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(57) Abstract: The present invention relates to delayed release pharmaceutical compositions comprising linaclotide or pharmaceutically acceptable salts thereof, as well as to various methods and processes for the preparation and use of the compositions.



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DELAYED RELEASE COMPOSITIONS OF LINACLOTIDE

FIELD OF THE INVENTION

[0001] The present invention relates to delayed release pharmaceutical compositions comprising linaclotide or pharmaceutically acceptable salts thereof, as well as to various methods and processes for the preparation and use of the compositions.

PRIORITY CLAIM

[0002] This application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Patent Application Number 61/914,951 filed on December 11, 2013, and to U.S. Provisional Patent Application Number 61/914,952 filed on December 11, 2013, the entire contents of which are hereby incorporated by reference.

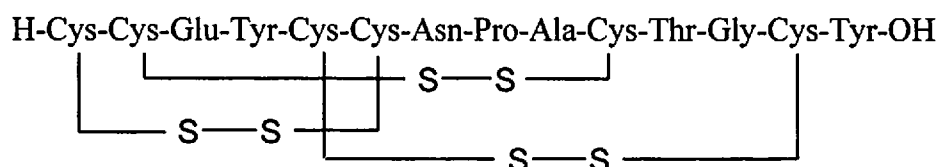
SEQUENCE LISTING

[0003] This application incorporates by reference in its entirety the Sequence Listing entitled "IW140PCT1_ST25.txt" (578 bytes) which was last modified on December 11, 2014 and filed electronically herewith.

BACKGROUND OF THE INVENTION

[0004] Various formulation techniques have been used to develop delayed release compositions for pharmaceutically active agents including the use of enteric coatings or pH responsive polymers. However, the specific components of these compositions vary greatly and depend significantly on the particular pharmaceutically active agent and the desired properties. For example, the formulation must be compatible with the pharmaceutically active agent and also provide the necessary dissolution performance and stability properties.

[0005] U.S. Patents 7,304,036 and 7,371,727, herein incorporated by reference, disclose peptides that act as agonists of the guanylate cyclase C (GC-C) receptor for the treatment of gastrointestinal (GI) disorders. One particular peptide disclosed is linaclotide, which consists of the following amino acid sequence: Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr. Linaclotide has the chemical structure of:



[0006] Linaclotide is orally administered and has been approved in the U.S. by the FDA for the treatment of irritable bowel syndrome with constipation (IBS-c) and chronic idiopathic constipation (CIC). In humans, linaclotide has been shown to effect GI physiology including reducing visceral pain, reducing bloating and increasing GI transit which can lead to increased stool frequency and improved stool consistency. Orally administered linaclotide acts locally by binding to and activating GC-C receptors at the luminal surface of the intestine. The GC-C receptor is a key regulator in mammals of intestinal function and is found throughout the luminal surface of the GI tract. The GC-C receptor responds to the endogenous hormones, guanylin and uroguanylin, and to enteric bacterial peptides from the heat stable enterotoxin family (ST peptide). When linaclotide binds to the GC-C receptor, there is an elevation of the second messenger, cyclic GMP (c-GMP), and an increase in chloride and bicarbonate secretion, resulting in an increase in intestinal fluid secretion and reducing pain.

[0007] As approved by the FDA, linaclotide is administered in an oral, solid, immediate-release capsule formulation manufactured by filling drug-layered beads into gelatin capsules. Due to the high expression of GC-C receptors throughout GI tract, linaclotide from an immediate release formulation activates the GC-C receptor starting from the upper GI tract, resulting in significant amount of intestinal fluid being brought to the lower GI tract. To reduce or mitigate this effect, delayed release compositions are needed which have targeted release of linaclotide in the distal or lower segment of the gastrointestinal tract. Targeting the lower GI for linaclotide release may help avoid excess fluid secretion but at the same time maintain or improve linaclotide efficacy for treating abdominal and bowel symptoms of GI disorders.

[0008] An estimated 13 million adults in the U.S. have IBS-c and 35 million adults have CIC. An estimated 15 million adults also suffer from IBS-m. Currently, 6.3 million adults are seeking care and not satisfied with current treatments for IBS-m. Abdominal or visceral pain is a pre-dominant symptom reported by patients suffering from IBS, CIC, and other gastrointestinal disorders. As a result, there is a need for therapies that provide improved relief of visceral pain and greater tolerability for adults suffering from IBS-c, IBS-m, and CIC.

[0009] Linaclotide has been previously demonstrated to reduce visceral pain which is thought to be mediated by increasing cGMP in the GI tract. Animal studies have shown that orally administered linaclotide can treat visceral pain originates in the lower GI tract. However, due to the reducing environment of the intestinal tract, it is believed that much of the oral linaclotide dose is degraded prior to reaching the distal colon. In human volunteers

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.

BRIEF DESCRIPTION OF THE FIGURES

[00014] Figure 1 shows the release profile at various pHs for delayed release tablet compositions comprising 100µg linaclotide.

[00015] Figure 2 shows the release profile at various pHs for delayed release tablet compositions comprising 25µg linaclotide.

[00016] Figure 3 shows a dissolution profile for an uncoated and coated acid resistant linaclotide capsule.

DETAILED DESCRIPTION OF THE INVENTION

[00017] Delayed release oral dosage forms of linaclotide (collectively, “DR”) are provided herein. Until now, the only approved formulation of linaclotide is a capsule that exhibits immediate release (“IR”). These IR dosage forms release most or all of the linaclotide contained therein in the upper GI. This, in turn, causes GC-C receptor activation and fluid secretion in both the upper GI and to a lesser extent in the lower GI. The difference between upper and lower GI activation and fluid secretion by the IR dosage form is due, in part, to the fact that linaclotide (once released from the dosage form) undergoes proteolytic digestion and loses some or all capacity to activate GC-C receptors, particularly by the time it reaches the lower GI (such as the ileum, terminal ileum, ileocecal valve, or colon).

[00018] The DR dosage forms described herein release most or all of the linaclotide contained therein within the lower GI, such as proximate to the ileocecal valve or within the colon (and less or no release in the stomach, duodenum and/or jejunum). Therefore, the inventive dosage forms have a capacity to achieve lower overall fluid secretion than IR dosage forms in the upper GI, while improving or still maintaining excellent efficacy for treating IBS-c, CIC, and for modulating the gastrointestinal pain sensory signaling. IBS patients report lower left quadrant abdominal pain as a symptom of their disorder, so it is believed that the pain of IBS originates from the colon. Moreover, the DR dosage forms are believed to be ideally suited for treating lower GI-associated diseases and disorders. Because the DR dosage forms will not release any (or a small percentage) of its linaclotide in the stomach and upper GI (which can cause rapid digestion of the linaclotide), some preferred embodiments of the DR dosage form will incorporate low doses of linaclotide (as compared to the amounts in the approved IR form) but will maintain the same efficacy levels as the IR in treating IBS-c and CIC symptoms.

[00019] In general, guanylate cyclase C (GC-C) receptor 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 is secreted bi-directionally from the epithelium into the mucosa and lumen. Normally, the pH of the GI tract gradually increases from stomach (pH 1.5-3) to terminal ileum (pH 7-8) before it drops in the colon to pH 5.5-7.0.

[00020] Linacotide binds to the intestinal GC-C receptor which is a regulator of fluid and electrolyte balance in the intestine. Linacotide is a peptide that consists of the amino acid sequence Cys₁ Cys₂ Glu₃ Tyr₄ Cys₅ Cys₆ Asn₇ Pro₈ Ala₉ Cys₁₀ Thr₁₁ Gly₁₂ Cys₁₃ Tyr₁₄. Any desired form of linacotide may be used in the composition, for example, any pharmaceutically acceptable salt or hydrate of the peptide, any isolated and/or purified form thereof, or any disulfide form thereof. Linacotide has disulfide bonds between Cys₁ and Cys₆, Cys₂ and Cys₁₀, and Cys₅ and Cys₁₃.

[00021] The DR compositions containing linacotide can be used to treat a variety of disorders. In various embodiments, the patient is suffering from a gastrointestinal disorder; the patient is suffering from a disorder selected from the group consisting of: gastrointestinal motility disorders, chronic intestinal pseudo-obstruction, colonic pseudo-obstruction, inflammatory bowel disease, Crohn's disease, duodenogastric reflux, dyspepsia, functional dyspepsia, nonulcer dyspepsia, a functional gastrointestinal disorder, functional heartburn, gastroesophageal reflux disease (GERD), gastroparesis, irritable bowel syndrome (e.g. diarrhea-predominant irritable bowel syndrome (IBS-d), constipation-predominant irritable bowel syndrome (IBS-c) and/or alternating or mixed irritable bowel syndrome (IBS-m)), post-operative ileus, ulcerative colitis, chronic constipation, constipation, interstitial cystitis, prostatitis, testicular pain, painful bladder syndrome, endometriosis, vulvodynia, rectal pain, diverticular disease or pain, pain associated with GI disorders, and disorders and conditions associated with constipation (e.g. constipation associated with use of opiate pain killers, post-surgical constipation, and constipation associated with neuropathic disorders as well as other conditions and disorders described herein). The patient can be diagnosed with a functional gastrointestinal disorder (e.g. IBS-c) according to the Rome Criteria (e.g. Rome II).

[00022] In some embodiments, the DR composition comprises enteric-coated beads comprising a pH- sensitive polymeric coating which be applied to core beads which have been coated with linacotide and potential polymeric sub-coat. In further embodiments, the beads with enteric and protective sub-coat coatings could be further filled into capsules to

achieve the desired unit dosage strengths. In some embodiments, the polymer acts as both a stabilizer, protective coating, or as a film forming agent within the delayed release composition. In other embodiments, the DR composition comprises enteric-coated tablets comprising an immediate release tablet core and containing a unit dose of linaclotide that dissolves only under pH conditions of the distal segment of intestine. In other embodiments, the DR composition comprises an enteric coated gelatin or HPMC capsule, achieving capsule disintegration in the lower GI tract. In some embodiments, the enteric or functional coating is selected from methyl acrylate-methacrylic acid copolymers (e.g. Eudragit®); cellulose acetate succinate (CAS); hydroxy propyl methyl cellulose phthalate (HPMCP); PVA; PVP; PVP-LP, 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. In further embodiments, the enteric coating is selected from 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.

[00023] The delayed release compositions may include any effective amount of linaclotide. In some embodiments, for example, the composition comprises from 0.05 µg to 6 mg of linaclotide. In some embodiments, for example, the composition comprises from 1 µg to 2 mg of linaclotide. In some embodiments, the composition comprises from 25 µg to 2 mg of linaclotide, for example, from 50 µg to 1 mg of linaclotide. In some embodiments, for example, the composition comprises from 0.1 µg to 90 µg of linaclotide. In some embodiments, for example, the composition comprises from 0.1 µg to 45 µg of linaclotide. In some embodiments, for example, the composition comprises from 0.1 µg to 25 µg of linaclotide. In some embodiments, for example, the composition comprises from 36 µg to 290 µg of linaclotide. In some embodiments, the composition comprises 0.05 µg, 0.1 µg, 0.15 µg, 0.25 µg, 0.5 µg, 0.75 µg, 1 µg, 1.5 µg, 2 µg, 2.5 µg, 3 µg, 3.5 µg, 4 µg, 4.5 µg, 5 µg, 7.5 µg, 9 µg, 10 µg, 15 µg, 20 µg, 25 µg, 30 µg, 35 µg, 36 µg, 40 µg, 45 µg, 50 µg, 60 µg, 72 µg, 75 µg, 90 µg, 100 µg, 145 µg, 150 µg, 200 µg, 250 µg, 290 µg, 300 µg, 350 µg, 400 µg, 450 µg, 500 µg, 550 µg, 579 µg, 600 µg, 650 µg, 700 µg, 750 µg, 800 µg, 850 µg, 900 µg, 950 µg or 1 mg of linaclotide. In some embodiments, the composition comprises from 100 µg to 600 µg of linaclotide. In some embodiments, the composition comprises 25 µg, 50 µg, 75 µg, 100 µg, 150 µg, 290 µg, 300 µg, 400 µg, 500 µg or 600 µg of linaclotide. In some embodiments, the composition comprises 9 µg, 10 µg, 15 µg, 36 µg, 72 µg, 75 µg, 145 µg, 290 µg, 579 µg, or 600 µg of linaclotide.

[00024] In some embodiments, the composition comprises 9 µg of linaclotide. In some embodiments, the composition comprises 10 µg of linaclotide. In some embodiments, the composition comprises 25 µg of linaclotide. In some embodiments, the composition comprises 50 µg of linaclotide. In some embodiments, the composition comprises 75 µg of linaclotide. In some embodiments, the composition comprises 100 µg of linaclotide. In some embodiments, the composition comprises 150 µg of linaclotide. In some embodiments, the composition comprises 145 µg of linaclotide. In some embodiments, the composition comprises 290 µg of linaclotide.

[00025] It has been found, in some embodiments, that the stability of delayed release compositions of linaclotide can be increased or improved by including in the compositions a suitable amount of a sterically hindered primary amine (*e.g.*, amino acid) component, a cation (*e.g.*, metal cation) component, and/or a polymer component. These components increase or enhance the stability of delayed release compositions of linaclotide, for example, by preventing, lessening, and/or decreasing degradation of linaclotide within the composition (for example, due to moisture-driven degradation reactions, *e.g.*, hydrolysis, deamidation, and/or multimerization reactions). For instance, it has been found in some embodiments that addition or inclusion of a suitable amount of a cation (*e.g.*, Mg^{2+} , Ca^{2+} , Zn^{2+}) in the composition increases the stability of the composition against oxidative degradation of linaclotide. Moreover, it has been found in some embodiments that inclusion of a suitable amount of a sterically hindered primary amine for an example in the form of an amino acid (*e.g.*, histidine) in the composition increases the stability of the composition against, for example, the nucleophilic addition of formaldehyde or a formaldehyde equivalent to the N-terminus of linaclotide, *e.g.* by acting as a scavenger, and/or by buffering the composition. Moreover, it has been found in some embodiments that inclusion of both a sterically hindered primary amine (*e.g.*, histidine) and a cation (*e.g.*, Ca^{2+}) in suitable amounts in the composition increases the stability of the composition against the formation of hydrolysis and formaldehyde (Cys¹-IMD) products of linaclotide. It has also been found in some embodiments that inclusion of a suitable amount of a polymer (*e.g.*, polyvinyl pyrrolidone or polyvinyl alcohol) in the delayed release composition increases the stability of the composition for example by decreasing the mobility and/or reactivity of linaclotide within the composition, *e.g.*, by forming a complex or matrix (for example, a glassy and/or rigid matrix) with linaclotide (*e.g.*, by vitrification reaction), by preventing or lessening hydrogen bond formation between linaclotide and water molecules, and/or by enhancing the three-dimensional structural integrity of linaclotide.

[00026] In this regard, it has been found in some embodiments that combining linaclotide in an delayed release pharmaceutical composition with specific concentrations or molar ratios of the cation and sterically hindered primary amine causes a synergistic enhancement or improvement in the stability of linaclotide within the composition, for example as compared to similar compositions not containing the cation and/or sterically hindered primary amine and/or the same concentrations of these components. In some embodiments, composition can comprise any stabilizing amount of a sterically hindered primary amine component. In other embodiments, the composition comprises a molar ratio of sterically hindered primary amine to linaclotide between 400:1 and 1:1. In further, embodiments, the composition comprises a molar ratio of sterically hindered primary amine to linaclotide between 200:1 and 50:1. In other embodiments, the composition can comprise a molar ratio of sterically hindered primary amine (*e.g.*, amino acid) to linaclotide between 100:1 and 1:100. In some embodiments, the composition comprises a molar ratio of sterically hindered primary amine to linaclotide between 100:1 and 1:1. In some embodiments, the composition comprises a molar ratio of sterically hindered primary amine to linaclotide between 90:1 and 2:1. In some embodiments, the composition comprises a molar ratio of sterically hindered primary amine to linaclotide between 80:1 and 5:1. In some embodiments, the composition comprises a molar ratio of sterically hindered primary amine to linaclotide between 70:1 and 10:1. In some embodiments, the composition comprises a molar ratio of sterically hindered primary amine to linaclotide between 60:1 and 20:1. In some embodiments, the composition comprises a molar ratio of sterically hindered primary amine to linaclotide between 50:1 and 30:1. In some embodiments, the composition comprises a molar ratio of sterically hindered primary amine to linaclotide between 40:1 and 20:1. In some embodiments, the composition comprises a molar ratio of sterically hindered primary amine to linaclotide between 100:1 and 20:1. In some embodiments, the composition comprises a molar ratio of sterically hindered primary amine to linaclotide between 100:1 and 25:1. In some embodiments, the composition comprises a molar ratio of sterically hindered primary amine to linaclotide between 100:1 and 30:1. In some embodiments, the composition comprises a molar ratio of sterically hindered primary amine to linaclotide between 100:1 and 40:1. In some embodiments, the composition comprises a molar ratio of sterically hindered primary amine to linaclotide between 100:1 and 50:1. In some embodiments, the composition comprises a molar ratio of sterically hindered primary amine to linaclotide between 100:1 and 60:1. In some embodiments, the composition comprises a molar ratio of sterically hindered primary amine to linaclotide between 100:1 and 70:1. In some embodiments, the composition comprises a molar ratio of sterically hindered

primary amine to linacotide of at least 5:1. In some embodiments, the composition comprises a molar ratio of sterically hindered primary amine to linacotide of at least 10:1. In some embodiments, the composition comprises a molar ratio of sterically hindered primary amine to linacotide of at least 20:1. In some embodiments, the composition comprises a molar ratio of sterically hindered primary amine to linacotide of at least 25:1. In some embodiments, the composition comprises a molar ratio of sterically hindered primary amine to linacotide of at least 30:1. In some embodiments, the composition comprises a molar ratio of sterically hindered primary amine to linacotide of at least 40:1.

[00027] Suitable sterically hindered primary amines for inclusion in the delayed release composition are, for example, naturally-occurring amino acids (*e.g.*, alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, meglumine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine), synthetic amino acids (*e.g.*, lanthionine, theanine or 1-amino cyclohexane), amino sugars (*e.g.*, chitosan or glucosamine), or combination or mixtures thereof. In some embodiments, the composition comprises an amino acid selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, or a mixture thereof. In some embodiments, the composition comprises an amino acid selected from leucine, isoleucine, asparagine, glutamine, glutamic acid, histidine, cysteine, alanine, serine, threonine, tyrosine, proline, tryptophan, or a combination or mixture thereof. In some embodiments, the composition comprises an amino acid selected from leucine, isoleucine, methionine, alanine, or a combination or mixture thereof. In some embodiments, the composition comprises an amino acid selected from leucine, isoleucine, alanine, or a combination or mixture thereof. In some embodiments, the composition comprises an amino acid selected from leucine, isoleucine, methionine, or a combination or mixture thereof. In some embodiments, the composition comprises an amino acid selected from leucine, methionine, alanine, or a combination or mixture thereof. In some embodiments, the composition comprises leucine, methionine, or a mixture thereof. In some embodiments, the composition comprises leucine, isoleucine, or a mixture thereof. In some embodiments, the composition comprises leucine, alanine, or a mixture thereof. In some embodiments, the composition comprises leucine. In some embodiments, the composition comprises isoleucine. In some embodiments, the composition comprises methionine. In some embodiments, the composition comprises alanine. In some embodiments, the composition comprises histidine.

[00028] The delayed release composition can comprise any stabilizing amount of a cation (*e.g.*, metal cation). In some embodiments, the composition comprises a molar ratio of cation to linacotide between 300:1 and 1:1. In further embodiments, the composition comprises a molar ratio of cation to linacotide between 250:1 and 30:1. In other embodiments, the composition can comprise a molar ratio of cation to linacotide between 100:1 and 1:100. In some embodiments, the composition comprises a molar ratio of cation to linacotide between 100:1 and 1:1. In some embodiments, the composition comprises a molar ratio of cation to linacotide between 90:1 and 2:1. In some embodiments, the composition comprises a molar ratio of cation to linacotide between 80:1 and 5:1. In some embodiments, the composition comprises a molar ratio of cation to linacotide between 70:1 and 10:1. In some embodiments, the composition comprises a molar ratio of cation to linacotide between 60:1 and 20:1. In some embodiments, the composition comprises a molar ratio of cation to linacotide between 50:1 and 30:1. In some embodiments, the composition comprises a molar ratio of cation to linacotide between 40:1 and 20:1. In some embodiments, the composition comprises a molar ratio of cation to linacotide between 100:1 and 20:1. In some embodiments, the composition comprises a molar ratio of cation to linacotide between 100:1 and 25:1. In some embodiments, the composition comprises a molar ratio of cation to linacotide between 100:1 and 30:1. In some embodiments, the composition comprises a molar ratio of cation to linacotide between 100:1 and 40:1. In some embodiments, the composition comprises a molar ratio of cation to linacotide between 100:1 and 50:1. In some embodiments, the composition comprises a molar ratio of cation to linacotide between 100:1 and 60:1. In some embodiments, the composition comprises a molar ratio of cation to linacotide between 100:1 and 70:1. In some embodiments, the composition comprises a molar ratio of cation to linacotide of at least 5:1. In some embodiments, the composition comprises a molar ratio of cation to linacotide of at least 10:1. In some embodiments, the composition comprises a molar ratio of cation to linacotide of at least 20:1. In some embodiments, the composition comprises a molar ratio of cation to linacotide of at least 25:1. In some embodiments, the composition comprises a molar ratio of cation to linacotide of at least 30:1. In some embodiments, the composition comprises a molar ratio of cation to linacotide of at least 40:1. In some embodiments, the composition comprises a molar ratio of cation to linacotide of at least 60:1.

[00029] Any suitable cation(s) can be included in the composition, for example, any suitable metal cation or organic cation. In some embodiments, the composition comprises a metal cation selected from calcium, potassium, magnesium, zinc, aluminum, iron, tin, manganese, chromium, cobalt, nickel, barium, sodium, or a combination or mixture thereof.

In some embodiments, the composition comprises a metal cation selected from calcium, potassium, magnesium, zinc, aluminum, manganese, chromium, cobalt, nickel, barium, sodium, or a combination or mixture thereof. In some embodiments, the composition comprises a metal cation selected from aluminum, calcium, potassium, sodium, magnesium, manganese, zinc, or a combination or mixture thereof. In some embodiments, the composition comprises a metal cation selected from calcium, magnesium, manganese, zinc, or a combination or mixture thereof. In some embodiments, the composition comprises a divalent metal cation. In some embodiments, the composition comprises a divalent metal cation selected from Al^{3+} , Ca^{2+} , Mg^{2+} , Zn^{2+} , Mn^{2+} , or a combination or mixture thereof. In some embodiments, the composition comprises Mg^{2+} . In some embodiments, the composition comprises Ca^{2+} . In some embodiments, the composition comprises Zn^{2+} . In some embodiments, the composition comprises aluminum.

[00030] Moreover, the metal cation can be added to the composition in any suitable form, for example any pharmaceutically acceptable salt with any appropriate counterion. Suitable metal salts include, for example, calcium chloride, calcium carbonate, calcium acetate, magnesium chloride, magnesium acetate, zinc acetate, zinc chloride, or mixtures thereof. In some embodiments, the composition comprises calcium chloride, magnesium chloride, zinc acetate, or any combination or mixture thereof. In some embodiments, the composition comprises calcium chloride. In some embodiments, the composition comprises magnesium chloride. In some embodiments, the composition comprises zinc acetate. Suitable organic cations include, for example, ammonium hydroxide, D-arginine, L-arginine, t-butylamine, calcium acetate hydrate, calcium carbonate, calcium DL-malate, calcium hydroxide, choline, ethanolamine, ethylenediamine, glycine, L-histidine, L-lysine, magnesium hydroxide, N-methyl-D-glucamine, L-ornithine hydrochloride, potassium hydroxide, procaine hydrochloride, L-proline, pyridoxine, L-serine, sodium hydroxide, DL-tryptophan, tromethamine, L-tyrosine, L-valine, carnitine, taurine, creatine malate, arginine alpha ketoglutarate, ornithine alpha ketoglutarate, spermine acetate, spermidine chloride, or combinations or mixtures thereof. In some embodiments, the organic cation is selected from the group consisting of N-methyl D-glucamine, choline, arginine, lysine, procaine, tromethamine (TRIS), spermine, N-methyl-morpholine, glucosamine, N,N-bis(2-hydroxyethyl) glycine, diazabicycloundecene, creatine, arginine ethyl ester, amantadine, rimantadine, ornithine, taurine, citrulline, or a combination or mixture thereof.

[00031] The composition can contain any stabilizing amount of a polymer. In some embodiments, the composition comprises between 1 and 25 % by weight of a polymer, relative to the total weight of the composition. In some embodiments, the composition

comprises between 1 and 10% by weight of a polymer, relative to the total weight of the composition.

[00032] In some embodiments, the composition comprises between 2 and 4 % by weight of a polymer, relative to the total weight of the composition. In some embodiments, the composition comprises between 0.1 and 75 wt.% of a polymer. In some embodiments, the composition comprises between 0.1 and 55 wt.% of a polymer. In some embodiments, the composition comprises between 0.1 and 35 wt.% of a polymer. In some embodiments, the composition comprises between 0.1 and 30 wt.% of a polymer. In some embodiments, the composition comprises between 0.1 and 25 wt.% of a polymer. In some embodiments, the composition comprises between 1 and 25 wt.% of a polymer. In some embodiments, the composition comprises between 5 and 25 wt.% of a polymer. In some embodiments, the composition comprises between 10 and 25 wt.% of a polymer. In some embodiments, the composition comprises between 15 and 25 wt.% of a polymer. In some embodiments, the composition comprises between 0.1 and 22 wt.% of a polymer. In some embodiments, the composition comprises between 1 and 22 wt.% of a polymer. In some embodiments, the composition comprises between 5 and 22 wt.% of a polymer. In some embodiments, the composition comprises between 10 and 22 wt.% of a polymer. In some embodiments, the composition comprises between 0.1 and 20 wt.% of a polymer. In some embodiments, the composition comprises between 1 and 20 wt.% of a polymer. In some embodiments, the composition comprises between 5 and 20 wt.% of a polymer. In some embodiments, the composition comprises between 10 and 20 wt.% of a polymer. In some embodiments, the composition comprises between 0.01 and 15 wt.% of a polymer. In some embodiments, the composition comprises between 0.01 and 10 wt.% of a polymer. In some embodiments, the composition comprises between 0.01 and 5 wt.% of a polymer. In some embodiments, the composition comprises between 0.1 and 95 wt.%, for example, between 5 and 95 wt.%, between 15 and 95 wt.%, between 25 and 95 wt.%, between 35 and 95 wt.%, between 45 and 95 wt.%, between 0.1 and 85 wt.%, between 1 and 85 wt.%, between 5 and 85 wt.%, between 15 and 85 wt.%, between 25 and 85 wt.%, between 35 and 85 wt.%, between 0.1 and 80 wt.%, between 1 and 80 wt.%, between 5 and 80 wt.%, between 15 and 80 wt.%, between 25 and 80 wt.%, between 35 and 80 wt.%, between 0.1 and 75 wt.%, between 1 and 75 wt.%, between 5 and 75 wt.%, between 15 and 75 wt.%, between 25 and 75 wt.%, between 35 and 75 wt.%, between 0.1 and 65 wt.%, between 1 and 65 wt.%, between 5 and 65 wt.%, between 15 and 65 wt.%, between 25 and 65 wt.%, between 35 and 65 wt.%, between 0.1 and 60 wt.%, between 1 and 60 wt.%, between 5 and 60 wt.%, between 15 and 60 wt.%, between 25 and 60 wt.%, or between 35 and 60 wt.% of a polymer.

[00033] In some embodiments, the polymer acts as both a stabilizer, protective coating, or as a film forming agent within the delayed release composition. In some embodiments, the delayed release composition comprises a molar ratio of polymer (e.g., PVP or PVA) to linaclotide between 80:1 and 300:1, for example, between 100:200:1, between 110:1 and 190:1, or even between 120:1 and 180:1. In some embodiments, the delayed release composition comprises a molar ratio of polymer (e.g., PVP or PVA) to linaclotide greater than about 80:1, for example, greater than about 100:1, or even greater than about 120:1. In some embodiments, the delayed release composition comprises a weight ration of polymer (e.g., PVP or PVA) to linaclotide between 10:1 and 300:1, for example, between 80:1 and 200:1, between 100:1 and 180:1, or even between 110:1 and 150:1. In some embodiments, the delayed release composition comprises a weight ration of polymer (e.g., PVP or PVA) to linaclotide between 100:1 and 500:1, for example, between 200:1 and 400:1, between 250:1 and 350:1, or even between 300:1 and 350:1.

[00034] Suitable polymers for inclusion in the delayed release compositions are, for example, polyvinyl pyrrolidone (PVP), polyvinyl alcohol (PVA), polyvinyl alcohol low peroxide (PVA-LP), hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC), methyl cellulose, methacrylate polymers, cyclodextrin, dextrin, dextran, polyacrylic acid, chitosan, guar gum, xanthan gum, polyethylene oxide (e.g., polyethylene polypropylene oxide), poly (sodium vinylsulfonate), polyethylene glycol, poly(arginine), poly carbophil, polyvinyl pyrrolidone-co-vinyl acetate, a poloxamer (e.g., Pluronic® products available from BASF), alginate, trehalose, sucrose, inulin, or a combination or mixture thereof. In some embodiments, the composition comprises a polymer selected from PVP, PVA, methacrylate polymers, cyclodextrin, dextran, polyacrylic acid, chitosan, guar gum, xanthan gum, polyethylene oxide, polyethylene glycol, poly(arginine), poly carbophil, polyvinyl pyrrolidone-co-vinyl acetate, a poloxamer, or a combination or mixture thereof. In some embodiments, the composition comprises PVP, PVA, polyethylene oxide, or a mixture thereof. In some embodiments, the composition comprises PVP, PVA, or a mixture thereof. In some embodiments, the composition comprises PVP. In some embodiments, the composition comprises PVA.

[00035] In some embodiments, the delayed release composition comprises two or more stabilizing agents. For example, the composition can include a stabilizing amount of a polymer and a stabilizing amount of a sterically hindered primary amine. Moreover, the composition can include a stabilizing amount of a polymer and a stabilizing amount of a cation (e.g., metal cation). In addition, the composition can include a stabilizing amount of a sterically hindered primary amine and a stabilizing amount of a cation (e.g., metal cation). In

some embodiments, the composition comprises a stabilizing amount of a polymer, a stabilizing amount of a sterically hindered primary amine, and a stabilizing amount of a cation (*e.g.*, metal cation).

[00036] In some embodiments, the delayed release composition comprises a stabilizing amount of PVP and a stabilizing amount of an amino acid selected from histidine, alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, or a mixture thereof. In some embodiments, the composition comprises a stabilizing amount of PVP and a stabilizing amount of an amino acid selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, or a mixture thereof. In some embodiments, the composition comprises a stabilizing amount of PVP and a stabilizing amount of leucine, isoleucine, methionine, alanine, or a combination or mixture thereof. In some embodiments, the composition comprises a stabilizing amount of PVP and a stabilizing amount of leucine.

[00037] In some embodiments, the delayed release composition comprises a stabilizing amount of PVA and a stabilizing amount of an amino acid selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, or a mixture thereof. In some embodiments, the composition comprises a stabilizing amount of PVA and a stabilizing amount of an amino acid selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, or a mixture thereof. In some embodiments, the composition comprises a stabilizing amount of PVA and a stabilizing amount of leucine, isoleucine, methionine, alanine, or a combination or mixture thereof. In some embodiments, the composition comprises a stabilizing amount of PVA and a stabilizing amount of leucine.

[00038] In some embodiments, the delayed release composition comprises a stabilizing amount of PVP and a stabilizing amount of a cation (*e.g.*, metal cation). In some embodiments, the composition comprises a stabilizing amount of PVP and a stabilizing amount of a divalent metal cation. In some embodiments, the composition comprises a stabilizing amount of PVP and a stabilizing amount of Mg^{2+} , Ca^{2+} , Zn^{2+} or a salt thereof or a combination or mixture thereof. In some embodiments, the composition comprises a stabilizing amount of PVP and a stabilizing amount of Ca^{2+} or a salt thereof. In some embodiments, the composition comprises a stabilizing amount of PVP and a stabilizing

amount of Mg^{2+} or a salt thereof. In some embodiments, the composition comprises a stabilizing amount of PVP and a stabilizing amount of Zn^{2+} or a salt thereof.

[00039] In some embodiments, the delayed release composition comprises a stabilizing amount of PVA and a stabilizing amount of a cation (*e.g.*, metal cation). In some embodiments, the composition comprises a stabilizing amount of PVA and a stabilizing amount of a divalent metal cation. In some embodiments, the composition comprises a stabilizing amount of PVA and a stabilizing amount of Mg^{2+} , Ca^{2+} , Zn^{2+} or a salt thereof or a combination or mixture thereof. In some embodiments, the composition comprises a stabilizing amount of PVA and a stabilizing amount of Ca^{2+} or a salt thereof. In some embodiments, the composition comprises a stabilizing amount of PVA and a stabilizing amount of Mg^{2+} or a salt thereof. In some embodiments, the composition comprises a stabilizing amount of PVA and a stabilizing amount of Zn^{2+} or a salt thereof.

[00040] In some embodiments, the delayed release composition comprises a stabilizing amount of an amino acid selected from leucine, isoleucine, methionine, alanine; and a stabilizing amount of a divalent metal cation selected from Mg^{2+} , Ca^{2+} , Zn^{2+} or a salt thereof or a combination or mixture thereof. In some embodiments, the composition comprises a stabilizing amount of an amino acid selected from leucine, and isoleucine; and a stabilizing amount of a divalent metal cation selected from Mg^{2+} , Ca^{2+} or a salt thereof or a combination or mixture thereof. In some embodiments, the composition comprises a stabilizing amount of an amino acid selected from leucine or methionine; and a stabilizing amount of a divalent metal cation selected from Ca^{2+} , Zn^{2+} or a salt thereof or a combination or mixture thereof. In some embodiments, the composition comprises a stabilizing amount of leucine and a stabilizing amount of Ca^{2+} or a salt thereof. In some embodiments, the composition comprises a stabilizing amount of a cation and a stabilizing amount of a sterically hindered primary amine. In some embodiments, the composition comprises a cation and a sterically hindered primary amine in a molar ratio of cation:sterically hindered primary amine (*e.g.*, Ca^{2+} :leucine) of at least 1.5:1, *e.g.*, at least 2:1, at least 2.5:1, at least 3:1, at least 4:1, or even at least 5:1 (for example, a molar ratio between 1.5:1 and 5:1, *e.g.*, between 2:1 and 4:1).

[00041] In some embodiments, the delayed release composition comprises (i) a stabilizing amount of PVP or PVA, (ii) a stabilizing amount of leucine, isoleucine, methionine, alanine, and (iii) a stabilizing amount of Mg^{2+} , Ca^{2+} , Zn^{2+} or a salt thereof or a combination or mixture thereof. In some embodiments, the composition comprises a stabilizing amount of PVP, a stabilizing amount of leucine, and a stabilizing amount of a metal cation. In some embodiments, the composition comprises a stabilizing amount of PVA, a stabilizing amount of histidine, and a stabilizing amount of Ca^{2+} or a salt thereof. In

some embodiments, the composition comprises a stabilizing amount of PVP, a stabilizing amount of leucine, and a stabilizing amount of Mg^{2+} or a salt thereof. In some embodiments, the composition comprises a stabilizing amount of PVP, a stabilizing amount of leucine, and a stabilizing amount of Zn^{2+} or a salt thereof. In some embodiments, the composition comprises a stabilizing amount of PVA, a stabilizing amount of leucine, and a stabilizing amount of Ca^{2+} or a salt thereof. In some embodiments, the composition comprises a stabilizing amount of PVA, a stabilizing amount of leucine, and a stabilizing amount of Mg^{2+} or a salt thereof. In some embodiments, the composition comprises a stabilizing amount of PVA, a stabilizing amount of leucine, and a stabilizing amount of Zn^{2+} or a salt thereof.

[00042] In some embodiments, the composition comprises (i) between 0.1 and 30 wt.% of a polymer, (ii) a sterically hindered primary amine (*e.g.*, an amino acid) in a molar ratio of primary amine to linacotide between 100:1 and 10:1, and (iii) a cation (*e.g.*, a metal cation) in a molar ratio of cation to linacotide between 100:1 and 40:1. In some embodiments, the composition comprises (i) between 5 and 25 wt.% of a polymer, (ii) a sterically hindered primary amine (*e.g.*, an amino acid) in a molar ratio of primary amine to linacotide 100:1 and 30:1 (*e.g.*, between 60:1 and 30:1 or even between 50:1 and 30:1), and (iii) a cation (*e.g.*, a metal cation) in a molar ratio of cation to linacotide between 100:1 and 60:1. In some embodiments, the composition comprises (i) between 0.1 and 30 wt.% of a polymer selected from PVP and PVA, (ii) an amino acid selected from leucine, isoleucine, alanine, and methionine in a molar ratio of amino acid to linacotide between 100:1 and 10:1, and (iii) a metal cation selected from Ca^{2+} , Mg^{2+} , and Zn^{2+} in a molar ratio of cation to linacotide between 100:1 and 40:1. In some embodiments, the composition comprises (i) between 5 and 25 wt.% of a polymer selected from PVP and PVA, (ii) an amino acid selected from leucine, isoleucine, alanine, and methionine in a molar ratio of amino acid to linacotide 100:1 and 30:1 (*e.g.*, between 60:1 and 30:1), and (iii) a metal cation selected from Ca^{2+} , Mg^{2+} , and Zn^{2+} in a molar ratio of cation to linacotide between 100:1 and 60:1. In some embodiments, the composition comprises (i) between 0.1 and 30 wt.% (*e.g.*, between 5 and 25 wt.%) of PVP or PVA, (ii) leucine in a molar ratio of leucine to linacotide between 100:1 and 30:1 (*e.g.*, between 60:1 and 30:1 or even between 50:1 and 30:1), and (iii) Ca^{2+} in a molar ratio of Ca^{2+} to linacotide between 100:1 and 60:1.

[00043] In some embodiments, the composition comprises (i) between 45 and 99 wt.% of a polymer, (ii) a sterically hindered primary amine (*e.g.*, an amino acid) in a molar ratio of primary amine to linacotide between 100:1 and 10:1, and (iii) a cation (*e.g.*, a metal cation) in a molar ratio of cation to linacotide between 100:1 and 40:1. In some embodiments, the composition comprises (i) between 45 and 70 wt.% of a polymer, (ii) a sterically hindered

primary amine (*e.g.*, an amino acid) in a molar ratio of primary amine to linacotide 100:1 and 30:1 (*e.g.*, between 60:1 and 30:1 or even between 50:1 and 30:1), and (iii) a cation (*e.g.*, a metal cation) in a molar ratio of cation to linacotide between 100:1 and 60:1. In some embodiments, the composition comprises (i) between 45 and 99 wt.% of a polymer selected from PVP and PVA, (ii) an amino acid selected from leucine, isoleucine, alanine, and methionine in a molar ratio of amino acid to linacotide between 100:1 and 10:1, and (iii) a metal cation selected from Ca^{2+} , Mg^{2+} , and Zn^{2+} in a molar ratio of cation to linacotide between 100:1 and 40:1. In some embodiments, the composition comprises (i) between 45 and 70 wt.% of a polymer selected from PVP and PVA, (ii) an amino acid selected from leucine, isoleucine, alanine, and methionine in a molar ratio of amino acid to linacotide 100:1 and 30:1 (*e.g.*, between 60:1 and 30:1), and (iii) a metal cation selected from Ca^{2+} , Mg^{2+} , and Zn^{2+} in a molar ratio of cation to linacotide between 100:1 and 60:1. In some embodiments, the composition comprises (i) between 45 and 99 wt.% (*e.g.*, between 45 and 70 wt.%) of PVP or PVA, (ii) leucine in a molar ratio of leucine to linacotide between 100:1 and 30:1 (*e.g.*, between 60:1 and 30:1 or even between 50:1 and 30:1), and (iii) Ca^{2+} in a molar ratio of Ca^{2+} to linacotide between 100:1 and 60:1.

[00044] The delayed release composition (*e.g.*, delayed release tablet) may also comprise any one or more filling agents. Suitable filling agents include, but are not limited to, starch, calcium carbonate, calcium sulfate, hydroxypropylmethyl cellulose, fructose, methyl cellulose, dextrates, dextrose, dextran, lactitol, maltose, sucrose, sorbitol, isomalt, pregelatinized starch, dicalcium phosphate, microcrystalline cellulose, mannitol, gelatin, trehalose, erythritol, maltitol, lactose, glucose, or a combination thereof, or a mixture thereof. In some embodiments, the filling agent is isomalt. In some embodiments, the filling agent is gelatin. In some embodiments, the filling agent is mannitol. In some embodiments, the filling agent is pregelatinized starch. In some embodiments, the filling agent is microcrystalline cellulose.

[00045] The delayed release composition (*e.g.*, delayed release tablet) can comprise any suitable concentration of filling agent. In some embodiments, for example, the composition comprises one or more filling agents in a concentration of 0.1-99 % by weight, relative to the total weight of the composition. In some embodiments, for example, the composition comprises one or more filling agents in a concentration of 1-95 wt.% of filling agent(s), relative to the total weight of the composition. In some embodiments, for example, the composition comprises one or more filling agents in a concentration of 10-90 wt.% of filling agent(s), relative to the total weight of the composition. In some embodiments, for example, the composition comprises one or more filling agents in a concentration of 20-90

wt.% of filling agent(s), relative to the total weight of the composition. In some embodiments, for example, the composition comprises one or more filling agents in a concentration of 25-85 wt.% of filling agent(s), relative to the total weight of the composition. In some embodiments, for example, the composition comprises one or more filling agents in a concentration of 30-80 wt.% of filling agent(s), relative to the total weight of the composition. In some embodiments, for example, the composition comprises one or more filling agents in a concentration of 40-70 wt.% of filling agent(s), relative to the total weight of the composition. In some embodiments, for example, the composition comprises one or more filling agents in a concentration of 10-60 wt.% of filling agent(s), relative to the total weight of the composition. In some embodiments, for example, the composition comprises one or more filling agents in a concentration of 20-50 wt.% of filling agent(s), relative to the total weight of the composition. In some embodiments, the composition comprises one or more filling agents in a concentration of at least 20 wt.%, for example, at least 40 wt.%, at least 60 wt.%, at least 70 wt.%, at least 80 wt.%, or at least 90 wt.%, relative to the total weight of the composition.

[00046] In some embodiments, the delayed release composition (e.g., delayed release film) comprises one or more plasticizers. Suitable plasticizers include, but are not limited to, polyethylene glycol, propylene glycol, glycerin, glycerol, monoacetin, diacetin, triacetin, dimethyl phthalate, diethyl phthalate, dibutyl phthalate, dibutyl sebacate, triethyl citrate, tributyl citrate, triethyl citrate, triethyl acetyl citrate, castor oil, acetylated monoglycerides, sorbitol or combinations thereof. In exemplary embodiments, the concentration of the plasticizer in the formulation may be about 0 to about 30 wt.%, for example, about 1 to about 20 wt.%, about 0 to about 10 wt.%, about 1 to about 5 wt.%, or even 0 to about 4 wt.%.

[00047] In some embodiments, the delayed release composition comprises a film forming agent, a water-soluble polymer, a pH sensitive polymer, biodegradable polymer, or combination thereof. Water soluble, pH sensitive, or biodegradable polymers that may be used in the orally dissolving formulations of the present invention include, but are not limited to, cellulose derivatives, synthetic polymers polyacrylates and natural gums. For example, the water soluble polymers used in the orally dissolving formulations of the present invention may include, but are not limited to, methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, cellulose acetate phthalate, cellulose acetate butyrate, amylose, dextran, casein, pullulan, gelatin, pectin, agar, carrageenan, xanthan gum, tragacanth, guar gum, acacia gum, arabic gum, polyethylene glycol, polyethylene oxide,

polyvinyl pyrrolidone, polyvinyl alcohol, cyclodextrin, carboxyvinyl polymers, sodium alginate, polyacrylic acid, methylmethacrylate or mixtures thereof. In exemplary embodiments, the concentration of the water-soluble polymer in the formulation may be about 20% to about 90% (by weight), preferably between about 40% to about 80% (by weight).

[00048] In some embodiments, the pH sensitive polymer is Eudagrit® L100 that has a threshold pH of 6.0. In some embodiments, the pH sensitive polymer is Eudagrit® S100 that has a threshold pH of 7.0. In some embodiments, the pH sensitive polymer is Eudagrit® L-30D that has a threshold pH of 5.6. In some embodiments, the pH sensitive polymer is Eudagrit® FS 30D that has a threshold pH of 6.8. In some embodiments, the pH sensitive polymer is Eudagrit® L00-55 that has a threshold pH of 5.5. In some embodiments, the pH sensitive polymer is Polyvinyl acetate phthalate that has a threshold pH of 5.0. In some embodiments, the pH sensitive polymer is Hydroxypropylmethylcellulose phthalate that has a threshold pH of 4.5-4.8. In some embodiments, the pH sensitive polymer is Hydroxypropylmethylcellulose phthalate 50 that has a threshold pH of 5.2. In some embodiments, the pH sensitive polymer is Hydroxypropylmethylcellulose phthalate 55 that has a threshold pH of 5.4. In some embodiments, the pH sensitive polymer is Cellulose acetate trimellitate that has a threshold pH of 4.8. In some embodiments, the pH sensitive polymer is Cellulose acetate phthalate that has a threshold pH of 5.0.

[00049] One skilled in the art, with the benefit of this disclosure, will understand that other components may be included to enhance one or more properties of the delayed release composition. In some embodiments, for example, the delayed release compositions may include one or more disintegrants, lubricants, anti-caking additives, anti-microbial agents, antifoaming agents, emulsifiers, surfactants, buffering agents, and/or coloring agents.

[00050] Suitable disintegrants include, for example, agar-agar, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, povidone, polacrillin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, clays, other algin, other celluloses, gums, and mixtures thereof. In some embodiments, the disintegrant is crospovidone. In some embodiments, the disintegrant is croscarmellose sodium.

[00051] Suitable lubricants include, for example, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil and soybean oil), zinc stearate, ethyl oleate, ethyl laurate, agar, syloid silica gel (AEROSIL® 200, W.R. Grace Co.,

Baltimore, MD USA), a coagulated aerosol of synthetic silica (Evonik Degussa Co., Plano, TX USA), a pyrogenic silicon dioxide (CAB-O-SIL, Cabot Co., Boston, MA USA), and mixtures thereof.

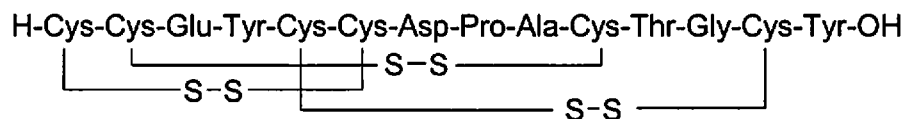
[00052] Suitable anti-caking additives include, for example, calcium silicate, magnesium silicate, silicon dioxide, colloidal silicon dioxide, talc, glyceryl, and mixtures thereof.

[00053] Suitable anti-microbial additives that may be used, *e.g.*, as a preservative for the linacotide compositions, include, for example, benzalkonium chloride, benzethonium chloride, benzoic acid, benzyl alcohol, butyl paraben, cetylpyridinium chloride, cresol, chlorobutanol, dehydroacetic acid, ethylparaben, methylparaben, phenol, phenylethyl alcohol, phenoxyethanol, phenylmercuric acetate, phenylmercuric nitrate, potassium sorbate, propylparaben, sodium benzoate, sodium dehydroacetate, sodium propionate, sorbic acid, thimersol, thymol, and mixtures thereof.

[00054] The composition may also comprise any suitable pharmaceutically acceptable carrier or medium. Suitable pharmaceutically acceptable carriers include, for example, any solvents, dispersants, pH buffering agents, coatings, absorption promoting agents, controlled release agents, and one or more inert excipients (*e.g.*, filling agents, starches, polyols, granulating agents, microcrystalline cellulose, diluents, lubricants, binders, disintegrating agents), or the like. In addition, the compositions can contain any desired additional components, additives, and/or species, for example, surface active additives, dispersing additives, humectants, suspending agents, solubilizers, buffering agents, disintegrants, preservatives, colorants, flavorants, and the like. In some embodiments, the composition comprises one or more ion species that interact with linaclotide.

