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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.

Table 1
The pH values and buffer agents used in the EUDRAGIT® S inner coats.

Formulation		F2	F3	F4	F5	F6
Polymer	EUDRAGIT® S	10 g	10 g	10 g	10 g	10 g
Buffer agent	Citric acid		1 g (10%[a])			
	KH_2PO_4			1 g (10%[a])	1 g (10%[a])	
	$(NH_4)_2CO_3$					1 g (10%[a])
Neutralising agent	1 M NaOH	35.2 g	57.7 g	42 g	45 g	56.2 g
Formulation pH		8.0	8.0	8.0	10.0	10.0
Buffer capacity (mM/L/pH unit, ±sd)		0.1 ± 0.01	1.9 ± 0.2	6.7 ± 0.2	1.3 ± 0.01	50 ± 1.4

[a] Based on polymer weight.

2.4. Buffer capacity measurement of the inner coat formulations

Buffer agents were added into the inner coat of the double-coating formulation to generate a buffer system and thus potentially facilitate coat dissolution. The buffer capacities of these buffer agents in aqueous solution, at the same pH as in the inner coat formulation, were measured. The buffer agents used were citric acid (pH 8.0), KH_2PO_4 (pH 8.0 and 10.0) and $(NH_4)_2CO_3$ (pH 10.0). The buffer capacity of deionised water at pH 8.0 was also measured to serve as a control. Two grams of the above mentioned buffer agents were dissolved in 340 g water; the concentration obtained was the same as in the inner coat formulations. The pH values of deionised water, citric acid, KH_2PO_4 and $(NH_4)_2CO_3$ solution were adjusted to their pre-determined pH using 1 M NaOH.

Buffer capacities of the above prepared solutions were determined by adding 0.1 M HCl into 100 ml solution to obtain a pH change (ΔpH) of approximate 0.3 units. The buffer capacity (β) was calculated using Eq. (1) [24].

$$\beta = \frac{\text{mmol/L(HCl)}}{\Delta\text{pH}} \quad (1)$$

2.5. Measurement of inner coat pH

It was hypothesized that in the case of the inner coat formulation containing $(NH_4)_2CO_3$, the pH of the deposited coating may be different from that of the original coating formulation, due to the possible evaporation of ammonia and carbon dioxide during the coating process. To assess this, the inner coat pH of F6 (10% $(NH_4)_2CO_3$, pH 10.0) was determined after coating by disintegrating the coated tablets in water. The inner coat pH of F5 (10% KH_2PO_4, pH 10.0) and the pH of the prednisolone tablet core disintegrated in deionised water were also measured for comparison purposes. Five prednisolone tablets (core or coated with the inner coat of F5 or F6) were placed in 10 ml water in a 15-ml vial. To obtain the highest salt concentration in water, minimum volume of water to disintegrate the tablets was used. The vial was closed with a lid and placed on a shaker until the coatings dissolved and the tablets disintegrated. The pH of the resultant tablet dispersion was measured with a pH meter.

2.6. 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 conditions. 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. Data were processed using Icalis software (Icalis Data Systems Ltd., Berkshire, UK). Tablets were tested for 2 h in 0.1 M HCl, and subsequently in pH 7.4 Krebs bicarbonate buffer which comprises 1.18 mM KH_2PO_4, 24 mM $NaHCO_3$, 118.07 mM NaCl, 4.69 mM KCl, 2.52 mM $CaCl_2$ and 1.18 mM $MgSO_4 \cdot 7H_2O$. The ionic composition and buffer capacity (5.45 mmol/L/pH unit) of stabilized Krebs buffer closely simulates that of human ileal fluid (buffer capacity 6.4 mmol/L/pH unit) [22,25]. To prevent the pH rise of Krebs buffer during dissolution due to the loss of CO_2 from the solution, the buffer was stabilized by applying an in-house seal device to completely seal each dissolution vessel. The method has been described previously [22]. The pH value of the medium was measured after completion of the dissolution experiments and was 7.4 ± 0.5.

3. Results and discussion

Prednisolone release from EUDRAGIT® S single-coated tablets (F1) in pH 7.4 Krebs bicarbonate buffer after pre-exposure to 0.1 M HCl for 2 h is shown in Fig. 1. The preparation was gastric-resistant with no drug release in the acid phase of the test (data not shown). Although EUDRAGIT® S has a dissolution pH threshold of 7.0, it took 2 h in pH 7.4 Krebs buffer for drug release to commence, attributable to the slow dissolution of the polymer coating in this physiological bicarbonate buffer. This slow release correlates to the reported slow dissolution of the coating *in vivo* which contributes to the inconsistency of performance of EUDRAGIT® S systems [4–10].

