CLAIMS

WHAT IS CLAIMED IS:

1. A solid pharmaceutical composition suitable for oral administration to a subject in need thereof, the pharmaceutical composition comprising:

a plurality of delivery constructs; and

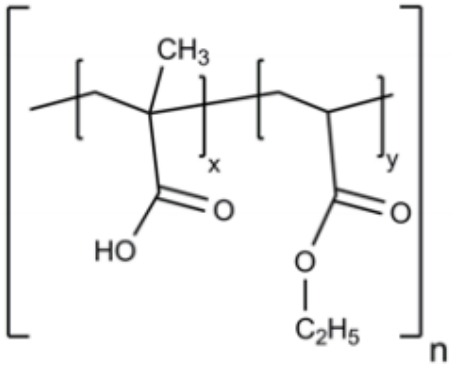
one or more pharmaceutically acceptable excipients;

wherein each of the delivery constructs comprises an amino acid sequence with at least 90% sequence identity to SEQ ID NO: 5 or SEQ ID NO: 13;

wherein at least 80% of the delivery constructs are in a dimer form;

wherein the pharmaceutical composition is formulated as an oral dosage form, the oral dosage form comprising (1) a first coat comprising two or more copolymers each having a different dissolution pH and (2) another coat interior to the first coat and exterior to the delivery constructs and the one or more pharmaceutically acceptable excipients; and

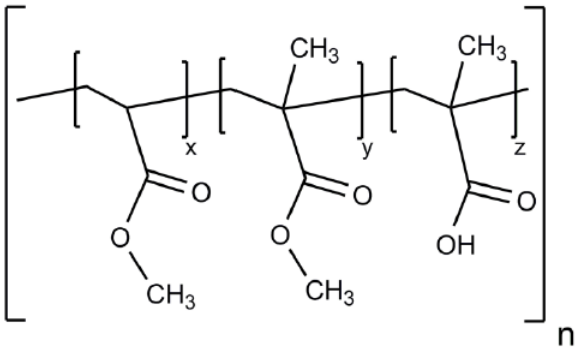
wherein a first copolymer of the first coat comprises a polymer of formula I:



Formula I;

wherein x, y, and n in Formula I are each greater than or equal to one; and

wherein a second copolymer of the first coat comprises a copolymer of formula II:



Formula II;

wherein x, y, z, and n in Formula II are each greater than or equal to one.

2. The pharmaceutical composition of claim 1 wherein in at least one of the one or more pharmaceutically acceptable excipients is a surfactant, wherein the surfactant comprises a poloxamer.

3. The pharmaceutical composition of claim 2, wherein the poloxamer is a poloxamer 188.

4. The pharmaceutical composition of any one of claims 1-3, wherein the one or more pharmaceutically acceptable excipients does not include a polysorbate.

5. The pharmaceutical composition of any one of claims 1-4, wherein the one or more pharmaceutically acceptable excipients comprises a non-ionic lubricant.

6. The pharmaceutical composition of claim 5, wherein the non-ionic lubricant is glyceryl behenate.

7. The pharmaceutical composition of any one of claims 1-6, wherein the one or more pharmaceutically acceptable excipients does not include a magnesium stearate.

8. The pharmaceutical composition of any one of claims 1-7, wherein the pharmaceutical composition is configured to release substantially none of the plurality of delivery constructs after a 1-hour exposure to a solution having a pH of 1.0 in a Type 4 dissolution apparatus in open mode, wherein the solution having the pH of 1.0 is a dissolution media containing hydrochloric acid.

9. The pharmaceutical composition of claim 8, wherein the pharmaceutical composition is configured to release at least 40% of the delivery construct after 2 hours of exposure to a solution having a pH of 7.0 in a Type 4 dissolution apparatus in open mode, wherein the solution having the pH of 7.0 is a citrate/phosphate buffer.

10. The pharmaceutical composition of any one of claims 1-9, wherein a ratio of free carboxyl groups to ester groups in the first copolymer is from 0.8:1 and 1.2:1 and wherein a ratio of free carboxyl groups to ester groups in the second copolymer is from 0.8:1 to 1.2:1.

11. The pharmaceutical composition of any one of claims 1-10, wherein a ratio of the first copolymer of the first coat to the second copolymer of the first coat is from 15:85 to 55:45.

12. The pharmaceutical composition of any one of claims 1-11, wherein the ratio of the first copolymer to the second copolymer is to 30:70.

