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Research paper

Improved drug delivery to the lower intestinal tract with tablets compression-coated with enteric/nonenteric polymer powder blends

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ABSTRACT

The objective of this study was to develop pH-erosion-controlled compression-coated tablets for potential colonic drug delivery with improved gastric resistance and pulsatile release based on compression-coatings of powder blends of the enteric polymer Eudragit® L100-55 and the extended release polymer ethylcellulose. Tablet cores containing model drugs of varying solubilities (acetaminophen, carbamazepine and chlorpheniramine maleate) were compression-coated with different ratios of Eudragit® L100-55:ethylcellulose 10cP FP at different compression forces and tablet core:compression-coat ratios. The compression-coated tablets were characterized by drug release, media uptake, erosion behaviour and wettability. All drugs were released in a pulsatile fashion in higher pH-media after a lag time, which was controlled by the erosion properties of the Eudragit L:ethylcellulose compression-coating. The addition of ethylcellulose avoided premature drug release in lower pH-media and significantly increased the lag time in higher pH-media because of a reduction in wettability, media uptake and erosion of the compression-coatings. Importantly, ethylcellulose also reduced the pH-dependency of the erosion process between pH 5.5 and 7.4. The lag time could also be increased by increasing the compression force and decreasing the core:compression-coat ratio. In conclusion, tablets compression-coated with blends of Eudragit L and ethylcellulose resulted in excellent release properties for potential targeting to the lower intestinal tract with no release in lower pH-media and rapid release after a controllable lag time in higher pH-media.

1. Introduction

Oral drug delivery to the colon has become attractive during the past two decades for reasons including a reduced dosing frequency, high local drug concentration for the treatment of large bowl diseases, chronotherapeutic drug delivery and the delivery of peptides/protein drugs and drugs unstable in the upper gastrointestinal tracts [1]. Colonic delivery systems include pH-, time-, bacterial- and pressure-responsive systems [2–4]. Also combinations of these approaches in the form of a pH-responsive and bacterially triggered system [5] or of a time- and microbial-controlled system [6] have been investigated. Among these approaches, pH- and time-responsive system are relatively simple to prepare, but their suitability as colonic delivery system has been doubtful because of the variable physiological or pathological conditions along the gastrointestinal (GI) tract [7]. Since the small intestinal transit time in humans is approximately 3 ± 1 h (both fasted and fed state) and less variable [5,8], combinations of pH- and time-controlled systems were successfully developed [9].

Colonic drug delivery systems should overcome problems associated with the variation of gastric emptying time (less than 2 h under fasting and 2–12 h under fed conditions in humans) [10] and with mechanical destructive forces in the gastrointestinal tract [11]. Feasible pH- and time-controlled systems include enteric coatings (with high pH-threshold and/or thicker film coating), enteric coatings on hydroxypropyl cellulose compression-coated tablets or matrix tablet [12–14] or coating blends of extended release and enteric polymer [15,16]. Besides gastric protection, the enteric coating has to be robust to ensure upper GI-tract passage of the delivery system.

Besides dry powder-coating techniques [17,18], compression-coating of tablets is attractive for thicker coatings since traditional liquid coating processes are time-consuming and often not solvent-free. Compression-coating provides thick coatings within short processing time. For example, hydroxypropylmethylcellulose acetate succinate (HPMCAS) compression-coated tablets have been investigated for colonic DDS [19], whereby the lag time was prolonged after prior acid treatments.

The purpose of this study was to develop compression-coated tablets suitable for colonic drug delivery. Eudragit® L100-55, a methacrylic acid-ethylacrylate copolymer, was chosen as enteric polymer for compression-coating because of its good flow properties (spray-dried powder), good compressibility and acid

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resistance. In particular, the addition of the water-insoluble polymer ethylcellulose was investigated to overcome the problems of only enteric coated colonic delivery systems, such as a too short gastric resistance and premature release [15].

