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Novel polymeric film coatings for colon targeting: Drug release from coated pellets

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ABSTRACT

The aim of this study was to prepare and characterize novel types of polymer coated pellets allowing for the site-specific delivery of drugs to the colon. 5-Aminosalicylic acid (5-ASA)-loaded beads were prepared by extrusion–spheronization and coated with different Nutriose:ethylcellulose blends. *In vitro* drug release from these systems was measured under various conditions, including the exposure to fresh fecal samples from inflammatory bowel disease patients under anaerobic conditions. Nutriose is a starch derivative, which is preferentially degraded by enzymes secreted by the microflora in the colon of Crohn's disease and ulcerative colitis patients. Interestingly, the release of 5-ASA (which is commonly used for the local treatment of inflammatory bowel diseases) could effectively be suppressed upon exposure to release media simulating the conditions in the upper GIT, irrespective of the degree of agitation and presence or absence of enzymes. But as soon as the pellets came into contact with fecal samples of inflammatory bowel disease patients, the release rate significantly increased and the drug was released in a time-controlled manner. Thus, this novel type of colon targeting system is adapted to the pathophysiology of the patient. Furthermore, culture media containing specific colonic bacteria are presented providing an interesting potential as substitutes for fresh fecal samples.

1. Introduction

The site-specific delivery of a drug to the colon can provide major advantages for a pharmacotherapy, for instance if inflammatory bowel diseases are to be treated locally. Conventional dosage forms lead to a rapid and complete drug release within the stomach and – generally – to subsequent absorption into the blood stream. Consequently, the systemic drug concentrations and related undesired side effects can be considerable. At the same time, the resulting drug concentrations at the site of action (the inflamed colon) are low, resulting in poor therapeutic efficacies. An ideal dosage form should effectively suppress drug release in the stomach and small intestine. But once the colon is reached, drug release should set on and be time-controlled (including –if desired –rapid and complete release). In the case of inflammatory bowel disease treatments (e.g., Crohn's disease and ulcerative colitis), the drug is, thus, released at its target site, providing optimal therapeutic effects and minimized undesired side effects.

Different types of advanced drug delivery systems have been described in the literature in order to provide such site-specific drug delivery to the colon. Generally, the drug is embedded within a polymeric matrix (Alias et al., 2007), or a drug reservoir (e.g., drug-loaded pellet, capsule or tablet) is surrounded by a polymeric film coating. The ideal polymers used for this purpose are poorly permeable for the drug in the upper GIT, but become permeable as soon as the colon is reached. In order to allow for such an increase in drug permeability different types of systems have been proposed, for instance based on: (i) changes in the pH along the GIT (Ibekwe et al., 2006), (ii) polymer degradation by enzymes that are preferentially located in the colon (Milojevic et al., 1996a,b; Cummings et al., 1996; Leong et al., 2002; Basit et al., 2004; Siew et al., 2004), or (iii) structural changes occurring in the polymeric networks, such as crack formation in poorly permeable film coatings (Yang et al., 2002; Gazzaniga et al., 2006). Alternatively, drug release might already start in the stomach, but at a rate that is sufficiently low to assure that the release still continues in the colon. An interest-

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ing example for an enzymatically triggered drug delivery system is COLAL (Thompson et al., 2001; McConnell et al., 2008a). The latter is based on an amylose:ethylcellulose coating and currently studied in clinical trials with prednisolone sodium metasulfabenzoate for the local treatment of ulcerative colitis.

However, great care has to be paid, because the pathophysiological conditions in the colon of patients suffering from inflammatory bowel diseases can be significantly different from those in healthy subjects (Siccardi et al., 2005; Friend, 2005; McConnell et al., 2008a). This concerns in particular: (i) the pH of the contents of the GIT (Fallingborg et al., 1993; McConnell et al., 2008b), (ii) the quality and quantity of the (enzyme secreting) microflora (El Yamani et al., 1992; Carrette et al., 1995; Favier et al., 1997), as well as (iii) the transit times in the various GIT segments (Hebden et al., 2000). Thus, a delivery system which successfully delivers the drug to the colon in a healthy subject might fail in a patient. Also, the inter- and intra-individual variability of the therapeutic effects might be considerable if the dosage form is not appropriately adapted to the disease state.

To overcome these restrictions, recently novel types of polymeric film coatings have been proposed based on blends of the starch derivative Nutriose and ethylcellulose (Karrout et al., 2009, in press). Nutriose is a water-soluble, branched dextrin with a high fiber content. It is produced by the chromatographic separation of a dextrin fraction derived from maize, wheat or other edible starches in the food industry (Wils et al., 2008). The investigated Nutriose type in this study is "Nutriose FB", which is prepared by roasting wheat starch under controlled conditions (essentially with respect to acidity, moisture, time and temperature). Upon purification with activated carbon and anionic and cationic resins, the hydrolyzed dextrin is subjected to a chromatographic separation, removing glucose and lower molecular weight oligosaccharides. The final product – Nutriose FB – is a blend of glucose polymers with a relatively narrow range of molecular weight (number average molecular weight, Mn = 2000–4000 Da; weight average molecular weight, Mw = 4000–6000 Da). The degree of polymerization is in the range of 12–25. Due to the presence of α-1,6 linkages and non-digestible glycoside linkages (e.g., α-1,2 and α-1,3), this starch derivative is only incompletely hydrolyzed and absorbed in the small intestine (approximately to 10–15%), but it is progressively fermented to about 85% in the colon. Furthermore, Nutriose is known to exhibit significant pre-biotic effects, normalizing the microflora in the colon (Van den Heuvel et al., 2004, 2005; Pasman et al., 2006; Lefranc-Millot et al., 2006). This is particularly beneficial for patients suffering from inflammatory bowel diseases, such as Crohn's diseases and ulcerative colitis. The presence of the ethylcellulose in the films avoids premature dissolution of the polymeric networks in the upper GIT (Nutriose being water-soluble) (Siew et al., 2000a,b; McConnell et al., 2007). Promising water uptake and dry mass loss rates and extents of such Nutriose:ethylcellulose blends have been reported (Karrout et al., 2009, in press). However, these results were obtained with thin, free films and, yet, it is unclear whether this type of polymer blends is able to appropriately control the resulting drug release kinetics from coated dosage forms.

