treated with linaclotide, only about 5% of the oral dose is found in feces. Delayed release ("DR") compositions of linaclotide that target the lower GI may improve linaclotide's efficacy towards relieving pain associated with various GI disorders by allowing for delivery of a higher dose of linaclotide to the colon. Such DR compositions of linaclotide would have the potential to release linaclotide predominantly (or fully) in the lower GI. As a result, for example, the DR formulation or composition would have an increased capacity to treat lower GI associated disorders. Moreover, it may have a capacity to cause lower incidences of adverse events (such as diarrhea) than the immediate-release dosage form, e.g., because it would cause lower overall intestinal fluid secretion by not activating GC-C receptors in the upper GI. This would occur while maintaining or even improving linaclotide efficacy for treating symptoms of GI disorders, such as pain.

[00010] Despite the need for delayed release compositions of linaclotide, difficulties exist in preparing such formulations due to the intrinsic chemical instability of linaclotide, for example, by moisture induced degradation reactions such as hydrolysis, deamidation, isomerization, and multimerization. These difficulties may be exacerbated when producing formulations having lower dosages of linaclotide.

[00011] Accordingly, there is an existing and continual need for delayed release compositions that provide stable and reliable delivery of linaclotide to targeted areas of the gastrointestinal tract.

SUMMARY OF THE INVENTION

[00012] The present inventions relates to stable, solid, oral dosage forms of linaclotide which exhibit delayed release of linaclotide to the lower gastrointestinal tract. In addition, the present invention provides methods of treating conditions by administering these delayed release compositions. The delayed release compositions of the present invention may be used to treat various conditions, but is particularly suited to treat gastrointestinal disorders, such as irritable bowel syndrome ("IBS") (for example, IBS with constipation "IBS-c", IBS with diarrhea "IBS-d", or mixed IBS with constipation and diarrhea "IBS-m"), constipation (for example, chronic idiopathic constipation), colon cancer, diverticulitis, interstitial cystitis, and abdominal or visceral pain.

[00013] According to some embodiments, methods are provided for the treatment of a gastrointestinal disorder or pain comprising administering to a patient in need thereof, a composition disclosed herein.

[00013a] In one aspect, provided herein is a composition comprising a combination of a delayed release (DR) bead, and an immediate release (IR) bead, the DR bead and the IR bead:

linaclotide; Ca^{2+}; histidine; and polyvinyl alcohol (PVA); wherein the DR bead further comprises an enteric coating.

[00013b] In one aspect, provided herein is a unit dosage form comprising the composition as described herein.

[00013c] In one aspect, provided herein is a method of making the composition of as described herein, comprising: i) preparing a DR bead comprising linaclotide, Ca^{2+}, histidine, and polyvinyl alcohol (PVA) and an enteric coating; ii) preparing an IR bead comprising linaclotide, Ca^{2+}, leucine, HPMC; and iii) blending and compressing the DR bead and the IR bead into a capsule.

[00013d] In one aspect, provided herein is a use of the composition as described herein in the manufacture of a medicament for treating a gastrointestinal disorder in a patient in need thereof.

[00013e] In one aspect, provided herein is a use of the composition as described herein in the manufacture of a medicament for treating a gastrointestinal disorder in a patient in need thereof.

[00013f] In one aspect, provided herein is a use of the composition as described herein in the manufacture of a medicament for treating or relieving pain in a patient in need thereof.

[00013g] In one aspect, provided herein is a use of the pharmaceutical composition as described herein in the manufacture of a medicament for increasing intestinal motility in a patient.

[00013h] In one aspect, provided herein is a use of a composition as described herein in the manufacture of a medicament for increasing guanylate cyclase C (GC-C) receptor activity in a biological sample or organism, wherein said biological sample or organism is to be contacted with the composition.

[00013i] In one aspect, provided herein is a composition comprising a combination of a delayed release (DR) formulation, and an immediate release (IR) formulation, wherein (i) the DR formulation comprises linaclotide; Ca^{2+}; histidine and a pH-responsive polymer; (ii) the IR formulation comprises linaclotide; Ca^{2+}; and leucine or histidine.

[00013j] In one aspect, provided herein is a composition as described herein for use in therapy.

