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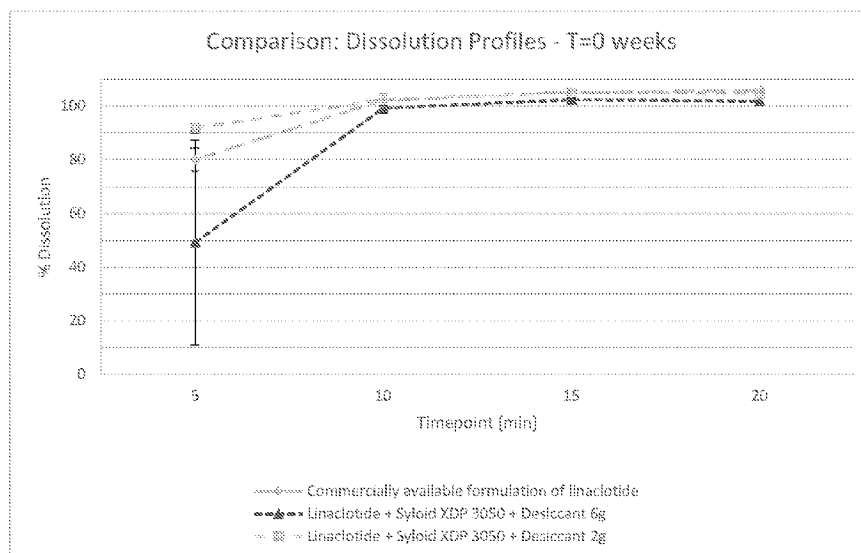


Figure 1

(57) **Abstract:** The present invention relates to a stable pharmaceutical composition for oral administration comprising Linaclotide or its pharmaceutically acceptable salts and a carrier. Methods of preparing and using the composition are also provided. In particular, the composition may be used in the treatment of gastrointestinal disorders, such as chronic constipation and irritable bowel syndrome.





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PHARMACEUTICAL COMPOSITION CONTAINING A PEPTIDE

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims the benefit Indian Patent Application Serial No. 201811025533, filed on July 9, 2018, the contents of which is hereby incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

The present invention relates generally to pharmaceutical compositions comprising a peptide. In particular, the invention relates to a composition comprising an adsorbate of a peptide on a carrier.

BACKGROUND OF THE PRESENT INVENTION

Many therapeutic polypeptides are formulated in aqueous solution because they are most active in this form. However, most polypeptides are not particularly stable in aqueous solution, such that the formulations often have a short half-life and require refrigeration. Although aqueous solutions of polypeptides can be dried by freeze-drying, spray-drying or other methods, such dried formulations may also be unstable and have reduced activity relative to an aqueous solution of the polypeptide. Typical break-down mechanisms that occur both in aqueous solution and in dried formulations include aggregation and oxidative or hydrolytic degradation. Thus, the majority of therapeutic polypeptides, whether in aqueous solution or dried, are stored under refrigerated conditions due to their limited stability.

Linaclotide is a tetradecapeptide having the amino acid sequence Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr that activates the guanylate cyclase-C (GC-C) receptor. Linaclotide, which may be administered orally, is useful for the treatment of gastrointestinal disorders and conditions, including irritable bowel syndrome (IBS) and chronic constipation (CC). Formulations comprising Linaclotide are susceptible to degradation including moisture -driven degradation reactions such as hydrolysis, oxidation, deamidation, isomerization, and multimerization. The

sensitivity of peptides to degradation due to oxidative or hydrolytic stress acts as a barrier to produce a stable drug formulation.

It is well known in the art that stabilization of proteins and peptides can be achieved by adding substances that stabilize the native protein structure by a preferential hydration of the proteins (Ref.: T Arakawa and S. N. Timasheff. The stabilization of Proteins by Osmolytes. Biophys. J. vol. 47 p.p. 411-414. 1985).

WO2007033427 discloses that proteins and peptides are susceptible to aggregation and/ or chemical degradation including oxidative or hydrolytic degradation. In order to improve the stabilization of peptides in pharmaceutical dosage forms, additives are required for peptide stabilization. Furthermore, additional drying steps such as lyophilization / freeze drying or spray drying are employed. Such freeze dried or spray dried products are very sensitive to moisture content and may need additional protective measures and such additional drying steps are very expensive.

U.S patent 20150005241 discloses that peptides are often sensitive against degradation, for example, due to oxidative or hydrolytic stress. Such formulations require the addition of stabilizers like Ca^{2+} ions and leucine to prevent hydrolytic and oxidative degradation of the peptide to achieve a stable drug product. In one embodiment, a coating solution of Linaclotide is prepared by adding stabilizers such as leucine and Ca^{2+} to the solution. After mixing, the solution is sprayed onto pellets made of microcrystalline cellulose (MCC). If stabilizers are not added, the impurities as well as multimers of the peptide increase substantially.

Additionally, WO/2016/024291 discloses the use of acesulfame to stabilize Linaclotide.

The drawback of using such stabilizers is that the stabilizers may present potential incompatibility with certain peptides. Further, the use of stabilizers may cause unwanted side effects such as allergic reactions. In addition, there may be potential incompatibilities with antibiotics and inorganic ions like calcium ions.

WO2010019266 describes that oxidation and hydrolysis occur in a significant manner if no stabilizers are added to the Linaclotide formulations.

The formation of multimers and/or impurities reduce the amount of the active pharmaceutical ingredient required to enable the required pharmacodynamical effect

in the respective therapy. Other stabilizers like trehalose, which are described in literature (Jai K. Kaushik and Rajiv Bhat. *J. Biol Chem.* Vol. 278, No. 29, Issue of July 18, pp. 26458–26465, 2003) were tested in an attempt to stabilize the Linaclotide peptide, but no stabilization was observed.

- 5 Currently, there are no Linaclotide peptide formulations available that are formulated without additional stabilizers.

Thus, in view of the above, there is a need to provide stable compositions of Linaclotide that are easy to manufacture and manufacture and do not require the use of additional stabilizers and the like.

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SUMMARY OF THE INVENTION

In one aspect, there is provided a pharmaceutical composition comprising a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), or a pharmaceutically acceptable salt thereof, on at
15 least one carrier, wherein X is any amino acid.

In another aspect, there is provided a process for preparing the composition as described herein, comprising the steps of: (a) preparing an aqueous solution of a peptide; (b) combining the aqueous solution of the peptide with a carrier; (c) drying the mixture of peptide and carrier under reduced pressure at a temperature of from about
20 30 to about 50°C.

In another aspect, there is provided a dosage form comprising the composition as described herein.

In another aspect there is provided, use of a composition as described herein in the manufacture of a medicament for treating of chronic constipation or irritable bowel
25 syndrome.

In yet another aspect there is provided a method of treating chronic constipation or irritable bowel syndrome comprising administering the composition as described herein or a dosage form as described herein, to a patient in need thereof.

In one aspect, there is provided use of a composition as described herein in the manufacture of a medicament for treating a gastrointestinal disorder in a patient, wherein the composition further comprises a probiotic or a prebiotic or a mixture thereof.

- 5 In another aspect, there is provided a method of treating a gastrointestinal disorder comprising administering the composition as described herein or a dosage form as described herein, to a patient in need thereof, wherein the composition or dosage form further comprises a probiotic or a prebiotic or a mixture thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

- 10 The invention will be better understood with reference to the detailed description when considered in conjunction with the non-limiting examples and the accompanying drawings, in which:

FIGURE 1 shows dissolution profile comparable to commercially available Linaclotide formulation at T=0 weeks.

- 15 FIGURE 2 shows dissolution profile comparable to commercially available Linaclotide formulation at T=4 weeks.

FIGURE 3 shows a comparison of impurity content to a commercially available Linaclotide formulation at T=0, 4, 8, 14 and 26 weeks.

- 20 FIGURE 4 shows a comparison of multimer content to a commercially available Linaclotide formulation at T=0, 4, 8, 14 and 26 weeks.

FIGURE 5 shows a comparison of water content to a commercially available Linaclotide formulation at T=0, 4, 8, 14 and 26 weeks.

FIGURE 6 shows a comparison recovery of label claim to a commercially available Linaclotide formulation at T=0, 4, 8, 14 and 26 weeks.

- 25 FIGURE 7 shows a comparison of dissolution profile to a commercially available Linaclotide formulation at T=0 weeks.

DETAILED DESCRIPTION OF THE PRESENT INVENTION

The present invention relates to a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 1) or a pharmaceutically acceptable salt thereof on at least one carrier, wherein X is any amino acid.

In various embodiments, the peptide Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr may be Linacotide or a pharmaceutically acceptable salt thereof.

The term "amino acid" refers to naturally occurring and non-naturally occurring amino acids, as well as amino acids such as proline, amino acid analogs and amino acid mimetics that function in a manner similar to naturally occurring amino acids. In particular, the term "amino acid" refers to naturally occurring and synthetic α , β , γ or δ amino acids. The backbone of the "amino acid" may be substituted with one or more groups selected from halogen, hydroxy, guanido, heterocyclic groups. Accordingly, the term "amino acid" also includes within its scope glycine, alanine, valine, leucine, isoleucine, methionine, proline, phenylalanine, tryptophan, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine and histidine, taurine, betaine, N-methylalanine and the like. Naturally encoded amino acids include the common amino acids (alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine) and the less common pyrrolysine and selenocysteine. Naturally encoded amino acids include post-translational variants of the naturally occurring amino acids such as prenylated amino acids, isoprenylated amino acids, myristoylated amino acids, palmitoylated amino acids, N-linked glycosylated amino acids, O-linked glycosylated amino acids, phosphorylated amino acids and acylated amino acids.

In certain embodiments, the amino acid may be in the L-configuration or D-configuration. Alternatively, the amino acid may be a derivative of alanyl, valinyl, leucinyl, isoleuccinyl, prolinyl, phenylalaninyl, tryptophanyl, methioninyl, glycyl, serinyl, threoninyl, cysteinyl, tyrosinyl, asparaginyl, glutaminyl, aspartoyl, glutaroyl, lysinyl, argininyl, histidinyl, β -alanyl, β -valinyl, β -leucinyl, β -isoleuccinyl, β -prolinyl, β -phenylalaninyl, β -tryptophanyl, β -methioninyl, β -glycyl, β -serinyl, β -threoninyl, β -

cysteiny, β -tyrosiny, β -asparaginy, β -glutaminy, β -aspartoy, β -glutaroy, β -lysiny, β -argininy or β -histidiny. In some embodiments the amino acid may be a modified amino acid.

The terms "polypeptide," "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues. That is, a description directed to a polypeptide applies equally to a description of a peptide and a description of a protein, and vice versa. The terms apply to naturally occurring amino acid polymers as well as amino acid polymers in which one or more amino acid residues is a modified amino acid.

In some embodiments, the peptide may be a derivative or variant of Linacotide. The term "derivative" or "variant" refers to a protein that differs from a related protein by substitutions in amino acid sequence. Such, substitutions may be conservative. One of skill will recognize that individual substitutions, deletions or additions to a peptide, polypeptide, or protein sequence which alters, adds or deletes a single amino acid or a small percentage of amino acids in the encoded sequence may be conservative, where the alteration results in the substitution of an amino acid with a chemically similar amino acid. Conservative substitution tables providing functionally similar amino acids are well known in the art. Such conservatively modified variants are in addition to and do not exclude polymorphic variants, interspecies homologs, and alleles. The term "variant" also refers to a protein sequence that has one or more residues that differ in amino acid identity from another similar protein sequence. Said similar protein sequence may be the natural wild type protein sequence, or another variant of the wild type sequence. Variants include proteins that have one or more amino acid insertions, deletions or substitutions. Variants also include proteins that have one or more post-translationally modified amino acids.

In a preferred embodiment, X may be selected from phenylalanine (Phe), Tyrosine (Tyr) or Tryptophan (Trp). Accordingly, the peptide according to the invention may comprise the following sequences: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2), or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3), or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4).

The peptides have six Cys residues. The six Cys residues form three disulfide bonds in the mature and active form of the peptide when fully folded. The six Cys residues may be identified, from the amino to carboxy terminus of the peptide, as A, B, C, D, E, and F as follows:

- 5 Cys(A)-Cys(B)-Glu-X-Cys(C)-Cys(D)-Asn-Pro-Ala-Cys(E)-Thr-Gly-Cys(F)-Tyr.

The disulfide bonds form as follows: A-D, B-E, and C-F.

In some embodiments, one or both members of one or more pairs of Cys residues which normally form a disulfide bond can be replaced by homocysteine, 3-
10 mercaptoproline; β , β dimethylcysteine or diaminopropionic acid to form alternative internal cross-links at the positions of the normal disulfide bonds.

In addition, one or more disulfide bonds may be replaced by alternative covalent cross-links, e.g., an amide bond, an ester linkage, an alkyl linkage, a thio-ester linkage, a lactam bridge, a carbamoyl linkage, a urea linkage, a thiourea linkage, a phosphonate
15 ester linkage, an alkyl linkage, and alkenyl linkage, an ether, a thioether linkage, or an amino linkage. In some cases, the generation of such alternative cross-links may require replacing the Cys residues with other residues such as Lys or Glu or non-naturally occurring amino acids.

In some embodiments, the peptide may be modified wherein at least one carboxyl
20 group of an amino acid residue of the peptide is modified to an alkyl ester. In some embodiments, at least one carboxyl group of an amino acid of the peptide is an alkyl ester. Methods of producing alkyl esters from carboxyl groups are readily known in those skilled in the relevant art. In some embodiments, the carboxylic acid of the side chain of a glutamate amino acid in a peptide sequence is modified into an alkyl ester.
25 As used herein, the term "alkyl" includes within its meaning monovalent ("alkyl") and divalent ("alkylene") straight chain or branched chain saturated aliphatic groups having from 1 to 10 carbon atoms, for example, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms. In other exemplary embodiments, the term alkyl includes, but is not limited to, methyl, ethyl, 1-propyl, isopropyl, 1-butyl, 2-butyl, isobutyl, tert-butyl, amyl, 1,2-dimethylpropyl,

1,1-dimethylpropyl, pentyl, isopentyl, hexyl, 4-methylpentyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1,2,2-trimethylpropyl, 1,1,2-trimethylpropyl, 2-ethylpentyl, 3-ethylpentyl, heptyl, 1-methylhexyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 4,4-dimethylpentyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,4-dimethylpentyl, 1,2,3-trimethylbutyl, 1,1,2-trimethylbutyl, 1,1,3-trimethylbutyl, 5-methylheptyl, 1-methylheptyl, octyl, nonyl, decyl, and the like. The term also includes both substituted and unsubstituted alkyl groups, including halogenated alkyl groups. In certain embodiments, the alkyl group is a fluorinated alkyl group. Non-limiting examples of moieties with which the alkyl group can be substituted are selected from the group consisting of halogen (fluoro, chloro, bromo or iodo), hydroxyl, carbonyl, sulfanyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art.

In further embodiments, the carboxylic acid on the side chain of a glutamate amino acid may be modified into an ethyl ester.

In other embodiments, the C-terminus carboxylic acid of a tyrosine amino acid may be modified into an alkyl ester. In particular, the C-terminus carboxylic acid of a tyrosine amino acid may be modified into an ethyl ester.

As used herein, the term "pharmaceutically acceptable salt" refers to any salt of a compound provided herein which retains its biological properties and which is not toxic or otherwise undesirable for pharmaceutical use. Such salts may be derived from a variety of organic and inorganic counter-ions well known in the art. Pharmaceutically acceptable salts further include, by way of example only and without limitation, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium and the like, and when the compound contains a basic functionality, salts of non-toxic organic or inorganic acids.

In accordance with the present disclosure, the at least one carrier may have a high surface area. In particular, the term "high surface area", as used herein, means that the carrier has a surface area of at least about 20 m²/g of carrier, at least about 30

m²/g, at least about 40 m²/g, at least about 50 m²/g, at least about 60 m²/g, at least about 70 m²/g, at least about 80 m²/g, at least about 90 m²/g, at least about 100 m²/g, at least about 110 m²/g, at least about 120 m²/g, at least about 130 m²/g, at least about 140 m²/g, at least about 150 m²/g, at least about 160 m²/g, at least about 170 m²/g, at least about 180 m²/g, at least about 190 m²/g, at least about 200 m²/g, at least about 210 m²/g, at least about 220 m²/g, at least about 230 m²/g, at least about 240 m²/g, at least about 250 m²/g, at least about 260 m²/g, at least about 270 m²/g, at least about 280 m²/g, at least about 290 m²/g, at least about 300 m²/g, at least about 310 m²/g, at least about 320 m²/g, at least about 330 m²/g, at least about 340 m²/g, at least about 350 m²/g, at least about 360 m²/g, at least about 370 m²/g, at least about 380 m²/g, at least about 390 m²/g, at least about 400 m²/g, at least about 450 m²/g at least about 500 m²/g, at least about 550 m²/g, at least about 600 m²/g, at least about 650 m²/g, at least about 700 m²/g. In one embodiment, the at least one carrier has a surface area of about 20 to about 320 m²/g or about 20 to about 350 m²/g. In another embodiment, the surface area may be from about 20 to about 700 m²/g of carrier. Preferably, the surface area may be about 300 to about 700 m²/g or about 320 to about 700 m²/g of carrier. The surface area of the carrier may be measured using standard procedures. Such standard procedures may include low-temperature nitrogen adsorption, based on the Brunauer, Emmett and Teller (BET) method which is well known in the art.

The at least one carrier may be selected from one or more of metal oxides, metal silicates, metal phosphates, metal carbonates or zeolites. Alternatively, the carrier may be selected from an acetate co-polymer or cellulosic polymer. In one embodiment, the acetate co-polymer may be a vinylpyrrolidone-vinyl acetate copolymer. In another embodiment, the cellulosic polymer may be hydroxypropyl cellulose or a methylcellulose ether, for example, hydroxypropyl methylcellulose or carboxymethyl cellulose. It will be appreciated that combinations of acetate copolymers and cellulosic polymers may also be used in some embodiments as described herein. In some embodiments, molecular sieves may also be used as a carrier. In a preferred embodiment, the at least one carrier is a porous carrier. In another embodiment, the at least one carrier is a porous carrier comprising a metal oxide. Suitable examples of metal oxides include silicon dioxide, titanium dioxide, zinc dioxide, zinc oxide and aluminium oxide. In a preferred embodiment, the metal oxide is silicon dioxide. In another embodiment, the at least one carrier is porous silicon dioxide. It will be

appreciated that the compositions described herein may contain at least one porous silicon dioxide carrier.

Suitable commercially available examples of porous silicon dioxide are Syloid® XDP 3050 and Syloid® XDP 3150, characterized by a pore volume of >1.70 ml/g and an average particle size of about 48-66 microns and about 120-170 microns, respectively. The aforementioned silicas Syloid® XDP 3050 and Syloid® XDP 3150 have typical surface areas of about 320 m²/g. Advantageously, the Syloid XDP particles offer a relatively high surface area with many free silanol units to interact and attach to hydrophilic areas of the peptide to achieve stabilization and avoid any aggregation of peptide molecules with each other. In particular, the Syloid XDP particles provide a highly inner porous structure. The relatively small peptide molecules may be absorbed in the inner pore region during the wet granulation process and upon removal of the water the peptides remain in the inner pore structure attached by the polar regions and the silanol units. The geometrical and structural conditions of the Syloid particles permit a stabilizing interaction with the polar regions of the peptide as described herein. The high surface area and the excess availability of the stabilizing silanol units permit an interaction with the peptide molecules in a way that minimizes the risk of peptide aggregation or multimer formation as the peptide molecules are geometrically separated from each other. Other suitable commercially available examples of porous silicon dioxide are Syloid® 244 FP and Syloid AL-1 FP/63FP. Syloid® 244 FP has an average particle size of about 3.5 to about 5.5 microns and a surface area of about 300 m²/g. Syloid AL-1 FP/63FP has an average particle size of about 6.5 to 8.1 microns and a surface area of about 700 m²/g.

The term average particle size as used herein refers to the particle size as measured using a Malvern Mastersizer. It will be appreciated that the term "average particle size" is intended to encompass particles sizes that are $\pm 10\%$ from the stated values.

It will be further appreciated that the compositions as described herein may comprise one or more Syloid carriers. For example, the composition may comprise one or more of Syloid® 244 FP, Syloid® XDP 3050, Syloid® XDP 3150 or Syloid® AL-1 FP/63FP as carriers. In some embodiments, the composition may comprise any one or more of Syloid® 244 FP, Syloid® XDP 3050 or Syloid® XDP 3150 in combination with Syloid® AL-1 FP/63FP as carriers. In some embodiments, the composition may

comprise Syloid® 244 FP and Syloid® AL-1 FP/63FP as carriers, or Syloid® XDP 3050 and Syloid® AL-1 FP/63FP as carriers, or Syloid® XDP 3150 and Syloid® AL-1 FP/63FP as carriers. It will be appreciated that any combination of these carriers is intended to be encompassed within the scope of the invention.

