syndrome that accounts for about 30% of cases seen by gastroenterologists, with FD representing about 60% of all such dyspepsia cases.

[0003] GP refers to abnormal gastric motility characterized by delayed gastric emptying in the absence of mechanical obstruction. GP may be idiopathic or may be caused by various conditions, including Type I or Type II diabetes mellitus, viral infection, scleroderma, nervous system disorders such as Parkinson's disease, metabolic disorders such as hypothyroidism, post-operative ileus, and certain medications, including narcotic pain medications, tricyclic antidepressants and calcium channel blockers. Treatment for cancer, including chemotherapeutic drugs and radiation to the chest and abdomen can also cause gastroparesis, either temporarily or permanently. The most common symptoms are nausea, vomiting, bloating, epigastric pain, weight loss and early satiation. Gastroparesis is a chronic condition that can lead to frequent hospitalization, decreased quality of life, and increased disability and, in severe cases, increased mortality. Severe, symptomatic GP is common in individuals suffering from diabetes, affecting from 5-10% of diabetics for a total patient population of 1 million in the U.S. alone.

[0004] Conventional treatment options for FD and GP, as well as other upper gastrointestinal disorders, have been of limited efficacy for many patients. Thus, there remains a need for new compounds and methods of treating FD, GP and other gastrointestinal disorders.

SUMMARY

[0005] The present ~~invention~~disclosure features peptides, compositions, and related methods for treating upper gastrointestinal disorders and conditions (e.g., dyspepsia, GP, post-operative gastric ileus, a functional esophageal disorder, a functional gastroduodenal disorder, gastroesophageal reflux disease (GERD), or a duodenal or stomach ulcer) as well as other conditions and disorders are described herein The compositions feature peptides that activate guanylate cyclase C (GC-C) in the upper GI but activate GC-C in the lower GI much more weakly or not at all. Without being bound by any particular theory, the peptides of the ~~invention~~present disclosure are useful because they may alleviate symptoms of upper GI disorders (in whole or in part by increasing upper GI motility and/or reducing epigastric pain/discomfort and bloating) without causing pronounced effects in the lower GI tract (e.g., dose-limiting alterations in bowel habits, including diarrhea) at dose levels and dosing frequency sufficient to reduce upper GI symptoms. The peptides of the ~~invention~~present disclosure are also useful for ameliorating gastrointestinal pain and discomfort.

[0006] A first ~~One~~ aspect of the present ~~invention~~disclosure provides a peptide or a pharmaceutically acceptable salt thereof, wherein the peptide comprises the amino acid sequence:

Xaa_1 Xaa_2 Xaa_3 Xaa_4 Cys_5 Xaa_6 Xaa_7 Xaa_8 Cys_9 Asn_{10} Pro_{11} Ala_{12} Cys_{13} Xaa_{14} Gly_{15} Xaa_{16} Xaa_{17}, or a pharmaceutically acceptable salt thereof; wherein

Xaa_1 is Asn, D-Asn, Gln, D-Gln, Pro, Ala, β-Ala, D-Ala, Val, D-Val, Gly, Thr, D-Thr, Asp, D-Asp, γ-carboxylated Asp, Glu, D-Glu, γ-carboxylated Glu, α-aminosuberic acid (Asu), α-aminoadipic acid (Aad), α-aminopimelic acid (Apm), or is absent;

Xaa_2 is Asp, γ-carboxylated Asp, Glu, γ-carboxylated Glu, Asu, Aad, Apm, or is absent;

Xaa_3 is Asp, γ-carboxylated Asp, Glu, γ-carboxylated Glu, Asu, Aad, Apm, or is absent;

Xaa_4 is Cys or D-Cys;

Xaa_6 is P-Ser, P-Thr, P-homo-Ser, 4-hydroxyvaline phosphate, P-homo-Thr, P-Cys or P-Tyr;

Xaa_7 is Tyr, Leu, Phe or Ile;

Xaa_8 is Cys or D-Cys;

Xaa_{14} is Thr, Ala or Phe;

Xaa_{16} is Cys or D-Cys; and

Xaa_{17} is Tyr, D-Tyr, or is absent;

wherein:

if Xaa_1 is present, Xaa_1 may be modified on its amino group by methyl, ethanedioic acid, propanedioic acid, butanedioic acid, pentanedioic acid, hexanedioic acid, heptanedioic acid or octanedioic acid;

if Xaa_1 is absent and Xaa_2 is present, then Xaa_2 may be modified on its amino group by methyl, ethanedioic acid, propanedioic acid, butanedioic acid, pentanedioic acid, hexanedioic acid, heptanedioic acid or octanedioic acid; or

if both Xaa_1 and Xaa_2 are absent, then Xaa_3 may be modified on its amino group by methyl, ethanedioic acid, propanedioic acid, butanedioic acid, pentanedioic acid, hexanedioic acid, heptanedioic acid or octanedioic acid.