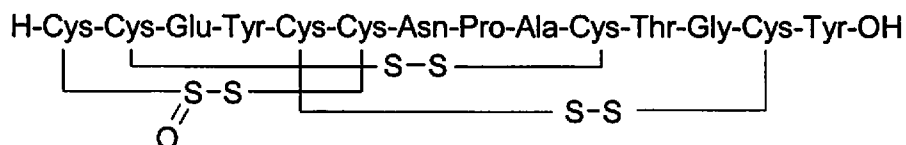
[00055] The composition can also comprise any suitable pH buffering agent. In some embodiments, the pH buffering agent is present in the composition in an amount sufficient to achieve the isoelectric point of linacotide. In the regard, the composition can have any desired pH. In some embodiments, the composition has a pH of 2 to 5 (for example, a pH of 2 to 4.5, a pH of 2 to 4, a pH of 2.5 to 4, a pH of 2.5 to 3.5, a pH of 2.5 to 3, or even a pH of 3).

[00056] In some embodiments, the composition comprises linacotide and a hydrolysis product, *e.g.*, a hydrolysis product comprising or having a structure of:



The composition can contain any desired concentration of the hydrolysis product. In some embodiments, the composition comprises less than 10 wt.% of the hydrolysis product. In some embodiments, the composition comprises less than 7 wt.% of the hydrolysis product. In some embodiments, the composition comprises less than 6 wt.% of the hydrolysis product. In some embodiments, the composition comprises less than 5 wt.% of the hydrolysis product. In some embodiments, the composition comprises less than 4 wt.% of the hydrolysis product. In some embodiments, the composition comprises less than 3 wt.% of the hydrolysis product. In some embodiments, the composition comprises less than 2 wt.% of the hydrolysis product. In some embodiments, the composition comprises less than 1 wt.% of the hydrolysis product. In some embodiments, the composition comprises between 0.01 and 10 wt.% of the hydrolysis product. In some embodiments, the composition comprises between 0.1 and 7 wt.% of the hydrolysis product. In some embodiments, the composition comprises between 0.1 and 5 wt.% of the hydrolysis product. In some embodiments, the composition comprises between 0.5 and 5 wt.% of the hydrolysis product. In some embodiments, the composition comprises between 1 and 5 wt.% of the hydrolysis product. In some embodiments, the composition comprises between 0.1 and 4 wt.% of the hydrolysis product. In some embodiments, the composition comprises between 0.5 and 4 wt.% of the hydrolysis product. In some embodiments, the composition comprises between 1 and 4 wt.% of the hydrolysis product. In some embodiments, the composition comprises between 0.1 and 3 wt.% of the hydrolysis product. In some embodiments, the composition comprises between 0.5 and 3 wt.% of the hydrolysis product. In some embodiments, the composition comprises between 1 and 3 wt.% of the hydrolysis product. In some embodiments, the composition comprises between 0.1 and 2.5 wt.% of the hydrolysis product. In some embodiments, the composition comprises between 0.5 and 2.5 wt.% of the hydrolysis product. In some embodiments, the composition comprises between 1 and 2.5 wt.% of the hydrolysis product. In some embodiments, the composition comprises between 0.1 and 2 wt.% of the hydrolysis product. In some embodiments, the composition comprises between 0.5 and 2 wt.% of the hydrolysis product. In some embodiments, the composition comprises between 1 and 2 wt.% of the hydrolysis product. In some embodiments, the composition comprises between 0.1 and 1.5 wt.% of the hydrolysis product. In some embodiments, the composition comprises between 0.5 and 1.5 wt.% of the hydrolysis product. In some embodiments, the composition comprises between 0.1 and 1 wt.% of the hydrolysis product. In some embodiments, the composition comprises between 0.5 and 1 wt.% of the hydrolysis product.

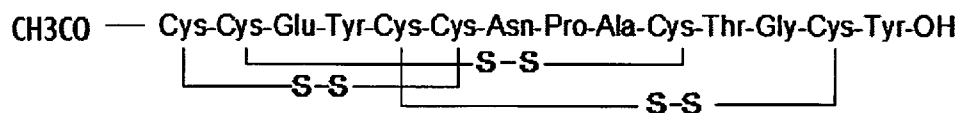
[00057] In some embodiments, the composition comprises linacotide and an oxidation product, *e.g.*, an oxidation product comprising or having a structure of:



Alternatively, or in addition, the composition comprises linaclotide and an oxidation product having the depicted structure but wherein oxidation occurs at any one or more of the six depicted cysteinyl sulfurs. The composition can contain any desired concentration of the oxidation product. In some embodiments, the composition comprises less than 10 wt.% of the oxidation product. In some embodiments, the composition comprises less than 7 wt.% of the oxidation product. In some embodiments, the composition comprises less than 6 wt.% of the oxidation product. In some embodiments, the composition comprises less than 5 wt.% of the oxidation product. In some embodiments, the composition comprises less than 4 wt.% of the oxidation product. In some embodiments, the composition comprises less than 3 wt.% of the oxidation product. In some embodiments, the composition comprises less than 2 wt.% of the oxidation product. In some embodiments, the composition comprises less than 1 wt.% of the oxidation product. In some embodiments, the composition comprises between 0.01 and 10 wt.% of the oxidation product. In some embodiments, the composition comprises between 0.1 and 7 wt.% of the oxidation product. In some embodiments, the composition comprises between 0.1 and 5 wt.% of the oxidation product. In some embodiments, the composition comprises between 0.5 and 5 wt.% of the oxidation product. In some embodiments, the composition comprises between 1 and 5 wt.% of the oxidation product. In some embodiments, the composition comprises between 0.1 and 4 wt.% of the oxidation product. In some embodiments, the composition comprises between 0.5 and 4 wt.% of the oxidation product. In some embodiments, the composition comprises between 1 and 4 wt.% of the oxidation product. In some embodiments, the composition comprises between 0.1 and 3 wt.% of the oxidation product. In some embodiments, the composition comprises between 0.5 and 3 wt.% of the oxidation product. In some embodiments, the composition comprises between 1 and 3 wt.% of the oxidation product. In some embodiments, the composition comprises between 0.1 and 2.5 wt.% of the oxidation product. In some embodiments, the composition comprises between 0.5 and 2.5 wt.% of the oxidation product. In some embodiments, the composition comprises between 1 and 2.5 wt.% of the oxidation product. In some embodiments, the composition comprises between 0.1 and 2 wt.% of the oxidation product. In some embodiments, the composition comprises between 0.5 and 2 wt.% of the oxidation product. In some embodiments, the composition comprises between 1 and 2 wt.% of the oxidation product. In some embodiments, the composition comprises between 0.1 and 1 wt.% of the oxidation product. In some embodiments, the composition comprises between 0.5 and 1 wt.% of the oxidation product. In some embodiments, the composition comprises between 1 and 1 wt.% of the oxidation product.

1.5 wt.% of the oxidation product. In some embodiments, the composition comprises between 0.5 and 1.5 wt.% of the oxidation product. In some embodiments, the composition comprises between 0.1 and 1 wt.% of the oxidation product. In some embodiments, the composition comprises between 0.5 and 1 wt.% of the oxidation product.

[00058] In some embodiments, the composition comprises linaclootide and an acetylation product, *e.g.*, an acetylation product comprising or having:

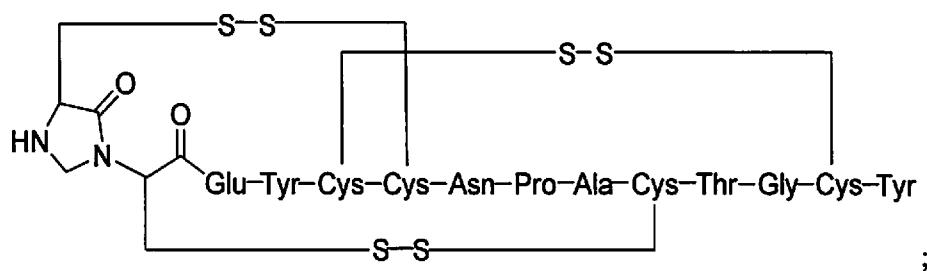


The composition can contain any desired concentration of the acetylation product. In some embodiments, the composition comprises less than 10 wt.% of the acetylation product. In some embodiments, the composition comprises less than 7 wt.% of the acetylation product. In some embodiments, the composition comprises less than 6 wt.% of the acetylation product. In some embodiments, the composition comprises less than 5 wt.% of the acetylation product. In some embodiments, the composition comprises less than 4 wt.% of the acetylation product. In some embodiments, the composition comprises less than 3 wt.% of the acetylation product. In some embodiments, the composition comprises less than 2 wt.% of the acetylation product. In some embodiments, the composition comprises less than 1 wt.% of the acetylation product. In some embodiments, the composition comprises between 0.01 and 10 wt.% of the acetylation product. In some embodiments, the composition comprises between 0.1 and 7 wt.% of the acetylation product. In some embodiments, the composition comprises between 0.1 and 5 wt.% of the acetylation product. In some embodiments, the composition comprises between 0.5 and 5 wt.% of the acetylation product. In some embodiments, the composition comprises between 1 and 5 wt.% of the acetylation product. In some embodiments, the composition comprises between 0.1 and 4 wt.% of the acetylation product. In some embodiments, the composition comprises between 0.5 and 4 wt.% of the acetylation product. In some embodiments, the composition comprises between 1 and 4 wt.% of the acetylation product. In some embodiments, the composition comprises between 0.1 and 3 wt.% of the acetylation product. In some embodiments, the composition comprises between 0.5 and 3 wt.% of the acetylation product. In some embodiments, the composition comprises between 1 and 3 wt.% of the acetylation product. In some embodiments, the composition comprises between 0.1 and 2.5 wt.% of the acetylation product. In some embodiments, the composition comprises between 0.5 and 2.5 wt.% of the acetylation product. In some embodiments, the composition comprises between 1 and 2.5 wt.% of the acetylation product. In some

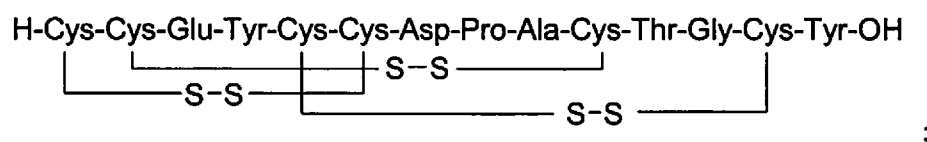
embodiments, the composition comprises between 0.1 and 2 wt.% of the acetylation product. In some embodiments, the composition comprises between 0.5 and 2 wt.% of the acetylation product. In some embodiments, the composition comprises between 1 and 2 wt.% of the acetylation product. In some embodiments, the composition comprises between 0.1 and 1.5 wt.% of the acetylation product. In some embodiments, the composition comprises between 0.5 and 1.5 wt.% of the acetylation product. In some embodiments, the composition comprises between 0.1 and 1 wt.% of the acetylation product. In some embodiments, the composition comprises between 0.5 and 1 wt.% of the acetylation product.

[00059] In some embodiments, there is provided a pharmaceutical composition comprising linacotide, and one or more peptides selected from:

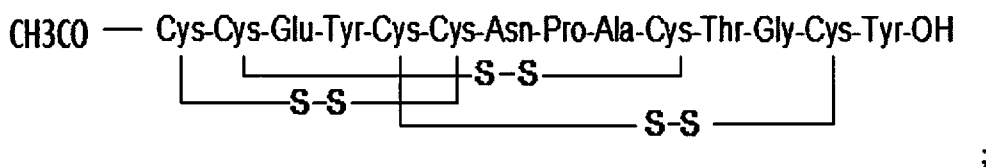
- i. a peptide (“Cys¹-IMD”) or a pharmaceutically acceptable salt thereof, wherein the peptide comprises the amino acid structure of:



- ii. a hydrolysis peptide (“Asp⁷”) or a pharmaceutically acceptable salt thereof, wherein the peptide comprises the amino acid structure of:

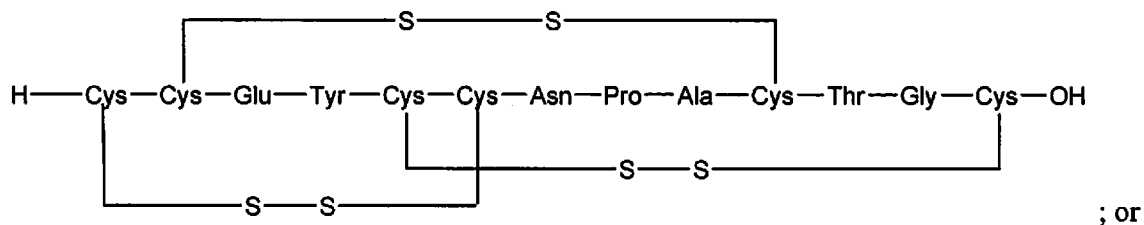


- iii. an acetylation peptide (“Cys¹-N-Acetyl”) or a pharmaceutically acceptable salt thereof, wherein the peptide comprises the amino acid structure of:

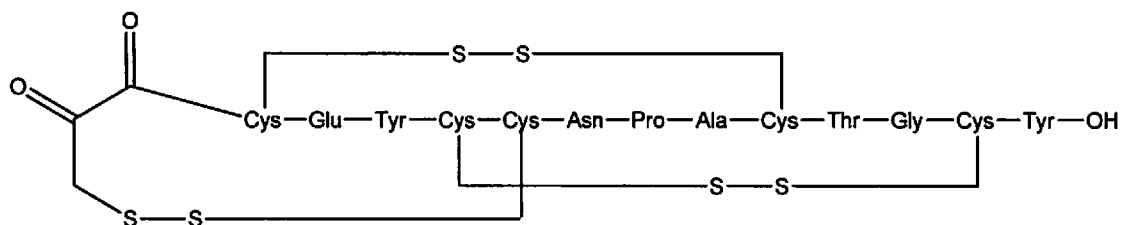


- iv. a linacotide trisulfide peptide or a pharmaceutically acceptable salt thereof, wherein the peptide comprises the amino acid sequence of Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr wherein an additional sulfur atom may be attached to any one of the six cysteinyl sulfurs;

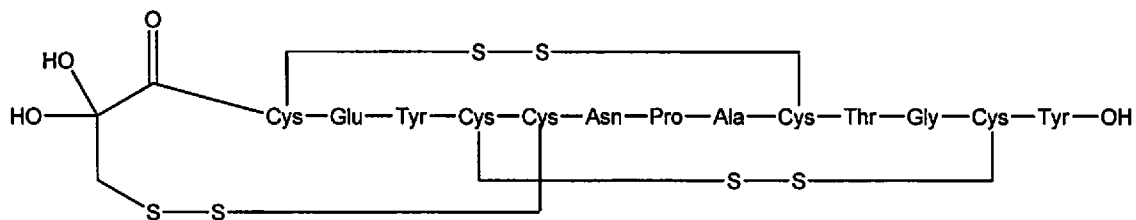
- v. a peptide ("Des-Tyr¹⁴") or a pharmaceutically acceptable salt thereof, wherein the peptide comprises the amino acid structure of:



- vi. a peptide (Cys¹- α -Ketone) or a pharmaceutically acceptable salt thereof, wherein the peptide comprises the amino acid structure of:



[00060] In some embodiments, the Cys¹- α -Ketone peptide may be present in its hydrated form or a pharmaceutically acceptable salt thereof, wherein the peptide comprises an amino acid structure of:



. One skilled in the art would recognize that the Cys¹- α -Ketone peptide would readily convert between its hydrate and ketone form.

[00061] In some embodiments, the Cys¹- α -Ketone peptide comprises less than about 15% by weight of the composition, less than about 10% by weight of the composition, less than about 7% by weight of the composition, less than about 5% by weight of the composition, less than about 4% by weight of the composition, less than about 3% by weight of the composition, less than about 2% by weight of the composition, less than about 1.5% by weight of the composition, or less than about 1% by weight of the composition. In other exemplary embodiments, the Cys¹- α -Ketone peptide comprises from about 0.01% to about 15% by weight of the composition, about 0.05% to about 10% by weight of the composition, about 0.05% to about 7% by weight of the composition or about 0.05% to about 5% by weight of the composition.

[00062] In some embodiments, the Cys¹-IMD peptide comprises less than about 15% by weight of the composition, less than about 10% by weight of the composition, less than about 7% by weight of the composition, less than about 5% by weight of the composition, less than about 4% by weight of the composition, less than about 3.5% by weight of the composition, less than about 3% by weight of the composition, less than about 2% by weight of the composition, or less than about 1% by weight of the composition. In other exemplary embodiments, the Cys¹-IMD peptide comprises from about 0.01% to about 15% by weight of the composition, about 0.05% to about 10% by weight of the composition, about 0.05% to about 7% by weight of the composition or about 0.05% to about 5% by weight of the composition.

[00063] In some embodiments, the hydrolysis peptide (“Asp⁷”) comprises less than about 15% by weight of the composition, less than about 10% by weight of the composition, less than about 7% by weight of the composition, less than about 5% by weight of the composition, less than about 4% by weight of the composition, less than about 3.5% by weight of the composition, less than about 3% by weight of the composition, less than about 2% by weight of the composition, or less than about 1% by weight of the composition. In other exemplary embodiments, the hydrolysis peptide (“Asp⁷”) comprises from about 0.01% to about 15% by weight of the composition, about 0.05% to about 10% by weight of the composition, about 0.05% to about 7% by weight of the composition or about 0.05% to about 5% by weight of the composition.

[00064] In some embodiments, the acetylation peptide (“Cys¹-N-Acetyl”) comprises less than about 15% by weight of the composition, less than about 10% by weight of the composition, less than about 7% by weight of the composition, less than about 5% by weight of the composition, less than about 4% by weight of the composition, less than about 3.5% by weight of the composition, less than about 3% by weight of the composition, less than about 2% by weight of the composition, or less than about 1% by weight of the composition. In other exemplary embodiments, the acetylation peptide (“Cys¹-N-Acetyl”) comprises from about 0.01% to about 15% by weight of the composition, about 0.05% to about 10% by weight of the composition, about 0.05% to about 7% by weight of the composition or about 0.05% to about 5% by weight of the composition.

[00065] In some embodiments, the linacotide trisulfide peptide comprises less than about 15% by weight of the composition, less than about 10% by weight of the composition, less than about 7% by weight of the composition, less than about 5% by weight of the composition, less than about 4% by weight of the composition, less than about 3.5% by weight of the composition, less than about 3% by weight of the composition, less than about

2% by weight of the composition, or less than about 1% by weight of the composition. In other exemplary embodiments, the linacotide trisulfide peptide comprises from about 0.01% to about 15% by weight of the composition, about 0.05% to about 10% by weight of the composition, about 0.05% to about 7% by weight of the composition or about 0.05% to about 5% by weight of the composition.

[00066] In some embodiments, the Des-Tyr¹⁴ peptide comprises less than about 15% by weight of the composition, less than about 10% by weight of the composition, less than about 7% by weight of the composition, less than about 5% by weight of the composition, less than about 4% by weight of the composition, less than about 3.5% by weight of the composition, less than about 3% by weight of the composition, less than about 2% by weight of the composition, or less than about 1% by weight of the composition. In other exemplary embodiments, the Des-Tyr¹⁴ peptide comprises from about 0.01% to about 15% by weight of the composition, about 0.05% to about 10% by weight of the composition, about 0.05% to about 7% by weight of the composition or about 0.05% to about 5% by weight of the composition.

[00067] In some embodiments, the composition comprises linacotide and any desired concentration of multimers. In some embodiments, the composition comprises less than 10 wt.% of multimer(s). In some embodiments, the composition comprises between 0.5 and 1 wt.% of multimer(s).

[00068] In some embodiments, the composition comprises an effective amount of linacotide and any desired amount of reduced form linacotide. As used herein, the term “reduced form linacotide” refers to linacotide having no disulfide bonds between cysteine amino acids. In some embodiments, the composition comprises less than 10 wt.% of reduced form linacotide. In some embodiments, the composition comprises between 0.5 and 1 wt.% of reduced form linacotide.

[00069] In some embodiments, the composition comprises an effective amount of linacotide and any desired amount of scrambled form linacotide. As used herein, the term “scrambled form linacotide” refers to linacotide having disulfide bonds between Cys₁ and Cys₁₀, between Cys₁ and Cys₁₃, between Cys₁ and Cys₅, between Cys₁ and Cys₂, between Cys₂ and Cys₆, between Cys₂ and Cys₁₃, between Cys₂ and Cys₅, between Cys₅ and Cys₆, and/or between Cys₅ and Cys₁₀. In some embodiments, the composition comprises between 0.5 and 1 wt.% of scrambled form linacotide. In some embodiments, the composition comprises less than 10 wt.% of scrambled form linacotide.

[00070] In some embodiments, the composition comprises a total degradant concentration of less than about 10 wt.%. In some embodiments, the composition comprises

a total degradant concentration of less than about 8 wt.%. In some embodiments, the composition comprises a total degradant concentration of less than about 7 wt.%. In some embodiments, the composition comprises a total degradant concentration of less than about 6.5 wt.%. In some embodiments, the composition comprises a total degradant concentration of less than about 6 wt.%. In some embodiments, the composition comprises a total degradant concentration of less than about 5.5 wt.%. In some embodiments, the composition comprises a total degradant concentration of less than about 5 wt.%. In some embodiments, the composition comprises a total degradant concentration of less than about 4 wt.%. In some embodiments, the composition comprises a total degradant concentration of less than about 3 wt.%. In some embodiments, the composition comprises a total degradant concentration of less than about 2.5 wt.%. In some embodiments, the composition comprises a total degradant concentration of less than about 2 wt.%. In some embodiments, the composition comprises a total degradant concentration of less than about 1 wt.%.

[00071] In some embodiments, the compositions can be prepared by spray drying, which is a technique used to prepare microparticles (e.g., microcapsules or microspheres) of drugs. Spray-dried peptides generally retain their biological activity upon dissolution and may have useful physical characteristics, including a uniform particle size and a spherical shape. In addition, the microparticles prepared by spray drying are often free flowing, which is helpful for pharmaceutical manufacturing processes such as forming tablets and filling capsules. Spray drying processes are also useful because they may be readily scaled up for clinical and commercial manufacturing. In one embodiment, the spray buffer comprises HCl, histidine, 1.5% PVA and 0.6% talc. This formulation can be used to produce lower dosing ranges between 36-290 μ g.

[00072] The composition, when administered, will dissolve to release linaclotide in targeted areas of the gastrointestinal tract. The formulation may release the linaclotide over a period of time that is determined by a number of different factors. These factors include the dimensions of the formulation, the concentration of the linaclotide, and how the linaclotide is dispersed throughout the formulation. For example, by varying the thickness and surface area of the formulations the rate of dissolution may be adjusted. A thick formulation will dissolve more slowly than an otherwise similar thin formulation and may be desirable to administer high dosages of linaclotide.

[00073] In some embodiments, the delayed release composition has a disintegration rate of less than about 60 minutes in the targeted pH conditions. In some embodiments, the delayed release composition has a disintegration rate of less than about 30 minutes in the targeted pH conditions. In some embodiments, the delayed release composition has a

disintegration rate of less than about 25 minutes. In some embodiments, the delayed release composition has a disintegration rate of less than about 20 minutes. In some embodiments, the delayed release composition has a disintegration rate of less than about 15 minutes. In some embodiments, the delayed release composition has a disintegration rate of less than about 10 minutes. In some embodiments, the delayed release composition disintegrates in less than about 30 minutes after entering a targeted environment. In some embodiments, the delayed release composition disintegrates in less than about 25 minutes after entering a targeted environment. In some embodiments, the delayed release composition disintegrates in less than about 20 minutes after entering a targeted environment. In some embodiments, the delayed release composition disintegrates in less than about 15 minutes after entering a targeted environment.

[00074] In some embodiments, the delayed release composition releases at least about 75% of the linaclotide contained therein within 60 minutes of entering a targeted environment. In some embodiments, the delayed release composition releases at least about 75% of the linaclotide contained therein within 30 minutes of entering a targeted environment. In some embodiments, the delayed release composition releases at least about 80% of the linaclotide contained therein within 30 minutes of entering a targeted environment. In some embodiments, the delayed release composition releases at least about 85% of the linaclotide contained therein within 30 minutes of entering a targeted environment. In some embodiments, the delayed release composition releases at least about 90% of the linaclotide contained therein within 30 minutes of entering a targeted environment. In some embodiments, the delayed release composition releases at least about 95% of the linaclotide contained therein within 30 minutes of entering a targeted environment. In some embodiments, the delayed release composition releases at least about 99% of the linaclotide contained therein within 30 minutes of entering a targeted environment.

[00075] In some embodiments, the delayed release composition releases at least about 40% of the linaclotide contained therein within 15 minutes of entering a targeted environment. In some embodiments, the delayed release composition releases at least about 50% of the linaclotide contained therein within 15 minutes of entering a targeted environment. In some embodiments, the delayed release composition releases at least about 60% of the linaclotide contained therein within 15 minutes of entering a targeted environment. In some embodiments, the delayed release composition releases at least about 70% of the linaclotide contained therein within 15 minutes of entering a targeted environment. In some embodiments, the delayed release composition releases at least about 80% of the linaclotide contained therein within 15 minutes of entering a targeted environment.

environment. In some embodiments, the delayed release composition releases at least about 85% of the linaclotide contained therein within 15 minutes of entering a targeted environment. In some embodiments, the delayed release composition releases at least about 90% of the linaclotide contained therein within 15 minutes of entering a targeted environment. In some embodiments, the delayed release composition releases at least about 95% of the linaclotide contained therein within 15 minutes of entering a targeted environment.

[00076] In some embodiments, the delayed release composition releases at least about 80% of the linaclotide contained therein between about 2 to about 2 hours of entering a targeted environment.

[00077] In some embodiments, the delayed release composition releases at least about 75% of the linaclotide contained therein within 30 minutes of contacting a pH greater than 5. In some embodiments, the delayed release composition releases at least about 80% of the linaclotide contained therein within 30 minutes of contacting a pH greater than 5. In some embodiments, the delayed release composition releases at least about 85% of the linaclotide contained therein within 30 minutes of contacting a pH greater than 5. In some embodiments, the delayed release composition releases at least about 90% of the linaclotide contained therein within 30 minutes of contacting a pH greater than 5. In some embodiments, the delayed release composition releases at least about 95% of the linaclotide contained therein within 30 minutes of contacting a pH greater than 5. In some embodiments, the delayed release composition releases at least about 99% of the linaclotide contained therein within 30 minutes of contacting a pH greater than 5.

[00078] In some embodiments, the delayed release composition releases at least about 75% of the linaclotide contained therein within 30 minutes of contacting a pH greater than 7. In some embodiments, the delayed release composition releases at least about 80% of the linaclotide contained therein within 30 minutes of contacting a pH greater than 7. In some embodiments, the delayed release composition releases at least about 85% of the linaclotide contained therein within 30 minutes of contacting a pH greater than 7. In some embodiments, the delayed release composition releases at least about 90% of the linaclotide contained therein within 30 minutes of contacting a pH greater than 7. In some embodiments, the delayed release composition releases at least about 95% of the linaclotide contained therein within 30 minutes of contacting a pH greater than 7. In some embodiments, the delayed release composition releases at least about 99% of the linaclotide contained therein within 30 minutes of contacting a pH greater than 7.

[00079] In some embodiments, linaclotide compositions can be formulated by combining IR and DR compositions of linaclotide in one dosage form. For example, a linaclotide DR capsule can be made by filling IR beads and DR beads into one capsule. Depending on the requirement for the drug release profile, the amount of IR and DR beads in such capsule can vary from 1 to 99% (wt%). In some embodiments, for example, the DR capsule comprises at least about 50% DR beads relative to IR beads. In some embodiments, the capsule comprises at least about 55% DR beads relative to IR beads. In some embodiments, the capsule comprises at least about 60% DR beads relative to IR beads. In some embodiments, the capsule comprises at least about 65% DR beads relative to IR beads. In some embodiments, the capsule comprises at least about 70% DR beads relative to IR beads. In some embodiments, the capsule comprises at least about 75% DR beads relative to IR beads. In some embodiments, the capsule comprises at least about 80% DR beads relative to IR beads. In some embodiments, the capsule comprises at least about 85% DR beads relative to IR beads. In some embodiments, the capsule comprises at least about 90% DR beads relative to IR beads. In some embodiments, the capsule comprises at least about 92% DR beads relative to IR beads. In some embodiments, the capsule comprises at least about 94% DR beads relative to IR beads. In some embodiments, the capsule comprises at least about 96% DR beads relative to IR beads. In some embodiments, the capsule comprises at least about 98% DR beads relative to IR beads.

[00080] In some embodiments, the linaclotide DR compositions are formulated for delivery of linaclotide to the ileum, terminal ileum, or colon.

[00081] In some embodiments, the linaclotide DR compositions are formulated for delivery of linaclotide to the colon.

[00082] The composition can be used to treat other diseases, disorders, or conditions that are responsive to treatment with agonists of the GC-C receptor. The composition can be used to treat any gastrointestinal disorders and/or conditions in a patient (*e.g.*, mammal or human) or inflammation or pain associated therewith. 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.

[00083] Suitable such gastrointestinal disorders and conditions, also include, but are not limited to, irritable bowel syndrome, irritable bowel syndrome with constipation, colon cancer, dyspepsia (including functional dyspepsia or non-ulcer dyspepsia), gastrointestinal

motility disorders, functional gastrointestinal disorders, gastroesophageal reflux disease (GERD), Crohn's disease, ulcerative colitis, inflammatory bowel disease, functional heartburn, gastroparesis, chronic intestinal pseudo-obstruction (or colonic pseudo-obstruction), and disorders and conditions associated with constipation, for example, chronic constipation, opioid induced constipation, post-surgical constipation (post-operative ileus), and constipation associated with neuropathic disorders or a combination of symptoms thereof (such as a combination of irritable bowel syndrome and chronic constipation), constipation associated with neuropathic disorders (e.g., constipation associated with Parkinson's Disease), constipation associated with cystic fibrosis or thyroid disease,. In some embodiments, a method is provided for treating gastrointestinal disorders in a patient (*e.g.*, mammal or human) diagnosed with one or more gastrointestinal disorders or conditions, wherein the method comprises administering an effective amount of the composition to the patient.

[00084] In some embodiments, a method of treating a gastrointestinal disorders comprising administering to a patient in need thereof, a therapeutically effective amount of compositions described herein. The gastrointestinal disorder is selected from the group consisting of: irritable bowel syndrome (IBS), constipation, a functional gastrointestinal disorder, gastroesophageal reflux disease, functional heartburn, inflammatory bowel disease, dyspepsia, diverticulitis pain, visceral pain, or abdominal pain, prostatitis, testicular pain, abdominal or visceral inflammation, painful bladder syndrome, endometriosis, vulvodynia, or rectal pain. In some embodiments, the constipation is chronic constipation, idiopathic constipation, chronic idiopathic constipation, constipation due to post-operative ileus, or constipation caused by opiate use. In other embodiments, the irritable bowel syndrome is irritable bowel syndrome with constipation (IBS-c), irritable bowel syndrome with diarrhea (IBS-d) or mixed irritable bowel syndrome (IBS-m).

[00085] In some embodiments, a method of treating a disorder is provided comprising administering to a patient in need thereof, a therapeutically effective amount of the composition described herein. In some embodiments, the disorder is cancer selected from colorectal/local metastasized colorectal cancer, intestinal polyps, Barrett's esophagus, gastrointestinal tract cancer, lung cancer, cancer or pre-cancerous growths or metastatic growths of epithelial cells, polyps, breast, colorectal, lung, ovarian, pancreatic, prostatic, renal, stomach, bladder, liver, esophageal and testicular carcinoma.

[00086] In some embodiments, methods are provided for preventing a cancer or hyperplasia of the gastrointestinal tract or preventing reoccurrence of cancer or hyperplasia of the gastrointestinal tract in a patient in need thereof comprising administering an effective

amount of the composition or the oral dosage form to the patient. In some embodiments, the cancer or hyperplasia is colorectal cancer, intestinal polyps or pre-cancerous growths or metastatic growths of gastrointestinal epithelial cells. In some embodiments, the composition or oral dosage form is administered simultaneously or sequentially with an effective amount of a COX-2 inhibitor. Examples of highly selective and selective COX-2 inhibitors include etoricoxib, rofecoxib, lumiracoxib, valdecoxib, celecoxib (Celebrex®), sulindac, diclofenac, meloxicam and etodolac. Non-selective NSAIDs that inhibit COX-2 include naproxen, ibuprofen, sodium salicylate and diflunisal. As used herein, the term “prevent” or “preventing” means to arrest, delay the onset (i.e., the period prior to clinical manifestation of a disease) or reoccurrence of cancer or hyperplasia, and/or reduce the risk of developing cancer or hyperplasia relative to a patient that has not been treated with a composition described herein.

[00087] In some embodiments, methods are provided for treating gastrointestinal disorders in pediatric patients with the compositions and oral dosage forms described herein. In some embodiments, methods are provided for treating gastrointestinal disorders in a pediatric patient diagnosed with one or more gastrointestinal disorders or conditions, wherein the method comprises administering an effective amount of the composition or the oral dosage form to the patient. In some embodiments, methods are provided to use the compositions and oral dosage forms for treating gastrointestinal disorders including, but not limited to, GI motility disorders, irritable bowel syndrome, constipation-predominant irritable bowel syndrome (IBS-c), mixed-type irritable bowel syndrome (IBS-m), chronic constipation, chronic idiopathic constipation, opioid induced constipation, post-surgical constipation (post-operative ileus), constipation associated with neuropathic disorders, constipation associated with cystic fibrosis or thyroid disease, dyspepsia (including functional dyspepsia or non-ulcer dyspepsia), gastroparesis, gastrointestinal motility disorders, functional gastrointestinal disorders, gastroesophageal reflux disease (GERD), inflammatory bowel disease, Crohn's disease, ulcerative colitis, functional heartburn, chronic intestinal pseudo-obstruction (or colonic pseudo-obstruction), visceral pain, abdominal pain, pelvic pain, anal fissure pain, pain associated with vulvodynia, pain associated with endometriosis, pain associated with fibromyalgia, functional abdominal pain, interstitial cystitis pain, diverticulitis, pain associated with diverticulitis, and pain associated with celiac sprue. In some embodiments, methods are provided to treat IBS-c, IBS-m or chronic constipation (e.g., chronic idiopathic constipation) in pediatric patients with the compositions and oral dosage forms described herein. In some embodiments, methods are provided to treat IBS-c in a

pediatric patient in need thereof. In some embodiments, methods are provided to treat chronic idiopathic constipation in a pediatric patient in need thereof.

[00088] In some embodiments, a method is for treating or relieving pain comprising administering to a patient in need thereof, a therapeutically effective amount of the composition described herein. In some embodiments, the pain is selected from visceral pain; abdominal pain; pelvic pain; or pain associated with gastrointestinal disorders, venereal diseases, bladder pain syndrome, diverticulitis pain, prostatitis, testicular pain, endometriosis, vulvodynia, rectal pain, or interstitial cystitis. In some embodiments, the pain is selected from pelvic pain, pain associated with proctitis, anal fissure pain, pain associated with vulvodynia, pain associated with endometriosis, pain associated with fibromyalgia, functional abdominal pain, interstitial cystitis pain, pain associated with venereal disease, diverticulitis, pain associated with diverticulitis, and pain associated with celiac sprue.

[00089] In another embodiment, the method is for increasing intestinal motility in a patient in need thereof, comprising administering an effective amount of the composition to the patient. Intestinal motility involves spontaneous coordinated dissensions and contractions of the stomach, intestines, colon and rectum to move food through the gastrointestinal tract during the digestive process. In some embodiments, the disorder is post-operative ileus, or constipation caused by opiate use.

[00090] In exemplary embodiments, the methods may comprise administering a therapeutically effective amount of the pharmaceutical composition to a patient in need thereof. An effective amount of a composition comprising linaclotide or a pharmaceutically acceptable salt thereof required to achieve desired results (such as desired treatment and/or symptom relief) of a subject is dependent on several understood factors, such as the identity and severity of the disorder being treated, as well as the age, weight, etc., of the patient being treated.

[00091] In some embodiments, the composition or oral dosage form is administered to a pediatric patient in need thereof as a tablet, capsule or sachet. In some embodiments, a sachet comprising the composition is opened and the contents are sprinkled on or stirred into food, such as applesauce, or into a beverage, such as water. In some embodiments, a capsule is swallowed whole with fluid, such as water, or is opened and sprinkled on or stirred into food or a beverage. Tablets may be swallowed whole, may be crushed and stirred into food or a beverage, or may be formulated as a chewable tablet.

[00092] A subject or patient in whom administration of the pharmaceutical composition is an effective therapeutic regimen for a disease or disorder is preferably a human, but can be any animal, including a laboratory animal in the context of a clinical trial

or screening or activity experiment. Thus, as can be readily appreciated by one of ordinary skill in the art, the methods, compounds and compositions described herein are particularly suited for administration to any animal, particularly a mammal, and including, but by no means limited to, humans, rodents and non-rodents, such as feline or canine subjects, farm animals, such as but not limited to bovine, equine, caprine, ovine, and porcine subjects, wild animals (whether in the wild or in a zoological garden), research animals, such as mice, rats, rabbits, goats, sheep, pigs, dogs, cats, etc., avian species, such as chickens, turkeys, songbirds, etc., *e.g.*, for veterinary medical use.

[00093] In some embodiments, the linacotide composition may be formulated as a rectal dosage form for rectal administration. Rectal dosage forms include, without limitation, rectal suppositories, rectal foams or aerosols, enemas, rectal gels and rectal ointments. In some embodiments, the rectal dosage form may be administered to a patient in need thereof. In some embodiments, the rectal dosage form may be administered to a patient to treat abdominal or rectal pain, pain from anal fissures, ulcerative colitis, Crohn's disease or inflammatory bowel disease. In some embodiments, the rectal dosage form may be administered to a pediatric or geriatric patient.

[00094] In some embodiments, the effective dose range of linacotide for adult humans is from 25 µg to 6 mg per day orally. In some embodiments, the dose range is 15 µg to 2 mg per day orally. In some embodiments, the dose range for adult humans is 50 µg to 1 mg per day orally (*e.g.*, 15 µg, 36 µg, 50 µg, 72 µg, 100 µg, 145 µg, 150 µg, 200 µg, 250 µg, 290 µg, 300 µg, 350 µg, 400 µg, 450 µg, 500 µg, 550 µg, 579 µg, 600 µg, 650 µg, 700 µg, 750 µg, 800 µg, 850 µg, 900 µg, 950 µg or 1 mg). In some embodiments, the dose range for adult humans is 36 µg to 290 µg per day orally. In some embodiments, the dose range is 100 µg to 600 µg per day orally. In some embodiments, the dose is 50 µg, 100 µg, 150 µg, 200 µg, 300 µg, 400 µg, 500 µg or 600 µg linacotide per day orally. In some embodiments, the dose is 50 µg linacotide per day orally. In some embodiments, the dose is 100 µg linacotide per day orally. In some embodiments, the dose is 145 µg linacotide per day orally. In some embodiments, the dose is 200 µg linacotide per day orally. In some embodiments, the dose is 290 µg linacotide per day orally. In some embodiments, the dose is 400 µg linacotide per day orally. In some embodiments, the dose is 500 µg linacotide per day orally. In some embodiments, the dose is 600 µg linacotide per day orally.

[00095] In some embodiments, the effective pediatric dose range of linacotide is from 0.05 µg to 2 mg per day orally. In some embodiments, the effective pediatric dose range of linacotide is from 0.05 µg to 100 µg per day orally. In some embodiments, the effective pediatric dose range of linacotide is from 0.1 µg to 90 µg per day orally. In some

embodiments, the effective pediatric dose range of linaclotide is from 0.1 μ g to 50 μ g per day orally. In some embodiments, the effective pediatric dose range of linaclotide is from 0.1 μ g to 25 μ g per day orally. In some embodiments, the effective pediatric dose range of linaclotide is from 0.1 μ g to 10 μ g per day orally. In some embodiments, the effective pediatric dose range of linaclotide is from 0.1 μ g to 5 μ g per day orally. In some embodiments, the effective pediatric dose range of linaclotide is from 0.1 μ g to 1 μ g per day orally. In some embodiments, the effective pediatric dose range of linaclotide is from 0.1 μ g to 0.5 μ g per day orally. In some embodiments, the effective pediatric dose range of linaclotide is 0.1 μ g per day orally. In some embodiments, the effective pediatric dose range of linaclotide is 0.15 μ g per day orally. In some embodiments, the effective pediatric dose range of linaclotide is 0.25 μ g per day orally. In some embodiments, the effective pediatric dose range of linaclotide is 0.5 μ g per day orally. In some embodiments, the effective pediatric dose range of linaclotide is 3.5 μ g per day orally. In some embodiments, the effective pediatric dose range of linaclotide is 15 μ g per day orally. In some embodiments, the effective pediatric dose range of linaclotide is 36 μ g per day orally. In some embodiments, the effective pediatric dose range of linaclotide is 45 μ g per day orally. In some embodiments, the effective pediatric dose range of linaclotide is 60 μ g per day orally. In some embodiments, the effective pediatric dose range of linaclotide is 90 μ g per day orally. In some embodiments, the unit dosage form and daily dose are equivalent.

[00096] In some embodiments, the unit dosage form is administered with food at any time of the day, without food at any time of the day, with food after an overnight fast (*e.g.*, with breakfast). In some embodiments, the unit dosage form is administered once a day, twice a day or three times a day. In some embodiments, one, two or three unit dosage forms will contain the daily oral dose of linaclotide. The precise amount of compound administered to a patient will be the responsibility of the attendant physician. However, the dose employed will depend on a number of factors, including the age and sex of the patient, the precise disorder being treated, and its severity.

[00097] In some embodiments, the compositions are administered as a monotherapy. In some embodiments, the composition consists essentially of an effective amount of linaclotide. In some embodiments, the composition consists of an effective amount of linaclotide.

[00098] In some embodiments, the compositions are directly administered to a patient, for example, in the form of delayed release tablet or delayed release capsule. In some embodiments, the compositions are dissolved, disintegrated and/or mixed on or within food or beverage prior to administration to patients (*e.g.*, elderly or pediatric patients). In some

embodiments, the composition is dissolved or disintegrated in a liquid, solution, or fluid optionally containing stabilizing agent(s), preservative(s), sweetener(s), or the like, etc. prior to administration to a patient (*e.g.*, elderly or pediatric patient). In some embodiments, the composition is a multiple dose composition, *i.e.*, containing two, three, five, seven, ten, fifteen, twenty, twenty-five, thirty, forty, fifty, sixty, seventy, eighty, ninety or more daily doses of linaclotide.

[00099] In other embodiments, the compositions are administered as part of a combination therapy. For example, a composition may be used in combination with other drugs or therapies that are used in the treatment, prevention, suppression, and/or amelioration of the diseases or conditions for which compounds of the invention are useful. The linaclotide can be co-administered or co-formulated with other medications. In one embodiment, the linaclotide composition can be co-administered with other medications used to treat gastrointestinal disorders including but not limited to acid suppressing agents such as Histamine-2 receptor agonists (H2As) and/or proton pump inhibitors (PPIs). In one embodiment, the linaclotide composition can be co-administered with other medications used to treat gastrointestinal disorders including 5-ASAs such as mesalamine.

[000100] Such other drug(s) may be administered, by a route and in an amount commonly used therefore, contemporaneously or sequentially with a compound of the invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical unit dosage form containing such other drugs in addition to the compound of the invention may be employed. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active components, in addition to a compound of invention.

[000101] Several methods can be used for evaluating the bioactivity of the linaclotide composition, including, but not limited to, immunoassays (*e.g.*, enzyme-linked immunosorbent assay), radioimmuno assays, immunoradiometric assays, gel electrophoresis (*e.g.*, SDS-PAGE), high performance liquid chromatography (HPLC), and/or high performance capillary electrophoresis (HPCE). In some embodiments, the bioactivity of the composition is assessed by a method comprising fixing linaclotide, incubating linaclotide with guanylate cyclase C (GCC), incubating GCC bound linaclotide with antibodies against GCC, incubating GCC antibody-bound linaclotide with fluorescently labeled antibodies against GCC antibodies, and detecting the linaclotide bound to the GCC antibodies by measuring the fluorescence intensity using a plate reader. The drug concentration can then be calculated based on the fluorescence reading of the solution.

[000102] For example, the bioactivity of the linaclotide compositions can be assessed and quantified using the following method, though other methods are available. The composition is added to a volumetric flask containing 60 ml of phosphate buffer having a pH of 4.5, and the flask is shaken for 60 minutes. 0.2 ml of the supernatant is then removed, and is added into one or more wells of a 96-well plate that is coated with GC-C receptors. The plate is sealed and incubated at 37°C for 2 hr. At the end of incubation, the sample is removed and the plate is washed with phosphate buffered saline (PBS). The bound linaclotide is then incubated for 1 hour, at room temperature, with GC-C (such as is available from Sigma-Aldrich Inc.) labeled with fluorescein isocyanate (FITC) in blocking buffer. After incubation, the well is washed with PBS. The fluorescence intensity of the end product is detected, for example, by using a plate reader. The linaclotide concentration is then calculated based on the fluorescence reading of the solution.

Definitions

[000103] As used herein, unless otherwise indicated, the term “delayed release” mean that the composition dissolves, melts, disintegrates, liquefies, etc. in a targeted area of the gastrointestinal tract such that substantially all of the linaclotide no longer remains in a formulation, composition, or dosage form. Delayed release compositions include sustained release compositions, gastro-retentive compositions, targeted release compositions (e.g. colonic-release compositions, or compositions that target the ileosecal valve, etc.), extended release compositions and/or combinations thereof.

[000104] As used herein, unless otherwise indicated, the term “delayed release composition” (“DR”) means that the composition is a dosage form that releases linaclotide at a time other than immediately following oral administration.

[000105] As used herein, unless otherwise indicated, the term “extended release composition” means that the composition is a dosage form that releases linaclotide over an extended period of time after administration. This allows a reduction in dosing frequency compared to immediate release compositions.

[000106] As used herein, unless otherwise indicated, the “disintegration” and “release” is used herein to mean that the capsule, film, bead, or tablet comprising linaclotide dissolves, melts, disintegrates, liquefies, etc. in the environment of an oral cavity such that substantially all of the linaclotide no longer remains in a formulation form, e.g., a pH greater than 5 or 7, or in a phosphate buffer solution and maintained at $37 \pm 1^\circ\text{C}$.

[000107] The term “released from”, when referring to the release of linaclotide from the composition, unless otherwise indicated, is used herein to mean that the linaclotide no longer remains in a composition form.

[000108] As used herein, unless otherwise indicated, the term “entry into a targeted environment” means contact of the composition within a patient at a targeted organ or segment thereof, or within a segment of the GI intended for linaclotide release, *e.g.*, having a pH greater than 5 or 7.

[000109] As used herein, unless otherwise indicated, the term “lower gastrointestinal (GI)” means the distal segment of the gastrointestinal tract, for example, the ileum, terminal ileum, ileocecal valve, or colon.

[000110] As used herein, unless otherwise indicated, the term “upper gastrointestinal (GI)” means the proximate segment of the gastrointestinal tract, for example, the stomach, duodenum and/or jejunum.

[000111] As used herein, unless otherwise indicated, “stabilizing agent” refers to a polymer, sterically hindered primary amine (*e.g.*, amino acid), or cation (*e.g.*, metal cation) component of the composition which is included in the composition in a stabilizing amount. For example, a polymeric stabilizing agent is a polymer that is included in the composition in a stabilizing amount. Similarly, a sterically hindered primary amine stabilizing agent is a sterically hindered primary amine that is included in the composition in a stabilizing amount. Moreover, a cationic stabilizing agent is a cation that is included in the composition in a stabilizing amount.

