragranular	Avicel PH 102 (mg)	36	82	76	38	77	72
	Magesium Stearate (mg)	2	4	7	3.5	4	4
Tablet Weight (mg)		200	400	700	350	400	400

[0065] Semaglutide was prepared according to the method described in WO2006/097537, Example 4, and subsequently freeze-dried. SNAC was prepared according to the method described in WO2008/028859. The compositions were prepared using the following manufacturing process:

1) The ingredients were first screened through a #35 mesh;
2) semaglutide and SNAC were geometrically blended in a mortar and pestle;
3) povidone was dissolved in water and the resulting solution was used to granulate the blend of semaglutide and SNAC;
4) the granules were dried at a temperature not exceeding 40°C to a moisture level of ≤4%; and
5) the resulting dried granules were milled through a #35 mesh;
6) finally, the granules were blended with the extra granular ingredients (see Table 1) and the final blend was compressed into tablets, wherein the compression was performed at a pressure of approximately 4.4 kN or higher.

[0066] The tablet hardness of was more than 50 N as determined by the Pharma Test (33AA02), which measures the force required to disrupt the tablet, and the test is based on the pharmacopeia method Ph Eur 2.9.8.

Results

[0067] Table 2 summarises the pharmacokinetic parameters for semaglutide from single dosing of the tablets shown in Table 1.

Table 2. Summary of pharmacokinetic parameters for semaglutide from single dosing of tablets comprising 10 mg semaglutide in combination with 150 mg (A), 300 mg (B) or 600 mg (C) SNAC.

Composition	SNAC (mg)	T_{max} (h)	C_{max} (pM)	AUCinf./D	F (%)
A	150	0.6	6222	0.62	0.17
B	300	0.8	21871	2.335	0.63
C	600	1.1	9972	1.09	0.29

[0068] Individual and mean (SD) calculated pharmacokinetic parameters following oral dosing appear from Tables 3 to 5 and following intravenous administration appear from Table 6.

*Table 3. Pharmacokinetic parameters for semaglutide following oral dosing of oral dosing of the combination of 10 mg semaglutide and 150 mg SNAC (Composition **A**) to 4 male and 4 female Beagle dogs.*

Dog no	Dose (nmol/kg)	T_{max} (h)	C_{max} (pM)	AUCinf./D (h*kg*pmol/l/pmol)	F (%)
1025	285	1.5	38300	4.08	1.1
1026	548	n.a.	0	0	0
1027	278	0.2	228	0	0.00003
1028	338	2.0	3410	0.31	0.08
1029	246	n.a.	0	0	0
1030	244	0.2	2030	0.07	0.02
1031	223	n.a.	0	0	0
1032	254	0.5	5810	0.47	0.13

(continued)

Dog no	**Dose** (nmol/kg)	**T_{max}** (h)	**C_{max}** (pM)	**AUCinf./D** (h*kg*pmol/l/pmol)	**F** (%)
Mean	302	0.6	6222	0.62	0.17
SD	105	0.5	13130	1.41	0.38
n.a.) not analysed					

*Table 4. Pharmacokinetic parameters for semaglutide following oral dosing of oral dosing of the combination of 10 mg semaglutide and 300 mg SNAC (Composition **B**) to 4 male and 4 female Beagle dogs.*

Dog no	**Dose** (nmol/kg)	**T_{max}** (h)	**C_{max}** (pM)	**AUCinf./D** (h*kg*pmol/l/pmol)	**F** (%)
1033	294	0.5	5540	0.35	0.09
1034	301	2.0	72000	6.83	1.8
1035	276	n.a.	0	0	0
1036	258	1.5	21100	2.52	0.68
1037	239	2.0	70000	8.73	2.3
1038	261	0.7	4050	0.28	0.07
1039	223	0.5	2010	0.07	0.02
1040	249	0.2	271	0.00	0.0001
Mean	263	0.8	21871	2.35	0.63
SD	26.7	0.5	31061	3.49	0.94
n.a.) not analysed					

*Table 5. Pharmacokinetic parameters for semaglutide following oral dosing of the combination of 10 mg semaglutide and 600 mg SNAC (Composition **C**) to 4 male and 4 female Beagle dogs.*