BRIEF DESCRIPTION OF THE FIGURES

WHAT IS CLAIMED IS:

~~1. A delayed release pharmaceutical~~1. A composition comprising ~~linaclotide or a pharmaceutically acceptable salt thereof.~~

~~2. The composition of claim 1, wherein the composition is~~ a combination of a delayed release ~~tablet or delayed release capsule.~~

~~3. The composition of claim 1, wherein the composition comprises delayed release tablet.~~

~~4. The composition of any one of claims 1-3, further comprising an enteric or functional coating.~~

~~5. The composition of any one of claims 1-3, further comprising an enteric coating~~(DR) bead, and ~~protective polymer film or subcoating.~~an immediate release (IR) bead, the DR bead and the IR bead:

~~The composition of claims 4 or 5,~~ linaclotide;

Ca^{2+};

histidine; and

polyvinyl alcohol (PVA);

wherein the DR bead further comprises an enteric coating ~~is selected from~~.

~~6.~~ 2. The composition of claim 1, wherein the enteric coating comprises methyl acrylate-methacrylic acid copolymers ~~(e.g. Eudragit®);~~; cellulose acetate succinate (CAS); hydroxy propyl methyl cellulose phthalate (HPMCP); ~~hydroxy propyl methyl cellulose acetate succinate (HPMCAS); polyvinyl acetate phthalate (PVAP); methyl methacrylate-methacrylic acid copolymers; sodium alginate and stearic acid; guar gum; and carbomers.~~

~~7. The composition of claims 4 or 5, wherein the enteric coating comprises Eudragit® FS30D, PlasAcryl®, Eudragit® S100, Eudragit®L100, Eudragit®L100-55, Eudragit® L30D-~~

~~55, Eudragit® S, Eudragit®RL30D, Eudragit®RS30D, Eudragit® RS, Eudragit® EC, or mixture thereof.~~

~~8. The composition of claims 5-7, wherein the subcoating comprises Opadry II®.~~

~~9. The composition of any of claims 1-8, wherein the composition releases at least 70% of the linaclotide at a pH greater than 5 or 7.~~

~~10. The composition of any of claims 1-8, wherein the composition releases at least 80% of the linaclotide at a pH greater than 5 or 7.~~

~~11. The composition of any of claims 1-10, wherein the composition has a disintegration rate of less than 30 seconds at a pH greater than 5 or 7.~~

~~12. The composition of any of claims 1-11, wherein the composition releases linaclotide in the ileum, terminal ileum, or colon.~~

~~13. The composition of any of claims 1-12, wherein the composition disintegrates in the ileum or colon.~~

~~14. The composition of any of claims 1-13, wherein the composition further comprises a polymer, a stabilizing amount of a sterically hindered primary amine, or a stabilizing amount of a cation, or a combination or mixture thereof.~~

~~15. The composition of any of claims 1-14, wherein the composition comprises a polymer.~~

~~16. The composition of any of claims 1-15, wherein the composition comprises 0.01 and 30 % by weight of a polymer, relative to the total weight of the composition.~~

~~17. The composition of any of claims 1-15, wherein the composition comprises between 1 and 25 % by weight of a polymer, relative to the total weight of the composition.~~

~~18. The composition of any of claims 1-15, wherein the composition comprises between 1 and 10% by weight of a polymer, relative to the total weight of the composition.~~

~~19. The composition of any of claims 1-15, wherein the composition comprises between 2 and 4 % by weight of a polymer, relative to the total weight of the composition.~~

~~20. The composition of any of claims 1-19, wherein the polymer is polyvinyl pyrrolidone (~~PVP~~), polyvinyl alcohol (PVA), or a combination or mixture thereof.~~

~~21. The composition of any of claims 1-20, wherein the composition comprises a stabilizing amount of a sterically hindered primary amine.~~

~~22. The composition of any of claims 1-21, wherein the composition comprises a molar ratio of sterically hindered primary amine to linaclotide between 400:1 and 1:1.~~

~~23. The composition of any of claims 1-21, wherein the composition comprises a molar ratio of sterically hindered primary amine to linaclotide between 200:1 and 50:1.~~

~~24. The composition of claim 23, wherein the sterically hindered primary amine is an amino acid.~~

~~25. The composition of claim 24, wherein the amino acid is histidine, leucine, isoleucine, methionine, alanine, or a combination or mixture thereof.~~