2. Materials and methods

2.1. Materials

Acetaminophen, carbamazepine (BASF AG, Ludwigshafen, Germany), chlorpheniramine maleate (STADA GmbH, Bad Vilbel, Germany), methacrylic acid-ethyl acrylate copolymer 1:1 (Eudragit L) (Eudragit® L100-55, Evonik Industries AG, Darmstadt, Germany), ethyl cellulose (EC) (Ethocel® Standard 10 Premium FP, Dow Chemical Company, Midland, MI, USA), direct compressible lactose (Ludipress®, BASF AG, Ludwigshafen, Germany), magnesium stearate (Herwe Chemisch-technische Erzeugnisse, Sinsheim Dühren, Germany) were used as received.

2.2. Methods

2.2.1. Preparation of tablet cores

Acetaminophen and carbamazepine biconvex tablet cores (6 mm diameter tablets: 15 mg drug, 85 mg Ludipress®, 0.5 mg magnesium stearate) and chlorpheniramine maleate tablet cores (6 mm diameter tablets: 40 mg drug, 60 mg Ludipress®, 0.5 mg magnesium stearate; 9 mm diameter tablets: 120 mg drug, 180 mg Ludipress®, 1.5 mg magnesium stearate) were prepared by direct compression (compression force, 15 kN; hardness for 6 and 9 mm tablets, 30 and 70 N; Korsch EKO, Korsch AG, Berlin, Germany). The drug content in the cores was different in order to allow UV detection without the dilution of the dissolution samples. Prior to compression, drug and Ludipress® were blended in a Turbula mixer (Willy A. Bachofen AG, Basel, Switzerland) for 10 min and additionally blended with 0.5% w/w magnesium stearate for 2 min.

2.2.2. Preparation of compression-coated tablets

Six millimeter diameter drug cores were compression-coated into 9 mm diameter tablets with Eudragit L or blends of Eudragit L:ethylcellulose (97.5:2.5, 95:5, 90:10, 85:15, 80:20 and 75:25). The compression-coated tablets (core:coat, 1:2) were prepared by first filling one-half (100 mg) of the polymer powder in the die cavity, then centrally positioning the tablet core on the powder bed followed by filling the remaining half (100 mg) of the polymer powder on top and then followed by compression at 10, 15, 20 and 25 kN (Korsch EKO, Korsch AG, Berlin, Germany). Compression-coated tablets with different core:coat ratios (3:1, 2:1, 1:1 and 1:2) were prepared by compression-coating chlorpheniramine