Dog no	**Dose** (nmol/kg)	**T_{max}** (h)	**C_{max}** (pM)	**AUCinf./D** (h*kg*pmol/l/pmol)	**F** (%)
1041	262	n.a.	0	0	0
1042	278	0.5	1890	0.52	0.14
1043	265	3.0	261	0	0.0005
1044	265	0.7	1270	0.02	0.01
1045	251	1.5	48400	5.2	1.4
1046	285	2.0	22900	2.53	0.68
1047	226	0.7	4100	0.4	0.11
1048	248	0.7	953	0.01	0.004
Mean	260	1.1	9972	1.09	0.29
SD	18	0.5	17298	1.87	0.50
n.a.) not analysed					

Table 6. Pharmacokinetic parameters for semaglutide following intravenous dosing of 2 nmol/kg semaglutide to 4 male and 4 female Beagle dogs.

Dog no	**Dose** (pmol/kg)	**T_{max}** (h)	**C_{max}** (pM)	**AUCinf./D** (h*kg*pmol/l/pmol)
1065	1980	0.5	31400	310
1066	1980	0.2	17400	227
1067	1980	0.2	28300	385
1068	1980	4.0	12900	384
1069	1980	0.2	28300	398
1070	1980	0.2	27400	383
1071	1980	0.2	31000	472
1072	1980	0.2	25700	418
Mean	1980	0.8	25300	372
SD	0	1.3	6638	73.8

Table 7. Summary of pharmacokinetic parameters for semaglutide from single dosing of composition comprising 300 mg SNAC in combination with 5, 10, 15 or 20 mg semaglutide.

Composition	**SNAC** (mg)	**Semaglutide** (mg)	**T_{max}** (h)	**C_{max}** (pM)	**AUCinf./D**	**F** (%)
D	300	5	0.5	4446	1.22	0.33
B	300	10	0.8	21871	2.33	0.63
E	300	15	1.0	42612	4.61	1.2
F	300	20	1.3	9603	5.09	1.4

*Table 8. Pharmacokinetic parameters for semaglutide following oral dosing of the combination of 5 mg semaglutide and 300 mg SNAC (Composition **D**) to 4 male and 4 female Beagle dogs.*

Dog no	**Dose** (nmol/kg)	**T_{max}** (h)	**C_{max}** (pM)	**AUCinf./D** (h*kg*pmol/l/pmol)	**F** (%)
1049	123	1	4490	1.54	0.41
1050	153	0.7	4420	0.5	0.13
1051	114	1	17200	4.27	1.1
1052	131	0.2	2390	0.52	0.14
1053	119	0.5	1860	0.31	0.08
1054	131	0.2	575	0.03	0.01
1055	113	0.7	3210	0.45	0.12
1056	107	0.5	1420	2.16	0.58
Mean	124	0.5	4446	1.22	0.33
SD	15	0.5	5335	1.42	0.38

*Table 9. Pharmacokinetic parameters for semaglutide following oral dosing of the combination of 15 mg semaglutide and 300 mg SNAC (Composition **E**) to 6 Beagle dogs.*

Dog no	**Dose** (nmol/kg)	T_{max} (h)	C_{max} (pM)	**AUCinf./D** (h*kg*pmol/l/pmol)	**F** (%)
1067	318	1	56500	5.18	1.4
1068	393	1.5	61000	4.75	1.3
1069	322	1	15100	1.23	0.3
1070	341	0.5	2090	0	0.01
1071	283	2.5	114000	16.00	4.3
1072	312	0.5	6980	0.47	0.1
Mean	328	1.0	42612	4.61	1.2
SD	37	0.8	43118	6.00	1.6

*Table 10. Pharmacokinetic parameters for semaglutide following oral dosing of the combination of 20 mg semaglutide and 300 mg SNAC (Composition **F**) to 4 male and 4 female Beagle dogs.*

Dog no	**Dose** (nmol/kg)	T_{max} (h)	C_{max} (pM)	**AUCinf./D** (h*kg*pmol/l/pmol)	**F** (%)
1057	588	1	197000	9.60	2.6
1058	619	1.5	144000	7.11	1.9
1059	508	1.5	77400	4.45	1.2
1060	519	1.5	91900	5.18	1.4
1061	519	2	70400	4.72	1.3
1062	519	1.5	155000	9.09	2.4
1063	460	0.7	1620	0.01	0.004
1064	487	1.5	11500	0.61	0.16
Mean	527	1.3	93603	5.09	1.4
SD	52	0.5	68667	3.52	0.95

Conclusion

[0069] Surprisingly, tablets comprising 300 mg SNAC showed improved bioavailability in the current study compared to tablets comprising 150 mg or 600 mg SNAC.