[0007] A second aspect of the present ~~invention~~disclosure provides pharmaceutical compositions comprising a peptide or pharmaceutically acceptable salt thereof according to~~of~~ the present ~~invention~~disclosure.

[0007a] In a third aspect, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier, a peptide as defined above and one or more agents selected from (i) a cation selected from Mg^{2+}, Ca^{2+}, Zn^{2+}, Mn^{2+}, K^{+}, Na^{+} or Al^{3+}, or (ii) a sterically hindered primary amine.

[0007b] In a fourth aspect, there is provided the pharmaceutical composition as defined above, further comprising a pharmaceutically acceptable antioxidant, binder, additive, or filler.

[0007c] In a fifth aspect, there is provided the pharmaceutical composition as defined above, further comprising an additional therapeutic agent.

[0007d] In a sixth aspect, there is provided a dosage unit comprising the pharmaceutical composition as defined above.

[0008] The present disclosure also~~A third aspect of the present invention~~ provides methods for treating a gastrointestinal disorder, which include administering a pharmaceutical composition according to the present ~~invention~~disclosure.

[0009] The details of one or more embodiments of the ~~invention~~present disclosure are set forth in the accompanying description.

BRIEF DESCRIPTION OF THE FIGURES

[00010] Figure 1A illustrates the reaction of an exemplary peptide of the present invention with alkaline phosphatase.

[00011] Figure 1B illustrates the hydrolysis of the control *p*-nitrophenylphosphate by phosphatases;

[00012] Figure 2 presents an example showing that Peptide 2 and Peptide 4 promote duodenal fluid secretion.

[00013] Figure 3 presents the results of a study on the stability of Peptide 2, Dephospho-peptide 2, and Peptide 3 in mouse intestinal (jejunum) fluid;

[00014] Figure 4 presents the results of a study on the effect of Peptides 2 and 3 on liquid gastric emptying in STZ-induced diabetic rats;

[00015] These figures are provided by way of example and are not intended to limit the scope of the present invention.

DETAILED DESCRIPTION

[00016] Guanylate cyclase C (GC-C) is a transmembrane receptor that is located on the apical surface of epithelial cells in the stomach and intestine. The receptor has an extracellular ligand-binding domain, a single transmembrane region and a C-terminal guanylyl cyclase domain. When a ligand binds to the extracellular domain of GC-C, the intracellular catalytic domain catalyzes the production of cGMP from GTP. *In vivo*, this increase in intracellular cGMP initiates a cascade of events that leads to increased secretion of chloride and bicarbonate into the intestinal lumen, increased luminal pH, decreased luminal sodium absorption, increased fluid secretion, and acceleration of intestinal transit. cGMP, which is secreted bidirectionally from the epithelium into the mucosa and lumen, has also been shown to dampen afferent C fiber firing, suggesting a potential mechanism for the observed analgesic effects of GC-C agonists on visceral pain.

[00017] Linaclotide, a peptide GC-C agonist that is orally administered and currently in clinical trials for treatment of irritable bowel syndrome with constipation (IBS-c) and chronic constipation (CC), has numerous effects on lower GI physiology including: (1) reduced visceral pain, (2) reduced bloating, and (3) increased GI transit, which can lead to increased stool frequency and improved stool consistency. Orally administered linaclotide acts locally

WHAT IS CLAIMED IS:

1. A peptide or a pharmaceutically acceptable salt thereof, wherein the peptide comprises the amino acid sequence

Xaa_1 Xaa_2 Xaa_3 Xaa_4 Cys_5 Xaa_6 Xaa_7 Xaa_8 Cys_9 Asn_{10} Pro_{11} Ala_{12} Cys_{13} Xaa_{14} Gly_{15} Xaa_{16} Xaa_{17}, or a pharmaceutically acceptable salt thereof; wherein

