Claims

1. A delayed release drug formulation for oral administration to deliver a drug to the colon of a subject, said formulation comprising:

a core and a coating for the core, the core comprising a drug and the coating comprising an outer layer and at least one layer between the core and the outer layer selected from the group consisting of an isolation layer and an inner layer,

said outer layer comprising a mixture of a first polymeric material which is susceptible to attack by colonic bacteria and a second polymeric material which has a pH threshold at about ~~pH 5~~ pH 6 or above,

said inner layer comprising a third polymeric material which is soluble in intestinal fluid or gastrointestinal fluid, said third polymeric material being selected from the group consisting of a polycarboxylic acid polymer that is at least partially neutralised, and a non-ionic polymer, provided that, where said third polymeric material is a non-ionic polymer, said inner layer comprises at least one additive selected from a buffer agent and a base,

said isolation layer comprising a non-ionic polymer which is soluble in intestinal fluid or gastrointestinal fluid,

wherein the outer layer is applied directly to the inner layer or the isolation layer using a coating preparation formed by combining said first polymeric material in an aqueous medium with said second polymeric material in an organic medium.

2. A delayed release drug formulation as claimed in Claim 1, wherein said organic medium is selected from the group consisting of C_1 to C_4 alcohols; methyl glycol; butyl glycol; acetone; methyl glycol acetate; and mixtures thereof.

3. A delayed release drug formulation as claimed in Claim 1 or Claim 2, wherein said organic medium comprises ethanol.

4. A delayed release drug delivery formulation as claimed in any of Claims 1 to 3, wherein said organic medium is 85 to 98% ethanol.

5. A delayed release drug delivery formulation as claimed in any of the preceding claims, wherein said organic medium contains from about 2% to about 10% polymer solids.

6. A delayed released drug formulation as claimed in any of the preceding claims, wherein said organic medium contains about 6% polymer solids.

7. A delayed release drug formulation as claimed in any of the preceding claims, wherein said aqueous medium is selected from the group consisting of water; C_1 to C_6 alcohol; and mixtures thereof.

8. A delayed release drug formulation as claimed in any of the preceding claims, wherein said aqueous medium is a mixture of water and a C_1 to C_6 alcohol, preferably butan-1-ol.

9. A delayed release drug formulation as claimed in Claim 8, wherein the ratio of water to alcohol in the mixture is at least 5:1, preferably about 11:1.

10. A delayed release drug formulation as claimed in any of the preceding claims, wherein the outer layer has a thickness from about 2 mg/cm^2 to about 10 mg/cm^2 based on the total polymeric material.

11. A delayed release drug formulation as claimed in any of the preceding claims, wherein the outer layer has a thickness of about 7 mg/cm^2 based on the total polymeric material.

12. A delayed release drug formulation as claimed in any of Claims 1 to 9, wherein the outer layer has a thickness from about 3% to about 8% total weight gain (TWG).

13. A delayed release drug formulation as claimed in any of Claims 1 to 9, wherein the outer layer has a thickness of about 5% TWG.

14. A delayed release drug formulation as claimed in any of the preceding claims, wherein the first and second polymeric materials are present in the outer layer in a ratio of up to about 60:40.

15. A delayed release drug formulation as claimed in any of the preceding claims, wherein the first and second polymeric materials are present in the outer layer in a ratio from about 25:75 to about 35:65, preferably about 30:70.

16. A delayed release drug formulation as claimed in any of the preceding claims, wherein the first polymeric material is starch.

17. A delayed release drug formulation as claimed in any of the preceding claims, wherein said

second polymeric material has a pH threshold of about pH 6.5 or above.

~~17.~~18. A delayed release drug formulation as claimed in any of the preceding claims wherein the second polymeric material is a poly(methacrylic acid/methyl methacrylate) copolymer having a molecular weight of about 125,000 g/mol, an acid:ester ratio of about 1:2 and a pH threshold of about pH 7.

