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A novel concept in enteric coating: A double-coating system providing rapid drug release in the proximal small intestine

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ABSTRACT

A novel double-coating enteric system was developed to accelerate drug release in conditions resembling the upper small intestine. The system comprises an inner coat (partially neutralised EUDRAGIT® L 30 D-55 and organic acid) and an outer coat (standard EUDRAGIT® L 30 D-55). Prednisolone tablets were coated with double layer formulations with inner coats neutralised to pH 5.6 in the presence of 10% citric acid or adipic acid. A conventional single coating was also applied for comparison purposes. There was no drug release from the single coated or double-coated tablets in 0.1M HCl for 2 h using USP II apparatus. The lag times of drug release in subsequent pH 5.6 phosphate buffer (to resemble the pH condition of the proximal small intestine) were 102, 42 and 28 min for the single coated, adipic acid and citric acid double-coated tablets respectively. The lag time for release from the double-coated tablets was further reduced to 5 min when the inner coat was neutralised to pH 6.0 in the presence of 10% citric acid. The rapid drug release from the double-coating system was associated with faster polymer dissolution rates compared to the single coating. The novel double-coated system has the potential to provide rapid drug release in the proximal small intestine, overcoming the limitations of conventional enteric coatings.

1. Introduction

The application of an enteric coating to a solid dosage form is a well established approach to prevent drug release in the stomach and allow release in the small intestine. It is used to preclude the degradation of acid-labile actives in the gastric environment or to protect the stomach from irritant compounds. The most commonly used enteric coatings employ pH-dependent polymers which contain carboxylic groups. These remain un-ionized in the low pH environment of the stomach, and become ionized in the higher pH conditions of the small intestine, thus allowing the dissolution of the coating and drug release.

The *in vitro* disintegration of products coated with common enteric polymers (cellulose esters, polyvinyl derivatives, and polymethacrylates) occurs over a very short period of time, normally within 30 min in pH 6.8 phosphate buffer [1–4]. However, this is not reflected *in vivo*; gamma scintigraphy studies have shown that it can take up to 2 h for such products to disintegrate in the human small intestine [1–8]. Drug release will then occur in the distal small intestine and cause a delayed response to medication and potentially reduce the bioavailability of those drugs having an absorption window in the proximal small intestine. This *in vivo*/*in vitro* discrepancy is due in part to the inadequacy of the commonly used *in vitro* dissolution medium (compendial pH 6.8 phosphate buffer) to resemble the luminal conditions of the upper small intestine in many respects such as pH, ionic composition, buffer capacity, viscosity and volume [9–14].

The purpose of the present study was to accelerate the dissolution of conventional enteric coatings and to achieve rapid drug release in conditions simulating the upper small intestine. A novel "double-coating" system was developed to facilitate this. The rationale for the double-coating design stems from the fact that the dissolution of an enteric polymer depends on the ionisation of its carboxylic acid groups at elevated pH. It is therefore conceivable that if some of the acid groups are neutralised to their ionised form (salt), the dissolution rate of the polymer would be increased. However, the inevitable pre-exposure to acidic medium for enteric coatings would transform the polymer salt back into its original acid form. It was hypothesised that the functionality of the neutralised film coating could be protected in acidic medium by over coating with a conventional enteric layer: the novel double-coating concept (Fig. 1). An organic acid was introduced to the neutralised inner layer to further accelerate dissolution by the formation of salt and so generating a buffer system. In this study, methacrylic acid-ethyl acrylate copolymer (EUDRAGIT® L 30 D-55), having a dissolution pH threshold of 5.5, was used as a

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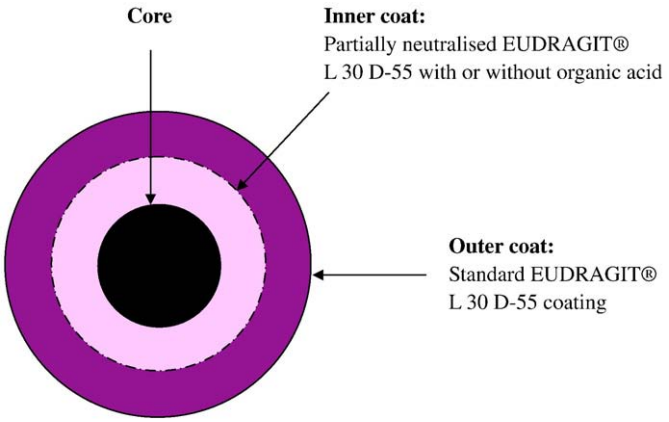

Fig. 1. Schematic of the double-coating concept.

model enteric polymer and *in vitro* performance of the double-coating system was assessed and compared to a conventional single coating.