5 The at least one carrier, or at least one porous silicon dioxide carrier, may be provided as a particle. The average particle size at least one carrier, or at least one porous silicon dioxide carrier, described herein may be about 2 to about 200 μm , about 2 to about 150 μm , about 4 to about 150 μm , about 5 to about 150 μm , about 10 to about 150 μm , about 25 to about 150 μm or about 50 to about 150 μm in diameter. In some
10 embodiments, the average particle size may be about 2 to about 195 μm , about 4 to about 195 μm , about 5 to about 195 μm , about 10 to about 195 μm , about 15 to about 190 μm , about 20 to about 185 μm , about 25 to about 180 μm , about 30 to about 175 μm , about 35 to about 170 μm , about 40 to about 170 μm , about 45 to about 170 μm , about 50 to about 170 μm , about 55 to about 170 μm , about 60 to about 170 μm , about
15 65 to about 170 μm , about 70 to about 170 μm , about 75 to about 170 μm , about 80 to about 170 μm , about 85 to about 170 μm , about 90 to about 170 μm , about 95 to about 170 μm , about 100 to about 170 μm , about 105 to about 170 μm , about 110 to about 170 μm , about 115 to about 170 μm or about 120 to about 170 μm in diameter. In another embodiment, the average particle size may be about 2 to about 100 μm ,
20 about 4 to about 100 μm , about 5 to about 100 μm , about 10 to about 100 μm , about 15 to about 95 μm , about 20 to about 90 μm , about 30 to about 85 μm , about 40 to about 80 μm , about 50 to about 75 μm or about 50 to about 70 μm in diameter.

In some embodiments, the average particle size of the at least one carrier, or at least one porous silicon dioxide carrier, may be about 3.0 μm to about 6.0 μm , about 3.1
25 μm to about 5.9 μm , about 3.2 μm to about 5.8 μm , about 3.3 μm to about 5.7 μm , about 3.4 μm to about 5.6 μm , and about 3.5 μm to about 5.5 μm .

In some embodiments, the average particle size of the at least one carrier, or at least one porous silicon dioxide carrier, may be about 6.0 μm to about 8.5 μm , about 6.1
30 μm to about 8.4 μm , about 6.2 μm to about 8.3 μm , about 6.3 μm to about 8.2 μm , about 6.4 μm to about 8.2 μm , and about 6.5 μm to about 8.1 μm .

In some embodiments, the average particle size of the at least one carrier, or at least one porous silicon dioxide carrier, may be about 40 μm to about 74 μm , about 41 μm

to about 73 μm , about 42 μm to about 72 μm , about 43 μm to about 71 μm , about 44 μm to about 70 μm , about 45 μm to about 69 μm , about 46 μm to about 68 μm , about 47 μm to about 67 μm , about 46 μm to about 66 μm .

In some embodiments, the average particle size of the at least one carrier, or at least one porous silicon dioxide carrier, may be about 110 μm to about 180 μm , about 111 μm to about 179 μm , about 112 μm to about 178 μm , about 113 μm to about 177 μm , about 114 μm to about 176 μm , about 115 μm to about 175 μm , about 116 μm to about 174 μm , about 117 μm to about 173 μm , about 118 μm to about 172 μm , about 119 μm to about 171 μm , about 120 μm to about 170 μm .

In some embodiments, the average particle size of the at least one carrier, or at least one porous silicon dioxide carrier, may be about 3.5, about 7.5, about 50 or about 150 μm .

In some embodiments, the ratio of the composition of the peptide to the at least one carrier ranges from about 0.1 to about 20 mg, about 0.2 to about 20 mg, about 0.3 to about 20 mg, about 0.4 to about 20 mg, about 0.5 to about 20 mg, about 0.6 to about 20 mg, about 0.7 to about 20 mg, about 0.8 to about 20 mg, about 0.9 to about 20 mg, about 1 to about 20 mg, about 1 to about 15 mg, about 2 to about 18 mg, about 3 to about 17 mg or about 4 to about 12 mg of peptide/g of the at least one carrier, or at least one porous carrier, or at least one porous silicon dioxide carrier. In some embodiments, the ratio of the composition of the peptide to the at least one carrier ranges from about 0.1 to about 20 mg, about 0.1 to about 15 mg, about 0.1 to about 12 mg, about 0.1 to about 10 mg, about 0.1 to about 9 mg, about 0.1 to about 8 mg, about 0.1 to about 7 mg, about 0.1 to about 6 mg, about 0.1 to about 5 mg, about 0.1 to about 4 mg, about 0.1 to about 3 mg, about 0.1 to about 2 mg, about 0.1 to about 1 mg, about 0.1 to about 0.9 mg, about 0.1 to about 0.8 mg, about 0.1 to about 0.7 mg, about 0.1 to about 0.6 mg, about 0.5 to about 4 mg, about 0.3 to about 4 mg or about 0.1 to about 0.2 mg of peptide/g of the at least one carrier, or at least one porous carrier, or at least one porous silicon dioxide carrier.

Preferably the composition may comprise about 4 mg of peptide, about 8 mg of peptide or about 12 mg of peptide/g of the at least one carrier, or at least one porous carrier, or at least one porous silicon dioxide carrier.

At least one carrier, or at least one porous silicon dioxide carrier, may be present in the pharmaceutical composition in an amount of about 50 to about 3000 mg by weight of the composition. In some embodiments, the at least one carrier, or at least one porous silicon dioxide carrier, may be present in the pharmaceutical composition in an amount of about 100 to about 3000 mg, about 150 to about 3000 mg, about 200 to about 3000 mg, about 250 to about 3000 mg, about 300 to about 3000 mg, about 350 to about 3000 mg, about 400 to about 3000 mg, about 450 to about 3000 mg, about 500 to about 3000 mg, about 550 to about 3000 mg, about 600 to about 3000 mg, about 650 to about 3000 mg, about 700 to about 3000 mg, about 750 to about 3000 mg, about 800 to about 3000 mg, about 850 to about 3000 mg, about 900 to about 3000 mg, about 950 to about 3000 mg, about 1000 to about 3000 mg, about 1100 to about 3000 mg, about 1300 to about 3000 mg, about 1400 to about 3000 mg, about 1500 to about 3000 mg, about 1600 to about 3000 mg, about 1700 to about 3000 mg, about 1800 to about 3000 mg, about 1900 to about 3000 mg, about 2000 to about 3000 mg, about 2100 to about 3000 mg, about 2200 to about 3000 mg, about 2300 to about 3000 mg, about 2400 to about 3000 mg, about 2500 to about 3000 mg, about 2600 to about 3000 mg, about 2700 to about 3000 mg, about 2800 to about 3000 mg or about 2900 to about 3000 mg by weight of the composition. Alternatively, in some embodiments, the at least one carrier, or at least one porous silicon dioxide carrier, may be present in the pharmaceutical composition in an amount of about 100 to about 2900 mg, about 100 to about 2800 mg, about 100 to about 2700 mg, about 100 to about 2600 mg, about 100 to about 2500 mg, about 100 to about 2400 mg, about 100 to about 2300 mg, about 100 to about 2200 mg, about 100 to about 2100 mg, about 100 to about 2000 mg, about 100 to about 1900 mg, about 100 to about 1800 mg, about 100 to about 1700 mg, about 100 to about 1600 mg, about 100 to about 1500 mg, about 100 to about 1400 mg, about 100 to about 1300 mg, about 100 to about 1200 mg, about 100 to about 1100 mg, about 100 to about 1000 mg, about 100 to about 950 mg, about 100 to about 900 mg, about 100 to about 850 mg, about 100 to about 800 mg, about 100 to about 750 mg, about 100 to about 700 mg, about 100 to about 650 mg, about 100 to about 600 mg, about 100 to about 550 mg, about 100 to about 500 mg, about 100 to about 450 mg, about 100 to about 400 mg, about 100 to about 350 mg, about 100 to about 300 mg, about 100 to about 250 mg, about 100 to about 200 mg or about 100 to about 150 mg by weight of the composition. In another

embodiment, the at least one carrier, or at least one porous silicon dioxide carrier, may be present in the pharmaceutical composition in an amount of about 50 to about 1500 or about 80 to about 300 mg by weight of the composition.

In some embodiments, the pharmaceutical composition, when in the form of a finished dosage form, may comprise about 10 to about 99.9 percent by weight of the composition of the carrier, or at least one porous silicon dioxide carrier. In some embodiments, the pharmaceutical composition, when in the form of a finished dosage form, may comprise about 10 to about 99.9, 15 to about 99.9, 20 to about 99.9, 30 to about 99.9, 35 to about 99.9, 40 to about 99.9, 45 to about 99.9, 50 to about 99.9, 55 to about 99.9, 60 to about 99.9, 65 to about 99.9, 70 to about 99.9, 75 to about 99.9, 80 to about 99.9, 85 to about 99.9, 90 to about 99.9 or 95 to about 99.9 percent by weight of the composition of the at least one carrier, or at least one porous silicon dioxide carrier. Alternatively, in other embodiments, the pharmaceutical composition when in the form of a finished dosage form, may comprise about 10 to about 95, 10 to about 90, 10 to about 85, 10 to about 80, 10 to about 75, 10 to about 70, 10 to about 65, 10 to about 60, 10 to about 55, 10 to about 50, 10 to about 45, 10 to about 40, 10 to about 35, 10 to about 30, 10 to about 25, 10 to about 20 or 10 to about 15 percent by weight of the composition of the at least one carrier, or at least one porous silicon dioxide carrier.

Preferably, the pharmaceutical composition, as described herein, may have a moisture content of about 5% or less, about 4.5% or less, about 4% or less, about 3.5% or less, about 3% or less, about 2.5% or less, about 2% or less, about 1.5% or less, or about 1% or less, inclusive of all ranges and subranges therebetween (i.e., any of about 1% to about 5%, about 1.5% to about 5%, about 2% to about 5%, about 2.5% to about 5%, about 3% to about 5%, about 3.5% to about 5%, about 4% to about 5%, about 4.5% to about 5, about 1% to about 5%, about 1% to about 4.5%, about 1% to about 4%, about 1% to about 3.5%, about 1% to about 3%, about 1% to about 2.5%, about 1% to about 2%, about 1% to about 1.5%, and the like). Compositions or dosage forms as described herein, maintained at low moisture content, have been found to be substantially more stable compared to conventional compositions maintained at higher moisture contents, e.g. above about 5% or higher. It will be appreciated that a similar moisture content will also apply to any dosage forms as described herein.

The term “moisture content”, also referred to as “water content”, means the amount of water that a composition contains. For compositions which do not change volume with changing moisture content, the moisture content can be expressed volumetrically (i.e., by volume) as the ratio of the mass of moisture to the dry volume of the material. For compositions that change volume with changing moisture content, the moisture content can be expressed gravimetrically (i.e., by weight) as the mass of water removed upon drying per unit dry mass of the specimen. Determination of moisture content can be achieved by any of the conventional methods known in the art. For example, the moisture content can be determined by chemical titration, such as Karl Fischer titration, in which a sample is dissolved in an electrochemical titration cell. Water from the sample is consumed in an electrochemical reaction whose endpoint is measured potentiometrically, thereby providing a direct measure of the amount of water in the sample. Alternatively, relatively simple thermogravimetric methods may be used such as “Loss on Drying” (LoD), in which the mass of a sample is measured prior to, and after controlled drying. The loss of mass after drying is attributed to loss of moisture. Commercially available moisture analyzers (e.g., available from Mettler Toledo, Sartorius AG, etc.) can also be used to determine moisture content. The moisture content of the compositions or dosage forms of the present invention can be measured by any suitable method known in the art, for example LoD.

The term “accelerated stability testing” or “accelerated storage testing” refers to test methods used to simulate the effects of relatively long-term storage conditions on enzyme activity, which can be carried out in a relatively short time. Accelerated stability testing methods are known in the art to be a reliable alternative to real-time stability testing, and can accurately predict the shelf-life of biological products. Such “accelerated stability testing” conditions are known in the art and are in accordance with the International Conference for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Stability Testing of New Drug Substances and Products Q1A, herein incorporated by reference in its entirety.

Advantageously, the pharmaceutical composition, as described herein, can be formulated in the substantial absence of other components such as glidants, lubricants, cations or amines and the like that have been previously required to stabilize peptide formulations and compositions. This results in a simpler, more robust

manufacture with minimal additional components. Furthermore, the use of at least one carrier having a high surface area results in a more stable formulation of peptides with a concomitant decrease in the formation of multimers compared to previous formulations.

5 In certain embodiments, a pharmaceutical composition described herein does not comprise a stabilizer or other component for stabilizing a peptide formulation and/or composition. In certain embodiments, a stabilizer may be a cation, an amine, or the like. Non-limiting examples of stabilizers include Ca^{2+} , Mg^{2+} , Zn^{2+} , polyvinyl pyrrolidone, polyvinyl alcohol, sucrose, cyclodextrin, xanthan, trehalose, sodium
10 chloride, inulin, primary amines (for example, glycine, alanine, serine, threonine, cysteine, valine, leucine, isoleucine, methionine, phenylalanine, tyrosine, aspartic acid, glutamic acid, arginine, lysine, ornithine, citrulline, taurine pyrrolysine, or a conjugate or a mixture thereof), L-histidine and acesulfame.

In certain embodiments, a pharmaceutical composition described herein may
15 comprise a stabilizer to provide additional stability to the pharmaceutical composition.

The invention also relates to a pharmaceutical composition consisting of an adsorbate of a peptide as described herein on at least one carrier having a surface area of about $300 \text{ m}^2/\text{g}$.

In another aspect, the invention also relates to a pharmaceutical composition
20 consisting of an adsorbate of a peptide as described herein on at least one porous carrier having a surface area of about $300 \text{ m}^2/\text{g}$. In another aspect, the invention also relates to a pharmaceutical composition consisting of an adsorbate of a peptide as described herein on at least one porous silicon dioxide carrier having a surface area of about $300 \text{ m}^2/\text{g}$. The invention also further relates to a pharmaceutical composition
25 consisting of an adsorbate of a peptide as described herein on at least one carrier having a surface area of about $300 \text{ m}^2/\text{g}$ to about $700 \text{ m}^2/\text{g}$. In another aspect, the invention also relates to a pharmaceutical composition consisting of an adsorbate of a peptide as described herein on at least one porous carrier having a surface area of about $300 \text{ m}^2/\text{g}$ to about $700 \text{ m}^2/\text{g}$. In another aspect, the invention also relates to a
30 pharmaceutical composition consisting of an adsorbate of a peptide as described herein on at least one porous silicon dioxide carrier having a surface area of about $300 \text{ m}^2/\text{g}$ to about $700 \text{ m}^2/\text{g}$.

Compositions comprising SEQ ID NO.1

In one embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein the at least one carrier has an average particle size of about 2 to about 200 μm .

In one embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one porous carrier, wherein the at least one porous carrier has an average particle size of about 2 to about 200 μm .

In one embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier, wherein the at least one porous silicon dioxide carrier has an average particle size of about 2 to about 200 μm .

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein said composition has moisture content of less than about 5%.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one porous carrier, wherein said composition has moisture content of less than about 5%.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is

any amino acid, or a pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier, wherein said composition has moisture content of less than about 5%.

5 In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein said at least one carrier has a surface area of at least about 20 m²/g.

10 In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one porous carrier, wherein said at least one porous carrier has a surface area of at least about 20 m²/g.

15 In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier, wherein said at least one porous silicon dioxide carrier has a surface area of at least about 20 m²/g.

20 In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein said at least one carrier has a surface area of at least about 300 m²/g.

25 In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one porous carrier, wherein said at least one porous carrier has a surface area of at least about 300 m²/g.

30

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier, wherein said at least one porous silicon dioxide carrier has a surface area of at least about 300 m²/g.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein said at least one carrier has a surface area of at least about 20 m²/g to about 700 m²/g.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one porous carrier, wherein said at least one porous carrier has a surface area of at least about 20 m²/g to about 700 m²/g.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier, wherein said at least one porous silicon dioxide carrier has a surface area of at least about 20 m²/g to about 700 m²/g.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein said at least one carrier has a surface area of at least about 300 m²/g to about 700 m²/g.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one porous carrier, wherein said at least one porous carrier has a surface area of at least about 300 m²/g to about 700 m²/g.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier, wherein said at least one porous silicon dioxide carrier has a surface area of at least about 300 m²/g to about 700 m²/g.

In another embodiment, the pharmaceutical composition as described herein may comprise an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein said composition has moisture content of less than about 5%, and the at least one carrier has an average particle size of about 2 to about 200 µm.

In another embodiment, the pharmaceutical composition as described herein may comprise an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one porous carrier, wherein said composition has moisture content of less than about 5%, and the at least one porous carrier has an average particle size of about 2 to about 200 µm.

In another embodiment, the pharmaceutical composition as described herein may comprise an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier, wherein said composition has moisture content of less than about 5%, and the at least one porous silicon dioxide carrier has an average particle size of about 2 to about 200 µm.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein the at least one carrier has a surface area of at least about 300 m²/g and an average particle size of about 2 to about 200 µm.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one porous carrier, wherein the at least one porous carrier has a surface area of at least about 300 m²/g and an average particle size of about 2 to about 200 µm.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier, wherein the at least one porous silicon dioxide carrier has a surface area of at least about 300 m²/g and an average particle size of about 2 to about 200 µm.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein the at least one carrier has a surface area of at least about 20 m²/g and an average particle size of about 2 to about 200 µm.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one porous carrier, wherein the at least one porous carrier has a surface area of at least about 20 m²/g and an average particle size of about 2 to about 200 µm.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier, wherein the at least one porous silicon dioxide carrier has a surface area of at least about 20 m²/g and an average particle size of about 2 to about 200 µm.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein the at least one carrier has a surface area of at least about 300 m²/g to about 700 m²/g and an average particle size of about 2 to about 200 µm.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one porous carrier, wherein the at least one porous carrier has a surface area of at least about 300 m²/g to about 700 m²/g and an average particle size of about 2 to about 200 µm.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier, wherein the at least one porous silicon dioxide carrier has a surface area of at least about 300 m²/g to about 700 m²/g and an average particle size of about 2 to about 200 µm.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on

at least one carrier, wherein the at least one carrier has a surface area of at least about 20 m²/g to about 700 m²/g and an average particle size of about 2 to about 200 μm.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one porous carrier, wherein the at least one porous carrier has a surface area of at least about 20 m²/g to about 700 m²/g and an average particle size of about 2 to about 200 μm.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier, wherein the at least one porous silicon dioxide carrier has a surface area of at least about 20 m²/g to about 700 m²/g and an average particle size of about 2 to about 200 μm.

In another embodiment, the pharmaceutical composition as described herein may comprise an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein said composition has moisture content of less than about 5%, and the at least one carrier has an average particle size of about 2 to about 200 μm, and a surface area of at least about 20 m²/g.

In another embodiment, the pharmaceutical composition as described herein may comprise an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one porous carrier, wherein said composition has moisture content of less than about 5%, and the at least one porous carrier has an average particle size of about 2 to about 200 μm, and a surface area of at least about 20 m²/g.

In another embodiment, the pharmaceutical composition as described herein may comprise an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier, wherein said composition has moisture content of less than about 5%, and the at least one porous silicon dioxide carrier has an average particle size of about 2 to about 200 μm , and a surface area of at least about 20 m^2/g .

In another embodiment, the pharmaceutical composition as described herein may comprise an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein said composition has moisture content of less than about 5%, and the at least one carrier has an average particle size of about 2 to about 200 μm , and a surface area of at least about 300 m^2/g .

In another embodiment, the pharmaceutical composition as described herein may comprise an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one porous carrier, wherein said composition has moisture content of less than about 5%, and the at least one porous carrier has an average particle size of about 2 to about 200 μm , and a surface area of at least about 300 m^2/g .

In another embodiment, the pharmaceutical composition as described herein may comprise an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier, wherein said composition has moisture content of less than about 5%, and the at least one porous silicon dioxide carrier has an average particle size of about 2 to about 200 μm , and a surface area of at least about 300 m^2/g .