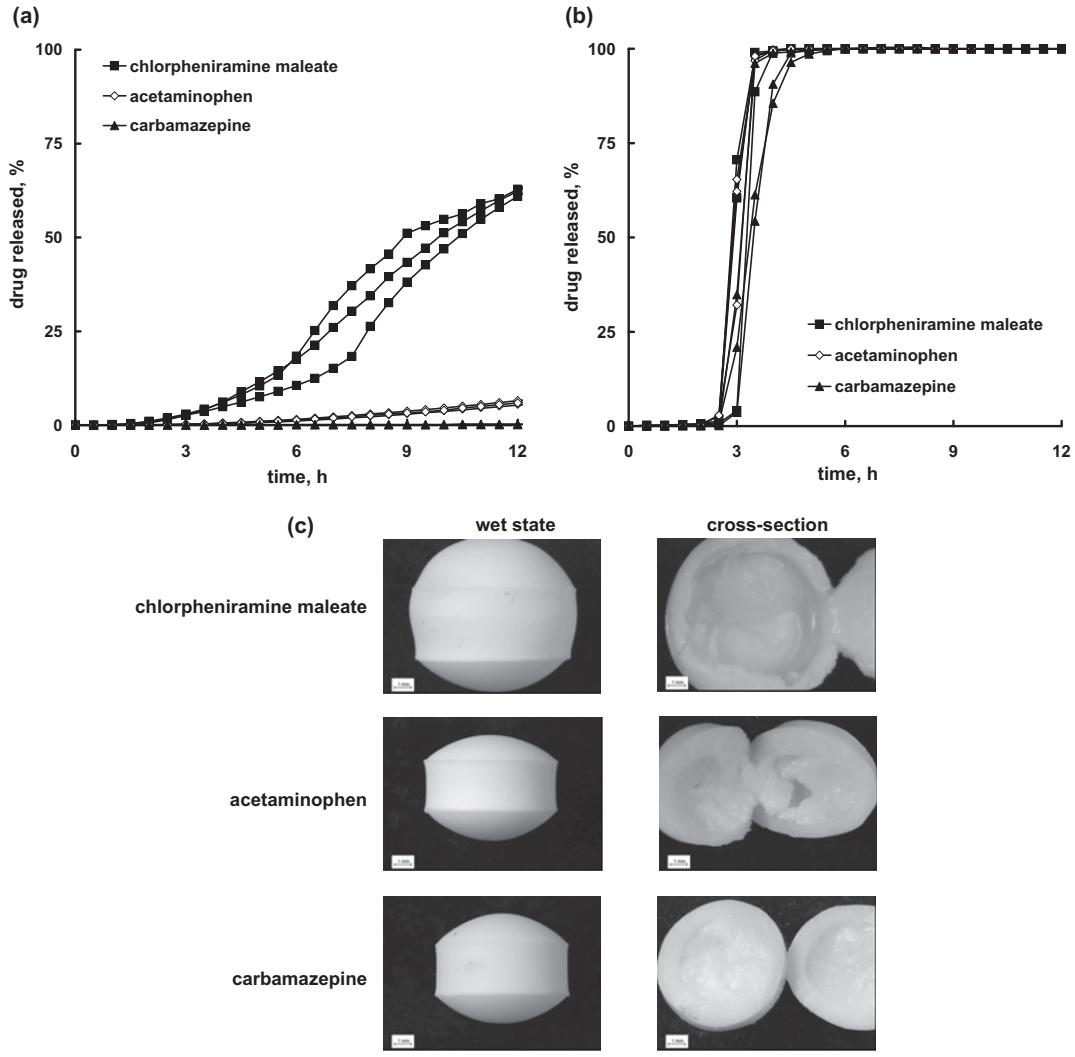

Fig. 1. Drug release of Eudragit L compression-coated tablets (core:coat, 1:2, 6 mm tablet cores in 9 mm compression-coated tablets, 25 kN compression force): (a) pH 1.0; (b) pH 7.4 ($n = 3$, individual release profiles shown); (c) wet state and cross section of compression-coated tablets in pH 1.0.

maleate cores (6 or 9 mm diameter) with different amounts of Eudragit L:ethylcellulose 75:25 (100, 150, 100 and 200 mg) resulting in compression-coated tablets with the dimensions of core/core + coat of 9/10, 9/11, 6/8 and 6/9 mm, respectively.

2.2.3. Drug release

Drug release was studied in a paddle apparatus (USP XXXIII) (Vankel® VK 7010, Vankel Industries, Edison, NJ, USA) [100 rpm, 37 °C, 900 ml, 0.1 N HCl (pH 1.0), 50 mM acetate buffer (pH 4.5), 50 mM of phosphate buffer (pH 5.5, 6.8 and 7.4), $n = 3$]. With the medium change method, the release was performed in pH 1.0 for 2 h followed by pH 6.8. Drug release was measured by UV spectrophotometer (Varian Cary 500 UV/Visible spectrophotometer, Varian Deutschland GmbH, Darmstadt, Germany) at wavelengths of 243.6, 285 and 261 nm for acetaminophen, carbamazepine and chlorpheniramine maleate, respectively. The lag time was taken as the time of <10% drug released. The percentage of acid uptake of compression-coated tablets was determined with the wet tablet weight after the release study in 0.1 N HCl based on the initial weight.