To accelerate drug release from EUDRAGIT® S systems in physiological buffer, the double-coating approach with partially neutralised EUDRAGIT® S as the inner coat and standard EUDRAGIT® S as the outer coat was investigated. Fig. 1 shows prednisolone release

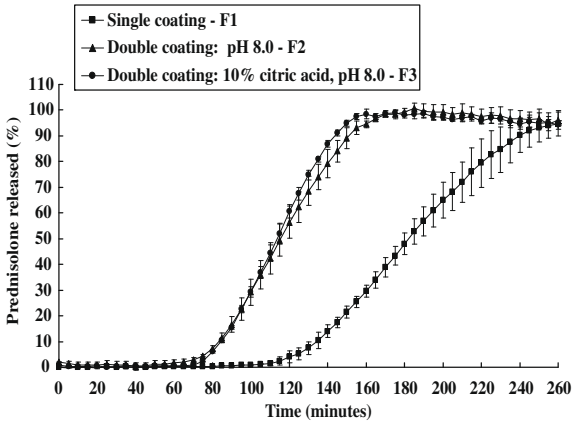

Fig. 1. *In vitro* prednisolone release from EUDRAGIT® S single-coated and double-coated tablets in pH 7.4 Krebs buffer after pre-exposure to 0.1 M HCl for 2 h.

from EUDRAGIT® S double-coated tablets with the inner coat polymer neutralised to pH 8.0 (F2). No drug release occurred in acidic medium (data not shown) and in subsequent bicarbonate buffer, the double-coating formulation substantially accelerated drug release compared to the single coating.

It was proposed that the generation of a buffer system in the inner coat can further facilitate the dissolution of the double-coating system [15]. In addition, elevated pH of the inner coat of the EUDRAGIT® S double-coating can also assist in the dissolution of the outer coat. To evaluate the interplay of these internal factors on drug release, inner coats with different buffer capacities and pH were investigated (F3–F6, Table 1). The addition of 10% citric acid as a buffering agent to the inner coat (F3) did not increase the rate of drug release compared to the formulation without additional acid (F2) in pH 7.4 buffer (Fig. 1). This observation was in contrast to our previous study where we reported that the inclusion of citric acid in the inner coat accelerated drug release from EUDRAGIT® L 30 D-55 double-coated formulations [15]. It is proposed that this is because the inner layer of the EUDRAGIT® S double-coating was neutralised to a higher pH value (8.0), compared to pH 6.0 in the case of EUDRAGIT® L 30 D-55, to completely dissolve the polymer. At this pH, citric acid, which has low p*K*a values (3.13, 4.76 and 6.4), has been largely neutralised to its salt form and the buffer capacity is therefore very low (Table 1) and any effect on drug release is limited.

A different buffer agent, KH_2PO_4, with a higher buffer capacity in solution than citric acid at pH 8.0 was also included in the inner coat of the double-coating system (Table 1). The corresponding dissolution data is shown in Fig. 2. The lag time of drug release in pH 7.4 buffer was markedly reduced for the KH_2PO_4 containing formulation (40 min, F4), compared to the citric acid containing formulation (70 min, F3). This suggests that in this instance the increase in buffer capacity is the predominant factor in accelerating the dissolution of the coating.

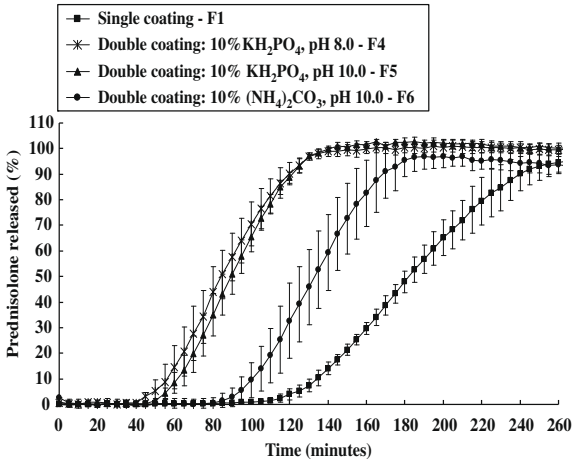

Fig. 2. *In vitro* prednisolone release from EUDRAGIT® S single-coated and double-coated tablets in pH 7.4 Krebs buffer after pre-exposure to 0.1 M HCl for 2 h.

Furthermore, the effect of inner coat pH on drug release was investigated by neutralising the inner coat containing KH_2PO_4 to a higher pH (pH 10.0) (Table 1). At this pH, KH_2PO_4 has a low buffer capacity due to the higher degree of ionization of its acid form, however, the drug release profile of this formulation (F5) in pH 7.4 buffer was similar to the formulation at pH 8.0 (F4) – Fig. 2. In this case, the high inner coat pH became the primary mechanism for coating dissolution and compensated for the low buffer capacity.