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one porous

silicon dioxide carrier selected from Syloid® XDP 3050, Syloid® XDP 3150, Syloid® 244 FP, Syloid AL-1 FP/63FP or any combination thereof.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-
5 Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier selected from Syloid® XDP 3050, Syloid® XDP 3150, Syloid® 244 FP, Syloid AL-1 FP/63FP or any combination thereof, wherein the at least one porous silicon dioxide carrier has a surface area of at least about 300 m²/g to about
10 700 m²/g and an average particle size of about 2 to about 200 µm.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-
Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, wherein at least one carboxyl group of the peptide is an alkyl ester,
15 or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein said at least one carrier has a surface area of at least about 20 m²/g to about 700 m²/g.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-
Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is
20 any amino acid, wherein at least one carboxyl group of the peptide is an alkyl ester, or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein said at least one carrier has a surface area of at least about 300 m²/g to about 700 m²/g.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-
25 Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, wherein at least one carboxyl group of the peptide is an alkyl ester, or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein the at least one carrier has a surface area of at least about 20 m²/g to about 700 m²/g and an average particle size of about 2 to about 200 µm.

30 In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-

Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, wherein at least one carboxyl group of the peptide is an alkyl ester, or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein the at least one carrier has a surface area of at least about 300 m²/g to about 700 m²/g and an average particle size of about 2 to about 200 μm.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, wherein at least one carboxyl group of the peptide is an alkyl ester, or a pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier selected from Syloid® XDP 3050, Syloid® XDP 3150, Syloid® 244 FP, Syloid AL-1 FP/63FP or any combination thereof.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, wherein at least one carboxyl group of the peptide is an alkyl ester, or a pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier selected from Syloid® XDP 3050, Syloid® XDP 3150, Syloid® 244 FP, Syloid AL-1 FP/63FP or any combination thereof, wherein the at least one porous silicon dioxide carrier has a surface area of at least about 300 m²/g to about 700 m²/g and an average particle size of about 2 to about 200 μm.

In another embodiment, the pharmaceutical composition as described herein may comprise an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier, wherein the at least one porous silicon dioxide carrier is Syloid® XDP 3150.

In another embodiment, the pharmaceutical composition as described herein may comprise an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one porous

silicon dioxide carrier, wherein the at least one porous silicon dioxide carrier is Syloid® XDP 3150, wherein said composition has moisture content of less than about 5%.

In one embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one carrier selected from an acetate co-polymer carrier, a cellulosic polymer carrier or a combination thereof.

In one embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one vinylpyrrolidone-vinyl acetate copolymer carrier.

In one embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one hydroxypropyl cellulose carrier.

In one embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one methylcellulose carrier.

In one embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino acid, or a pharmaceutically acceptable salt thereof, on at least one hydroxypropyl methylcellulose carrier.

In one embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino

acid, or a pharmaceutically acceptable salt thereof, on at least one carboxymethyl cellulose carrier.

Compositions comprising SEQ ID NOs.2, 3 and 4

In one embodiment, there is also provided a pharmaceutical composition comprising
5 an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-
Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-
Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-
Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable
salt thereof, on at least one carrier, wherein the at least one carrier has an average
10 particle size of about 2 to about 200 μm .

In one embodiment, there is also provided a pharmaceutical composition comprising
an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-
Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-
Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-
15 Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable
salt thereof, on at least one porous carrier, wherein the at least one porous carrier has
an average particle size of about 2 to about 200 μm .

In one embodiment, there is also provided a pharmaceutical composition comprising
an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-
20 Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.1), wherein X is any amino
acid, or a pharmaceutically acceptable salt thereof, on at least one porous silicon
dioxide carrier, wherein the at least one porous silicon dioxide carrier has an average
particle size of about 2 to about 200 μm .

In another embodiment, there is also provided a pharmaceutical composition
25 comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-
Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-
Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-
Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically
acceptable salt thereof, on at least one carrier, wherein said composition has moisture
30 content of less than about 5%.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one porous carrier, wherein said composition has moisture content of less than about 5%.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier, wherein said composition has moisture content of less than about 5%.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein said at least one carrier has a surface area of at least about 20 m²/g.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one porous carrier, wherein said at least one porous carrier has a surface area of at least about 20 m²/g.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-

Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier, wherein said at least one porous silicon dioxide carrier has a surface area of at least about 20 m²/g.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein said at least one carrier has a surface area of at least about 300 m²/g.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one porous carrier, wherein said at least one porous carrier has a surface area of at least about 300 m²/g.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier, wherein said at least one porous silicon dioxide carrier has a surface area of at least about 300 m²/g.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein said at least one carrier has a surface area of at least about 20 m²/g to about 700 m²/g.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one porous carrier, wherein said at least one porous carrier has a surface area of at least about 20 m²/g to about 700 m²/g.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier, wherein said at least one porous silicon dioxide carrier has a surface area of at least about 20 m²/g to about 700 m²/g.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein said at least one carrier has a surface area of at least about 300 m²/g to about 700 m²/g.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one porous carrier, wherein said at least one porous carrier has a surface area of at least about 300 m²/g to about 700 m²/g.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-

Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier, wherein said at least one porous silicon dioxide carrier has a surface area of at least about 300 m²/g to about 700 m²/g.

In another embodiment, the pharmaceutical composition as described herein may comprise an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein said composition has moisture content of less than about 5%, and the at least one carrier has an average particle size of about 2 to about 200 µm.

In another embodiment, the pharmaceutical composition as described herein may comprise an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one porous carrier, wherein said composition has moisture content of less than about 5%, and the at least one porous carrier has an average particle size of about 2 to about 200 µm.

In another embodiment, the pharmaceutical composition as described herein may comprise an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier, wherein said composition has moisture content of less than about 5%, and the at least one porous silicon dioxide carrier has an average particle size of about 2 to about 200 µm.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-

Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein the at least one carrier has a surface area of at least about 300 m²/g and an average particle size of about 2 to about 200 µm.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one porous carrier, wherein the at least one porous carrier has a surface area of at least about 300 m²/g and an average particle size of about 2 to about 200 µm.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier, wherein the at least one porous silicon dioxide carrier has a surface area of at least about 300 m²/g and an average particle size of about 2 to about 200 µm.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein the at least one carrier has a surface area of at least about 20 m²/g and an average particle size of about 2 to about 200 µm.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-

Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one porous carrier, wherein the at least one porous carrier has a surface area of at least about 20 m²/g and an average particle size of about 2 to about 200 µm.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier, wherein the at least one porous silicon dioxide carrier has a surface area of at least about 20 m²/g and an average particle size of about 2 to about 200 µm.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein the at least one carrier has a surface area of at least about 300 m²/g to about 700 m²/g and an average particle size of about 2 to about 200 µm.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one porous carrier, wherein the at least one porous carrier has a surface area of at least about 300 m²/g to about 700 m²/g and an average particle size of about 2 to about 200 µm.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-

Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier, wherein the at least one porous silicon dioxide carrier has a surface area of at least about 300 m²/g to about 700 m²/g and an average particle size of about 2 to about 200 µm.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein the at least one carrier has a surface area of at least about 20 m²/g to about 700 m²/g and an average particle size of about 2 to about 200 µm.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one porous carrier, wherein the at least one porous carrier has a surface area of at least about 20 m²/g to about 700 m²/g and an average particle size of about 2 to about 200 µm.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier, wherein the at least one porous silicon dioxide carrier has a surface area of at least about 20 m²/g to about 700 m²/g and an average particle size of about 2 to about 200 µm.

In another embodiment, the pharmaceutical composition as described herein may comprise an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-

Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein said composition has moisture content of less than about 5%, and the at least one carrier has an average particle size of about 2 to about 200 μm , and a surface area of at least about 20 m^2/g .

In another embodiment, the pharmaceutical composition as described herein may comprise an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one porous carrier, wherein said composition has moisture content of less than about 5%, and the at least one porous carrier has an average particle size of about 2 to about 200 μm , and a surface area of at least about 20 m^2/g .

In another embodiment, the pharmaceutical composition as described herein may comprise an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier, wherein said composition has moisture content of less than about 5%, and the at least one porous silicon dioxide carrier has an average particle size of about 2 to about 200 μm , and a surface area of at least about 20 m^2/g .

In another embodiment, the pharmaceutical composition as described herein may comprise an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein said composition has moisture content of less than about 5%, and the at least one carrier has an average particle size of about 2 to about 200 μm , and a surface area of at least about 300 m^2/g .

In another embodiment, the pharmaceutical composition as described herein may comprise an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one porous carrier, wherein said composition has moisture content of less than about 5%, and the at least one porous carrier has an average particle size of about 2 to about 200 μm , and a surface area of at least about 300 m^2/g .

In another embodiment, the pharmaceutical composition as described herein may comprise an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier, wherein said composition has moisture content of less than about 5%, and the at least one porous silicon dioxide carrier has an average particle size of about 2 to about 200 μm , and a surface area of at least about 300 m^2/g .

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier selected from Syloid® XDP 3050, Syloid® XDP 3150, Syloid® 244 FP, Syloid AL-1 FP/63FP or any combination thereof wherein the at least one porous silicon dioxide carrier has a surface area of at least about 300 m^2/g to about 700 m^2/g and an average particle size of about 2 to about 200 μm .

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-

Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier selected from Syloid® XDP 3050, Syloid® XDP 3150, Syloid® 244 FP, Syloid AL-1 FP/63FP or any combination thereof.

- 5 In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), wherein at least one
10 carboxyl group of the peptide is an alkyl ester, or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein said at least one carrier has a surface area of at least about 20 m²/g to about 700 m²/g.

- In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), wherein at least one
15 carboxyl group of the peptide is an alkyl ester, or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein said at least one carrier has a surface area of at least about 300 m²/g to about 700 m²/g.
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- In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), wherein at least one
25 carboxyl group of the peptide is an alkyl ester, or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein the at least one carrier has a surface area of at least about 20 m²/g to about 700 m²/g and an average particle size of about 2 to about 200 µm.

- 30 In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-

Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), wherein at least one carboxyl group of the peptide is an alkyl ester, or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein the at least one carrier has a surface area of
5 at least about 300 m²/g to about 700 m²/g and an average particle size of about 2 to about 200 µm.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-
10 Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), wherein at least one carboxyl group of the peptide is an alkyl ester, or a pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier selected from Syloid® XDP 3050, Syloid® XDP 3150, Syloid® 244 FP, Syloid AL-1 FP/63FP or any combination thereof,
15 wherein the at least one porous silicon dioxide carrier has a surface area of at least about 300 m²/g to about 700 m²/g and an average particle size of about 2 to about 200 µm.

In another embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-
20 Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), wherein at least one carboxyl group of the peptide is an alkyl ester, or a pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier selected from Syloid® XDP 3050, Syloid® XDP 3150, Syloid® 244 FP, Syloid AL-1 FP/63FP or any combination thereof.
25

In another embodiment, the pharmaceutical composition as described herein may comprise an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a
30 pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier, wherein the at least one porous silicon dioxide carrier is Syloid® XDP 3150.

In another embodiment, the pharmaceutical composition as described herein may comprise an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier, wherein the at least one porous silicon dioxide carrier is Syloid® XDP 3150, wherein said composition has moisture content of less than about 5%.

In one embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one carrier selected from an acetate co-polymer carrier, a cellulosic polymer carrier or a combination thereof.

In one embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one vinylpyrrolidone-vinyl acetate copolymer carrier.

In one embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one hydroxypropyl cellulose carrier.

In one embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-

Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one methylcellulose carrier.

In one embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one hydroxypropyl methylcellulose carrier.

In one embodiment, there is also provided a pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one carboxymethyl cellulose carrier.

Advantageously, the pharmaceutical composition in accordance with the present invention is in the form of a free-flowing powder, with excellent handling properties. The adsorbate is very suitable to be used for the preparation of dosage forms. Dosage forms contemplated in the present disclosure include a tablet, a powder filled capsule or a powder filled sachet. "Dosage form" as used herein may refer to physically discrete units suited as unitary dosages for the individual to be treated; each unit containing a predetermined quantity of the composition, as described herein, is calculated to produce the desired therapeutic effect. The composition may be formulated for convenient and effective administration in effective amounts in an acceptable dosage unit.

In the case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients.

In one embodiment of the invention, the pharmaceutical composition or dosage forms as described herein may be administered orally. The free-flowing powder may be enclosed in a hard or soft-shell gelatin capsule, tablets, or incorporated directly into an

individual's diet. For oral therapeutic administration, the dosage form comprising the pharmaceutical composition as described herein may be used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like

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Another form of a pharmaceutical composition is a dosage form formulated as enterically coated granules, tablets or capsules suitable for oral administration. Also included in the scope of this invention are delayed release formulations.

10 Suitable pharmaceutical compositions in accordance with the invention will generally include an amount of the active compound(s) with an acceptable pharmaceutical diluent or excipient, such as a sterile aqueous solution, to give a range of final concentrations, depending on the intended use. The techniques of preparation are generally well known in the art, as exemplified by Remington's Pharmaceutical
15 Sciences (18th Edition, Mack Publishing Company, 1995).

In some embodiments, the composition may comprise capsules/tablets/sachets that comprise about 20-600 mcg of Linaclotide to be taken orally once daily on an empty stomach. In some embodiments, the Linaclotide composition comprises
20 capsules/tablets/sachets that comprise at least about 20, about 25, about 30, about 35, about 45, about 50, about 55, about 60, about 65, about 70, about 75, about 80, about 85, about 90, about 100, about 145 or about 290 mcg which are to be taken orally once daily on an empty stomach for treating IBS-C (IBS with constipation). In some embodiments, the Linaclotide composition comprises capsules/tablets/sachets
25 that comprise at least about 20, about 25, about 30, about 35, about 45, about 50, about 55, about 60, about 65, about 70, about 72, about 75, about 80, about 85, about 90, about 100, about 145 or about 290 mcg which are to be taken orally once daily on an empty stomach for treating chronic idiopathic constipation. In some embodiments, the Linaclotide composition comprises capsules/tablets/sachets that comprise at least
30 about 30 mcg to 1500 mcg of Linaclotide, or 10mg to 500mg of Linaclotide.

The Linaclotide composition may include additional ingredients or excipients. In certain embodiments, one or more therapeutic agents of the dosage unit may exist in an

extended or control release formulation and additional therapeutic agents may not exist in extended release formulation. For example, a peptide described herein may exist in a controlled release formulation or extended release formulation in the same dosage unit with another agent that may or may not be in either a controlled release or extended release formulation. Thus, in certain embodiments, it may be desirable to provide for the immediate release of one or more of the agents described herein, and the controlled release of one or more other agents.

Single or multiple administrations of the pharmaceutical compositions or dosage forms, as described herein, may be carried out. It will be appreciated that, one skilled in the art would be able, by routine experimentation, to determine effective, non-toxic dosage levels of the composition as described herein and an administration pattern which would be suitable for treating the diseases to which the compositions are applicable.

Further, it will be apparent to one of ordinary skill in the art that the optimal course of treatment, such as the number of doses of the composition or dosage form, as described herein, given per day for a defined number of days, can be ascertained using conventional course of treatment determination tests.

Also provided is a process for preparing the pharmaceutical composition as defined herein comprising the steps of: (a) preparing an aqueous solution of a peptide; (b) combining the aqueous solution of the peptide with a carrier; and (c) drying the mixture of peptide and carrier under reduced pressure at a temperature of from about 30 to about 50°C.

Preferably the aqueous solution of the peptide is acidic with a pH in the range of about 1 to about 3, about 1 to about 2.9, about 1 to about 2.8, about 1 to about 2.7, about 1 to about 2.6, about 1 to about 2.5, about 1 to about 2.4, about 1 to about 2.3, about 1 to about 2.2. Alternatively, in some embodiments, the pH may be in the range of about 1.1 to about 3, about 1.2 to about 3, about 1.3 to about 3, about 1.4 to about 3, about 1.5 to about 3, about 1.6 to about 3, about 1.7 to about 3, about 1.8 to about 3, about 1.9 to about 3, about 2 to about 3, about 2.1 to about 3 or about 2.2 to about 3. In a preferred embodiment, the pH is in the range of about 1.7 to about 2.2.

Additionally, the combining step (step B) may comprise spraying or rinsing the aqueous solution of peptide onto a carrier powder.

The drying step (step C) may be performed in a vacuum dryer, spray drier or a fluidized bed dryer. Examples of equipment that can be used are fluid bed, high shear mixed and spray drying. The dried powder may be further milled or granulated. The dried powder or granulated powder may be encapsulated in HPMC or gelatin or hard gelatin capsules.

In one embodiment the carrier is a porous carrier. In some embodiments, the porous carrier is porous silicon dioxide.

It will be appreciated that the methods and equipment to carry out the process to form the adsorbate are well known in the art.

In some embodiments the composition may be formed by an extrusion process, for example by twin screw extrusion.

In one aspect, there is provided the use of a composition as described herein in the manufacture of a medicament for treating a gastrointestinal disorder in a patient in need thereof.

In another aspect, there is provided a method of treating a gastrointestinal disorder comprising administering the composition, as described herein, or a dosage form, as described herein, to a patient in need thereof.

In various embodiments, a patient diagnosed with a gastrointestinal disorder may be provided with the composition described herein, wherein the gastrointestinal disorder may be selected from the group consisting of irritable bowel syndrome (IBS) (such as constipation-predominant IBS), constipation (such as chronic idiopathic constipation), a functional gastrointestinal disorder, gastroesophageal reflux disease, functional heartburn, dyspepsia, visceral pain, gastroparesis, chronic intestinal pseudo-obstruction, colonic pseudo-obstruction, Crohn's disease, ulcerative colitis, and inflammatory bowel disease, chronic constipation or irritable bowel syndrome (IBS).

In a further embodiment, the gastrointestinal disorder may be constipation. The constipation may be chronic idiopathic constipation, idiopathic constipation, due to

post-operative ileus, or caused by opiate use. Clinically accepted criteria that define constipation include the frequency of bowel movements, the consistency of feces and the ease of bowel movement. Constipation may be idiopathic (functional constipation or slow transit constipation) or secondary to other causes including neurologic, metabolic or endocrine disorders. These disorders include diabetes mellitus, hypothyroidism, hyperthyroidism, hypocalcaemia, Multiple Sclerosis, Parkinson's disease, spinal cord lesions, Neurofibromatosis, autonomic neuropathy, Chagas disease, Hirschsprung's disease and Cystic fibrosis. Constipation may also be the result of surgery (postoperative ileus) or due to the use of drugs such as analgesics (like opioids), antihypertensives, anticonvulsants, antidepressants, antispasmodics and antipsychotics.

In other embodiments, the gastrointestinal disorder may be irritable bowel syndrome (IBS). The irritable bowel syndrome can be constipation-predominant irritable bowel syndrome (IBS-C), diarrhea-predominant irritable bowel syndrome (IBS-D) or alternating between the two irritable bowel syndromes (IBS-A).

In other embodiments, the gastrointestinal disorder may be dyspepsia.

In other embodiments, the gastrointestinal disorder may be gastroparesis. The gastroparesis may be selected from idiopathic, diabetic or post-surgical gastroparesis.

In still other embodiments, the gastrointestinal disorder may be chronic intestinal pseudo obstruction.

In other embodiments, the gastrointestinal disorder may be Crohn's disease.

In some embodiments, the gastrointestinal disorder may be ulcerative colitis.

Preferably the gastrointestinal disorder may be selected from IBS or chronic constipation. More preferably, the IBS is IBS-C (IBS with predominant constipation).

In one embodiment, there is provided the use of a composition as described herein in the manufacture of a medicament for treating IBS-C (IBS with predominant constipation) or chronic constipation.

In another aspect, there is provided a method of treating IBS-C (IBS with predominant constipation) or chronic constipation comprising administering the composition, as described herein, or a dosage form, as described herein, to a patient in need thereof.

It will be appreciated that the composition as described may further comprise one or more supplementary active ingredients or medicaments useful for the treatment of gastrointestinal disorders. Alternatively, the composition as described herein may be administered in combination with a supplementary active ingredient or medicament, either separately, sequentially or simultaneously.

The supplementary active ingredient or medicament may be a probiotic or a prebiotic or a mixture thereof. As used herein, the term "probiotic" refers to live bacteria (also referred to as microflora or microorganisms) that confer a beneficial effect when introduced into the gastrointestinal tract of a mammal. The term "prebiotic" refers to any substance that may be consumed by a relevant probiotic, or that otherwise assists in keeping the relevant probiotic alive or stimulates its growth, and may include mucopolysaccharides, oligosaccharides, polysaccharides, amino acids, vitamins, nutrient precursors and proteins. The term "gastrointestinal tract" refers to the tract from the mouth to the anus and includes the stomach and intestines (including the ileum, duodenum, jejunum, caecum, crassum (large intestine), rectum, and tenue (small intestine, which includes the intestinum tenue mesenteriale).

