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Research paper

A novel coating concept for ileo-colonic drug targeting: Proof of concept in humans using scintigraphy

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ABSTRACT

The *in vivo* proof of concept of a novel double-coating system, based on enteric polymers, which accelerated drug release in the ileo-colonic region, was investigated in humans. Prednisolone tablets were coated with a double-coating formulation by applying an inner layer composed of EUDRAGIT® S neutralised to pH 8.0 and a buffer salt (10% KH_2PO_4), which was overcoated with layer of standard EUDRAGIT® S organic solution. For comparison, a single coating system was produced by applying the same amount of EUDRAGIT® S organic solution on the tablet cores. Dissolution tests on the tablets were carried out using USP II apparatus in 0.1 N HCl for 2 h and subsequently in pH 7.4 Krebs bicarbonate buffer. For comparison, tablets were also tested under the USP method established for modified release mesalamine formulations. Ten fasted volunteers received the double-coated and single-coated tablets in a two-way crossover study. The formulations were radiolabelled and followed by gamma scintigraphy; the disintegration times and positions were recorded. There was no drug release from the single-coated or double-coated tablets in 0.1 N HCl for 2 h. The single-coated tablets showed slow release in subsequent Krebs bicarbonate buffer with a lag time of 120 min, while in contrast drug release from the double-coated tablets was initiated at 60 min. In contrast, using the USP dissolution method, normally employed for modified release mesalamine products, no discrimination was attained. The *in vivo* disintegration of the single-coated EUDRAGIT® S tablets in the large intestine was erratic. Furthermore, in 2 volunteers, the single-coated tablet was voided intact. Double-coated tablets disintegrated in a more consistent way, mainly in the ileo-caecal junction or terminal ileum. The accelerated *in vivo* disintegration of the double-coating EUDRAGIT® S system can overcome the limitations of conventional enteric coatings targeting the colon and avoid the pass-through of intact tablets. Moreover, Krebs bicarbonate buffer has the ability to discriminate between formulations designed to target the ileo-colonic region.

1. Introduction

Enteric coatings are widely used to delay the release of medicaments to the lower regions of the gastrointestinal tract. In the case of colonic drug targeting, delivery is intrinsically dependent upon the use of such polymer coatings in order to circumvent conditions in the stomach and small intestine. These formulations have in recent years gained increasing popularity for the localised targeting of drugs to treat or ameliorate conditions such as inflammatory bowel disease [1–4], and to which end multiple drug products utilising pH-dependent EUDRAGIT® S coating technologies have been developed including mesalazine and budesonide, for instance.

In spite of the many advantages proffered by such coatings, however, they have historically featured numerous shortcomings [5–8]. EUDRAGIT® S polymer coated formulations are those designed to dissolve in fluids of pH > 7.0, being refractive to dissolution in both low pH stomach fluids and fluids of the upper gastrointestinal tract. However, inadequate exposure of these coated dosage forms to sufficient fluid volumes of pH 7.0 or higher through transit in the distal gut has been associated with inconsistent *in vivo* performance and disintegration failure observed both in single- and multiple-unit coated dosage forms [6,8]. Furthermore, the fluid available in the distal small intestine and large intestine is scarce and often found in pockets [9], which complicates the process of coating dissolution in these regions. A summative table highlighting pH-responsive dosage forms based on EUDRAGIT® S and their *in vivo* performances is provided in a previous review [10], based on cumulated data where high numbers of coated tablets were seen to be voided intact in healthy and diseased human volunteers.

Recently, our group developed a novel double-coating enteric polymer-based technology which provides faster coating dissolution and drug release on initiation of a pH trigger in the small intestine [11]. The concept of double coating *per se* involves the

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application of two separate layers of discrete polymer coating formulations to the dosage form: an inner layer of partially neutralised polymer along with a buffer salt, and an outer layer of standard enteric polymer. We have already demonstrated the success of this concept using EUDRAGIT® L30D-55 to accelerate drug release *in vitro* and within the human proximal small intestine as compared to a conventional single coating [12]. The concept was further adapted in the design of an ileo-colonic drug delivery system based on EUDRAGIT® S, providing accelerated drug release for both single- [11] and multiple-unit dosage forms [13] *in vitro*. However, proof of the concept for drug release acceleration in the ileo-colonic region needs to be assessed *in vivo*, and so the purpose of this study was to investigate the performance of the aforementioned EUDRAGIT® S double-coated colonic delivery technology by means of gamma scintigraphy in man. Additional investigations were also carried out to ascertain the drug release from double-coated and single-coated tablets in Krebs physiological bicarbonate buffer of pH 7.4, with the aim of providing greater *in vitro–in vivo* correlation between drug release profiles by close mimicry of human ileal fluid [14,15].

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 [16]. Potassium dihydrogen phosphate was 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.

2.3. Coating of prednisolone tablets

2.3.1. EUDRAGIT® S single coating

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 (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. EUDRAGIT® S double coating

2.3.2.1. Inner coat. The inner coat comprises EUDRAGIT® S partially neutralised by 1 M NaOH as the optimised formulation taken from our previous publication [11]. Briefly, the inner coat formulation was prepared by dissolving triethyl citrate (50% w/w, based on polymer) and potassium dihydrogen phosphate (10% w/w, based on polymer) into water. EUDRAGIT® S was dispersed into the above solution under stirring, and the dispersion was then neutralised to pH 8.0 using 1 M NaOH. 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 tablet 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 coating was applied on tablets (previously coated with the inner layer) as described for the single coating in Section 2.3.1. The coating thickness of the outer coating was controlled by applying 5 mg EUDRAGIT® S/cm^2 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.

2.4. In vitro drug release

The dissolution method specified in the USP for delayed-release mesalamine products was used to mimic three sequential stages to which tablets are exposed during transit through the gastrointestinal tract, and until the ileo-colonic region is reached. Given that the products specified are coated with EUDRAGIT® S polymers, this method was logically applied to our *in vitro* dissolutions of EUDRAGIT® S single- and double-coated prednisolone tablets using a USP II apparatus (Model PTWS, Pharmatest, Hainburg, Germany). The parameters outlined by the USP for test conditions are as follows: 0.1 N hydrochloric acid, 500 ml for acid stage; pH 6.0 phosphate buffer, 900 ml for buffer stages; 100 rpm paddle speed for acid stage and buffer stage 1, with 50 rpm paddle speed for buffer stage 2. The tests were conducted in triplicate in 900 ml dissolution medium maintained at 37 + 0.5 °C. All tests were conducted under sink conditions, with tablets exposed to 0.1 N HCl for 2 h, followed by 1 h exposure to phosphate buffer pH 6.0, and thereafter, tablets were transferred to a phosphate buffer of pH 7.2. The amount of prednisolone released from the coated tablets was determined at 5-min intervals by an in-line UV spectrophotometer at a wavelength of 247 nm, with data processed using Icalis software (Icalis Data Systems Ltd., Berkshire, UK).

For comparison purposes, tablets were tested for 2 h in 0.1 N HCl, and subsequently in pH 7.4 Krebs bicarbonate buffer, comprising 1.18 mM KH_2PO_4, 24 mM $NaHCO_3$, 118.07 mM NaCl, 4.69 mM