[000112] As used herein, unless otherwise indicated, “stabilizing amount” refers to a concentration, within the composition, of a polymer, sterically hindered primary amine (*e.g.*, amino acid), or metal cation component at which the component increases the stability of linaclotide in the composition, as compared to a similar composition not having a stabilizing amount of the same component.

[000113] As used herein, unless otherwise indicated, the term “substantially all” means at least about 90%, for example, at least about 95% or even at least about 99%.

[000114] As used herein, unless otherwise indicated, the term “isolated and purified” means at least 95 percent pure (for example, at least 96% pure, at least 97% pure, at least 98% pure, or even at least 99% pure), as measured, for example, by chromatographic purity using HPLC.

[000115] As used herein, unless otherwise indicated, “therapeutically effective amount” means the amount of a linaclotide or a pharmaceutically acceptable salt thereof that, when administered to a mammal for treating a state, disorder or condition, is sufficient to effect a

treatment (as defined below). The “therapeutically effective amount” will vary depending on the compound, the disease and its severity and the age, sex, weight, physical condition and responsiveness of the mammal to be treated. For example, a therapeutically effective amount of linaclotide, or its pharmaceutically acceptable salt or hydrate, can be an amount effective to treat gastrointestinal disorders, including irritable bowel syndrome, constipation-predominant irritable bowel syndrome, chronic constipation, opioid induced constipation and/or dyspepsia.

[000116] As used herein, unless other indicated, “pharmaceutically acceptable” means biologically or pharmacologically compatible for *in vivo* use in animals or humans, and preferably means, approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans.

[000117] As used herein, unless otherwise indicated, the term “treat”, in all its verb forms, is used herein to mean to relieve, alleviate, prevent, and/or manage at least one symptom of a disorder in a subject, the disorder including, for example, a gastrointestinal disorder, such as, irritable bowel syndrome, constipation-predominant irritable bowel syndrome, chronic constipation, opioid induced constipation, dyspepsia, or a combination of symptoms thereof. Within the meaning of the present invention, the term “treat” also denotes, to arrest, delay the onset (*i.e.*, the period prior to clinical manifestation of a disease) and/or reduce the risk of developing or worsening a disease. The term “treatment” means the act of “treating” as defined above.

[000118] As used herein, unless otherwise indicated, the term “additives” refers to a pharmaceutically acceptable additive. Pharmaceutically acceptable additives include, without limitation, binders, disintegrants, dispersing additives, lubricants, glidants, antioxidants, coating additives, diluents, surfactants, flavoring additives, humectants, absorption promoting additives, controlled release additives, anti-caking additives, anti-microbial agents (e.g., preservatives), colorants, desiccants, plasticizers and dyes.

[000119] As used herein, unless otherwise indicated, an “excipient” is any pharmaceutically acceptable additive, filler, binder or agent.

[000120] As used herein, unless otherwise indication, “stressed conditions” refer to 40°C and 75% relative humidity (RH).

[000121] As used here, unless otherwise indicated, the terms “about” and “approximately” mean within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend, in part, on how the value is measured or determined, *i.e.*, the limitations of the measurement system. For example, “about” can mean

within 1 or more than 1 standard deviation, per practice in the art. Alternatively, “about” with respect to the compositions can mean plus or minus a range of up to 20%, preferably up to 10%. Alternatively, particularly with respect to biological systems or processes, the term can mean within an order of magnitude, preferably within 5-fold, and more preferably within 2-fold, of a value. Particular values are described in the application and claims, unless otherwise stated the term “about” means within an acceptable error range for the particular value.

[000122] All weight percentages (*i.e.*, “% by weight” and “wt.%” and w/w) referenced herein, unless otherwise indicated, are measured relative to the total weight of the pharmaceutical composition.

[000123] The term “consisting essentially of”, and variants thereof, when used to refer to the composition, are used herein to mean that the composition includes linacotide and other desired pharmaceutically inactive additives, excipients, and/or components (*e.g.*, polymers, sterically hindered primary amines, cations, filling agents, binders, carriers, excipients, diluents, disintegrating additives, lubricants, solvents, dispersants, coating additives, absorption promoting additives, hydrolysis products, formaldehyde imine products, oxidation products, acetylation products, deamidation products, multimers, controlled release additives, anti-caking additives, anti-microbial additives, preservatives, sweetening additives, colorants, flavors, desiccants, plasticizers, dyes, or the like), and no other active pharmaceutical ingredient(s).

EXAMPLES

[000124] The following examples are merely illustrative of the present invention and should not be construed as limiting the scope of the invention in any way as many variations and equivalents that are encompassed by the present invention will become apparent to those skilled in the art upon reading the present disclosure.

[000125] Several formulation approaches are used to target linacotide to the lower GI tract. (i) Enteric-coated beads comprising a pH- sensitive polymeric coating may be applied to core beads which have been coated with linacotide and potentially a sub-coat. These beads could be further filled into capsules to achieve the desired unit dosage strengths. (ii) Enteric-coated tablets comprising a core immediate release tablet containing a unit dose of linacotide can be coated with coatings that dissolve only under pH conditions of the distal segment of intestine, so that linacotide will be released in lower GI tract. (iii) Enteric coatings may be applied to a gelatin or HPMC capsule, making the capsule disintegrates and dissolves only in the lower GI tract. Linacotide-loaded beads or tablets can be filled into the capsule to

achieve the delayed release. (iv) Additionally, immediate release beads filled to the appropriate dosage strength in whereby the capsule shell is made of an enteric polymeric materials. This enteric capsule shell can be used as such or further coated with pH sensitive polymers to achieve the desired pH release profile and site of release.

[000126] Linacotide or a pharmaceutically acceptable salt thereof may be produced and purified using standard techniques known in the art, e.g., chemical synthesis or recombinant expression followed by purification using standard techniques.

[000127] Preparation of the linacotide coating solution for beads: Approximately 32 g to 42 g of purified water is mixed with hydrochloric acid to create a solution with a pH between 1.5 and 2.0. The cation, if used, is added to the solution in a quantity to provide the desired concentration, and the solution is mixed for sufficient time to produce a clear solution. The sterically hindered primary amine, if used, is added to the solution in a quantity to provide the desired concentration, and the solution is mixed for sufficient time to produce a clear solution. Other additives, such as antioxidants, are then added, if desired. The pH of the solution is tested, and hydrochloric acid is added, if necessary, to produce a solution having a pH between 1.5 and 2.0. The binder is then added to the solution and the mixture is then stirred for sufficient time to achieve a clear solution. The desired amount of linacotide is added to the solution and mixed for 30-100 minutes to provide the coating solution.

[000128] In one embodiment, the coating solution comprises linacotide, histidine, 1.5% PVA and 0.6% talc. This formulation can be used to produce dosing ranges between 36-290µg.

[000129] Preparation of the Active Beads: Approximately 30-36 g of dried microcrystalline cellulose beads are added to a Mini Column Fluid Bed Coater. The microcrystalline cellulose beads are fluidized and heated prior to layering. Next, the coating solution is layered to the beads. The spraying temperature is controlled between 24°C and 55°C by controlling inlet temperature, spray rate, atomization pressure, and air volume. After the entire coating solution is layered to the beads, the beads are dried. The product of this process is referred to as active beads.

[000130] Preparation of Active Beads with Protective Coating: Approximately 35 g of Active Beads are added to a Mini Column Fluid Bed Coater. The Active Beads are fluidized and heated prior to coating with Aquacoat® (e.g. Aquacoat® Ethylcellulose Aquaeous Dispersion, 15% w/w, FMC Biopolymer, ECD-30), Eudragit® (e.g. Eudragit®E PO PE-EL, Roehm Pharma Polymers) or Opadry® (e.g Opadry® AMB dispersion, 20% w/w, Colorcon). Next, the coating solution is layered to the beads. The spraying temperature is controlled

between 24°C and 55°C by controlling inlet temperature, spray rate, atomization pressure, and air volume. After the entire coating solution is layered to the beads, the beads are dried.

Example 1

Delayed release Linacotide beads

[000131] Delayed release beads may be manufactured in several ways:

A. Enteric-coated beads

[000132] Delayed release beads comprise coatings which may be engineered to be resistant to low pH in stomach but rapidly break down and release active linacotide only under the pH of the lower GI tract (pH>5). Functional polymers of this category include: 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.

[000133] Enteric coating solution/suspension may comprise an enteric dissolving polymer or combination of a plasticizer, wetting material, anti-caking agent and diluent (aqueous or organic). Plasticizers are normally added to the polymeric coating to assist film coat formation. A sub-coat could be applied to the linacotide-layered beads prior to the enteric coating to separate linacotide and the enteric polymer for improved stability.

Example 2

Eudragit®FS30D coated DR linacotide beads

Table 1 Linacotide core bead composition

<i>Item</i>	<i>Name</i>	<i>Wt Percentage%</i>	<i>Wt/batch(Grams)</i>
1	Linacotide*	0.06	16.1
2	PVA	1.00	250

3	Calcium chloride	0.32	80
4	Histidine	0.68	170
5	MCC Beads	97.48	24,370
6	Talc, Imperial	0.5	125
7	Purified water*	95.56	13,000
8	Hydrochloric acid	Q.S.	--
	Total dry weight	100.04	25,011.1

Table 2 Eudragit®FS30D Coated linacotide DRrelease bead composition

<i>Item</i>	<i>Name</i>	<i>Wt Percentage%</i>	<i>Quantity/batch (g)</i>
1	Linacotide layered beads	75.19	1000
2	Eudragit® FS 30D	22.56	1000
3	PlasACRYL™	2.25	150
4	Purified Water*	-	500
	Total Dry weight	100	1330

* Water is removed during the coating process

Manufacturing process:

A. Coating solution preparation

[000134] Bead-coating starts with the preparation of the coating solution.

PlasACRYL™ is weighed into a container and agitate it using a stand mixer. Eudragit® FS30D is weighed and slowly added to the PlasACRYL™ container under agitation.

Purified water is weighed and slowly added to the PlasACRYL™/ Eudragit® suspension under agitation. The suspension is mixed for 10 min and then passed through a 0.5 mm sieve. The polymer suspension is ready for bead coating.

B. Bead coating

[000135] A fluid bed of a Wurster is warmed to 40°C. Linacotide core beads are weighed and added to the Wurster. The beads are warmed to 35°C. Bead coating proceeds with Eudragit® FS 30 D suspension while keeping the temperature at 28° to 32°C, and atomization air pressure at 3 bar. At the end of coating, the discharged beads are placed into a circulated air oven and dried for 2h at 40 °C.

Example 3

Eudragit® FS30D coated DR linacotide beads with PVP sub-coat

Table 3 Eudragit® FS30D Coated linacotide delayed release bead composition with PVP sub-coat

<i>Item</i>	<i>Name</i>	<i>Wt Percentage%</i>	<i>Quantity/batch (g)</i>
1	Linacotide layered beads	72.46	1000
2.	Polyvinyl pyrrolidone (PVP k30)	3.62	50
3	Eudragit® FS 30D	21.74	1000
4	PlasACRYL™	2.17	150
5	Purified Water*	-	1500
	Total Dry weight	100	1380

Manufacturing process:

A. Sub-coat solution preparation

[000136] In a container, purified water is weighed to 1000 g and added to the pre-weighed PVP under agitation. The solution is mixed until clear.

B. Beads coating with sub-coat

[000137] A fluid bed of the Wurster is warmed to 60°C. Linacotide core beads are weighed and added to the Wurster. The beads are warmed to 50°C before starting the bead coating. During coating the product temperature is controlled at 45° to 50°C. Once finish coating, the beads are dried for 30 min at product temperatures of 45° to 50°C.

C. Eudragit® FS30D coating

[000138] Manufacturing steps for Eudragit® FS30D coated linacotide beads are provided in Example 1.

[000139] Materials that can be used as a sub-coat include polymers such as polyvinyl alcohol (PVA), Polyvinyl pyrrolidone (PVP), Hypromellose (HPMC), Hydroxypropyl cellulose (HPC), methyl cellulose, starch, gelatin, dextrin, maltodextrin, poloxamer, polydextrose, shellac, chitosan, alginate, pectin, polyethylene glycol, guar gum, albumin, and sugars such as mannitol, lactose, isomalt, sorbitol, xylitol, maltitol, sucrose, trehalose, fructose, glucose, dextrose, erythritol, sucralose, etc., or their combinations. The level of sub-coat varies from 1 to 60 wt.% in the bead formula.

Example 4**Acryl-EZE® (Eudragit® L100-55) coated linacotide beads***Table 4 Acryl-EZE® Coated linacotide delayed release (DR) bead composition*

#	Ingredients	Wt. in gms	Wt. %
1.	Linacotide	5.87	0.24
2	GalenIQ™ 980	1930	78.4
3	Leucine	13.7	0.56
4	Calcium chloride dihydrate	30.8	1.25
5	Kollidon® 30 LP	20	3.25
6.	Acryl-Eze® (Eudragit® L100)	1600	16.3
7	0.01N HCl	Q.S.	--
8	Purified water*	Q.S.	--
	TOTAL	3600.37	100.0

*Water is removed during the coating process

Manufacturing process:**A. PVP solution preparation**

[000140] In a stainless steel jar, water is weighed to 2000 g. PVP is added under agitation. The solution is mixed until clear. Leucine and calcium chloride are weighed and added to the

PVP solution under agitation. The solution is mixed until clear. The solution is adjusted to pH 2, then linacotide is added and mixed until a clear solution is once again obtained.

B. Acryl-EZE® suspension preparation

[000141] In a stainless steel jar, distilled water is weighed to 8000 g. Acryl-EZE® is weighed and added to the water. The suspension is mixed using a stand mixer for 20 min. The suspension is passed through a #60 mesh screen.

C. Coating

[000142] Weigh Isomalt beads and add to the Wurster of a fluid bed warmed to 50°C. Start spraying the drug solution, with product temperature around 40°C. Upon finishing spraying the drug solution, dry the beads for 30 min with product temperature of around 40°C. Start spraying the Acryl-EZE® coat, keep the product temperature ~30°C. At the end of Acryl-EZE® coating, dry the beads for 30 min with product temperature ~30°C.

Dissolution of Acryl-EZE® coated linacotide DR beads

Beads	0.1 N HCl	Acetate Buffer, pH 4.5	Phosphate buffer saline, pH 7.4
BN0005656B (40% Wt Gain)	N.D.*	79.9	86.58
BN0005656B (50% Wt Gain)	N.D.	79.47	87.09
BN0005656B (60% Wt Gain)	N.D.	79.97	88.19

[000143] To achieve drug dissolution in different intestinal pH, Acryl-EZE® (Eudragit® L100-55, dissolves at pH higher than 5.5) can be replaced by other methacrylate polymers, such as Eudragit® L (dissolves at pH 6), Eudragit® S & Eudragit® FS30D (dissolves at pH 7), or their combinations. For example, (i) Form 1: drug dissolution at pH > 5.5 using Acryl-EZE®-coated beads; (ii) Form 2: drug releases at pH>6.5 by using coating

with Eudragit® L/S (50:50); (iii) Form 4: drug releases at pH 7 by coating the beads with Eudragit® FS30D. In addition, two or more of these types of beads can be placed in a capsule to provide pulsatile delivery at different regions of the GI tract. For example, in one capsule DR beads are combined with beads in Form 1, or using a combination of beads from Form 1 and Form 2, or a combination of beads of Form 2 and Form 3, or a combination of beads of Form 1 and Form 2 and Form 3, etc.

Example 5

HPMCAS coated linacotide DR beads

Table 5 HPMCAS Coated linacotide delayed release (DR) bead composition

<i>Item</i>	<i>Name</i>	<i>Wt Percentage%</i>	<i>Quantity/batch (g)</i>
1	Linacotide layered beads	75.3	1000
2	Aquacoat® AS-LG (HPMCAS)	15.06	200
3	Triethyl citrate	4.43	58.8
4	Talc	4.74	63
5	Sodium lauryl sulfate	0.47	6.3
6	Purified Water*	-	3000
	Total Dry weight	100	1328.1

Example 6

Ethyl cellulose coated linacotide DR beads

Table 6 Ethyl cellulose Coated linacotide delayed release (DR) bead composition

<i>Item</i>	<i>Name</i>	<i>Wt Percentage%</i>	<i>Quantity/batch (g)</i>
1	Linacotide layered beads	75.3	1000
2	Ethyl cellulose	15.06	200
3	Triethyl citrate	4.43	58.8
4	Talc	4.74	63
5	Sodium lauryl sulfate	0.47	6.3
6	Purified Water*	-	3000

	Total Dry weight	100	1328.1
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[000144] Similarly, linaclotide beads may be coated with other enteric polymers such as cellulose acetate phthalate (CAP), cellulose acetate trimilliate (CAT), cellulose acetate succinate (CAS), polyvinyl acetate phthalate (PVAP), and other copolymer. To assist polymer film formation, plasticizers such as triethyl citrate (TEC), polyethylene glycol (PEG), acetylated monoglyceride (AMG), or their combinations are added to the polymer coating solution. In addition, surfactants such as sodium lauryl sulfate, polysorbate, are added to the coating solution as wetting agent. To ensure enteric drug release, the polymer coating is applied at weight percentage of 5 to 80% depending on the size and make of the beads and the properties of sub-coat.

Example 7

Delayed release Linaclotide Tablet

[000145] Linaclotide can be formulated into a tablet for delayed drug release. Compared to an equal volume of beads, tablets have much smaller specific surface area, which makes them potentially less prone to degradation induced by environmental factors such as humidity, oxidation, deamidation, etc. In addition, the smaller surface area of the tablet can become advantageous when an enteric coating are needed since much less coating material is required to cover the surface of the dosage form.

Enteric Coated Tablet

[000146] Enteric coatings may be applied in a tablet coating pan, and coatings that are used for delayed release beads can be used for tablets to form delayed release tablets. The amount of coating polymer on the tablet can vary from 5 to 60% (weight gain) depending on the size, shape and surface properties of the tablet. A sub-coat can be applied to the tablets to separate linaclotide from the enteric or functional coat.

Example 8

Table 7 Eudragit® FS30D Coated linaclotide delayed release (DR) tablet composition

	Ingredients	Wt. %	Wt. in kg
Fluid bed Granulation			
1.	Linaclotide	0.3	2.94

2	Isomalt	93.7	937
3	Histidine	0.46	4.6
4	Calcium chloride dihydrate	2.57	25.7
5	Polyvinyl pyrrolidone (PVP)	3	30
6	0.01N HCl	Q.S.	Q.S.
7	Purified Water	Q.S.	Q.S.
Blending and compression			
i	Linacotide granules	27.85	139.25
ii	Isomalt	60.9	304.5
iii	Crospovidone	10	50
iv	Magnesium stearate	0.75	3.75
vi	Talc	0.5	2.5
Enteric coating			
	Linacotide tablet	75.19	1000
	Eudragit® FS 30D	22.56	1000
	PlasACRYL™	2.25	150
	Purified Water*	-	500
	Total Dry weight	100	1330

Manufacturing process:

A. Tablet

[000147] The granulation solution may be prepared by dissolving PVP, histidine and calcium chloride in water, adjusting solution pH to 2, and dissolving linacotide. Granulation is performed in a fluid bed by spraying the granulation solution onto filler isomalt. At the end of granulation, dry the granules for 30 min. The granules are then blended with tablet components including isomalt, crospovidone, Mg stearate and talc until uniform, and compressed into tablets.

B. Enteric coating

[000148] Eudragit® FS30D suspension can be prepared as described in Example 1. For tablet coating, linacotide core tablets are placed into a pan coater and warmed up to 35°C.

Start tablets coating with Eudragit® FS 30 D suspension, keep the product temperature at 28° to 32°C, and atomization air pressure at 3 bar. At the end of coating, discharge the tablets and place them into a circulated air oven and dry for 2 h at 40°C.

[000149] Similarly, other enteric coatings such as Eudragit® L, S, ethyl cellulose, HPMCAS, PVAP, CAP, CAS, etc. may also be applied to form delayed release tablets at various weight gains.

Enteric Coated Granules

[000150] Enteric coatings may also be applied to drug granules, and delayed release tablets can be manufactured by compressing the enteric coated granules into tablets. The granules have increased surface area and require larger quantities of coating to fully cover the granule surface. Once the tablet disintegrates, enteric coated granules release linaclotide in a more consistent way compared to tablets. Coating failure on single or a few granules will have a lesser impact on the overall performance of the dosage form of linaclotide.

Example 9

Table 8 Eudragit® FS30D Coated linaclotide delayed release (DR) granule composition

	Ingredients	Wt. %	Wt. in grams
Fluid bed Granulation			
1.	Linaclotide	0.3	2.94
2	Isomalt	93.7	937
3	Histidine	0.46	4.6
4	Calcium chloride dihydrate	2.57	25.7
5	Polyvinyl pyrrolidone (PVP)	3	30
6	0.01N HCl	Q.S.	Q.S.
7	Purified Water	Q.S.	Q.S.
Granules Enteric coating			
a	Linaclotide graules	75.19	1000
b	Eudragit® FS 30D	22.56	1000

c	PlasACRYL™	2.25	150
d	Purified Water	-	500
Blending and compression			
i	Enteric coated Linacotide granules	37.04	185.2
ii	Isomalt	51.71	258.55
iii	Crospovidone	10	50
iv	Magnesium stearate	0.75	3.75
vi	Talc	0.5	2.5
	Total	100	500

DR Matrix Tablet

[000151] Matrix tablet may also be formulated to achieve delayed drug release.

Polymers for enteric coating may be used either as filler for linacotide granules, or as matrix (filler) for the tablet.

Example 10

Table 9 Linacotide DRmatrix tablet made with DRgranules

	Ingredients	Wt. %	Wt. in kg
Fluid bed Granulation			
1.	Linacotide	0.3	2.94
2	Eudragit® L100	93.7	937
3	Histidine	0.46	4.6
4	Calcium chloride dihydrate	2.57	25.7
5	Polyvinyl pyrrolidone (PVP)	3	30
6	0.01N HCl	Q.S.	Q.S.
7	Purified Water	Q.S.	Q.S.
Blending and compression			
i	Linacotide granules	27.85	139.25
ii	Isomalt	60.9	304.5

iii	Crospovidone	10	50
iv	Magnesium stearate	0.75	3.75
vi	Talc	0.5	2.5

Example 11*Table 10 Linacotide DR Matrix Tablet*

	Ingredients	Wt. %	Wt. in kg
Fluid bed Granulation			
1.	Linacotide	0.3	2.94
2	Isomalt	93.7	937
3	Histidine	0.46	4.6
4	Calcium chloride dihydrate	2.57	25.7
5	Polyvinyl pyrrolidone (PVP)	3	30
6	0.01N HCl	Q.S.	Q.S.
7	Purified Water	Q.S.	Q.S.
Blending and compression			
i	Linacotide granules	27.85	139.25
ii	Eudragit® L100	60.9	304.5
iii	Crospovidone	10	50
iv	Magnesium stearate	0.75	3.75
vi	Talc	0.5	2.5

[000152] In above two examples, Eudragit® L100 may be replaced by other enteric dissolving polymers (Eudragit® S, Eudragit® FS30D, Acryl-EZE®, HPMCAS, HPMCP, CAP, CAS, PVAP, etc.) at a weight percentage or gain of 5 to 90% in a tablet.

Example 12**Enteric coated capsules for delayed release of linacotide**

[000153] Other than directly applied to beads, granules or tablets, enteric coatings may also be applied to capsules. Capsule coating may be performed on filled capsules. The

capsules will be de-dusted first to create a clean and smooth surface. To avoid coating defects around the connection between capsule cap and body, the cleaned capsules are banded before coating. The banded capsules are coated with an enteric coating in a coating pan.

Enteric coatings could be applied to either gelatin or HPMC capsules and depending on the size and property of the capsule coating can be applied at 5 to 60% weight gain.

Example 13

Delayed release compositions comprising linaclotide

[000154] Delayed release capsules comprising linaclotide may be formulated to target the ileum or colon. The composition is formulated to include a pH triggered release based on enteric coating of a linaclotide tablet, capsule or linaclotide coated beads contained in a hard gelatin capsule. The composition may be formulated to further comprise stabilizing additives such as a divalent cation and an amino acid. PVA can be used as binder as well as protective layer in between linaclotide and enteric coating. Linaclotide or linaclotide with PVA overcoat (as beads, capsule or tablet) may be coated with an additional enteric coating (e.g. Eudragit® FS30D, Eudragit® S100, Eudragit® L100, Eudragit® L100-55, Eudragit® L30D-55) that dissolves in a pH dependent manner to release at the appropriate pH of 7 in the ileum of the GI tract. The enteric coatings may consist of blends combining different types of Eudragit® - Eudragit® S100 / Eudragit® L100 in different ratios; Eudragit® S100 / Eudragit® L100-55 in various ratios; Eudragit® FS30D/Eudragit® L30D-55, Eudragit® FS30D/Eudragit® S / Eudragit® RS or EC in various ratios. The compositions may further comprise other excipients including plasticizing agents such as triethylcitrate. The coatings may further comprising disintegrants as suspended solid to expedite the relevant pH triggered release – resulting in mixed systems as croscarmellose sodium / Eudragit® S. For ease of processing, anti-tacking agent (e.g., talc, Aerosil® 200 or PlasAcryl™) may be used to prevent the beads from sticking.

[000155] Additionally, two Eudragit® coatings may be applied to ensure swift release once the desired pH region in the GI tract is reached – including partially neutralized coating systems. Buffering agents such as potassium hydrogen phosphate can be included into one of the two Eudragit® films. Alternative non-Eudragit® pH dependent film coatings include hydroxypropylmethylcellulose acetate succinate (HPMCAS, e.g. Aqoat® AS-HF), cellulose acetate phthalate (CAP, e.g. Aquateric®) or shellac.

Example 14**Linacotide compositions with DR granules/beads and IR granules/beads**

[000156] DR tablet can be formulated by compressing IR granules and DR granules into one tablet. Alternatively, the IR and DR formulation can be integrated into one formulation to achieve desired dissolution kinetics. For example, an immediate release drug layer can be applied as an outer layer or an under layer on beads/granules containing the DR portion, as illustrated below.

Table 11 Composition of Linacotide DR Beads with IR outer layer

Ingredient	wt%	Wt (kg) per batch
Linacotide IR beads		
Linacotide*	0.06	16.1
PVA	1.00	250
Calcium chloride	0.32	80
Histidine	0.68	170
MCC Beads	97.48	24,370
Talc, Imperial	0.5	125
Purified water*	95.56	13,000
Linacotide DR beads coated with Eudragit FS30D		
Linacotide layered beads	75.19	1000
Eudragit FS 30D	22.56	1000
PlasACRYL™	2.25	150
Purified Water*	-	500
Linacotide DR beads with IR outer layer		
Linacotide DR beads	98.47	299.25
Linacotide	0.05	0.145
PVA	0.74	2.25
Calcium chloride	0.24	0.72
Histidine	0.50	1.53
Purified Water*	-	117
Total wt	100	303.895

[000157] *Water is removed from the product during the manufacturing process

Example 15**Linacotide Sustained Release (SR) formulation**

[000158] In a sustained release formulation, linacotide is released in a slow and steady mode over a period of hours to days, so as to maintain effect drug level in blood stream over prolonged period of time and increase the patient compliance by reducing dosing frequencies.

The most frequently used approach for sustaining drug release is through the formation of a matrix system in which the active drug is embedded. Matrix system often involves using release controlling materials in the following categories: 1) hydrophilic polymers with high gelling capacity such as hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC), methyl cellulose, sodium carboxy methyl cellulose, carbopol, guar gum, agar-agar, alginate, mannose, galactose, Xanthan gum, chitosan, modified starch, polyacrylamide, cross-linked polyvinyl pyrrolidone, cross-linked polyvinyl alcohol, Polyhydroxyethylene methylacrylate (PHEMA), etc.;

2) Hydrophobic materials such as polyethylene, polyvinyl chloride, ethyl cellulose, acrylate polymers and their co-polymers; 3) biodegradable polymers such as polylactic acid (PLA), polyglycolic acid (PGA), poly (lactic-glycolic) acid (PLGA), polycaprolactone (PCL), polyanhydride, polyorthoesters, etc.

Example 16

pH and time release compositions comprising linaclotide

[000159] Delayed release compositions that combine an enteric coating (pH dependent release) with a time release coating could be applied to a linaclotide tablet, capsule or linaclotide coated beads contained in a hard gelatin capsule. The compositions could be formulated with stabilizing additives such as a divalent cation and an amino acid. PVA can be used as binder as well as protective layer in between linaclotide and the enteric coating.

[000160] Hydroxypropyl cellulose can be used as a time release polymer or as an overcoat over linaclotide or linaclotide coated with an additional protective PVA layer. The compositions can be coated with a pH dependent release enteric coating (e.g. Eudragit®). Two different Eudragit® coatings could be applied with an outer Eudragit® FS coating dissolving at pH 6.8 (for release in the area of ileum and ileo-caecal valve). The coating formula for the inner coating with Eudragit® FS could contain: Eudragit® FS30D, Eudragit® L 30D-55, glyceryl monostearate, Tween® 80 and water. An internal Eudragit® RL-RS layer could be applied to allow for sustained release of the drug in the colon. Both layers would be applied as previously described over beads coated with linaclotide or with linaclotide with a protective PVA coat. The coating formula for the inner coating with Eudragit® RL – RS may comprise Eudragit® RL30D, Eudragit® RS30D, glyceryl monostearate, triethyl citrate, Tween® 80 and water.

Example 17

pH and microbially triggered release compositions comprising linacotide

[000161] Delayed release compositions of linacotide could be formulated with a combination of an enteric coating for pH dependent release and a microbially triggered release layer (e.g. biodegradable polymer) which may be applied to a linacotide tablet, capsule or linacotide coated beads contained in a hard gelatin capsule. The compositions may further comprise stabilizing additives such as a divalent cation or an amino acid. PVA may be used as binder as well as protective layer in between linacotide and the enteric coating. A biodegradable polymer can be used as a release function as an overcoat over linacotide or linacotide coated with an additional protective PVA layer. The biodegradable polymer could be a film coating based on naturally occurring polysaccharides of plant, animal or microbial origin such as pectin, chitosan, chondroitin sulphate, galactomannan and amylose. These compositions can include mixed coatings or coating combination for example with HPMC/pectin, ethyl cellulose/pectin, cellulose acetate/pectin, chitosan/pectin or pectin/ Eudragit® (e.g. Eudragit® RS 30D). The compositions may include additional excipients such as plasticizers. PVA can be used as the film forming polymer, for example, in a combination with chitosan. These compositions may further include an additional pH dependent enteric coating (e.g. Eudragit®) for more effective release of linacotide to the ileum.

Example 18

Measurement of content and purity of exemplary peptides

[000162] Content and purity of linacotide may be determined by reverse phase gradient liquid chromatography using an Agilent Series 1100 LC System with Chemstation Rev A.09.03 software or equivalent. A YMC Pro™ C18 column (dimensions: 3.0 x 150 mm, 3.5 µm, 120 Å; Waters Corp., Milford, MA) or equivalent is used and is maintained at 40°C. Mobile phase A (MPA) consists of water with 0.1% trifluoroacetic acid while mobile phase B (MPB) consists of 95% acetonitrile:5% water with 0.1% trifluoroacetic acid. Elution of the linacotide is accomplished with a gradient from 0% to 47% MPB in 28 minutes followed by a ramp to 100% MPB in 4 minutes with a 5 minute hold at 100% MPB to wash the column.

Re-equilibration of the column is performed by returning to 0% MPB in 1 minute followed by a 10 minute hold at 100% MPA. The flow rate is 0.6 mL/min and detection is accomplished by UV at 220 nm.

Example 19

In vitro drug release testing

[000163] Linacotide release from the coated tablets can be assessed by dissolution testing using a USP XXIV type II paddle dissolution apparatus (model PTWS, Pharma Test, Hainburg, Germany). The tests are conducted in triplicates, at a paddle speed of 100 rpm in 900 ml dissolution medium maintained at $37.0 \pm 0.5^{\circ}\text{C}$. Tablets are tested first in 0.1 N hydrochloric acid (pH 1.2) for 30 minutes or 2 hours to simulate gastric residence and then for 6 hours in buffer media of varying pH and ionic composition, akin to small intestinal pH conditions. Linacotide release may be assessed at pH 6.8–7.4 in two compendial buffer media: 0.067 M mixed sodium and potassium phosphate (Sorensen's) buffer and 0.05 M potassium phosphate buffer as well as in a pH 7.4 multi-electrolyte salt solution (Hanks) buffer which is similar in ionic composition to intestinal fluid. All the buffers are freshly prepared with de-ionized water and de-aerated by sparging with helium prior to use. The amount of linacotide released from the dosage form can be determined by reverse phase gradient liquid chromatography as described in example 16.

Example 20

Dissolution studies with beads coated with pectin and ethylcellulose

[000164] Three coat formulations containing different amounts of pectin and Surelease® may be prepared and coated onto the linacotide beads to different film thickness. Coat formulation one (F1) is prepared by mixing a 2% (w/v) solution of pectin USP in distilled water with Surelease® and distilled water to result in a ratio of pectin (P) to Surelease® (S) of 1:12 by weight. Coat formulation two (F2) is prepared in a similar way but by using a 3% (w/v) solution of pectin USP in distilled water with Surelease® and distilled water to result in a ratio of pectin (P) to Surelease® (S) of 1:6 by weight. Coat formulation three (F3) is prepared by mixing a 5% (w/v) solution of pectin USP in distilled water with Surelease® and distilled water to result in a ratio of pectin (P) to Surelease® (S) of 1:3 by

weight. Coating is performed using a laboratory Aeromatic Strea-1 fluidized bed coater (Niro-Aeromatic, Columbia, MD). Coating is performed at 50°C inlet temperature and coating solution was applied through a 1.0mm spray nozzle at a spray rate of 2 ml/min using a rabbit peristaltic pump (Rainin Instrument Co. Inc., Woburn, MA) and 25 psi atomizing air pressure. Coating solutions are coated onto linacotide beads to result in a different coat thickness. The film thickness is expressed as the theoretical percentage of the weight gained (TWG) used relative to the weight of the uncoated beads. Beads were coated with 9%, 14%, 16% and 18% weight gains for coat formulation F1, 12%, 25%, 30% and 35% weight gains for coat formulation F2, and 25%, 35%, 45% and 55% weight gains for coat formulation F3. Coated beads were cured for 30 min at 50°C.

[000165] Linacotide release from coated beads may be assessed in a dissolution tester (VK 7000 Dissolution Testing Station, Vankel Industries, Inc., NJ), following the USP basket method. All tests are conducted in 900 ml dissolution medium maintained at $37 \pm 0.5^\circ\text{C}$ with a paddle rotation speed at 50 rpm. Dissolution studies are carried out under conditions simulating pH and times likely to be encountered during transit in the GI tract. Tests are carried out using simulated gastric fluid (SGF) for 2 h at pH 1.4, followed by simulated small intestinal fluid (SSIF) for 4 h at pH 7.4, followed by simulated cecal fluid (SCF) at pH 6 for at least 6 h (or until 100% drug release) with or without the addition of 3 ml enzymes. The buffer pH 6 was used to compromise between the mean pH of the cecum and the optimum pH for the activity of the enzymes. The amount of linacotide released from the dosage form is determined by reverse phase gradient liquid chromatography as described in Example 16. For each dissolution experiment, a duplicate is run at the same time under the same conditions. After the 4 h in SSIF, pectinolytic enzymes are added to one of the dissolution vessels but not to the other. Thus, one is a release study with enzymes and the other one is a release study without enzymes. Each dissolution experiment is repeated 3 times ($n=3$).

Example 21

Linacotide Tablet Release Profiles

[000166] Linacotide tablet release profiles have been tested at various pHs for three delayed release formulations. Sample 181-64B contains a 100 µg dose of linacotide, a subcoat of Opadry® II, and a functional coat of Eudragit® FS 30D and talc. Sample 181-64C contains a 100 µg dose of linacotide, a subcoat of Opadry II, and a functional coat of Eudragit® FS 30D and Eudragit® PlasAcryl™. The release profiles for Lot 181-64B and Lot 181-64C are provided in Figure 1. The release profile of a 25 µg dose of linacotide is provided in Figure 2.

Example 22

Linacotide Tablet Preparation

[000167] Delayed release tablets may be prepared by first preparing the following core tablet components: a placebo base, a linacotide 750 µg/225 mg base, and pre-granulated fillers.

Granulation manufacturing process:

[000168] The tablet components may be prepared into separate granulations for blending before tablet compression. Use of separate tablet components, such as, the placebo base and pregranulated filler base provided, among other things, advantageous properties for stability and release profiles for the tablets. For example, all the tablets components listed in Table 12 could be separately prepared by wet granulation and blended before compression or blended together and processed as a mixture for wet granulation. In another process, the tablets components listed in Table 12 could be separately prepared by dry granulation and blended before compression or blended together and processed as a mixture for dry granulation. In another process, the tablet components are direct blended for compression. In a preferred process, the pregranulated filler base and/or placebo base are prepared through wet granulation and dried before mixing with the 750 µg/225 mg linacotide base. The linacotide base could be prepared by wet granulation processes or by Wurster coating process. This preferred process, exhibited further gains in stability for the tablet by reducing moisture exposure to linacotide during processing and minimizing residue moisture in the table core.

Table 12: Components for various tablet strengths

Strength	Placebo	25 µg	50 µg	75 µg	100 µg	150 µg	290 µg
Placebo base (%)	20.00	16.67	13.33	10.00	6.67	3.33	0.00
Linacotide base (i.e. 750 ug/225 mg base (%))	0.00	3.33	6.67	10.00	13.33	16.67	38.67
Pregranulated fillers (%)	78.75	78.75	78.75	78.75	78.75	78.75	62.58
Magnesium Stearate (%)	1.25	1.25%	1.25%	1.25%	1.25%	1.25%	1.25%

Total (%)	100.0	100.0	100.0	100.0	100.0	100.0	100.0
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[000169] Then compress the above blends on a suitable tablet press to target core table weight of 225 mg. In a perforated pan coater, add a sub-coat (OPADRY® II) at a weight gain of 4% w/w. Coating conditions should be set and monitored so that moisture uptake during coating is kept to a minimum. When measured by loss on drying (LOD), the sub-coated tablets should have no more than 1.5% LOD. In a perforated pan coater, add a functional coat on the subcoated tablets. The functional coat is either Eudragit® FS30D or Eudragit® S100. Apply the functional coat at 5 mg polymer weight/cm² of the tablet surface. This comes to be approximately 4.5% total polymer weight gain during functional coating. Coating conditions should be set and monitored so that moisture uptake during coating is kept to a minimum. When measured by loss on drying, the functionally coated tablet should have no more than 2.0% LOD.

Placebo Base Preparation:

[000170] Table 13 represents the formulation for the placebo base granulation:

Table 13: Formulation of the placebo base granulation

Component	%w/w	Quantity (g)
L-Histidine	2.26	112.9
Calcium Chloride Dihydrate	1.07	53.5
polyvinyl alcohol	1.50	75.0
microcrystalline cellulose	95.17	4758.6
Hydrochloric acid, pure, fuming, 37% solution in water		
Treated water		
Total	100	5000

[000171] The placebo base preparation may be prepared by first dispensing the raw materials of Table 14.

Table 14: Raw materials for placebo base preparation

Component	Quantity (g)
L-Histidine	242.2
Calcium Chloride Dihydrate	114.8
polyvinyl alcohol	160.9
microcrystalline cellulose	4758.6

[000172] Tare the mix container and add 2682.1 ± 5.0 g of treated water into the container. Set up a mixer and begin to stir the water. Add the EMPROVE® to the water while stirring and start the timer. Cover and heat solution to 70C while stirring and maintain temperature until material is visually dissolved.

[000173] Adjust the pH of solution to 1.5 with hydrochloric acid. Add calcium chloride dihydrate to the solution while stirring. Mix until dissolved. Add L-Histidine to the solution while stirring. Stir for approximately 15 minutes. Record the initial pH. Adjust pH of solution to 5.0 with hydrochloric acid. Record final pH of solution and hydrochloric acid addition. Mix until all material is dissolved. While mixing, adjust the pH solution to 2.5 with hydrochloric acid. Record final pH of solution and hydrochloric acid addition. Ensure that the high shear granulator is set up properly for granulating with the 25L bowl, mixing blade and chopper. Pass microcrystalline cellulose through 16 mesh screen into granulator bowl. Calculate the net weight of granulation solution to add. Pump the granulation solution into the granulator at a rate of approximately 300g/min while mixing with the below parameters: Impeller speed 1(290 rpm, 5.5m/s tip speed), Chopper speed 1(1760 rpm). Stop the granulator and scrape down the sides and the bottom of the bowl. Mix for an additional 3 minutes according to the following parameters: Impeller speed 1(290 rpm, 5.5m/s tip speed), Chopper speed 1(1760 rpm). Tare a poly bag and discharge the completed wet granulation into it. Weigh the granulation. Transfer the wet granulation to the FLM-3 fluid bed for drying. Dry the granulation using the following approximate settings. Dry until the granulation LOD is no more than 1.2% moisture. Discharge the dried granulation into a tared poly bag.

Parameters	Target Range
Product Temperature	40°C
Process (Drying) Air	30 – 60 CFM
Inlet Temperature	60°C

Settings are suggested settings only and may be adjusted for optimum drying.

[000174] Screen the dried granulation through a #30 mesh sieve. Tare a poly bag and discharge the dried granulation into it. Weigh the granulation. Package dried granulation into foil sealed bags with desiccant.

Linacotide Base Preparation (i.e. 750µg/225mg):

[000175] Table 15 represents the formulation for the 750µg/225mg base granulation:

Table 15: Formulation for the 750µg/225mg base granulation

Component	% w/w	Quantity (g)
Linacotide	0.39	19.3
L-Histidine	2.26	112.9
Calcium Chloride Dihydrate	1.07	53.5
polyvinyl alcohol	1.50	75.0
microcrystalline cellulose	94.79	4,739.3
Hydrochloric acid, pure, fuming, 37% solution in water	-----	-----
Treated water	-----	-----
Total	100.00	5,000.0

[000176] The 750µg/225mg base granulation may be prepared by first dispensing the raw materials of Table 16.

Table 16: Raw materials of the linacotide base granulation

Raw Material	Required Quantity (g)
Linacotide	19.3
microcrystalline cellulose	4,739.3
Granulation solution	

[000177] While mixing, add the linacotide to the granulation solution. Mix until dissolved. Ensure that the high shear granulator is set up properly for granulating with the 25L bowl, mixing blade and chopper. Pass microcrystalline cellulose through 16 mesh screen into granulator bowl. Pump the granulation solution into the granulator at a rate of approximately 300g/min while mixing with the below parameters: Impeller speed 1(290 rpm, 5.5m/s tip speed), Chopper speed 1(1760 rpm). Tare a poly bag and discharge the completed wet granulation into it. Weigh the granulation. Transfer the wet granulation to the FLM-3 fluid bed for drying. Dry the granulation using the following approximate settings. Dry until the granulation LOD is no more than 1.2% moisture. Discharge the dried granulation into a tared poly bag.

Parameters	Target Range
Product Temperature	40°C
Process (Drying) Air	30 – 60 CFM
Inlet Temperature	60°C

Note: Settings are suggested settings only and may be adjusted for optimum drying.

[000178] Screen the dried granulation through a #30 mesh sieve. Tare a poly bag and discharge the dried granulation into it. Weigh the granulation. Package dried granulation into foil sealed bags with desiccant.

Pregranulated Filler Preparation:

[000179] Table 17 represents the formulation for the pregranulated fillers.

Table 17: Formulation of the fillers granulation

Component	% w/w	Total Quantity(g)	Qty per sublot (g)
microcrystalline cellulose	19.4	4,074	1,358
croscarmellose sodium	5.1	1,071	357
mannitol	71.7	15,057	5,019
polyvinyl alcohol	3.8	798	266
Treated water	-----	-----	-----
Total	100.0	21,000	7,000

[000180] The fillers preparation may be prepared by first dispensing the raw materials of Table 18.

Table 18: Raw materials for preparation of fillers granulation

Raw Material	Required Quantity (g)
polyvinyl alcohol	840
microcrystalline cellulose – Granulation 1	1,358
microcrystalline cellulose – Granulation 2	1,358
microcrystalline cellulose – Granulation 3	1,358
croscarmellose sodium – Granulation 1	357
croscarmellose sodium – Granulation 2	357
croscarmellose sodium – Granulation 3	357
mannitol – Granulation 1	5,019
mannitol – Granulation 2	5,019

mannitol - Granulation 3	5,019
Total	---

[000181] Then record the tare weight of the stainless steel container. Tare the container and weigh the required quantity of treated water into the container. Transfer the water into a jacketed kettle. Set up the mixer and begin to stir the water in the kettle. Add the EMPROVE® (polyvinyl alcohol) to the water while stirring and start the timer. Cover and heat solution to 70°C while stirring and maintain temperature until material is visually dissolved. Calculate weight of water lost due to evaporation during heating. Add this amount of treated water to the solution. Add one bag each of microcrystalline cellulose, Ac-Di-Sol (i.e. croscarmellose sodium) , and Pearlitel 100SD (i.e. mannitol) to a high shear granulator bowl. Mix for approximately 2 minutes according to the following parameters: Impeller speed 1(290 rpm, 5.5m/s tip speed), Chopper speed 1(1760 rpm). Pump 2217 ± 5 g of the granulation solution into the granulator at a rate of approximately 300g/min while mixing with the below parameters: Impeller speed 1(290 rpm, 5.5m/s tip speed), Chopper speed 1(1760 rpm). Stop the granulator and scrape down the sides and the bottom of the bowl. Mix for an additional 30 seconds to 1 minute according to the following parameters: Impeller speed 1(290 rpm, 5.5m/s tip speed), Chopper speed 1(1760 rpm). Tare a poly bag and discharge the completed wet granulation into it. Weigh the granulation. Pass the wet granulation through the Comil with 2A375Q03763 screen with 5-10% power. Transfer the wet granulation to the FLM-3 fluid bed for drying. Dry the granulation using the following approximate settings. Dry until the granulation LOD is no more than 1.0% moisture. Discharge the dried granulation into a tared poly bag.

Parameters	Target Range
Product Temperature	40°C
Process (Drying) Air	30 – 60 CFM
Inlet Temperature	60°C

Settings are suggested settings only and may be adjusted for optimum drying.

[000182] Mill the granulation with Comil, round impeller, 2A045R03137 screen. Perform particle size analysis with a sonic sifter using the following screen sizes (in micron): 38,75,106,150,180,250. Tare a poly bag and discharge the dried and milled granulation into it. Weigh the granulation. Package dried granulation into foil sealed bags with desiccant.

Example 23**25µg Tablet Blending and Compression**

[000183] According to the procedure of Example 22, a 25µg dose table of linaclotide may be prepared with the formulation of Table 19.

Table 19: Formulation of a 25 µg Linaclotide Tablet:

Component	% w/w	Quantity (g)
Pregranulated Fillers	78.750	5118.8
Linaclotide Base	3.333	216.7
Placebo Base	16.667	1083.4
Magnesium Stearate	1.250	81.3
Total	100	6500

[000184] First, dispense the raw materials of Table 20.

Table 20: Raw materials for preparation of 25µg linaclotide tablet

Raw Material	Required Quantity (g)
Pregranulated Fillers Sub Blend A	2559.4
Pregranulated Fillers Sub Blend B	2559.4
Linaclotide Base	227.5
Placebo Base	1137.5
Magnesium Stearate Sub Blend A	40.6
Magnesium Stearate Sub Blend B	40.6
Total	6565.0

[000185] Preblend: Set up an 8 qt blender and add the 750µg/225mg Base and Placebo Base. Close lids and blend for 10 minutes. Tare a poly bag, and discharge the preblend into it.

[000186] Sub-Blend A: Add 650g of the preblend to a 16 qt v-blender. Add the Pregranulated Fillers for sub-blend A to the 16 qt v-blender. Close lids and blend for 10 minutes. Pass the Magnesium Stearate for sub-blend A through the 40 mesh screen. Add to

the 16 qt v-blender. Close lids and blend for 3 minutes. Tare a poly bag, and discharge the blend into it.