Accordingly, in one aspect, there is provided use of a composition as described herein in the manufacture of a medicament for treating a gastrointestinal disorder in a patient in need thereof, wherein the composition further comprises a probiotic, a prebiotic or a mixture thereof.

In another aspect, there is provided a method of treating a gastrointestinal disorder comprising administering the composition as described herein or a dosage form as described herein, to a patient in need thereof, wherein the composition or dosage form further comprises a probiotic, a prebiotic or a mixture thereof.

The probiotic may comprise lactic acid bacteria, including Lactobacilli (abbreviated to "L." herein), Bifidobacteria (abbreviated to "B." herein), and Streptococci (abbreviated to "S." herein); anaerobic bacteria; or aerobic bacteria or mixtures thereof. Non-

- limiting examples of probiotics that may be used include, but are not limited to, one or more of *L. acidophilus*, *L. reuteri*, *L. curvatus*, *L. bulgaricus*, *L. grasseri*, *L. casei*, *L. fermentum*, *L. caveasicus*, *L. helveticus*, *L. lactis*, *L. salivarius*, *L. rhamnosus*, *L. brevis*, *L. leichmanni*, *L. plantarum*, *L. cellobiosus*, *L. buchneri*, *B. laterosporus*, *B. breve*, *B. subtilis*, *L. sporogenes* (also known as *Bacillus coagulans*), *pediococcus acidilactici*, *pediococcus pentosaceus*, *enterococcus faecium*, *B. adolescentis*, *B. infantis*, *B. longum*, *B. thermophilum*, *B. animalis*, and *B. bifidum* and *S. thermophilus*. Other probiotics that may be used include *Lactococcus lactis cremoris*, *S. diacetylactis* and *S. intermedius*.
- As will be appreciated by those of skill in the art, there is no published standard for the amount of bacteria that should be in a probiotic product or dosage form, only estimated figures ranging from 10^6 to 10^{10} bacteria per day, depending on the condition of the host. However, probiotics are generally considered to be safe and well tolerated by humans even at high dosages.
- In some embodiments, the prebiotic may comprise one or more of the following (a) a mucopolysaccharide or glycosaminoglycan, e.g. hyaluronic acid, agar, carrageenan or chitin or the like (b) an oligosaccharide, (c) a fructo-oligosaccharide ("FOS"), such as a soy fructo-oligosaccharide, inulin or banana fiber, (d) a pectin or pectic polysaccharide, (e) a mannan, such as guar gum, locust bean gum, konjac, or xanthan gum, (f) a pentosan, beta-glucan, arabinan and galactan, and arabinogalactans and (g) mixtures thereof. In some embodiments, the prebiotic may be selected to be complementary to the probiotic (for example, a complimentary prebiotic is consumed by, or otherwise assists in keeping alive or stimulates the growth of, a relevant probiotic).
- As used herein, the term "about", in the context of concentrations of components of the formulations, typically means $\pm 5\%$ of the stated value, more typically $\pm 4\%$ of the stated value, more typically $\pm 3\%$ of the stated value, more typically, $\pm 2\%$ of the stated value, even more typically $\pm 1\%$ of the stated value, and even more typically $\pm 0.5\%$ of the stated value.
- Throughout this disclosure, certain embodiments may be disclosed in a range format. It should be understood that the description in range format is merely for convenience

and brevity and should not be construed as an inflexible limitation on the scope of the disclosed ranges. Accordingly, the description of a range should be considered to have specifically disclosed all the possible sub-ranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be
5 considered to have specifically disclosed sub-ranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

Certain embodiments may also be described broadly and generically herein. Each of
10 the narrower species and subgeneric groupings falling within the generic disclosure also form part of the disclosure. This includes the generic description of the embodiments with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

15 Unless the context requires otherwise or specifically stated to the contrary, integers, steps, or elements of the invention recited herein as singular integers, steps or elements clearly encompass both singular and plural forms of the recited integers, steps or elements.

The invention illustratively described herein may suitably be practiced in the absence
20 of any element or elements, limitation or limitations, not specifically disclosed herein. Thus, for example, the terms "comprising", "including", "containing", etc. shall be read expansively and without limitation. Additionally, the terms and expressions employed herein have been used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the
25 features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the inventions embodied therein herein disclosed may be resorted to by those skilled in
30 the art, and that such modifications and variations are considered to be within the scope of this invention.

The invention has been described broadly and generically herein. Each of the narrower species and subgeneric groupings falling within the generic disclosure also form part of the invention. This includes the generic description of the invention with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

Other embodiments are within the following claims and non-limiting examples. In addition, where features or aspects of the invention are described in terms of Markush groups, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group.

EXAMPLES

Non-limiting examples of the invention, including the best mode, and a comparative example will be further described in greater detail by reference to specific Examples, which should not be construed as in any way limiting the scope of the invention.

Example 1 - Preparation of Linaclotide Carrier Compositions

Linaclotide carrier compositions were prepared at 4, 8 and 12 mg/g of carrier.

Batches of Linaclotide carrier compositions were prepared using a Diosna laboratory mixer. Briefly, 1 kg Syloid (either Syloid® XDP 3150 or Syloid® FP 244 or Syloid® XDP 3050) was weighted in a steel box and transferred into the 10 L container of the Diosna mixer. Linaclotide was then added to a hydrochloric acid (HCl) solution at a pH of from 1.7-2.2 to form an acidic Linaclotide solution. 1 kg of Linaclotide solution was sprayed on the Syloid® for approximately 6 minutes. The mixture was then stirred for a further 5 minutes to form a wet granulate. The resulting wet granulate was then dried using a vacuum dryer. Dried Linaclotide carrier composition granules were then encapsulated into hard gelatin (HG) capsules under controlled humidity conditions below 40%, or formed into tablets, using techniques well known to those in the art and packed in HDPE (high-density polyethylene) bottles under nitrogen either with or without a desiccant, for example MiniPax®.

Tables 1 to 5 show the specific compositions of the granulate Linaclotide carrier composition produced in accordance with the invention as described herein. Table 1

shows the composition of Linaclotide formulated as an absorbate on Syloid®3150. Table 2 shows the composition of Linaclotide formulated as an absorbate on Syloid®3150 and including Syloid®AL as an additional Syloid. Table 3 shows the composition of Linaclotide formulated as an absorbate on Syloid®244. Table 4 shows the composition of Linaclotide formulated as an absorbate on Syloid®XDP3050.

Table 1: Linaclotide formulated as an absorbate on Syloid®3150

Ingredients	Quantity (Granules)	mg	Quantity (Granules)	mg	Quantity (Granules)	mg
Linaclotide	200		200		300	
Syloid® XDP 3150	50000		25000		25000	
HCL Solution pH 1.7 (ml)	50		25		25	

Table 2: Linaclotide formulated as an absorbate on Syloid®3150 and including Syloid®AL.

Ingredients	Quantity mg (Granules)	Quantity mg (Granules)
Linaclotide	80	80
Syloid® XDP 3150	20000	20000
HCL Solution pH 1.7 (ml)	20	20
Syloid®AL	1004	13,386

10

Table 3: Linaclotide formulated as an absorbate on Syloid®244.

Ingredients	Quantity mg (Granules)	Quantity mg (Granules)
Linaclotide	80	80
Syloid®244 FP	20000	20000
HCL Solution pH 1.7 (ml)	20	20

Table 4: Linaclotide formulated as an absorbate on Syloid®3050.

Ingredients	Quantity (Granules) mg	Quantity (Granules) mg	Quantity (Granules) mg
Linacotide	200	200	300
Syloid® XDP 3050	50000	25000	25000
HCL Solution pH 1.7 (ml)	50	25	25

Example 2 - Determination of Linacotide Multimer Content by SEC-UV in Linacotide Carrier Formulations

Linacotide aggregate and multimer formation in the compositions and formulations as described herein and a commercially available preparation of Linacotide were determined. The pellets of 10 capsules from each of the formulations prepared as described in Example 1 and those of the commercially available formulation were pooled and homogenized.

The pellets in the pellet pool were placed into a glass beaker and weighed. A solvent was then added to the beaker to achieve a target concentration of 250µg Linacotide per ml. The pellets were then stirred for 15 minutes until a suspension was obtained. The suspension was then centrifuged for 3 min at 21380 rcf (15000 rpm) until a clear supernatant was obtained. The clear supernatant was subsequently decanted and used for further analysis.

Size exclusion chromatography (SEC) was used to analyze Linacotide multimers. Briefly, the sample supernatant was added to a 100 Å SEC column. Linacotide multimers were then isocratically eluted using 0.017 M Na₂HPO₄ as the eluent. The elution was monitored by UV absorption at a wavelength of 220 nm. Evaluation was performed using data collected from the peaks of the chromatogram obtained and then analyzing these using the area% method which is well known in the art.

In the absence of any generally accepted standard for Linacotide formulations, the Linacotide carrier compositions in accordance with the present invention, as described herein, were compared to that of a commercially available Linacotide formulation.

Table 5 below shows the results of the analysis.

Ingredients	A			B			C			D			E		
Linacotide [mg]	2.65			2.65			0.13			0.13			-		
Syloid® XDP3050 [mg]	1000			1000			49.87			49.87			-		
HCL pH 1.7 [mL]	1000			1000			-			-			-		
Lactose 200 DFE	-			-			14.0			14.0			-		
L-HPC LH-11	-			-			16.0			16.0			-		
Emcompress Anhydrous Powder	-			-			14.0			14.0			-		
Crosscarmelos e sodium	-			-			5.0			5.0			-		
Magnesium stearate	-			-			1.0			1.0			-		
T= x weeks at 40°C	0	1	4	0	1	4	0	1	4	0	1	4	0	1	4
Linacotide Area% by SEC-UV method	98. 9	99. 1	98. 8	99. 1	99. 1	99. 0	98. 8	98. 5	98. 0	98. 8	N/ A	95. 6	98. 4	N/ A	98. 2
Area% (Multimers)	1.1	0.9	1.2	0.9	0.9	1.0	1.2	1.5	2.0	1.2	N/ A	4.4	1.6	N/ A	1.8

Table 5

A= Linacotide 290 µg HG Capsules in HDPE bottle with 2 g desiccant in lid of HDPE container.

5 **B=** Linacotide 290 µg HG Capsules in HDPE bottle with 3 x 2g desiccant.

C= Linacotide 290 µg HG tablets in HDPE bottle with 2 g desiccant in lid of HDPE container.

D= Linacotide 290 µg HG tablets in HDPE bottle in twist-off glass without desiccant.

10 **E=** Commercially available Linacotide formulation.

The commercially available Linacotide formulation comprises 290 µg Linacotide in hard gelatin capsules. The capsules also generally contain microcrystalline cellulose, hypromellose, calcium chloride dihydrate and leucine. The capsule shell comprises red iron oxide, titanium dioxide, yellow iron oxide and gelatin. The commercially available Linacotide formulation is packed in a white HDPE bottle with a tamper evident seal and a child resistant screw cap, together with one or more desiccant canisters containing silica gel. Calcium chloride dihydrate and leucine are present as additional stabilizers which are not present in the Linacotide formulations according to the present invention as prepared in Example 1.

20 The level of multimer formation is shown in the bottom row of Table 5 as Area% (multimers). The commercially available Linacotide formulation is shown in Batch E.

Here, the level of multimers in the commercially available formulation is shown to be from 1.6% to 1.8% over 4 weeks. The composition in accordance with the present invention is shown in batches A-D. Batches A and B show the multimer content for the composition in HG capsules to be from 1.1% to 1.2% in Batch A and from 0.9% to 1.0% in Batch B. This clearly demonstrates that the compositions provided by the present invention have a significantly lower multimer content than the commercially available Linaclotide formulation over the same period of testing. The compositions in the form of tablets shown in batches C and D had higher concentrations of multimers than the commercially available Linaclotide formulation.

Additionally, another Linaclotide carrier composition using a different Syloid was also tested (see Table 6 below). This composition was tested in the absence of a desiccant. As was to be expected, the multimer formation (see Area% (Multimers) in last row of Table 6) was slightly higher than that of the Syloid formulations tested with a desiccant. However, the level of multimer in this Linaclotide composition (1.7% to 1.8%) is still comparable to the commercially available Linaclotide formulation (1.6 to 1.8%) over the same period of testing.

Ingredients	F		
Linaclotide [mg]	2.65		
Syloid® 244 [mg]	1000		
HCL pH 2.2 [ml]	1000		
Lactose 200 DFE	-		
L-HPC LH-11	-		
Emcompress Anhydrous Powder	-		
Crosscarmellose sodium	-		
Magnesium stearate	-		
T= x weeks at 40°C	0	1	4
Linaclotide Area% by SEC-UV method	98.3	98.3	98.2
Area% (Multimers)	1.7	1.7	1.8

Table 6

F= Linaclotide 290 µg HG capsules HDPE bottle in twist-off glass without desiccant.

Example 3 - Determination of Moisture Content in Linacotide Carrier Compositions and Formulations

The moisture content in the Linacotide carrier compositions and formulations as described herein was determined using the Karl-Fischer Oven-Method with coulometric detection. The compositions were prepared as previously described in Example 1.

Powder Active Ingredient and Formulation

The determination of the moisture content of the Linacotide carrier composition as described herein was performed on samples ranging from 10-350 mg.

Pellets and Capsules

The determination of moisture content for pellets was performed samples ranging from 10-350 mg.

Samples of the composition or pellets were added to sample vials. The sample vials were then placed into a Karl Fischer autosampler. The samples were then automatically transferred to an oven on the sampler. Water located in the vial and within the sample was heated in the oven at a defined temperature and the water vapour transferred to a measuring cell using nitrogen gas. The mass of the transferred water vapor was determined coulometrically in the measuring cell that had been preconditioned with the Karl Fischer reagent and methanol. The measurement was automatically carried out with a Stopdrift (μg water/min) and the moisture content of the sample in % (w/w) was then calculated.

Ingredients	A	B	C	D	E
Linacotide [mg]	2.65	2.65	0.13	0.13	-
Syloid® XDP3050 [mg]	1000	1000	49.87	49.87	-
HCL pH 1.7 [ml]	1000	1000	-	-	-
Lactose 200 DFE	-	-	14.0	14.0	-
L-HPC LH-11	-	-	16.0	16.0	-
Emcompress Anhydrous Powder	-	-	14.0	14.0	-

Crosscarmellose sodium	-			-			5.0			5.0			-		
Magnesium stearate	-			-			1.0			1.0			-		
T= x weeks at 40°C	0	1	4	0	1	4	0	1	4	0	1	4	0	1	4
Moisture%	3.1	2.7	2.9	2.6	1.9	2.3	2.6	2.1	2.2	3.8	N/A	3.6	N/A	N/A	2.7

Table 7

A= Linacotide 290 µg HG Capsules in HDPE bottle with 2 g desiccant in lid of HDPE container.

5 **B=** Linacotide 290 µg HG Capsules in HDPE bottle with 3 x 2g desiccant.

C= Linacotide 290 µg HG tablets in HDPE bottle with 2 g desiccant in lid of HDPE container.

D= Linacotide 290 µg HG tablets in HDPE bottle in twist-off glass without desiccant.

10 **E=** Commercially available Linacotide formulation.

The commercially available Linacotide formulation comprises 290 µg Linacotide in hard gelatin capsules. The capsules also generally contain microcrystalline cellulose, hypromellose, calcium chloride dihydrate and leucine. The capsule shell comprises red iron oxide, titanium dioxide, yellow iron oxide and gelatin. The commercially available Linacotide formulation is packed in a white HDPE bottle with a tamper evident seal and a child resistant screw cap, together with one or more desiccant canisters containing silica gel. Calcium chloride dihydrate and leucine are present as additional stabilizers which are not present in the Linacotide formulations according to the present invention as prepared in Example 1.

15 The percentage of moisture content is shown in the last row of Table 7, above. The commercially available Linacotide formulation is shown in Batch E. Here the moisture content in the commercially available formulation is shown to be 2.7% over a four-week period of testing. The composition in accordance with the present invention is shown in batches A-D. Batches A and B show the moisture content for the composition in HG capsules to be from 3.1% to 2.7% in Batch A and from 1.9% to 2.6% in Batch B. This demonstrates that the Linacotide carrier compositions of the present invention have a comparable level of moisture content, and in some cases a lower degradation product content, to that found in the commercially available

formulation over the same period of testing, in the absence of additional stabilizers. The compositions in the form of tablets shown in batches C and D. Batch C also demonstrates a comparable level of moisture content to the commercially available Linaclotide formulation over the same period of testing.

5 **Example 4 - Determination of Impurity/Degradation Product Content by RP-HPLC-UV in Linaclotide Carrier Compositions and Formulations**

The content of Linaclotide and any impurities in the Linaclotide carrier compositions and formulations was determined by RP-HPLC-UV. In this example, the level of impurities and degradation products, distinct from multimer content, in the Linaclotide
10 carrier compositions and a commercially available Linaclotide formulation was analyzed. The compositions for testing were prepared as described in Example 1.

Linaclotide was eluted by applying distinct organic solvent concentrations. A gradient with an increasing amount of acetonitrile was used for the separation on a C18 column. The protein elution was monitored by UV absorption at a wavelength of 227 nm.
15 Quantitation was carried out using external standard method. Single point calibration was performed using the mean of 4 injections.

Solvent preparation:

Potassium dihydrogen phosphate solution, pH 7,0

Approximately 13.61 g potassium dihydrogen phosphate was dissolved in 800 mL
20 water. pH was adjusted with 4 M sodium hydroxide to a pH of 7.0 ± 0.1 . The solution was filled up to 1000 mL with water. Volumes were adjusted as necessary. The solvent was cooled to $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$.

Mobile Phase A: Water + 0.05% trifluoro acetic acid (v/v)

1,0 ml TFA was added to 1800 ml water in a volumetric flask and filled up to 2000 ml.
25 Volumes were adjusted if necessary.

Mobile Phase B: Acetonitrile + 0.05% trifluoro acetic acid (v/v)

0,5 ml TFA was added to 800 ml acetonitrile in a volumetric flask and filled up to 1000 ml.

Volumes were adjusted if necessary.

Sample preparation for Linaclotide and Reference Standard

A Linaclotide test solution was prepared by dissolving Linaclotide (content of reference substance was taken into account) in an ice-cold solvent to a final concentration of 100 µg/mL (e.g. weigh approx. 2.5 mg Linaclotide into a 25 ml volumetric flask and filled up to the required volume with solvent).

Sample preparation for Linaclotide formulation:

Linaclotide carrier formulations were weighed into a beaker, after addition of ice-cold solvent to a target concentration of 100 µg Linaclotide per mL the samples were extracted on a magnetic stirrer for 15 minutes. The obtained suspension was centrifuged at 22 °C for 3 min at 21380 rcf using 2ml Eppendorf Tubes (PP, disposal). The clear supernatant was used for analysis.

Sample preparation for capsules

For the determination of impurities and degradation products of Linaclotide in Linaclotide preparations, the pellets of not less than five capsules were pooled and homogenized.

Drug product pellets out of the pellet pool were weighed into a beaker, after addition of ice cold solvent to a target concentration of 100 µg Linaclotide per mL the samples were extracted on a magnetic stirrer for 15 minutes. The obtained suspension was centrifuged at 22 °C for 3 min at 21380 rcf using 2ml Eppendorf Tubes (PP, disposal). The clear supernatant was used for subsequent analysis.

Ingredients	A			B			C			D			E		
Linaclotide [mg]	2.65			2.65			0.13			0.13			-		
Syloid® XDP3050 [mg]	1000			1000			49.87			49.87			-		
HCL pH 1.7 [ml]	1000			1000			-			-			-		
Lactose 200 DFE	-			-			14.0			14.0			-		
L-HPC LH-11	-			-			16.0			16.0			-		
Emcompress Anhydrous Powder	-			-			14.0			14.0			-		
Crosscarmelos e sodium	-			-			5.0			5.0			-		
Magnesium stearate	-			-			1.0			1.0			-		
T= x weeks at 40°C	0	1	4	0	1	4	0	1	4	0	1	4	0	1	4
Linaclotide area % by RP-HPLC method	99, 2	98, 7	98, 0	99, 1	98, 7	98, 5	98, 3	96, 8	94, 5	98, 3	N/A	81, 3	97, 8	N/A	96, 9

Sum of Degradation Products (distinct from multimers) Area%	0.8	1.3	2.0	0.9	1.3	1.5	1.7	3.2	5.5	1.7	N/A	18.1	2.2	N/A	3.1
---	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	------	-----	-----	-----

Table 8

A= Linacotide 290 µg HG Capsules in HDPE bottle with 2 g desiccant in lid of HDPE container.