~~26. The composition of any of claims 1-25, wherein the composition comprises a stabilizing amount of a cation.~~

~~27. The composition of claim 26, wherein the composition comprises a molar ratio of cation to linaclotide between 300:1 and 1:1.~~

~~28. The composition of claim 26, wherein the composition comprises a molar ratio of cation to linaclotide between 250:1 and 30:1.~~

~~29. The composition of any of claims 26-28, wherein the cation is calcium, magnesium, manganese, zinc, potassium, sodium, or a mixture thereof.~~

~~30. The composition of any of claims 26-29, wherein the cation is a divalent metal cation.~~

~~31. The composition of claim 30, wherein the divalent metal cation is Ca^{2+}, Mg^{2+}, Mn^{2+}, Zn^{2+}, or a mixture thereof.~~

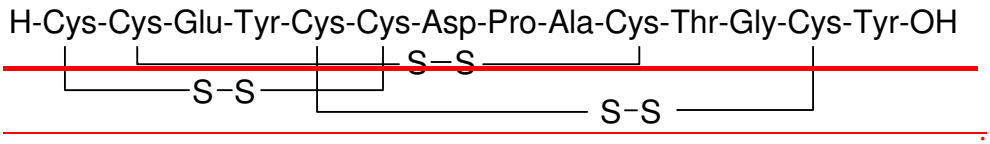
~~32. The composition of any of claims 1-31, wherein the composition comprises a polymer, stabilizing amount of a sterically hindered primary amine, and stabilizing amount of a cation.~~

~~33. The composition of claim 32, wherein the composition comprises a stabilizing amount of a polymer selected from PVP and PVA; a stabilizing amount of an amino acid selected from histidine, leucine, isoleucine, alanine, and methionine; and a stabilizing amount of a cation selected from Ca^{2+}, Mg^{2+}, Zn^{2+}, or a mixture thereof.~~

~~34. The composition of claim 33, wherein the composition comprises (i) between 0.01 and 30 % by weight of a polymer selected from PVP and PVA, (ii) an amino acid selected from histidine, leucine, isoleucine, alanine, and methionine in a molar ratio of amino acid to linaclotide between 400:1 and 1:1, and (iii) a cation selected from Ca^{2+}, Mg^{2+}, Zn^{2+}, or a mixture thereof, in a molar ratio of cation to linaclotide between 300:1 and 1:1.~~

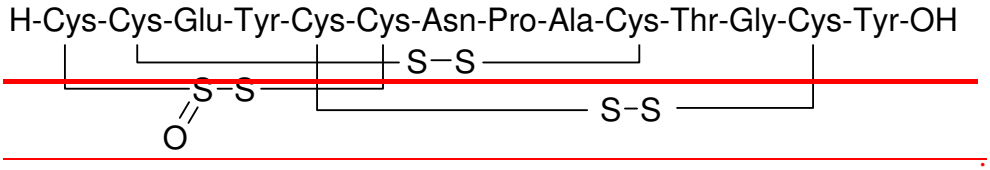
~~35. The composition of claim 33, wherein the composition comprises (i) between 1 and 10% by weight of PVA, (ii) histidine in a molar ratio of histidine to linaclotide between 400:1 and 50:1, and (iii) Ca^{2+} in a molar ratio of Ca^{2+} to linaclotide between 300:1 and 30:1.~~

~~36. The composition of any of claims 1-35, wherein the composition further comprises a hydrolysis product having a structure of:~~



37. The composition of claim 36, wherein the composition comprises less than 5% by weight of the hydrolysis product.

38. The composition of any of claims 1-37, wherein the composition further comprises an oxidation product having a structure of:



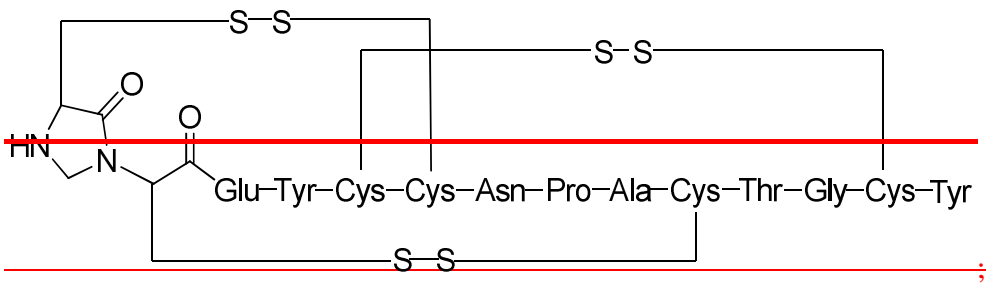
39. The composition of claim 38, wherein the composition comprises less than 5% by weight of the oxidation product.