13. The pharmaceutical composition of any one of claims 1-12, wherein the first coat further comprises an anti-tacking agent, a plasticizer, a surfactant, or a combination thereof.

14. The pharmaceutical composition of any one of claims 1-13, further comprising an additional coat exterior to the first coat.

15. The pharmaceutical composition of claim 14, wherein the additional coat exterior to the first coat comprises hydroxypropylmethylcellulose (HPMC).

16. The pharmaceutical composition of any one of claims 1-15, wherein the another coat comprises HPMC.

17. The pharmaceutical composition of any one of claims 1-16, wherein the oral formulation is in a tablet or a capsule form.

18. The pharmaceutical composition of any one of claims 1-17, wherein the oral formulation is in a unit dose form.

19. The pharmaceutical composition of claim 18, wherein the first coat has a mass from 10 mg to 100 mg per unit dose form.

20. The pharmaceutical composition of claim 18, wherein the plurality of delivery constructs are present in an amount from 1 mg to 20 mg per unit dose of the formulation.

21. The pharmaceutical composition of any one of claims 1-20, wherein each of the delivery constructs comprises the amino acid sequence set forth in SEQ ID NO: 5.

22. The pharmaceutical composition of any one of claims 1-20, wherein each of the delivery constructs comprises the amino acid sequence set forth in SEQ ID NO: 13.

23. A method for producing a solid pharmaceutical composition for oral administration that comprises a plurality of coats according to any one of claims 1-22, the method comprising:

obtaining the delivery constructs that comprise an amino acid sequence with at least 90% sequence identity to SEQ ID NO: 5 or SEQ ID NO: 13;

applying a plurality of coats around the delivery construct, wherein the plurality of coats comprises (1) the first coat comprising two or more copolymers each having a different dissolution pH and (2) the another coat interior to the first coat and exterior to the delivery constructs; and

adding of one or more pharmaceutically suitable excipients to the pharmaceutical composition.

24. The method of claim 23, wherein the method further comprises lyophilizing or spray-drying of the delivery constructs.

25. The method of claim 23, wherein the method further comprises compacting the delivery constructs with the one or more pharmaceutically suitable excipients.

26. Use of the pharmaceutical composition of any one of claims 1-22 in the manufacture of a medicament for the treatment of an inflammatory disease in a subject, wherein the medicament is to be administered orally.

27. The use of claim 26, wherein the inflammatory disease is ulcerative colitis, proctitis, pouchitis, Crohn's disease, multiple sclerosis (MS), systemic lupus erythematosus (SLE), graft versus host disease (GVHD), rheumatoid arthritis, inflammatory bowel disease (IBD), celiac disease, psoriatic arthritis, or psoriasis.

28. The use of claim 26 or claim 27, wherein the administration of the medicament to the subject results in an immunomodulatory response selected from the group consisting of: (i) a decrease in a concentration of fecal calprotectin (FCP) relative to an FCP baseline concentration level present in the subject prior to administration, (ii) a decrease in a concentration of C-reactive protein (CRP) relative to a CRP baseline concentration level present in the subject prior to administration, (iii) a decrease in a Geboes score relative a Geboes score baseline present in the subject prior to administration, or (iv) a combination thereof.

29. The use of claim 27, wherein the inflammatory disease is ulcerative colitis.

30. The use of claim 27, wherein the inflammatory disease is rheumatoid arthritis.

31. The use of claim 27, wherein the inflammatory disease is pouchitis.

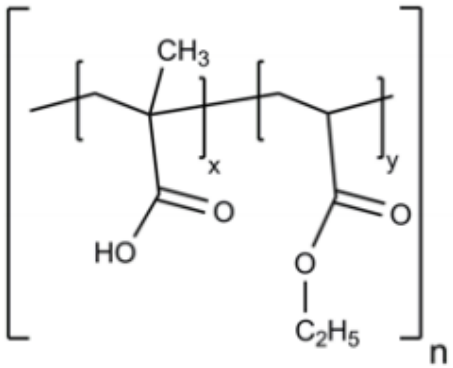
32. A solid oral formulation comprising:

a) a delivery construct consisting of an amino acid sequence set forth in SEQ ID NO: 5 or SEQ ID NO: 13, wherein the delivery construct comprises a carrier that promotes transcytosis of the delivery construct across a polarized gut epithelial cell;

b) one or more excipients; wherein the one or more excipients comprise a non-ionic lubricant; and

c) a first coat comprising two or more copolymers each having a different nominal dissolution pH

