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Mucoadhesive platforms for targeted delivery to the colon

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ABSTRACT

A novel platform system, comprising a mucoadhesive core and a rapid release carrier, was designed for targeted drug delivery to the colon. Prednisolone pellets containing different carbomers, including Carbopol 971P, Carbopol 974P and Polycarbophil AA-1, with or without organic acids, were produced by extrusion–spheronization. Mucoadhesive pellets were coated with a new enteric double-coating system, which dissolves at pH 7. This system comprises an inner layer of partially neutralized Eudragit® S and buffer salt and an outer coating of standard Eudragit® S. A single layer of standard Eudragit S was also applied for comparison purposes. Dissolution of the coated pellets was assessed in USP II apparatus in 0.1 N HCl followed by Krebs bicarbonate buffer pH 7.4. Visualization of the coating dissolution process was performed by confocal laser scanning microscopy using fluorescent markers in both layers. The mucoadhesive properties of uncoated, single-coated and-double coated pellets were evaluated *ex vivo* on porcine colonic mucosa. Mucoadhesive pellets coated with a single layer of Eudragit® S release its cargo after a lag time of 120 min in Krebs buffer. In contrast, drug release from the double-coated mucoadhesive pellets was significantly accelerated, starting at 75 min. In addition, the mucoadhesive properties of the core of the double coated pellets were higher than those from single-coated pellets after the core had been exposed to the buffer medium. This novel platform technology has the potential to target the colon and overcome the variability in transit and harmonize drug release and bioavailability.

1. Introduction

The complexity and variability in gastrointestinal physiology presents a challenge for oral drug delivery, particularly in the case of modified release dosage forms (McConnell et al., 2008a). One such physiological parameter, which is subject to marked variability, is gastrointestinal transit. Total transit through the gut can be as short as a few hours or as long as a several days (Varum et al., 2010a). For example, the total gastrointestinal transit time of the osmotic-pump system (Oros®) ranged from 5.1 to 58.3 h in healthy volunteers (John et al., 1985). Transit through the colon makes the greatest contribution to overall variability in gastrointestinal transit. For instance, it has been reported that the transit time of dosage forms through the colon can range from 0 to 72 h (Coupe et al., 1991; Wilding, 2001) and in a recent study, pellets were still present in the colon 5 days after oral administration (Basit et al., 2009).

In a study designed to evaluate the *in vivo* behavior of a bacteria-sensitive colonic delivery system, in one subject the coated capsule was voided intact due to rapid transit through the gut (Tuleu et al., 2002). A failure to disintegrate was also observed with pH-sensitive polymer coated tablets (Schroeder et al., 1987; Sinha et al., 2003; Ibekwe et al., 2006, 2008). This is not restricted to tablets, as enteric coated pellets are also not immune to the pass-through effect (McConnell et al., 2008b). Therefore, the impact of colonic transit variability on formulation performance is independent of the type of dosage form and the trigger mechanism.

Considering this variability, an increased or harmonized residence time in the colon would be beneficial. This can be achieved using the mucoadhesion approach. This concept would offer significant therapeutic advantages, such as an increase in drug absorption or an improvement in topical efficacy (Smart et al., 1984; Ch'ng et al., 1985). Acrylic acid polymers have been recently suggested as potential candidates for the development of mucoadhesive dosage forms intended to target the lower gut (McGirr et al., 2009; Varum et al., 2010b). However, these materials present technical problems when formulated in solid dosage forms if a wetting step is required, due to the gelling and swelling properties, resulting in tacking. This problem has been addressed by using strong electrolytes, such as calcium chloride solutions (Neau et al., 1996, 2000) or high levels of spheronization aid (Awad et al., 2002; Mezreb et al., 2004). However, a significant reduction in mucoadhesive properties was observed *in vitro* (Gómez-Carracedo et al., 2001).

The combination of the mucoadhesion concept with a colon-specific drug delivery vehicle would contribute to a more efficient colonic targeting and avoid the pass-through effects. Recently, a novel enteric double-coating system with accelerated drug release

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in the intestine was developed (Liu et al., 2009a; Liu and Basit, 2010). This concept was further developed to target the ileo-colonic region (Liu et al., 2010). This double-coating system successfully accelerated drug release from tablets compared to the standard Eudragit® S single-coating. Furthermore, rapid coating dissolution may trigger an earlier exposure of a mucoadhesive platform in the ascending colon, where the mucus turnover and colonic motility are lower (Lehr et al., 1991; Rubinstein and Tirosh, 1994) and mucus is thicker compared to the small intestine (Varum et al., 2010b).

The aim of this work was to investigate the combination of an ileo-colonic drug delivery platform with mucoadhesive characteristics for improved colonic targeting. In order to attain this, the usefulness of organic acids in reducing tack of carbomer polymers during the extrusion–spheronization process was assessed. Further developments were made towards the application and optimization of a novel double-coating system based on Eudragit® S and its implications in the mucoadhesive properties after exposure to media resembling the lower gut. The mechanisms underlying the acceleration process in this system were also elucidated.