[000187] Sub-Blend B: Add 650g of the preblend to a 16 qt v-blender. Add the Pregranulated Fillers for sub-blend B to the 16 qt v-blender. Close lids and blend for 10 minutes. Pass the Magnesium Stearate for sub-blend B through the 40 mesh screen. Add to the 16 qt v-blender. Close lids and blend for 3 minutes. Tare a poly bag, and discharge the blend into it.

[000188] Compression: Ensure a Korsch XL 100 tablet press with 0.32" sc toolings is set up per SOP E-59 with 0.32" round concave tooling (10 stations desired), paddle feeder, and that all other components are properly secured. Manually rotate die table at least one full revolution to ensure proper installation. Visually confirm presence of all dies and punches, and that dies are flush with the die table. Verify that the table specifications meet the In-Process Tablet Specifications of Table 21.

Table 21: In-Process Tablet Specifications

Parameters	Target
Average Tablet Weight	225 mg
Individual Thickness	4.0 - 4.5 mm (guideline only)
Individual Tablet Hardness	10 kP
Friability (100 drops)	NO MORE THAN 0.6%
Individual Disintegration	NO MORE THAN 15 min

[000189] Charge the blend into the hopper. Set the turret speed to 20 RPM. Adjust the die fill amount and compression parameters to yield a tablet with a target weight of 225 mg and with a target hardness of 8-12 kP. All waste material should be collected in the tableting waste poly bag. Start timer and compress tablets.

Example 24

100µg Tablet Blending and Compression

[000190] According to the procedure of Example 22, a 100µg dose table of linaclotide may be prepared with the formulation of Table 22.

Table 22: Formulation of a 100 µg Linaclotide Tablet:

Component	% w/w	Quantity (g)
Pregranulated Fillers	78.750	9843.8
Linaclotide Base	3.333	1666.6

Placebo Base	16.667	833.4
Magnesium Stearate	1.250	156.3
Total	100	12500

[000191] First, dispense the raw materials of Table 23.

Table 23: Raw materials for preparation of 100µg linacotide tablet

Raw Material	Required Quantity (g)
Pregranulated Fillers	9843.8
Linacotide Base	1750.0
Placebo Base	875.0
Magnesium Stearate	156.3
Total	12,625.0

[000192] Preblend: Set up an 16 qt blender and add the 750µg/225mg Base and Placebo Base. Close lids and blend for 10 minutes. Tare a poly bag, and discharge the preblend into it.

[000193] Add 2500g of the preblend to a 1 cubic foot v-blender. Add the Pregranulated Fillers to the 1 cubic foot v-blender. Close lids and blend for 10 minutes. Pass the Magnesium Stearate through the 40 mesh screen. Add to the 1 cubic foot v-blender. Close lids and blend for 3 minutes. Tare a poly bag, and discharge the blend into it.

[000194] Compression: Ensure a Korsch XL 100 tablet press with 0.32" sc toolings is set up per SOP E-59 with 0.32" round concave tooling (10 stations desired), paddle feeder, and that all other components are properly secured. Manually rotate die table at least one full revolution to ensure proper installation. Visually confirm presence of all dies and punches, and that dies are flush with the die table. Verify that the table specifications meet the In-Process Tablet Specifications of Table 24.

Table 24: In-Process Tablet Specifications

Parameters	Target
Average Tablet Weight	225 mg
Individual Thickness	4.0 - 4.5 mm (guideline only)
Individual Tablet Hardness	10 kP
Friability (100 drops)	NO MORE THAN 0.6%
Individual Disintegration	NO MORE THAN 15 min

[000195] Charge the blend into the hopper. Set the turret speed to 20 RPM. Adjust the die fill amount and compression parameters to yield a tablet with a target weight of 225 mg and with a target hardness of 8-12 kP. All waste material should be collected in the tableting waste poly bag. Start timer and compress tablets.

Example 25

290µg Tablet Blending and Compression

[000196] According to the procedure of Example 22, a 290µg dose table of linacotide may be prepared with the formulation of Table 25.

Table 25: Formulation of a 290 µg Linacotide Tablet:

Component	% w/w	Quantity (g)
Pregranulated Fillers	60.10	3906.5
Linacotide Base	38.65	2512.3
Magnesium Stearate	1.25	81.3
Total	100	6500

[000197] First, dispense the raw materials of Table 26.

Table 26: Raw materials for preparation of 290µg linacotide tablet

Raw Material	Required Quantity (g)
Pregranulated Fillers Sub Blend A	1953.3
Pregranulated Fillers Sub Blend B	1953.3
Linacotide Base Sub Blend A	1256.1
Linacotide Base Sub Blend B	1256.1
Magnesium Stearate Sub Blend A	40.6
Magnesium Stearate Sub Blend B	40.6
Total	6500.0

[000198] Sub-blend A: Add the Pregranulated Fillers and Linacotide base for sub-blend A to a 16 qt v-blender. Close lids and blend for 10 minutes. Pass the Magnesium Stearate for

sub-blend A through the 40 mesh screen. Add to the 16 qt v-blender. Close lids and blend for 3 minutes. Tare a poly bag, and discharge the blend into it.

[000199] Sub-blend B: Add the Pregranulated Fillers and Linaclotide Base for sub-blend B to a 16 qt v-blender. Close lids and blend for 10 minutes. Pass the Magnesium Stearate for sub-blend B through the 40 mesh screen. Add to the 16 qt v-blender. Close lids and blend for 3 minutes. Tare a poly bag, and discharge the blend into it.

[000200] Compression: Ensure a Korsch XL 100 tablet press with 0.32" sc toolings is set up per SOP E-59 with 0.32" round concave tooling (10 stations desired), paddle feeder, and that all other components are properly secured. Manually rotate die table at least one full revolution to ensure proper installation. Visually confirm presence of all dies and punches, and that dies are flush with the die table. Verify that the table specifications meet the In-Process Tablet Specifications of Table 27.

Table 27: In-Process Tablet Specifications

Parameters	Target
Average Tablet Weight	225 mg
Individual Thickness	4.0 - 4.5 mm (guideline only)
Individual Tablet Hardness	10 kP
Friability (100 drops)	NO MORE THAN 0.6%
Individual Disintegration	NO MORE THAN 15 min

[000201] Charge the blend into the hopper. Set the turret speed to 20 RPM. Adjust the die fill amount and compression parameters to yield a tablet with a target weight of 225 mg and with a target hardness of 8-12 kP. All waste material should be collected in the tableting waste poly bag. Start timer and compress tablets.

Example 26

Sub-Coating of Linaclotide 25 µg Tablets

[000202] The 25µg tablets of Example 23 may be sub-coated with an Opadry® II sub-coating. The formula of Table 28 represents the amounts needed to prepare the coating material, which is prepared in excess to account for losses in the coating process.

Table 28: Sub-Coating formula for 25µg tablets

Component	%w/w	g/batch
Opadry II White	20	400
Purified water	80	1600

Total	100	2000
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[000203] Dispense 1600g of purified water into a suitably sized container. Dispense 400g of Opadry® II into a suitably sized container. Add Opadry® to the water. Calculate the theoretical amount of solution needed to apply a 4.0% weight gain, with 85% theoretical efficiency. Prepare a poly bag for the waste tablets collected during the coating process. Ensure the Compu-Lab has been set up with the 19 inch pan and plenum assembly. Verify the liquid feed lines are Tygon 17 tubing. Verify the gun assembly is installed in the pan. The spray gun assembly should consist of 1 x ¼ JAU spray gun mounted with a 40100 AB liquid spray nozzle and matching air cap. The gun assembly should be mounted as far as possible from the tablet bed, with the spray angle perpendicular to the top third of the bed. Verify initial tablet weight by weighing 100 uncoated tablets. Calculate the average weight of a single tablet by dividing the weight of the tablets by 100. Test the initial tablet moisture by crushing approximately 1 gram of tablets and running LOD for 10 minutes at 105°C. Adjust the pump so that the liquid flow rate is approximately 10 g/min. Prime the lines past the guns and verify that there is no leaking in the lines or gun. Charge the tablets into the coating pan and begin warming for 20 minutes with an inlet temperature of 50°C and airflow of 350 CFM. Jog occasionally during warm-up.

[000204] Once target bed temperature is reached, begin spraying the coating suspension according to the target process parameters outlined in Table 29 below. Test and report tablet moisture content periodically as desired. Once the theoretical amount of solution has been applied check the tablets for weight gain. When 4% weight gain has been achieved, stop spray and dry tablets for 30 minutes with an inlet temperature of 50°C, reducing pan speed to a minimum or jogging. Discharge the tablets and determine the new weight of the coated tablets.

Table 29: Target Process Parameters

Parameters	Target
Spray rate	10 g/min
Inlet temperature	65°C
Airflow	350 CFM
Atomization air	40 PSI
Pan speed	11 RPM
Exhaust temperature	47°C
Bed Temperature	50°C

Example 27**Sub-Coating of 100 µg Linacotide Tablets**

[000205] The 100µg tablets of Example 24 may be sub-coated with an Opadry® II coating. The formula of Table 30 represents the amounts needed to prepare the coating material, which is prepared in excess to account for losses in the coating process.

Table 30: Sub-Coating formula for 100µg tablets

Component	%w/w	g/batch
Opadry II White	20	1000
Purified water	80	4000
Total	100	5000

[000206] Dispense 4000g of purified water into a suitably sized container. Dispense 1000g of Opadry® II into a suitably sized container. Add Opadry® to the water. Calculate the theoretical amount of solution needed to apply a 4.0% weight gain, with 85% theoretical efficiency. Ensure the Compu-Lab has been set up with the 24 inch pan and plenum assembly. Verify the liquid feed lines are Tygon 17 tubing. Verify the gun assembly is installed in the pan. The spray gun assembly should consist of 2 x ¼ JAU spray gun mounted with a 40100 AB liquid spray nozzle and matching air cap. The gun assembly should be mounted as far as possible from the tablet bed, with the spray angle perpendicular to the top third of the bed. Verify initial tablet weight by weighing 100 uncoated tablets. Calculate the average weight of a single tablet by dividing the weight of the tablets by 100. Test the initial tablet moisture by crushing approximately 1 gram of tablets and running LOD for 10 minutes at 105°C. Adjust the pump so that the liquid flow rate is approximately 20 g/min. Prime the lines past the guns and verify that there is no leaking in the lines or gun. Charge the tablets into the coating pan and begin warming for 20 minutes with an inlet temperature of 50°C and airflow of 400 CFM. Jog occasionally during warm-up.

[000207] Once target bed temperature is reached, begin spraying the coating suspension according to the target process parameters outlined in Table 31 below. Test and report tablet moisture content periodically as desired. Once the theoretical amount of solution has been applied check the tablets for weight gain. When 4% weight gain has been achieved, stop spray and dry tablets for 30 minutes with an inlet temperature of 50°C, reducing pan speed to a minimum or jogging. Discharge the tablets and determine the new weight of the coated tablets.

Table 31: Target Process Parameters

Parameters	Target
Spray rate	20 g/min
Inlet temperature	65°C
Airflow	400 CFM
Atomization air	40 PSI
Pan speed	10 RPM
Exhaust temperature	47°C
Bed Temperature	50°C

Example 28**Sub-Coating of 290 µg Linacotide Tablets**

[000208] The 290µg tablets of Example 25 may be sub-coated with an Opadry® II coating. The formula of Table 32 represents the amounts needed to prepare the coating material, which is prepared in excess to account for losses in the coating process.

Table 32: Sub-Coating formula for 100µg tablets

Component	%w/w	g/batch
Opadry II White	20	400
Purified water	80	1600
Total	100	2000

[000209] Dispense 1600g of purified water into a suitably sized container. Dispense 400g of Opadry® II into a suitably sized container. Add Opadry® to the water. Calculate the theoretical amount of solution needed to apply a 4.0% weight gain, with 85% theoretical efficiency. Ensure the Compu-Lab has been set up with the 19 inch pan and plenum assembly. Verify the liquid feed lines are Tygon 17 tubing. Verify the gun assembly is installed in the pan. The spray gun assembly should consist of 1 x ¼ JAU spray gun mounted with a 40100 AB liquid spray nozzle and matching air cap. The gun assembly should be mounted as far as possible from the tablet bed, with the spray angle perpendicular to the top third of the bed. Verify initial tablet weight by weighing 100 uncoated tablets. Calculate the average weight of a single tablet by dividing the weight of the tablets by 100. Test the initial tablet moisture by crushing approximately 1 gram of tablets and running LOD for 10 minutes at 105°C. Adjust the pump so that the liquid flow rate is approximately 10 g/min. Prime the lines past the guns and verify that there is no leaking in the lines or gun. Charge the tablets

into the coating pan and begin warming for 20 minutes with an inlet temperature of 50°C and airflow of 350 CFM. Jog occasionally during warm-up.

[000210] Once target bed temperature is reached, begin spraying the coating suspension according to the target process parameters outlined in Table 33 below. Test and report tablet moisture content periodically as desired. Once the theoretical amount of solution has been applied check the tablets for weight gain. When 4% weight gain has been achieved, stop spray and dry tablets for 30 minutes with an inlet temperature of 50°C, reducing pan speed to a minimum or jogging. Discharge the tablets and determine the new weight of the coated tablets.

Table 33: Target Process Parameters

Parameters	Target
Spray rate	10 g/min
Inlet temperature	65°C
Airflow	350 CFM
Atomization air	40 PSI
Pan speed	1 RPM
Exhaust temperature	47°C
Bed Temperature	50°C

Example 29

Functional or Enteric Coating of Linaclotide Tablets

[000211] The tablets of previous examples may be prepared with a functional coating. The formulation of Table 34 represents the amounts needed to prepare the coating material, which is prepared in excess to account for losses in the coating process:

Table 34: Formulation for functional coating process

Component	%w/w
Eudragit® S100	9.94
1N NH ₃	6.75
Triethyl Citrate	4.97
Talc	4.97
Purified water	73.37
Total	100

[000212] To prepare the functional coating, dispense the required quantity of Eudragit® S100 into a suitably sized container. Dispense 2/3 of the required quantity of purified water into a suitably sized container. Begin agitation of water until a vortex is achieved. Add S100

slowly to the water and mix until the powder is thoroughly wetted and lump or foam formation has dissipated (about 5 minutes).

[000213] Dispense the required quantity of 1N NH₃ into a suitable sized container. Add the 1N NH₃ slowly into the Eudragit® suspension and mix for a minimum of 60 minutes. Dispense the required quantity of Triethyl Citrate into a suitable sized container. Add the Triethyl Citrate into the Eudragit® suspension and mix for a minimum of 60 minutes. Dispense the required quantity of Talc into a suitable sized container. Homogenize the talc in the remaining 1/3 of purified water for 10 minutes (or until homogenous) using a Silverson Homogenizer. Pour the talc suspension into the Eudragit® suspension while mixing. Mix for no longer than 5 minutes. Screen the coating suspension through a #30 mesh screen.

[000214] Calculate the theoretical amount of solution needed to apply a 9.0% weight gain, with 90% theoretical efficiency. Ensure the Compu-Lab has been set up with the 19 inch pan and plenum assembly. Verify the liquid feed lines are Tygon 17 tubing. Verify the gun assembly is installed in the pan. The spray gun assembly should consist of 1 x ¼ JAU spray gun mounted with a 40100 AB liquid spray nozzle and matching air cap. The gun assembly should be mounted as far as possible from the tablet bed, with the spray angle perpendicular to the top third of the bed. Charge the tablets into the coating pan. Warm the tablets with an inlet temperature of 30 degrees. Ensure bed temperature reaches approximately 30 degrees before proceeding to next step. Adjust the pump so that the liquid flow rate is approximately 12 g/min. Prime the lines past the guns and verify that there is no leaking in the lines or gun. Test the starting tablet moisture by crushing approximately 2 gram of tablets and running LOD for 10 minutes at 105°C.

[000215] Once target bed temperature is reached, begin spraying the coating suspension according to the target process parameters outlined in Table 35 below. Test and report tablet moisture content periodically as desired. Once the theoretical amount of solution has been applied check the tablets for weight gain. When 9% weight gain has been achieved, stop spray and dry tablets for 5-10 minutes with an inlet temperature of 40°C, reducing pan speed to a minimum or jogging.

Table 35: Target process parameters for spray coating process

Parameters	Target
Spray rate	12 – 20 g/min ¹
Inlet temperature	43°C ¹
Airflow	300 CFM
Atomization air	35 PSI
Pan speed	12 RPM
Exhaust temperature	33°C
Bed Temperature	35°C

¹ Adjust as needed to maintain bed temperature.

[000216] Test the final tablet moisture by crushing approximately 2 gram of tablets and running LOD for 10 minutes at 105°C. Moisture should be $\leq$ the initial tablet moisture. Discharge the tablets and determine the new weight of the coated tablets. Dry tablets for at least 2 hours in a mechanical convection oven with the temperature set to 40°C. Allow tablets to reach 25-30°C before bulk packaging. Bulk package tablets in foil bag with desiccants and store at 5°C.

Example 30

Acid Resistant Linacotide Capsule and Coated Acid Resistant Capsule Formulation

[000217] Acid resistant linacotide capsules and coated capsules may be prepared for targeted release. A formulation of an acid resistant linacotide capsule is provided in Table 36.

Table 36: Formulation of acid resistant linacotide capsule

Low dose/Pediatric Bead Strength 145µg/225mg			
Ingredient	%	mg/g	kg/batch
Calcium Chloride,	0.32%	3.200	0.080
Histidine USP	0.68%	6.800	0.170
PVA, USP	1.50%	15.000	0.375
Linacotide	0.06%	0.645	0.0161
Talc	0.60%	6.000	0.1500
Microcrystalline Cellulose, NF (Celphere CP305 beads)	96.85%	968.500	24.213
Purified Water, USP	NA	-	13.000
Hydrochloric Acid (10%), USP	NA	-	0.142
Sub coating of low dose Beads			
Low dose Linacotide beads, 145µg/225mg	90.9	909.0	2.00
Polyvinyl Pyrrolidone (Kollidon k30 LP) or Poly Vinyl Alcohol USP	8.6	86.0	0.190
Talc, Luzenac	0.5	5.0	0.011
Purified water*	-	-	2.5
Total Dry Weight	100.0	-	2.201

Encapsulation of Low dose Sub coated Beads in Acid resistance Capsules

[000218] Acid resistant capsules may also include a coating. An acid resistant linacotide capsule formulation is provided in Table 35. Figure 3 shows a dissolution profile of uncoated and coated acid resistant capsules in acidic media.

<i>Coating of Encapsulated AR Capsules</i>		
<i>Name</i>	<i>Wt Percentage %</i>	<i>Wt/batch (kg)Solid</i>
AR Capsules Size 1 filled with 10% PVPLP subcoat	84.49	0.390
FS30D	10.18	0.157
L30D-55	3.39	0.052
TEC	0.68	0.0031
Talc, Pharma M	0.43	0.0020
PlasAcryl T20	0.81	0.0125
Purified water*	-	0.130
Total %	100.00	-

OTHER EMBODIMENTS

[000219] The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims. It is further to be understood that all values are approximate, and are provided for description.

[000220] All patents, patent applications, publications, product descriptions, and protocols are cited throughout this application, the disclosures of which are incorporated herein by reference in their entireties for all purposes.

WHAT IS CLAIMED IS:

1. A delayed release pharmaceutical composition comprising linaclotide or a pharmaceutically acceptable salt thereof.
2. The composition of claim 1, wherein the composition is 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 and protective polymer film or subcoating.
6. The composition of claims 4 or 5, wherein the enteric coating is selected from 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 linacotide 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.

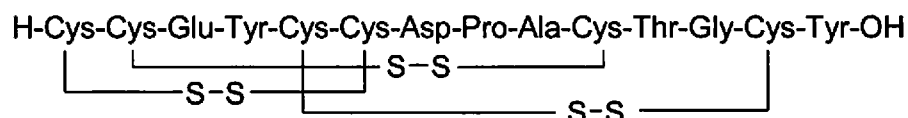
22. The composition of any of claims 1-21, wherein the composition comprises a molar ratio of sterically hindered primary amine to linacotide between 400:1 and 1:1.
23. The composition of any of claims 1-21, wherein the composition comprises a molar ratio of sterically hindered primary amine to linacotide 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 linacotide between 300:1 and 1:1.
28. The composition of claim 26, wherein the composition comprises a molar ratio of cation to linacotide 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 linacotide 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 linacotide between 300:1 and 1:1.

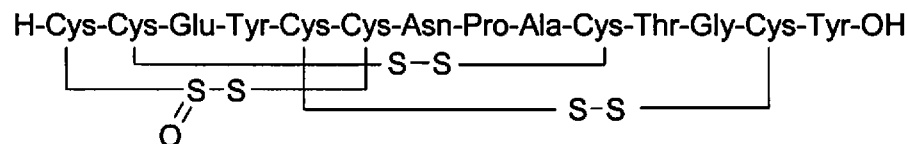
35. The composition of claim 33, wherein the composition comprises (i) between 1 and 10% by weight of PVA, (ii) histidine in a molar ratio of histidine to linacotide between 400:1 and 50:1, and (iii) Ca^{2+} in a molar ratio of Ca^{2+} to linacotide between 300:1 and 30:1.

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:



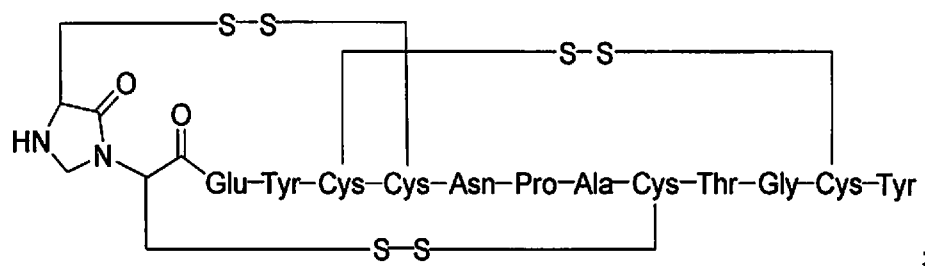
39. The composition of claim 38, wherein the composition comprises less than 5% by weight of the oxidation product.

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

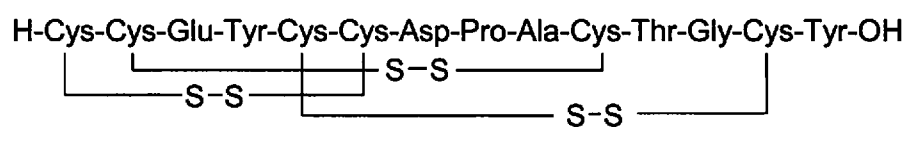
41. The composition of claim 40, wherein the composition comprises less than 5% by weight of the reduced form linacotide.

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

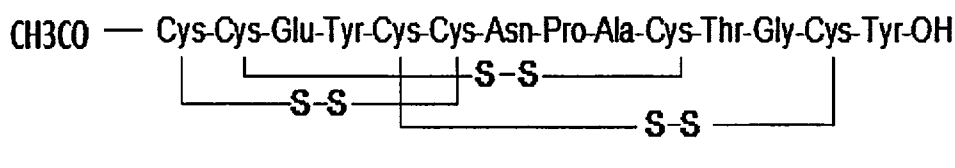
i. a peptide ("Cys¹-IMD") or a pharmaceutically acceptable salt thereof, wherein the peptide comprises the amino acid structure of:



ii. a hydrolysis peptide ("Asp⁷") or a pharmaceutically acceptable salt thereof, wherein the peptide comprises the amino acid structure of:

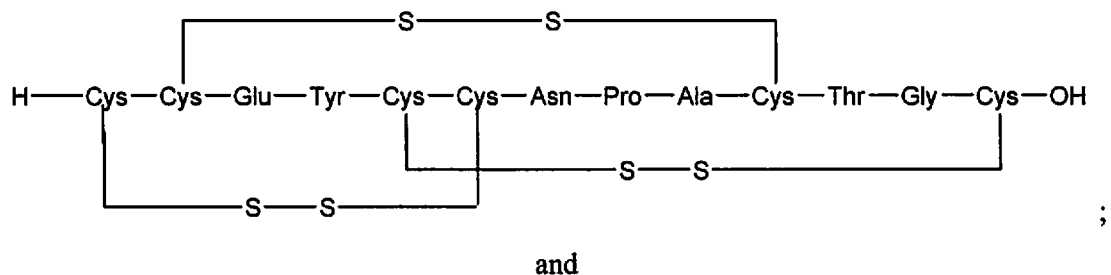


iii. an acetylation peptide ("Cys¹-N-Acetyl") or a pharmaceutically acceptable salt thereof, wherein the peptide comprises the amino acid structure of:

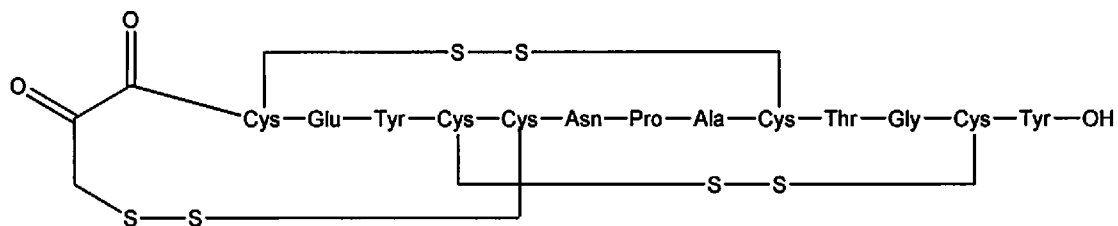


iv. a linacotide trisulfide peptide or a pharmaceutically acceptable salt thereof, wherein the peptide comprises the amino acid sequence of Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr wherein an additional sulfur atom may be attached to any one of the six cysteinyl sulfurs;

v. a peptide ("Des-Tyr¹⁴") or a pharmaceutically acceptable salt thereof, wherein the peptide comprises the amino acid structure of:



- vi. a peptide ("Cys¹- 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 linacлотide is present in the composition in a concentration of 1 μ g to 2 mg.
44. The composition of any of claims 1-43, wherein the linacлотide is present in the composition in a concentration of 25 μ g, 36 μ g, 50 μ g, 72 μ g, 75 μ g, 100 μ g, 145 μ g, 150 μ g, 290 μ g, 300 μ g, or 600 μ g.
45. The composition of claim 44, wherein the linacлотide is present in the composition in a concentration of 25 μ g.
46. The composition of claim 44, wherein the linacлотide is present in the composition in a concentration of 50 μ g.
47. The composition of claim 44, wherein the linacлотide is present in the composition in a concentration of 75 μ g.
48. The composition of claim 44, wherein the linacлотide is present in the composition in a concentration of 100 μ g.
49. The composition of claim 44, wherein the linacлотide is present in the composition in a concentration of 150 μ g.

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. The composition of claims 51 or 52, 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.

54. The composition of any one of claims 51-53, further comprising an enteric coating and a protective polymer film or subcoating.

55. The composition of claim 54, wherein the subcoating comprises Opadry II®.

56. The composition of any of claims 51-55, wherein the composition releases at least 70% of the linaclotide at a pH greater than 5 or 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 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 the composition disintegrates in the ileum or colon.
61. A unit dosage form comprising the pharmaceutical composition of claim 51.
62. The unit dosage form of claim 61, wherein the linaclotide is present in the pharmaceutical composition in an amount between 1 μ g to 300 μ g.
63. A method of making the composition of any one of claims 1-60, comprising:
i) preparing a linaclotide base, pregranulated filler, and placebo base; and
ii) blending and compressing the linaclotide base, pregranulated filler, and placebo base into a tablet.
64. The method of claim 63, wherein the pregranulated filler is prepared through wet granulation and dried before blending and compressing into a tablet.
65. The method of claims 63 and 64, wherein the method further comprises applying a subcoat to the tablet.
66. The method of claim 65, wherein the subcoat comprises Opadry II®.
67. The method of any of claims 63-66, wherein the method further comprises applying an enteric or functional coating to the tablet.
68. The composition of claim 67, 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. The composition of claims 67 or 68, 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.

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

70. A method of treating a gastrointestinal disorder comprising administering to a patient in need thereof, a therapeutically effective amount of the composition of any of claims 1-60 or 70.

71. The method of claim 70, 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.

72. The method of claim 71, wherein the gastrointestinal disorder is constipation.

73. The method of claim 72, wherein the constipation is chronic constipation, idiopathic constipation, chronic idiopathic constipation, constipation due to post-operative ileus, or constipation caused by opiate use.

74. The method of claim 71, wherein the gastrointestinal disorder is irritable bowel syndrome (IBS).

75. The method of claim 74, 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).

76. The method of claim 71, wherein the gastrointestinal disorder is dyspepsia.

77. The method of claim 71, wherein the gastrointestinal disorder is gastroparesis.

78. The method according to claim 77, wherein said gastroparesis is idiopathic, diabetic or post-surgical gastroparesis.
79. The method of claim 71, wherein the gastrointestinal disorder is chronic intestinal pseudo obstruction.
80. The method of claim 71, wherein the gastrointestinal disorder is Crohn's disease.
81. The method of claim 71, wherein the gastrointestinal disorder is ulcerative colitis.
82. The method of claim 71, wherein the gastrointestinal disorder is inflammatory bowel disease.
83. The method of claim 71, wherein the gastrointestinal disorder is visceral pain.
84. The method of claim 71, wherein the gastrointestinal disorder is diverticulitis.
85. The method of claim 71, wherein the gastrointestinal disorder is abdominal pain.
86. A method of treating a disorder comprising administering to a patient in need thereof, a therapeutically effective amount of the composition of any of claims 1-60 or 70.
87. The method of claim 86, 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.
88. A method of treating or relieving pain comprising administering to a patient in need thereof, a therapeutically effective amount of the composition of any of claims 1-60 or 70.
89. The method of claim 88, 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.

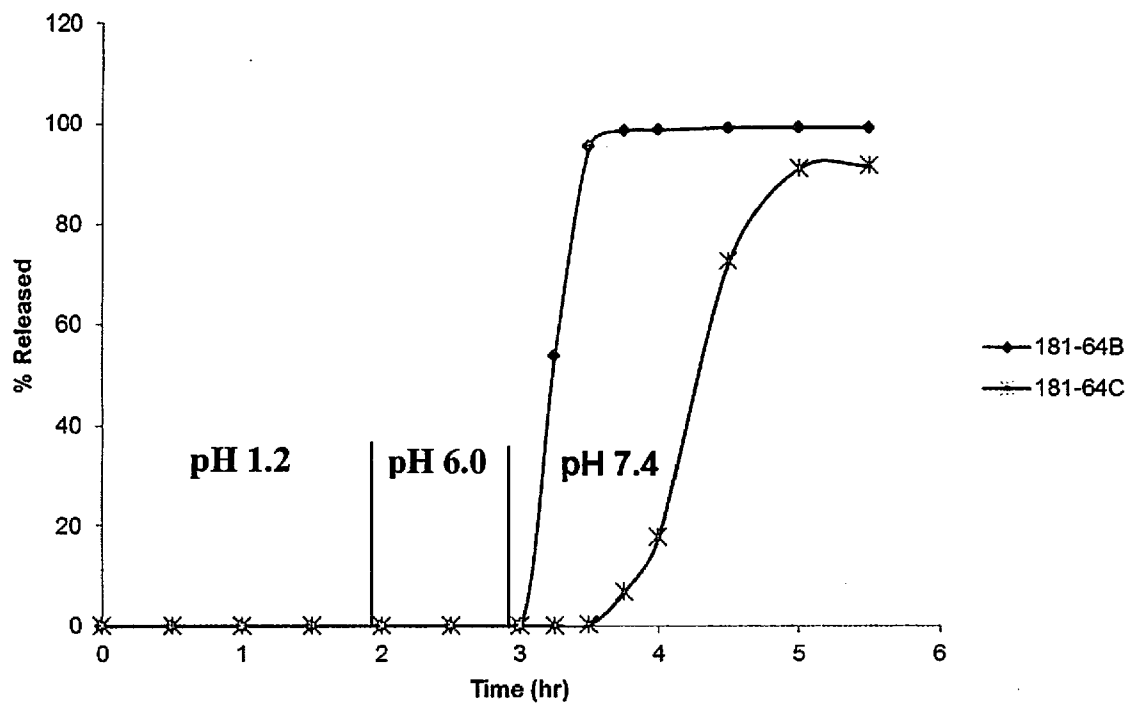
90. A method for increasing intestinal motility in a patient, the method comprising administering to the patient the pharmaceutical composition according to any one of claims 1-60 or 70.

91. A method of increasing guanylate cyclase C (GC-C) receptor activity in a biological sample or organism, comprising contacting said biological sample or organism with a composition according to any one of claims 1-60 or 70.

92. 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.

93. A composition prepared by the method of claim 92.

**FIGURE 1**

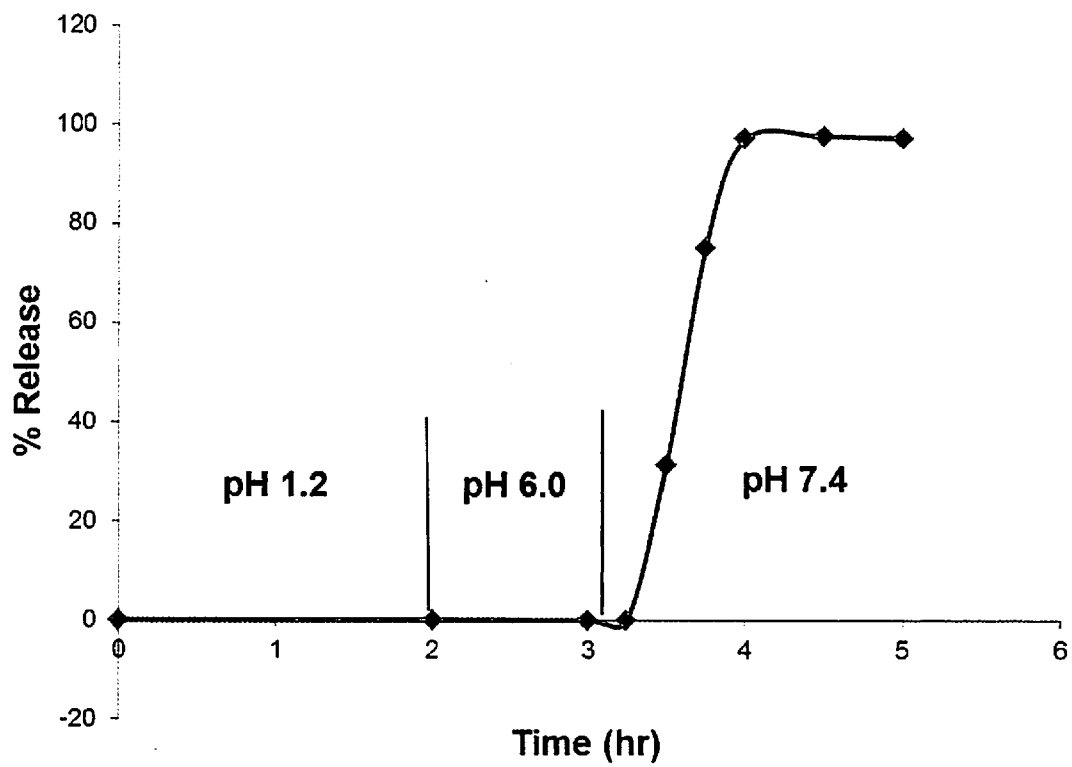


FIGURE 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/069838

A. CLASSIFICATION OF SUBJECT MATTER		
INV.	A61K9/16	A61K9/20
	A61K38/10	
		A61K9/28
		A61K9/48
		A61K9/50
ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols)		
A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
EPO-Internal, WPI Data, BIOSIS, EMBASE, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Section Ch, Week 201326 Thomson Scientific, London, GB; Class A96, AN 2013-F10566 XP002736499, ASHIHARA K ET AL: "Particulate form pharmaceutical composition useful for treating gastrointestinal disorders, obtained by coating nucleus with layer containing material having damp-proofing function, and drug layer containing linaclotide", -& WO 2013/047795 A ((ASTE) ASTELLAS PHARMA INC) 4 April 2013 (2013-04-04) the whole document -& US 2014/242158 A1 (NISHIURA MARE [JP] ET AL) 28 August 2014 (2014-08-28) the whole document ----- -/-	1-87, 89-94
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
9 March 2015		17/03/2015
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Gómez Gallardo, S

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International application No

PCT/US2014/069838

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/020054 A1 (IRONWOOD PHARMACEUTICALS INC [US]) 17 February 2011 (2011-02-17) page 2, last paragraph - page 3, last paragraph page 4, last paragraph page 7, paragraph 4 - page 9, paragraph 1 page 17, paragraph 8 - page 20, paragraph 1 claims 1-211 -----	1-87, 89-94
X	US 2011/059903 A1 (FRETZEN ANGELIKA [US] ET AL) 10 March 2011 (2011-03-10) the whole document -----	1-87, 89-94
X	WO 2010/019266 A2 (IRONWOOD PHARMACEUTICALS INC [US]) 18 February 2010 (2010-02-18) the whole document -----	1-87, 89-94
X	WO 2013/025969 A1 (IRONWOOD PHARMACEUTICALS INC [US]) 21 February 2013 (2013-02-21) -----	1-87, 89-94
Y	page 2, paragraph 9 page 3, paragraph 12 page 12, paragraph 56 - page 25, paragraph 108 page 28, paragraph 131 page 29, paragraph 134 - page 30, paragraph 145 claims 1-81 -----	88
X	WO 2012/034068 A1 (IRONWOOD PHARMACEUTICALS INC [US]) 15 March 2012 (2012-03-15) the whole document -----	1-87, 89-94
Y	BLOMAIN ERIK S ET AL: "Translating colorectal cancer prevention through the guanylyl cyclase C signaling axis", EXPERT REVIEW OF CLINICAL PHARMACOLOGY, vol. 6, no. 5, 1 September 2013 (2013-09-01), pages 557-564, XP008175159, ISSN: 1751-2441 the whole document -----	88
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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2014/069838

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2014/131024 A2 (SYNERGY PHARMACEUTICALS INC [US]) 28 August 2014 (2014-08-28) page 2, lines 5-7 page 2, line 24 - page 3, line 5 page 4, lines 21-27 page 9 - page 11; table 2 page 39, line 11 - page 59, line 13 claims 1-16 -----	1,4,6, 9-16, 21-31, 43,44, 71-76, 83,87, 91,92,94

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2014/069838

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2013047795 A	04-04-2013	JP 5553132 B2 JP 2014159480 A TW 201328703 A US 2014242158 A1 WO 2013047795 A1	16-07-2014 04-09-2014 16-07-2013 28-08-2014 04-04-2013
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WO 2013025969 A1	21-02-2013	CA 2846230 A1 CN 104053449 A EP 2776055 A1 JP 2014524444 A WO 2013025969 A1	21-02-2013 17-09-2014 17-09-2014 22-09-2014 21-02-2013
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(51)Int.Cl.

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A61K 9/20(2006.01)

A61K 9/28(2006.01)

A61K 9/48(2006.01)

A61K 9/50(2006.01)

A61K 38/10(2006.01)

权利要求书7页 说明书52页

序列表1页 附图2页

(54)发明名称

利那洛肽的延迟释放组合物

(57)摘要

本发明涉及包含利那洛肽(linaclotide)或其可药用盐的延迟释放药物组合物,以及涉及用于制备和使用所述组合物的各种方法和工艺。

1. 一种包含利那洛肽或其可药用盐的延迟释放药物组合物。
2. 根据权利要求1所述的组合物,其中所述组合物为延迟释放片剂或延迟释放胶囊。
3. 根据权利要求1所述的组合物,其中所述组合物包含延迟释放片剂。
4. 根据权利要求1至3中任一项所述的组合物,还包含肠溶性或功能性包衣。
5. 根据权利要求1至3中任一项所述的组合物,还包含肠溶性包衣和保护性聚合物膜或底包衣。
6. 根据权利要求4或5所述的组合物,其中所述肠溶性包衣选自丙烯酸甲酯-甲基丙烯酸共聚物(例如,Eudragit[®]);醋酸纤维素琥珀酸酯(CAS);羟丙基甲基纤维素邻苯二甲酸酯(HPMCP);醋酸羟丙基甲基纤维素琥珀酸酯(HPMCAS);聚醋酸乙烯邻苯二甲酸酯(PVAP);甲基丙烯酸甲酯-甲基丙烯酸共聚物;海藻酸钠和硬脂酸;瓜尔胶;以及卡波姆。
7. 根据权利要求4或5所述的组合物,其中所述肠溶性包衣包含Eudragit[®]FS30D、PlasAcryl[®]、Eudragit[®]S100、Eudragit[®]L100、Eudragit[®]L100-55、Eudragit[®]L30D-55、Eudragit[®]S、Eudragit[®]RL30D、Eudragit[®]RS30D、Eudragit[®]RS、Eudragit[®]EC或它们的混合物。
8. 根据权利要求5至7所述的组合物,其中所述底包衣包含Opadry II[®]。
9. 根据权利要求1至8中任一项所述的组合物,其中所述组合物在大于5或7的pH下释放至少70%的所述利那洛肽。
10. 根据权利要求1至8中任一项所述的组合物,其中所述组合物在大于5或7的pH下释放至少80%的所述利那洛肽。
11. 根据权利要求1至10中任一项所述的组合物,其中所述组合物在大于5或7的pH下具有小于30秒的崩解速率。
12. 根据权利要求1至11中任一项所述的组合物,其中所述组合物在回肠、回肠末端或结肠中释放利那洛肽。
13. 根据权利要求1至12中任一项所述的组合物,其中所述组合物在回肠或结肠中崩解。
14. 根据权利要求1至13中任一项所述的组合物,其中所述组合物还包含聚合物、起稳定作用的量的空间位阻伯胺或起稳定作用的量的阳离子,或者它们的组合或混合物。
15. 根据权利要求1至14中任一项所述的组合物,其中所述组合物包含聚合物。
16. 根据权利要求1至15中任一项所述的组合物,其中相对于所述组合物的总重量计,所述组合物包含0.01重量%至30重量%的聚合物。
17. 根据权利要求1至15中任一项所述的组合物,其中相对于所述组合物的总重量计,所述组合物包含1重量%至25重量%的聚合物。
18. 根据权利要求1至15中任一项所述的组合物,其中相对于所述组合物的总重量计,所述组合物包含1重量%至10重量%的聚合物。
19. 根据权利要求1至15中任一项所述的组合物,其中相对于所述组合物的总重量计,所述组合物包含2重量%至4重量%的聚合物。
20. 根据权利要求1至19中任一项所述的组合物,其中所述聚合物为聚乙烯吡咯烷酮

(PVP)、聚乙烯醇(PVA),或者它们的组合或混合物。

21. 根据权利要求1至20中任一项所述的组合物,其中所述组合物包含起稳定作用的量的空间位阻伯胺。

22. 根据权利要求1至21中任一项所述的组合物,其中所述组合物包含的空间位阻伯胺与利那洛肽的摩尔比介于400:1与1:1之间。

23. 根据权利要求1至21中任一项所述的组合物,其中所述组合物包含的空间位阻伯胺与利那洛肽的摩尔比介于200:1与50:1之间。

24. 根据权利要求23所述的组合物,其中所述空间位阻伯胺为氨基酸。

25. 根据权利要求24所述的组合物,其中所述氨基酸为组氨酸、亮氨酸、异亮氨酸、甲硫氨酸、丙氨酸,或者它们的组合或混合物。

26. 根据权利要求1至25中任一项所述的组合物,其中所述组合物包含起稳定作用的量的阳离子。

27. 根据权利要求26所述的组合物,其中所述组合物包含的阳离子与利那洛肽的摩尔比介于300:1与1:1之间。

28. 根据权利要求26所述的组合物,其中所述组合物包含的阳离子与利那洛肽的摩尔比介于250:1与30:1之间。

29. 根据权利要求26至28中任一项所述的组合物,其中所述阳离子为钙、镁、锰、锌、钾、钠或它们的混合物。

30. 根据权利要求26至29中任一项所述的组合物,其中所述阳离子为二价金属阳离子。

31. 根据权利要求30所述的组合物,其中所述二价金属阳离子为 Ca^{2+} 、 Mg^{2+} 、 Mn^{2+} 、 Zn^{2+} 或它们的混合物。

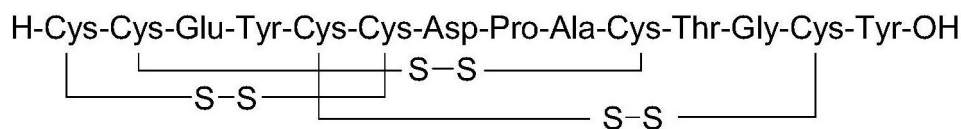
32. 根据权利要求1至31中任一项所述的组合物,其中所述组合物包含聚合物、起稳定作用的量的空间位阻伯胺和起稳定作用的量的阳离子。

33. 根据权利要求32所述的组合物,其中所述组合物包含:起稳定作用的量的选自PVP和PVA的聚合物;起稳定作用的量的选自组氨酸、亮氨酸、异亮氨酸、丙氨酸和甲硫氨酸的氨基酸;以及起稳定作用的量的选自 Ca^{2+} 、 Mg^{2+} 、 Zn^{2+} 或它们的混合物的阳离子。

34. 根据权利要求33所述的组合物,其中所述组合物包含:(i) 0.01重量%至30重量%的选自PVP和PVA的聚合物,(ii) 选自组氨酸、亮氨酸、异亮氨酸、丙氨酸和甲硫氨酸的氨基酸,其中氨基酸与利那洛肽的摩尔比介于400:1与1:1之间,以及(iii) 选自 Ca^{2+} 、 Mg^{2+} 、 Zn^{2+} 或它们的混合物的阳离子,其中阳离子与利那洛肽的摩尔比介于300:1与1:1之间。

35. 根据权利要求33所述的组合物,其中所述组合物包含:(i) 1重量%至10重量%的PVA,(ii) 组氨酸,其中组氨酸与利那洛肽的摩尔比介于400:1与50:1之间,以及(iii) Ca^{2+} ,其中 Ca^{2+} 与利那洛肽的摩尔比介于300:1与30:1之间。

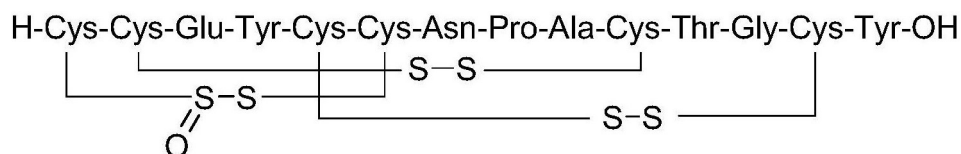
36. 根据权利要求1至35中任一项所述的组合物,其中所述组合物还包含具有以下结构的水解产物:



37. 根据权利要求36所述的组合物,其中所述组合物包含少于5重量%的所述水解产

物。

38. 根据权利要求1至37中任一项所述的组合物, 其中所述组合物还包含具有以下结构的氧化产物:



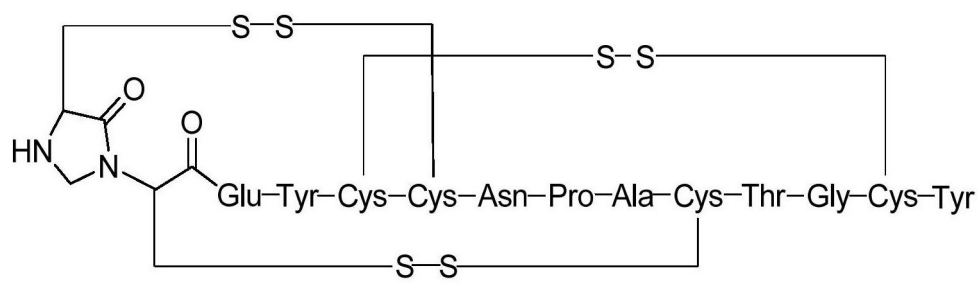
39. 根据权利要求38所述的组合物, 其中所述组合物包含少于5重量%的所述氧化产物。