2.2.4. Swelling and erosion studies of Eudragit L:ethylcellulose matrices

Three hundred milligrams of tablets (10 mm diameter) containing different Eudragit L:ethylcellulose blends was compressed at 25 kN. Swelling and erosion of Eudragit L:ethylcellulose tablets were performed in pH 1.0 and pH 7.4 buffers at 100 rpm and 37 °C (Vankel® VK 7010, Vankel Industries, Edison, NJ, USA). In addition, the erosion of Eudragit L tablets was performed in different pH media (5.5, 5.8, 6.0, 6.8 and 7.4). The initial tablet weight (w_i), tablet weight in the wet state (w_t) and tablet weight after drying (w_d) (60 °C, until constant weight) were measured to determine the percentage of weight increase (reflecting swelling) and weight remaining (reflecting erosion) as swelling in 0.1 N HCl and erosion in pH 7.4 as follows:

$$\text{Weight increase } (\%) = \frac{w_t - w_i}{w_i} \times 100$$

$$\text{Weight remaining } (\%) = \frac{w_d}{w_i} \times 100$$

2.2.5. Drug solubility determinations

The solubility of the drugs was determined by adding an excess amount of drug in vials with 5 ml phosphate buffer pH 7.4 and shaking at 37 °C in an incubator (GFL® 3033, GFL Gesellschaft für Labortechnik, Burgwedel, Germany). After 48 h equilibration, the drug suspensions were adjusted to pH 7.4, if necessary, and further shaken. The suspensions were centrifuged at 13,000 rpm for 10 min (Biofuge 13/Haemo, Heraeus Instruments GmbH, Osterode, Germany) and filtered through a 0.2 μm filter. The filtrate was