5 **B=** Linacotide 290 µg HG Capsules in HDPE bottle with 3 x 2g desiccant.

C= Linacotide 290 µg HG tablets in HDPE bottle with 2 g desiccant in lid of HDPE container.

D= Linacotide 290 µg HG tablets in HDPE bottle in twist-off glass without desiccant.

10 **E=** Commercially available Linacotide formulation.

The commercially available Linacotide formulation comprises 290 µg Linacotide in hard gelatin capsules. The capsules also generally contain microcrystalline cellulose, hypromellose, calcium chloride dihydrate and leucine. The capsule shell comprises red iron oxide, titanium dioxide, yellow iron oxide and gelatin. The commercially available Linacotide formulation is packed in a white HDPE bottle with a tamper evident seal and a child resistant screw cap, together with one or more desiccant canisters containing silica gel. Calcium chloride dihydrate and leucine are present as additional stabilizers which are not present in the Linacotide formulations according to the present invention as prepared in Example 1.

20 The level of impurities and degradation products is shown in the bottom row of Table 8 as Sum of Degradation Products (distinct from multimers) Area%. The commercially available Linacotide formulation is shown in Batch E. Here, the level of impurities and degradation products in the commercially available formulation is shown to be from 2.2% to 3.1% over 4 weeks. The composition in accordance with the present invention is shown in batches A-D. Batches A and B show the level of impurities and degradation products for the composition in HG capsules to be from 0.8% to 2.0% in Batch A and from 0.9% to 1.5% in Batch B. This clearly demonstrates that the compositions provided by the present invention have a significantly lower multimer content than the commercially available Linacotide formulation over the same period of testing. The compositions in the form of tablets shown in batches C and D had

higher concentrations of multimers than the commercially available Linaclotide formulation over the same period of testing.

Example 5 - Dissolution of Linaclotide Carrier Formulations

- 5 The dissolution of Linaclotide was performed according to FDA recommendations. In particular, the dissolution testing of the HG capsules comprising granules of the Linaclotide carrier composition in accordance with the present invention were tested according to the USP (United States Pharmacopeia) basket method.

One Linaclotide carrier dosage form as prepared in accordance with Example 1 was
10 added to a dissolution medium comprising 50mM phosphate buffer at pH 4.5. The solution was then stirred at 50 rpm and samples were taken at 5, 10, 15 and 20 minute time intervals.

The dosage forms were stored at 40°C at 75% relative humidity for 0 and 4 weeks prior to the dissolution testing.

- 15 Sample analysis was performed using high pressure liquid chromatograph (HPLC). Linaclotide was eluted by applying distinct organic solvent concentrations. A gradient with an increasing amount of acetonitrile was used for the elution on a C18 column. The protein elution was monitored by UV absorption at a wavelength of 208 nm. Quantitation was carried out using an external standard method. Four-point calibration
20 was performed.

As can be seen from the dissolution results, the Linaclotide carrier compositions in accordance with the present invention have a comparable dissolution profile to the commercially available formulation of Linaclotide at the 20 minute time interval at both T=0 (Fig. 1) and T=4 (Fig. 2). In particular, the Linaclotide carrier formulation of
25 Syloid® XDP 3050 and 2g of desiccant has a better dissolution profile from 5 to 10 minutes at T=0 than the commercially available formulation (Fig. 1).

Example 6 - Comparison of Surface Area of Linaclotide Carrier Compositions

In the following example, the relatively high surface area Linaclotide carrier compositions provided by the present invention were compared to a relatively low

surface area Suglet carrier. The batches were tested at T=0 days, T=7 days at 40°C
T=9 days at 40°C.

Ingredients	Group 1 (Suglets)						Group 2 (Syloid)					
	all quantities in mg											
Batch	1			2			3			4		
Linacotide	740			740			30			30		
Hypromellose	1750			1750								
Trehalose				4430								
Syloid® 244 FP							10000					
Syloid® XDP 3050										10000		
Suglets 500/600	241900			241900								
HCl solution pH 2,2	254000			254000			10000			10000		
Remarks												
T = x days	0	7d/ 40° C	9d/25 °C	0	7d/ 40° C	9d/25 °C	0	7d/40 °C	9d/25 °C	0	7d/4 0°C	9d/2 5°C
Linacotide area% by RP-HPLC method	97,7	69,5	90,3	97,7	54,1	87,4	99,2	98,7	98,9	99,1	98,7	98,9
Sum of degradation Products (distinct from multimers). Area%	2,3	30,5	9,7	2,3	45,9	12,6	0,8	1,3	1,1	0,9	1,3	1,1
Area% Multimers	2,6	2,2	3,5	2,3	2,3	4,1	1,7	1,7	1,8	1,3	1,1	1,1
Moisture [%]	2,9	2,1	1,9	3,3	3,0	3,0	2,1	2,3	2,5	2,5	1,8	1,5

Table 9

- 5 Table 9 shows a comparison of surface area between Group 1 comprising Linacotide on Suglets, a relatively low surface area carrier, and Group 2, the Linacotide-Syloid carrier compositions in accordance with the present invention, which provide a relatively higher surface area. The Suglets used in this example have a particle size of from about 500-600 microns. The surface area of Suglets 500/600 is generally in the region of 0.015 m²/g to 0.010 m²/g, which is substantially lower than the surface area of the syloids used in this example.
- 10

Two different Syloids were used in Group 2 offering slightly different surface areas (Syloid® 244 FP = 300 m²/g and Syloid® XDP 3050 = 320 m²/g). An assessment

between the two groups was made on the basis of the following parameters: 1) multimer content, 2) impurity and degradation product levels. These two parameters were tested and analysed as described previously in examples 2 and 4 above. The compositions were prepared as previously described in Example 1.

- 5 The levels of multimer content and impurity and degradation product levels of the compositions in Group 2 were significantly lower than those levels seen in Group 1. In particular, the multimer levels for Group 2, Batch 3 were 1.7% to 1.8% over 9 days. For Batch 4 the multimer levels were 1.3% to 1.1% over 9 days. This is compared with Group 1, Batch1 multimer levels of 2.6% to 3.5% and Batch 2 multimer levels of
10 2.3% to 4.1%.

Additionally, looking at the results with respect to impurities and degradation products we can see that for Group 2, Batch 3 the levels were 0.8% to 1.1% over 9 days. For Batch 4 the levels were 0.9% to 1.1% over 9 days. This is compared with Group 1, Batch1 levels of 2.3% to 9.7% and Batch 2 levels of 2.3% to 12.6%.

- 15 Accordingly, the Linacotide-Syloid carrier compositions, as provided by the present invention, provide clear advantages with respect to impurities and degradation product levels and multimer formation compared to the use of lower surface area carriers such as Suglets.

20 **Example 7 – 6 Month Stability of Linacotide-Syloid Carrier Compositions**

The stability of Linacotide-Syloid compositions was investigated. Dried granules comprising the Linacotide-Syloid composition as described herein were prepared as previously described in Example 1 and subsequently tested after 6 months of storage.

Ingredients	Group 1 (Granules)					
Batch	1		2		3	
All quantities in mg						
Linacotide [mg]	2655		2655		2655	
Syloid® XDP 3050 [mg]	1000100		1000100		1000100	
HCl solution pH 1.7	1010000		1010000		1010000	
Remarks						

T [months]	0	6	0	6	0	6
Linacotide Area% by RP-HPLC method	99,4	98,5	99,3	98,4	99,3	98,4
Sum of Degradation Products (distinct from multimers) Area%	0,6	1,5	0,7	1,6	0,7	1,6
Sum of Multimer Area%	1,1	1,1	1,4	1,3	1,2	1,3
Moisture [%]	0,9	1,9	2,5	2,5	2,9	2,7

Table 10

Table 10, above, shows the results of stability testing over 6 months using three batches of dried granules comprising the Linacotide compositions in accordance with the present invention. An assessment between the two groups was made on the basis of the following parameters: 1) multimer content, 2) impurity and degradation product levels. These two parameters were tested and analysed as described previously in examples 2 and 4 above.

The results show that the degradation product levels of all three batches after 6 months were comparable and had not shown any signs of significant increase between the batches: 1.5% (Batch 1) vs. 1.6% (Batch 2) vs. 1.6% (Batch 3), and is still relatively low.

Additionally, the multimer levels in all three batches after 6 months were comparable and had not shown any signs of significant increase between the batches: 1.1% (Batch 1) vs. 1.3% (Batch 2) vs. 1.3% (Batch 3), and is still relatively low.

Example 8 – Comparison of Linacotide carrier compositions comprising Syloid® XDP 3150 or Syloid® XDP 3050

A comparison between different the effects of different Syloids on the Linacotide-Syloid compositions was investigated. Two Syloid formulations were compared. Linacotide was adsorbed on either Syloid® XDP 3150 or Syloid® XDP 3050. These were prepared as previously described in Example 1.

Ingredients	Granules in twist off bottle without desiccant		Granules in HG caps in HDPE Bottles with 1.5g desiccant	
	1	2	3	4
Batch				
	all quantities in mg			
Linacotide	2650	2640	2650	2640

Syloid® XDP 3050	1000				1000					
Syloid® XDP 3150			1000						1000	
HCl solution pH 1.7										
Remarks										
T [weeks]	0	4	0	4	0	4	10	0	4	10
Linacotide Area% by RP-HPLC method	99,5	97,8	99,4	98,3	99,6	98,3	97,6	99,6	99,1	98,3
Sum of Degradation Products (distinct from multimers). Area%	0,5	2,2	0,6	1,7	0,4	1,7	2,4	0,4	0,9	1,7
Sum of Multimers. Area%	1,0	1,4	1,3	1,9	0,7	1,1	1,9	0,9	1,3	1,9
Moisture [%]	2,7	2,8	2,5	3,1	2,7	2,8	3,3	2,7	2,6	3,2

Table 11

Table 11 shows the results of a comparison between two Syloid formulations. Linacotide was adsorbed on either Syloid® XDP 3150 or Syloid® XDP 3050 and either prepared as dried granules or encapsulated in HG capsules. The comparison between the formulations was made using the following parameters: 1) multimer content, 2) impurity and degradation product levels. These two parameters were tested and analysed as described previously in examples 2 and 4 above.

Batch 1 comprising Linacotide adsorbed on Syloid® XDP 3050 and Batch 2, comprising Linacotide adsorbed on Syloid® XDP 3150 demonstrate comparable levels of multimer formation at 1 month (1.4% vs. 1.9%). These batches also show comparable levels of impurities and degradation products (2.2% vs. 1.7%) over the same period of testing.

The capsules were tested over a 10-week period. Batch 3, comprising HG capsules of Linacotide adsorbed on Syloid® XDP 3050 and Batch 2, comprising HG capsules of Linacotide adsorbed on Syloid® XDP 3150, demonstrate comparable levels of multimer formation at 10 weeks (1.9% vs. 1.9%). These batches also show comparable levels of impurities and degradation products (2.4% vs. 1.7%) over the same period of testing.

Additionally, this analysis was performed on an encapsulated formulation that had been stored using a reduced level of desiccant (1.5g versus 2g or 6g of desiccant). This demonstrates that the Linacotide carrier formulations using different Syloid carriers are stable under a reduced desiccant content.

Example 9 – Comparison of Encapsulated Linacotide Compositions in the Absence of a Desiccant

An analysis of Linacotide carrier compositions encapsulated in HG capsule and stored in HDPE bottles under nitrogen with and without desiccant was performed. The encapsulated compositions were compared against dried granules. The results are presented in Table 12 below.

Ingredients	Group 1 (Granules)						Group 2 (HG capsules) with/without desiccant				
	all quantities in mg										
Batch	1		2		3		4		5		
Linacotide	180		40		40		180		180		
Syloid XDP 3050	45000		10000		10000		45000		45000		
HCl solution pH 2.2	60000		10000				60000		60000		
HCl solution pH 1.7					10000						
Remark							HG; 2g des.		HG; w/o des.		
T = x days		0	7d/40°C	0	7d/40°C	0	7d/40°C	0	7d/40°C	0	7d/40°C
Linacotide Area% by RP-HPLC method		98,6	98,2	99,2	98,7	99,6	99,2	99,4	99,1	99,3	99,0
Sum of Degradation Products (distinct from multimers) Area%		1,4	1,8	0,8	1,3	0,4	0,8	0,6	0,9	0,7	1,0
Multimer Area%		1,2	1,4	1,2	0,9	1,2	1,0	1,1	1,2	1,1	1,6
Moisture [%]		1,9	1,8	1,6	1,5	1,9	1,5	3,4	3,7	4,4	4,6

Table 12

Table 12 shows the results of a comparison of Linacotide carrier compositions. Batch 4 represents an encapsulated Linacotide carrier composition in HG capsules stored in HDPE bottles under nitrogen with a desiccant. Batch 5 represents an encapsulated Linacotide carrier composition in HG capsules stored in HDPE bottles under nitrogen without a desiccant. Batches 1-3 are dried granules comprising an equivalent Linacotide carrier composition.

The comparison between the formulations was made using the following parameters:

1) multimer content, 2) impurity and degradation product levels. These two

parameters were tested and analysed as described previously in examples 2 and 4 above.

As can be seen, the encapsulated Linaclotide carrier compositions demonstrate comparable levels of degradation products, multimer formation and moisture content.

- 5 In particular, Batch 4 and Batch 5 do not differ significantly in multimer content (1.2% vs. 1.6%), degradation products (0.9% vs. 1.0%) or moisture content (3.7% vs. 4.6%) over a 7 day period, showing that the encapsulated compositions either with or without desiccant are comparable. In particular, batches 4 and 5 demonstrate comparable, and in some cases, lower degradation product levels than the dried granule
10 preparations (0.9% and 1.0%, for batches 3 and 4, vs 1.8%, 1.3% and 0.8% for batches 1 to 3).

This demonstrates that the Linaclotide carrier compositions are stable even when encapsulated in the absence of a desiccant. This is advantageous, as such compositions in accordance with the present invention may be used in sachets or the
15 like.

Example 10 – Combination of Syloid® XDP 3150 and Syloid® AL-1FP

A Linaclotide combination comprising Syloid® AL-1FP and Syloid® XDP 3150 was also prepared, as described previously in Example 1, and subsequently analysed. The results can be seen in Table 13.

Ingredients	Granules in twist off bottle without desiccant.					Granules in HG caps in HDPE Bottles without desiccant	
	1	2	3	4	5	6	7
Batch	1	2	3	4	5	6	7
Linaclotide	4,11	8,46	11,95	3,91	2,46	3,91	2,46
Syloid® XDP 3150	x	x	x	x	x	x	x
Syloid® AL -1FP	-	-	-	x	x	x	x
HCl solution pH 1.	x	x	x	x	x	x	x
T = x days	0	0	0	0	0	0	0
Remark				5% AL	67% AL	5% AL	67% AL
Linaclotide Area% by RP-HPLC method	99,5	99,8	99,8	99,3	99,4	99,4	97,0
Sum of Degradation Products (distinct from multimers) Area%	0,5	0,2	0,2	0,7	0,6	0,6	3,0

Area% Multimer	0,6	0,3	0,4	0,6	0,6	0,5	0,7
Moisture [%]	1,6	3,1	3,2	1,7	2,6	4,2	5,8

Table 13

Table 13 shows a comparison of Linaclotide compositions containing either Syloid® XDP 3150 (batches 1, 2 and 3) or a combination of Syloid® XDP 3150 and Syloid® AL-1FP (batch 4 and 5), in a composition in accordance with the present invention.

- 5 Batches 6 and 7 show a comparison of a Linaclotide composition containing a combination of Syloid® XDP 3150 and Syloid® AL-1FP encapsulated in HG Capsules and packaged in HDPE bottles without desiccant under nitrogen as previously described in Example 1.

The comparison between the formulations was made using the following parameters:

- 10 1) multimer content, 2) impurity and degradation product levels. These two parameters were tested and analysed as described previously in examples 2 and 4 above.

- Batch 6 and 7 comprise 5% or 67% of Syloid® AL-1FP, respectively. The results from batch 6 and 7 suggest that a lower content (5%) of Syloid® AL-1FP is preferable, with
15 respect to degradation products (0.6% vs. 3.0%) and multimer formation (0.5% vs. 0.7%).

- The presence of a combination of Syloid® AL-1FP 5% and Syloid® XDP 3150 as in batches 4 and 5 has no significant effect on the degradation product level or multimer formation, when compared to compositions comprising a single Syloid carrier (batches
20 1, 2 or 3), with all batches 1 to 5 having comparable levels of degradation products and multimer content. In particular, Batch 4 has a degradation product level and multimer content of 0.7% and 0.6%, respectively. Batch 5 has a degradation product level and multimer content of 0.5% and 0.6%, respectively. Batch 1 has a degradation product level and multimer content of 0.5% and 0.6%, respectively. Batch 2 has a
25 degradation product level and multimer content of 0.2% and 0.3%, respectively. Batch 3 has a degradation product level and multimer content of 0.2% and 0.4%, respectively.

- These results demonstrate that Linaclotide carrier compositions in accordance with the present invention are stable and do not require the use of any additional stabilisers
30 or the like.

Example 11 - Preparation of Alternative Linaclotide Carrier Compositions

Linaclotide carrier compositions were prepared at 4, 8 and 12 mg/g of carrier.

A Linaclotide stock solution was prepared by adding 0.5g linaclotide into a 500mL Schott flask and 200g of HCl solution (pH 1.7) was then added. The solution was stirred using a magnetic stirrer for 30 minutes until the linaclotide had dissolved and the solution was clear.

Preparation of Batch 813392:

25 g of HPC-SSL was weighed into the 250 mL bin of a Mini-Diosna mixer. 25 g of Linaclotide stock solution was sprayed onto the HPC-SSL for approximately 60 seconds using a 0.4 mm spray nozzle. The mixture was stirred (mixer 500 rpm, chopper 750 rpm) for approximately 5 minutes. The resulting slightly yellow liquid was transferred to a glass dish.

Preparation of Batch 813393

25 g CompactCel P204 were weighed into the 250 mL bin of a Mini-Diosna mixer. 25 g of Linaclotide stock solution was sprayed onto the CompactCel P204 for about 60 seconds using a 0.4 mm spray nozzle. The mixture was stirred (mixer 500 rpm, chopper 750 rpm) for approximately five minutes. The resulting white sticky paste was transferred to a glass dish.

Preparation of Batch 813395

25 g Kollidon VA 64 was weighed into the 250 mL bin of a Mini-Diosna mixer. 25 g of Linaclotide stock solution was sprayed onto the Kollidon VA 64 for about 60 seconds using a 0.4 mm spray nozzle. The mixture was stirred (mixer 500 rpm, chopper 750 rpm) for approximately five minutes. The resulting slight reddish liquid material was transferred to a metal dish.

All three batches (813392, 813393 and 813395) were dried in a vacuum dryer at 40°C and 10 mbar pressure overnight. All three batches were removed from their respective dishes and subsequently milled for 5 minutes in a plastic mortar. A 5g sample of each batch was taken for a LOD measurement – the remaining material was filled into a 125 ml twist-off glassflask for subsequent analytical testing.

Table 14 shows the specific compositions of the alternative granulate Linaclotide carrier composition produced in accordance with the invention as described herein. Table 14 shows the composition of Linaclotide formulated on HPC-SSL, CompactCel P204 and Kollidon VA 64.

5 **Table 14:** Linaclotide formulated on alternative carrier materials

Ingredients	Quantity (g)		
	813392	813393	813395
Linaclotide	0.5	0.5	0.5
HCl Solution (g)	200	200	200
Concentration (linaclotide/stock solution) mg/g	2.49	2.49	2.49
Stock solution (g)	25	25	25
HPC-SSL (g)	25	-	-
CompactCel P204 (g)	-	25	-
Kollidon VA 64 (g)	-	-	25
Concentration (linaclotide/granules) mg/g	2.49	2.49	2.49
Vacuum Drying (overnight)	40°C/10mbar	40°C/10mbar	40°C/10mbar
Milling (plastic mortar)	~ 5 mins	~ 5 mins	~ 5 mins
Remarks (LOD <2.5%)	2.38%	1.67%	2.05%

Example 12 – Second Preparation of Alternative Linaclotide Carrier Compositions

In this Example a different concentration of linaclotide stock solution was used.

10 CompactCel P204

A Linaclotide stock solution was prepared by adding 0.220g linaclotide into a Schott flask and 24g of HCl solution (pH 1.7) was then added. The solution was stirred using a magnetic stirrer for 30 minutes until the linaclotide had dissolved and the solution was clear.