Ammonium carbonate ($(NH_4)_2CO_3$) was found to have a very high buffer capacity (this buffer agent can form a multiple buffer system with both acidic [carbonate/bicarbonate] buffer and basic [ammonium] buffer species) at pH 10.0 (Table 1); this combination of high buffer capacity and high pH were expected to achieve more rapid drug release. However, despite its high buffer capacity, when ammonium carbonate was included in the double-coating system (F6), drug release from the coated prednisolone tablets was slower compared to the KH_2PO_4 containing formulations (F4 and F5) – Fig. 2. This was attributed to a pH change of the ammonium carbonate-containing inner coat during coating. During the drying stage of the coating process, both ammonia and carbon dioxide can evaporate from the coating formulation: the loss of ammonia decreases the coat pH, whereas the loss of carbon dioxide increases the pH. After coating it was found that the pH of this inner coat (F6) was 7.5 in water, while the corresponding pH of F5 was 10.0 (the pH of prednisolone tablet core when dispersed in water was 7.0). This pH drop of the final inner coat can contribute to the slow dissolution from the $(NH_4)_2CO_3$ containing formulation. Further evidence for the removal of ammonia and CO_2 was also seen when the film coats were examined visually.

It is summarised from the above results that drug release from the double-coated system was affected by the combination of the inner coat pH and buffer capacity. The effect of a buffer agent will depend on the employed inner coat pH which in turn affects its buffer capacity. Fig. 3 shows the SEM images of the surface of the single-coated (F1) and the double-coated tablets with inner coats containing KH_2PO_4 – F4 or $(NH_4)_2CO_3$ – F6. In contrast to the KH_2PO_4-containing inner coat which showed a smooth surface, bubbles presented on the surface of the $(NH_4)_2CO_3$-containing inner coat, indicating the possible evaporation of ammonia and carbon dioxide from the formulation during coating.

The dissolution mechanisms of the EUDRAGIT® L 30 D-55 double-coating system have been investigated in a previous paper [16]. Similar mechanisms can be applied here to the EUDRAGIT® S system. As aforementioned, the inner coat is partially neutralised and can more easily dissolve than the outer coat. Once buffer medium starts to penetrate through the outer coat, as starts to occur upon exposure to this pH 7.4 Krebs buffer, the neutralised inner coat rapidly dissolves. This produces a fluid and dynamic internal component of high pH (>dissolution threshold of polymer) and var-

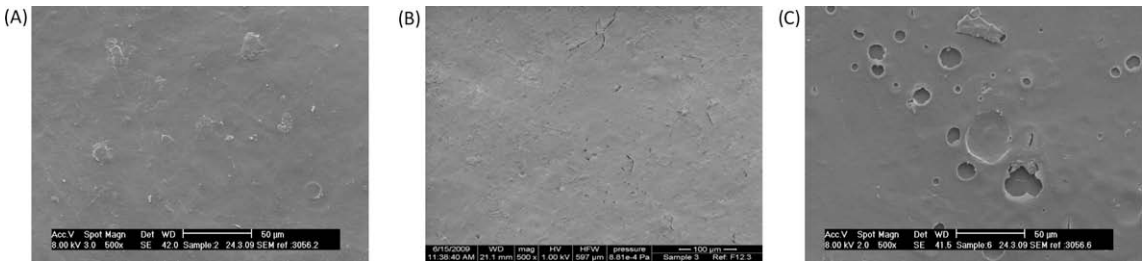

Fig. 3. Scanning electron micrographs of the surface of the single-coated and the double-coated tablets. (A) Surface of single-coated tablet; (B) inner coat surface of 10% KH_2PO_4 double-coated tablet; (C) inner coat surface of 10% $(NH_4)_2CO_3$ double-coated tablet.

iable (formulation dependant) buffer capacity. Due to the high pH and buffer capacity of the inner layer, the outer coat, which is immediately adjacent to the dissolved inner layer, can start to dissolve from its inner surface. Meanwhile, the outer surface also undergoes dissolution. This latter mechanism (dissolution from outer surface) is the only method by which a normal single coating can dissolve. To summarise, in contrast to the single coating, the outer coat of the double-coating system dissolves from both its inner and outer surfaces which results in rapid dissolution and expedited drug release.

4. Conclusions

A novel double-coating system based on EUDRAGIT® S was developed for improved drug delivery to the ileo-colonic segments of the gastrointestinal tract. The inner and outer coats of the system comprise partially neutralised and standard EUDRAGIT® S coating respectively. Drug release from coated tablets was substantially accelerated from this double-coating system compared to the conventional single EUDRAGIT® S coating in pH 7.4 physiological bicarbonate buffer. The inclusion of a buffer agent in the inner coat was found to further facilitate drug release from the double-coating system and the inner coat pH and buffer capacity were the main factors influencing double-coating dissolution. The accelerated coat dissolution of this novel system may be able to overcome the lack of fluid in the distal gut and the variability in intestinal transit, and thus potentially improve drug delivery.

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