40. 根据权利要求1至39中任一项所述的组合物, 其中所述组合物还包含还原形式利那洛肽。

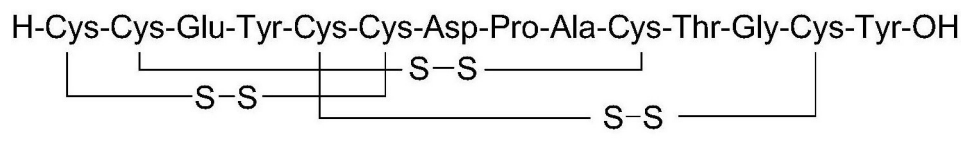
41. 根据权利要求40所述的组合物, 其中所述组合物包含少于5重量%的所述还原形式利那洛肽。

42. 根据权利要求1至41中任一项所述的药物组合物, 还包含一种或多种选自以下的肽:

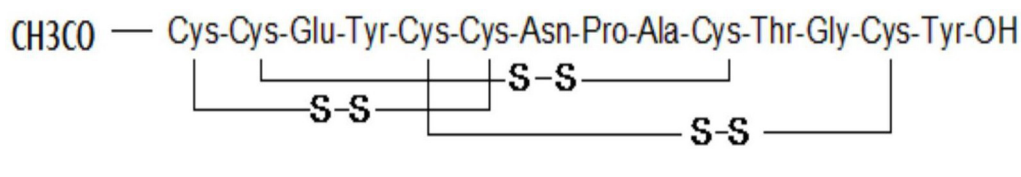
i. 肽 (“Cys¹-IMD”) 或其可药用盐, 其中所述肽包含以下氨基酸结构:



ii. 水解肽 (“Asp⁷”) 或其可药用盐, 其中所述肽包含以下氨基酸结构:

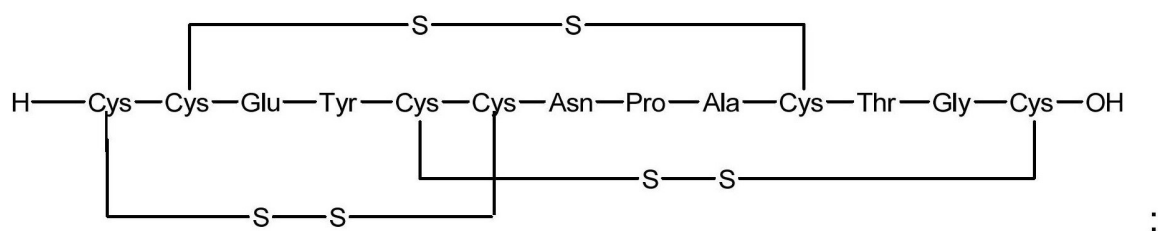


iii. 乙酰化肽 (“Cys¹-N-乙酰基”) 或其可药用盐, 其中所述肽包含以下氨基酸结构:



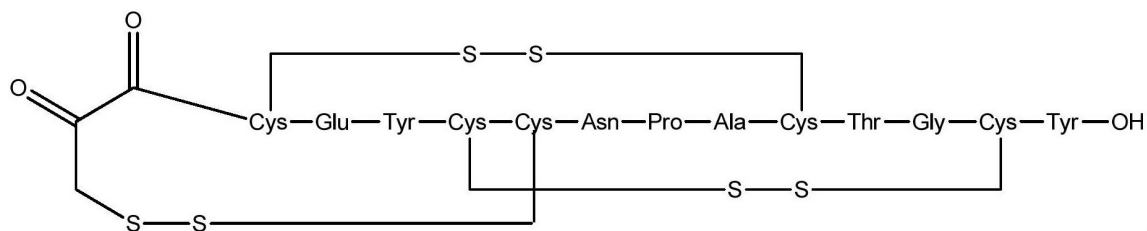
iv. 利那洛肽三硫化物肽或其可药用盐, 其中所述肽包含氨基酸序列Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr, 其中附加的硫原子可连接到所述六个半胱氨酸硫中的任何一个;

v. 肽 (“Des-Tyr¹⁴”) 或其可药用盐, 其中所述肽包含以下氨基酸结构:



以及

vi. 肽 (“Cys¹-α-酮肽”) 或其可药用盐或水合物, 其中所述肽包含以下氨基酸结构:



43. 根据权利要求1至42中任一项所述的组合物, 其中所述利那洛肽以1μg至2mg的浓度存在于所述组合物中。

44. 根据权利要求1至43中任一项所述的组合物, 其中所述利那洛肽以25μg、36μg、50μg、72μg、75μg、100μg、145μg、150μg、290μg、300μg或600μg的浓度存在于所述组合物中。

45. 根据权利要求44所述的组合物, 其中所述利那洛肽以25μg的浓度存在于所述组合物中。

46. 根据权利要求44所述的组合物, 其中所述利那洛肽以50μg的浓度存在于所述组合物中。

47. 根据权利要求44所述的组合物, 其中所述利那洛肽以75μg的浓度存在于所述组合物中。

48. 根据权利要求44所述的组合物, 其中所述利那洛肽以100μg的浓度存在于所述组合物中。

49. 根据权利要求44所述的组合物, 其中所述利那洛肽以150μg的浓度存在于所述组合物中。

50. 根据权利要求44所述的组合物, 其中所述利那洛肽以290μg的浓度存在于所述组合物中。

51. 一种包含肠溶性包衣片剂的延迟释放组合物, 其中所述片剂包含:

利那洛肽;

Ca²⁺;

组氨酸; 以及

聚乙烯醇 (PVA)。

52. 根据权利要求51所述的组合物, 其中所述肠溶性包衣包含丙烯酸甲酯-甲基丙烯酸共聚物 (例如, Eudragit[®]); 醋酸纤维素琥珀酸酯 (CAS); 羟丙基甲基纤维素邻苯二甲酸酯 (HPMCP); PVP; PVA; 醋酸羟丙基甲基纤维素琥珀酸酯 (HPMCAS); 聚醋酸乙烯邻苯二甲酸酯 (PVAP); 甲基丙烯酸甲酯-甲基丙烯酸共聚物; 海藻酸钠和硬脂酸; 瓜尔胶; 卡波姆; 或它们的混合物。

53. 根据权利要求51或52所述的组合物,其中所述肠溶性包衣包含Eudragit[®]FS30D、PlasAcryl[®]、Eudragit[®]S100、Eudragit[®]L100、Eudragit[®]L100-55、Eudragit[®]L30D-55、Eudragit[®]S、Eudragit[®]RL30D、Eudragit[®]RS30D、Eudragit[®]RS、Eudragit[®]EC或它们的混合物。

54. 根据权利要求51至53中任一项所述的组合物,还包含肠溶性包衣和保护性聚合物膜或底包衣。

55. 根据权利要求54所述的组合物,其中所述底包衣包含Opadry II[®]。

56. 根据权利要求51至55中任一项所述的组合物,其中所述组合物在大于5或7的pH下释放至少70%的所述利那洛肽。

57. 根据权利要求51至55中任一项所述的组合物,其中所述组合物在大于5或7的pH下释放至少80%的所述利那洛肽。

58. 根据权利要求51至57中任一项所述的组合物,其中所述组合物在大于5或7的pH下具有小于30秒的崩解速率。

59. 根据权利要求51至58中任一项所述的组合物,其中所述组合物在回肠、回肠末端或结肠中释放利那洛肽。

60. 根据权利要求51至59中任一项所述的组合物,其中所述组合物在回肠或结肠中崩解。

61. 一种包含根据权利要求51所述的药物组合物的单位剂型。

62. 根据权利要求61所述的单位剂型,其中所述利那洛肽以1 μ g至300 μ g之间的量存在于所述药物组合物中。

63. 一种制备根据权利要求1至60中任一项所述的组合物的方法,包括:

i) 制备利那洛肽基料、预先粒化的填充剂和安慰剂基料;以及

ii) 将所述利那洛肽基料、预先粒化的填充剂和安慰剂基料共混并压制成片剂。

64. 根据权利要求63所述的方法,其中所述预先粒化的填充剂通过湿法制粒制备,并且在共混并压制成片剂之前先干燥。

65. 根据权利要求63和64所述的方法,其中所述方法还包括将底包衣施加于所述片剂。

66. 根据权利要求65所述的方法,其中所述底包衣包含Opadry II[®]。

67. 根据权利要求63至66中任一项所述的方法,其中所述方法还包括将肠溶性或功能性包衣施加于所述片剂。

68. 根据权利要求67所述的组合物,其中所述肠溶性包衣包含丙烯酸甲酯-甲基丙烯酸共聚物(例如,Eudragit[®]);醋酸纤维素琥珀酸酯(CAS);羟丙基甲基纤维素邻苯二甲酸酯(HPMCP);PVP;PVA;醋酸羟丙基甲基纤维素琥珀酸酯(HPMCAS);聚醋酸乙烯邻苯二甲酸酯(PVAP);甲基丙烯酸甲酯-甲基丙烯酸共聚物;海藻酸钠和硬脂酸;瓜尔胶;卡波姆;或它们的混合物。

69. 根据权利要求67或68所述的组合物,其中所述肠溶性包衣包含Eudragit[®]FS30D、PlasAcryl[®]、Eudragit[®]S100、Eudragit[®]L100、Eudragit[®]L100-55、Eudragit[®]L30D-55、

Eudragit[®]S、Eudragit[®]RL30D、Eudragit[®]RS30D、Eudragit[®]RS、Eudragit[®]EC或它们的混合物。

70.一种通过根据权利要求63所述的方法制备的组合物。

70.一种治疗胃肠疾病的方法,包括向有需要的患者施用治疗有效量的根据权利要求1至60或70中任一项所述的组合物。

71.根据权利要求70所述的方法,其中所述胃肠疾病选自:肠易激综合征(IBS)、便秘、功能性胃肠疾病、胃食管反流病、功能性烧心、消化不良、憩室炎、内脏痛、腹痛、胃轻瘫、慢性假性肠梗阻、结肠假性梗阻、克罗恩氏病、溃疡性结肠炎以及炎性肠病。

72.根据权利要求71所述的方法,其中所述胃肠疾病为便秘。

73.根据权利要求72所述的方法,其中所述便秘为慢性便秘、特发性便秘、慢性特发性便秘、术后肠梗阻所致便秘或由使用阿片类药物所引起的便秘。

74.根据权利要求71所述的方法,其中所述胃肠疾病为肠易激综合征(IBS)。

75.根据权利要求74所述的方法,其中所述肠易激综合征是便秘为主型肠易激综合征(IBS-c)、腹泻为主型肠易激综合征(IBS-d)或混合型肠易激综合征(IBS-m)。

76.根据权利要求71所述的方法,其中所述胃肠疾病为消化不良。

77.根据权利要求71所述的方法,其中所述胃肠疾病为胃轻瘫。

78.根据权利要求77所述的方法,其中所述胃轻瘫为特发性胃轻瘫、糖尿病性胃轻瘫或术后胃轻瘫。

79.根据权利要求71所述的方法,其中所述胃肠疾病为慢性假性肠梗阻。

80.根据权利要求71所述的方法,其中所述胃肠疾病为克罗恩氏病。

81.根据权利要求71所述的方法,其中所述胃肠疾病为溃疡性结肠炎。

82.根据权利要求71所述的方法,其中所述胃肠疾病为炎性肠病。

83.根据权利要求71所述的方法,其中所述胃肠疾病为内脏痛。

84.根据权利要求71所述的方法,其中所述胃肠疾病为憩室炎。

85.根据权利要求71所述的方法,其中所述胃肠疾病为腹痛。

86.一种治疗疾病的方法,包括向有需要的患者施用治疗有效量的根据权利要求1至60或70中任一项所述的组合物。

87.根据权利要求86所述的方法,其中所述疾病为选自以下的癌症:结肠直肠/局部转移结肠直肠癌、胃癌、肠息肉、胃肠道癌、上皮细胞的癌或癌前期生长或转移生长、或结肠直肠组织的息肉。

88.一种治疗或缓解疼痛的方法,包括向有需要的患者施用治疗有效量的根据权利要求1至60或70中任一项所述的组合物。

89.根据权利要求88所述的方法,其中所述疼痛选自:内脏痛;憩室炎疼痛;骨盆痛;腹痛;或与胃肠疾病、性病、膀胱疼痛综合征或间质性膀胱炎相关的疼痛。

90.一种用于提高患者的肠动力的方法,所述方法包括向所述患者施用根据权利要求1至60或70中任一项所述的药物组合物。

91.一种提高生物样品或生物体中的鸟苷酸环化酶C(GC-C)受体活性的方法,包括使所述生物样品或生物体与根据权利要求1至60或70中任一项所述的组合物接触。

92.一种制备根据权利要求1至60或70中任一项所述的组合物的方法,包括:

- i) 制备包含利那洛肽或其可药用盐的水溶液;以及
 - ii) 将所述水溶液施加于可药用的载体。
93. 一种通过根据权利要求92所述的方法制备的组合物。

利那洛肽的延迟释放组合物

技术领域

[0001] 本发明涉及包含利那洛肽(linaclotide)或其可药用盐的延迟释放药物组合物,以及涉及用于制备和使用所述组合物的各种方法和工艺。

优先权声明

[0002] 本申请按美国法典第35卷第119条第(e)款的规定,要求2013年12月11日提交的美国临时专利申请No.61/914,951和2013年12月11日提交的美国临时专利申请No.61/914,952的优先权,这两份临时专利申请的全部内容特此以引用方式并入本文。

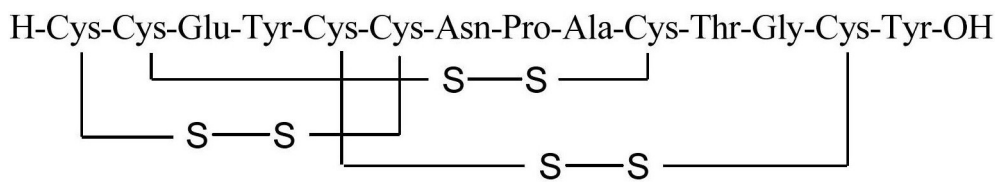
序列表

[0003] 本申请以引用方式合并了名称为“IW140PCT1_ST25.txt”的序列表的全部内容(578字节),该序列表最后修订于2014年12月11日,且以电子方式与本申请一同提交。

背景技术

[0004] 本领域已使用各种配制技术来开发药物活性剂的延迟释放组合物,包括使用肠溶性包衣或pH响应性聚合物。然而,这些组合物的具体组分差别很大,并显著依赖于特定药物活性剂和所需的特性。例如,配制技术必须与药物活性剂相容,还必须提供必要的溶出性能和稳定性特性。

[0005] 美国专利No.7,304,036和No.7,371,727(均以引用方式并入本文)公开了充当鸟苷酸环化酶C(GC-C)受体激动剂的肽,这些肽用于治疗胃肠(GI)疾病。所公开的一种特定肽是利那洛肽,其由下列氨基酸序列组成:Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr。利那洛肽的化学结构为:



[0006] 利那洛肽经口施用,在美国已由FDA批准用于治疗伴有便秘的肠易激综合征(IBS-c)和慢性特发性便秘(CIC)。利那洛肽已显示出能影响人类胃肠的生理机能,包括可减轻内脏痛、减轻腹胀和加快胃肠转运,这可引起大便次数增加以及大便稠度改善。经口施用的利那洛肽结合至肠腔面的GC-C受体后将该受体激活,由此在局部发挥作用。GC-C受体是哺乳动物肠道功能的关键调节因子,存在于整个胃肠道腔面。GC-C受体响应内源激素鸟苷蛋白和尿鸟苷蛋白,还响应来自热稳定肠毒素家族的肠道细菌肽(ST肽)。当利那洛肽结合至GC-C受体时,第二信使环GMP(c-GMP)升高,氯离子和碳酸氢根分泌增加,引起肠液分泌增多、疼痛减轻。

[0007] 经FDA批准,利那洛肽以口服固体速释胶囊制剂的形式施用,这种制剂是将层积了药物的微丸填充到明胶胶囊内而制成的。由于GC-C受体在整个胃肠道内高水平表达,速释制剂中的利那洛肽从上胃肠道开始激活GC-C受体,从而导致大量肠液流入下胃肠道。为减轻或缓解这种效应,需要能将利那洛肽靶向释放到胃肠道远段(即下段)的延迟释放组合

物。利那洛肽在下胃肠道靶向释放可有助于避免胃肠道分泌过多流体,同时仍保持或改善利那洛肽治疗胃肠疾病的腹部症状和肠道症状的功效。

[0008] 据估计,美国有1300万成人患有IBS-c,3500万成人患有CIC。还估计有1500万成人罹患IBS-m。目前630万成人正寻求治疗,但他们并不满意目前IBS-m治疗的效果。罹患IBS、CIC和其他胃肠疾病的患者主诉的症状是腹痛或内脏痛。因此,有必要开发疗法,来进一步缓解罹患IBS-c、IBS-m和CIC的成人感受到的内脏痛,并增强这部分人群对疼痛的耐受度。

[0009] 此前已证实利那洛肽能减轻内脏痛,这种内脏痛被认为是由胃肠道内cGMP水平升高介导的。动物研究已表明,经口施用的利那洛肽可治疗源于下胃肠道的内脏痛。然而,由于肠道内环境具有还原性,据信大部分的口服利那洛肽剂量在到达远端结肠之前就已被降解。在接受利那洛肽治疗的人类志愿者中,发现排泄物内只有约5%的口服剂量。靶向下胃肠道的利那洛肽延迟释放(“DR”)组合物可促使较高剂量的利那洛肽递送到结肠,从而改善利那洛肽缓解与各种胃肠疾病相关的疼痛的功效。利那洛肽的这种DR组合物有可能将利那洛肽主要(或完全)释放到下胃肠道中。因此,例如,DR制剂或组合物治疗下胃肠道相关疾病的能力有望增强。另外,DR制剂或组合物相比速释剂型可能可以降低不良事件(诸如腹泻)发生率,原因是例如,其不会激活上胃肠道内的GC-C受体,从而引起肠液总分泌量下降。与此同时,DR制剂或组合物还能保持或甚至改善利那洛肽治疗胃肠疾病症状(诸如疼痛)的功效。

[0010] 尽管需要利那洛肽的延迟释放组合物,但制备此类制剂仍困难重重,原因是利那洛肽的化学性质本身不稳定,例如在水分作用下会发生降解反应,诸如水解、脱酰胺、异构化和多聚化。在生产利那洛肽剂量较低的制剂时,这些困难可能加重。

[0011] 因此,目前一直需要利那洛肽的延迟释放组合物,用于稳定可靠地将利那洛肽递送到胃肠道内的目标区域。

发明内容

[0012] 本发明涉及表现出利那洛肽在下胃肠道延迟释放的稳定的利那洛肽固体口服剂型。此外,本发明提供了通过施用这些延迟释放组合物来治疗病症的方法。本发明的延迟释放组合物可用于治疗各种病症,但特别适用于治疗胃肠疾病,诸如肠易激综合征(“IBS”) (例如,伴有便秘的IBS(即“IBS-c”)、伴有腹泻的IBS(即“IBS-d”)、或伴有便秘和腹泻的混合型IBS(即“IBS-m”))、便秘(例如,慢性特发性便秘)、结肠癌、憩室炎、间质性膀胱炎,以及腹痛或内脏痛。

[0013] 根据一些实施例,提供了用于治疗胃肠疾病或疼痛的方法,所述方法包括向有需要的患者施用本文公开的组合物。

附图说明

[0014] 图1示出了包含100μg利那洛肽的延迟释放片剂组合物在各种pH下的释放曲线。

[0015] 图2示出了包含25μg利那洛肽的延迟释放片剂组合物在各种pH下的释放曲线。

[0016] 图3示出了不带包衣和带包衣的耐酸利那洛肽胶囊的溶出曲线。

具体实施方式

[0017] 本文提供了利那洛肽的延迟释放口服剂型(统称“DR”)。迄今为止,利那洛肽唯一获批的制剂是表现出速释(“IR”)的胶囊。这些IR剂型在上胃肠道内释放其中所装的大部分或全部利那洛肽。释出的利那洛肽不仅在上胃肠道内激活GC-C受体,刺激肠液分泌,也在下胃肠道内发挥这些效应,但程度较轻。IR剂型在上下胃肠道内激活受体、刺激肠液分泌的程度之所以存在差异,部分归因于下述事实:利那洛肽(一旦从IR剂型释放)经历蛋白水解消化,因而部分甚至完全丧失激活GC-C受体的能力,尤其是其到达下胃肠道(诸如回肠、回肠末端、回盲瓣或结肠)的时候。

[0018] 本文所述的DR剂型在下胃肠道内诸如靠近回盲瓣或在结肠内(几乎不在或完全不在胃、十二指肠和/或空肠内)释放其中所装的大部分或全部利那洛肽。因此,本发明的剂型能够实现在上胃肠道内引起的流体总分泌量相比IR剂型减少,同时仍保持或改善治疗IBS-c、CIC以及调节胃肠痛觉信号传导的出色功效。IBS患者主诉的疾病症状是左下腹疼痛,故据信IBS的疼痛源自结肠。此外,DR剂型被认为非常适合治疗下胃肠道相关的疾病和障碍。由于DR剂型完全不会将(或只将很少一部分)利那洛肽释放到胃和上胃肠道内(利那洛肽在其中可被快速消化),所以DR剂型的一些优选实施例将掺入低剂量利那洛肽(与获批IR剂型中的量相比),尽管如此,仍将保持与用IR治疗IBS-c和CIC症状时相同的功效水平。

[0019] 一般来讲,鸟苷酸环化酶C(GC-C)受体是位于胃肠上皮细胞顶端表面上的跨膜受体。这种受体具有细胞外配体结合结构域、单次跨膜区和C端鸟苷酸环化酶结构域。配体结合至GC-C的细胞外结构域后,细胞内催化结构域便催化GTP生成cGMP。在活体内,细胞内cGMP的这种增加引发了一系列级联事件,导致氯离子和碳酸氢根向肠腔的分泌量增多、腔内pH升高、腔内钠吸收减少、流体分泌增多以及肠道转运加快。cGMP从上皮双向分泌到粘膜和肠腔内。通常,胃肠道的pH从胃(pH 1.5-3)到回肠末端(pH 7-8)逐渐升高,之后在结肠内下降到5.5-7.0。

[0020] 利那洛肽结合至肠GC-C受体,这种受体是肠内流体与电解质平衡的调节因子。利那洛肽是由氨基酸序列Cys₁Cys₂Glu₃Tyr₄Cys₅Cys₆Asn₇Pro₈Ala₉Cys₁₀Thr₁₁Gly₁₂Cys₁₃Tyr₁₄组成的肽。利那洛肽的任何合乎需要的形式都可用于组合物中,例如,利那洛肽的任何可药用的盐或水合物、任何分离和/或纯化形式、或任何二硫化物形式。利那洛肽中的Cys₁与Cys₆之间、Cys₂与Cys₁₀之间、Cys₅与Cys₁₃之间具有二硫键。

[0021] 包含利那洛肽的DR组合物可用于治疗多种疾病。在各种实施例中,患者正罹患胃肠疾病;患者正罹患选自下列的疾病:胃肠动力障碍、慢性假性肠梗阻、结肠假性梗阻、炎性肠病、克罗恩氏病、十二指肠胃反流、消化不良、功能性消化不良、非溃疡性消化不良、功能性胃肠疾病、功能性烧心、胃食管反流病(GERD)、胃轻瘫、肠易激综合征(例如,腹泻为主型肠易激综合征(IBS-d)、便秘为主型肠易激综合征(IBS-c)和/或交替型(即混合型)肠易激综合征(IBS-m))、术后肠梗阻、溃疡性结肠炎、慢性便秘、便秘、间质性膀胱炎、前列腺炎、睾丸痛、疼痛膀胱综合征、子宫内膜异位症、外阴痛、直肠疼痛、憩室疾病或疼痛、与胃肠疾病相关的疼痛,以及与便秘相关的疾病和病症(例如,与使用阿片止痛药相关的便秘、术后便秘、与神经病变相关的便秘,以及本文所述的其他病症和疾病)。患者可依据罗马标准(例如,罗马II标准)被诊断患有功能性胃肠疾病(例如IBS-c)。

[0022] 在一些实施例中,DR组合物包括肠溶性包衣微丸,这些微丸的微丸芯上施加有pH敏感性聚合物包衣,其中微丸芯已包被有利那洛肽且可能包被有聚合物底包衣。在另外的

实施例中,可将具有肠溶性底包衣和保护性底包衣的微丸进一步填充到胶囊中,以实现所需的单位剂量强度。在一些实施例中,所述聚合物在延迟释放组合物内充当稳定剂、保护性包衣,或充当成膜剂。在其他实施例中,DR组合物包括肠溶性包衣片剂,这些片剂包含速释片剂芯并包含单位剂量的利那洛肽,其中的利那洛肽只在肠远段的pH条件下溶出。在其他实施例中,DR组合物包括肠溶性包衣明胶或HPMC胶囊,从而胶囊在下胃肠道内崩解得以实现。在一些实施例中,肠溶性或功能性包衣选自丙烯酸甲酯-甲基丙烯酸共聚物(例如,Eudragit[®])、醋酸纤维素琥珀酸酯(CAS)、羟丙基甲基纤维素邻苯二甲酸酯(HPMCP)、PVA、PVP、PVP-LP、醋酸羟丙基甲基纤维素琥珀酸酯(HPMCAS)、聚醋酸乙烯邻苯二甲酸酯(PVAP)、甲基丙烯酸甲酯-甲基丙烯酸共聚物、海藻酸钠和硬脂酸、瓜尔胶以及卡波姆。在另外的实施例中,肠溶性包衣选自Eudragit[®]FS30D、PlasAcryl[®]、Eudragit[®]S100、Eudragit[®]L100、Eudragit[®]L100-55、Eudragit[®]L30D-55、Eudragit[®]S、Eudragit[®]RL30D、Eudragit[®]RS30D、Eudragit[®]RS、Eudragit[®]EC或它们的混合物。

[0023] 延迟释放组合物可包含任何有效量的利那洛肽。在一些实施例中,例如,所述组合物包含0.05 μ g至6mg利那洛肽。在一些实施例中,例如,所述组合物包含1 μ g至2mg利那洛肽。在一些实施例中,所述组合物包含25 μ g至2mg利那洛肽,例如,50 μ g至1mg利那洛肽。在一些实施例中,例如,所述组合物包含0.1 μ g至90 μ g利那洛肽。在一些实施例中,例如,所述组合物包含0.1 μ g至45 μ g利那洛肽。在一些实施例中,例如,所述组合物包含0.1 μ g至25 μ g利那洛肽。在一些实施例中,例如,所述组合物包含36 μ g至290 μ g利那洛肽。在一些实施例中,所述组合物包含0.05 μ g、0.1 μ g、0.15 μ g、0.25 μ g、0.5 μ g、0.75 μ g、1 μ g、1.5 μ g、2 μ g、2.5 μ g、3 μ g、3.5 μ g、4 μ g、4.5 μ g、5 μ g、7.5 μ g、9 μ g、10 μ g、15 μ g、20 μ g、25 μ g、30 μ g、35 μ g、36 μ g、40 μ g、45 μ g、50 μ g、60 μ g、72 μ g、75 μ g、90 μ g、100 μ g、145 μ g、150 μ g、200 μ g、250 μ g、290 μ g、300 μ g、350 μ g、400 μ g、450 μ g、500 μ g、550 μ g、579 μ g、600 μ g、650 μ g、700 μ g、750 μ g、800 μ g、850 μ g、900 μ g、950 μ g或1mg利那洛肽。在一些实施例中,所述组合物包含100 μ g至600 μ g利那洛肽。在一些实施例中,所述组合物包含25 μ g、50 μ g、75 μ g、100 μ g、150 μ g、290 μ g、300 μ g、400 μ g、500 μ g或600 μ g利那洛肽。在一些实施例中,所述组合物包含9 μ g、10 μ g、15 μ g、36 μ g、72 μ g、75 μ g、145 μ g、290 μ g、579 μ g或600 μ g利那洛肽。

[0024] 在一些实施例中,所述组合物包含9 μ g利那洛肽。在一些实施例中,所述组合物包含10 μ g利那洛肽。在一些实施例中,所述组合物包含25 μ g利那洛肽。在一些实施例中,所述组合物包含50 μ g利那洛肽。在一些实施例中,所述组合物包含75 μ g利那洛肽。在一些实施例中,所述组合物包含100 μ g利那洛肽。在一些实施例中,所述组合物包含150 μ g利那洛肽。在一些实施例中,所述组合物包含145 μ g利那洛肽。在一些实施例中,所述组合物包含290 μ g利那洛肽。

[0025] 在一些实施例中已发现,利那洛肽延迟释放组合物的稳定性可通过在组合物中包含适量空间位阻伯胺(如氨基酸)组分、阳离子(如金属阳离子)组分和/或聚合物组分来提高或改善。这些组分(例如)通过防止利那洛肽延迟释放组合物内的利那洛肽降解(例如,水分引起的降解反应,如水解反应、脱酰胺反应和/或多聚化反应),减轻并/或降低该组合物内利那洛肽降解的程度,来提高或增强这种组合物的稳定性。例如,在一些实施例中已发现,向这种组合物中添加或加入适量阳离子(如Mg²⁺、Ca²⁺、Zn²⁺)提高了组合物在防止利那洛

肽氧化降解方面的稳定性。此外,在一些实施例中已发现,向组合物中加入适量空间位阻伯胺(例如氨基酸形式的空间位阻伯胺,如组氨酸)提高了组合物在防止(例如)甲醛或甲醛等同物与利那洛肽N端亲核加成方面的稳定性,例如通过充当清除剂并且/或者对组合物进行缓冲。此外,在一些实施例中已发现,向组合物中加入适量的空间位阻伯胺(如组氨酸)和阳离子(如 Ca^{2+})两者,提高了组合物防止利那洛肽水解及形成甲醛($\text{Cys}^1\text{-IMD}$)产物方面的稳定性。在一些实施例中还已发现,向延迟释放组合物中加入适量聚合物(如聚乙烯吡咯烷酮或聚乙烯醇)提高了组合物的稳定性,机理例如为:降低组合物内利那洛肽的迁移率和/或反应性(例如,通过与利那洛肽形成复合物或基质(例如,玻璃态基质和/或刚性基质)(如经由玻璃化反应));防止利那洛肽与水分子之间形成氢键或减少两者间形成的氢键的数量;以及/或者增强利那洛肽的三维结构完整性。

[0026] 就这一点而言,在一些实施例中已发现,例如相比不包含阳离子和/或空间位阻伯胺和/或相同浓度的这些组分的类似组合物,将利那洛肽与特定浓度或摩尔比的阳离子和空间位阻伯胺组合于延迟释放药物组合物中,可引起组合物内利那洛肽的稳定性协同增强或改善。在一些实施例中,组合物可包含任何起稳定作用的量的空间位阻伯胺组分。在其他实施例中,所述组合物包含的空间位阻伯胺与利那洛肽的摩尔比介于400:1与1:1之间。在另外的实施例中,所述组合物包含的空间位阻伯胺与利那洛肽的摩尔比介于200:1与50:1之间。在其他实施例中,所述组合物包含的空间位阻伯胺(如氨基酸)与利那洛肽的摩尔比可介于100:1与1:100之间。在一些实施例中,所述组合物包含的空间位阻伯胺与利那洛肽的摩尔比介于100:1与1:1之间。在一些实施例中,所述组合物包含的空间位阻伯胺与利那洛肽的摩尔比介于90:1与2:1之间。在一些实施例中,所述组合物包含的空间位阻伯胺与利那洛肽的摩尔比介于80:1与5:1之间。在一些实施例中,所述组合物包含的空间位阻伯胺与利那洛肽的摩尔比介于70:1与10:1之间。在一些实施例中,所述组合物包含的空间位阻伯胺与利那洛肽的摩尔比介于60:1与20:1之间。在一些实施例中,所述组合物包含的空间位阻伯胺与利那洛肽的摩尔比介于50:1与30:1之间。在一些实施例中,所述组合物包含的空间位阻伯胺与利那洛肽的摩尔比介于40:1与20:1之间。在一些实施例中,所述组合物包含的空间位阻伯胺与利那洛肽的摩尔比介于100:1与20:1之间。在一些实施例中,所述组合物包含的空间位阻伯胺与利那洛肽的摩尔比介于100:1与25:1之间。在一些实施例中,所述组合物包含的空间位阻伯胺与利那洛肽的摩尔比介于100:1与30:1之间。在一些实施例中,所述组合物包含的空间位阻伯胺与利那洛肽的摩尔比介于100:1与40:1之间。在一些实施例中,所述组合物包含的空间位阻伯胺与利那洛肽的摩尔比介于100:1与50:1之间。在一些实施例中,所述组合物包含的空间位阻伯胺与利那洛肽的摩尔比介于100:1与60:1之间。在一些实施例中,所述组合物包含的空间位阻伯胺与利那洛肽的摩尔比介于100:1与70:1之间。在一些实施例中,所述组合物包含的空间位阻伯胺与利那洛肽的摩尔比至少为5:1。在一些实施例中,所述组合物包含的空间位阻伯胺与利那洛肽的摩尔比至少为10:1。在一些实施例中,所述组合物包含的空间位阻伯胺与利那洛肽的摩尔比至少为20:1。在一些实施例中,所述组合物包含的空间位阻伯胺与利那洛肽的摩尔比至少为25:1。在一些实施例中,所述组合物包含的空间位阻伯胺与利那洛肽的摩尔比至少为30:1。在一些实施例中,所述组合物包含的空间位阻伯胺与利那洛肽的摩尔比至少为40:1。

[0027] 用于加入延迟释放组合物中的合适空间位阻伯胺例如为天然存在的氨基酸(如丙

氨酸、精氨酸、天冬酰胺、天冬氨酸、半胱氨酸、谷氨酸、谷氨酰胺、甘氨酸、组氨酸、异亮氨酸、亮氨酸、赖氨酸、葡甲胺、甲硫氨酸、苯丙氨酸、脯氨酸、丝氨酸、苏氨酸、色氨酸、酪氨酸、缬氨酸)、合成氨基酸(如羊毛硫氨酸、茶氨酸或1-氨基环己烷)、氨基糖(如壳聚糖或葡萄糖胺),或者它们的组合或混合物。在一些实施例中,所述组合物包含选自下列的氨基酸:丙氨酸、精氨酸、天冬酰胺、天冬氨酸、半胱氨酸、谷氨酸、谷氨酰胺、组氨酸、异亮氨酸、亮氨酸、赖氨酸、甲硫氨酸、苯丙氨酸、脯氨酸、丝氨酸、苏氨酸、色氨酸、酪氨酸、缬氨酸,或它们的混合物。在一些实施例中,所述组合物包含选自下列的氨基酸:亮氨酸、异亮氨酸、天冬酰胺、谷氨酰胺、谷氨酸、组氨酸、半胱氨酸、丙氨酸、丝氨酸、苏氨酸、酪氨酸、脯氨酸、色氨酸,或者它们的组合或混合物。在一些实施例中,所述组合物包含选自下列的氨基酸:亮氨酸、异亮氨酸、甲硫氨酸、丙氨酸,或者它们的组合或混合物。在一些实施例中,所述组合物包含选自下列的氨基酸:亮氨酸、异亮氨酸、丙氨酸,或者它们的组合或混合物。在一些实施例中,所述组合物包含选自下列的氨基酸:亮氨酸、异亮氨酸、甲硫氨酸,或者它们的组合或混合物。在一些实施例中,所述组合物包含选自下列的氨基酸:亮氨酸、甲硫氨酸、丙氨酸,或者它们的组合或混合物。在一些实施例中,所述组合物包含亮氨酸、甲硫氨酸,或它们的混合物。在一些实施例中,所述组合物包含亮氨酸、异亮氨酸,或它们的混合物。在一些实施例中,所述组合物包含亮氨酸、丙氨酸,或它们的混合物。在一些实施例中,所述组合物包含亮氨酸。在一些实施例中,所述组合物包含异亮氨酸。在一些实施例中,所述组合物包含甲硫氨酸。在一些实施例中,所述组合物包含丙氨酸。在一些实施例中,所述组合物包含组氨酸。

[0028] 延迟释放组合物可包含任何起稳定作用的量的阳离子(如金属阳离子)。在一些实施例中,所述组合物包含的阳离子与利那洛肽的摩尔比介于300:1与1:1之间。在另外的实施例中,所述组合物包含的阳离子与利那洛肽的摩尔比介于250:1与30:1之间。在其他实施例中,所述组合物包含的阳离子与利那洛肽的摩尔比可介于100:1与1:100之间。在一些实施例中,所述组合物包含的阳离子与利那洛肽的摩尔比介于100:1与1:1之间。在一些实施例中,所述组合物包含的阳离子与利那洛肽的摩尔比介于90:1与2:1之间。在一些实施例中,所述组合物包含的阳离子与利那洛肽的摩尔比介于80:1与5:1之间。在一些实施例中,所述组合物包含的阳离子与利那洛肽的摩尔比介于70:1与10:1之间。在一些实施例中,所述组合物包含的阳离子与利那洛肽的摩尔比介于60:1与20:1之间。在一些实施例中,所述组合物包含的阳离子与利那洛肽的摩尔比介于50:1与30:1之间。在一些实施例中,所述组合物包含的阳离子与利那洛肽的摩尔比介于40:1与20:1之间。在一些实施例中,所述组合物包含的阳离子与利那洛肽的摩尔比介于100:1与20:1之间。在一些实施例中,所述组合物包含的阳离子与利那洛肽的摩尔比介于100:1与25:1之间。在一些实施例中,所述组合物包含的阳离子与利那洛肽的摩尔比介于100:1与30:1之间。在一些实施例中,所述组合物包含的阳离子与利那洛肽的摩尔比介于100:1与40:1之间。在一些实施例中,所述组合物包含的阳离子与利那洛肽的摩尔比介于100:1与50:1之间。在一些实施例中,所述组合物包含的阳离子与利那洛肽的摩尔比介于100:1与60:1之间。在一些实施例中,所述组合物包含的阳离子与利那洛肽的摩尔比介于100:1与70:1之间。在一些实施例中,所述组合物包含的阳离子与利那洛肽的摩尔比至少为5:1。在一些实施例中,所述组合物包含的阳离子与利那洛肽的摩尔比至少为10:1。在一些实施例中,所述组合物包含的阳离子与利那洛肽的摩尔比至少为20:1。在一些实施例中,所述组合物包含的阳离子与利那洛肽的摩尔比至少为25:1。在一

些实施例中,所述组合物包含的阳离子与利那洛肽的摩尔比至少为30:1。在一些实施例中,所述组合物包含的阳离子与利那洛肽的摩尔比至少为40:1。在一些实施例中,所述组合物包含的阳离子与利那洛肽的摩尔比至少为60:1。

[0029] 可向所述组合物中加入任何合适的阳离子,例如任何合适的金属阳离子或有机阳离子。在一些实施例中,所述组合物包含选自下列的金属阳离子:钙、钾、镁、锌、铝、铁、锡、锰、铬、钴、镍、钡、钠,或者它们的组合或混合物。在一些实施例中,所述组合物包含选自下列的金属阳离子:钙、钾、镁、锌、铝、锰、铬、钴、镍、钡、钠,或者它们的组合或混合物。在一些实施例中,所述组合物包含选自下列的金属阳离子:铝、钙、钾、钠、镁、锰、锌,或者它们的组合或混合物。在一些实施例中,所述组合物包含选自下列的金属阳离子:钙、镁、锰、锌,或者它们的组合或混合物。在一些实施例中,所述组合物包含二价金属阳离子。在一些实施例中,所述组合物包含选自下列的二价金属阳离子: Al^{3+} 、 Ca^{2+} 、 Mg^{2+} 、 Zn^{2+} 、 Mn^{2+} ,或者它们的组合或混合物。在一些实施例中,所述组合物包含 Mg^{2+} 。在一些实施例中,所述组合物包含 Ca^{2+} 。在一些实施例中,所述组合物包含 Zn^{2+} 。在一些实施例中,所述组合物包含铝。

[0030] 此外,可将金属阳离子以任何合适的形式添加到组合物中,例如,作为具有任何适当的抗衡离子的任何可药用盐来加入。合适的金属盐包括(例如)氯化钙、碳酸钙、醋酸钙、氯化镁、醋酸镁、醋酸锌、氯化锌,或它们的混合物。在一些实施例中,所述组合物包含氯化钙、氯化镁、醋酸锌,或者它们的任何组合或混合物。在一些实施例中,所述组合物包含氯化钙。在一些实施例中,所述组合物包含氯化镁。在一些实施例中,所述组合物包含醋酸锌。合适的有机阳离子包括(例如)氢氧化铵、D-精氨酸、L-精氨酸、叔丁胺、水合醋酸钙、碳酸钙、DL-苹果酸钙、氢氧化钙、胆碱、乙醇胺、乙二胺、甘氨酸、L-组氨酸、L-赖氨酸、氢氧化镁、N-甲基-D-葡萄糖胺、L-鸟氨酸盐酸盐、氢氧化钾、盐酸普鲁卡因、L-脯氨酸、吡哆醇、L-丝氨酸、氢氧化钠、DL-色氨酸、氨丁三醇、L-酪氨酸、L-缬氨酸、肉毒碱、牛磺酸、肌酸苹果酸、精氨酸 α 酮戊二酸、鸟氨酸 α 酮戊二酸、醋酸精胺、氯化亚精胺,或者它们的组合或混合物。在一些实施例中,有机阳离子选自N-甲基D-葡萄糖胺、胆碱、精氨酸、赖氨酸、普鲁卡因、氨丁三醇(TRIS)、精胺、N-甲基-吗啉、葡萄糖胺、N,N-双(2-羟乙基)甘氨酸、二氮杂二环十一烯、肌酸、精氨酸乙酯、金刚烷胺、金刚烷乙胺、鸟氨酸、牛磺酸、瓜氨酸,或者它们的组合或混合物。

[0031] 所述组合物可包含任何起稳定作用的量的聚合物。在一些实施例中,所述组合物包含按其总重量计1重量%至25重量%的聚合物。在一些实施例中,所述组合物包含按其总重量计1重量%至10重量%的聚合物。

[0032] 在一些实施例中,所述组合物包含按其总重量计2重量%至4重量%的聚合物。在一些实施例中,所述组合物包含0.1重量%至75重量%的聚合物。在一些实施例中,所述组合物包含0.1重量%至55重量%的聚合物。在一些实施例中,所述组合物包含0.1重量%至35重量%的聚合物。在一些实施例中,所述组合物包含0.1重量%至30重量%的聚合物。在一些实施例中,所述组合物包含0.1重量%至25重量%的聚合物。在一些实施例中,所述组合物包含1重量%至25重量%的聚合物。在一些实施例中,所述组合物包含5重量%至25重量%的聚合物。在一些实施例中,所述组合物包含10重量%至25重量%的聚合物。在一些实施例中,所述组合物包含15重量%至25重量%的聚合物。在一些实施例中,所述组合物包含0.1重量%至22重量%的聚合物。在一些实施例中,所述组合物包含1重量%至22重量%的

聚合物。在一些实施例中,所述组合物包含5重量%至22重量%的聚合物。在一些实施例中,所述组合物包含10重量%至22重量%的聚合物。在一些实施例中,所述组合物包含0.1重量%至20重量%的聚合物。在一些实施例中,所述组合物包含1重量%至20重量%的聚合物。在一些实施例中,所述组合物包含5重量%至20重量%的聚合物。在一些实施例中,所述组合物包含10重量%至20重量%的聚合物。在一些实施例中,所述组合物包含0.01重量%至15重量%的聚合物。在一些实施例中,所述组合物包含0.01重量%至10重量%的聚合物。在一些实施例中,所述组合物包含0.01重量%至5重量%的聚合物。在一些实施例中,所述组合物包含0.1重量%至95重量%,例如,5重量%至95重量%、15重量%至95重量%、25重量%至95重量%、35重量%至95重量%、45重量%至95重量%、0.1重量%至85重量%、1重量%至85重量%、5重量%至85重量%、15重量%至85重量%、25重量%至85重量%、35重量%至85重量%、0.1重量%至80重量%、1重量%至80重量%、5重量%至80重量%、15重量%至80重量%、25重量%至80重量%、35重量%至80重量%、0.1重量%至75重量%、1重量%至75重量%、5重量%至75重量%、15重量%至75重量%、25重量%至75重量%、35重量%至75重量%、0.1重量%至65重量%、1重量%至65重量%、5重量%至65重量%、15重量%至65重量%、25重量%至65重量%、35重量%至65重量%、0.1重量%至60重量%、1重量%至60重量%、5重量%至60重量%、15重量%至60重量%、25重量%至60重量%、或35重量%至60重量%的聚合物。

[0033] 在一些实施例中,所述聚合物在延迟释放组合物内充当稳定剂、保护性包衣,或充当成膜剂。在一些实施例中,延迟释放组合物包含的聚合物(如PVP或PVA)与利那洛肽的摩尔比介于80:1与300:1之间,例如介于100:1与200:1之间,介于110:1与190:1之间,或甚至介于120:1与180:1之间。在一些实施例中,延迟释放组合物包含的聚合物(如PVP或PVA)与利那洛肽的摩尔比大于约80:1,例如大于约100:1,或甚至大于约120:1。在一些实施例中,延迟释放组合物包含的聚合物(如PVP或PVA)与利那洛肽的重量比介于10:1与300:1之间,例如介于80:1与200:1之间,介于100:1与180:1之间,或甚至介于110:1与150:1之间。在一些实施例中,延迟释放组合物包含的聚合物(如PVP或PVA)与利那洛肽的重量比介于100:1与500:1之间,例如介于200:1与400:1之间,介于250:1与350:1之间,或甚至介于300:1与350:1之间。

[0034] 用于加入延迟释放组合物中的合适聚合物例如为聚乙烯吡咯烷酮(PVP)、聚乙烯醇(PVA)、聚乙烯醇低过氧化物(PVA-LP)、羟丙基甲基纤维素(HPMC)、羟丙基纤维素(HPC)、甲基纤维素、甲基丙烯酸酯聚合物、环糊精、糊精、葡聚糖、聚丙烯酸、壳聚糖、瓜尔胶、黄原胶、聚氧化乙烯(如聚乙烯聚丙烯氧化物)、聚乙烯基磺酸钠、聚乙二醇、聚精氨酸、聚卡波非、聚乙烯吡咯烷酮醋酸乙烯酯共聚物、泊洛沙姆(如,购自巴斯夫公司(BASF)的Pluronic®产品)、藻酸盐、海藻糖、蔗糖、菊粉,或者它们的组合或混合物。在一些实施例中,所述组合物包含选自下列的聚合物:PVP、PVA、甲基丙烯酸酯聚合物、环糊精、葡聚糖、聚丙烯酸、壳聚糖、瓜尔胶、黄原胶、聚氧化乙烯、聚乙二醇、聚精氨酸、聚卡波非、聚乙烯吡咯烷酮醋酸乙烯酯共聚物、泊洛沙姆,或者它们的组合或混合物。在一些实施例中,所述组合物包含PVP、PVA、聚氧化乙烯,或它们的混合物。在一些实施例中,所述组合物包含PVP、PVA,或它们的混合物。在一些实施例中,所述组合物包含PVP。在一些实施例中,所述组合物包含PVA。

[0035] 在一些实施例中,延迟释放组合物包含两种或更多种稳定剂。例如,所述组合物可

包含起稳定作用的量的聚合物和起稳定作用的量的空间位阻伯胺。此外,所述组合物可包含起稳定作用的量的聚合物和起稳定作用的量的阳离子(如金属阳离子)。另外,所述组合物可包含起稳定作用的量的空间位阻伯胺和起稳定作用的量的阳离子(如金属阳离子)。在一些实施例中,所述组合物包含起稳定作用的量的聚合物、起稳定作用的量的空间位阻伯胺和起稳定作用的量的阳离子(如金属阳离子)。

[0036] 在一些实施例中,延迟释放组合物包含起稳定作用的量的PVP,和起稳定作用的量的选自下列的氨基酸:组氨酸、丙氨酸、精氨酸、天冬酰胺、天冬氨酸、半胱氨酸、谷氨酸、谷氨酰胺、甘氨酸、组氨酸、异亮氨酸、亮氨酸、赖氨酸、甲硫氨酸、苯丙氨酸、脯氨酸、丝氨酸、苏氨酸、色氨酸、酪氨酸、缬氨酸或这些氨基酸的混合物。在一些实施例中,所述组合物包含起稳定作用的量的PVP,和起稳定作用的量的选自下列的氨基酸:丙氨酸、精氨酸、天冬酰胺、天冬氨酸、半胱氨酸、谷氨酸、谷氨酰胺、组氨酸、异亮氨酸、亮氨酸、赖氨酸、甲硫氨酸、苯丙氨酸、脯氨酸、丝氨酸、苏氨酸、色氨酸、酪氨酸、缬氨酸或这些氨基酸的混合物。在一些实施例中,所述组合物包含起稳定作用的量的PVP,和起稳定作用的量的亮氨酸、异亮氨酸、甲硫氨酸、丙氨酸或者这些氨基酸的组合或混合物。在一些实施例中,所述组合物包含起稳定作用的量的PVP和起稳定作用的量的亮氨酸。