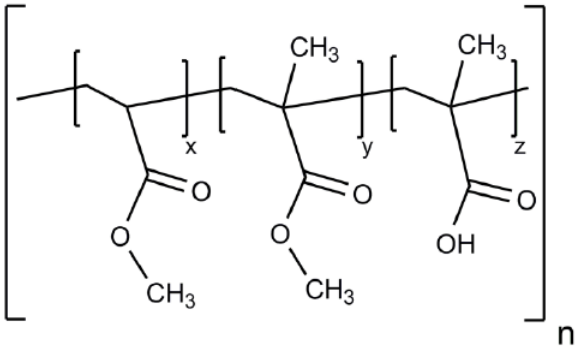
wherein the oral formulation is configured to release substantially none of the IL-10 delivery construct after 1 h exposure to a solution having a pH of 1.0 in a Type 4 dissolution apparatus in open mode, wherein the first copolymer comprises a polymer of formula I:



Formula I;

wherein x, y, and n of Formula I are each greater than or equal to one; and

wherein the second copolymer comprises a polymer of formula II:



Formula II;

wherein x, y, z, and n of Formula II are each greater than or equal to one.

33. The solid oral formulation of claim 32, wherein:

(a) the solution having the pH of 1.0 is a dissolution media containing 0.1M hydrochloric acid; and/or

(b) the formulation is configured to release at least 40% of the delivery construct after 2 hours of exposure to a solution having a pH of 7.0 in a Type 4 dissolution apparatus in open mode, wherein the solution having the pH of 7.0 is a citrate/phosphate buffer, optionally wherein at least 5%, at least 10%, at least 20%, or at least 25% of the delivery construct released following 2 hours of exposure to the solution having the pH of 7.0 is in a dimer form.

34. The solid oral formulation of any one of claims 32-33, wherein:

(a) a ratio of free carboxyl groups to ester groups in the first copolymer is from 0.8:1 and 1.2:1 and wherein a ratio of free carboxyl groups to ester groups in the second copolymer is from 0.8:1 to 1.2:1; and/or

(b) the first copolymer comprises methacrylic acid and ethyl acrylate; and/or

(c) the second copolymer comprises methacrylic acid, methyl methacrylate, and methyl acrylate; and/or

(d) a ratio of the first copolymer to the second copolymer in the first coat is from 15:85 to 55:45; optionally the ratio of the first copolymer to the second copolymer is 20:80, 30:70, 40:60, or 50:50; and/or

(e) the first coat further comprises an anti-tacking agent, a plasticizer, a surfactant, or a combination thereof.

35. The solid oral formulation of any one of claims 32-34, wherein the oral formulation further comprises a second coat located interior of the first coat and external of the IL-10 and one or more

pharmaceutically acceptable excipients, wherein the second coat comprises hydroxypropyl methylcellulose.

36. The solid oral formulation of claim 35, further comprising a third coat interior to the first coat and exterior of the IL-10 delivery constructs and the one or more pharmaceutically acceptable excipients, optionally wherein the third coat comprises HPMC.

37. The solid oral formulation of any one of claims 32-36, wherein:

(a) the IL-10 delivery constructs are present in the formulation in an amount from 1 mg to 20 mg; and/or

(b) the one or more pharmaceutically acceptable excipients comprise a surfactant, optionally wherein the surfactant is a poloxamer, and optionally wherein the poloxamer is a poloxamer 188.

38. The solid oral formulation of claim 32, wherein:

(a) the non-ionic lubricant is glyceryl behenate; and/or

(b) the formulation lacks magnesium stearate.

39. The solid oral formulation of claim any one of claims 32-38, wherein:

(a) the formulation is lyophilized or spray dried; and/or

(b) the formulation is in a tablet or a capsule form.

40. Use of the solid oral formulation of any one of claims 32-39, in the manufacture of a medicament for the treatment of an inflammatory disease in a subject, optionally wherein the inflammatory disease is ulcerative colitis, proctitis, pouchitis, Crohn's disease, multiple sclerosis (MS), systemic lupus erythematosus (SLE), graft versus host disease (GVHD), rheumatoid arthritis, psoriatic arthritis, or psoriasis.

41. The pharmaceutical composition of any one of claims 1-22, or the solid oral formulation of any one of claims 32-39, for use in therapy.