Preparation of Batch 813476:

25 g of CompactCel P204 was weighed into the 250 mL bin of a Mini-Diosna mixer. 6 g of Linacotide stock solution was sprayed onto CompactCel P204 for approximately 30 seconds using a 0.4 mm spray nozzle. During spraying the mixture was stirred.

- 5 The mixture was then stirred (mixer 500 rpm, chopper 750 rpm) for approximately 5 minutes after all water was introduced by spraying. The resulting white coarse particles were transferred to a glass dish.

Preparation of Batch 813477

50 g CompactCel P204 were weighed into the 250 mL bin of a Mini-Diosna mixer. 25 g of Linacotide stock solution was sprayed onto the CompactCel P204 for about 60 seconds using a 0.4 mm spray nozzle. During spraying the mixture was stirred. The mixture was then stirred (mixer 500 rpm, chopper 750 rpm) for approximately five minutes after all water was introduced by spraying. The resulting white fluffy material was transferred to a glass dish.

15 Copovidon VA64

A Linacotide stock solution was prepared by adding 0.220g Linacotide into a Schott flask and 20g of HCl solution (pH 1.7) was then added. The solution was stirred using a magnetic stirrer for 30 minutes until the Linacotide had dissolved and the solution was clear.

20 Preparation of Batch 813479

25 g Copovidon VA 64 was weighed into the 250 mL bin of a Mini-Diosna mixer. 5 g of Linacotide stock solution was sprayed onto the Copovidon VA 64 for about 30 seconds using a 0.4 mm spray nozzle. During spraying the mixture was stirred. The mixture was then stirred (mixer 500 rpm, chopper 750 rpm) for approximately five minutes after all water was introduced by spraying. The resulting white sticky material was transferred to a glass dish.

All three batches (813476, 813477 and 813479) were dried in a vacuum dryer at 40°C and 10 mbar pressure overnight. All three batches were removed from their respective dishes and subsequently milled for 5 minutes in a plastic mortar. A 2g sample of each batch was taken for a LOD measurement.

30

All three batches were filled into size 1 capsules using an Aponorm capsule filling device.

Table 15 shows the composition of Linacotide formulated on CompactCel P204 (813476 and 813477) and Kollidon VA 64 (813479).

5 **Table 15:** Linacotide formulated on alternative carrier materials

Ingredients	Quantity (g)		
	813476	813477	813479
Linacotide	0.220	0.220	0.5
HCl Solution (g)	24	24	20
Concentration (linacotide/stock solution) mg/g	9.1	9.1	10.9
Stock solution (g)	6	6	5
CompactCel P204 (g)	25	50	-
Kollidon VA 64 (g)	-	-	25
Concentration (linacotide/granules) mg/g	2.08	1.04	2.09
Vacuum Drying (overnight)	40°C/10mbar	40°C/10mbar	40°C/10mbar
Milling (plastic mortar)	~ 5 mins	~ 5 mins	~ 5 mins
Remarks (LOD <2.5%)	1.52%	1.31%	2.14%

Table 16 shows the details of the size 1 capsules filled with batches of linacotide formulation (813476, 813477 and 813479) using the Aponorm capsule filling device.

Table 16: Capsule composition

	813476	813477	813479
Target amount of linacotide per capsule (mg)	139.4	139.4	69.4
60 empty capsules (g)	4.51	4.56	3.02
60 filled capsules (g)	17.67	12.99	10.77

Example 13 – Stability of Linacotide Carrier Compositions Prepared Using Vacuum Drying

This example relates to the use of an external desiccant on stability of the Linacotide carrier compositions together with a further investigation on the use of an additional Syloid (AL-1FP) in the Linacotide carrier compositions described herein.

Materials

Materials
Linacotide API Selectchemie
Syloid XDP 3150
Syloid AL-1FP
Hard Gelatine Capsules size 1
Hard Gelatine Capsules size 2

Summary of Manufacturing Process

Linacotide solution (2.38 mg/g)

0.143 g Linacotide was weighed in a 0.2 L Schott bottle. A magnetic stir bar and 60 g HCl-solution (pH=1.7) were added. The mixture was stirred on a magnetic stirrer for 0.5 h. The pH was controlled at pH=1.7. The stock solution was split in to two 0.1 L Schott bottles.

Linacotide solution (3.25 mg/g)

0.098 g Linacotide was weighed in a 0.1 L Schott bottle. A magnetic stir bar and 30 g HCl-solution (pH=1.7) were added. The mixture was stirred on a magnetic stirrer for 0.5 h. The pH was controlled at pH=1.7.

Linacotide granulation & drying (2.38 mg/g batch)

2 x 30 g Syloid XDP 3150 was weighed in a steel box and transferred into the 0.25 L container of a Diosna mixer. Each time, 30g of the Linacotide stock solution was sprayed on the Syloid for about 6 min under stirring. A Schott bottle, pipe and spray nozzle were rinsed with 5 mL HCl solution pH=1.7. The wet mixtures were stirred for a further 5 min. The wet mixtures were combined and dried in a vacuum cabinet for ~

17 h at 40°C and 10 mbar. The water content was checked via LOD 2.0 %.

Linacotide granulation & drying (3.25 mg/g batch)

30 g Syloid XDP 3150 was weighed in a steel box and transferred into the 0.25 L container of the Diosna mixer. 30 g of Linacotide solution was sprayed on the Syloid for about 6 min under stirring. A Schott bottle, pipe and spray nozzle were rinsed with 5 mL HCl solution pH:1.7. The wet mixture was stirred for a further 5 min. The wet mixture was dried in a vacuum cabinet for ~ 17 h at 40°C and at the end 10 mbar. The water content was checked via LOD 2.5 %.

Linacotide mixture (2.49 mg/g batch with 10 % Syloid AL-1FP)

25.000g of an existing batch of granules comprising a linacotide API content of 2.49mg/g (batch 812899) and 2.500 g of Syloid AL-1FP (pre-dried LOD 0.1 %) were weighed in a 125 mL Twist-off glass. The blend was mixed for 15 min at 42 rpm using a Turbula T2C mixer. The water content was checked via LOD 2.5 %.

Linacotide capsules batch 812959 (batch 812899 + 10% Syloid AL-1FP)

120 HG capsules size 1 were filled completely with batch 812959 with the semi-automated encapsulation system CAPIII. 5 HG capsules size 1 were filled manually with batch 812959. The capsules were filled under controlled humidity conditions in 5 HDPE bottles (20 pcs.) and 2 Twist-off glasses (5 pcs. and 20 pcs.). All container systems were flushed with nitrogen.

Linacotide capsules batch 812968 (batch 812968)

125 HG capsules size 1 were filled completely with batch 812968 with the semi-automated encapsulation system CAPIII. The capsules were filled under controlled humidity conditions in 5 HDPE bottles (20 pcs.) and 2 Twist-off glasses (5 pcs. and 20 pcs.). A 1.5 g desiccant pouch were placed in all HDPE bottles. All container systems were flushed with nitrogen.

Linacotide capsules batch 812975 (batch 812968)

120 HG capsules size 1 were filled completely with batch 812968 with the semi-automated encapsulation system CAPIII. The capsules were filled under controlled

humidity conditions in 5 HDPE bottles (20 pcs.) and 1 Twist-off glass (20 pcs.). A 2.0 g desiccant pouch was placed in all HDPE bottles. All container systems were flushed with nitrogen.

5 Linacotide capsules batch 812976 (batch 812968)

120 HG capsules size 1 were filled completely with batch 812968 with the semi-automated encapsulation system CAPIII. The capsules were filled under controlled humidity conditions in 5 HDPE bottles (20 pcs.) and 1 Twist-off glass (20 pcs.). A 3.0 g desiccant pouch was placed in all HDPE bottles. All container systems were flushed
10 with nitrogen.

Linacotide capsules batch 812969 (batch 812969)

120 HG capsules size 1 were filled for 73% (target 93.6 mg) manually with batch 812969. The capsules were filled under controlled humidity conditions in 5 HDPE
15 bottles (20 pcs.) and 2 Twist-off glasses (5 pcs. and 15 pcs.). A 2.0 g desiccant pouch was placed in all HDPE bottles. All container systems were flushed with nitrogen.

Linacotide capsules batch 812977 (batch 812968)

115 HG capsules size 2 were filled completely with batch 812969 with the semi-automated encapsulation system CAPIII. 5 HG capsules size 2 were filled manually
20 with batch 812969. The capsules were filled under controlled humidity conditions in 5 HDPE bottles (20 pcs.) and 2 Twist-off glasses (5 pcs. and 15 pcs.). A 2.0 g desiccant pouch was placed in all HDPE bottles. All container systems were flushed with
25 nitrogen.

The composition and batch overview can be seen in tables 17 and 18.

Component	Group 1 (Granules)	Group 2 (HG Cps.)			Group 1 (Granules)	Group 2 (HG Cps.)	
Batch No.	812968 (I)	812968 (II)	812975 (III)	812976 (IV)	812969 (V)	812969 (VI)	812977(VII)
Linacotide API [mg]	143	Granule batch (I) 812968			98	Granule batch (V) 812969	
Syloid 3150 (core material) [g]	60				30		
HCl Solution pH 1.7 [g]	60				30		
Calculated Linacotide content [mg/g]	2.38				3.26		
Capsule Size	n.a.	1	1	1	n.a.	1	2
Filling Level [%]	n.a.	100	100	100	n.a.	~ 73	~ 100
HDPE Bottle		x	x	x		x	x
Twist-Off glass	x				x		
Desiccant in pouch (external desiccant)	-	1.5	2.0	3.0	-	2.0	2.0

Table 17 Composition and Batch overview of Linacotide Granules and Hard Gelatine Capsules 290 µg/cps

Component	Group 1 (Granules)	Group 2 (Capsules)
Batch No.	812959 (VIII)	812959 (IX)
Linacotide API [mg]	Granule batch 812899 (25 g)	Granule batch 812959
Syloid 3150 (core material) [g]		
HCl Solution pH 1.7 [ml]		
Syloid AL (internal desiccant)	10 % (2.5 g)	
Calculated Linacotide content [mg/g]	2.27	
Capsule Size	n.a.	1
Filling Level [%]	n.a.	100
HDPE Bottle	-	×
Twist-Off glass	×	-
Desiccant in pouch (external desiccant)	-	-

Table 18: Composition and Batch overview of Linacotide Granules mixed with Syloid AL and Hard Gelatine Capsules 290 µg/cps. Granules batch 812959 was manufactured using an already existing granule batch having a Linacotide API content of 2.49 mg/g formulation.

Results Summary

Group 1

Batch 812968 – 2.38 mg/g Linacotide

Batch 812969 – 3.26 mg/g Linacotide

Batch 812959 – 2.27 mg/g Linacotide (including 10 % Syloid AL)

Water content

The water content was 2.8 %, 3.9 % and 4.7 % (w/w) for batches 812968, 812969 and 812959 respectively.

Multimers

Multimers levels were measured with 0.9, 1.0 and 1.2 % for batches 812968, 812969 and 812959 respectively.

Purity/Content

The purity was about 99.4 % for batches without Syloid AL (812968, 812969) with a recovery between 101.3 and 102.0 whereas the purity for batch 812959 (with 10 % Syloid AL) was 98.8 % and the recovery with 98.4 %.

Table 19 summarizes the results for Group 1.

Batch	812968 (I)	812969 (V)	812959 (VIII)
Time Point	0	0	0
LOD [%]	1.99	2.51	2.47
Water Content [%w/w]	2.8	3.9	4.7
Multimers [Area%]	0.9	1.0	1.2
Recovery of Linacotide [%]	101.3	102.0	98.4
Purity [Area %]	99.5	99.4	98.8
Sum of Impurities [Area %]	0.5	0.6	1.2

Table 19: Granules with different API load (2.38 mg/g; 3.26 mg/g; 2.27 mg/g) in TOG (Twist-off glass)

Group 2Appearance/Brittleness

Batches 812968, 812975, 812976 (all HG 1; all 100 % fill; 1.5, 2.0, 3.0 g desiccant in pouches)

Batches 812969, 812977 (HG 1 and HG 2; 73 % and 100 % fill; all 2.0 g desiccant in pouches)

5 Batch 812959 (HG 1; 100 % fill; 10 % Syloid AL, no desiccant in pouches)

For batches 812968, 812975, 812976, 812977 and 812959 no capsule brittleness (before capsule opening) could be observed after 26 weeks of storage at 40°C/75% RH. The partially filled capsule batch 812969 showed at
10 time 4 and 10 weeks one brittle capsule before capsule opening however no capsule broke during actual opening of the capsule.

Water content

15 812968, 812975, 812976 (all HG 1; all 100 % fill; 1.5, 2.0, 3.0 g desiccant in pouches):

The initial water content was 3.8 % (w/w). For all three batches the water content decreased after 4 weeks of storage at 40°C/75% RH up to 2.5 % (w/w)
20 using the maximum amount of desiccant (3.0 g) in pouches. After 10 weeks of storage 40°C/75% RH the water content increased for two batches (812968 and 812975) and stayed the same for 812976 (3.0 g desiccant). The highest water content was detected using the minimum amount of desiccant (1.5 g) with 4.4 % (w/w) after 26 weeks of storage at 40°C/75% RH.

25 812969, 812977 (HG 1 and HG 2; 73 % and 100 % fill; all 2.0 g desiccant in pouches)

Batch 812959 (HG 1; 100 % fill; 10 % Syloid AL, no desiccant in pouches):

30 The same tendency could be observed for batches 812969 and 812977. However, when using 10 % Syloid AL (batch 812959) as an internal desiccant the water content increased during the stability from initially 4.8 % (w/w) to

5.9 % (w/w) after 26 weeks.

Multimers

5 Batches 812968, 812975, 812976 (all HG 1; all 100 % fill; 1.5, 2.0, 3.0 g desiccant in pouches):

The initial multimer level was about 0.5 %. After 26 weeks of storage at 40°C/75% RH multimers increased to 8.1 %, 6.0 % and 4.0 % depending on the amount of desiccant in pouches used.

10

Batches 812969, 812977 (HG 1 and HG 2; 73 % and 100 % fill; all 2.0 g desiccant in pouches):

The initial multimer level was about 0.5 %. After 26 weeks of storage at 40°C/75% RH multimers increased to 6.7 % for batch 812969 and 6.3 % for batch 812977.

15

Batch 812959 (HG 1; 100 % fill; 10 % Syloid AL, no desiccant in pouches):

The initial multimer level was 0.6 %. However, after 26 weeks of storage at 40°C/75% RH multimers increased to 18.1 % due to high water content within the granules.

20

Purity/Content

25 Batches 812968, 812975, 812976 (all HG 1; all 100 % fill; 1.5, 2.0, 3.0 g desiccant in pouches):

The initial impurity level was about 0.4 %, hence a purity of 99.6 %. After 26 weeks of storage at 40°C/75% RH impurities increased to 4.3 %, 3.9 % and 3.2 % depending on the amount of desiccant in pouches used.

30

The initial recovery of label claim was about 109.6 %, 109.9 % and 108.5 %, respectively batch 812968, 812975 and 812976. After 26 weeks of storage at 40°C/75% RH recovery of label claim decreased to 86.7 %, 91.1 % and 92.0 %

depending on the amount of desiccant in pouches used.

Batches 812969, 812977 (HG 1 and HG 2; 73 % and 100 % fill; all 2.0 g desiccant in pouches):

5 The initial impurity level was about 0.6 %, hence a purity of 99.4 %. After 26 weeks of storage at 40°C/75% RH impurities increased to 5.1 % and 4.0 %.
The initial recovery of label claim was about 109.0 % and 118.5 %, respectively batch 812969 and 812977. For batch 812969 this was unexpected, since we have aimed for about 105 % of label claim. After 26 weeks of storage at
10 40°C/75% RH recovery of label claim decreased to 88.7 % and 97.8 %.

Batch 812959 (HG 1; 100 % fill; 10 % Syloid AL, no desiccant in pouches):

The initial impurity level was 0.7 %, hence a purity of 99.3 %. After 26 weeks of storage at 40°C/75% RH impurities increased to 16.4 %.
15 The initial recovery of label claim was about 107.6 %. After 26 weeks of storage at 40°C/75% RH recovery of label claim decreased to 65.5 %.

Dissolution

20 All batches showing immediate release properties with more than 85 % after 15 mins.

Batches 812968, 812975, 812976 (all HG 1; all 100 % fill; 1.5, 2.0, 3.0 g desiccant in pouches):

25 Batch 812968 – 1.5 g desiccant in pouches
The recovery of label claim decreases 18 % from 114 % (T=0) to 96 % (T=26 weeks).

30 Batch 812975 – 2.0 g desiccant in pouches
The recovery of label claim decreases 13 % from 114 % (T=0) to 101 % (T=26 weeks).

Batch 812976 – 3.0 g desiccant in pouches

The recovery of label claim decreases 14 % from 114 % (T=0) to 100 % (T=26 weeks).

- 5 Batches 812969, 812977 (HG 1 and HG 2; 73 % and 100 % fill; all 2.0 g desiccant in pouches):

Batch 812969 – 2.0 g desiccant in pouches

The recovery of label claim decreases 13 % from 111 % (T=0) to 98 % (T=26 weeks).

10

Batch 812977 – 2.0 g desiccant in pouches

The recovery of label claim decreases 10 % from 117 % (T=0) to 107 % (T=26 weeks).

- 15 Batch 812959 (HG 1; 100 % fill; 10 % Syloid AL, no desiccant in pouches):

Batch 812959 – no external desiccant

The recovery of label claim decreases 40 % from 115 % (T=0) to 75 % (T=26 weeks).

20

Conclusion

As can be seen from the results, the alternative Linaclotide carrier compositions, as described herein, have acceptable product characteristics with respect to impurities, multimer content, water content, recovery of label claim and dissolution profiles.

- 25 Tables 20, 21 and 22 summarize the results for Group 2.

Batch	812968 (II)				812975 (III)				812976 (IV)			
Time Point [weeks]	0	4	10	26	0	4	10	26	0	4	10	26
Brittleness - before opening - while opening	0/10 0/10	0/10 1/10	0/10 0/10	0/10 0/10	0/10 0/10	0/10 0/10	0/10 0/10	0/10 0/10	0/10 0/10	0/10 0/10	0/10 1/10	0/10 0/10
Mean Fill weight [mg]	133.3 0	130.9 1	130. 41	133. 23	133.0 6	127.2 5	129.6 4	133. 07	132.7 1	126.1 3	128.0 2	130.4 1
Dissolution	114	n.d.	95	96	n.d.	n.d.	101	101	n.d.	n.d.	93	100
Water Content [%w/w]	3.8	3.0	3.3	4.4	3.8	2.8	2.9	4.0	3.8	2.5	2.5	3.3
Water content in capsule shell [%w/w]	12.9	9.1	8.8	10.8	12.6	7.8	7.7	10.0	12.4	7.2	6.6	8.2
Multimers [Area%]	0.5	1.1	2.2	8.1	0.4	0.9	1.9	6.0	0.5	0.9	1.7	4.0
Recovery of - Label Claim [%]	109.6	106.5	99.1	86.7	109.9	104.2	100.5	91.1	108.5	104.4	99.0	92.0
Purity [Area %]	99.5	98.9	98.3	95.7	99.6	99.1	98.5	96.1	99.6	99.1	98.4	96.8
Sum of Impurities [Area %]	0.5	1.1	1.7	4.3	0.4	0.9	1.5	3.9	0.4	0.9	1.6	3.2

Table 20: HG Capsules size 1 in HDPE bottles with different amount of desiccant (1.5, 2.0 and 3.0 g)

Batch	812969 (VI)				812977 (VII)			
Time Point [weeks]	0	4	10	26	0	4	10	26
Brittleness - before opening - while opening	0/10 0/10	1/10 0/10	1/10 0/10	0/10 0/10	0/10 0/10	0/10 1/10	0/10 0/10	0/10 0/10
Fill weight [mg]	94.42	91.79	90.17	94.45	103.27	99.82	100.46	102.19
Dissolution [% LC]	111	n.d.	98	98	117	n.d.	105	107
Water Content [%w/w]	4.1	3.0	3.0	4.0	4.1	2.5	2.9	4.0
Water content in capsule shell [%w/w]	13.3	8.2	8.0	10.2	13.5	8.5	7.7	10.5
Multimers [Area%]	0.5	1.1	2.2	6.7	0.5	1.3	1.9	6.3
Recovery of - Label Claim [%]	109.0	104.5	95.2	88.7	118.5	111.9	107.1	97.8
Purity [Area %]	99.4	98.9	98.2	94.9	99.5	98.9	98.2	96.0
Sum of Impurities [Area %]	0.6	1.1	1.8	5.1	0.5	1.1	1.8	4.0

Table 21: Granules in HG Capsules size 1 (73% filled) and size 2 (100% filled) in HDPE bottles with 2.0g desiccant

Batch	812959 (IX)			
Time Point	0	4	10	26
Brittleness				
- before opening	0/10	0/10	0/10	0/10
- while opening	0/10	0/10	0/10	0/10
Fill weight [mg]	137.58	140.13	139.73	140.88
Dissolution [% LC]	115	n.d.	86	75
Water Content [%w/w]	4.8	5.3	5.6	5.9
Water content in capsule shell [%w/w]	12.8	15.1	12.7	14.0
Multimers [Area%]	0.6	2.3	6.4	18.1
Recovery of - Label Claim [%]	107.6	101.7	89.4	65.5
Purity [Area %]	99.3	97.0	93.6	83.6
Sum of Impurities [Area %]	0.7	3.0	6.3	16.4

- 5 **Table 22:** Granules + 10% Syloid AL-1FP in HG Capsules size 1 in HDPE bottles without desiccant, initial in TOG

Example 14 – Stability of Linaclotide Carrier Compositions Prepared Using Fluid Bed Drying

This example relates to the use of an external desiccant on stability of the Linaclotide carrier compositions together with a further investigation on the use of an additional Syloid (AL-1FP).