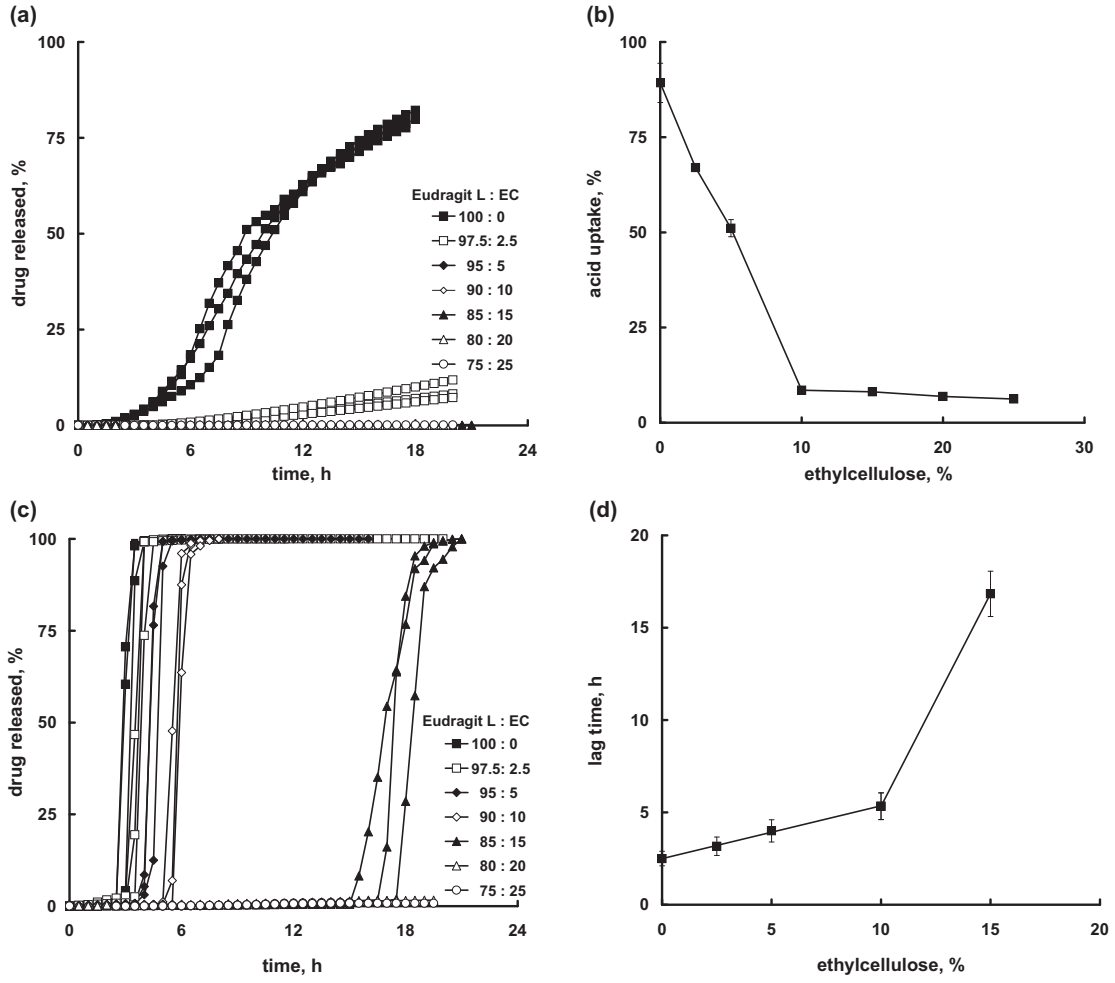

Fig. 2. Influence of Eudragit L:ethylcellulose (EC) in the compression-coating on chlorpheniramine maleate release from compression-coated tablets (core:coat, 1:2, 6 mm tablet cores in 9 mm compression-coated tablets, 25 kN compression force): (a) drug release in pH 1.0; (b) acid uptake in pH 1.0; (c) drug release in pH 7.4 ($n = 3$, individual release profiles shown); (d) lag time in pH 7.4.

diluted and analyzed UV-spectrophotometrically (Shimadzu UV-2101PC, Shimadzu Europa, Duisburg, Germany) at the same wavelengths used for drug release studies.

2.2.6. Wettability of Eudragit L:ethylcellulose matrices with release media

The wettability of matrix tablets prepared from different Eudragit L:ethylcellulose ratios (100:0, 95:5, 85:15 and 75:25 w/w) was investigated by placing a drop of media (approximately 50 μl) on the flat surface of the tablets. Pictures of the water droplet as a function of time were taken with a macroscope (INTEQ GmbH, Berlin, Germany). The contact angle on Eudragit L:ethylcellulose matrix tablets was measured with a goniometer (Contact Angle Meter G1, Krüss GmbH, Hamburg, Germany).

2.2.7. Tapped density

Tapped densities of Eudragit L and ethylcellulose were determined by a tap density volumeter (Erweka® type SYM 202, Erweka® GmbH, Heusenstamm, Germany). The tapped volume of 35 g polymer powder (2500 tappings, stroke height 15 mm, 300 strokes/min) was measured.

3. Results and discussion

Colonic drug delivery systems should not release the drug in the stomach/upper intestine but in the lower intestinal tract after about 3–4 h intestinal passage. An erosion-controlled enterically compression-coated tablet was investigated in this study as a potential delivery system to the large intestine. Eudragit L (soluble at pH > 5.5) and blends of Eudragit L with the nonenteric, water-insoluble polymer ethylcellulose were evaluated as pH-controlled erodible coatings resulting ideally in drug release only after erosion of the coating. Drugs of varying solubility (solubilities of carbamazepine, acetaminophen and chlorpheniramine maleate are 0.2, 20 and 562 mg/ml, respectively) were incorporated into the core in order to evaluate the flexibility/limitations of the compression-coated system with regard to different drug candidates.

All drug cores (without compression-coating) resulted in complete release within 15 min (data not shown). Thus, in the ideal case, a rapid drug release after erosion of the coat in intestinal fluids was guaranteed. Eudragit L compression-coated tablets released less than 10% chlorpheniramine maleate in 4 h and less than 10% acetaminophen in 12 h in 0.1 N HCl (Fig. 1a). The water-insoluble carbamazepine was not released at all. The Eudragit L coating is insoluble in gastric juice; however, it swells (Fig. 1c). Drugs could thus only be released in 0.1 N HCl by diffusion through the swollen coating; this occurred to a higher extent with the more water-soluble chlorpheniramine maleate (approximately 75% released in 12 h) than with the other two drugs. Interestingly, chlorpheniramine maleate tablets swelled more than the other two less water-soluble drugs, probably because of the higher osmotic activity of the chlorpheniramine maleate (Fig. 1c). Although Eudragit L is brittle and not flexible in the dry state, it is very flexible upon contact with dissolution media because of the plasticization effect of water [20], thus explaining the expansion of the chlorpheniramine maleate tablets.