~~18.~~19. A delayed release drug formulation as claimed in any of the preceding claims, wherein said third polymeric material is said polycarboxylic acid polymer that is at least partially neutralised.

~~19.~~20. A delayed release drug formulation as claimed in Claim 18, wherein at least 10%, preferably at least 25%, more preferably at least 50%, and most preferably at least 90%, of the carboxylic acid groups of said polycarboxylic acid polymer are in the form carboxylate anions.

~~20.~~21. A delayed release drug formulation as claimed in Claim 18 or Claim 19, wherein said polycarboxylic acid polymer is fully neutralised.

~~21.~~22. A delayed release drug formulation as claimed in any of Claims 18 to 20, wherein said second polymeric material is based on the same polycarboxylic acid polymer as said third polymeric material, said the third polymeric material having a higher degree of neutralisation than the second polymeric material.

~~22.~~23. A delayed release drug formulation as claimed in any of Claims 18 to 21, wherein said polycarboxylic acid polymer of said third polymeric material is selected from polymethacrylates; cellulose acetate phthalate (CAP); polyvinyl acetate phthalate (PVAP); hydroxypropyl methylcellulose phthalate (HPMCP); hydroxypropyl methylcellulose acetate succinate (HPMC AS); cellulose acetate trimellitate (CAT); xanthan gum; alginates; and shellac.

~~23.~~24. A delayed release drug formulation as claimed in any of Claims 18 to 22, wherein said third polymeric material is an at least partially neutralised co-polymer of (meth)acrylic acid and a (meth)acrylic acid C_{1-4} alkyl ester.

~~24.~~25. A delayed release drug formulation as claimed in any of Claims 18 to 23, wherein said third polymeric material is a fully neutralised co-polymer of (meth)acrylic acid and (meth)acrylic acid methyl ester.

~~25.~~26. A delayed release drug formulation as claimed in any of Claims 18 to 24, wherein said

inner layer comprises at least one additive selected from a buffer agent and a base.

26.27. A delayed release drug formulation as claimed in any of the preceding claims, wherein said non-ionic polymer of the inner layer and said non-ionic polymer of the isolation layer are selected independently from the group consisting of methylcellulose (MC); hydroxypropyl cellulose (HPC); hydroxypropyl methylcellulose (HPMC); poly(ethyleneoxide)-graft-polyvinylalcohol; polyvinylpyrollidone (PVP); polyethylene glycol (PEG); and polyvinylalcohol (PVA).

27.28. A delayed release drug formulation as claimed in any of the preceding claims, wherein the formulation comprises said isolation layer and said inner layer.

28.29. A delayed release drug formulation as claimed in Claim 2728, wherein said third polymeric material is the same non-ionic polymer as the non-ionic polymer of the isolation layer.

29.30. A delayed release drug formulation as claimed in any of the preceding claims, wherein the inner layer comprises at least one buffer agent and at least one base.

30.31. A delayed release drug formulation as claimed in any of the preceding claims, wherein the buffer is selected from the group consisting of a carboxylic acid having from 1 to 16 carbon atoms, an alkali metal salt, an alkali earth metal salt, an ammonium salt and a soluble metal salt.

31.32. A delayed release drug formulation as claimed in any of the preceding claims, wherein the buffer is a phosphate salt.

32.33. A delayed release drug formulation as claimed in any of the preceding claims, wherein the buffer is potassium dihydrogen phosphate.

33.34. A delayed release drug formulation as claimed in any of the preceding claims, wherein the buffer is present in the inner layer an amount from about 0.1 wt % to about 20 wt % based on the dry weight of the third polymeric material.

34.35. A delayed release drug formulation as claimed in any of the preceding claims, wherein the base is selected from the group consisting of hydroxide bases, alkali metal bicarbonates, alkali metal carbonates, alkali metal phosphates, alkali metal citrates, or physiologically tolerated amines.

