The inner layer coating preparation was sprayed on to the isolation layer coated cores using the same pan coater as for the isolation layer until the coating amount of HPMC reached 3 mg polymer/cm^2 to form inner layer coated cores. The spray coating parameters were as follows:

Table 8

	Comparative Example 3 and Example 1
Drum speed (rpm)	10 - 12
Nozzle diameter (mm)	0.8
Spray rate (g/min)	2.5
Spray pressure (bar)	0.6
Pattern pressure (bar)	0.8
Air flow (m^3/h)	30
Inlet air temperature (ºC)	62 - 70
Outlet air temperature (ºC)	40.6 - 40.9
Product temperature (ºC)	30.5 - 31

Outer layer

The inner layer coated tablet cores were coated with an outer coating formed of 70% Eudragit® S 100 and 30% high amylose starch.

The outer coating was applied from a mixture of an aqueous starch dispersion and an ethanolic Eudragit® S 100 solution in the following amounts (based on Eudragit® S 100 dry polymer weight):

Table 9

	Comparative Example 3 and Example 1
	mg/cm^2
Starch (raw)	2.45
Glyceryl monostearate	0.36
Polysorbate 80	0.14
Iron Oxide yellow	0.11
Iron Oxide red	0.66
Eudragit® S 100	5
Triethyl citrate	1.43

The aqueous starch dispersion was prepared by dispersing high amylose maize starch, (Eurylon® 6 also known as Amylo N-400) into butan-1-ol, followed by water, under magnetic stirring. The resulting dispersion was heated to boiling and then cooled under stirring overnight.

The Eudragit® S 100 solution was prepared by dispersing Eudragit® S 100 in 96% ethanol under high speed stirring.

The aqueous starch dispersion was added dropwise to the Eudragit® S 100 solution under stirring to obtain a ratio of Eudragit® S 100:starch of 70:30 (Example 1 and 2) or 50:50 (Example 3). The mixture was stirred for 1 hour and triethyl citrate and a GMS emulsion (previously prepared with Polysorbate 80) were added and mixed for further 30 minutes. A suspension of iron oxide red and iron oxide yellow was added and the mixture was stirred for a further 10 minutes.

The GMS emulsion was prepared at a concentration of 5% w/w. Polysorbate 80 (Tween®, 40% based on GMS weight) was dissolved in distilled water followed by dispersion of the GMS. The dispersion was heated at 75 °C for 15 minutes under strong magnetic stirring in order to form an emulsion. The emulsion was cooled at room temperature under stirring.

The pigment suspension was formed by suspending red and yellow iron oxide pigments in 96% ethanol for 10 minutes under homogenization.

The final outer layer coating preparation was sprayed on to the inner layer coated cores using the same pan coater as used to apply the isolation layer having a 0.8 L drum on a batch size of 400 g until the coating amount of Eudragit® S 100 reached 5 mg polymer/cm^2. The spray coating parameters were as follows:

Table 10

Drum speed (rpm)	12
Nozzle diameter (mm)	0.8
Spray rate (g/min)	3.8
Spray pressure (bar)	0.4
Pattern pressure (bar)	0.5
Air flow (m^3/h)	40
Inlet air temperature (ºC)	55-57
Outlet air temperature (ºC)	41-43
Product temperature (ºC)	32.5-33

EXAMPLE 2 and EXAMPLE 3 (5-ASA tablet cores coated with a PVA-based isolation layer/inner layer of HPMC with a buffer and a base/outer layer of a 70:30 mixture of Eudragit® S 100 and high amylose starch)

Isolation layer

The isolation layer was applied from an aqueous dispersion of Opadry® AMB at 3.1 mg/cm^2 (total solids).

Opadry® AMB is a fully formulated coating system based on polyvinyl alcohol (PVA). Opadry® AMB was diluted with purified water under magnetic stirring for 30 minutes to prepare a isolation layer coating preparation.

The isolation layer coating preparation was sprayed onto the 5-ASA cores using a pan coater having a 0.8 L drum on a batch size of 400 g until the coating amount of Opadry® AMB reached the target amount to form isolation layer coated cores. The spray coating parameters were the same as for Comparative Example 3 and Examples 1.

Inner layer

CLAIMS

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

a core, a coating for the core and an isolation layer between the core and the coating, the core comprising a drug, the coating comprising an outer layer and an inner layer and the isolation layer comprising a film-forming non-ionic polymer,

in which the outer layer comprises a mixture of an enzymatically degradable polysaccharide that is degraded by colonic enzymes and a film-forming enteric acrylate polymer having a pH threshold at pH 6 or above,

in which the inner layer comprises a film-forming non-ionic polymer that is soluble in intestinal or gastrointestinal fluid, and a buffer agent in an amount in a range from 25 wt % to 60 wt %, based on the dry weight of the non-ionic polymer of the inner layer, and

in which the non-ionic polymers of the isolation layer and the inner layer are independently selected from the group consisting of methylcellulose (MC), hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC), poly(ethyleneoxide)-graft-polyvinylalcohol, polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), PVP-grafted PEG and polyvinylalchohol (PVA).

2. A delayed release drug formulation according to Claim 1, in which the non-ionic polymer of the inner layer is HPMC.

3. A delayed release drug formulation according to Claim 1 or 2 in which the non-ionic polymer of the isolation layer is HPMC or PVA.