Materials

Materials
Linaclotide API Selectchemie
Syloid XDP 3150
Hard Gelatine Capsules size 1
Desiccant (pouches) 0.5 g
Desiccant (pouches) 1.0 g
HDPE bottle 35 ml
Closure without desiccant
Twist-off glas (TOG) clear bottle 50 ml
Twist-off closure white
Originator Constella® Batch 1M

Summary of Manufacturing Process

- 10 The batches were produced by wet granulation using a 10 L Diosna high shear mixer.
- Linaclotide solution (7.10 mg/g)

2.86 g Linacotide was weighed in a 1 L Schott bottle. A magnetic stir bar and 400 g HCl-solution (pH=1.7) were added. The mixture was stirred on a magnetic stirrer for 0.5 h.

Linacotide granulation & drying (2.38 mg/g batch)

- 5 1200g of Syloid XDP 3150 was weighed in a steel box and transferred into the 10 L container of the Diosna mixer. 402.86 g of Linacotide solution was sprayed on the Syloid in about 20 min under stirring. Schott bottle, pipe and spray nozzle were rinsed with 50 mL HCl solution pH=1.7. The wet mixture was stirred for a further 15 min. 3x ~530 g wet mixtures were dried in a fluid bed dryer, pre-heated at ~65°C with an air flow of 65 m³/h at ≤ 65°C. For the first trial, after 17 min of drying a LOD of 1.82 % was measured. For the second trial, after 15 min of drying a LOD of 2.15 %. For the third trial, after 10 min of drying a LOD of 2.48 % was measured. For this the encapsulation was done with product of the second run.

Linacotide capsules batch 813254

- 15 HG capsules size 1 were filled completely with batch 813253 with the semi-automated encapsulation system CAPIII. 20 capsules per bottle were each filled into 35 ml HDPE bottles under controlled humidity conditions. 9 bottles each with 1.5 g desiccant, 9 HDPE bottles each with 2.0 g desiccant, 9 HDPE bottles with 2.5 g desiccant and 3 HDPE bottles with 2.0 g desiccant in the lid. All HDPE bottles were flushed with nitrogen. 2 Twist-off glass were each filled with 20 capsules (cps). without nitrogen flushing.

The composition and batch overview can be seen in Table 23

Component	Group 1 (Granules)	Group 2 (HG Cps.)				Group 3 - Originator
Batch No.	813253 (I)	(II)	(III)	(IV)	(V)	1M
Linacotide API [mg]	2860	Granule batch (I)				290 µg Linacotide per Capsule (Label Claim)
Syloid 3150 (core material) [g]	1200					

HCl Solution pH 1.7 [g]	400					
Calculated Linacotide content [mg/g]	2.38					n.a.
Capsule Size	n.a.	1	1	1	1	2
Filling Level [%]	n.a.	100	100	100	100	n.a.
HDPE Bottle		x	x	x	x	x
Twist-Off glass	x					
Desiccant in pouches	-	1.5 g	2.0 g	2.5 g		3.3 g in a cylindric can
Desiccant in lid					2.0 g	

Table 23: Composition and Batch overview of Linacotide Granules and Hard Gelatine Capsules 290 µg/cps

Analytical Methods:

5 Appearance / Brittleness of Capsules

After opening the container (e.g HDPE bottle, twist off glass) the integrity of the capsules were checked visually for integrity and the absence of any defects. The outcome of this initial assessment was then noted and reported (I).

Before opening, the capsules were taken between thumb and index finger applying moderate mechanical stress whilst rolling between these fingers. This aims to mimic the handling of a capsule by a patient. Afterwards, the closed capsules were visually checked for integrity and the absence of any defects. The outcome of this assessment was then noted and reported (II).

The brittleness was judged by the assessments given above (I+II).

15 During opening of the capsules more mechanical stress was applied which could lead to capsule breaking. The outcome of this assessment was also noted and reported for information only.

Water Content

A sample, located in a “head-space” vial, was heated in an oven and the evaporated water transferred to the measuring cell/senor with the help of a nitrogen gas stream. The coulometric determination of water is an absolute method and it is based on a quantitative reaction of water with an anhydrous solution of sulphur dioxide and iodine in the presence of a buffer, which in turn captures hydronium ions:



- 10 Iodine (I_2) is generated electrochemically from iodide (I^-). When iodine (I_2) encounters the water in the sample, water is titrated according to the above-mentioned reaction scheme. Once all the water available has reacted, the reaction is complete. The amount of water in the sample is calculated by measuring the current needed for the electrochemical generation of iodine (I_2) from iodide (I^-).
- 15 Titration was performed with a modified Karl-Fischer (KF)-solution using biamperometric indication (dead-stop-method).

Assay and Purity

- The analysis of content and purity of Linaclotide was performed using high pressure liquid chromatography. Linaclotide and Linaclotide related compounds were eluted by applying distinct organic solvent concentrations. A gradient with an increasing amount of acetonitrile was used for the separation on a C18 column. The protein elution was monitored by UV absorption at a wavelength of 227 nm. Quantitation was carried out using external standard method.

Multimers

- 25 The analysis of Linaclotide multimers was performed using size exclusion chromatography. Linaclotide multimers and aggregates were eluted isocratic with 0.017 M Na_2HPO_4 as eluent on a 100 Å SEC column. The protein elution was monitored by UV absorption at a wavelength of 220 nm. Quantitation was carried out using area% method.

Dissolution

The dissolution testing was performed using a basket apparatus, 500 ml potassium phosphate buffer at pH 4.5 with 50 rpm at 37°C. A dissolution profile was generated up to 20 min. Samples were analyzed a gradient HPLC method.

5

Results Summary**Group 1**Water content

Water content was 2.7 % (w/w).

10

Multimers

Multimers level was measured at 0.9 %

Purity/Content

15 The purity was 99.4 % with a recovery of 98.7 %.

Table 30 summarizes the results for Group 1:

Batch	813254 (I)
Time Point	0
LOD [%]	2.15
Water Content [%w/w]	2.7
Multimers [Area%]	0.9
Recovery of Linaclotide [%]	98.7
Purity [Area %]	99.4
Sum of Impurities [Area %]	0.6

Table 24: Granules with API load (2.38 mg/g) in TOG

Group 2Appearance/Brittleness

20 For all batches no capsules brittleness ("rolling test") could be observed after 26 weeks of storage at 30°C/65% RH.

Water content

The initial water content was 3.9 % (w/w). After 26 weeks of storage at 30°C/65% RH

all three batches (just desiccant in pouches) decreased to 3.4 %, 3.1 % and 3.1 % (w/w) depending on the amount of desiccant used.

Multimers

- 5 After 26 weeks of storage at 30°C/65% RH an increase for all three batches (just desiccant in pouches) to about 1.5 – 1.7 % could be observed.

Purity/Content

The initial impurity level was about 0.4 %, hence a purity of 99.6 %.

10

After 26 weeks of storage at 30°C/65% RH a moderate increase for all three batches (just desiccant in pouches) to about 1.6 – 1.8 % could be observed.

15

The initial recovery of label claim was about 104.3 %. After 26 weeks of storage at 30°C/65% RH a decrease in recovery for all three batches (just desiccant in pouches) to about 97.0 – 99.6 % could be observed.

Table 25 summarizes the results for Group 2:

Batch	813254	813254 (II)				813254 (III)				813254 (IV)			
Time Point [weeks]	0	4	8	14	26	4	8	14	26	4	8	14	26
Brittleness - after bottle opening - moderate stress (rolling test) - during capsules opening	0/10 0/10 0/10			0/20 0/10 0/10	0/20 0/10 0/10			0/20 0/10 0/10	0/20 0/10 1/10			0/20 0/10 0/10	0/20 0/10 0/10
Mean Fill weight [mg]	132.36			128.72	129.89			127.52	128.87			126.14	127.66
Dissolution	108			n.d.	n.d.			n.d.	n.d.			n.d.	n.d.
Water Content [%w/w]	3.9			3.2	3.4			3.0	3.1			2.8	3.1
Water content in capsule shell [%w/w]	13.6			9.5	9.1			8.6	8.3			7.9	7.8
Multimers [Area%]	0.6			1.0	1.5			0.9	1.7			0.9	1.7
Recovery of - Label Claim [%]	104.3			103.7	99.6			103.6	98.4			103.4	97.0
Purity [Area %]	99.6			98.7	98.2			98.8	98.4			98.8	98.4
Sum of Impurities [Area %]	0.4			1.3	1.8			1.2	1.6			1.2	1.6

Table 25: Granules (API load 2.38 mg/g) in HG Capsules size 1 in HDPE bottles with different amount of desiccant in pouches (1.5, 2.0 and 2.5 g), initial in TOG, Intermediate Condition **30°C/65% RH**, closed)

Group 3Appearance/Brittleness

No capsule brittleness could be observed when Originator sample was stored at 30°C/65% RH.

Water content

The initial water content was 3.4 % (w/w). No significant decrease or increase of water content could be observed over the course of the stability for 30°C/65% RH.

Multimers

The initial multimer level was about 1.0 %. After 26 weeks of storage at 30°C/65% RH a slight increase to 1.4 % could be observed.

Purity/Content

The initial impurity level was about 1.6 %, hence a purity of 98.4 %.

After 14 weeks of storage at 30°C/65% RH an increase to 2.5 % could be observed. However, after 26 weeks 1.7 % of impurities were measured.

The initial recovery of label claim was about 103.4 %. After 26 weeks of storage at 30°C/65% RH no significant change occurred. However, after 14 weeks an increase of recovery to 111.6 % could be observed.

Dissolution

No significant change occurred.

Table 26 summarizes the results for Group 3:

Batch	1M				
	0	4	8	14	26
Time Point [weeks]					
Brittleness					
- after bottle opening	1/28			0/28	0/28
- moderate stress (rolling test)	2/10			0/10	0/10
- during capsules opening	0/14			0/14	0/14
Fill weight [mg]	111.94			112.37	112.10

Batch	1M				
Time Point [weeks]	0	4	8	14	26
Dissolution [% LC]	106			n.d.	n.d.
Water Content [%w/w]	3.4			3.5	2.8
Water content in capsule shell [%w/w]	9.2			9.0	8.4
Multimers [Area%]	1.0			1.1	1.4
Recovery of - Label Claim [%]	103.4			111.6	103.4
Purity [Area %]	98.4			97.5	98.3
Sum of Impurities [Area %]	1.6			2.5	1.7

Table 26: Originator in HG Capsules size 2 in HDPE bottles with about 3.3g desiccant in cylindric can, Intermediate Condition **30°C/65% RH**, closed)

5 Conclusion

As can be seen from the results, the Linaclotide carrier compositions having Syloid 3150 as a carrier demonstrate comparable product qualities compared to the originator formulation with respect to impurities (Fig. 3), multimer content (Fig. 4), water content (Fig.5), recovery of label claim (Fig. 6) and dissolution profiles (Fig. 7). In particular, the linaclotide formulation demonstrates a lower impurity content than the originator formulation at 0 to 14 weeks and a comparable impurity level at 26 weeks (Fig. 3).

CLAIMS

1. A pharmaceutical composition comprising an adsorbate of a peptide having the following amino acid sequence: Cys-Cys-Glu-X-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 1), or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein X is any amino acid.
2. The pharmaceutical composition according to claim 1, wherein X is selected from phenylalanine (Phe), Tyrosine (Tyr) or Tryptophan (Trp).
3. The pharmaceutical composition according to claim 1 or 2, wherein the peptide comprises a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4).
4. The pharmaceutical composition according to any one of claims 1 to 3, wherein at least one carboxyl group of an amino acid of the peptide is modified to an alkyl ester.
5. The pharmaceutical composition according to any one of claims 1 to 4, wherein the at least one carrier has a surface area of about 20 - 700 m²/g.
6. The pharmaceutical composition according to anyone of claims 1 to 5, wherein the at least one carrier is selected from one or more of metal oxides, metal silicates, metal phosphates, metal carbonates or zeolites.
7. The pharmaceutical composition according to any one of claims 1 to 6, wherein the at least one carrier is a porous carrier comprising a metal oxide.
8. The pharmaceutical composition according to claim 7, wherein the metal oxide is a silicon dioxide.
9. The pharmaceutical composition according to any one of claims 1 to 8, wherein the ratio of the composition of the peptide to the at least one carrier ranges from about 0.1mg/g to about 15mg/g of the at least one carrier.
10. The pharmaceutical composition according to any one of claims 1 to 9, wherein the at least one carrier is present in an amount of about 50 to 3000 mg by weight of the composition.

11. The pharmaceutical composition according to any one of claims 1 to 10, when in the form of a finished dosage form, may comprise about 10 – 99.9 percent by weight of the composition of at least one carrier.
12. The pharmaceutical composition according to any one of claims 1 to 11, wherein said composition has moisture content of about 5% or less.
13. The pharmaceutical composition according to any one of claims 1 to 12, wherein the at least one carrier has an average particle size of about 2 to about 200 μm .
14. The pharmaceutical composition according to any one of claims 1 to 12, wherein said composition has moisture content of less than about 5% and a surface area of at least about 20 m^2/g .
15. The pharmaceutical composition according to any one of claims 1 to 12, wherein said at least one carrier has a surface area of at least about 20 m^2/g .
16. The pharmaceutical composition according to any one of claims 1 to 12, wherein said composition has moisture content of less than about 5%, and the at least one carrier has an average particle size of about 2 to about 200 μm .
17. The pharmaceutical composition according to any one of claims 1 to 12, wherein the at least one carrier has a surface area of at least about 20 m^2/g and an average particle size of about 2 to about 200 μm .
18. The pharmaceutical composition according to any one of claims 1 to 12, wherein said composition has moisture content of less than about 5%, and the at least one carrier has an average particle size of about 2 to about 200 μm , and a surface area of at least about 20 m^2/g .
19. The pharmaceutical composition according to any one of claims 1 to 12, comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein said at least one carrier has a surface area of at least about 20 m^2/g to about 700 m^2/g .
20. The pharmaceutical composition according to any one of claims 1 to 12, comprising an adsorbate of a peptide comprising a sequence selected from:

Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein said at least one carrier has a surface area of at least about 300 m²/g to about 700 m²/g.

21. The pharmaceutical composition according to any one of claims 1 to 12, comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein the at least one carrier has a surface area of at least about 20 m²/g to about 700 m²/g and an average particle size of about 2 to about 200 µm.
22. The pharmaceutical composition according to any one of claims 1 to 12, comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein the at least one carrier has a surface area of at least about 300 m²/g to about 700 m²/g and an average particle size of about 2 to about 200 µm.
23. The pharmaceutical composition according to any one of claims 1 to 12, comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4), or a pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier selected from Syloid® XDP 3050, Syloid® XDP 3150, Syloid® 244 FP, Syloid AL-1 FP/63FP or any combination thereof, wherein the at least one porous silicon dioxide carrier has a surface area of at least about 300 m²/g to about 700 m²/g and an average particle size of about 2 to about 200 µm.

24. The pharmaceutical composition according to any one of claims 1 to 12, comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4) wherein at least one carboxyl group of an amino acid of the peptide is an alkyl ester, or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein said at least one carrier has a surface area of at least about 20 m²/g to about 700 m²/g.
25. The pharmaceutical composition according to any one of claims 1 to 12, comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4) wherein at least one carboxyl group of an amino acid of the peptide is an alkyl ester, or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein said at least one carrier has a surface area of at least about 300 m²/g to about 700 m²/g.
26. The pharmaceutical composition according to any one of claims 1 to 12, comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4) wherein at least one carboxyl group of an amino acid of the peptide is an alkyl ester, or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein the at least one carrier has a surface area of at least about 20 m²/g to about 700 m²/g and an average particle size of about 2 to about 200 μ m.
27. The pharmaceutical composition according to any one of claims 1 to 12, comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID

- NO.: 4) wherein at least one carboxyl group of an amino acid of the peptide is an alkyl ester, or a pharmaceutically acceptable salt thereof, on at least one carrier, wherein the at least one carrier has a surface area of at least about 300 m²/g to about 700 m²/g and an average particle size of about 2 to about 200 µm.
28. The pharmaceutical composition according to any one of claims 1 to 12, comprising an adsorbate of a peptide comprising a sequence selected from: Cys-Cys-Glu-Phe-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 2) or Cys-Cys-Glu-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 3) or Cys-Cys-Glu-Trp-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr (SEQ ID NO.: 4) wherein at least one carboxyl group of an amino acid of the peptide is an alkyl ester, or a pharmaceutically acceptable salt thereof, on at least one porous silicon dioxide carrier selected from Syloid® XDP 3050, Syloid® XDP 3150, Syloid® 244 FP or Syloid AL-1 FP/63FP, wherein the at least one porous silicon dioxide carrier has a surface area of at least about 300 m²/g to about 700 m²/g and an average particle size of about 2 to about 200 µm.
29. A process for preparing the pharmaceutical composition according to any one of claims 1 to 28 comprising the steps of:
- (a) preparing an aqueous solution of a peptide;
 - (b) combining the aqueous solution of the peptide with a carrier; and
 - (c) drying the mixture of peptide and carrier under reduced pressure at a temperature of from about 30 to about 50°C.
30. The process according to claim 29, wherein the aqueous solution of the peptide is acidic with a pH in the range of from about 1.7 to about 2.2.
31. The process according to claim 29 or claim 30, wherein step (b) comprises spraying or rinsing the aqueous solution of peptide onto a carrier powder.
32. The process according to any one of claims 29 to 31, wherein step (c) is performed in a vacuum dryer, spray drier or a fluidized bed dryer.
33. The process of any one of claims 29 to 32, wherein the process further comprises encapsulating the dried powder in capsules.

34. The process of any one of claims 29 to 33, wherein the carrier is a porous carrier.
35. A dosage form comprising said composition of any one of claims 1 to 28.
36. The dosage form according to claim 35, wherein said dosage form is selected from a tablet, a powder filled capsule or a powder filled sachet.
37. The dosage form according to claim 35 or claim 36, wherein the dosage form is a HPMC or a gelatin capsule.
38. Use of a composition according to any one of claims 1 to 28, in the manufacture of a medicament for treating a gastrointestinal disorder in a patient in need thereof.
39. A method of treating a gastrointestinal disorder comprising administering the composition of any one of claims 1 to 28 or a dosage form according to any one of claims 35 to 37, to a patient in need thereof.
40. Use of a composition according to any one of claims 1 to 28, in the manufacture of a medicament for treating a gastrointestinal disorder in a patient in need thereof, wherein the composition further comprises a probiotic, a prebiotic or a mixture thereof.
41. A method of treating a gastrointestinal disorder comprising administering the composition according to any one of claims 1 to 28, or a dosage form according to any one of claims 35 to 37, to a patient in need thereof, wherein the composition or dosage form further comprises a probiotic, a prebiotic or a mixture thereof.

