DELAYED RELEASE DRUG FORMULATION COMPRISING AN OUTER LAYER WITH AN ENZYMATICALLY DEGRADABLE POLYMER, ITS COMPOSITION AND ITS METHOD OF MANUFACTURING

The present invention relates to a method of producing a delayed release drug formulation with a core comprising a drug and a delayed release coating. In particular, it relates to a delayed release formulation for delivering a drug to the colon.

The targeting of drugs to the intestine is well known and has been known for over one hundred years. Commonly, the target of the drugs is the small intestine although the colon can be utilised as a means of achieving local therapy or systemic treatment. The requirements for the coatings on the drugs are different depending on the target site. In order to reach the colon, it is necessary for the drugs to pass through the small intestine, and therefore it is a requirement that a delayed release coating intended to release the drug in the colon does not release the drug in the small intestine.

Coated products for release in the small intestine commonly use polymer coatings which dissolve or disintegrate in a pH dependent manner. In the low pH environment of the stomach, the polymer coating is insoluble. However, on reaching the small intestine, the pH rises to 5 and above and the polymeric coating dissolves or disintegrates. A commonly used coating is one containing ionizable carboxylic groups. At higher pH levels, the carboxylic groups ionize, allowing the polymer coatings to disintegrate or dissolve. Common polymers of this type which are used include Eudragit® L and Eudragit® S.

Various methods of improving the release in the small intestine by ensuring an earlier release of the drug are known. US2008/0200482 is one of a number of references which discloses partially neutralizing the carboxylic groups in order to reduce the pH at which disintegration occurs. WO2008/135090 discloses a tablet with an inner coat of partially neutralized material and an outer coat with less or no neutralization. This is said to result in disintegration at an earlier time point when transferred from the stomach.

Release of drugs in the colon typically requires an alternative approach. The colon is susceptible to a number of disease states, including inflammatory bowel disease, irritable bowel syndrome, constipation, diarrhoea, infection and carcinoma. In such conditions, drug targeting to the colon would maximise the therapeutic effectiveness of the treatment. The colon can also be utilised as a portal for the entry of drugs into the systemic circulation. Various formulations have been developed for colonic drug delivery, including pro-drugs as

CLAIMS

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

forming a core comprising a drug;

combining a first aqueous preparation of an enzymatically degradable starch which is degradable by colonic bacterial enzymes; a second aqueous preparation of a film-forming enteric acrylate polymer having a pH threshold of pH 6 or above; and an organic anti-tack agent selected from glyceryl monostearate and stearic acid, to form an outer layer coating preparation; and

coating the core with the outer layer coating preparation to form an outer layer coated core;

in which the proportion of the enzymatically degradable starch to the film-forming enteric acrylate polymer in the outer coating preparation is in a range from 10:90 to 50:50; and

in which the outer layer coating preparation comprises no more than 5% v/v organic solvent.

2. A method according to Claim 1, in which the second aqueous preparation is formed by suspending the enteric polymer in water under stirring to form a suspension, and partially neutralising the suspension with a base.

3. A method according to Claim 2, in which the base is added to the suspension in an amount sufficient to neutralise from 10% to 30%, preferably from 15% to 20%, of the carboxylic acid groups in the enteric polymer.

4. A method according to Claim 2 or 3, in which the suspension is partially neutralised using aqueous ammonia.

5. A method according to Claim 4, in which the aqueous ammonia has a concentration from 0.5 N to 2 N, preferably 1 N.

6. A method according to any preceding claim, in which the organic anti-tack agent is in the form of an aqueous dispersion.

7. A method according to Claim 6, in which the aqueous dispersion comprises a surfactant.

8. A method according to Claim 7, in which the surfactant is non-ionic.

9. A method according to Claim 7 or 8, in which the surfactant is hydrophilic.

10. A method according to any preceding claim, in which the core is pre-coated with either an isolation layer comprising a film-forming non-ionic polymer that is soluble in gastrointestinal fluid; or an inner layer comprising a polymeric material which is soluble in intestinal or gastrointestinal fluid, the 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 the polymeric material is a non-ionic polymer, the inner layer comprises at least one additive selected from a buffer agent and a base; or both the isolation layer and the inner layer.

11. A method according to Claim 10, in which the inner layer comprises a buffer agent and a base.

12. A delayed release drug formulation for oral administration to deliver a drug to the colon, the formulation produced according to a method according to any preceding claim, comprising:

a core comprising a drug, and

an outer coating layer for the core, the outer coating layer comprising a mixture of an enzymatically degradable starch which is degradable by colonic bacterial enzymes, a film-forming enteric acrylate polymer having a pH threshold at pH 6 or above, and an organic anti-tack agent selected from glyceryl monostearate and stearic acid;

in which the outer coating layer comprises no more than 5000 ppm residual free organic solvent;

and

in which the proportion of the enzymatically degradable starch to the film-forming enteric acrylate polymer in the outer coating preparation is in a range from 10:90 to 50:50.

13. A delayed release drug formulation according to Claim 12, in which the outer coating layer comprises at least 10% by weight of at least one plasticiser based on the weight of the film-forming enteric polymer.

14. A delayed release drug formulation according to Claim 12 or 13 comprising an inner layer located between the core and the outer coating layer, in which the inner layer comprises a film-forming non-ionic polymer that is soluble in gastrointestinal fluid, a buffer agent, and a base.

15. A delayed release drug formulation according to Claim 12, 13 or 14 comprising an isolation layer located on the surface of the core, the isolation layer comprising a film-forming non-ionic polymer that is soluble in gastrointestinal fluid.