[0037] 在一些实施例中,延迟释放组合物包含起稳定作用的量的PVA,和起稳定作用的量的选自下列的氨基酸:丙氨酸、精氨酸、天冬酰胺、天冬氨酸、半胱氨酸、谷氨酸、谷氨酰胺、甘氨酸、组氨酸、异亮氨酸、亮氨酸、赖氨酸、甲硫氨酸、苯丙氨酸、脯氨酸、丝氨酸、苏氨酸、色氨酸、酪氨酸、缬氨酸或这些氨基酸的混合物。在一些实施例中,所述组合物包含起稳定作用的量的PVA,和起稳定作用的量的选自下列的氨基酸:丙氨酸、精氨酸、天冬酰胺、天冬氨酸、半胱氨酸、谷氨酸、谷氨酰胺、组氨酸、异亮氨酸、亮氨酸、赖氨酸、甲硫氨酸、苯丙氨酸、脯氨酸、丝氨酸、苏氨酸、色氨酸、酪氨酸、缬氨酸或这些氨基酸的混合物。在一些实施例中,所述组合物包含起稳定作用的量的PVA,和起稳定作用的量的亮氨酸、异亮氨酸、甲硫氨酸、丙氨酸或者这些氨基酸的组合或混合物。在一些实施例中,所述组合物包含起稳定作用的量的PVA和起稳定作用的量的亮氨酸。

[0038] 在一些实施例中,延迟释放组合物包含起稳定作用的量的PVP和起稳定作用的量的阳离子(如金属阳离子)。在一些实施例中,所述组合物包含起稳定作用的量的PVP和起稳定作用的量的二价金属阳离子。在一些实施例中,所述组合物包含起稳定作用的量的PVP,和起稳定作用的量的 Mg^{2+} 、 Ca^{2+} 、 Zn^{2+} 或其盐,或者这些二价金属阳离子或其盐的组合或混合物。在一些实施例中,所述组合物包含起稳定作用的量的PVP,和起稳定作用的量的 Ca^{2+} 或其盐。在一些实施例中,所述组合物包含起稳定作用的量的PVP,和起稳定作用的量的 Mg^{2+} 或其盐。在一些实施例中,所述组合物包含起稳定作用的量的PVP,和起稳定作用的量的 Zn^{2+} 或其盐。

[0039] 在一些实施例中,延迟释放组合物包含起稳定作用的量的PVA和起稳定作用的量的阳离子(如金属阳离子)。在一些实施例中,所述组合物包含起稳定作用的量的PVA和起稳定作用的量的二价金属阳离子。在一些实施例中,所述组合物包含起稳定作用的量的PVA,和起稳定作用的量的 Mg^{2+} 、 Ca^{2+} 、 Zn^{2+} 或其盐,或者这些二价金属阳离子或其盐的组合或混合物。在一些实施例中,所述组合物包含起稳定作用的量的PVA,和起稳定作用的量的 Ca^{2+} 或其盐。在一些实施例中,所述组合物包含起稳定作用的量的PVA,和起稳定作用的量的 Mg^{2+} 或其

盐。在一些实施例中,所述组合物包含起稳定作用的量的PVA,和起稳定作用的量的 Zn^{2+} 或其盐。

[0040] 在一些实施例中,延迟释放组合物包含起稳定作用的量的选自亮氨酸、异亮氨酸、甲硫氨酸、丙氨酸的氨基酸;以及起稳定作用的量的选自 Mg^{2+} 、 Ca^{2+} 、 Zn^{2+} 的二价金属阳离子或其盐,或者这些二价金属阳离子或其盐的组合或混合物。在一些实施例中,所述组合物包含起稳定作用的量的选自亮氨酸和异亮氨酸的氨基酸;以及起稳定作用的量的选自 Mg^{2+} 、 Ca^{2+} 的二价金属阳离子或其盐,或者这些二价金属阳离子或其盐的组合或混合物。在一些实施例中,所述组合物包含起稳定作用的量的选自亮氨酸和甲硫氨酸的氨基酸;以及起稳定作用的量的选自 Ca^{2+} 、 Zn^{2+} 的二价金属阳离子或其盐,或者这些二价金属阳离子或其盐的组合或混合物。在一些实施例中,所述组合物包含起稳定作用的量的亮氨酸,和起稳定作用的量的 Ca^{2+} 或其盐。在一些实施例中,所述组合物包含起稳定作用的量的阳离子和起稳定作用的量的空间位阻伯胺。在一些实施例中,所述组合物包含阳离子和空间位阻伯胺,其中阳离子与空间位阻伯胺的摩尔比(如 Ca^{2+} 与亮氨酸的摩尔比)至少为1.5:1,例如至少为2:1、至少为2.5:1、至少为3:1、至少为4:1、或甚至至少为5:1(例如,摩尔比介于1.5:1与5:1之间,例如,介于2:1与4:1之间)。

[0041] 在一些实施例中,延迟释放组合物包含:(i)起稳定作用的量的PVP或PVA,(ii)起稳定作用的量的亮氨酸、异亮氨酸、甲硫氨酸、丙氨酸,以及(iii)起稳定作用的量的 Mg^{2+} 、 Ca^{2+} 、 Zn^{2+} 或其盐,或者这些二价金属阳离子或其盐的组合或混合物。在一些实施例中,所述组合物包含起稳定作用的量的PVP、起稳定作用的量的亮氨酸和起稳定作用的量的金属阳离子。在一些实施例中,所述组合物包含起稳定作用的量的PVA、起稳定作用的量的组氨酸,以及起稳定作用的量的 Ca^{2+} 或其盐。在一些实施例中,所述组合物包含起稳定作用的量的PVP、起稳定作用的量的亮氨酸,以及起稳定作用的量的 Mg^{2+} 或其盐。在一些实施例中,所述组合物包含起稳定作用的量的PVP、起稳定作用的量的亮氨酸,以及起稳定作用的量的 Zn^{2+} 或其盐。在一些实施例中,所述组合物包含起稳定作用的量的PVA、起稳定作用的量的亮氨酸,以及起稳定作用的量的 Ca^{2+} 或其盐。在一些实施例中,所述组合物包含起稳定作用的量的PVA、起稳定作用的量的亮氨酸,以及起稳定作用的量的 Mg^{2+} 或其盐。在一些实施例中,所述组合物包含起稳定作用的量的PVA、起稳定作用的量的亮氨酸,以及起稳定作用的量的 Zn^{2+} 或其盐。

[0042] 在一些实施例中,所述组合物包含:(i)0.1重量%至30重量%的聚合物;(ii)空间位阻伯胺(如氨基酸),其中伯胺与利那洛肽的摩尔比介于100:1与10:1之间;(iii)阳离子(如金属阳离子),其中阳离子与利那洛肽的摩尔比介于100:1与40:1之间。在一些实施例中,所述组合物包含:(i)5重量%至25重量%的聚合物;(ii)空间位阻伯胺(如氨基酸),其中伯胺与利那洛肽的摩尔比介于100:1与30:1之间(例如,介于60:1与30:1之间,或甚至介于50:1与30:1之间);(iii)阳离子(如金属阳离子),其中阳离子与利那洛肽的摩尔比介于100:1与60:1之间。在一些实施例中,所述组合物包含:(i)0.1重量%至30重量%的选自PVP和PVA的聚合物;(ii)选自亮氨酸、异亮氨酸、丙氨酸和甲硫氨酸的氨基酸,其中氨基酸与利那洛肽的摩尔比介于100:1与10:1之间;(iii)选自 Ca^{2+} 、 Mg^{2+} 和 Zn^{2+} 的金属阳离子,其中阳离子与利那洛肽的摩尔比介于100:1与40:1之间。在一些实施例中,所述组合物包含:(i)5重量%至25重量%的选自PVP和PVA的聚合物;(ii)选自亮氨酸、异亮氨酸、丙氨酸和甲硫氨酸

的氨基酸,其中氨基酸与利那洛肽的摩尔比介于100:1与30:1之间(例如,介于60:1与30:1之间);(iii)选自 Ca^{2+} 、 Mg^{2+} 和 Zn^{2+} 的金属阳离子,其中阳离子与利那洛肽的摩尔比介于100:1与60:1之间。在一些实施例中,所述组合物包含:(i) 0.1重量%至30重量%(如5重量%至25重量%)的PVP或PVA;(ii) 亮氨酸,其中亮氨酸与利那洛肽的摩尔比介于100:1与30:1之间(例如,介于60:1与30:1之间,或甚至介于50:1与30:1之间);(iii) Ca^{2+} ,其中 Ca^{2+} 与利那洛肽的摩尔比介于100:1与60:1之间。

[0043] 在一些实施例中,所述组合物包含:(i) 45重量%至99重量%的聚合物;(ii) 空间位阻伯胺(如氨基酸),其中伯胺与利那洛肽的摩尔比介于100:1与10:1之间;(iii) 阳离子(如金属阳离子),其中阳离子与利那洛肽的摩尔比介于100:1与40:1之间。在一些实施例中,所述组合物包含:(i) 45重量%至70重量%的聚合物;(ii) 空间位阻伯胺(如氨基酸),其中伯胺与利那洛肽的摩尔比介于100:1与30:1之间(例如,介于60:1与30:1之间,或甚至介于50:1与30:1之间);(iii) 阳离子(如金属阳离子),其中阳离子与利那洛肽的摩尔比介于100:1与60:1之间。在一些实施例中,所述组合物包含:(i) 45重量%至99重量%的选自PVP和PVA的聚合物;(ii) 选自亮氨酸、异亮氨酸、丙氨酸和甲硫氨酸的氨基酸,其中氨基酸与利那洛肽的摩尔比介于100:1与10:1之间;(iii) 选自 Ca^{2+} 、 Mg^{2+} 和 Zn^{2+} 的金属阳离子,其中阳离子与利那洛肽的摩尔比介于100:1与40:1之间。在一些实施例中,所述组合物包含:(i) 45重量%至70重量%的选自PVP和PVA的聚合物;(ii) 选自亮氨酸、异亮氨酸、丙氨酸和甲硫氨酸的氨基酸,其中氨基酸与利那洛肽的摩尔比介于100:1与30:1之间(例如,介于60:1与30:1之间);(iii) 选自 Ca^{2+} 、 Mg^{2+} 和 Zn^{2+} 的金属阳离子,其中阳离子与利那洛肽的摩尔比介于100:1与60:1之间。在一些实施例中,所述组合物包含:(i) 45重量%至99重量%(如45重量%至70重量%)的PVP或PVA;(ii) 亮氨酸,其中亮氨酸与利那洛肽的摩尔比介于100:1与30:1之间(例如,介于60:1与30:1之间,或甚至介于50:1与30:1之间);(iii) Ca^{2+} ,其中 Ca^{2+} 与利那洛肽的摩尔比介于100:1与60:1之间。

[0044] 延迟释放组合物(如延迟释放片剂)还可包含任何一种或多种填充剂。合适的填充剂包括但不限于淀粉、碳酸钙、硫酸钙、羟丙基甲基纤维素、果糖、甲基纤维素、葡萄糖结合剂(dextrates)、右旋糖、葡聚糖、乳糖醇、麦芽糖、蔗糖、山梨醇、异麦芽酮糖醇(isomalt)、预糊化淀粉、磷酸二钙、微晶纤维素、甘露醇、明胶、海藻糖、赤藓醇、麦芽糖醇、乳糖、葡萄糖,或者它们的组合或混合物。在一些实施例中,填充剂为异麦芽酮糖醇。在一些实施例中,填充剂为明胶。在一些实施例中,填充剂为甘露醇。在一些实施例中,填充剂为预糊化淀粉。在一些实施例中,填充剂为微晶纤维素。

[0045] 延迟释放组合物(如延迟释放片剂)可包含任何适宜浓度的填充剂。在一些实施例中,例如,所述组合物包含按其总重量计浓度为0.1重量%至99重量%的一种或多种填充剂。在一些实施例中,例如,所述组合物包含按其总重量计浓度为1重量%至95重量%的一种或多种填充剂。在一些实施例中,例如,所述组合物包含按其总重量计浓度为10重量%至90重量%的一种或多种填充剂。在一些实施例中,例如,所述组合物包含按其总重量计浓度为20重量%至90重量%的一种或多种填充剂。在一些实施例中,例如,所述组合物包含按其总重量计浓度为25重量%至85重量%的一种或多种填充剂。在一些实施例中,例如,所述组合物包含按其总重量计浓度为30重量%至80重量%的一种或多种填充剂。在一些实施例中,例如,所述组合物包含按其总重量计浓度为40重量%至70重量%的一种或多种填充剂。

在一些实施例中,例如,所述组合物包含按其总重量计浓度为10重量%至60重量%的一种或多种填充剂。在一些实施例中,例如,所述组合物包含按其总重量计浓度为20重量%至50重量%的一种或多种填充剂。在一些实施例中,所述组合物包含按其总重量计浓度为至少20重量%,例如至少40重量%、至少60重量%、至少70重量%、至少80重量%或至少90重量%的一种或多种填充剂。

[0046] 在一些实施例中,延迟释放组合物(如延迟释放膜)包含一种或多种增塑剂。合适的增塑剂包括但不限于聚乙二醇、丙二醇、甘油、丙三醇、甘油一醋酸酯、甘油二醋酸酯、甘油三醋酸酯、邻苯二甲酸二甲酯、邻苯二甲酸二乙酯、邻苯二甲酸二丁酯、癸二酸二丁酯、柠檬酸三乙酯、柠檬酸三丁酯、柠檬酸三乙酯、乙酰柠檬酸三乙酯、蓖麻油、乙酰化单酸甘油酯、山梨醇或它们的组合。在示例性实施例中,制剂中增塑剂的浓度可为约0重量%至约30重量%,例如,约1重量%至约20重量%、约0重量%至约10重量%、约1重量%至约5重量%,或者甚至0重量%至约4重量%。

[0047] 在一些实施例中,延迟释放组合物包含成膜剂、水溶性聚合物、pH敏感性聚合物、可生物降解的聚合物或它们的组合。可用于本发明的口腔溶出制剂的水溶性聚合物、pH敏感性聚合物或可生物降解的聚合物包括但不限于纤维素衍生物、合成聚合物、聚丙烯酸酯和天然树胶。例如,用于本发明的口腔溶出制剂的水溶性聚合物可包括但不限于甲基纤维素、羟丙基纤维素、羟丙基甲基纤维素、乙基纤维素、羟乙基纤维素、羟丙基纤维素、羧甲基纤维素、醋酸纤维素邻苯二甲酸酯、醋酸丁酸纤维素、直链淀粉、葡聚糖、酪蛋白、普鲁兰、明胶、果胶、琼脂、卡拉胶、黄原胶、黄芪胶、瓜尔胶、金合欢胶、阿拉伯胶、聚乙二醇、聚氧化乙烯、聚乙烯吡咯烷酮、聚乙烯醇、环糊精、羧基乙烯基聚合物、海藻酸钠、聚丙烯酸、甲基丙烯酸甲酯或它们的混合物。在示例性实施例中,制剂中水溶性聚合物的浓度可为约20重量%至约90重量%,优选介于约40重量%至约80重量%之间。

[0048] 在一些实施例中,pH敏感性聚合物是Eudagrit[®] L100,其pH阈值为6.0。在一些实施例中,pH敏感性聚合物是Eudagrit[®] S100,其pH阈值为7.0。在一些实施例中,pH敏感性聚合物是Eudagrit[®] L-30D,其pH阈值为5.6。在一些实施例中,pH敏感性聚合物是Eudagrit[®] FS 30D,其pH阈值为6.8。在一些实施例中,pH敏感性聚合物是Eudagrit[®] L00-55,其pH阈值为5.5。在一些实施例中,pH敏感性聚合物为聚醋酸乙烯邻苯二甲酸酯,其pH阈值为5.0。在一些实施例中,pH敏感性聚合物为羟丙基甲基纤维素邻苯二甲酸酯,其pH阈值为4.5-4.8。在一些实施例中,pH敏感性聚合物为羟丙基甲基纤维素邻苯二甲酸酯50,其pH阈值为5.2。在一些实施例中,pH敏感性聚合物为羟丙基甲基纤维素邻苯二甲酸酯55,其pH阈值为5.4。在一些实施例中,pH敏感性聚合物为醋酸纤维素偏苯三酸酯,其pH阈值为4.8。在一些实施例中,pH敏感性聚合物为醋酸纤维素邻苯二甲酸酯,其pH阈值为5.0。

[0049] 本领域技术人员阅读本发明后应当理解,可加入其他组分来增强延迟释放组合物的一种或多种特性。在一些实施例中,例如,延迟释放组合物可包含一种或多种崩解剂、润滑剂、防结块添加剂、抗微生物剂、消泡剂、乳化剂、表面活性剂、缓冲剂和/或着色剂。

[0050] 合适的崩解剂包括(例如)琼脂、碳酸钙、微晶纤维素、交联羧甲基纤维素钠、交联聚维酮、聚维酮、波拉克林钾、羟基乙酸淀粉钠、马铃薯或木薯淀粉、其他淀粉、预糊化淀粉、粘土、其他褐藻胶、其他纤维素、树胶,以及它们的混合物。在一些实施例中,崩解剂为交联

聚维酮。在一些实施例中,崩解剂为交联羧甲基纤维素钠。

[0051] 合适的润滑剂包括(例如)硬脂酸钙、硬脂酸镁、矿物油、轻质矿物油、甘油、山梨醇、甘露醇、聚乙二醇、其他二醇、硬脂酸、月桂基硫酸钠、滑石、氢化植物油(如花生油、棉籽油、葵花油、芝麻油、橄榄油、玉米油、大豆油)、硬脂酸锌、油酸乙酯、月桂酸乙酯、琼脂、syloid硅胶(AEROSIL® 200,美国马里兰州巴尔的摩格雷斯公司(W.R.Grace Co., Baltimore, MD USA))、合成二氧化硅的凝聚型气溶胶(美国德克萨斯州普莱诺赢创德固赛公司(Evonik Degussa Co., Plano, TX USA))、热解二氧化硅(CAB-O-SIL,美国马萨诸塞州波士顿卡博特公司(Cabot Co., Boston, MA USA)),以及它们的混合物。

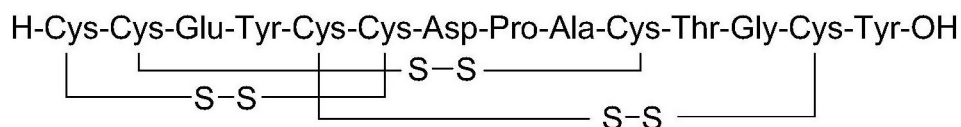
[0052] 合适的防结块添加剂包括(例如)硅酸钙、硅酸镁、二氧化硅、胶态二氧化硅、滑石、甘油酯(glyceryl),以及它们的混合物。

[0053] 可(例如)用作利那洛肽组合物的防腐剂的合适抗微生物添加剂包括(例如)苯扎氯铵、苄索氯铵、苯甲酸、苯甲醇、对羟基苯甲酸丁酯、氯化十六烷基吡啶、甲酚、氯丁醇、脱氢醋酸、对羟基苯甲酸乙酯、对羟基苯甲酸甲酯、苯酚、苯乙醇、苯氧乙醇、醋酸苯汞、硝酸苯汞、山梨酸钾、对羟基苯甲酸丙酯、苯甲酸钠、脱氢醋酸钠、丙酸钠、山梨酸、硫柳汞、百里酚,以及它们的混合物。

[0054] 所述组合物还可包含任何合适的可药用的载体或介质。合适的可药用载体包括(例如)任何溶剂、分散剂、pH缓冲剂、包衣、促吸收剂、控释剂,以及一种或多种惰性赋形剂(如填充剂、淀粉、多元醇、成粒剂、微晶纤维素、稀释剂、润滑剂、粘结剂、崩解剂)等等。另外,所述组合物可包含任何所需的附加组分、添加剂和/或物质,例如,表面活性添加剂、分散添加剂、保湿剂、助悬剂、增溶剂、缓冲剂、崩解剂、防腐剂、着色剂、调味剂等。在一些实施例中,所述组合物包含一种或多种与利那洛肽相互作用的离子物质。

[0055] 所述组合物还可包含任何合适的pH缓冲剂。在一些实施例中,pH缓冲剂以足以实现利那洛肽等电点的量存在于所述组合物中。就这一点而言,所述组合物可具有任何所需的pH。在一些实施例中,所述组合物的pH为2至5(例如,pH为2至4.5,pH为2至4,pH为2.5至4,pH为2.5至3.5,pH为2.5至3,或者甚至pH为3)。

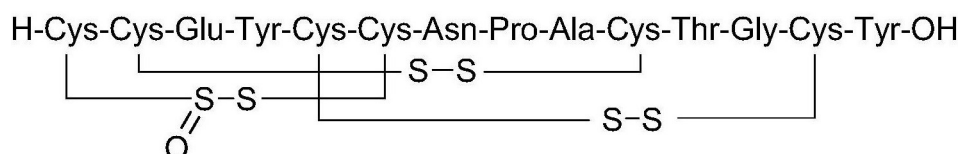
[0056] 在一些实施例中,所述组合物包含利那洛肽和水解产物,例如,包含或具有以下结构的水解产物:



所述组合物可包含任何所需浓度的水解产物。在一些实施例中,所述组合物包含少于10重量%的水解产物。在一些实施例中,所述组合物包含少于7重量%的水解产物。在一些实施例中,所述组合物包含少于6重量%的水解产物。在一些实施例中,所述组合物包含少于5重量%的水解产物。在一些实施例中,所述组合物包含少于4重量%的水解产物。在一些实施例中,所述组合物包含少于3重量%的水解产物。在一些实施例中,所述组合物包含少于2重量%的水解产物。在一些实施例中,所述组合物包含少于1重量%的水解产物。在一些实施例中,所述组合物包含0.01重量%至10重量%的水解产物。在一些实施例中,所述组合物包含0.1重量%至7重量%的水解产物。在一些实施例中,所述组合物包含0.1重量%至5重量%的水解产物。在一些实施例中,所述组合物包含0.5重量%至5重量%的水解产物。在

一些实施例中,所述组合物包含1重量%至5重量%的水解产物。在一些实施例中,所述组合物包含0.1重量%至4重量%的水解产物。在一些实施例中,所述组合物包含0.5重量%至4重量%的水解产物。在一些实施例中,所述组合物包含1重量%至4重量%的水解产物。在一些实施例中,所述组合物包含0.1重量%至3重量%的水解产物。在一些实施例中,所述组合物包含0.5重量%至3重量%的水解产物。在一些实施例中,所述组合物包含1重量%至3重量%的水解产物。在一些实施例中,所述组合物包含0.1重量%至2.5重量%的水解产物。在一些实施例中,所述组合物包含0.5重量%至2.5重量%的水解产物。在一些实施例中,所述组合物包含1重量%至2.5重量%的水解产物。在一些实施例中,所述组合物包含0.1重量%至2重量%的水解产物。在一些实施例中,所述组合物包含0.5重量%至2重量%的水解产物。在一些实施例中,所述组合物包含1重量%至2重量%的水解产物。在一些实施例中,所述组合物包含0.1重量%至1.5重量%的水解产物。在一些实施例中,所述组合物包含0.5重量%至1.5重量%的水解产物。在一些实施例中,所述组合物包含0.1重量%至1重量%的水解产物。在一些实施例中,所述组合物包含0.5重量%至1重量%的水解产物。

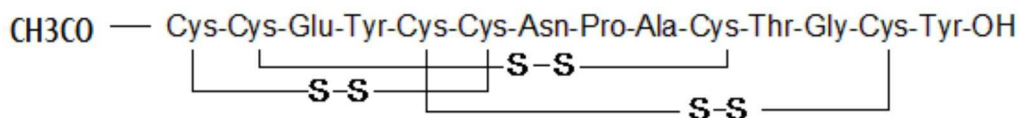
[0057] 在一些实施例中,所述组合物包含利那洛肽和氧化产物,例如,包含或具有以下结构的氧化产物:



另外，或作为替代，所述组合物包含利那洛肽和下述氧化产物：其具有示出的结构，但在示出的六个半胱氨酰硫中的任一个或多个处发生氧化。所述组合物可包含任何所需浓度的氧化产物。在一些实施例中，所述组合物包含少于10重量%的氧化产物。在一些实施例中，所述组合物包含少于7重量%的氧化产物。在一些实施例中，所述组合物包含少于6重量%的氧化产物。在一些实施例中，所述组合物包含少于5重量%的氧化产物。在一些实施例中，所述组合物包含少于4重量%的氧化产物。在一些实施例中，所述组合物包含少于3重量%的氧化产物。在一些实施例中，所述组合物包含少于2重量%的氧化产物。在一些实施例中，所述组合物包含少于1重量%的氧化产物。在一些实施例中，所述组合物包含0.01重量%至10重量%的氧化产物。在一些实施例中，所述组合物包含0.1重量%至7重量%的氧化产物。在一些实施例中，所述组合物包含0.1重量%至5重量%的氧化产物。在一些实施例中，所述组合物包含0.5重量%至5重量%的氧化产物。在一些实施例中，所述组合物包含1重量%至5重量%的氧化产物。在一些实施例中，所述组合物包含0.1重量%至4重量%的氧化产物。在一些实施例中，所述组合物包含0.5重量%至4重量%的氧化产物。在一些实施例中，所述组合物包含1重量%至4重量%的氧化产物。在一些实施例中，所述组合物包含0.1重量%至3重量%的氧化产物。在一些实施例中，所述组合物包含0.5重量%至3重量%的氧化产物。在一些实施例中，所述组合物包含1重量%至3重量%的氧化产物。在一些实施例中，所述组合物包含0.1重量%至2.5重量%的氧化产物。在一些实施例中，所述组合物包含0.5重量%至2.5重量%的氧化产物。在一些实施例中，所述组合物包含1重量%至2.5重量%的氧化产物。在一些实施例中，所述组合物包含0.1重量%至2重量%的氧化产物。在一些实施例中，所述组合物包含0.5重量%至2重量%的氧化产物。在一些实施例中，所述组合

物包含1重量%至2重量%的氧化产物。在一些实施例中,所述组合物包含0.1重量%至1.5重量%的氧化产物。在一些实施例中,所述组合物包含0.5重量%至1.5重量%的氧化产物。在一些实施例中,所述组合物包含0.1重量%至1重量%的氧化产物。在一些实施例中,所述组合物包含0.5重量%至1重量%的氧化产物。

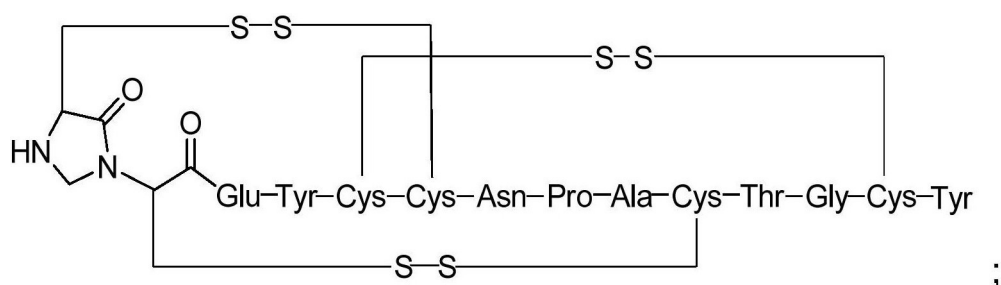
[0058] 在一些实施例中,所述组合物包含利那洛肽和乙酰化产物,例如,包含或具有以下结构的乙酰化产物:



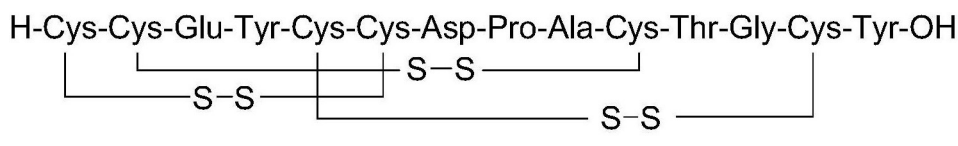
所述组合物可包含任何所需浓度的乙酰化产物。在一些实施例中,所述组合物包含少于10重量%的乙酰化产物。在一些实施例中,所述组合物包含少于7重量%的乙酰化产物。在一些实施例中,所述组合物包含少于6重量%的乙酰化产物。在一些实施例中,所述组合物包含少于5重量%的乙酰化产物。在一些实施例中,所述组合物包含少于4重量%的乙酰化产物。在一些实施例中,所述组合物包含少于3重量%的乙酰化产物。在一些实施例中,所述组合物包含少于2重量%的乙酰化产物。在一些实施例中,所述组合物包含少于1重量%的乙酰化产物。在一些实施例中,所述组合物包含0.01重量%至10重量%的乙酰化产物。在一些实施例中,所述组合物包含0.1重量%至7重量%的乙酰化产物。在一些实施例中,所述组合物包含0.1重量%至5重量%的乙酰化产物。在一些实施例中,所述组合物包含0.5重量%至5重量%的乙酰化产物。在一些实施例中,所述组合物包含1重量%至5重量%的乙酰化产物。在一些实施例中,所述组合物包含0.1重量%至4重量%的乙酰化产物。在一些实施例中,所述组合物包含0.5重量%至4重量%的乙酰化产物。在一些实施例中,所述组合物包含1重量%至4重量%的乙酰化产物。在一些实施例中,所述组合物包含0.1重量%至3重量%的乙酰化产物。在一些实施例中,所述组合物包含0.5重量%至3重量%的乙酰化产物。在一些实施例中,所述组合物包含1重量%至3重量%的乙酰化产物。在一些实施例中,所述组合物包含0.1重量%至2.5重量%的乙酰化产物。在一些实施例中,所述组合物包含0.5重量%至2.5重量%的乙酰化产物。在一些实施例中,所述组合物包含1重量%至2.5重量%的乙酰化产物。在一些实施例中,所述组合物包含0.1重量%至2重量%的乙酰化产物。在一些实施例中,所述组合物包含0.5重量%至2重量%的乙酰化产物。在一些实施例中,所述组合物包含1重量%至2重量%的乙酰化产物。在一些实施例中,所述组合物包含0.1重量%至1.5重量%的乙酰化产物。在一些实施例中,所述组合物包含0.5重量%至1.5重量%的乙酰化产物。在一些实施例中,所述组合物包含0.1重量%至1重量%的乙酰化产物。在一些实施例中,所述组合物包含0.5重量%至1重量%的乙酰化产物。

[0059] 在一些实施例中,提供了一种药物组合物,该药物组合物包含利那洛肽和一种或多种选自下列的肽:

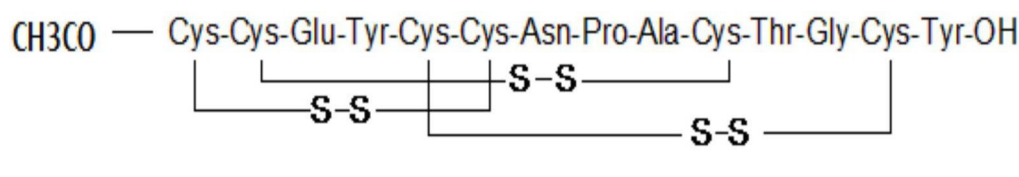
i. 肽 (“Cys¹-IMD”) 或其可药用盐,其中所述肽包含以下氨基酸结构:



ii. 水解肽 (“Asp⁷”) 或其可药用盐, 其中所述肽包含以下氨基酸结构:

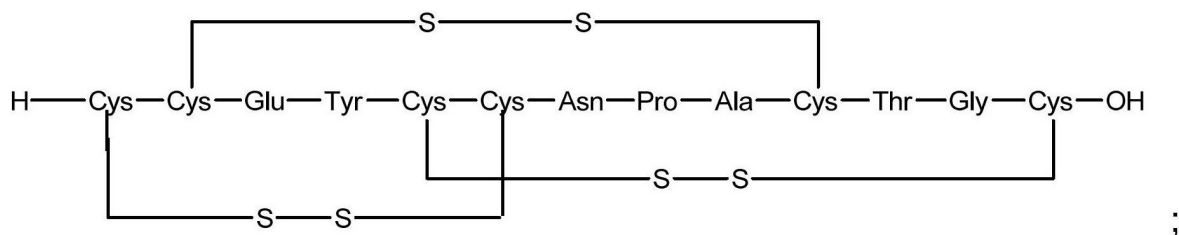


iii. 乙酰化肽 (“Cys¹-N-乙酰基”) 或其可药用盐, 其中所述肽包含以下氨基酸结构:



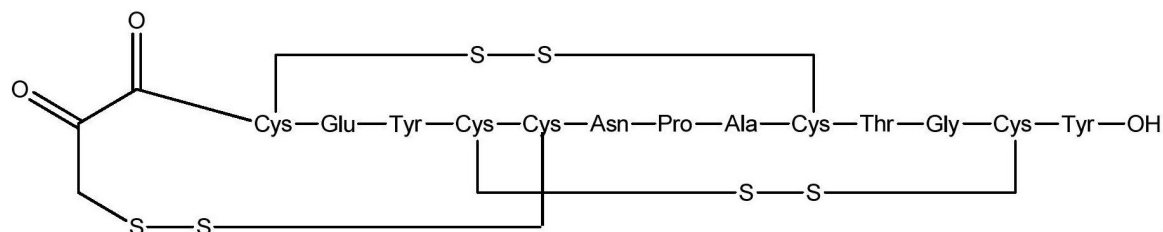
iv. 利那洛肽三硫化物肽或其可药用盐, 其中所述肽包含氨基酸序列Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr, 其中附加的硫原子可连接到六个半胱氨酰硫中的任一个上;

v. 肽 (“Des-Tyr¹⁴”) 或其可药用盐, 其中所述肽包含以下氨基酸结构:

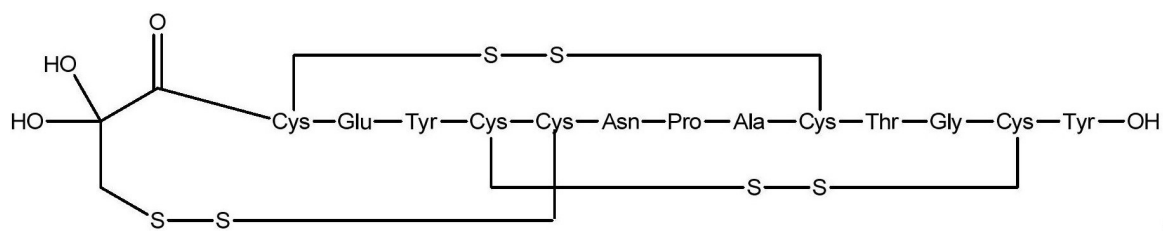


或者

vi. 肽 (Cys¹-α-酮) 或其可药用盐, 其中所述肽包含以下氨基酸结构:



[0060] 在一些实施例中, 肽Cys¹-α-酮可以以其水合形式或其可药用盐形式存在, 其中所述肽包含以下氨基酸结构:



本领域的技术人员会认识到,肽Cys¹-α-酮易于在其水合物与酮形式之间转化。

[0061] 在一些实施例中,肽Cys¹-α-酮占所述组合物重量不足约15%,占所述组合物重量不足约10%,占所述组合物重量不足约7%,占所述组合物重量不足约5%,占所述组合物重量不足约4%,占所述组合物重量不足约3%,占所述组合物重量不足约2%,占所述组合物重量不足约1.5%,或占所述组合物重量不足约1%。在其他示例性实施例中,肽Cys¹-α-酮占所述组合物重量约0.01%至约15%,占所述组合物重量约0.05%至约10%,占所述组合物重量约0.05%至约7%,或占所述组合物重量约0.05%至约5%。

[0062] 在一些实施例中,肽Cys¹-IMD占所述组合物重量不足约15%,占所述组合物重量不足约10%,占所述组合物重量不足约7%,占所述组合物重量不足约5%,占所述组合物重量不足约4%,占所述组合物重量不足约3.5%,占所述组合物重量不足约3%,占所述组合物重量不足约2%,或占所述组合物重量不足约1%。在其他示例性实施例中,肽Cys¹-IMD占所述组合物重量约0.01%至约15%,占所述组合物重量约0.05%至约10%,占所述组合物重量约0.05%至约7%,或占所述组合物重量约0.05%至约5%。

[0063] 在一些实施例中,水解肽(“Asp⁷”)占所述组合物重量不足约15%,占所述组合物重量不足约10%,占所述组合物重量不足约7%,占所述组合物重量不足约5%,占所述组合物重量不足约4%,占所述组合物重量不足约3.5%,占所述组合物重量不足约3%,占所述组合物重量不足约2%,或占所述组合物重量不足约1%。在其他示例性实施例中,水解肽(“Asp⁷”)占所述组合物重量约0.01%至约15%,占所述组合物重量约0.05%至约10%,占所述组合物重量约0.05%至约7%,或占所述组合物重量约0.05%至约5%。

[0064] 在一些实施例中,乙酰化肽(“Cys¹-N-乙酰基”)占所述组合物重量不足约15%,占所述组合物重量不足约10%,占所述组合物重量不足约7%,占所述组合物重量不足约5%,占所述组合物重量不足约4%,占所述组合物重量不足约3.5%,占所述组合物重量不足约3%,占所述组合物重量不足约2%,或占所述组合物重量不足约1%。在其他示例性实施例中,乙酰化肽(“Cys¹-N-乙酰”)占所述组合物重量约0.01%至约15%,占所述组合物重量约0.05%至约10%,占所述组合物重量约0.05%至约7%,或占所述组合物重量约0.05%至约5%。

[0065] 在一些实施例中,利那洛肽三硫化物肽占所述组合物重量不足约15%,占所述组合物重量不足约10%,占所述组合物重量不足约7%,占所述组合物重量不足约5%,占所述组合物重量不足约4%,占所述组合物重量不足约3.5%,占所述组合物重量不足约3%,占所述组合物重量不足约2%,或占所述组合物重量不足约1%。在其他示例性实施例中,利那洛肽三硫化物肽占所述组合物重量约0.01%至约15%,占所述组合物重量约0.05%至约10%,占所述组合物重量约0.05%至约7%,或占所述组合物重量约0.05%至约5%。

[0066] 在一些实施例中,肽Des-Tyr¹⁴占所述组合物重量不足约15%,占所述组合物重量不足约10%,占所述组合物重量不足约7%,占所述组合物重量不足约5%,占所述组合物重量不足约4%,占所述组合物重量不足约3.5%,占所述组合物重量不足约3%,占所述组合物重量不足约2%,或占所述组合物重量不足约1%。在其他示例性实施例中,肽Des-Tyr¹⁴占所述组合物重量约0.01%至约15%,占所述组合物重量约0.05%至约10%,占所述组合物重量约0.05%至约7%,或占所述组合物重量约0.05%至约5%。

[0067] 在一些实施例中,所述组合物包含利那洛肽和任何所需浓度的多聚体。在一些实

施例中,所述组合物包含少于10重量%的多聚体。在一些实施例中,所述组合物包含0.5重量%至1重量%的多聚体。

[0068] 在一些实施例中,所述组合物包含有效量的利那洛肽和任何所需量的还原形式利那洛肽。如本文所用,术语“还原形式利那洛肽”是指在半胱氨酸氨基酸之间没有二硫键的利那洛肽。在一些实施例中,所述组合物包含少于10重量%的还原形式利那洛肽。在一些实施例中,所述组合物包含0.5重量%至1重量%的还原形式利那洛肽。

[0069] 在一些实施例中,所述组合物包含有效量的利那洛肽和任何所需量的凑集形式(scrambled form)利那洛肽。如本文所用,术语“凑集形式利那洛肽”是指在Cys₁与Cys₁₀之间、Cys₁与Cys₁₃之间、Cys₁与Cys₅之间、Cys₁与Cys₂之间、Cys₂与Cys₆之间、Cys₂与Cys₁₃之间、Cys₂与Cys₅之间、Cys₅与Cys₆之间和/或Cys₅与Cys₁₀之间有二硫键的利那洛肽。在一些实施例中,所述组合物包含0.5重量%至1重量%的凑集形式利那洛肽。在一些实施例中,所述组合物包含少于10重量%的凑集形式利那洛肽。

[0070] 在一些实施例中,所述组合物的总降解物浓度小于约10重量%。在一些实施例中,所述组合物的总降解物浓度小于约8重量%。在一些实施例中,所述组合物的总降解物浓度小于约7重量%。在一些实施例中,所述组合物的总降解物浓度小于约6.5重量%。在一些实施例中,所述组合物的总降解物浓度小于约6重量%。在一些实施例中,所述组合物的总降解物浓度小于约5.5重量%。在一些实施例中,所述组合物的总降解物浓度小于约5重量%。在一些实施例中,所述组合物的总降解物浓度小于约4重量%。在一些实施例中,所述组合物的总降解物浓度小于约3重量%。在一些实施例中,所述组合物的总降解物浓度小于约2.5重量%。在一些实施例中,所述组合物的总降解物浓度小于约2重量%。在一些实施例中,所述组合物的总降解物浓度小于约1重量%。

[0071] 在一些实施例中,所述组合物可通过喷雾干燥制备,其中喷雾干燥是用于制备药物微粒(如微胶囊或微球)的技术。经喷雾干燥的肽在溶出时通常保留其生物活性,而且可具有有用的物理特征(包括均匀粒度和球体形状)。另外,由喷雾干燥制备的微粒通常是自由流动的,这有助于药物制造工艺(诸如形成片剂和填充胶囊)。喷雾干燥工艺还因为可易于按比例放大以便临床制造与商业制造而具有实用性。在一个实施例中,喷雾缓冲剂包含HCl、组氨酸、1.5%PVA和0.6%滑石。该配方可用于生产36μg至290μg之间的较低剂量范围。

[0072] 所述组合物在施用时会溶出,从而在胃肠道内的目标区域中释放利那洛肽。所述制剂可在由多种不同因素决定的时间段内释放利那洛肽。这些因素包括制剂的尺寸、利那洛肽的浓度,以及利那洛肽分散于整个制剂的方式。例如,通过改变制剂的厚度与表面积,可调节溶出速率。厚制剂的溶出速率将小于其他方面类似的薄制剂,因而可能需要施用高剂量利那洛肽。

[0073] 在一些实施例中,延迟释放组合物在目标pH条件下的崩解时间短于约60分钟。在一些实施例中,延迟释放组合物在目标pH条件下的崩解时间短于约30分钟。在一些实施例中,延迟释放组合物的崩解时间短于约25分钟。在一些实施例中,延迟释放组合物的崩解时间短于约20分钟。在一些实施例中,延迟释放组合物的崩解时间短于约15分钟。在一些实施例中,延迟释放组合物的崩解时间短于约10分钟。在一些实施例中,延迟释放组合物在进入目标环境后,在不到约30分钟内崩解。在一些实施例中,延迟释放组合物在进入目标环境后,在不到约25分钟内崩解。在一些实施例中,延迟释放组合物在进入目标环境后,在不到

约20分钟内崩解。在一些实施例中，延迟释放组合物在进入目标环境后，在不到约15分钟内崩解。

[0074] 在一些实施例中，延迟释放组合物在进入目标环境后60分钟内释放其中所含的利那洛肽的至少约75%。在一些实施例中，延迟释放组合物在进入目标环境后30分钟内释放其中所含的利那洛肽的至少约75%。在一些实施例中，延迟释放组合物在进入目标环境后30分钟内释放其中所含的利那洛肽的至少约80%。在一些实施例中，延迟释放组合物在进入目标环境后30分钟内释放其中所含的利那洛肽的至少约85%。在一些实施例中，延迟释放组合物在进入目标环境后30分钟内释放其中所含的利那洛肽的至少约90%。在一些实施例中，延迟释放组合物在进入目标环境后30分钟内释放其中所含的利那洛肽的至少约95%。在一些实施例中，延迟释放组合物在进入目标环境后30分钟内释放其中所含的利那洛肽的至少约99%。

[0075] 在一些实施例中，延迟释放组合物在进入目标环境后15分钟内释放其中所含的利那洛肽的至少约40%。在一些实施例中，延迟释放组合物在进入目标环境后15分钟内释放其中所含的利那洛肽的至少约50%。在一些实施例中，延迟释放组合物在进入目标环境后15分钟内释放其中所含的利那洛肽的至少约60%。在一些实施例中，延迟释放组合物在进入目标环境后15分钟内释放其中所含的利那洛肽的至少约70%。在一些实施例中，延迟释放组合物在进入目标环境后15分钟内释放其中所含的利那洛肽的至少约80%。在一些实施例中，延迟释放组合物在进入目标环境后15分钟内释放其中所含的利那洛肽的至少约85%。在一些实施例中，延迟释放组合物在进入目标环境后15分钟内释放其中所含的利那洛肽的至少约90%。在一些实施例中，延迟释放组合物在进入目标环境后15分钟内释放其中所含的利那洛肽的至少约95%。

[0076] 在一些实施例中，延迟释放组合物在进入目标环境后约2至约2小时之间，释放其中所含的利那洛肽的至少约80%。

[0077] 在一些实施例中，延迟释放组合物在接触大于5的pH后30分钟内释放其中所含的利那洛肽的至少约75%。在一些实施例中，延迟释放组合物在接触大于5的pH后30分钟内释放其中所含的利那洛肽的至少约80%。在一些实施例中，延迟释放组合物在接触大于5的pH后30分钟内释放其中所含的利那洛肽的至少约85%。在一些实施例中，延迟释放组合物在接触大于5的pH后30分钟内释放其中所含的利那洛肽的至少约90%。在一些实施例中，延迟释放组合物在接触大于5的pH后30分钟内释放其中所含的利那洛肽的至少约95%。在一些实施例中，延迟释放组合物在接触大于5的pH后30分钟内释放其中所含的利那洛肽的至少约99%。

[0078] 在一些实施例中，延迟释放组合物在接触大于7的pH后30分钟内释放其中所含的利那洛肽的至少约75%。在一些实施例中，延迟释放组合物在接触大于7的pH后30分钟内释放其中所含的利那洛肽的至少约80%。在一些实施例中，延迟释放组合物在接触大于7的pH后30分钟内释放其中所含的利那洛肽的至少约85%。在一些实施例中，延迟释放组合物在接触大于7的pH后30分钟内释放其中所含的利那洛肽的至少约90%。在一些实施例中，延迟释放组合物在接触大于7的pH后30分钟内释放其中所含的利那洛肽的至少约95%。在一些实施例中，延迟释放组合物在接触大于7的pH后30分钟内释放其中所含的利那洛肽的至少约99%。

[0079] 在一些实施例中,可通过将利那洛肽的IR组合物和DR组合物合并并在一种剂型中,来配制利那洛肽组合物。例如,可通过将IR微丸与DR微丸填充到一个胶囊内,来制备利那洛肽DR胶囊。视药物释放曲线的要求而定,这种胶囊内的IR微丸和DR微丸的量可从1重量%至99重量%变化。在一些实施例中,例如,DR胶囊包含至少约50%DR微丸,其余的是IR微丸。在一些实施例中,胶囊包含至少约55%DR微丸,其余的是IR微丸。在一些实施例中,胶囊包含至少约60%DR微丸,其余的是IR微丸。在一些实施例中,胶囊包含至少约65%DR微丸,其余的是IR微丸。在一些实施例中,胶囊包含至少约70%DR微丸,其余的是IR微丸。在一些实施例中,胶囊包含至少约75%DR微丸,其余的是IR微丸。在一些实施例中,胶囊包含至少约80%DR微丸,其余的是IR微丸。在一些实施例中,胶囊包含至少约85%DR微丸,其余的是IR微丸。在一些实施例中,胶囊包含至少约90%DR微丸,其余的是IR微丸。在一些实施例中,胶囊包含至少约92%DR微丸,其余的是IR微丸。在一些实施例中,胶囊包含至少约94%DR微丸,其余的是IR微丸。在一些实施例中,胶囊包含至少约96%DR微丸,其余的是IR微丸。在一些实施例中,胶囊包含至少约98%DR微丸,其余的是IR微丸。