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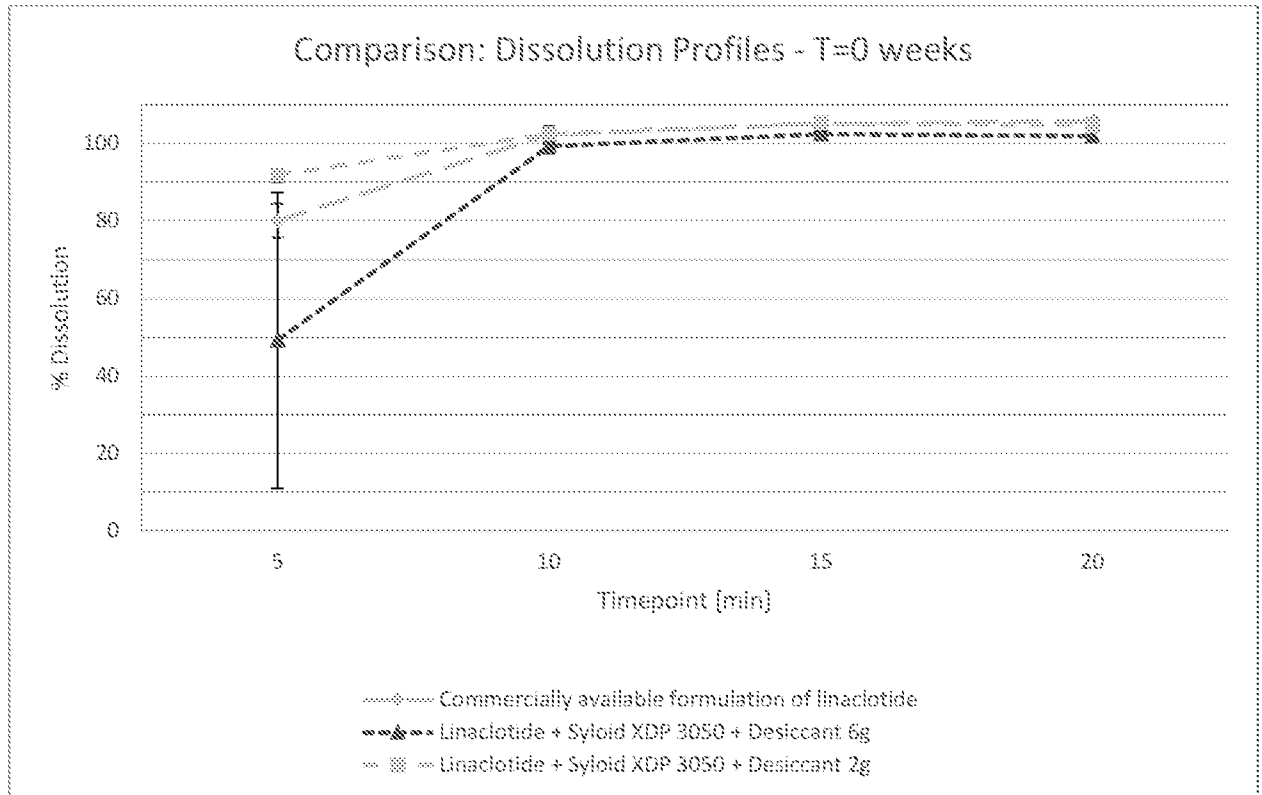


Figure 1

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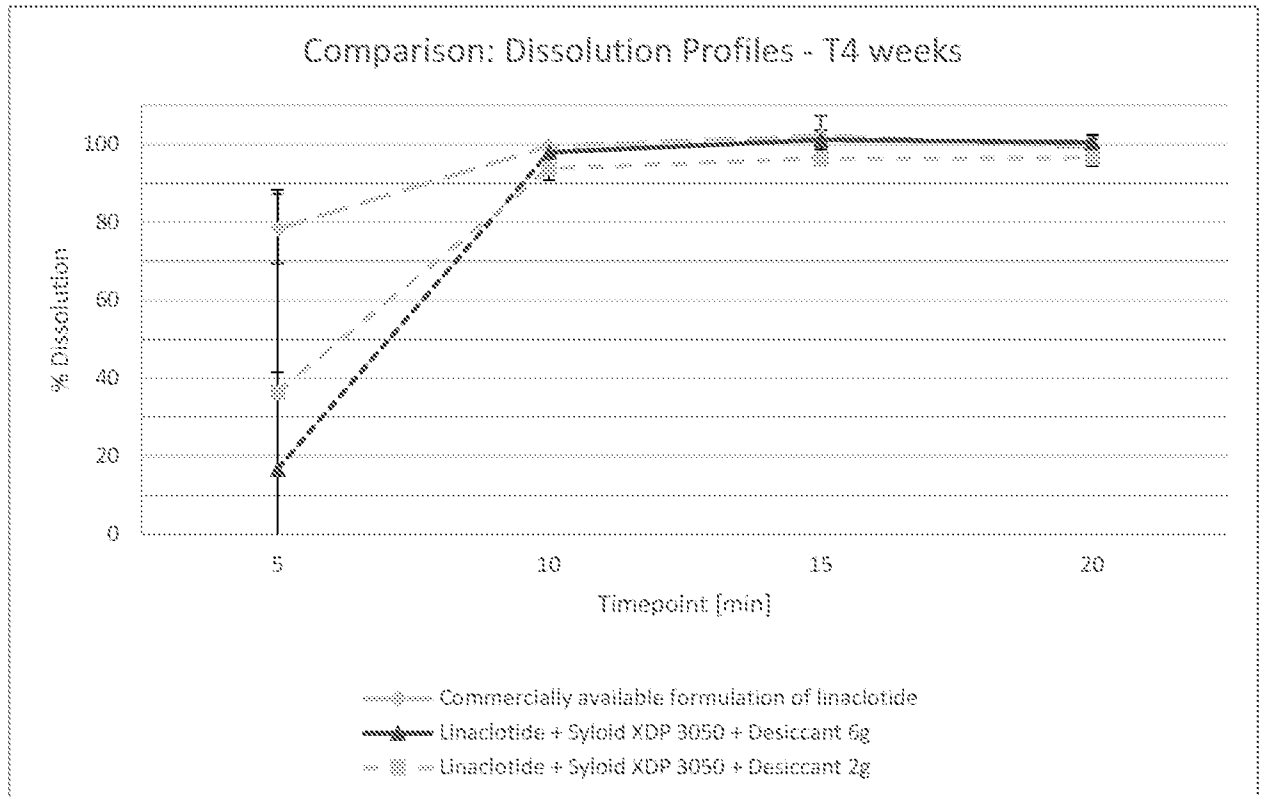


Figure 2

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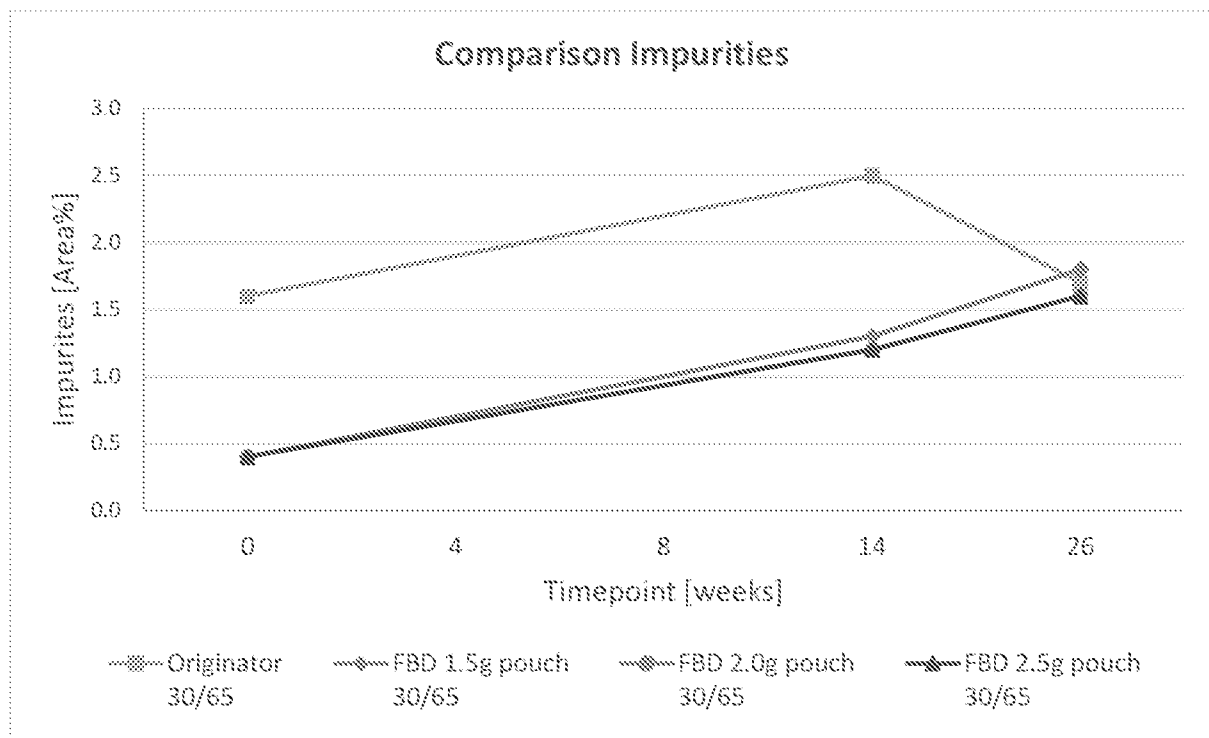


Figure 3

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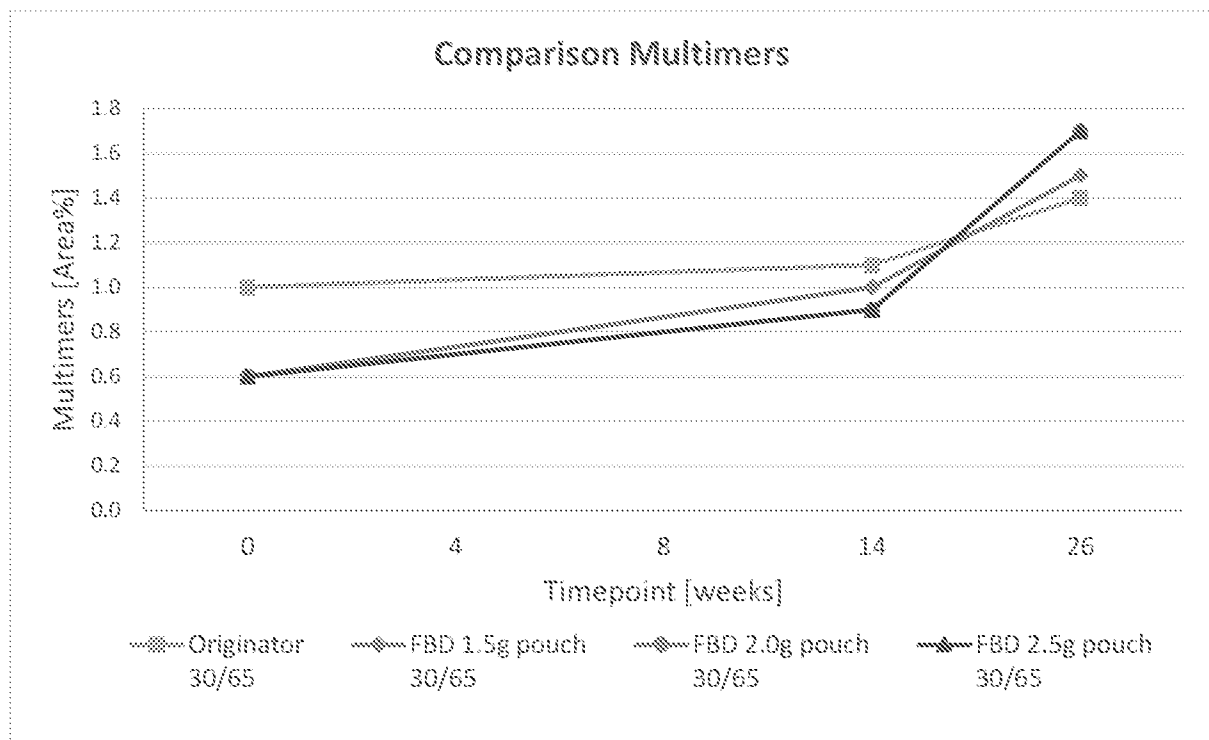


Figure 4

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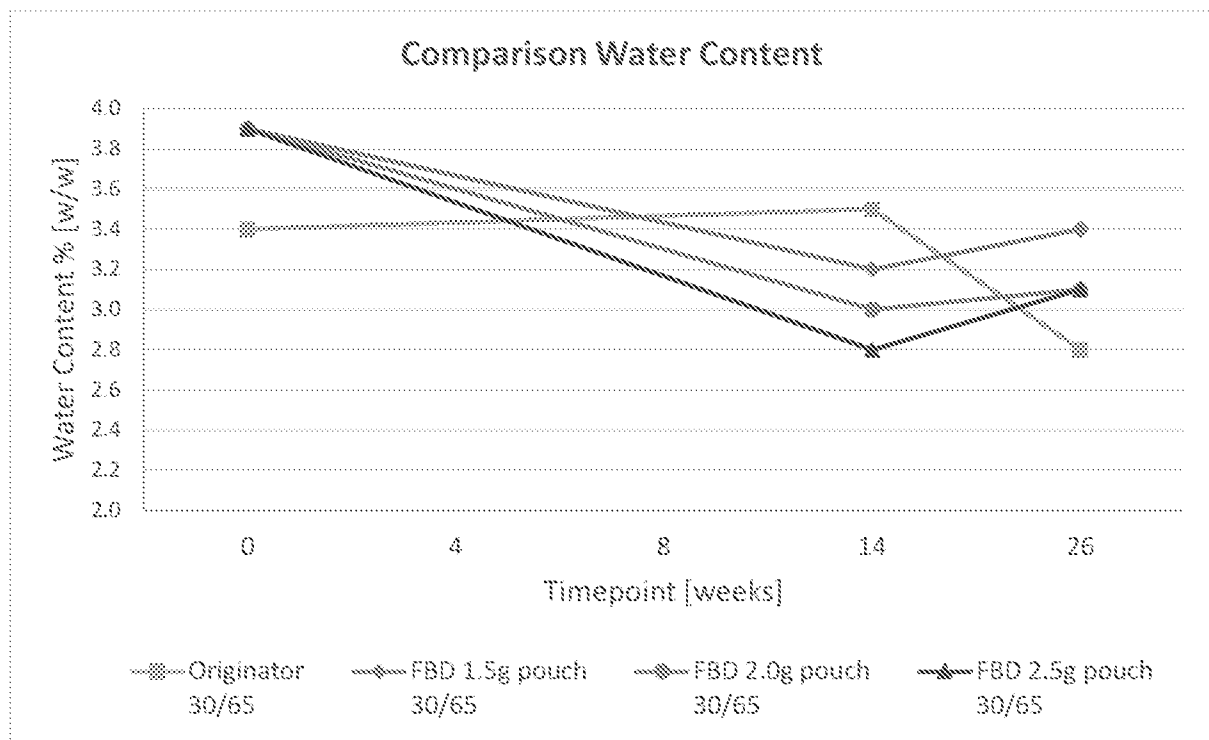


Figure 5

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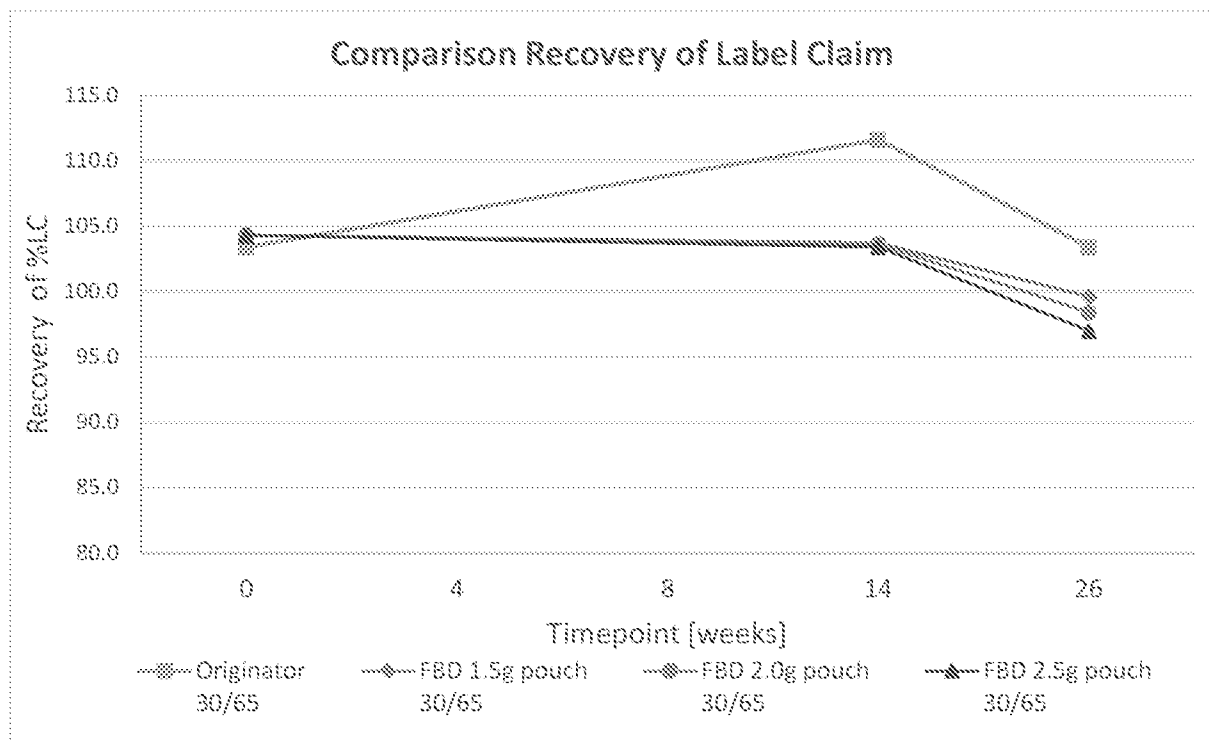


Figure 6

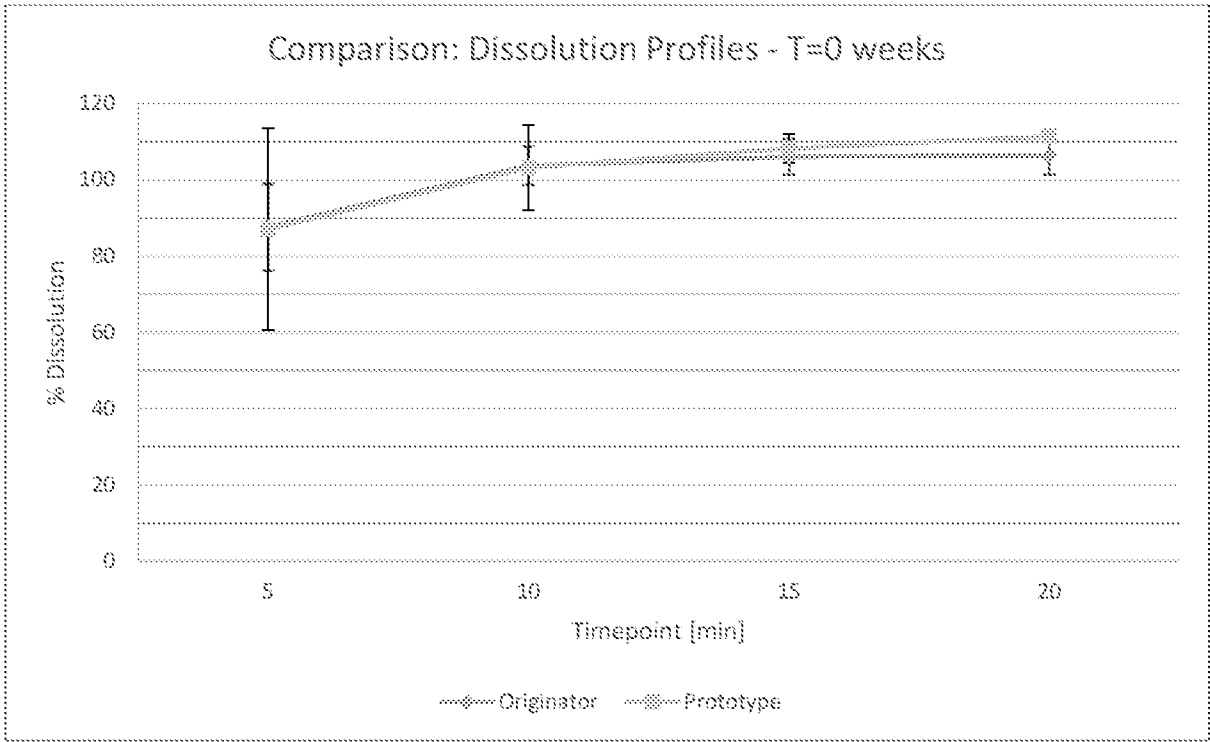


Figure 7