2. Materials and methods

2.1. Materials

Prednisolone was purchased from Aventis Pharma., Antony France. Microcrystalline cellulose (Avicel® PH101) was obtained from FMC Biopolymer, Philadelphia, USA. Lactose monohydrate and polyvinylpirrolidone (K30) and citric acid anhydrous were purchased from VWR International Ltd., Poole, UK. Carbopol 974P NF, Carbopol 971P NF and Polycarbophil AA-1 were kindly donated by Lubrizol Advanced Materials Europe BVBA, Brussels, Belgium. Eudragit® S was kindly donated by Evonik Röhm GmbH, Darmstadt, Germany. Eudragit® S is a methacrylic acid and methyl methacrylate copolymer in the ratio 1:2 with a dissolution pH threshold of 7. It is composed of 27.6–30.7% methacrylic acid units on dry substance and has an acid value equivalent to 180–200 mg KOH/g polymer. Potassium dihydrogen phosphate and polysorbate 80 were purchased from Sigma–Aldrich Co. Ltd., Dorset, UK. Triethyl citrate was supplied by Lancaster Synthesis, Lancashire, UK. Glyceryl monostearate (Inwitor 900) was purchased from Hüls AG, Witten, Germany. Fluorescein and rhodamine B were purchased from Sigma–Aldrich Co. Ltd., Dorset, UK.

2.2. Rheological analysis

0.5% (w/v) carbomer (Carbopol 974 NF, Carbopol 971 NF and Polycarbophil AA-1) solutions were prepared by dispersing polymer into 20 ml of distilled water and stirring overnight. Carbomer solutions with citric acid were prepared at different carbomer:citric acid ratios (1:0, 1:1, 1:0.5, 1:0.25) as described above. Viscosity of carbomer aqueous solutions was determined using a rotational rheometer (Bohlin Instruments, Cirencester, UK). Briefly, 2 ml of carbomer dispersion were gently spread on the base of the rheometer and the cone and plate geometry was used with a radius of 50 mm and angle of 2° for frequency measurements. All measurements were performed at 25 °C, controlled by a thermostatic system. Viscosity of carbomer dispersions was measured in the shear rate range of 1–200 (1/s), in triplicate. The pH of these carbomer dispersions was measured with a pH meter (Hanna Instruments, Bedfordshire, UK).

2.3. Pellet manufacture

Prednisolone was chosen as a model drug. Microcrystalline cellulose was used as a spheronization aid and citric acid as a pH modifier (5%, w/w). Three different grades of carbomer polymers were used, namely, Carbopol 971P NF, Carbopol 974P NF and Polycarbophil AA-1, at concentrations ranging from 0 to 20% (w/w) of the total powder batch (50 g). Distilled water was used as a binding liquid and the required amount of water was optimized in order to achieve a high yield of pellets within a size range of 1.0–1.4 mm and acceptable sphericity. Briefly, dry powders were mixed in a planetary mixer (Kenwood Major) for 10 min, the required amount of distilled water was then added dropwise and the mixing continued for an additional 15 min.

The resultant wet mass was tightly packed into the ram extrusion assembly and extruded at 200 mm/min through a 1 mm diameter multiple hole die. The equipment used was the Instron® (Instron, High Wycombe, United Kingdom) equipped with a 10 kN load cell which was connected to an *in*-house designed device to fit the piston inserted into the ram extrusion assembly. The extrudate was spheronized until spherical pellets were obtained using a spheronizer (Caleva model 120, G.B. Caleva Ltd., Sturminster Newton, UK). Pellets were dried overnight at 40 °C (Gallenkamp, Weiss-Gallenkamp, United Kingdom) sieved using a nest of standard sieves (Endecott, Endecott Ltd., London, UK) on a $\sqrt{2}$ progression (500, 710, 1000, 1400, 1700, 2360 μm aperture). The size range of pellets between 1000 and 1400 μm was used for further characterization.

2.4. Eudragit® S double-coating of pellets

2.4.1. Inner coating

The 1.0–1.4 mm pellet fraction was used for the coating and 1.2 mm was considered as a mean diameter for coating calculations. The inner coating comprises a partially neutralized Eudragit S dispersion and a buffer agent. Triethyl citrate (TEC 50%, w/w) and potassium dihydrogen phosphate (10%, w/w), both based on polymer weight, were dissolved in water under mechanical stirring (Heidolph RZR1 stirrer, Heidolph Instruments, Schwabach, Germany) for 15 min. Eudragit® S was dispersed into the above solution under stirring and then the dispersion was neutralized to pH 8 using 1 M NaOH and stirring continued for 60 min. Glyceryl monostearate (GMS, 10%, w/w, based on polymer weight) was added into the Eudragit® S solution and mixed for 15 min prior to coating. The final dispersion contained 10% (w/w) of total solid contents. The coating level was set to 5 mg polymer/cm^2. Batches of 30 g of pellets were coated using a Strea-1 bottom spray fluidized bed coater (Aeromatic AG, Bubendorf, Switzerland) and the coating conditions were: inlet air temperature 50 °C, outlet air temperature 40 °C, fan capacity 15, atomizing pressure 0.2 and flow process rate 1.0 ml/min. Coated pellets were further fluidized for 15 min and cured at 40 °C for at least 2 h, before applying the outer coating.

2.4.2. Outer coating

TEC (20%, w/w, based on polymer weight) was dissolved into 90% ethanol for 10 min and Eudragit® S was slowly added into the ethanolic solution under stirring and mixing continued for 60 min. GMS (10% based on polymer weight) was added to the above solution and mixed for 15 min. The final dispersion contained 10% (w/w) of total solid contents. The coating level was controlled by the amount of polymer applied onto the pellets surface. The coating was performed as reported above but using a slower flow rate (0.8 ml/min). Pellets were further air dried for 15 min in the coating equipment and cured in the oven at 40 °C for at least 2 h.

For comparison purposes, single-coated pellets were prepared as reported here at the same coating level (5 mg/cm^2).

2.5. In vitro drug release

In order to closely resemble the conditions of the ileo-colonic region, Krebs bicarbonate buffer pH 7.4 was used as a dissolution medium after the acid stage (Fadda and Basit, 2005; Fadda