40. The composition of any of claims 1-39, wherein the composition further comprises reduced form linaclotide.

41. The composition of claim 40, wherein the composition comprises less than 5% by weight of the reduced form linaclotide.

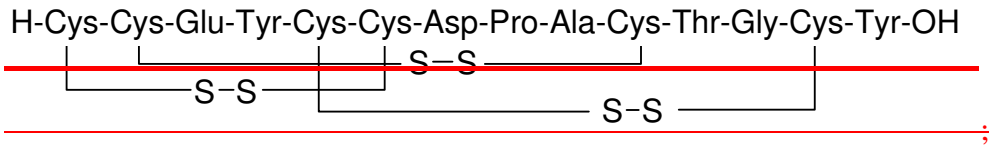
42. The pharmaceutical composition of any one of claims 1-41 further comprising one or more peptides selected from:

i. a peptide ("Cys^1 IMD") or a pharmaceutically acceptable salt thereof, wherein the peptide comprises the amino acid structure of:



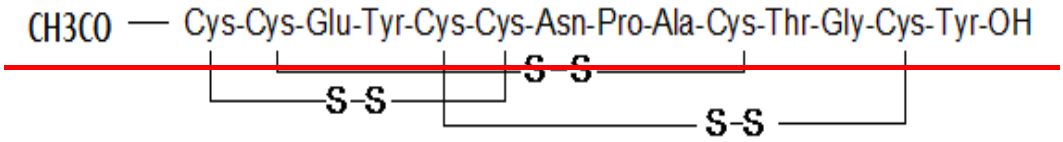
;

ii. a hydrolysis peptide ("Asp[7]") or a pharmaceutically acceptable salt thereof, wherein the peptide comprises the amino acid structure of:



;

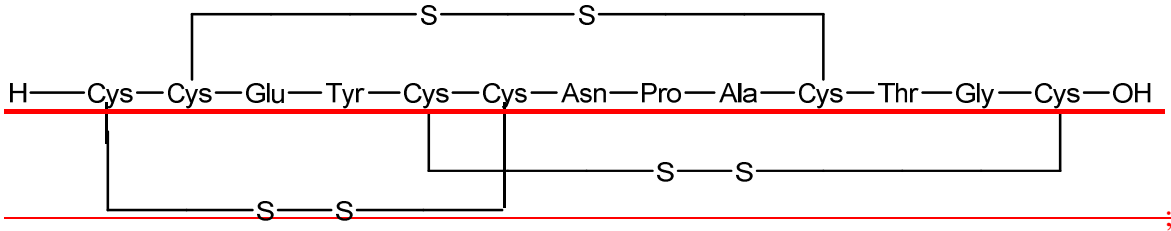
iii. an acetylation peptide ("Cys[1]-N-Acetyl") or a pharmaceutically acceptable salt thereof, wherein the peptide comprises the amino acid structure of:



;

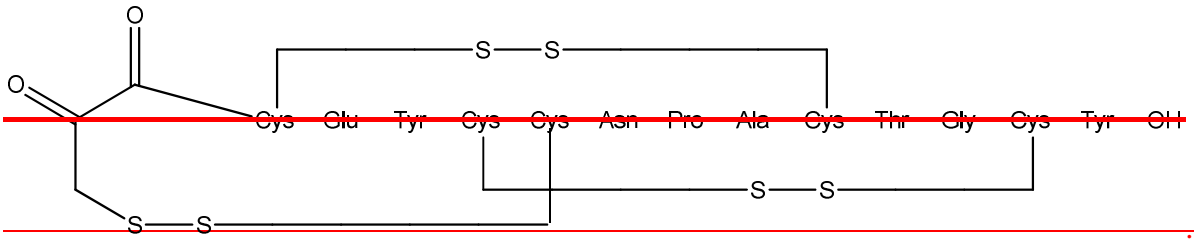
iv. a linaclotide trisulfide peptide or a pharmaceutically acceptable salt thereof, wherein the peptide comprises the amino acid sequence of Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr wherein an additional sulfur atom may be attached to any one of the six cysteinyl sulfurs;

v. a peptide ("Des-Tyr[14]") or a pharmaceutically acceptable salt thereof, wherein the peptide comprises the amino acid structure of:



; and

vi. a peptide ("Cys[1]-α Ketone peptide"), or a pharmaceutically acceptable salt or hydrate thereof, wherein the peptide comprises the amino acid structure of:



43. The composition of any of claims 1-42, wherein the linaclotide is present in the composition in a concentration of 1µg to 2 mg.

44. The composition of any of claims 1-43, wherein the linaclotide is present in the composition in a concentration of 25 µg, 36 µg, 50 µg, 72 µg, 75 µg, 100 µg, 145 µg, 150 µg, 290 µg, 300 µg, or 600 µg.

45. The composition of claim 44, wherein the linaclotide is present in the composition in a concentration of 25 µg.

46. The composition of claim 44, wherein the linaclotide is present in the composition in a concentration of 50 µg.

47. The composition of claim 44, wherein the linaclotide is present in the composition in a concentration of 75 µg.

48. The composition of claim 44, wherein the linaclotide is present in the composition in a concentration of 100 µg.

49. The composition of claim 44, wherein the linaclotide is present in the composition in a concentration of 150 µg.

50. The composition of claim 44, wherein the linaclotide is present in the composition in a concentration of 290 µg.

~~51. A delayed release composition comprising an enteric coated tablet, wherein the tablet is comprises:~~

~~linaclotide;~~

~~Ca^{2+};~~

~~histidine; and~~

~~polyvinyl alcohol (PVA).~~

~~52. The composition of claim 51, wherein the enteric coating comprises methyl acrylate-methacrylic acid copolymers (e.g. Eudragit®); cellulose acetate succinate (CAS); hydroxy propyl methyl cellulose phthalate (HPMCP); PVP; PVA~~; hydroxy propyl methyl cellulose acetate succinate (HPMCAS); polyvinyl acetate phthalate (PVAP); methyl methacrylate-methacrylic acid copolymers; sodium alginate and stearic acid; guar gum; carbomers; or mixtures thereof.

~~53.~~ 3. The composition of ~~claims 51 or 52~~claim 2, wherein the enteric coating comprises ~~Eudragit® FS30D, PlasAcryl®, Eudragit® S100, Eudragit®L100, Eudragit®L100-55, Eudragit® L30D-55, Eudragit® S, Eudragit®RL30D, Eudragit®RS30D, Eudragit® RS, Eudragit® EC, or mixtures thereof.~~a methyl methacrylate-methacrylic acid copolymer.

~~54.~~ 4. The composition of ~~any one of claims 51-53,~~claim 3, wherein the DR bead further ~~comprising an enteric coating and~~ comprises a protective polymer film or subcoating.

~~55.~~ 5. The composition of claim ~~5~~4, wherein the subcoating comprises ~~Opadry II®.~~polyvinyl alcohol.

6. The composition of any one of claims ~~51-55~~1-5, wherein the ~~composition releases at least 70% of~~DR bead and the ~~linaclotide at~~IR bead are compressed into a ~~pH greater than 5~~tablet, or the IR bead is applied to the DR bead as an outer layer or an under layer.

~~56.~~ 7.

~~57.~~ The composition of ~~any of claims 51-55, wherein the composition releases at least 80% of the linaclotide at a pH greater than 5 or 7.~~

~~58. The composition of any of claims 51-57, wherein the composition has a disintegration rate of less than 30 seconds at a pH greater than~~claim 5~~ or 7.~~

~~59. The composition of any of claims 51-58~~, wherein the composition ~~releases linaclotide in the ileum, terminal ileum, or colon.~~

~~60. The composition of any of claims 51-59, wherein~~further comprises a plurality of the DR beads and the ~~composition disintegrates in the ileum or colon~~IR beads, wherein the plurality of the DR beads and the IR beads are in an amount ranging from about 1% to about 99% (w/w) of the total weight of the composition.