Xaa_1 is Asn, D-Asn, Gln, D-Gln, Pro, Ala, β-Ala, D-Ala, Val, D-Val, Gly, Thr, D-Thr, Asp, D-Asp, γ-carboxylated Asp, Glu, D-Glu, γ-carboxylated Glu, α-aminosuberic acid (Asu), α-aminoadipic acid (Aad), α-aminopimelic acid (Apm), or is absent;

Xaa_2 is Asp, γ-carboxylated Asp, Glu, γ-carboxylated Glu, Asu, Aad, Apm, or is absent;

Xaa_3 is Asp, γ-carboxylated Asp, Glu, γ-carboxylated Glu, Asu, Aad, Apm, or is absent;

Xaa_4 is Cys or D-Cys;

Xaa_6 is P-Ser, P-Thr, P-homo-Ser, 4-hydroxyvaline phosphate, P-homo-Thr, P-Cys or P-Tyr;

Xaa_7 is Tyr, Leu, Phe or Ile;

Xaa_8 is Cys or D-Cys;

Xaa_{14} is Thr, Ala or Phe;

Xaa_{16} is Cys or D-Cys; and

Xaa_{17} is Tyr, D-Tyr, or is absent;

wherein:

if Xaa_1 is present, Xaa_1 may be modified on its amino group by methyl, ethanedioic acid, propanedioic acid, butanedioic acid, pentanedioic acid, hexanedioic acid, heptanedioic acid or octanedioic acid;

if Xaa_1 is absent and Xaa_2 is present, then Xaa_2 may be modified on its amino group by methyl, ethanedioic acid, propanedioic acid, butanedioic acid, pentanedioic acid, hexanedioic acid, heptanedioic acid or octanedioic acid; or

if both Xaa_1 and Xaa_2 are absent, then Xaa_3 may be modified on its amino group by methyl, ethanedioic acid, propanedioic acid, butanedioic acid, pentanedioic acid, hexanedioic acid, heptanedioic acid or octanedioic acid.

2. The peptide or pharmaceutically acceptable salt thereof according to claim 1, wherein: Xaa_1, Xaa_2 and Xaa_3 are absent;

Xaa_1 is Asn, D-Asn, Gln, D-Gln, Pro, Ala, β-Ala, D-Ala, Val, D-Val, Gly, Thr, D-Thr, Asp, D-Asp, Glu or D-Glu;

Xaa_2 and Xaa_3 are both absent;

Xaa_2 is Asp or Glu and Xaa_3 is absent;

Xaa_2 is Asp or Glu and Xaa_3 is Asp or Glu

Xaa_6 is P-Ser or P-Thr;

Xaa_7 is Tyr or Leu;

Xaa_{14} is Thr;

Xaa_{17} is Tyr or is absent.

3. The peptide or pharmaceutically acceptable salt thereof according to claim 1, wherein Xaa_2 is Asp or Glu and Xaa_3 is absent.

4. The peptide or pharmaceutically acceptable salt thereof according to claim 1, wherein Xaa_2 is Asp or Glu and Xaa_3 is Asp or Glu.

5. The peptide or pharmaceutically acceptable salt thereof according to any one of claims 1-4, wherein Xaa_7 is Tyr or Leu.

6. The peptide or pharmaceutically acceptable salt thereof according to any one of claims 1-5, wherein Xaa_{14} is Thr.

7. The peptide or pharmaceutically acceptable salt thereof according to any one of claims 1-6, wherein Xaa_{17} is Tyr or is absent.

8. The peptide or pharmaceutically acceptable salt thereof according to any one of claims 1-7, wherein Xaa_1 is Asn, D-Asn, Gln, D-Gln, Pro, Ala, β-Ala, D-Ala, Val, D-Val, Gly, Thr, D-Thr, Asp, D-Asp, Glu or D-Glu.

9. The peptide or pharmaceutically acceptable salt thereof according to claim 8, wherein Xaa_1 is Asp, D-Asp, Glu or D-Glu.

10. The peptide or pharmaceutically acceptable salt thereof according to any one of claims 1-9, wherein Xaa_6 is P-Ser or P-Thr.

11. The peptide or pharmaceutically acceptable salt thereof according to claim 10, wherein Xaa_6 is P-Ser.

12. The peptide or pharmaceutically acceptable salt thereof according to claim 1, wherein Xaa_1, Xaa_2 and Xaa_3 are absent.

