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Research paper

A novel double-coating approach for improved pH-triggered delivery to the ileo-colonic region of the gastrointestinal tract

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ABSTRACT

Oral pH-responsive systems for drug delivery to the ileo-colonic region of the gastrointestinal tract show poor site specificity. Here, we describe a novel double-coating concept, based on the acrylic polymer EUDRAGIT® S, which provides improved functionality for targeting performance. The coating system comprises an inner layer of partially neutralised EUDRAGIT® S and buffer agent and an outer coat of standard EUDRAGIT® S. Tablets containing prednisolone were coated with double-layer formulations with different inner coat compositions. A conventional single coating was also applied for comparison purposes. Dissolution of the coated tablets was assessed using USP II apparatus in 0.1 M HCl for 2 h followed by pH 7.4 physiological bicarbonate buffer (Krebs buffer), a medium which closely resembles the ionic composition and buffer capacity of the fluid in the distal small intestine. Following acid exposure, drug release from the EUDRAGIT® S single-layer-coated tablets in pH 7.4 Krebs buffer was delayed for 120 min. Release from the double-coated tablets was significantly faster compared to the single-coated tablets and was found to be affected by the pH and buffer capacity of the inner coat. The drug release lag time from the optimised double-coating formulation with an inner coat consisting of 10% KH_2PO_4 (neutralisation pH of 8.0) was 40 min. The accelerated coat dissolution and subsequent rapid drug release from the double-coating system can potentially overcome the limitations of conventional EUDRAGIT® S coatings for ileo-colonic delivery.

1. Introduction

The distal segments of the gastrointestinal (GI) tract have been extensively explored as a site for drug delivery, both systemic and topical [1]. The use of pH-responsive systems is one of the most commonly exploited approaches for ileo-colonic targeting. These systems utilise polymers which are insoluble in the low-pH environment of the proximal gut (1–2.5 in the stomach and 6.6 ± 0.5 in the proximal small intestine) and dissolve at the higher pH of the distal gastrointestinal tract (7.5 ± 0.4 in the distal small intestine) [2]. Gastrointestinal pH normally reaches a peak at the ileo-caecal junction and is often followed by a drop on entry into the colon [3]. The polymethacrylate polymer EUDRAGIT® S (dissolves at pH > 7.0) has been routinely used as a coating material for pH-dependent ileo-colonic release systems. A number of drug products based on EUDRAGIT® S are commercially available for the treatment of inflammatory bowel disease, such as mesalazine (Asacol®, Lialda®/Mezavant®) and budesonide (Budenofalk®).

Despite their widespread clinical application and commercial success, inherent problems have been reported with EUDRAGIT® S-coated preparations. Failure of disintegration has been reported for EUDRAGIT® S-coated tablets *in vivo* [4–9]. McConnell et al. recently reported the same phenomenon of disintegration failure with EUDRAGIT® S-coated pellets [10]. The inconsistency in performance has been attributed to variability in intestinal pH and transit [7,11]. Such coated dosage forms need to be exposed to high-pH conditions, typically found at the terminal end of the small intestine, for substantial periods of time for dissolution of the polymer coating to occur. The lack of free fluid in the colon [12] also contribute to the slow and incomplete dissolution of EUDRAGIT® S coatings and the consequent failure of drug release. Hence, there is a clear need to develop coatings which dissolve quickly and fully upon reaching the colon.

A number of approaches have been proposed to improve the performance of pH-dependent ileo-colonic release systems. For example, Schellekens et al. [13] described a pulsatile system containing disintegrants in an EUDRAGIT® S coating. Once the dissolution pH threshold of EUDRAGIT® S is reached, the swelling of the disintegrant can expedite the rupture of the coat. Ibekwe et al. [14] introduced a new concept based on a combination of

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pH-responsive (EUDRAGIT® S) and bacterially-triggered (resistant starch) mechanisms in a single-layer matrix film. Both trigger mechanisms contribute to site-specific delivery to the ileo-colonic region, with each trigger acting as a failsafe to ensure appropriate drug targeting. This was confirmed in a recent comprehensive human study using scintigraphic techniques [14].

In this paper, we propose to apply a novel concept that we recently introduced, a concept which was shown to accelerate the dissolution of pH-sensitive coatings for drug delivery to the upper small intestine [15,16]. Enteric drug delivery systems in the small intestine can often suffer a lag time before coating dissolution occurs, similar to that described in the colon. To decrease this lag time a novel system was developed consisting of a double-coating based on EUDRAGIT® L 30 D-55 (which dissolves at pH > 5.5); the inner coat consists of partially neutralised enteric polymer (and organic acid) and the outer coat of a standard enteric polymer. This can be applied to solid dosage forms. With this concept, substantially accelerated coating dissolution was observed along with rapid drug release in simulated upper small intestine conditions *in vitro*. The expedited coat dissolution was attributed to the elevated buffer capacity and ionic strength of the inner coat. The concept is extended here to EUDRAGIT® S coatings for ileo-colonic delivery to potentially improve their performance by accelerating the dissolution process once the threshold dissolution pH of the polymer coating is reached.