8. The composition of claim 7, wherein the composition comprises about 50% to about 98% of the DR beads, relative to the IR beads.

9. The composition of any of claims 1-5, wherein the composition has a ratio of DR bead to IR bead (DR:IR) that is about 1:2 to about 49:50.

~~61.~~ 10. A unit dosage form comprising the ~~pharmaceutical~~ composition of claim ~~51~~1.

~~62.~~ 11. The unit dosage form of claim ~~61~~10, wherein the linaclotide is present in the ~~pharmaceutical~~ composition in an amount between ~~1µg~~25 µg to ~~300µg~~2 mg.

~~63.~~ 12. A method of making the composition of any one of claims 1-~~60~~9, comprising:

i) preparing a DR bead comprising linaclotide ~~base, pregranulated filler~~, Ca^{2+}, histidine, and ~~placebo base;~~polyvinyl alcohol (PVA) and an enteric coating;

~~ii)~~ ii) preparing an IR bead comprising linaclotide, Ca^{2+}, leucine, HPMC; and

iii) blending and compressing the ~~linaclotide base, pregranulated filler,~~DR bead and ~~placebo base~~the IR bead into a ~~tablet~~capsule.

~~64.~~ 13. The method of claim ~~63~~12, wherein the DR bead and the IR bead further comprises a pregranulated filler ~~is~~, and wherein each of the DR bead and IR bead are prepared through wet granulation and dried before blending and compressing into ~~a tablet~~the capsule.

~~65.~~ 14. The method of claims ~~63~~12 and ~~64~~13, wherein the method further comprises applying a subcoat to the tablet.

~~66.~~ 15. The method of claim ~~65~~14, wherein the subcoat comprises ~~Opadry II®.~~polyvinyl alcohol.

~~67. The method of any of claims 63-66, wherein the method further comprises applying an enteric or functional coating to the tablet.~~

~~68.~~ 16. The ~~composition~~ method of claim ~~67~~12, wherein the enteric coating comprises methyl acrylate-methacrylic acid copolymers ~~(e.g. Eudragit®);~~ cellulose acetate succinate (CAS); hydroxy propyl methyl cellulose phthalate (HPMCP); PVP~~; PVA~~; hydroxy propyl methyl cellulose acetate succinate (HPMCAS); polyvinyl acetate phthalate (PVAP); methyl methacrylate-methacrylic acid copolymers; sodium alginate and stearic acid; guar gum; carbomers; or mixtures thereof.

~~69.~~ 17. The method~~composition~~ of ~~claims 67 or 68~~claim 16, wherein the enteric coating comprises ~~Eudragit® FS30D, PlasAcryl®, Eudragit® S100, Eudragit®L100, Eudragit®L100-55, Eudragit® L30D-55, Eudragit® S, Eudragit®RL30D, Eudragit®RS30D, Eudragit® RS, Eudragit® EC, or mixtures thereof~~a methyl methacrylate-methacrylic acid copolymer.

~~70. A composition prepared by the method of claim 63.~~

~~71.~~ 18. Use of ~~a therapeutically effective amount of~~ the composition of any of claims 1-~~60 or 70~~9 in the manufacture of a medicament for treating a gastrointestinal disorder in a patient in need thereof.

~~72.~~ 19. The use of claim ~~71~~18, wherein the gastrointestinal disorder is selected from the group consisting of: irritable bowel syndrome (IBS), constipation, a functional gastrointestinal disorder, gastroesophageal reflux disease, functional heartburn, dyspepsia, diverticulitis, visceral pain, abdominal pain, gastroparesis, chronic intestinal pseudo-obstruction, colonic pseudo-obstruction, Crohn's disease, ulcerative colitis, and inflammatory bowel disease.

~~73.~~ 20. The use of claim ~~72~~19, wherein the gastrointestinal disorder is constipation.

~~74.~~ 21. The use of claim ~~73~~20, wherein the constipation is chronic constipation, idiopathic constipation, chronic idiopathic constipation, constipation due to post-operative ileus, or constipation caused by opiate use.

~~75.~~ 22. The use of claim ~~72~~19, wherein the gastrointestinal disorder is irritable bowel syndrome (IBS).