13. The peptide or pharmaceutically acceptable salt thereof according to claim 12, wherein Xaa_7 is Tyr or Leu.

~~14. The peptide or pharmaceutically acceptable salt thereof according to either of claims 12 or 13, wherein Xaa_{14} is Thr.~~

~~15. The peptide or pharmaceutically acceptable salt thereof according to any one of claims 12-14, wherein Xaa_{17} is Tyr or is absent.~~

~~16. The peptide or pharmaceutically acceptable salt thereof according to any one of claims 12-15, wherein Xaa_6 is P-Ser.~~

~~17. The peptide or pharmaceutically acceptable salt thereof according to claim 16, wherein said peptide comprises the amino acid sequence Cys_4-Cys_5-P-Ser_6-Xaa_7-Cys_8-Cys_9-Asn_{10}-Pro_{11}-Ala_{12}-Cys_{13}-Thr_{14}-Gly_{15}-Cys_{16}-Xaa_{17}, wherein Xaa_7 is Tyr or Leu.~~

~~18.~~3. The peptide or pharmaceutically acceptable salt thereof according to claim 1, wherein said peptide comprises the amino acid sequence:
Asp Asp Cys Cys P-Ser Leu Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr;
Asp Asp Cys Cys P-Ser Leu Cys Cys Asn Pro Ala Cys Thr Gly Cys;
Asp Asp Cys Cys P-Ser Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr;
Asp Asp Cys Cys P-Ser Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys;
Cys Cys P-Ser Leu Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr;
Cys Cys P-Ser Leu Cys Cys Asn Pro Ala Cys Thr Gly Cys;
Cys Cys P-Ser Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr; or
Cys Cys P-Ser Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys.

~~19.~~ 4. The peptide or pharmaceutically acceptable salt thereof according to any one of claims 1-3~~18~~, wherein said peptide comprises no more than 50, 40, 30, ~~or~~ 20, ~~amino acids.~~

~~20. The peptide or pharmaceutically acceptable salt thereof according to claim 19, wherein said peptide comprises no more than~~ 19, 18, 17, 16, 15 or 14 amino acids.

~~21. A peptide consisting of the amino acid sequence~~

~~Xaa_1-Xaa_2-Xaa_3-Xaa_4-Cys_5-Xaa_6-Xaa_7-Cys_8-Cys_9-Asn_{10}-Pro_{11}-Ala_{12}-Cys_{13}-Xaa_{14}-Gly_{15}-Cys_{16}-Xaa_{17}, or a pharmaceutically acceptable salt thereof; wherein~~

~~Xaa_1 is Asn, D-Asn, Gln, D-Gln, Pro, Ala, β-Ala, D-Ala, Val, D-Val, Gly, Thr, D-Thr, Asp, D-Asp, γ-carboxylated Asp, Glu, D-Glu, γ-carboxylated Glu, α-aminosuberic acid (Asu), α-aminoadipic acid (Aad), α-aminopimelic acid (Apm), or is absent;~~

~~Xaa_2 is Asp, γ-carboxylated Asp, Glu, γ-carboxylated Glu, Asu, Aad, Apm, or is absent;~~

~~Xaa_3 is Asp, γ-carboxylated Asp, Glu, γ-carboxylated Glu, Asu, Aad, Apm, or is absent;~~

~~Xaa_4 is Cys or D-Cys;~~

~~Xaa_6 is P-Ser, P-Thr, P-homo-Ser, 4-hydroxyvaline phosphate, P-homo-Thr, P-Cys or P-Tyr;~~

~~Xaa_7 is Tyr, Leu, Phe or Ile;~~

~~Xaa_8 is Cys or D-Cys;~~

~~Xaa_{14} is Thr, Ala or Phe;~~

~~Xaa_{16} is Cys or D-Cys; and~~

~~Xaa_{17} is Tyr, D-Tyr, or is absent;~~

~~wherein:~~

~~if Xaa_1 is present, Xaa_1 may be modified on its amino group by methyl, ethanedioic acid, propanedioic acid, butanedioic acid, pentanedioic acid, hexanedioic acid, heptanedioic acid or octanedioic acid;~~

~~if Xaa_1 is absent and Xaa_2 is present, then Xaa_2 may be modified on its amino group by methyl, ethanedioic acid, propanedioic acid, butanedioic acid, pentanedioic acid, hexanedioic acid, heptanedioic acid or octanedioic acid; or~~

~~if both Xaa_1 and Xaa_2 are absent, then Xaa_3 may be modified on its amino group by methyl, ethanedioic acid, propanedioic acid, butanedioic acid, pentanedioic acid, hexanedioic acid, heptanedioic acid or octanedioic acid.~~

~~22. The peptide or pharmaceutically acceptable salt thereof according to claim 21, wherein Xaa_2 and Xaa_3 are both absent.~~

~~23. The peptide or pharmaceutically acceptable salt thereof according to claim 21, wherein Xaa_2 is Asp or Glu and Xaa_3 is absent.~~

24. The peptide or pharmaceutically acceptable salt thereof according to claim 21, wherein Xaa_2 is Asp or Glu and Xaa_3 is Asp or Glu.