4. A delayed release drug formulation according to Claim 1, 2 or 3, in which the non-ionic polymer is present in the inner layer in an amount from 2 mg/cm2 to 5 mg/cm2, preferably 3 mg/cm2, based on the dry weight of the non-ionic polymer of the inner layer.

5. A delayed release drug formulation according to any preceding claim, in which the buffer agent is present in the inner layer in an amount in a range from 25 wt % to 50 wt %, preferably from 25 wt % to 40 wt %, more preferably 30 wt %, based on the dry weight of the non-ionic polymer in the inner layer.

6. A delayed release drug formulation according to any preceding claim, in which the buffer agent 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.

7. A delayed release drug formulation according to any preceding claim, in which the buffer agent is a phosphate salt, preferably in which the buffer agent is potassium dihydrogen phosphate.

8. A delayed release drug formulation according to any preceding claim, in which the buffer agent is combined with a base.

9. A delayed release drug formulation according to Claim 8, in which 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.

10. A delayed release drug formulation according to Claim 8 or 9, in which the base is a hydroxide base, preferably in which the base is sodium hydroxide.

11. A delayed release drug formulation according to any preceding claim, in which the enzymatically degradable polysaccharide and the enteric acrylate polymer are present in the outer coating in a ratio of at least 10:90, optionally at least 25:75, or from 25:75 to 60:40, or 30:70 or 50:50.

12. A delayed release drug formulation according to any preceding claim, in which the enteric acrylate polymer is present in the outer layer in an amount from 3 to 10 mg/cm2, preferably 5 mg/cm2, based on the dry weight of the enteric acrylate polymer.

13. A delayed release drug formulation according to in any preceding claim, in which the film-forming non-ionic polymer of the isolation layer is the same film-forming non-ionic polymer as present in the inner layer.

14. A method of producing a delayed release drug formulation for oral administration to deliver a drug to the colon according to Claim 1, the method comprising:

forming a core comprising a drug;

initially coating the core with an isolation layer coating preparation comprising a film forming non-ionic polymer in a solvent to form an isolated core;

dissolving a film-forming non-ionic polymer that is soluble in intestinal or gastrointestinal fluid in an aqueous solvent with a buffer agent in an amount in a range from 25 wt % to 60 wt %, based on the dry weight of the non-ionic polymer, to form an inner layer coating preparation having a pH of greater than pH 7;

coating the isolated core using the inner layer coating preparation to form an inner layer coated core; and

coating the inner layer coated core with an outer layer coating preparation comprising a mixture of an enzymatically degradable polysaccharide that is degraded by colonic enzymes and a film-forming enteric acrylate polymer having a pH threshold of pH 6 or above in a solvent system, to form an outer coated core

in which the non-ionic polymers of the isolation layer and the inner layer are independently selected from the group consisting of methylcellulose (MC), hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC), poly(ethyleneoxide)-graft-polyvinylalcohol, polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), PVP-grafted PEG and polyvinylalchohol (PVA).

15. A method according to Claim 14, in which the method comprises adding base to the inner coating layer preparation in an amount sufficient to raise the pH to the required level.

16. A method according to Claim 15, in which the amount of base added to the inner layer coating preparation is sufficient to raise the pH of the inner layer coating preparation to be in a range from pH 7.5 to pH 10, preferably in a range from pH 7.5 to pH 8.5, and more preferably pH 8.

17. A method according to Claim 15 or 16, in which 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.

18. A method according to Claim 15, 16 or 17, in which the base is a hydroxide base, preferably in which the base is sodium hydroxide.

19. A method according to any of Claims 15 to 18, in which the non-ionic polymer the inner layer coating preparation is HPMC.

20. A method according to any of Claims 15 to 19, in which the non-ionic polymer of the isolation layer coating preparation is HPMC or PVA.

21. A method according to any of Claims 15 to 20, in which the core is coated with the inner layer coating preparation until the non-ionic polymer is coated on to the isolated core in an amount from 2 to 5 mg/cm2, preferably 3 mg/cm2, based on the dry weight of the non-ionic polymer of the inner layer coating preparation.

22. A method according to any of Claims 15 to 21, in which the buffer agent is present in the inner layer coating preparation in an amount in a range from 25 wt% to 50 wt %, optionally from 25 wt % to 40 wt %, or 30 wt %, based on the dry weight of the non-ionic polymer of the inner layer coating preparation.

23. A method according to any of Claims 15 to 22, in which the buffer agent 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.

24. A method according to any of Claims 15 to 23, in which the buffer agent is a phosphate salt, preferably in which the buffer agent is potassium dihydrogen phosphate.

25. A method according to any of Claims 15 to 24, in which the enzymatically degradable polysaccharide and the enteric acrylate polymer are present in the outer layer coating preparation in a ratio of at least 10:90, optionally at least 25:75, or from 25:75 to 60:40, or 30:70, or 50:50.

26. A method according to any of Claims 15 to 25, in which the inner coated core is coated with the outer layer coating preparation until the enteric polymer is coated on to the inner coated core in an amount from 3 to 10 mg/cm2, preferably 5 mg/cm2, based on the dry weight of the enteric polymer.

27. A method according to any of Claims 15 to 26, in which the identity of the non-ionic polymer of the isolation layer coating preparation is the same as that for the non-ionic polymer of the inner layer coating preparation.