[0080] 在一些实施例中,利那洛肽DR组合物被配制用于将利那洛肽递送到回肠、回肠末端或结肠。

[0081] 在一些实施例中,利那洛肽DR组合物被配制用于将利那洛肽递送到结肠。

[0082] 所述组合物可用于治疗响应于GC-C受体激动剂治疗的其他疾病、障碍或病症。所述组合物可用于治疗患者(如哺乳动物或人类)的任何胃肠疾病和/或病症,或者与此相关的炎症或疼痛。本发明的延迟释放组合物可用于治疗各种病症,但特别适用于治疗胃肠疾病,诸如肠易激综合征(“IBS”) (例如,伴有便秘的IBS(即“IBS-c”)、伴有腹泻的IBS(即“IBS-d”)、或伴有便秘和腹泻的混合型IBS(即“IBS-m”))、便秘(例如,慢性特发性便秘)、结肠癌、憩室炎、间质性膀胱炎,以及腹痛或内脏痛。

[0083] 适当的此类胃肠疾病和病症还包括但不限于肠易激综合征、伴有便秘的肠易激综合征、结肠癌、消化不良(包括功能性消化不良或非溃疡性消化不良)、胃肠动力障碍、功能性胃肠疾病、胃食管反流病(GERD)、克罗恩氏病、溃疡性结肠炎、炎性肠病、功能性烧心、胃轻瘫、慢性假性肠梗阻(或结肠假性梗阻),与便秘相关的疾病和病症例如慢性便秘、阿片类药物所致便秘、术后便秘(术后肠梗阻),以及与神经病变相关的便秘,或这些胃肠疾病和病症的症状的组合(诸如肠易激综合征与慢性便秘的组合)、与神经病变相关的便秘(例如,与帕金森氏病相关的便秘)、与囊性纤维化或甲状腺疾病相关的便秘。在一些实施例中,提供了用于治疗被诊断患有的一种或多种胃肠疾病或病症的患者(如哺乳动物或人类)的胃肠疾病的方法,其中该方法包括向该患者施用有效量的所述组合物。

[0084] 在一些实施例中,治疗胃肠疾病的方法包括向有需要的患者施用治疗有效量的本文所述组合物。所述胃肠疾病选自:肠易激综合征(IBS)、便秘、功能性胃肠疾病、胃食管反流病、功能性烧心、炎性肠病、消化不良、憩室炎疼痛、内脏痛或腹痛、前列腺炎、睾丸痛、腹腔炎症或内脏炎症、膀胱疼痛综合征、子宫内膜异位症、外阴痛或直肠疼痛。在一些实施例中,便秘为慢性便秘、特发性便秘、慢性特发性便秘、术后肠梗阻所致便秘、或使用阿片类药物引起的便秘。在其他实施例中,肠易激综合征为伴有便秘的肠易激综合征(IBS-c)、伴有腹泻的肠易激综合征(IBS-d)或混合型肠易激综合征(IBS-m)。

[0085] 在一些实施例中,提供了治疗疾病的方法,该方法包括向有需要的患者施用治疗

有效量的本文所述组合物。在一些实施例中,所述疾病是选自下列的癌症:结肠直肠/局部转移结肠直肠癌、肠息肉、巴雷特食道症、胃肠道癌、肺癌、上皮细胞癌或癌前期生长或转移性生长、息肉、乳腺癌、结肠直肠癌、肺癌、卵巢癌、胰腺癌、前列腺癌、肾癌、胃癌、膀胱癌、肝癌、食道癌、睾丸癌。

[0086] 在一些实施例中,提供了用于在有需要的患者中预防胃肠道癌或增生或者预防胃肠道癌或增生复发的方法,该方法包括向该患者施用有效量的所述组合物或口服剂型。在一些实施例中,癌或增生为结肠直肠癌、肠息肉或胃肠上皮细胞的癌前期生长或转移性生长。在一些实施例中,所述组合物或口服剂型与有效量的COX-2抑制剂同时施用或循序施用。高度选择性COX-2抑制剂和选择性COX-2抑制剂的例子包括依托考昔、罗非考昔、鲁米考昔、伐地考昔、塞来考昔(Celebrex[®])、舒林酸、双氯芬酸、美洛昔康和依托度酸。抑制COX-2的非选择性NSAID包括萘普生、布洛芬、水杨酸钠和二氟尼柳。如本文所用,术语“预防”或“防止”意指相比未用本文所述组合物治疗过的患者,阻止、延缓癌或增生的发作(即,延长疾病有临床表现之前的时间)或复发,并且/或者降低患上癌或增生的风险。

[0087] 在一些实施例中,提供了用本文所述的组合物和口服剂型治疗小儿患者的胃肠疾病的方法。在一些实施例中,提供了用于治疗被诊断患有的一种或多种胃肠疾病或病症的小儿患者的胃肠疾病的方法,其中该方法包括向该患者施用有效量的所述组合物或口服剂型。在一些实施例中,提供了使用所述组合物和口服剂型治疗胃肠疾病的方法,所述胃肠疾病包括但不限于胃肠动力障碍、肠易激综合征、便秘为主型肠易激综合征(IBS-c)、混合型肠易激综合征(IBS-m)、慢性便秘、慢性特发性便秘、阿片类药物所致便秘、术后便秘(术后肠梗阻)、与神经病变相关的便秘、与囊性纤维化或甲状腺疾病相关的便秘、消化不良(包括功能性消化不良或非溃疡性消化不良)、胃轻瘫、胃肠动力障碍、功能性胃肠疾病、胃食管反流病(GERD)、炎症肠病、克罗恩氏病、溃疡性结肠炎、功能性烧心、慢性假性肠梗阻(或结肠假性梗阻)、内脏痛、腹痛、骨盆痛、肛裂疼痛、与外阴痛相关的疼痛、与子宫内膜异位症相关的疼痛、与纤维肌痛相关的疼痛、功能性腹痛、间质性膀胱炎疼痛、憩室炎、与憩室炎相关的疼痛,以及与腹型口炎性腹泻相关的疼痛。在一些实施例中,提供了用本文所述的组合物和口服剂型治疗小儿患者的IBS-c、IBS-m或慢性便秘(如慢性特发性便秘)的方法。在一些实施例中,提供了在有需要的小儿患者中治疗IBS-c的方法。在一些实施例中,提供了在有需要的小儿患者中治疗慢性特发性便秘的方法。

[0088] 在一些实施例中,用于治疗或缓解疼痛的方法包括向有需要的患者施用治疗有效量的本文所述组合物。在一些实施例中,所述疼痛选自内脏痛;腹痛;骨盆痛;或与下列相关的疼痛:胃肠疾病、性病、膀胱疼痛综合征、憩室炎疼痛、前列腺炎、睾丸痛、子宫内膜异位症、外阴痛、直肠疼痛或间质性膀胱炎。在一些实施例中,所述疼痛选自骨盆痛、与直肠炎相关的疼痛、肛裂疼痛、与外阴痛相关的疼痛、与子宫内膜异位症相关的疼痛、与纤维肌痛相关的疼痛、功能性腹痛、间质性膀胱炎疼痛、与性病相关的疼痛、憩室炎、与憩室炎相关的疼痛,以及与腹型口炎性腹泻相关的疼痛。

[0089] 在另一个实施例中,所述方法用于在有需要的患者中提高肠动力,包括向该患者施用有效量的所述组合物。肠动力涉及胃、小肠、结肠和直肠的自发协调舒张(dissention)和收缩,作用是在消化过程中运送食物通过胃肠道。在一些实施例中,所述疾病为术后肠梗阻或使用阿片类药物引起的便秘。

[0090] 在示例性实施例中,所述方法可包括向有需要的患者施用治疗有效量的所述药物组合物。为实现受试对象的期望结果(诸如期望的治疗和/或症状缓解)所需的包含利那洛肽或其可药用盐的组合物的有效量取决于若干公知的因素,诸如待治疗疾病的类别和严重程度,以及待治疗患者的年龄、体重,等等。

[0091] 在一些实施例中,所述组合物或口服剂型作为片剂、胶囊或小药囊施用给有需要的小儿患者。在一些实施例中,打开装有所述组合物的小药囊,将内容物撒在食物(诸如苹果酱)上或搅拌进食物(诸如苹果酱)中,或者搅拌进饮料(诸如水)中。在一些实施例中,用流体(诸如水)送服整粒胶囊,或打开胶囊将内容物撒在食物上、或搅拌进食物或饮料中。片剂可被整个吞下,可被压碎并搅拌进食物或饮料中,或者可被配制成咀嚼片。

[0092] 所述药物组合物的施用是其疾病或障碍的有效治疗方案的受试对象或患者优选地是人类,但也可用于任何动物,包括临床试验、筛选实验或活性实验背景下的试验动物。因此,本领域普通技术人员容易理解,本文所述的方法、化合物和组合物特别适用于施用给任何动物(尤其是哺乳动物),包括但不限于人类、啮齿动物和非啮齿动物(诸如猫科或犬科受试对象)、农畜(诸如但不限于牛科、马科、山羊、绵羊和猪科受试对象)、野生动物(不论是生活在野外、还是在动物园里)、研究动物(诸如小鼠、大鼠、兔、山羊、绵羊、猪、狗、猫等)、禽类物种(诸如鸡、火鸡、鸣禽等)例如用于兽医医疗应用的禽类物种。

[0093] 在一些实施例中,利那洛肽组合物可被配制为经直肠施用的直肠剂型。直肠剂型包括但不限于直肠栓剂、直肠泡沫剂或气雾剂、灌肠剂、直肠凝胶剂和直肠软膏剂。在一些实施例中,直肠剂型可施用给有需要的患者。在一些实施例中,直肠剂型可施用给患者以治疗腹痛或直肠疼痛,源自肛裂、溃疡性结肠炎、克罗恩氏病或炎性肠病的疼痛。在一些实施例中,直肠剂型可施用给小儿患者或老年患者。

[0094] 在一些实施例中,利那洛肽的成人有效剂量范围为每天口服25 μ g至6mg。在一些实施例中,剂量范围为每天口服15 μ g至2mg。在一些实施例中,成人剂量范围为每天口服50 μ g至1mg(例如,15 μ g、36 μ g、50 μ g、72 μ g、100 μ g、145 μ g、150 μ g、200 μ g、250 μ g、290 μ g、300 μ g、350 μ g、400 μ g、450 μ g、500 μ g、550 μ g、579 μ g、600 μ g、650 μ g、700 μ g、750 μ g、800 μ g、850 μ g、900 μ g、950 μ g或1mg)。在一些实施例中,成人剂量范围为每天口服36 μ g至290 μ g。在一些实施例中,剂量范围为每天口服100 μ g至600 μ g。在一些实施例中,剂量为每天口服50 μ g、100 μ g、150 μ g、200 μ g、300 μ g、400 μ g、500 μ g或600 μ g利那洛肽。在一些实施例中,剂量为每天口服50 μ g利那洛肽。在一些实施例中,剂量为每天口服100 μ g利那洛肽。在一些实施例中,剂量为每天口服145 μ g利那洛肽。在一些实施例中,剂量为每天口服200 μ g利那洛肽。在一些实施例中,剂量为每天口服290 μ g利那洛肽。在一些实施例中,剂量为每天口服400 μ g利那洛肽。在一些实施例中,剂量为每天口服500 μ g利那洛肽。在一些实施例中,剂量为每天口服600 μ g利那洛肽。

[0095] 在一些实施例中,利那洛肽的小儿有效剂量范围为每天口服0.05 μ g至2mg。在一些实施例中,利那洛肽的小儿有效剂量范围为每天口服0.05 μ g至100 μ g。在一些实施例中,利那洛肽的小儿有效剂量范围为每天口服0.1 μ g至90 μ g。在一些实施例中,利那洛肽的小儿有效剂量范围为每天口服0.1 μ g至50 μ g。在一些实施例中,利那洛肽的小儿有效剂量范围为每天口服0.1 μ g至25 μ g。在一些实施例中,利那洛肽的小儿有效剂量范围为每天口服0.1 μ g至10 μ g。在一些实施例中,利那洛肽的小儿有效剂量范围为每天口服0.1 μ g至5 μ g。在一些实施例中,利那洛肽的小儿有效剂量范围为每天口服0.1 μ g至1 μ g。在一些实施例中,利那洛肽的

小儿有效剂量范围为每天口服0.1 μ g至0.5 μ g。在一些实施例中,利那洛肽的小儿有效剂量范围为每天口服0.1 μ g。在一些实施例中,利那洛肽的小儿有效剂量范围为每天口服0.15 μ g。在一些实施例中,利那洛肽的小儿有效剂量范围为每天口服0.25 μ g。在一些实施例中,利那洛肽的小儿有效剂量范围为每天口服0.5 μ g。在一些实施例中,利那洛肽的小儿有效剂量范围为每天口服3.5 μ g。在一些实施例中,利那洛肽的小儿有效剂量范围为每天口服15 μ g。在一些实施例中,利那洛肽的小儿有效剂量范围为每天口服36 μ g。在一些实施例中,利那洛肽的小儿有效剂量范围为每天口服45 μ g。在一些实施例中,利那洛肽的小儿有效剂量范围为每天口服60 μ g。在一些实施例中,利那洛肽的小儿有效剂量范围为每天口服90 μ g。在一些实施例中,单位剂型等于日剂量。

[0096] 在一些实施例中,单位剂型在当天任何时间随食物一同施用、在当天任何时间不随食物一同施用,或在整夜禁食后随食物一同施用(例如,随早餐一同施用)。在一些实施例中,单位剂型一天施用一次、一天施用两次或一天施用三次。在一些实施例中,一份、两份或三份单位剂型将包含口服日剂量的利那洛肽。判断施用给患者的化合物的精确量将是主治医师的责任。然而,所用剂量将取决于多种因素,包括患者的年龄和性别、待治疗的确切疾病及其严重程度。

[0097] 在一些实施例中,所述组合物作为单一疗法施用。在一些实施例中,所述组合物基本上由有效量的利那洛肽组成。在一些实施例中,所述组合物由有效量的利那洛肽组成。

[0098] 在一些实施例中,所述组合物直接施用给患者,例如以延迟释放片剂或延迟释放胶囊的形式施用。在一些实施例中,所述组合物先溶出、崩解并且/或者混合于食物或饮料之上或之内,再施用给患者(如老年患者或小儿患者)。在一些实施例中,所述组合物先溶出或崩解于任选包含稳定剂、防腐剂、甜味剂等物质的液体、溶液或流体中,再施用给患者(如老年患者或小儿患者)。在一些实施例中,所述组合物为多剂量组合物,也就是说,包含两份、三份、五份、七份、十份、十五份、二十份、二十五份、三十份、四十份、五十份、六十份、七十份、八十份、九十份或更多份日剂量的利那洛肽。

[0099] 在其他实施例中,所述组合物作为联合疗法的一部分施用。例如,组合物可与其他药物或疗法联合使用,所述其他药物或疗法用于治疗、预防、抑制和/或缓解本发明化合物可对其起作用的疾病或病症。利那洛肽可与其他药物共同施用或共同配制。在一个实施例中,利那洛肽组合物可与用于治疗胃肠疾病的其他药物共同施用,所述其他药物包括但不限于抑酸剂,诸如组胺-2受体激动剂(H2A)和/或质子泵抑制剂(PPI)。在一个实施例中,利那洛肽组合物可与用于治疗胃肠疾病的其他药物共同施用,所述其他药物包括5-ASA(诸如美沙拉嗪)。

[0100] 此类其他药物可按此前常用的途径和量,与本发明化合物同时施用或循序施用。在同时使用本发明化合物与一种或多种其他药物时,可采用除该本发明化合物之外还包含此类其他药物的药物单位剂型。因此,本发明的药物组合物包括除了包含本发明化合物之外还包含一种或多种其他活性组分的那些组合物。

[0101] 可使用若干方法来评价利那洛肽组合物的生物活性,包括但不限于免疫测定法(如酶联免疫吸附测定法)、放射免疫测定法、免疫放射测定法、凝胶电泳法(如SDS-PAGE)、高效液相色谱法(HPLC)和/或高效毛细管电泳法(HPCE)。在一些实施例中,采用包括下列步骤的方法来评估所述组合物的生物活性:固定利那洛肽,将利那洛肽与鸟苷酸环化酶C

(GCC)一起温育,将GCC结合的利那洛肽与抗GCC的抗体一起温育,将GCC抗体结合的利那洛肽与抗GCC抗体的荧光标记抗体一起温育,然后通过使用读板机测量荧光强度来检测结合于GCC抗体的利那洛肽。随后可根据溶液的荧光读数来计算药物浓度。

[0102] 例如,可使用以下方法(但也可使用其他方法)评估和定量利那洛肽组合物的生物活性。将所述组合物加入装有60ml磷酸盐缓冲剂(pH为4.5)的容量瓶中,振摇容量瓶60分钟。然后取出0.2ml上清液,加入涂有GC-C受体的96孔板的一个或多个孔中。将板密封,37℃下温育2小时。温育结束后,取出样品,用磷酸盐缓冲盐水(PBS)对板进行洗涤。然后将结合的利那洛肽与标记有异氰酸荧光素(FITC)的GC-C(诸如购自西格玛奥德里奇股份有限公司(Sigma-Aldrich Inc.))一同置于封闭缓冲液中,室温下温育1小时。温育后,用PBS洗涤各孔。例如使用读板机,检测最终产物的荧光强度。然后根据溶液的荧光读数来计算利那洛肽浓度。

定义

[0103] 如本文所用,术语“延迟释放”除非另外指明,否则是指所述组合物在胃肠道的目标区域内溶出、融化、崩解、液化等,使得基本上所有利那洛肽不再留存于制剂、组合物或剂型中。延迟释放组合物包括持续释放组合物、胃内滞留组合物、靶向释放组合物(例如,结肠释放组合物或靶向回盲瓣的组合物等)、延长释放组合物和/或这些组合物的组合。

[0104] 如本文所用,术语“延迟释放组合物”(“DR”)除非另外指明,否则是指所述组合物是在口服施用后不立即释放利那洛肽而在之后的其他时间释放利那洛肽的剂型。

[0105] 如本文所用,术语“延长释放组合物”除非另外指明,否则是指所述组合物是在施用后的一段延长时间内释放利那洛肽的剂型。这使得给药频率比速释组合物低。

[0106] 如本文所用,“崩解”和“释放”除非另外指明,否则在本文中是指包含利那洛肽的胶囊、膜、微丸或片剂在口腔环境中溶出、融化、崩解、液化等,使得基本上所有利那洛肽不再留存于制剂形式中(例如,pH高于5或7)或磷酸盐缓冲溶液中,并保持在 $37 \pm 1^\circ\text{C}$ 。

[0107] 术语“从……释放”在涉及利那洛肽从所述组合物释放时,除非另外指明,否则在本文中是指利那洛肽不再留存于组合物形式中。

[0108] 如本文所用,术语“进入目标环境”除非另外指明,否则是指所述组合物接触患者体内的目标器官或其区段,或患者体内打算让利那洛肽在其中释放的一段胃肠道(例如pH高于5或7)。

[0109] 如本文所用,术语“下胃肠道(GI)”除非另外指明,否则是指胃肠道的远段,例如回肠、回肠末端、回盲瓣或结肠。

[0110] 如本文所用,术语“上胃肠道(GI)”除非另外指明,否则是指胃肠道的近段,例如胃、十二指肠和/或空肠。

[0111] 如本文所用,术语“稳定剂”除非另外指明,否则是指以起稳定作用的量加入所述组合物中的聚合物、空间位阻伯胺(如氨基酸)或阳离子(如金属阳离子)组分。例如,聚合物稳定剂是以起稳定作用的量加入所述组合物中的聚合物。相似地,空间位阻伯胺稳定剂是以起稳定作用的量加入所述组合物中的空间位阻伯胺。此外,阳离子稳定剂是以起稳定作用的量加入所述组合物中的阳离子。

[0112] 如本文所用,“起稳定作用的量”除非另外指明,否则是指所述组合物内聚合物、空间位阻伯胺(如氨基酸)或金属阳离子组分的这样的浓度,在该浓度下,该组分使组合物中

利那洛肽的稳定性相比不含起稳定作用的量的同一组分的类似组合物提高。

[0113] 如本文所用,术语“基本上所有”除非另外指明,否则是指至少约90%,例如至少约95%,或者甚至至少约99%。

[0114] 如本文所用,术语“分离和纯化的”除非另外指明,否则是指纯度至少为95%(例如,纯度至少为96%、至少为97%、至少为98%,或者甚至至少为99%),其中纯度例如由使用HPLC测得的色谱纯度衡量。

[0115] 如本文所用,“治疗有效量”除非另外指明,否则是指将在将利那洛肽或其可药用盐施用于哺乳动物以便治疗病况、疾病或病症时,利那洛肽或其可药用盐的足以实现治疗(如下文所定义)的量。“治疗有效量”将视化合物、疾病及其严重程度以及待治疗的哺乳动物的年龄、性别、体重、身体状况和响应性而变化。例如,利那洛肽或其可药用盐或水合物的治疗有效量可为能有效治疗胃肠疾病的量,所述胃肠疾病包括肠易激综合征、便秘为主型肠易激综合征、慢性便秘、阿片类药物所致便秘和/或消化不良。

[0116] 如本文所用,“可药用”除非另外指明,否则是指对于动物或人类活体内的应用来说,在生物学或药理学上是相容的,优选地是指已获得联邦政府或州政府的管理机构批准或已载入美国药典或其他公认的药典,可用于动物,更具体而言可用于人体。

[0117] 如本文所用,术语“治疗”除非另外指明,否则在本文中用来指缓解、减轻、预防和/或管理受试对象所患疾病的至少一种症状,所述疾病包括例如胃肠疾病,诸如肠易激综合征、便秘为主型肠易激综合征、慢性便秘、阿片类药物所致便秘、消化不良或这些疾病的症状的组合。在本发明的含义内,术语“治疗”也表示阻止、延缓疾病发作(即,延长疾病有临床表现之前的时间),并且/或者降低患上疾病或疾病恶化的风险。术语“治疗”还用来指与如上所定义的术语“治疗”对应的行为。

[0118] 如本文所用,术语“添加剂”除非另外指明,否则是指可药用的添加剂。可药用的添加剂包括但不限于粘结剂、崩解剂、分散添加剂、润滑剂、助流剂、抗氧化剂、包衣添加剂、稀释剂、表面活性剂、调味添加剂、保湿剂、促吸收添加剂、控释添加剂、防结块添加剂、抗微生物剂(如防腐剂)、着色剂、干燥剂、增塑剂和染料。

[0119] 如本文所用,“赋形剂”除非另外指明,否则是指任何可药用的添加剂、填充剂、粘结剂或物质。

[0120] 如本文所用,“应激条件”除非另外指明,否则是指40℃和75%相对湿度(RH)。

[0121] 如本文所用,术语“约”和“大约”除非另外指明,否则是指本领域普通技术人员所确定的特定值的可接受误差范围,该可接受误差范围将部分取决于该特定值的测量或测定方式,也就是测量系统的局限性。例如,根据本领域的实践,“约”可意指在1个标准偏差或超过1个标准偏差的范围内。作为另一种选择,与所述组合物有关的“约”可意指加上或减去最多20%、优选最多10%的范围。作为另一种选择,尤其是与生物体系或生物过程有关的术语“约”,可意指处于数值的数量级内,优选处于数值的5倍范围内,更优选处于数值的2倍范围内。本申请和权利要求书中描述的具体数值,除非另有说明,否则术语“约”意指在该具体数值的可接受误差范围内。

[0122] 除非另外指明,否则本文中引用的所有重量百分比(即,“重量%”和w/w)都是相对于药物组合物的总重量测得的。

[0123] 术语“基本上由……组成”及其变型形式在用于指涉组合物时,在本文中用来指所

述组合物包含利那洛肽和其他所需的不具药物活性的添加剂、赋形剂和/或组分(例如,聚合物、空间位阻伯胺、阳离子、填充剂、粘结剂、载体、赋形剂、稀释剂、崩解添加剂、润滑剂、溶剂、分散剂、包衣添加剂、促吸收添加剂、水解产物、甲醛亚胺产物、氧化产物、乙酰化产物、脱酰胺产物、多聚体、控释添加剂、防结块添加剂、抗微生物添加剂、防腐剂、增甜添加剂、着色剂、调味剂、干燥剂、增塑剂、染料等),而且不包含其他活性药物成分。

实例

[0124] 以下实例仅仅是举例说明本发明,不应理解为以任何方式限制本发明的范围,因为在阅读本公开内容后,被本发明所涵盖的许多变型形式和等同形式对于本领域技术人员将变得显而易见。

[0125] 使用几种配制方法来将利那洛肽靶向下胃肠道。(i) 可将包含pH敏感性聚合物包衣的肠溶性包衣微丸施加于微丸芯,所述微丸芯已包被有利那洛肽并可能包被有底包衣。可将这些微丸进一步填充到胶囊中,以实现所需的单位剂量强度。(ii) 具有含单位剂量利那洛肽的速释片剂芯的肠溶性包衣片剂可用仅在肠远段的pH条件下才溶出的包衣进行包被,使得利那洛肽将在下胃肠道中释放。(iii) 可将肠溶性包衣施加于明胶或HPMC胶囊,使得胶囊仅在下胃肠道中崩解和溶出。可将载有利那洛肽的微丸或片剂填充到胶囊中,以实现延迟释放。(iv) 另外,将速释微丸填充到适当的剂量强度,其中胶囊壳由肠溶性聚合物材料制成。该肠溶性胶囊壳可原样使用,或可用pH敏感性聚合物进一步包被,以实现所需的pH释放曲线和释放部位。

[0126] 利那洛肽或其可药用盐可使用本领域已知的标准技术制备和纯化,例如,使用标准技术进行化学合成或重组表达,然后进行纯化。

[0127] 用于微丸的利那洛肽包衣溶液的制备:将大约32g至42g纯化水与盐酸混合,以形成pH介于1.5与2.0之间的溶液。将阳离子(如果使用的话)以一定量加入溶液中以提供所需的浓度,并且将溶液混合足够的时间以产生澄清的溶液。将空间位阻伯胺(如果使用的话)以一定量加入溶液中以提供所需的浓度,并且将溶液混合足够的时间以产生澄清的溶液。然后根据需要加入其他添加剂,诸如抗氧化剂。测试溶液的pH,并视需要加入盐酸以产生pH介于1.5与2.0之间的溶液。然后将粘结剂加入溶液中,接着将混合物搅拌足够的时间以获得澄清的溶液。将所需量的利那洛肽加入溶液中,并混合30至100分钟以提供包衣溶液。

[0128] 在一个实施例中,包衣溶液包含利那洛肽、组氨酸、1.5%PVA和0.6%滑石。该配方可用于产生36至290 μ g之间的剂量范围。

[0129] 活性微丸的制备:将大约30至36g干燥微晶纤维素微丸加入微型柱流化床包衣机(Mini Column Fluid Bed Coater)中。在微晶纤维素微丸进行层积之前,对微晶纤维素微丸进行流化和加热。接下来,将包衣溶液层积到微丸上。通过控制入口温度、喷雾速率、雾化压力和空气体积,将喷雾温度控制在24 $^{\circ}$ C至55 $^{\circ}$ C之间。将全部包衣溶液层积到微丸上后,干燥微丸。该过程的产物被称为活性微丸。

[0130] 具有保护性包衣的活性微丸的制备:将大约35g活性微丸加入微型柱流化床包衣机中。先对活性微丸进行流化和加热,然在用Aquacoat[®](例如,Aquacoat[®]乙基纤维素水分散体,15%w/w,FMC生物聚合物公司(FMC Biopolymer),ECD-30)、Eudragit[®](例如,Eudragit[®] E PO PE-EL,Roehm药用聚合物公司(Roehm Pharma Polymers))或Opadry[®](例

如, Opadry® AMB分散体, 20%w/w, 卡乐康公司 (Colorcon)) 进行包被。接下来, 将包衣溶液层积到微丸上。通过控制入口温度、喷雾速率、雾化压力和空气体积, 将喷雾温度控制在24℃至55℃之间。将全部包衣溶液层积到微丸上后, 干燥微丸。

实例1

延迟释放利那洛肽微丸

[0131] 延迟释放微丸可以几种方式制造:

A. 肠溶性包衣微丸

[0132] 延迟释放微丸包含可被设计成耐受胃中的低pH, 而仅在下胃肠道的pH (pH>5) 下快速分解并释放活性利那洛肽的包衣。该类别的功能性聚合物包括: 丙烯酸甲酯-甲基丙烯酸共聚物 (例如, Eudragit®)、醋酸纤维素琥珀酸酯 (CAS)、羟丙基甲基纤维素邻苯二甲酸酯 (HPMCP)、醋酸羟丙基甲基纤维素琥珀酸酯 (HPMCAS)、聚醋酸乙烯邻苯二甲酸酯 (PVAP)、甲基丙烯酸甲酯-甲基丙烯酸共聚物、海藻酸钠和硬脂酸、瓜尔胶以及卡波姆。

[0133] 肠溶性包衣溶液/悬浮液可包含肠溶聚合物, 或者增塑剂、润湿材料、抗结块剂和(水性的或有机的) 稀释剂的组合。通常将增塑剂加入聚合物包衣中以促进膜包衣形成。可先将底包衣施加于利那洛肽层积微丸上, 然后施加肠溶性包衣, 以将利那洛肽与肠溶性聚合物分隔开, 从而改善稳定性。

实例2

包被Eudragit®FS30D的DR利那洛肽微丸

表1利那洛肽微丸芯组合物

编号	名称	重量百分比%	重量/批次(克)
1	利那洛肽*	0.06	16.1
2	PVA	1.00	250
3	氯化钙	0.32	80
4	组氨酸	0.68	170
5	MCC微丸	97.48	24,370
6	滑石, Imperial	0.5	125
7	纯化水*	95.56	13,000
8	盐酸	适量	--
	总干重	100.04	25,011.1

表2包被Eudragit®FS30D的利那洛肽延迟释放微丸组合物

编号	名称	重量百分比%	量/批(g)
1	利那洛肽层积微丸	75.19	1000
2	Eudragit® FS 30D	22.56	1000
3	PlasACRYL™	2.25	150
4	纯化水*	-	500
	总干重	100	1330

*在包被过程中去除水

制造工艺:

A. 包衣溶液的制备

[0134] 微丸包被从包衣溶液的制备开始。称取PlasACRYL™放入容器中,并用立式混合器对其进行搅拌。称取Eudragit®FS30D,并一边搅拌一边将其缓慢加入PlasACRYL™容器中。称取纯化水,并一边搅拌一边将其缓慢加入PlasACRYL™/Eudragit®悬浮液中。将悬浮液混合10分钟,然后使其通过0.5mm筛子。由此制得的聚合物悬浮液就可用于微丸包被。

B. 微丸包被

[0135] 将Wurster流化床升温至40℃。称取利那洛肽微丸芯,并加入Wurster中。将微丸升温至35℃。在保持温度为28℃至32℃、雾化空气压力为3巴的同时,用Eudragit®FS 30D悬浮液进行微丸包被。包被结束时,将排出的微丸放入空气循环的烘箱中,在40℃下干燥2小时。

实例3

具有PVP底包衣且包被Eudragit®FS30D的延迟释放利那洛肽微丸

表3具有PVP底包衣且包被Eudragit®FS30D的利那洛肽延迟释放微丸组合物

编号	名称	重量百分比%	量/批(g)
1	利那洛肽层积微丸	72.46	1000
2	聚乙烯吡咯烷酮(PVP k30)	3.62	50
3	Eudragit® FS 30D	21.74	1000
4	PlasACRYL™	2.17	150
5	纯化水*	-	1500
	总干重	100	1380

制造工艺:

A. 底包衣溶液的制备

[0136] 在容器中,称取1000g纯化水,并一边搅拌一边将其加入预先称取的PVP中。混合该溶液直至澄清。

B. 使微丸包被底包衣

[0137] 将Wurster流化床升温至60℃。称取利那洛肽微丸芯,并加入Wurster中。先将微丸升温至50℃,然后开始微丸包被。在包被期间,将产品温度控制在45℃至50℃。完成包被后,将微丸在45℃至50℃的产品温度下干燥30分钟。

C. Eudragit®FS30D包被

[0138] 实例1提供了包被Eudragit®FS30D的利那洛肽微丸的制造步骤。

[0139] 可用作底包衣的材料包括聚合物(诸如聚乙烯醇(PVA)、聚乙烯吡咯烷酮(PVP)、羟丙甲纤维素(HPMC)、羟丙基纤维素(HPC)、甲基纤维素)、淀粉、明胶、糊精、麦芽糖糊精、泊洛

沙姆、聚右旋糖、虫胶、壳聚糖、藻酸盐、果胶、聚乙二醇、瓜尔胶、白蛋白,以及糖类(诸如甘露醇、乳糖、异麦芽酮糖醇、山梨醇、木糖醇、麦芽糖醇、蔗糖、海藻糖、果糖、葡萄糖、右旋糖、赤藓醇、三氯蔗糖等),或它们的组合。底包衣在微丸配方中的含量在1重量%至60重量%范围内变化。

实例4

包被Acryl-EZE[®] (Eudragit[®] L100-55)的利那洛肽微丸

表4包被Acryl-EZE[®]的利那洛肽延迟释放(DR)微丸组合物

编号	成分	重量(克)	重量%
1	利那洛肽	5.87	0.24
2	GalenIQ [™] 980	1930	78.4
3	亮氨酸	13.7	0.56
4	二水氯化钙	30.8	1.25
5	Kollidon [®] 30 LP	20	3.25
6	Acryl-Eze [®] (Eudragit [®] L100)	1600	16.3
7	0.01N HCl	适量	--
8	纯化水*	适量	--
	总计	3600.37	100.0

*在包被过程中去除水

制造工艺:

A. PVP溶液的制备

[0140] 在不锈钢广口瓶中,称取2000g水。一边搅拌一边加入PVP。混合该溶液直至澄清。称取亮氨酸和氯化钙,并一边搅拌一边将其加入PVP溶液中。混合该溶液直至澄清。将该溶液调节至pH 2,然后加入利那洛肽,并混合直至再次获得澄清溶液。

B. Acryl-EZE[®]悬浮液的制备

[0141] 在不锈钢广口瓶中,称取8000g蒸馏水。称取Acryl-EZE[®]并加入水中。用立式混合器将悬浮液混合20分钟。使悬浮液通过#60目筛网。

C. 包被

[0142] 称取异麦芽酮糖醇微丸并加入升温至50℃的Wurster流化床中。开始喷射药物溶液,产品温度在40℃左右。完成喷射药物溶液后,干燥微丸30分钟,产品温度在40℃左右。开始喷射Acryl-EZE[®]包衣,保持产品温度为约30℃。Acryl-EZE[®]包被结束时,干燥微丸30分钟,产品温度为约30℃。

包被Acryl-EZE[®]的利那洛肽DR微丸的溶出

微丸	0.1 N HCl	醋酸盐缓冲液, pH 4.5	磷酸盐缓冲液, pH 7.4
BN0005656B (40%增重率)	未检测*	79.9	86.58
BN0005656B (50%增重率)	未检测	79.47	87.09
BN0005656B (60%增重率)	未检测	79.97	88.19

[0143] 为了在不同肠道pH中实现药物溶出,可将Acryl-EZE[®] (Eudragit[®] L100-55,在高于5.5的pH下溶出) 替换为其他甲基丙烯酸酯聚合物,诸如Eudragit[®] L(在pH 6下溶出)、Eudragit[®] S和Eudragit[®] FS30D(在pH7下溶出) 或它们的组合。例如, (i) 形式1: 使用包被Acryl-EZE[®] 的微丸,在pH>5.5下实现药物溶出; (ii) 形式2: 使用具有Eudragit[®] L/S (50:50) 的包衣,在pH>6.5下实现药物释放; (iii) 形式4: 用Eudragit[®] FS30D包被微丸,在pH 7下实现药物释放。另外,可将这些类型的微丸中的两种或更多种放入胶囊中,以在胃肠道的不同区域提供脉冲给药。例如,在一个胶囊中,将DR微丸与形式1的微丸组合,或使用形式1和形式2的微丸的组合,或形式2和形式3的微丸的组合,或形式1、形式2和形式3的微丸的组合等。

实例5

包被HPMCAS的利那洛肽DR微丸

表5包被HPMCAS的利那洛肽延迟释放 (DR) 微丸组合物

编号	名称	重量百分比%	量/批(g)
1	利那洛肽层积微丸	75.3	1000
2	Aquacoat [®] AS-LG (HPMCAS)	15.06	200
3	柠檬酸三乙酯	4.43	58.8
4	滑石	4.74	63
5	月桂基硫酸钠	0.47	6.3
6	纯化水*	-	3000
	总干重	100	1328.1

实例6

包被乙基纤维素的利那洛肽DR微丸

表6包被乙基纤维素的利那洛肽延迟释放 (DR) 微丸组合物

编号	名称	重量百分比%	量/批(g)
1	利那洛肽层积微丸	75.3	1000
2	乙基纤维素	15.06	200
3	柠檬酸三乙酯	4.43	58.8
4	滑石	4.74	63
5	月桂基硫酸钠	0.47	6.3

6	纯化水*	—	3000
	总干重	100	1328.1

[0144] 同样,可用其他肠溶性聚合物(诸如,醋酸纤维素邻苯二甲酸酯(CAP)、醋酸纤维素偏苯三酸酯(CAT)、醋酸纤维素琥珀酸酯(CAS)、聚醋酸乙烯邻苯二甲酸酯(PVAP))和其他共聚物包被利那洛肽微丸。为促进聚合物膜形成,将增塑剂(诸如,柠檬酸三乙酯(TEC)、聚乙二醇(PEG)、乙酰化单酸甘油酯(AMG)或它们的组合)加入聚合物包衣溶液中。另外,将表面活性剂(诸如,月桂基硫酸钠、聚山梨醇酯)加入包衣溶液中作为润湿剂。为了确保肠溶性药物释放,以5%至80%的重量百分比施加聚合物包衣,具体取决于微丸的尺寸和组成以及底包衣的特性。

实例7

延迟释放利那洛肽片剂

[0145] 可将利那洛肽配制成用于延迟药物释放的片剂。与等体积的微丸相比,片剂具有小得多的比表面积,这使得它们可能较不易发生环境因素(诸如,湿度、氧化、脱酰胺等)引起的降解。另外,当需要肠溶性包衣时,较小表面面积的片剂可变得有利,因为覆盖该剂型的表面需要少得多的包衣材料。

肠溶性包衣片剂

[0146] 可将肠溶性包衣施加于片剂包衣锅中,并且用于延迟释放微丸的包衣可用于片剂,以形成延迟释放片剂。片剂上的包衣聚合物量可在5%至60%(增重率)范围内变化,具体取决于片剂的尺寸、形状和表面特性。可将底包衣施加于片剂上,以将利那洛肽与肠溶性或功能性包衣分隔开。

实例8

表7包被 *Eudragit*[®] FS30D 的利那洛肽延迟释放 (DR) 片剂组合物

	成分	重量%	重量 (千克)
流化床制粒			
1	利那洛肽	0.3	2.94
2	异麦芽酮糖醇	93.7	937
3	组氨酸	0.46	4.6
4	二水氯化钙	2.57	25.7
5	聚乙烯吡咯烷酮(PVP)	3	30
6	0.01N HCl	适量	适量

7	纯化水	适量	适量
共混和压制			
i	利那洛肽颗粒	27.85	139.25
ii	异麦芽酮糖醇	60.9	304.5
iii	交联聚维酮	10	50
iv	硬脂酸镁	0.75	3.75
vi	滑石	0.5	2.5
肠溶性包衣			
	利那洛肽片剂	75.19	1000
	Eudragit [®] FS 30D	22.56	1000
	PlasACRYL [™]	2.25	150
	纯化水*	-	500
	总干重	100	1330

制造工艺:

A. 片剂

[0147] 可通过如下方式制备制粒溶液:将PVP、组氨酸和氯化钙溶于水中,调节溶液pH至2,然后溶解利那洛肽。通过将制粒溶液喷射到填充剂异麦芽酮糖醇上,在流化床中进行制粒。制粒结束时,干燥颗粒30分钟。然后将颗粒与片剂组分(包括异麦芽酮糖醇、交联聚维酮、硬脂酸镁和滑石)共混直至均匀,并压制成片剂。

B. 肠溶性包衣

[0148] Eudragit[®] FS30D悬浮液可按照实例1所述那样制备。为进行片剂包被,将利那洛肽片剂芯放入包衣锅中并升温至35℃。开始用Eudragit[®] FS30D悬浮液进行片剂包被,保持产品温度为28℃至32℃、雾化空气压力为3巴。包被结束时,排出片剂并将其放入空气循环的烘箱中,在40℃下干燥2小时。

[0149] 同样,还可施加其他肠溶性包衣(诸如,Eudragit[®] L、S、乙基纤维素、HPMCAS、PVAP、CAP、CAS等),以形成各种增重率的延迟释放片剂。

肠溶性包衣颗粒

[0150] 还可将肠溶性包衣施加于药物颗粒上,并且可通过将肠溶性包衣颗粒压制成片剂来制造延迟释放片剂。颗粒具有增大的表面积,需要更大量的包衣才能完全覆盖颗粒表面。片剂崩解后,肠溶性包衣颗粒以比片剂更一致的方式释放利那洛肽。如果单个或几个颗粒的包被失效,这将对利那洛肽剂型的总体性能具有较小影响。

实例9

表8包被Eudragit[®] FS30D的利那洛肽延迟释放(DR)颗粒组合物

	成分	重量%	重量 (克)
流化床制粒			
1	利那洛肽	0.3	2.94
2	异麦芽酮糖醇	93.7	937
3	组氨酸	0.46	4.6
4	二水氯化钙	2.57	25.7
5	聚乙烯吡咯烷酮(PVP)	3	30
6	0.01N HCl	适量	适量
7	纯化水	适量	适量
颗粒肠溶性包衣			
a	利那洛肽颗粒	75.19	1000
b	Eudragit [®] FS 30D	22.56	1000
c	PlasACRYL [™]	2.25	150
d	纯化水	-	500
共混和压制			
i	肠溶性包衣利那洛肽颗粒	37.04	185.2
ii	异麦芽酮糖醇	51.71	258.55
iii	交联聚维酮	10	50
iv	硬脂酸镁	0.75	3.75
vi	滑石	0.5	2.5
	总计	100	500

DR基质片剂

[0151] 还可配制基质片剂以实现延迟药物释放。用于肠溶性包衣的聚合物可用作利那洛肽颗粒的填充剂,或用作片剂的基质(填充剂)。

实例10

表9用DR颗粒制成的利那洛肽DR基质片剂

	成分	重量%	重量 (千克)
流化床制粒			
1	利那洛肽	0.3	2.94
2	Eudragit [®] L100	93.7	937
3	组氨酸	0.46	4.6
4	二水氯化钙	2.57	25.7
5	聚乙烯吡咯烷酮(PVP)	3	30
6	0.01N HCl	适量	适量
7	纯化水	适量	适量
共混和压制			
i	利那洛肽颗粒	27.85	139.25
ii	异麦芽酮糖醇	60.9	304.5
iii	交联聚维酮	10	50
iv	硬脂酸镁	0.75	3.75
vi	滑石	0.5	2.5

实例11

表10利那洛肽DR基质片剂

	成分	重量%	重量 (千克)
流化床制粒			
1	利那洛肽	0.3	2.94
2	异麦芽酮糖醇	93.7	937
3	组氨酸	0.46	4.6
4	二水氯化钙	2.57	25.7
5	聚乙烯吡咯烷酮(PVP)	3	30
6	0.01N HCl	适量	适量
7	纯化水	适量	适量
共混和压制			
i	利那洛肽颗粒	27.85	139.25
ii	Eudragit [®] L100	60.9	304.5
iii	交联聚维酮	10	50
iv	硬脂酸镁	0.75	3.75
vi	滑石	0.5	2.5

[0152] 在上述两个实例中,可将Eudragit[®]L100替换为在片剂中的重量百分比或增重率为5%至90%的其他肠溶聚合物(Eudragit[®]S、Eudragit[®]FS30D、Acryl-EZE[®]、HPMCAS、HPMCP、CAP、CAS、PVAP等)。

实例12

用于延迟释放利那洛肽的肠溶性包衣胶囊

[0153] 除了将肠溶性包衣直接施加于微丸、颗粒或片剂上,还可将其施加于胶囊上。可在填充的胶囊上进行胶囊包被。首先要对胶囊进行除尘,以形成干净光滑的表面。为了避免在胶囊帽与胶囊体之间的连接部周围形成包衣缺陷,在包被之前对经清洁的胶囊进行镶边。在包衣锅中用肠溶性包衣包被经镶边的胶囊。

可将肠溶性包衣施加于明胶或HPMC胶囊上,并且可根据胶囊的尺寸和特性,以5%至60%的增重率施加该肠溶性包衣。

实例13

包含利那洛肽的延迟释放组合物

[0154] 可将包含利那洛肽的延迟释放胶囊配制成靶向回肠或结肠。将所述组合物配制成包括基于肠溶性包衣的pH触发释放,所述肠溶性包衣属于硬明胶胶囊中所含的利那洛肽片剂、胶囊或者包被利那洛肽的微丸。可将所述组合物配制成还包含稳定添加剂,诸如二价阳离子和氨基酸。PVA可用作利那洛肽与肠溶性包衣之间的粘结剂和保护层。利那洛肽或具有PVA外包衣的利那洛肽(作为微丸、胶囊或片剂)可包被有额外的肠溶性包衣(例如,Eudragit[®]FS30D、Eudragit[®]S100、Eudragit[®]L100、Eudragit[®]L100-55、Eudragit[®]L 30D-55),这些肠溶性包衣以pH依赖的方式溶解,以在适当的pH 7下释放到胃肠道的回肠中。肠溶性包衣可由共混物组成,所述共混物将不同类型的Eudragit[®]-Eudragit[®]S100/Eudragit[®]L100以不同比率组合、将Eudragit[®]S100/Eudragit[®]L100-55以各种比率组合、将Eudragit[®]FS30D/Eudragit[®]L 30D-55、Eudragit[®]FS30D/Eudragit[®]S/Eudragit[®]RS或EC以各种比率组合。所述组合物还可包含其他赋形剂,包括增塑剂,诸如柠檬酸三乙酯。所述包衣还可包含作为悬浮固体的崩解剂,以加快相关pH触发释放,从而得到作为交联羧甲基纤维素钠/Eudragit[®]S的混合体系。为便于加工,可使用抗粘剂(例如,滑石、Aerosil[®]200或PlasAcryl[™])防止微丸粘结。

[0155] 另外,可施加两种Eudragit[®]包衣(包括部分中和的包衣体系),以确保到达胃肠道中的所需pH区域后,就能迅速释放。可将缓冲剂(诸如,磷酸氢钾)包含在两种Eudragit[®]膜中的一种中。另外的非Eudragit[®]pH依赖性膜包衣包括醋酸羟丙基甲基纤维素琥珀酸酯(HPMCAS,例如,Aqoat[®]AS-HF)、醋酸纤维素邻苯二甲酸酯(CAP,例如,Aquateric[®])或虫胶。

实例14

具有DR颗粒/微丸和IR颗粒/微丸的利那洛肽组合物

[0156] 可通过将IR颗粒和DR颗粒压制成一个片剂来配制DR片剂。或者,可将IR和DR制剂

整合成一种制剂,以实现所需的溶出动力学。例如,可将速释药物层作为外层或下层施加于包含DR部分的微丸/颗粒上,如下文所示。

表11具有IR外层的利那洛肽DR微丸组合物

成分	重量%	重量/批次 (千克)
利那洛肽 IR 微丸		
利那洛肽*	0.06	16.1
PVA	1.00	250
氯化钙	0.32	80
组氨酸	0.68	170
MCC 微丸	97.48	24,370
滑石, Imperial	0.5	125
纯化水*	95.56	13,000
包被 Eudragit FS30D 的利那洛肽 DR 微丸		
利那洛肽层积微丸	75.19	1000
Eudragit FS 30D	22.56	1000
PlasACRYL™	2.25	150
纯化水*	-	500
具有 IR 外层的利那洛肽 DR 微丸		
利那洛肽 DR 微丸	98.47	299.25
利那洛肽	0.05	0.145
PVA	0.74	2.25
氯化钙	0.24	0.72
组氨酸	0.50	1.53
纯化水*	-	117
总重量	100	303.895