25. The peptide or pharmaceutically acceptable salt thereof according to any one of claims 21-24, wherein Xaa_7 is Tyr or Leu.

26. The peptide or pharmaceutically acceptable salt thereof according to any one of claims 21-25, wherein Xaa_{14} is Thr.

27. The peptide or pharmaceutically acceptable salt thereof according to any one of claims 21-26, wherein Xaa_{17} is Tyr or is absent.

28. The peptide or pharmaceutically acceptable salt thereof according to any one of claims 21-27, wherein Xaa_1 is Asn, D-Asn, Gln, D-Gln, Pro, Ala, β-Ala, D-Ala, Val, D-Val, Gly, Thr, D-Thr, Asp, D-Asp, Glu or D-Glu.

29. The peptide or pharmaceutically acceptable salt thereof according to claim 28, wherein Xaa_1 is Asp, D-Asp, Glu or D-Glu.

30. The peptide or pharmaceutically acceptable salt thereof according to any one of claims 21-29, wherein Xaa_6 is P-Ser or P-Thr.

31. The peptide or pharmaceutically acceptable salt thereof according to claim 30, wherein Xaa_6 is P-Ser.

32. The peptide or pharmaceutically acceptable salt thereof according to claim 21, wherein Xaa_1, Xaa_2 and Xaa_3 are absent.

33. The peptide or pharmaceutically acceptable salt thereof according to claim 32, wherein Xaa_7 is Tyr or Leu.

34. The peptide or pharmaceutically acceptable salt thereof according to either of claims 32 or 33, wherein Xaa_{14} is Thr.

~~35. The peptide or pharmaceutically acceptable salt thereof according to any one of claims 32-34, wherein Xaa_{17} is Tyr or is absent.~~

~~36. The peptide or pharmaceutically acceptable salt thereof according to any one of claims 32-35, wherein Xaa_6 is P-Ser.~~

~~37. The peptide or pharmaceutically acceptable salt thereof according to claim 36, wherein said peptide consists of the amino acid sequence~~

~~Cys_4-Cys_5-P-Ser_6-Xaa_7-Cys_8-Cys_9-Asn_{10}-Pro_{11}-Ala_{12}-Cys_{13}-Thr_{14}-Gly_{15}-Cys_{16}-Xaa_{17}, wherein Xaa_7 is Tyr or Leu.~~

~~38. The peptide or pharmaceutically acceptable salt thereof according to claim 32, wherein said peptide consists of the amino acid sequence:~~

~~Asp-Asp-Cys-Cys-P-Ser-Leu-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr;~~

~~Asp-Asp-Cys-Cys-P-Ser-Leu-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys;~~

~~Asp-Asp-Cys-Cys-P-Ser-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr;~~

~~Asp-Asp-Cys-Cys-P-Ser-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys;~~

~~Cys-Cys-P-Ser-Leu-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr;~~

~~Cys-Cys-P-Ser-Leu-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys;~~

~~Cys-Cys-P-Ser-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys-Tyr; or~~

~~Cys-Cys-P-Ser-Tyr-Cys-Cys-Asn-Pro-Ala-Cys-Thr-Gly-Cys.~~

~~39~~5. The peptide or pharmaceutically acceptable salt thereof according to any one of claims 1-~~38~~4, wherein said peptide or pharmaceutically acceptable salt thereof is isolated~~.~~

~~40. The peptide or pharmaceutically acceptable salt thereof according to claim 39, wherein said peptide or pharmaceutically acceptable salt thereof is~~ or purified.

~~41~~6. A pharmaceutical composition comprising a peptide or pharmaceutically acceptable salt thereof according to any one of claims 1-~~40~~5.