2. Materials and methods

2.1. Materials

EUDRAGIT® L 30 D-55 was donated by Evonik Röhm GmbH, Darmstadt, Germany. EUDRAGIT® L 30 D-55 is the aqueous dispersion of the methacrylic acid-ethyl acrylate copolymer (monomer pK_a 4.6) with 30% solid content. The dissolution pH threshold of the enteric polymer is 5.5. The polymer has an acid value equivalent to 300–330 mg KOH/1g polymer [15]. The pH of the dispersion is 2.8–3.0; the mean particle size in the dispersion is 0.25 μm [16]. Citric acid (pK_a values of 3.13, 4.76 and 6.4, aqueous solubility of 380 mg/ml) and adipic acid (pK_a values of 4.41 and 5.41, aqueous solubility of 0.32 mg/ml) were purchased from Sigma-Aldrich Co. Ltd., Dorset, UK. Triethyl citrate was obtained from Lancaster Synthesis, Lancashire, UK. Talc (fine powder, <15 μm) was purchased from VWR International Ltd, Poole, UK. Prednisolone was purchased from Aventis Pharma., Antony, France. Lactose (Pharmatose) was obtained from Ellis & 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. Placebo glass beads (spherical, 5 mm diameter) were obtained from Peco Laborbedarf GmbH, Darmstadt, Germany.

2.2. Preparation of prednisolone tablets

Tablets were prepared containing 5% prednisolone, 88.5% lactose, 5% polyvinylpyrrolidone, 0.5% cross-linked sodium carboxymethylcellulose and 1% 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-granulary (50:50). A biconvex 8 mm punch and die set (Holland, Nottingham, UK) was 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. Single coating

Triethyl citrate (10% w/w, based on polymer weight) was dissolved into EUDRAGIT® L 30 D-55 dispersion. Talc (50% w/w, based on polymer weight), used as an anti-tacking agent, was homogenized in water and added into the above dispersion. The total solid content for the final dispersion was 20% w/w.

The recommended coating level for EUDRAGIT® L 30 D-55 to achieve enteric properties on tablets is in the range of 4–6 mg polymer (pure polymer) per cm^2 surface area of the core [15]. In the present study, 5 mg/cm^2 polymer was applied for the single coating. The tablets were coated using Strea-1 bottom spray fluidised bed spray coater (Aeromatic AG, Bubendorf, Switzerland). The coating conditions were: 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 2.0 ml/min. After coating, the tablets were further fluidised for 15 min in the coater and cured in an oven at 40 °C for 2 h.

2.3.2. Double-coating

2.3.2.1. Inner coat. The formulation variables of the inner coat of the double-coating are summarised in Table 1. The coating formulations were prepared by dissolving triethyl citrate (5% w/w, based on polymer weight) into EUDRAGIT® L 30 D-55 dispersion. The dispersion was then neutralised to pH 5.6 (unless otherwise stated) using 1 M NaOH with or without the addition of organic acid (adipic acid or citric acid). Since the dissolution pH threshold of the polymer is 5.5, the polymer particles in the dispersion completely dissolved and the dispersion turned into a clear solution at pH 5.6. Talc (50% w/w, based on polymer weight) was homogenized in water and added to these solutions to prepare a dispersion of 10% w/w total solid content.

As for the single coating the amount of polymer applied on the inner coats was 5 mg/cm^2. The coating conditions for the inner coating formulations were the same as the single coating except lower spray rate (1.0 ml/min) was applied. After coating, the tablets were further fluidised for 15 min in the coater and subjected to the outer coating process.

2.3.2.2. Outer coat. The outer coat of the double-coating 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 cured in an oven at 40 °C for 2 h.

2.4. Scanning electron microscopy

The surfaces and cross-sections of the single coated and the double-coated tablets were examined by scanning electron microscopy (SEM), using a JEOL JSM-35 Scanning Microscope. The electron energy applied was 5–10 keV. Samples were gold coated using an EMITEC K500 sputter coater for 3 min at 40 mA.

2.5. In vitro drug release

The drug release profiles from the coated prednisolone tablets were carried out using a USP II apparatus (Model PTWS, Pharmatest, Hainburg, Germany). The tests were conducted in triplicate, in 900 ml dissolution medium maintained at 37±0.5 °C. A paddle speed of 50 rpm was employed. The tests were conducted under sink

Table 1
Formulation variables of the inner coat of the double-coating

Concentration of organic acids (%)*		pH of the inner coating solutions
Without organic acid		5.6
Adipic acid	10	5.6
	15	5.6
	20	5.6
Citric acid	10	5.6, 5.8, 6.0
	15	5.6
	20	5.6

*The concentrations of the organic acid were based on the dry weight of the polymer.