[0157] *在制造过程中去除产品中的水

实例15

利那洛肽持续释放 (SR) 制剂

[0158] 在持续释放制剂中,利那洛肽以缓慢而稳定的模式在数小时至数天时间内释放,从而长时间保持血流中的有效药物含量,并通过降低给药频率来提高患者的依从性。

使药物持续释放的最常用方法是通过形成基质体系,在基质体系中埋植活性药物。基质体系通常涉及使用以下类别的释放控制材料:1) 具有高胶凝能力的亲水聚合物,诸如羟丙基甲基纤维素 (HPMC)、羟丙基纤维素 (HPC)、甲基纤维素、羧甲基纤维素钠、carbopol、瓜尔胶、琼脂、藻酸盐、甘露糖、半乳糖、黄原胶、壳聚糖、改性淀粉、聚丙烯酰胺、交联聚乙烯吡咯烷酮、交联聚乙烯醇、聚甲基丙烯酸羟乙酯 (PHEMA) 等;

2) 疏水材料,诸如聚乙烯、聚氯乙烯、乙基纤维素、丙烯酸酯聚合物以及它们的共聚物;

3) 可生物降解的聚合物, 诸如聚乳酸 (PLA)、聚乙醇酸 (PGA)、聚(乳酸-乙醇酸) (PLGA)、聚己内酯 (PCL)、聚酸酐、聚原酸酯等。

实例16

包含利那洛肽的pH和定时释放组合物

[0159] 可将组合了肠溶性包衣 (pH依赖性释放) 和定时释放包衣的延迟释放组合物施加于硬明胶胶囊中所含的利那洛肽片剂、胶囊或包被利那洛肽的微丸上。所述组合物可用稳定添加剂 (诸如, 二价阳离子和氨基酸) 配制。PVA可用作利那洛肽与肠溶性包衣之间的粘结剂和保护层。

[0160] 羟丙基纤维素可用作定时释放聚合物, 或用作利那洛肽或包被有额外保护性PVA层的利那洛肽上方的外包衣。所述组合物可包被有pH依赖性释放肠溶性包衣 (例如, Eudragit[®])。可在两种不同Eudragit[®]包衣上施加在pH 6.8下溶解的Eudragit[®]FS外包衣 (以便释放到回肠和回盲瓣区域中)。具有Eudragit[®]FS的内包衣的包衣配方可包含: Eudragit[®]FS30D、Eudragit[®]L 30D-55、单硬脂酸甘油酯、Tween[®]80和水。可施加Eudragit[®]RL-RS内层, 以允许药物持续释放到结肠中。如此前所述那样将两层施加于包被有利那洛肽或包被有具有保护性PVA包衣的利那洛肽的微丸上。具有Eudragit[®]RL-RS的内包衣的包衣配方可包含Eudragit[®]RL30D、Eudragit[®]RS30D、单硬脂酸甘油酯、柠檬酸三乙酯、Tween[®]80和水。

实例17

包含利那洛肽的pH和微生物触发释放组合物

[0161] 可用pH依赖性释放肠溶性包衣与微生物触发释放层 (例如, 可生物降解的聚合物) 的组合来配制利那洛肽的延迟释放组合物, 所述组合可施加于硬明胶胶囊中所含的利那洛肽片剂、胶囊或包被利那洛肽的微丸上。所述组合物还可包含稳定添加剂, 诸如二价阳离子或氨基酸。PVA可用作利那洛肽与肠溶性包衣之间的粘结剂和保护层。可生物降解的聚合物可用作利那洛肽或包被有额外保护性PVA层的利那洛肽上方的外包衣, 起到释放功能。可生物降解的聚合物可为基于植物、动物或微生物来源的天然多糖 (诸如, 果胶、壳聚糖、硫酸软骨素、半乳甘露聚糖和直链淀粉) 的膜包衣。这些组合物可包含混合包衣或包衣组合, 例如这些包衣具有HPMC/果胶、乙基纤维素/果胶、醋酸纤维素/果胶、壳聚糖/果胶或果胶/Eudragit[®] (例如, Eudragit[®]RS 30D)。所述组合物可包含额外的赋形剂, 诸如增塑剂。PVA可例如与壳聚糖组合用作成膜聚合物。这些组合物还可包含额外的pH依赖性肠溶性包衣 (例如, Eudragit[®]), 以更有效地将利那洛肽释放到回肠。

实例18

示例性肽的含量和纯度的测量

[0162] 可使用配有Chemstation Rev A.09.03软件或等同物的Agilent 1100系列LC系统, 通过反相梯度液相色谱法测定利那洛肽的含量和纯度。使用YMC Pro[™]C18柱 (尺寸: 3.0 × 150mm, 3.5μm, 120Å; 马萨诸塞州米尔福德的沃特世公司 (Waters Corp., Milford, MA)) 或等同物, 并将其保持在40℃。流动相A (MPA) 由含0.1%三氟乙酸的水组成, 而流动相B

(MPB) 由95%乙腈:5%水(含0.1%三氟乙酸)组成。使用如下梯度完成利那洛肽的洗脱:在28分钟内0%至47%MPB,然后在4分钟内升至100%MPB,在100%MPB下保持5分钟以洗涤柱子。通过如下方式进行柱的再平衡:在1分钟内返回至0%MPB,然后在100%MPA下保持10分钟。流速为0.6mL/min,并在220nm处完成紫外检测。

实例19

体外药物释放测试

[0163] 使用USP XXIV II型桨式溶出度仪(型号PTWS,德国海恩堡的Pharma Test公司(Pharma Test,Hainburg,Germany)),通过溶出度测试评估包被片剂的利那洛肽释放。将900ml溶出介质保持在 $37.0 \pm 0.5^\circ\text{C}$ 下,以100rpm的桨速一式三份地进行测试。首先将片剂在0.1N盐酸(pH 1.2)中测试30分钟或2小时,模拟胃内滞留,然后在与小肠pH条件类似的不同pH和离子组成的缓冲介质中测试6小时。可在如下两种药典级缓冲介质中并在pH 6.8至7.4下评估利那洛肽释放:0.067M混合磷酸钠与磷酸钾(索伦森氏)缓冲液和0.05M磷酸钾缓冲液,以及离子组成与肠液相似的pH 7.4多元电解质盐溶液(汉克斯)缓冲液。所有缓冲液均用去离子水新鲜制备,并在使用之前鼓入氦气,以除去空气。从该剂型释放的利那洛肽量可通过如实例16中所述的反相梯度液相色谱法测定。

实例20

使用包被有果胶和乙基纤维素的微丸进行溶出度研究

[0164] 可制备包含不同量的果胶和Surelease®的三种包衣制剂,并将其在利那洛肽微丸上包被至不同的膜厚度。通过如下方式制备包衣制剂1(F1):将蒸馏水中2%(w/v)的果胶USP溶液与Surelease®和蒸馏水混合,得到按重量计1:12的果胶(P)与Surelease®(S)比率。以类似方式制备包衣制剂2(F2),但使用蒸馏水中3%(w/v)的果胶USP溶液与Surelease®和蒸馏水,得到按重量计1:6的果胶(P)与Surelease®(S)比率。通过如下方式制备包衣制剂3(F3):将蒸馏水中5%(w/v)的果胶USP溶液与Surelease®和蒸馏水混合,得到按重量计1:3的果胶(P)与Surelease®(S)比率。使用实验室Aeromatic Strea-1流化床包衣机(马里兰州哥伦比亚的Niro-Aeromatic公司(Niro-Aeromatic,Columbia,MD))进行包被。在50℃的入口温度下进行包被,并且使用兔式蠕动泵(马萨诸塞州沃本的瑞宁仪器公司(Rainin Instrument Co.Inc.,Woburn,MA))和25psi雾化空气压力,以2ml/min喷射速率通过1.0mm喷嘴施加包衣溶液。将包衣溶液包被到利那洛肽微丸上,得到不同的包衣厚度。膜厚度表示为相对于未包被微丸的重量所使用的理论增重百分比(TWG)。就包衣制剂F1而言,以9%、14%、16%和18%的增重率对微丸进行包被;就包衣制剂F2而言,以12%、25%、30%和35%的增重率对微丸进行包被;就包衣制剂F3而言,以25%、35%、45%和55%的增重率对微丸进行包被。将包被的微丸在50℃下固化30分钟。

[0165] 可按照USP转篮法,在溶出度测试仪(VK 7000溶出度测试台,新泽西州的Vankel工业公司(Vankel Industries,Inc.,NJ))中评估包被的微丸的利那洛肽释放。所有测试均在保持于 $37 \pm 0.5^\circ\text{C}$ 下的900ml溶出介质中以50rpm的桨转速进行。溶出度研究在模拟胃肠道中转运期间可能遇到的pH和时间的条件下进行。在添加或不添加3ml酶的情况下,使用模拟胃液(SGF)在pH 1.4下测试2小时,之后使用模拟小肠液(SSIF)在pH 7.4下测试4小时,然后使用模拟盲肠液(SCF)在pH 6下测试至少6小时(或直到100%药物释放)。使用pH 6的缓冲

剂在盲肠的平均pH与酶活性的最适pH之间进行折中。从该剂型释放的利那洛肽量通过如实例16中所述的反相梯度液相色谱法测定。就每个溶出度实验而言,均在相同条件下同时运行两次平行实验。在SSIF中测试4小时后,将果胶分解酶加入其中一个溶出容器,但不加入另一个溶出容器中。因此,一者是含酶的释放研究,另一者是不含酶的释放研究。每个溶出度实验重复3次(n=3)。

实例21

利那洛肽片剂释放曲线

[0166] 在不同pH下测试了三种延迟释放制剂的利那洛肽片剂释放曲线。样品181-64B包含100 μ g剂量的利那洛肽、Opadry® II的底包衣以及Eudragit® FS 30D和滑石的功能性包衣。样品181-64C包含100 μ g剂量的利那洛肽、Opadry II的底包衣以及Eudragit® FS 30D和Eudragit® PlasAcryl™的功能性包衣。图1提供了批次181-64B和批次181-64C的释放曲线。图2提供了25 μ g剂量的利那洛肽释放曲线。

实例22

利那洛肽片剂的制备

[0167] 可通过首先制备以下片剂芯组分来制备延迟释放片剂:安慰剂基料、利那洛肽750 μ g/225mg基料以及预先粒化的填充剂。

颗粒制造工艺:

[0168] 可将片剂组分制备成单独颗粒,以便在片剂压制之前进行共混。单独片剂组分(诸如,安慰剂基料和预先粒化的填充剂基料)的使用提供了有利的片剂稳定性特性和释放曲线等优点。例如,表12中所列的所有片剂组分可通过湿法制粒单独地制备并在压制之前进行共混,或共混在一起并加工成用于湿法制粒的混合物。在另一种工艺中,表12中所列的片剂组分可通过干法制粒单独地制备并在压制之前进行共混,或共混在一起并加工成用于干法制粒的混合物。在另一种工艺中,直接共混片剂组分,以用于压制。在一种优选的工艺中,预先粒化的填充剂基料和/或安慰剂基料通过湿法制粒制备,并在与750 μ g/225mg利那洛肽基料混合之前进行干燥。利那洛肽基料可通过湿法制粒工艺或通过Wurster包衣工艺制备。该优选的工艺通过降低加工期间利那洛肽的水分暴露并最大程度减少片剂芯中的残余水分,而表现出片剂稳定性进一步增加。

表12:用于各种片剂强度的组分

强度	安慰剂	25 μ g	50 μ g	75 μ g	100 μ g	150 μ g	290 μ g
安慰剂基料(%)	20.00	16.67	13.33	10.00	6.67	3.33	0.00
利那洛肽基料(即, 750 μ g/225mg 基料(%))	0.00	3.33	6.67	10.00	13.33	16.67	38.67
预先粒化的填充剂(%)	78.75	78.75	78.75	78.75	78.75	78.75	62.58
硬脂酸镁(%)	1.25	1.25%	1.25%	1.25%	1.25%	1.25%	1.25%
总计(%)	100.0	100.0	100.0	100.0	100.0	100.0	100.0

[0169] 然后在合适的压片机上将上述共混物压制成重量为225mg的目标片剂芯。在有孔

包衣锅中,以4%w/w的增重率加入底包衣(OPADRY®II)。应设定并监测包衣条件,使得包被期间的水分吸收保持在最小限度。当通过干燥失重(LOD)进行测量时,包被底包衣的片剂的LOD应不超过1.5%。在有孔包衣锅中,将功能性包衣加到包被底包衣的片剂上。该功能性包衣为Eudragit®FS30D或Eudragit®S100。以5mg聚合物重量/cm²片剂表面施加功能性包衣。这在功能性包被期间得到大约4.5%的总聚合物增重率。应设定并监测包衣条件,使得包被期间的水分吸收保持在最小限度。当通过干燥失重进行测量时,功能性包被的片剂的LOD应不超过2.0%。

安慰剂基料的制备:

[0170] 表13表示安慰剂基料颗粒的配方:

表13:安慰剂基料颗粒的配方

组分	%w/w	量(g)
L-组氨酸	2.26	112.9
二水氯化钙	1.07	53.5
聚乙烯醇	1.50	75.0
微晶纤维素	95.17	4758.6
盐酸(高纯、发烟、37%水溶液)		
经处理的水		
总计	100	5000

[0171] 可通过首先分配表14的原料来制备安慰剂基料制剂。

表14:用于制备安慰剂基料的原料

组分	量(g)
L-组氨酸	242.2
二水氯化钙	114.8
聚乙烯醇	160.9
微晶纤维素	4758.6

[0172] 将混合容器去皮重,并将2682.1±5.0g经处理的水加入该容器中。设置混合器并开始搅拌水。一边搅拌一边将EMPROVE®加入水中,并开始计时。盖上溶液,一边搅拌一边将溶液加热到70℃,并保持该温度直到肉眼观察到材料溶解。

[0173] 用盐酸将溶液的pH调节至1.5。一边搅拌一边将二水氯化钙加入溶液中。混合直到溶解。一边搅拌一边将L-组氨酸加入溶液中。搅拌大约15分钟。记录初始pH。用盐酸将溶液的pH调节至5.0。记录溶液的最终pH和盐酸的加入量。混合直到所有材料都溶解。一边混合一边用盐酸将溶液的pH调节至2.5。记录溶液的最终pH和盐酸的加入量。确保正确设定高剪切制粒机,以使用25L缸、混合叶片和切碎机进行制粒。使微晶纤维素通过16目筛网进入制粒机缸中。计算要加入的制粒溶液的净重。将制粒溶液以大约300g/min的速率泵送到制粒机中,同时在以下参数下进行混合:叶轮速度1(290rpm,5.5m/s端速),切碎机速度1(1760rpm)。关闭制粒机并刮下缸侧面和底部的材料。根据以下参数再混合3分钟:叶轮速度1(290rpm,5.5m/s端速),切碎机速度1(1760rpm)。将塑料袋(poly bag)去皮重,并将完成的湿制颗粒排入到塑料袋中。对颗粒进行称重。将湿制颗粒转移到FLM-3流化床中进行干燥。

使用以下近似设置干燥颗粒。干燥直到颗粒LOD不超过1.2%水分。将干燥的颗粒排入到去皮重的塑料袋中。

参数	目标范围
产品温度	40°C
工艺(干燥) 空气	30至60CFM
入口温度	60°C

这些设置仅为建议的设置,可对其进行调节以达到最佳干燥效果。

[0174] 通过#30目筛子筛选经干燥的颗粒。将塑料袋去皮重,并将经干燥的颗粒排入到塑料袋中。对颗粒进行称重。将经干燥的颗粒包装到加有干燥剂的箔密封袋中。

利那洛肽基料的制备(即,750 μ g/225mg):

[0175] 表15表示750 μ g/225mg基料颗粒的配方:

表15:750 μ g/225mg基料颗粒的配方

组分	%w/w	量(g)
利那洛肽	0.39	19.3
L-组氨酸	2.26	112.9
二水氯化钙	1.07	53.5
聚乙烯醇	1.50	75.0
微晶纤维素	94.79	4,739.3
盐酸(高纯、发烟、37%水溶液)	-----	-----
经处理的水	-----	-----
总计	100.00	5,000.0

[0176] 可通过首先分配表16的原料来制备750 μ g/225mg基料颗粒。

表16:利那洛肽基料颗粒的原料

原料	所需的量(g)
利那洛肽	19.3
微晶纤维素	4,739.3
制粒溶液	

[0177] 一边混合一边将利那洛肽加入制粒溶液中。混合直到溶解。确保正确设定高剪切制粒机,以使用25L缸、混合叶片和切碎机进行制粒。使微晶纤维素通过16目筛网进入制粒机缸中。将制粒溶液以大约300g/min的速率泵送到制粒机中,同时在以下参数下进行混合:叶轮速度1(290rpm,5.5m/s端速),切碎机速度1(1760rpm)。将塑料袋去皮重,并将完成的湿制颗粒排入到塑料袋中。对颗粒进行称重。将湿制颗粒转移到FLM-3流化床中进行干燥。使用以下近似设置干燥颗粒。干燥直到颗粒LOD不超过1.2%水分。将干燥的颗粒排入到去皮重的塑料袋中。

参数	目标范围
产品温度	40°C
工艺(干燥) 空气	30 至 60CFM

入口温度	60°C
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注意：这些设置仅为建议的设置，可对其进行调节以达到最佳干燥效果。

[0178] 通过#30目筛子筛选经干燥的颗粒。将塑料袋去皮重，并将经干燥的颗粒排入到塑料袋中。对颗粒进行称重。将经干燥的颗粒包装到加有干燥剂的箔密封袋中。

预先粒化的填充剂的制备：

[0179] 表17表示预先粒化的填充剂的配方。

表17：填充剂颗粒的配方

组分	%w/w	总量 (g)	量/子批 (g)
微晶纤维素	19.4	4,074	1,358
交联羧甲基纤维素钠	5.1	1,071	357
甘露醇	71.7	15,057	5,019
聚乙烯醇	3.8	798	266
经处理的水	-----	-----	-----
总计	100.0	21,000	7,000

[0180] 可通过首先分配表18的原料来制备填充剂制剂。

表18：用于制备填充剂颗粒的原料

原料	所需的量(g)
聚乙烯醇	840
微晶纤维素-颗粒 1	1,358
微晶纤维素-颗粒 2	1,358
微晶纤维素-颗粒 3	1,358
交联羧甲基纤维素钠-颗粒 1	357
交联羧甲基纤维素钠-颗粒 2	357
交联羧甲基纤维素钠-颗粒 3	357
甘露醇-颗粒 1	5,019
甘露醇-颗粒 2	5,019
甘露醇-颗粒 3	5,019
总计	---

[0181] 然后记录不锈钢容器的皮重。将容器去皮重，并将所需量的经处理的水称取到该容器中。将水转移到夹层釜中。设置混合器并开始搅拌釜中的水。一边搅拌一边将EMPROVE® (聚乙烯醇) 加入水中，并开始计时。盖上溶液，一边搅拌一边将溶液加热到70℃，并保持该温度直到肉眼观察到材料溶解。计算加热过程中因蒸发而损失的水的重量。将这个量的经处理的水加入溶液中。将各一袋的微晶纤维素、Ac-Di-Sol (即，交联羧甲基纤维素钠) 和Pearlitol 100SD (即，甘露醇) 加入高剪切制粒机缸中。根据以下参数混合大约2分钟：叶轮速度1 (290rpm, 5.5m/s端速)，切碎机速度1 (1760rpm)。将2217±5g制粒溶液以大约

300g/min的速率泵送到制粒机中,同时在以下参数下进行混合:叶轮速度1 (290rpm,5.5m/s端速),切碎机速度1 (1760rpm)。关闭制粒机并刮下缸侧面和底部的材料。根据以下参数再混合30秒至1分钟:叶轮速度1 (290rpm,5.5m/s端速),切碎机速度1 (1760rpm)。将塑料袋去皮重,并将完成的湿制颗粒排入到塑料袋中。对颗粒进行称重。以5-10%功率使湿制颗粒通过配有2A375Q03763筛网的Comil。将湿制颗粒转移到FLM-3流化床中进行干燥。使用以下近似设置干燥颗粒。干燥直到颗粒LOD不超过1.0%水分。将干燥的颗粒排入到去皮重的塑料袋中。

参数	目标范围
产品温度	40°C
工艺(干燥)空气	30至60CFM
入口温度	60°C

这些设置仅为建议的设置,可对其进行调节以达到最佳干燥效果。

[0182] 用Comil、圆形叶轮、2A045R03137筛网研磨颗粒。利用具有以下筛网尺寸(单位为微米)的声波筛进行粒度分析:38、75、106、150、180、250。将塑料袋去皮重,并将经干燥且研磨的颗粒排入到塑料袋中。对颗粒进行称重。将经干燥的颗粒包装到加有干燥剂的箔密封袋中。

实例23

25μg片剂共混和压制

[0183] 可根据实例22的工序,用表19的配方制备利那洛肽的25μg剂量片剂。

表19:25μg利那洛肽片剂的配方:

组分	%w/w	量(g)
预先粒化的填充剂	78.750	5118.8
利那洛肽基料	3.333	216.7
安慰剂基料	16.667	1083.4
硬脂酸镁	1.250	81.3
总计	100	6500

[0184] 首先,分配表20的原料。

表20:用于制备25μg利那洛肽片剂的原料

原料	所需的量(g)
预先粒化的填充剂次级共混物A	2559.4
预先粒化的填充剂次级共混物B	2559.4
利那洛肽基料	227.5
安慰剂基料	1137.5
硬脂酸镁次级共混物A	40.6
硬脂酸镁次级共混物B	40.6
总计	6565.0

[0185] 预混物:设置8夸脱混合器,并加入750μg/225mg基料和安慰剂基料。盖上盖子并共混10分钟。将塑料袋去皮重,并将预混物排入到塑料袋中。

[0186] 次级共混物A:将650g的预混物加入到16夸脱V形混合器中。将用于次级共混物A的

预先粒化的填充剂加入到16夸脱V形混合器中。盖上盖子并共混10分钟。使用于次级共混物A的硬脂酸镁通过40目筛网。再将其加入到16夸脱V形混合器中。盖上盖子并共混3分钟。将塑料袋去皮重,并将共混物排入到塑料袋中。

[0187] 次级共混物B:将650g的预混物加入到16夸脱V形混合器中。将用于次级共混物B的预先粒化的填充剂加入到16夸脱V形混合器中。盖上盖子并共混10分钟。使用于次级共混物B的硬脂酸镁通过40目筛网。再将其加入到16夸脱V形混合器中。盖上盖子并共混3分钟。将塑料袋去皮重,并将共混物排入到塑料袋中。

[0188] 压制:确保按照SOP E-59为具有0.32"sc模具的Korsch XL 100压片机设置0.32"圆形凹面模具(所需的10个工位)、桨叶式加料器,并且所有其他部件均恰当固定。将冲模台手动旋转至少完整一周,以确保正确安装。目视确认所有冲模和冲头均在,并且冲模与冲模台齐平。核实片剂规格是否满足表21的过程中片剂规格。

表21:过程中片剂规格

参数	目标值
平均片剂重量	225mg
单片厚度	4.0-4.5mm (仅供参考)
单片硬度	10kP
脆碎度(100次下落)	不超过0.6%
单片崩解	不超过15min

[0189] 将共混物加入到料斗中。将转台速度设定为20RPM。调节冲模填充量和压制参数,以得到目标重量为225mg且目标硬度为8-12kP的片剂。所有废弃材料应收集在压片废料塑料袋中。启动计时器,并压制片剂。

实例24

100μg片剂共混和压制

[0190] 可根据实例22的工序,用表22的配方制备利那洛肽的100μg剂量片剂。

表22:100μg利那洛肽片剂的配方:

组分	% w/w	量(g)
预先粒化的填充剂	78.750	9843.8
利那洛肽基料	3.333	1666.6
安慰剂基料	16.667	833.4
硬脂酸镁	1.250	156.3
总计	100	12500

[0191] 首先,分配表23的原料。

表23:用于制备100μg利那洛肽片剂的原料

原料	所需的量(g)
预先粒化的填充剂	9843.8
利那洛肽基料	1750.0
安慰剂基料	875.0

硬脂酸镁	156.3
总计	12,625.0

[0192] 预混物：设置16夸脱混合器，并加入750 μ g/225mg基料和安慰剂基料。盖上盖子并共混10分钟。将塑料袋去皮重，并将预混物排入到塑料袋中。

[0193] 将2500g的预混物加入到1立方英尺V形混合器中。将预先粒化的填充剂加入到1立方英尺V形混合器中。盖上盖子并共混10分钟。使硬脂酸镁通过40目筛网。加入到1立方英尺V形混合器中。盖上盖子并共混3分钟。将塑料袋去皮重，并将共混物排入到塑料袋中。

[0194] 压制：确保按照SOP E-59为具有0.32"sc模具的Korsch XL 100压片机设置0.32"圆形凹面模具（所需的10个工位）、桨叶式加料器，并且所有其他部件均恰当固定。将冲模台手动旋转至少完整一周，以确保正确安装。目视确认所有冲模和冲头均在，并且冲模与冲模台齐平。核实片剂规格是否满足表24的过程中片剂规格。

表24：过程中片剂规格

参数	目标值
平均片剂重量	225mg
单片厚度	4.0-4.5mm (仅供参考)
单片硬度	10kP
脆碎度 (100次下落)	不超过0.6%
单片崩解	不超过15min

[0195] 将共混物加入到料斗中。将转台速度设定为20RPM。调节冲模填充量和压制参数，以得到目标重量为225mg且目标硬度为8-12kP的片剂。所有废弃材料应收集在压片废料塑料袋中。启动计时器，并压制片剂。

实例25

290 μ g片剂共混和压制

[0196] 可根据实例22的工序，用表25的配方制备利那洛肽的290 μ g剂量片剂。

表25：290 μ g利那洛肽片剂的配方：

组分	%w/w	量(g)
预先粒化的填充剂	60.10	3906.5
利那洛肽基料	38.65	2512.3
硬脂酸镁	1.25	81.3
总计	100	6500

[0197] 首先，分配表26的原料。

表26：用于制备290 μ g利那洛肽片剂的原料

原料	所需的量(g)
预先粒化的填充剂次级共混物 A	1953.3
预先粒化的填充剂次级共混物 B	1953.3
利那洛肽基料次级共混物 A	1256.1
利那洛肽基料次级共混物 B	1256.1
硬脂酸镁次级共混物 A	40.6
硬脂酸镁次级共混物 B	40.6
总计	6500.0

[0198] 次级共混物A:将用于次级共混物A的预先粒化的填充剂和利那洛肽基料加入到16夸脱V形混合器中。盖上盖子并共混10分钟。使用于次级共混物A的硬脂酸镁通过40目筛网。再将其加入到16夸脱V形混合器中。盖上盖子并共混3分钟。将塑料袋去皮重,并将共混物排入到塑料袋中。

[0199] 次级共混物B:将用于次级共混物B的预先粒化的填充剂和利那洛肽基料加入到16夸脱V形混合器中。盖上盖子并共混10分钟。使用于次级共混物B的硬脂酸镁通过40目筛网。再将其加入到16夸脱V形混合器中。盖上盖子并共混3分钟。将塑料袋去皮重,并将共混物排入到塑料袋中。

[0200] 压制:确保按照SOP E-59为具有0.32"sc模具的Korsch XL 100压片机设置0.32"圆形凹面模具(所需的10个工位)、桨叶式加料器,并且所有其他部件均恰当固定。将冲模台手动旋转至少完整一周,以确保正确安装。目视确认所有冲模和冲头均在,并且冲模与冲模台齐平。核实片剂规格是否满足表27的过程中片剂规格。

表27:过程中片剂规格

参数	目标值
平均片剂重量	225mg
单片厚度	4.0-4.5mm (仅供参考)
单片硬度	10kP
脆碎度(100次下落)	不超过0.6%
单片崩解	不超过15min

[0201] 将共混物加入到料斗中。将转台速度设定为20RPM。调节冲模填充量和压制参数,以得到目标重量为225mg且目标硬度为8-12kP的片剂。所有废弃材料应收集在压片废料塑料袋中。启动计时器,并压制片剂。

实例26

利那洛肽25μg片剂的底包衣

[0202] 可用Opadry® II底包衣对实例23的25μg片剂进行底包被。表28的配方示出制备包衣材料所需的量,所述包衣材料被过量地制备,以弥补包被过程中的损失。

表28:25μg片剂的底包衣配方

组分	%w/w	g/批次
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Opadry II白色	20	400
纯化水	80	1600
总计	100	2000

[0203] 将1600g的纯化水分配到适当尺寸的容器中。将400g的Opadry® II分配到适当尺寸的容器中。将Opadry®加入水中。计算以85%理论效率施加4.0%增重率所需的理论溶剂量。准备塑料袋,以在包被过程中收集废片剂。确保已为Compu-Lab设置19英寸锅与增压组件。核实液体进料管线为Tygon 17管。核实枪组件安装在锅中。喷枪组件应由安装有40100AB液体喷嘴和相配气帽的1×1/4JAU喷枪组成。枪组件应尽可能远离片剂床安装,且喷射角垂直于片剂床的上三分之一。通过称量100个不带包衣的片剂,核实初始片剂重量。通过将片剂的重量除以100,来计算单个片剂的平均重量。通过如下方式测试初始片剂水分:将大约1克的片剂碾碎并在105℃下运行LOD 10分钟。调节泵,以使得液体流量为大约10g/min。将液体注入管线,使之超过枪,并核实管线或枪中没有渗漏。将片剂加入到包衣锅中,并以50℃的入口温度和350CFM的气流开始温热20分钟。在升温期间偶尔轻摇。

[0204] 一旦达到目标床温,就开始根据下表29中概述的目标工艺参数喷射包衣悬浮液。视需要定期测试并报告片剂水分含量。一旦已施加理论量的溶液,就检查片剂的增重率。当已达到4%增重率时,停止喷射,然后以50℃的入口温度使片剂干燥30分钟,降低锅转速至最低限度或轻摇。排出片剂并测定包衣片剂的新重量。

表29:目标工艺参数

参数	目标值
喷射速率	10g/min
入口温度	65℃
气流	350CFM
雾化空气	40PSI
锅转速	11RPM
排气温度	47℃
床温	50℃

实例27

100μg利那洛肽片剂的底包衣

[0205] 可对实例24的100μg片剂底包被上Opadry® II包衣。表30的配方示出制备包衣材料所需的量,所述包衣材料被过量地制备,以弥补包被过程中的损失。

表30:100μg片剂的底包衣配方

组分	% w/w	g/批次
Opadry II白色	20	1000
纯化水	80	4000
总计	100	5000

[0206] 将4000g的纯化水分配到适当尺寸的容器中。将1000g的Opadry® II分配到适当尺寸的容器中。将Opadry®加入水中。计算以85%理论效率施加4.0%增重率所需的理论溶

液量。确保已为Compu-Lab设置24英寸锅与增压组件。核实液体进料管线为Tygon 17管。核实枪组件安装在锅中。喷枪组件应由安装有40100AB液体喷嘴和相配气帽的2×1/4JAU喷枪组成。枪组件应尽可能远离片剂床安装,且喷射角垂直于片剂床的上三分之一。通过称量100个不带包衣的片剂,核实初始片剂重量。通过将片剂的重量除以100,来计算单个片剂的平均重量。通过如下方式测试初始片剂水分:将大约1克的片剂碾碎并在105℃下运行LOD 10分钟。调节泵,以使得液体流量为大约20g/min。将液体注入管线,使之超过枪,并核实管线或枪中没有渗漏。将片剂加入到包衣锅中,并以50℃的入口温度和400CFM的气流开始温热20分钟。在升温期间偶尔轻摇。

[0207] 一旦达到目标床温,就开始根据下表31中概述的目标工艺参数喷射包衣悬浮液。视需要定期测试并报告片剂水分含量。一旦已施加理论量的溶液,就检查片剂的增重率。当已达到4%增重率时,停止喷射,然后以50℃的入口温度使片剂干燥30分钟,降低锅转速至最低限度或轻摇。排出片剂并测定包衣片剂的新重量。

表31:目标工艺参数

参数	目标值
喷射速率	20g/min
入口温度	65℃
气流	400CFM
雾化空气	40PSI
锅转速	10RPM
排气温度	47℃
床温	50℃

实例28

290μg利那洛肽片剂的底包衣

[0208] 可对实例25的290μg片剂底包被上Opadry® II包衣。表32的配方示出制备包衣材料所需的量,所述包衣材料被过量地制备,以弥补包被过程中的损失。

表32:100μg片剂的底包衣配方

组分	% w/w	g/批次
Opadry II白色	20	400
纯化水	80	1600
总计	100	2000

[0209] 将1600g的纯化水分配到适当尺寸的容器中。将400g的Opadry® II分配到适当尺寸的容器中。将Opadry® 加入到水中。计算以85%理论效率施加4.0%增重率所需的理论溶液量。确保已为Compu-Lab设置19英寸锅与增压组件。核实液体进料管线为Tygon 17管。核实枪组件安装在锅中。喷枪组件应由安装有40100AB液体喷嘴和相配气帽的1×1/4JAU喷枪组成。枪组件应尽可能远离片剂床安装,且喷射角垂直于片剂床的上三分之一。通过称量100个不带包衣的片剂,核实初始片剂重量。通过将片剂的重量除以100,来计算单个片剂的平均重量。通过如下方式测试初始片剂水分:将大约1克的片剂碾碎并在105℃下运行LOD 10分钟。调节泵,以使得液体流量为大约10g/min。将液体注入管线,使之超过枪,并核实管

线或枪中没有渗漏。将片剂加入到包衣锅中,并以50℃的入口温度和350CFM的气流开始温热20分钟。在升温期间偶尔轻摇。

[0210] 一旦达到目标床温,就开始根据下表33中概述的目标工艺参数喷射包衣悬浮液。视需要定期测试并报告片剂水分含量。一旦已施加理论量的溶液,就检查片剂的增重率。当已达到4%增重率时,停止喷射,然后以50℃的入口温度使片剂干燥30分钟,降低锅转速至最低限度或轻摇。排出片剂并测定包衣片剂的新重量。

表33:目标工艺参数

参数	目标值
喷射速率	10g/min
入口温度	65℃
气流	350CFM
雾化空气	40PSI
锅转速	1RPM
排气温度	47℃
床温	50℃

实例29

利那洛肽片剂的功能性或肠溶性包衣

[0211] 前述实例的片剂可被制备成具有功能性包衣。表34的配方示出制备包衣材料所需的量,所述包衣材料被过量地制备,以弥补包被过程中的损失:

表34:功能性包衣工艺的配方

组分	% w/w
Eudragit [®] S100	9.94
1N NH ₃	6.75
柠檬酸三乙酯	4.97
滑石	4.97
纯化水	73.37
总计	100

[0212] 为了制备功能性包衣,将所需量的Eudragit[®] S100分配到适当尺寸的容器中。将2/3所需量的纯化水分配到适当尺寸的容器中。开始搅拌水直到获得涡流。将S100缓慢加入水中,并混合直到粉末被彻底润湿并且所形成的团块或泡沫已消散(约5分钟)。

[0213] 将所需量的1N NH₃分配到适当尺寸的容器中。将1N NH₃缓慢加入到Eudragit[®]悬浮液中,并且混合最少60分钟。将所需量的柠檬酸三乙酯分配到适当尺寸的容器中。将柠檬酸三乙酯加入到Eudragit[®]悬浮液中,并且混合最少60分钟。将所需量的滑石分配到适当尺寸的容器中。使用Silverson均质器使滑石在剩余1/3的纯化水中均质化10分钟(或直到均匀)。在混合的同时,将滑石悬浮液倒入Eudragit[®]悬浮液中。混合不长于5分钟。使包衣悬浮液过#30目筛网。

[0214] 计算以90%理论效率施加9.0%增重率所需的理论溶液量。确保已为Compu-Lab设置19英寸锅与增压组件。核实液体进料管线为Tygon 17管。核实枪组件安装在锅中。喷枪组件应由安装有40100AB液体喷嘴和相配气帽的1×1/4JAU喷枪组成。枪组件应尽可能远离片剂床安装,且喷射角垂直于片剂床的上三分之一。将片剂加入到包衣锅中。以30度的入口温度温热片剂。确保床温达到大约30度后再进行下一步。调节泵,以使得液体流量为大约12g/min。将液体注入管线,使之超过枪,并核实管线或枪中没有渗漏。通过如下方式测试初始片剂水分:将大约2克的片剂碾碎并在105℃下运行LOD 10分钟。

[0215] 一旦达到目标床温,就开始根据下表35中概述的目标工艺参数喷射包衣悬浮液。视需要定期测试并报告片剂水分含量。一旦已施加强理论量的溶液,就检查片剂的增重率。当已达到9%增重率时,停止喷射,然后以40℃的入口温度使片剂干燥5-10分钟,降低锅转速至最低限度或轻摇。

表35:喷雾包衣工艺的目标工艺参数

参数	目标值
喷射速率	12-20g/min ¹
入口温度	43℃ ¹
气流	300CFM
雾化空气	35PSI
锅转速	12RPM
排气温度	33℃
床温	35℃

1视需要进行调节以保持床温。

[0216] 通过如下方式测试最终片剂水分:将大约2克的片剂碾碎并在105℃下运行LOD 10分钟。水分应≤初始片剂水分。排出片剂并测定包衣片剂的新重量。在温度设定为40℃的机械对流烘箱中使片剂干燥至少2小时。在成批包装之前,使片剂达到25-30℃。将片剂成批包装在加有干燥剂的金属箔袋中,并保存于5℃下。

实例30

耐酸利那洛肽胶囊和带包衣的耐酸胶囊制剂

[0217] 可制备用于靶向释放的耐酸利那洛肽胶囊和包衣胶囊。耐酸利那洛肽胶囊的配方提供于表36中。

表36:耐酸利那洛肽胶囊的配方

低剂量/小儿微丸强度 145μg/225mg			
成分	%	mg/g	kg/批次

氯化钙	0.32%	3.200	0.080
组氨酸 USP	0.68%	6.800	0.170
PVA , USP	1.50%	15.000	0.375
利那洛肽	0.06%	0.645	0.0161
滑石	0.60%	6.000	0.1500
微晶纤维素, NF (Celphere CP305 微丸)	96.85%	968.500	24.213
纯化水, USP	NA	-	13.000
盐酸(10%), USP	NA	-	0.142
低剂量微丸的底包衣			
低剂量利那洛肽微丸, 145µg/225mg	90.9	909.0	2.00
聚乙烯吡咯烷酮(Kollidon k30 LP) 或 聚乙烯醇 USP	8.6	86.0	0.190
滑石, 鲁兹那克(Luzenac)	0.5	5.0	0.011
纯化水*	-	-	2.5
总干重	100.0	-	2.201
在耐酸胶囊中包封低剂量带底包衣的微丸			

[0218] 耐酸胶囊还可包含包衣。耐酸利那洛肽胶囊配方提供于表35中。

图3示出了不带包衣和带包衣的耐酸胶囊在酸性介质中的溶出曲线。

经包封的 AR 胶囊的包衣		
名称	重量百分比%	重量/批次(kg)固形物
填充有 10% PVPLP 底包衣的 AR 胶囊尺寸 1	84.49	0.390
FS30D	10.18	0.157
L30D-55	3.39	0.052
TEC	0.68	0.0031
滑石, Pharma M	0.43	0.0020
PlasAcryl T20	0.81	0.0125
纯化水*	-	0.130
总计%	100.00	-

其他实施例

[0219] 本发明的范围不受本文所述的特定实施例限制。实际上,除本文所述的那些之外,通过前面的描述和附图,本发明的各种修改形式对于本领域技术人员而言将变得显而易

见。这些修改形式旨在落入所附权利要求书的范围之内。还应当理解,所有值是近似的,并且是为说明而提供的。

[0220] 本申请通篇引用了所有专利、专利申请、出版物、产品说明和方案,它们的公开内容全文以引用方式并入本文中以用于所有目的。

序列表

<110> 硬木药品公司

<120> 利那洛肽的延迟释放组合物

<130> 223355/140PCT1/366281

<140> PCT/US2014/069838

<141> 2014-12-11

<150> 61/914,951

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<160> 1

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<212> PRT

<213> 人工序列

<220>

<223> 合成产生的肽

<400> 1

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1

5

10

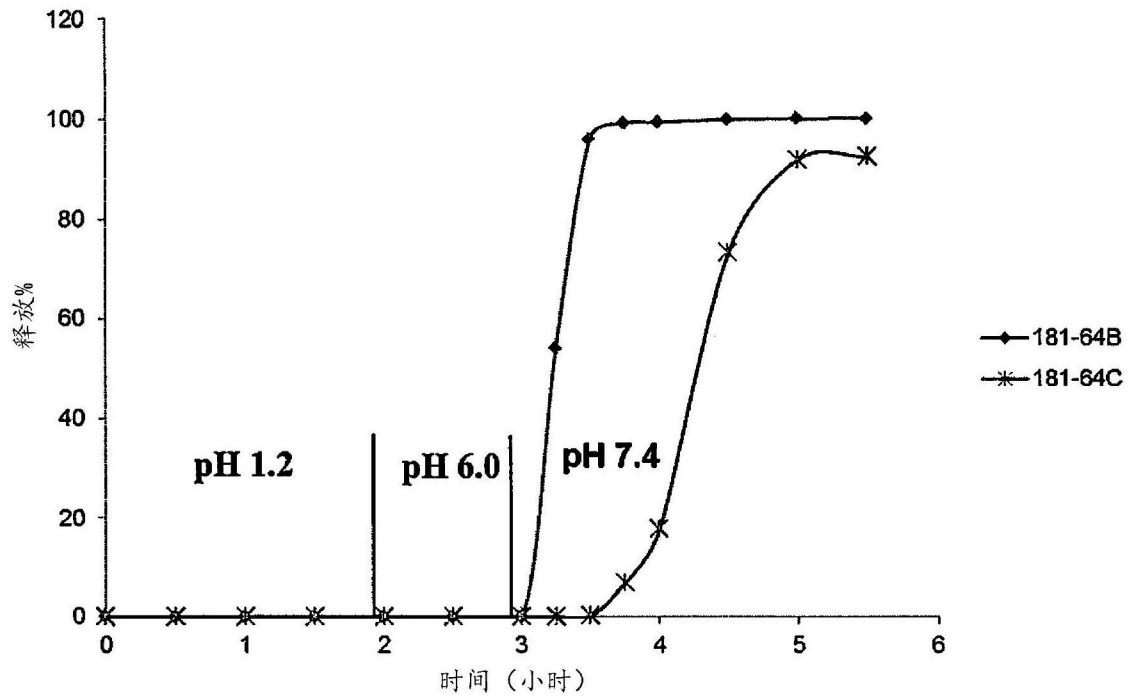


图1

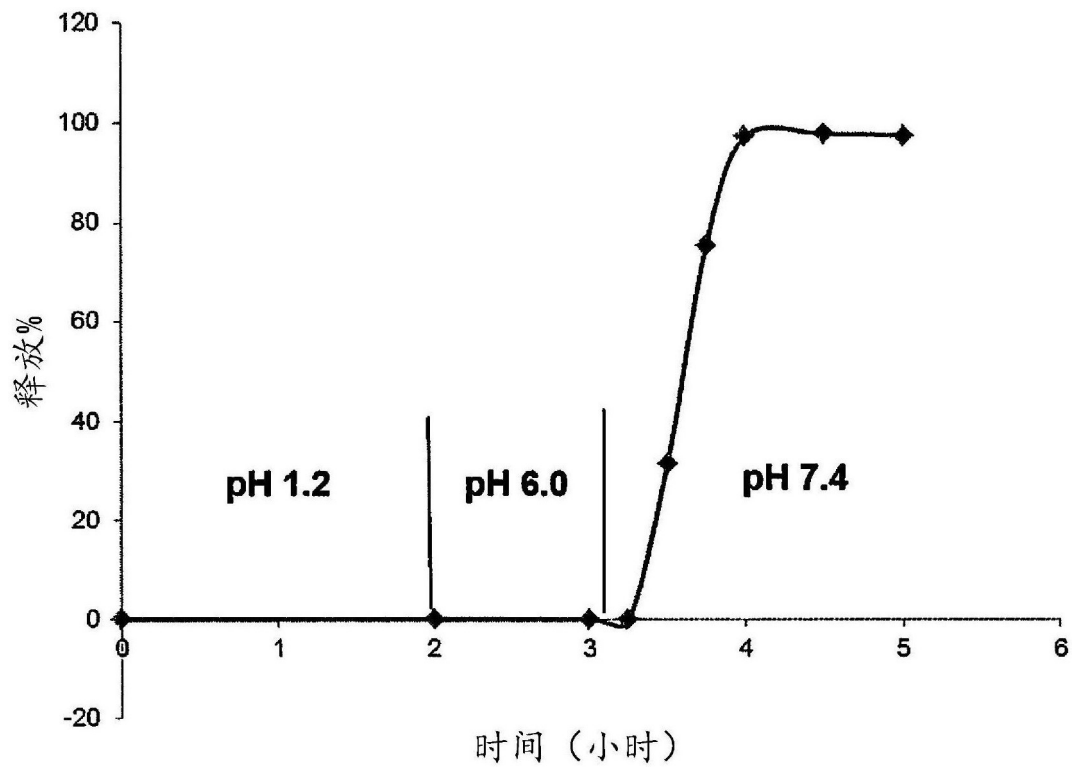


图2

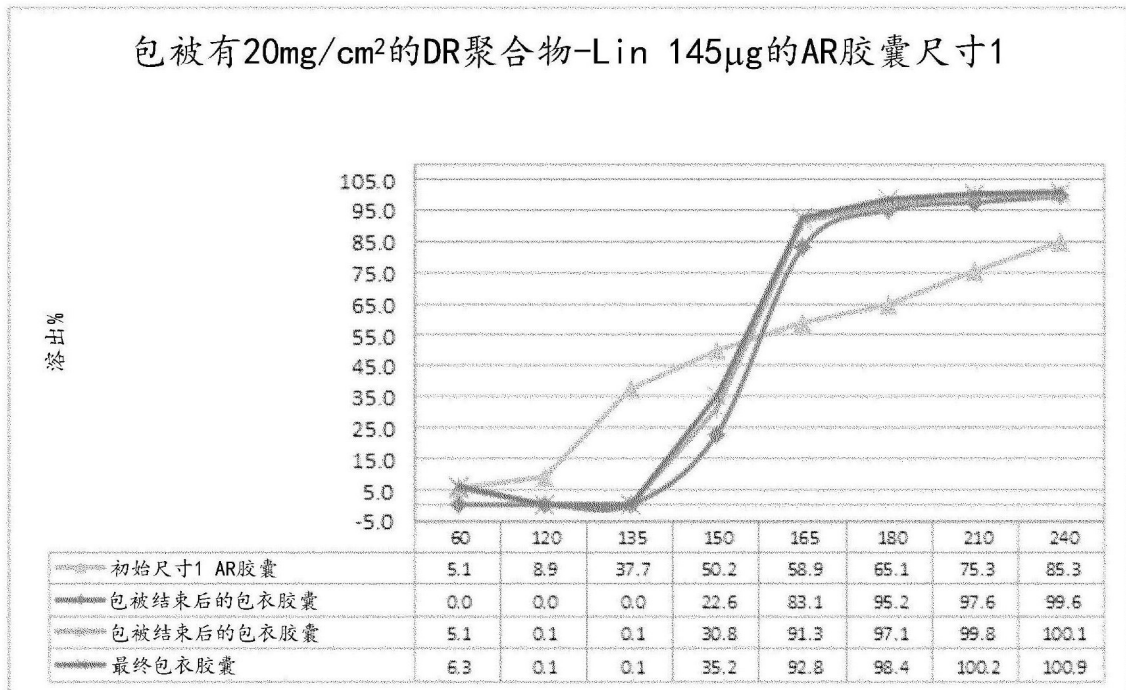


图3