~~42~~7. A pharmaceutical composition comprising a pharmaceutically acceptable carrier, a peptide according to any one of claims 1-~~40~~5 and one or more agents selected from (i) a cation

selected from Mg^{2+}, Ca^{2+}, Zn^{2+}, Mn^{2+}, K^+, Na^+ or Al^{3+}, or (ii) a sterically hindered primary amine.

~~43. The pharmaceutical composition according to claim 42, wherein said agent is Mg^{2+}, Ca^{2+}, Zn^{2+}, Mn^{2+}, K^+, Na^+ or Al^{3+}.~~

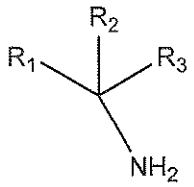
448. The pharmaceutical composition according to claim 742 or 43, wherein said Mg^{2+}, Ca^{2+}, Zn^{2+}, Mn^{2+}, K^+, Na^+ or Al^{3+} is provided as magnesium acetate, magnesium chloride, magnesium phosphate, magnesium sulfate, calcium acetate, calcium chloride, calcium phosphate, calcium sulfate, zinc acetate, zinc chloride, zinc phosphate, zinc sulfate, manganese acetate, manganese chloride, manganese phosphate, manganese sulfate, potassium acetate, potassium chloride, potassium phosphate, potassium sulfate, sodium acetate, sodium chloride, sodium phosphate, sodium sulfate, aluminum acetate, aluminum chloride, aluminum phosphate or aluminum sulfate.

~~45. The pharmaceutical composition according to claim 42, wherein said agent is a sterically hindered primary amine.~~

469. The pharmaceutical composition according to claim 457, wherein the sterically hindered primary amine is an amino acid.

~~47. The pharmaceutical composition according to claim 46, wherein the amino acid is~~ selected from a naturally-occurring amino acid, a non-naturally occurring amino acid or an amino acid derivative;.

~~48. The pharmaceutical composition according to claim 47,~~ wherein the naturally-occurring amino acid is histidine, phenylalanine, alanine, glutamic acid, aspartic acid, glutamine, leucine, methionine, asparagine, tyrosine, threonine, isoleucine, tryptophan or valine; and ~~or~~ the non-naturally occurring amino acid is 1-aminocyclohexane carboxylic acid, lanthanine or theanine.

~~49~~10. The pharmaceutical composition according to claim ~~42~~7, wherein the sterically hindered primary amine has the formula: 

, wherein R_1, R_2 and R_3 are independently selected from: H, C(O)OH, C_1-C_6 alkyl, C_1-C_6 alkylether, C_1-C_6 alkylthioether, C_1-C_6 alkyl carboxylic acid, C_1-C_6 alkyl carboxylamide and alkylaryl, wherein any group can be singly or multiply substituted with: halogen or amino, and provided that no more than one of R_1, R_2 and R_3 is H.

~~50~~11. The pharmaceutical composition according to claim ~~49~~7, wherein the sterically hindered primary amine is cyclohexylamine, ~~or~~ 2-methylbutylamine~~.~~.

~~51. The pharmaceutical composition according to claim 42, wherein the sterically hindered primary amine is~~ a polymeric amine~~.~~.

~~52. The pharmaceutical composition according to claim 51, wherein the polymeric amine is~~ or chitosan.

~~53. The pharmaceutical composition according to any one of claims 45-52, wherein said pharmaceutical composition further comprises Mg^{2+}, Ca^{2+}, Zn^{2+}, Mn^{2+}, K^+, Na^+ or Al^{3+}.~~

~~54. The pharmaceutical composition according to claim 50, wherein said Mg^{2+}, Ca^{2+}, Zn^{2+}, Mn^{2+}, K^+, Na^+ or Al^{3+} is provided as magnesium acetate, magnesium chloride, magnesium phosphate, magnesium sulfate, calcium acetate, calcium chloride, calcium phosphate, calcium sulfate, zinc acetate, zinc chloride, zinc phosphate, zinc sulfate, manganese acetate, manganese chloride, manganese phosphate, manganese sulfate, potassium acetate, potassium chloride, potassium phosphate, potassium sulfate, sodium acetate, sodium chloride, sodium phosphate, sodium sulfate, aluminum acetate, aluminum chloride, aluminum phosphate or aluminum sulfate.~~

~~55~~12. The pharmaceutical composition according to any one of claims 6-11~~42-54~~, further comprising ~~an~~ pharmaceutically acceptable antioxidant~~.~~.

