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

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

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

SUMMARY OF THE INVENTION

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

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

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

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

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

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

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

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

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

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

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

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

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

BRIEF DESCRIPTION OF THE FIGURES

WHAT IS CLAIMED IS:

1. A composition comprising a combination of a delayed release (DR) bead, and an immediate release (IR) bead, the DR bead and the IR bead:

linaclotide;

Ca^{2+};

histidine; and

polyvinyl alcohol (PVA);

wherein the DR bead further comprises an enteric coating.

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

3. The composition of claim 2, wherein the enteric coating comprises a methyl methacrylate-methacrylic acid copolymer.

4. The composition of claim 3, wherein the DR bead further comprises a protective polymer film or subcoating.

5. The composition of claim 4, wherein the subcoating comprises polyvinyl alcohol.

6. The composition of any one of claims 1-5, wherein the DR bead and the IR bead are compressed into a tablet, or the IR bead is applied to the DR bead as an outer layer or an under layer.

7. The composition of claim 5, wherein the composition further comprises a plurality of the DR beads and the IR beads, wherein the plurality of the DR beads and the IR beads are in an amount ranging from about 1% to about 99% (w/w) of the total weight of the composition.

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

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

10. A unit dosage form comprising the composition of claim 1.

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

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

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

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

iii) blending and compressing the DR bead and the IR bead into a capsule.

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

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

15. The method of claim 14, wherein the subcoat comprises polyvinyl alcohol.

16. The method of claim 12, wherein the enteric coating comprises methyl acrylate-methacrylic acid copolymers cellulose acetate succinate (CAS); hydroxy propyl methyl cellulose phthalate (HPMCP); PVP; hydroxy propyl methyl cellulose acetate succinate (HPMCAS);

polyvinyl acetate phthalate (PVAP); methyl methacrylate-methacrylic acid copolymers; sodium alginate and stearic acid; guar gum; carbomers; or mixtures thereof.

17. The method of claim 16, wherein the enteric coating comprises a methyl methacrylate-methacrylic acid copolymer.

18. Use of the composition of any of claims 1-9 in the manufacture of a medicament for treating a gastrointestinal disorder in a patient in need thereof.

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

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

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

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

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

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

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

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

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

28. The use of claim 19, wherein the gastrointestinal disorder is Crohn's disease.

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

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

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

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

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

34. Use of the composition of any of claims 1-9 in the manufacture of a medicament for treating a gastrointestinal disorder in a patient in need thereof.

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

36. Use of the composition of any of claims 1-9 in the manufacture of a medicament for treating or relieving pain in a patient in need thereof.

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

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

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

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

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

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

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

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

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

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