SEQUENCE LISTING

[0070]

<110> Novo Nordisk A/S

<120> SOLID COMPOSITIONS COMPRISING A GLP-1 AGONIST AND A SALT OF N-(8-(2-HYDROXYBENZOYL) AMINO)CAPRYLATE

<130> 8253EP01

<150> 10195285.1
<151> 2010-12-16

<150> PCT/EP2011/073060
<151> 2011-12-16

<160> 2

<170> PatentIn version 3.3

<210> 1
<211> 31
<212> PRT
<213> Homo sapiens

<400> 1

```
His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly
1               5                   10                  15

Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly
            20                  25                  30
```

<210> 2
<211> 40
<212> PRT
<213> Heloderma suspectum

<400> 2

```
His Gly Glu Gly Thr Phe Ile Thr Ser Asp Leu Ser Lys Gln Met Glu
1               5                   10                  15

Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro
            20                  25                  30

Ser Ser Gly Ala Pro Pro Pro Ser
        35                  40
```

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- WO 2010020978 A **[0002]**
- US 20050148497 A **[0002]**
- WO 2010092163 A **[0002]**
- WO 9808871 A **[0008] [0021]**
- WO 2006097537 A **[0017] [0021] [0065]**
- WO 9319175 A **[0021]**
- WO 9629342 A **[0021]**
- WO 9943707 A **[0021]**
- WO 9943706 A **[0021]**
- WO 9943341 A **[0021]**
- WO 9943708 A **[0021]**
- WO 2005027978 A **[0021]**
- WO 2005058954 A **[0021]**
- WO 2005058958 A **[0021]**
- WO 2006005667 A **[0021]**
- WO 2006037810 A **[0021]**
- WO 2006037811 A **[0021]**
- WO 2006097538 A **[0021]**
- WO 2008023050 A **[0021]**
- WO 2009030738 A **[0021]**
- WO 2009030771 A **[0021]**
- WO 2009030774 A **[0021]**
- WO 96030036 A **[0025]**
- WO 00046182 A **[0025]**
- WO 01092206 A **[0025]**
- WO 2008028859 A **[0025] [0065]**
- WO 2007121318 A **[0026]**
- WO 2008145728 A **[0040]**
- WO 10195285 A **[0070]**
- EP 2011073060 W **[0070]**

Non-patent literature cited in the description

- **STEINERT et al.** *Am J Clin Nutr,* October 2010, vol. 92, 810-817 **[0002]**
- **BEGLINGER et al.** *Clinical Pharmacology and therapeutics,* October 2008, vol. 84 (4), 468-474 **[0002]**
- Handbook of Pharmaceutical Excipients. American Pharmaceuticals Association and the Pharmaceutical Press, 2009 **[0032]**
- Remington: the Science and Practice of Pharmacy. Lippincott Williams & Wilkins, 2005 **[0032]**

Patent

1. Fast sammensætning til oral administration omfattende semaglutid og et salt af N-(8-(2-hydroxybenzoyl)amino)caprylsyre, hvor nævnte sammensætning omfatter mindst 60% (vægt/vægt) af nævnte salt af N-(8-(2-hydroxybenzoyl)-amino)caprylsyre.

2. Sammensætning ifølge krav 1, hvor nævnte sammensætning omfatter mindst 70% (vægt/vægt) eller mindst 75% (vægt/vægt) af nævnte salt af N-(8-(2-hydroxybenzoyl)-amino)caprylsyre.

3. Sammensætning ifølge et hvilket som helst af de foregående krav, hvor molforholdet mellem semaglutid og nævnte salt af N-(8-(2-hydroxybenzoyl)amino)caprylsyre i sammensætningen er mindre end 10, såsom mindre end 5 eller mindre end 1.

4. Sammensætning ifølge et hvilket som helst af de foregående krav, hvor mængden af semaglutid er i intervallet fra 1 til 20 mg, såsom i intervallet fra 5 til 20 mg, såsom i intervallet fra 5 til 15 mg, såsom 10 mg.

5. Sammensætning ifølge et hvilket som helst af de foregående krav, hvor mængden af semaglutid er i intervallet fra 0,05 til 25 µmol, såsom i intervallet fra 0,5 til 2,5 µmol.