~~56. The pharmaceutical composition according to claim 55, wherein said antioxidant is BHA, vitamin E or propyl gallate.~~

~~57. The pharmaceutical composition according to any one of claims 42-56, further comprising a pharmaceutically acceptable~~ binder, ~~or~~ additive~~.~~, or filler.

~~58~~13. The pharmaceutical composition according to claim ~~57~~ 12 wherein the pharmaceutically acceptable binder or additive is selected from polyvinyl alcohol, polyvinylpyrrolidone (povidone), a starch, maltodextrin or a cellulose ether.

~~59. The pharmaceutical composition according to claim 58, wherein the pharmaceutically acceptable binder or additive is polyvinyl alcohol.~~

~~60~~14. The pharmaceutical composition of claim ~~59~~ 12 wherein the pharmaceutically acceptable binder or additive is a cellulose ether~~.~~

~~61. The pharmaceutical composition of claim 60 wherein the cellulose ether is~~ selected from: methylcellulose, ethylcellulose, carboxymethylcellulose, hydroxyethyl cellulose, hydroxyethyl methylcellulose, hydroxypropyl cellulose and hydroxypropyl methylcellulose.

~~62. The pharmaceutical composition of any of claims 42-61, further comprising a pharmaceutically acceptable filler.~~

~~63~~15. The pharmaceutical composition according to claim ~~62~~12, wherein the pharmaceutically acceptable filler is cellulose, isomalt, mannitol, lactose or dibasic calcium phosphate.

~~64~~16. The pharmaceutical composition of claim ~~63~~ 15 wherein the pharmaceutically acceptable filler is cellulose is selected from microfine cellulose and microcrystalline cellulose.

~~65~~17. The pharmaceutical composition according to any one of claims 6-16~~41-64~~, further comprising an additional therapeutic agent.

~~66~~18. The pharmaceutical composition according to claim ~~65~~17, wherein said additional therapeutic agent is selected from one or more of an analgesic agent, an antidepressant, a

promotility or prokinetic agent, an antiemetic, an antibiotic, a proton pump inhibitor, an acid blocker, a PDE5 inhibitor, an acid pump antagonist, a GABA-B agonist, a bile acid sequestrant or a mucosal protecting agent.

~~67~~19. A dosage unit comprising the pharmaceutical composition according to any one of claims 6-18~~41-67~~.

~~68~~20. The dosage unit according to claim ~~67~~19, wherein said dosage unit is a capsule~~, or~~ tablet~~.~~, or

~~69. The dosage unit according to claim 69, wherein each of said dosage units~~ comprises 5 µg to 1 mg of said peptide.

~~70. A method for treating a gastrointestinal disorder comprising administering the pharmaceutical composition according to any one of claims 41-69.~~

~~71. The method according to claim 70, wherein said gastrointestinal disorder is gastroparesis, post-operative gastric ileus, a functional esophageal disorder, a functional gastroduodenal disorder, gastroesophageal reflux disease (GERD), celiac disease, mucositis, or a duodenal or stomach ulcer.~~

~~72. The method according to claim 71, wherein said gastrointestinal disorder is gastroparesis.~~

~~73. The method according to claim 72, wherein said gastroparesis is idiopathic, diabetic or post-surgical gastroparesis.~~

~~74. The method according to claim 71, wherein said gastrointestinal disorder is post-operative gastric ileus.~~

~~75. The method according to claim 71, wherein said gastrointestinal disorder is a functional esophageal disorder.~~

~~76. The method according to claim 75, wherein said functional esophageal disorder is functional heartburn, functional chest pain of presumed esophageal origin, functional dysphagia or globus.~~

~~77. The method according to claim 71, wherein said gastrointestinal disorder is a functional gastroduodenal disorder.~~

~~78. The method according to claim 77, wherein said functional gastroduodenal disorder is functional dyspepsia, a belching disorder, a nausea or vomiting disorder, or rumination syndrome.~~

~~79. The method according to claim 78, wherein said functional dyspepsia is postprandial distress syndrome or epigastric pain syndrome.~~

~~80. The method according to claim 78, wherein said belching disorder is aerophagia or unspecified excessive belching.~~

~~81. The method according to claim 78, wherein said nausea or vomiting disorder is chronic idiopathic nausea, functional vomiting or cyclic vomiting syndrome.~~

~~82. The method according to claim 71, wherein said gastrointestinal disorder is gastroesophageal reflux disease (GERD).~~

~~83. The method according to claim 71, wherein said gastrointestinal disorder is a duodenal or stomach ulcer.~~