35.36. A delayed release drug formulation as claimed in any of the preceding claims, wherein the base is a hydroxide base.

36.37. A delayed release drug formulation as claimed in any of the preceding claims, wherein the base is sodium hydroxide.

37.38. A method of producing a delayed release drug formulation for oral administration to deliver a drug to the colon as claimed in Claim 1, said method comprising:

forming a core comprising a drug;

coating the core using at least one coating preparation selected from the group consisting of an isolation layer coating preparation comprising a non-ionic polymer that is soluble in intestinal fluid or gastrointestinal fluid, in a solvent system, and an inner layer coating preparation comprising a third polymeric material that is soluble in intestinal fluid or gastrointestinal fluid, in a solvent system, to form an intermediate coated core and;

combining an aqueous preparation of a first polymeric material which is susceptible to attack by colonic bacteria with an organic preparation of a second polymeric material which has a pH threshold of about ~~pH 5~~ pH 6 or above, to form an outer layer coating preparation

coating the intermediate coated core with the outer layer coating preparation to form an outer layer coated core,

wherein the third polymeric material is selected from the group consisting of a polycarboxylic acid that is at least partially neutralised, and a non-ionic polymer, provided that, where the third polymeric material is a non-ionic polymer, said inner coating preparation comprises at least one additive selected from a buffer agent and a base.

38.39. A method as claimed in Claim ~~37~~38, wherein the core is coated directly using said isolation layer coating preparation to form said intermediate coated core.

39.40. A method as claimed in Claim ~~37~~38, wherein the core is coated directly using said inner layer coating preparation to form said intermediate coated core.

40.41. A method as claimed in Claim ~~37~~38, wherein the core is coated directly using said isolation layer coating preparation to form an isolation layer coated core which is then coated directly using said inner layer coating preparation to form said intermediate coated core.

41.42. A method as claimed in any of Claims ~~37~~38 to ~~40~~41, wherein the formulation is as defined in any of Claims 2 to ~~36~~37.

42.43. A method as claimed in any of Claims 3738 to 4142, wherein the solvent system of the inner layer coating preparation or the isolation layer coating preparation is aqueous.

43.44. A method as claimed in any of Claims 3738 to 4243, wherein said third polymeric material is said polycarboxylic acid polymer that is at least partially neutralised, said method comprising dispersing a polycarboxylic acid polymer in a solvent, optionally with a buffer agent, and adding base to at least partially neutralise the polycarboxylic acid polymer to form the inner coating preparation.

44.45. A method as claimed in Claim 4344, wherein the amount of base added is at least sufficient to neutralise at least 10%, preferably at least 25%, more preferably at least 50%, and most preferably at least 90%, of the carboxylic acid groups in the polycarboxylic acid polymer.

45.46. A method as claimed in Claim 4344 or Claim 4445, wherein the amount of base added is more than sufficient to fully neutralise the polycarboxylic acid polymer.

46.47. A method as claimed in any of Claims 3738 to 4243, wherein said third polymeric material is said non-ionic polymer, the pH of the inner coating preparation being adjusted prior to coating to be at least 0.5 pH units higher than the pH threshold of the second polymeric material.

47.48. A method as claimed in any of Claims 3738 to 4647, wherein the pH of the inner coating preparation is adjusted to be from about pH 7.5 to about pH 10, preferably from about pH 7.5 to about pH 8.5, more preferably about pH 8.

48.49. A method as claimed in any of Claims 3738 to 4748, wherein the base is selected from the group consisting of hydroxide bases, alkali metal bicarbonates, alkali metal carbonates, alkali metal phosphates, alkali metal citrates, or physiologically tolerated amines.

49.50. A method as claimed in any of Claims 3738 to 4849, wherein the base is a hydroxide.

50.51. A method as claimed in any of Claims 3738 to 4950, wherein the base is sodium hydroxide.