In this study, coated pellets have been studied as advanced drug delivery systems. The use of small, multiparticulate dosage forms (e.g., pellets and mini-matrices) provides the following major advantage compared to single unit dosage forms (e.g., tablets or capsules): (i) the all-or-nothing effect can be avoided: if a tablet gets accidentally damaged within the upper GIT, the entire drug dose is lost and (ii) the gastric emptying time is less variable, because the pylorus can be passed even in the contracted state (Digenis, 1994). Furthermore, significant drug amounts can be incorporated in the core of coated dosage forms. This is particularly important for highly dosed drugs, such as 5-aminosalicylic acid (5-ASA), which is the standard drug for the local treatment of inflammatory bowel diseases (Crohn's disease and ulcerative colitis) (Desreumaux et al., 2001; Rousseaux et al., 2005; Dubuquoy et al., 2006).

The major aim of this study was to evaluate the ability of Nutriose:ethylcellulose blends to provide site-specific drug delivery to the colon. 5-ASA release from coated pellets was monitored in the presence and absence of fecal samples from inflammatory bowel disease patients. For reasons of comparison, also drug release from commercially available products was determined.

2. Materials and methods

2.1. Materials

Nutriose FB 06 (Nutriose; Roquette Freres, Lestrem, France); aqueous ethylcellulose dispersion (Aquacoat ECD 30; FMC Biopolymer, Philadelphia, USA); triethylcitrate (TEC; Morflex, Greensboro, USA); 5-aminosalicylic acid (5-ASA; Sigma–Aldrich, Isle d'Abeau Chesnes, France); microcrystalline cellulose (Avicel PH 101; FMC Biopolymer, Brussels, Belgium); bentonite and polyvinylpyrrolidone (PVP, Povidone K 30) (Cooperation Pharmaceutique Francaise, Melun, France); pancreatin (from mammalian pancreas = mixture of amylase, protease and lipase) and pepsin (Fisher Bioblock, Illkirch, France); extracts from beef and yeast as well as tryptone (=pancreatic digest of casein) (Becton Dickinson, Sparks, USA); L-cysteine hydrochloride hydrate (Acros Organics, Geel, Belgium); cysteinated Ringer solution (Merck, Darmstadt, Germany). Pentasa (pellets, batch number: JX 155), Asacol (capsules filled with coated granules, batch number: TX 143) and Lialda (tablets, batch number: NA 647 D) are commercially available products produced by Ferring, Meduna and Shire, respectively.

2.2. Preparation of drug-loaded pellet cores

Drug-loaded pellet cores (diameter: 710–1000 μm; 60% 5-ASA, 32% microcrystalline cellulose, 4% bentonite, 4% PVP) were prepared by extrusion and spheronization. The powders were blended in a high speed granulator (Gral 10; Collette, Antwerp, Belgium) and purified water was added until a homogeneous mass was obtained (41 g of water for 100 g of powder blend). The wetted mixture was passed through a cylinder extruder (SK M/R, holes: 1 mm diameter, 3 mm thickness, rotation speed: 96 rpm; Alexanderwerk, Remscheid, Germany). The extrudates were subsequently spheronized at 520 rpm for 2 min (Spheronizer Model 15; Calveva, Dorset, UK) and dried in a fluidized bed (ST 15; Aeromatic, Muttenz, Switzerland) at 40 °C for 30 min. The size fraction "710–1000 μm" was obtained by sieving.

2.3. Preparation of coated pellets

Nutriose was dissolved in purified water (5%, w/w), blended with plasticized aqueous ethylcellulose dispersion (25% TEC, overnight stirring; 15% (w/w) polymer content) at a ratio of 1:2, 1:3, 1:4, 1:5 (w/w, based on the non-plasticized polymer dry mass) and stirred for 6 h prior to coating. The drug-loaded pellet cores were coated in a fluidized bed coater equipped with a Wurster insert (Strea 1; Aeromatic-Fielder, Bubendorf, Switzerland) until a weight gain of 5, 10, 15 and 20% (w/w) was achieved. The process parameters were as follows: inlet temperature = 39 ± 2 °C, product temperature = 40 ± 2 °C, spray rate = 1.5–3 g/min, atomization pressure = 1.2 bar, nozzle diameter = 1.2 mm. After coating, the beads were further fluidized for 10 min and subsequently cured in an oven for 24 h at 60 °C.