To be able to prove the concept *in vitro*, it is important to test the system in an appropriate manner. Compendial phosphate buffer systems are often used to assess drug release from pH-responsive dosage forms but these do not fully reflect the complex nature of gastrointestinal fluid and consequently often give poor *in vivo in vitro* correlations [17–20]. This can be significantly improved by using physiological bicarbonate buffers, fluids which better simulate the intestinal environment when used as dissolution media [8,18,21,22]. The objective of the present study was therefore to design a novel double-coated system based on EUDRAGIT® S to provide accelerated coating dissolution and drug release in conditions resembling the ileo-colonic region of the gastrointestinal tract.

2. Materials and methods

2.1. Materials

EUDRAGIT® S was donated by Evonik Röhm GmbH, Darmstadt, Germany. EUDRAGIT® S is a methacrylic acid and methyl methacrylate copolymer (1:2), with a dissolution pH threshold of 7.0. The polymer has 27.6–30.7% methacrylic acid units on dry substance and an acid value equivalent to 180–200 mg KOH/1 g polymer [23]. Citric acid, potassium dihydrogen phosphate and ammonium carbonate were purchased from Sigma–Aldrich Co. Ltd., Dorset, UK. Triethyl citrate was obtained from Lancaster Synthesis, Lancashire, UK. Glyceryl monostearate (Imwitor 900) was obtained from Hüls AG (Witten, Germany). Polysorbate 80 was purchased from Sigma–Aldrich Co. Ltd., Dorset, UK. Prednisolone was purchased from Aventis Pharma., Antony, France. Lactose (Pharmatose) was obtained from Ellis and Everard, Essex, UK. Cross-linked sodium carboxymethylcellulose was donated by FMC International, Cork, Ireland. Polyvinylpyrrolidone 44000 was purchased from VWR International Ltd, Poole, UK. Magnesium stearate was purchased from Sigma–Aldrich Co. Ltd., Dorset, UK.

2.2. Preparation of prednisolone tablets

Tablets were prepared containing 5% (w/w) prednisolone, 88.5% (w/w) lactose, 5% (w/w) polyvinylpyrrolidone, 0.5% (w/w) cross-linked sodium carboxymethylcellulose and 1% (w/w) magnesium stearate. Tablets were prepared by wet granulation and were produced using a single punch tableting machine (Manesty, Speke, UK). Cross-linked sodium carboxymethylcellulose (disintegrant) was added both intra- and extra-granularly (50:50). A biconcave 8-mm punch and die set (Holland, Nottingham, UK) were used to obtain tablets of mass 200 mg (containing 10 mg drug) and crushing strength of 80 N. The friability of the tablets was measured as per USP specifications and found to be less than 0.05%.

2.3. Coating of prednisolone tablets

2.3.1. EUDRAGIT® S single coating (formulation 1 – [F1])

Triethyl citrate (20% (w/w), based on polymer) was dissolved into ethanol. EUDRAGIT® S powder (10 g) was poured slowly into the above solution under stirring and stirring was continued until a clear solution was obtained. Glyceryl monostearate (GMS, 5% (w/w), based on polymer) was used as a glidant. A 10% (w/w) GMS dispersion was prepared by emulsification in water at 70–80 °C using polysorbate 80 (40% (w/w), based on GMS). The dispersion was then cooled to room temperature and added into the EUDRAGIT® S solution. The total solid content for the final dispersion was 10% (w/w).

The tablets (40 g/batch) were coated using Strea-1 bottom spray fluidised bed coater (Aeromatic AG, Bubendorf, Switzerland). The coating conditions were as follows: inlet air temperature 40 °C, outlet air temperature 30 °C, fan capacity 15 (equivalent to air flow 150 m^3/h), atomising pressure 0.2 bar and spray rate 1.0 ml/min. The coating thickness of the single coating was controlled by applying 5 mg polymer (pure EUDRAGIT® S polymer) per cm^2 surface area of the tablet core. After coating, the tablets were further fluidised for 15 min in the coater and dried in an oven at 40 °C for 2 h.

2.3.2. Double-coating (formulations 2–6 [F2–F6])

2.3.2.1. Inner coat. The inner coat of the double-coating comprises EUDRAGIT® S which was partially neutralised by adding 1 M NaOH to the formulation until the polymer was completely dissolved. Buffer agents were also included into the inner coat formulations to generate a buffer system (as specified in Table 1). The coating formulations were prepared by dissolving triethyl citrate (10% (w/w), based on polymer) and buffer agent (as specified in Table 1 for the individual formulations) into water. EUDRAGIT® S was dispersed into the above solution under stirring. The dispersion was then neutralised to a pre-determined pH (pH 8 or 10, as specified in Table 1) using 1 M NaOH. Since the pH was above the dissolution pH threshold of the polymer (pH 7.0), the polymer dispersion dissolved to a clear solution. Glyceryl monostearate (GMS, 5% (w/w), based on polymer) was used as a glidant. A 10% (w/w) GMS dispersion was prepared according to Section 2.3.1 and added into the EUDRAGIT® S solution to prepare a coating suspension of 10% (w/w) total solid content.

The coating conditions for the inner coating formulations were the same as the single coating. The coating thickness of the inner coats was also controlled by the amount of polymer applied on the core (5 mg/cm^2). The tablets were further fluidised for 15 min in the coater after coating and subjected to the outer coating process.

2.3.2.2. Outer coat. The outer coat of the double-coating formulations was identical to the single coating. The coating level was also 5 mg/cm^2 polymer. After applying the outer coat, the tablets were further fluidised for 15 min in the coater and dried in an oven at 40 °C for 2 h.