6. Sammensætning ifølge et hvilket som helst af de foregående krav, hvor nævnte salt af N-(8-(2-hydroxybenzoyl)amino)caprylsyre er valgt fra gruppen bestående af natriumsaltet, kaliumsaltet og calciumsaltet af N-(8-(2-hydroxybenzoyl)amino)caprylsyre.

7. Sammensætning ifølge et hvilket som helst af de foregående krav, hvor nævnte salt af N-(8-(2-hydroxybenzoyl)amino)caprylsyre er natrium-N-(8-(2-hydroxybenzoyl)amino)caprylsyre (SNAC).

8. Sammensætning ifølge krav 7, hvor mængden af SNAC er op til 575 mg, såsom en mængde valgt fra gruppen bestående af op til 550 mg, op til 525 mg, op til 500 mg, op til 475 mg, op til 450 mg, op til 425 mg, op til 400 mg, op til 375 mg, op til 350 mg og op til 325 mg.

9. Sammensætning ifølge krav 7 eller 8, hvor mængden af SNAC er mindst 175 mg, såsom en mængde valgt fra gruppen bestående af mindst 200 mg, mindst 210 mg, mindst 220 mg, mindst 230 mg, mindst 240 mg, mindst 250 mg, mindst 260 mg, mindst 270 mg og mindst 280 mg.

10. Sammensætning ifølge krav 7, hvor mængden af SNAC i sammensætningen er i intervallet fra 175-575 mg, såsom 200-500 mg eller 250-400 mg

11. Sammensætning ifølge krav 7, hvor mængden af SNAC er 300 mg.

12. Sammensætning ifølge et hvilket som helst af de foregående krav, hvor sammensætningen er i form af en tablet, og hvor tabletten har en vægt i intervallet fra 175-1000 mg, såsom i intervallet fra 200-800 mg.

13. Sammensætning ifølge et hvilket som helst af de foregående krav, hvor nævnte sammensætning omfatter mindst en yderligere farmaceutisk acceptabel excipiens, hvor nævnte excipiens er valgt fra en eller flere af grupperne bestående af bindemidler, fyldstoffer, disintegrationsmidler og smøremidler og/eller glidemidler.

14. Sammensætning ifølge et hvilket som helst af de foregående krav, hvor nævnte sammensætning omfatter 0,1-10% (vægt/vægt) bindemiddel.

15. Sammensætning ifølge krav 14, hvor nævnte bindemiddel er povidon.

16. Sammensætning ifølge et hvilket som helst af de foregående krav, hvor nævnte sammensætning omfatter 5-40% (vægt/vægt) fyldstof.

17. Sammensætning ifølge krav 16, hvor nævnte fyldstof er mikrokrystallinsk cellulose.

18. Sammensætning ifølge et hvilket som helst af de foregående krav, hvor nævnte sammensætning omfatter 0,1-10% (vægt/vægt) eller 0,5-5% (vægt/vægt) smøremiddel og/eller et glidemiddel.

19. Sammensætning ifølge et hvilket som helst af de foregående krav, hvor nævnte sammensætning omfatter 1-3,5% (vægt/vægt) eller 1 % (vægt/vægt) smøremiddel og/eller et glidemiddel.

20. Sammsætning ifølge et hvilket som helst af de foregående krav 18-19, hvor nævnte smøremiddel er magnesiumstearat.

21. Sammensætning ifølge et hvilket som helst af de foregående krav, hvor nævnte sammensætning omfatter mindst 60% (vægt/vægt) af et salt af N-(8-(2-hydroxybenzoyl)amino)caprylsyre, mindre end 10% (vægt/vægt) bindemiddel, 5-40% (vægt/vægt) fyldstof og mindre end 10% (vægt/vægt) smøremiddel eller glidemiddel.

22. Sammensætning ifølge et hvilket som helst af de foregående krav, hvor nævnte sammensætning er i form af en tablet.

23. Sammensætning ifølge et hvilket som helst af de foregående krav, hvor nævnte sammensætning omfatter en intragranulær del og en ekstragranulær del.

24. Sammensætning som defineret i et hvilket som helst af de foregående krav til anvendelse i medicin.

25. Sammensætning ifølge et hvilket som helst af de foregående krav, til anvendelse i behandlingen af type II diabetes eller fedme.