~~76.~~ 23. The use of claim ~~75~~22, wherein the irritable bowel syndrome is constipation-predominant irritable bowel syndrome (IBS-c), diarrhea-predominant irritable bowel syndrome (IBS-d) or mixed irritable bowel syndromes (IBS-m).

~~77.~~ 24. The use of claim ~~72~~19, wherein the gastrointestinal disorder is dyspepsia.

~~78.~~ 25. The use of claim ~~72~~19, wherein the gastrointestinal disorder is gastroparesis.

~~79.~~ 26. The use according to claim ~~78~~25, wherein said gastroparesis is idiopathic, diabetic or post-surgical gastroparesis.

~~80.~~ 27. The ~~use~~used of claim ~~72~~19, wherein the gastrointestinal disorder is chronic intestinal pseudo obstruction.

~~81.~~ 28. The use of claim ~~72~~19, wherein the gastrointestinal disorder is Crohn’s disease.

~~82.~~ 29. The use of claim ~~72~~19, wherein the gastrointestinal disorder is ulcerative colitis.

~~83.~~ 30. The use of claim ~~72~~19, wherein the gastrointestinal disorder is inflammatory bowel disease.

~~84.~~ 31. The use of claim ~~72~~19, wherein the gastrointestinal disorder is visceral pain.

~~85.~~ 32. The use of claim ~~72~~19, wherein the gastrointestinal disorder is diverticulitis.

~~86.~~ 33. The use of claim ~~72~~19, wherein the gastrointestinal disorder is abdominal pain.

~~87.~~ 34. Use of ~~a therapeutically effective amount of~~ the composition of any of claims 1-~~60 or 70~~9 in the manufacture of a medicament for treating a gastrointestinal disorder in a patient in need thereof.

~~88.~~ 35. The use of claim ~~87~~34, wherein the disorder is cancer selected from colorectal/local metastasized colorectal cancer, gastric cancer, intestinal polyps, gastrointestinal tract cancer, cancer or pre-cancerous growths or metastatic growths of epithelial cells or polyps of colorectal tissue.

~~89.~~ 36. Use of ~~a therapeutically effective amount of~~ the composition of any of claims 1-~~60 or 70~~9 in the manufacture of a medicament for treating or relieving pain in a patient in need thereof.

~~90.~~ 37. The use of claim ~~89~~36, wherein the pain is selected from visceral pain; diverticulitis pain; pelvic; abdominal pain; or pain associated with gastrointestinal disorders, venereal diseases, bladder pain syndrome, or interstitial cystitis.

~~91.~~ 38. Use of the pharmaceutical composition according to any one of claims 1-~~60 or 70~~9 in the manufacture of a medicament for increasing intestinal motility in a patient.

~~92.~~ 39. Use of a composition according to any one of claims 1-~~60 or 70~~9 in the manufacture of a medicament for increasing guanylate cyclase C (GC-C) receptor activity in a biological sample or organism, wherein said biological sample or organism is to be contacted with the ~~medicament~~composition.

~~93. A method of making the composition of any of claims 1-60 or 70, comprising:~~

~~i) preparing an aqueous solution comprising linaclotide, or a pharmaceutically acceptable salt thereof; and~~

~~ii) applying the aqueous solution to a pharmaceutically acceptable carrier.~~

~~94. A composition prepared by the method of claim 93.~~

40. A composition comprising a combination of a delayed release (DR) formulation, and an immediate release (IR) formulation, wherein

(i) the DR formulation comprises linaclotide; Ca^{2+}; histidine and a pH-responsive polymer;

(ii) the IR formulation comprises linaclotide; Ca^{2+}; and leucine or histidine.

41. The composition of claim 40, wherein the pH-responsive polymer comprises methyl acrylate-methacrylic acid copolymers; cellulose acetate succinate (CAS); hydroxy propyl methyl cellulose phthalate (HPMCP); PVP; hydroxy propyl methyl cellulose acetate succinate (HPMCAS); polyvinyl acetate phthalate (PVAP); methyl methacrylate-methacrylic acid copolymers; sodium alginate and stearic acid; guar gum; carbomers; or mixtures thereof.

42. The composition of claim 41, wherein the DR formulation and the IR formulation are each beads or granules.

43. The composition of claim 42, wherein the beads or granules are compressed as a tablet.

44. The composition of any one of claims 1-9 for use in therapy.