As desired, the release was independent of drug type in pH 7.4 (Fig. 1b). All three drugs were released rapidly and similar after a lag time of about 2.5 h. The release profile was pulsatile; no drug was released until almost complete dissolution/erosion of the Eudragit L compression-coat. The individual release profiles ($n = 3$) were very close in most cases and showed the good

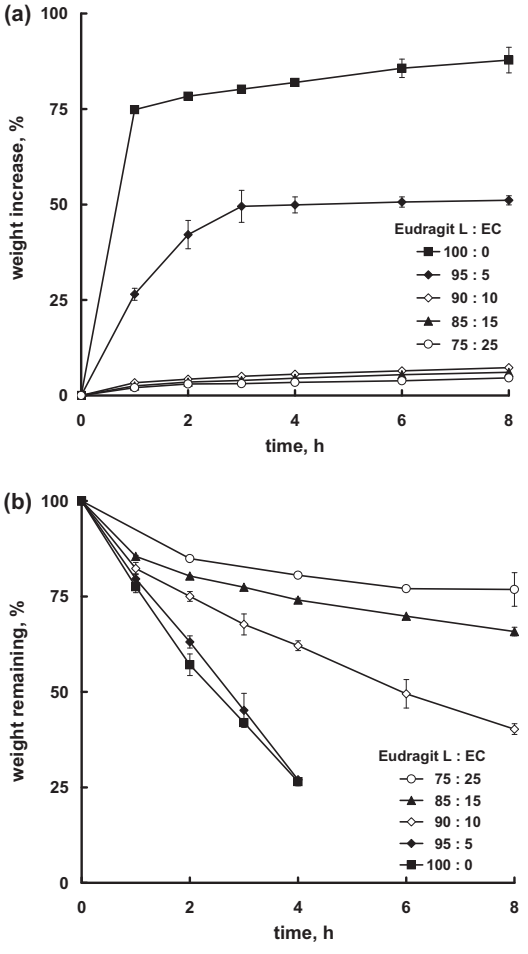

Fig. 3. Weight increase (reflecting swelling) and weight remaining (reflecting erosion) of drug-free Eudragit L:ethylcellulose (EC) matrix tablets (9 mm diameter, 25 kN compression force): (a) pH 1.0; (b) pH 7.4 ($n = 3$).

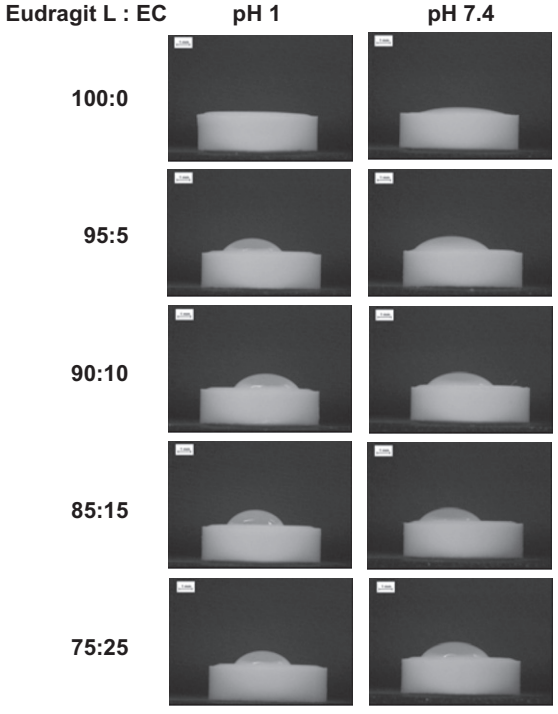

Fig. 4. Influence of ethylcellulose on the wettability of drug-free Eudragit L:ethylcellulose (EC) matrix tablets (300 mg, 9 mm diameter, 25 kN compression force) with pH 1.0 and pH 7.4 after 6 min.

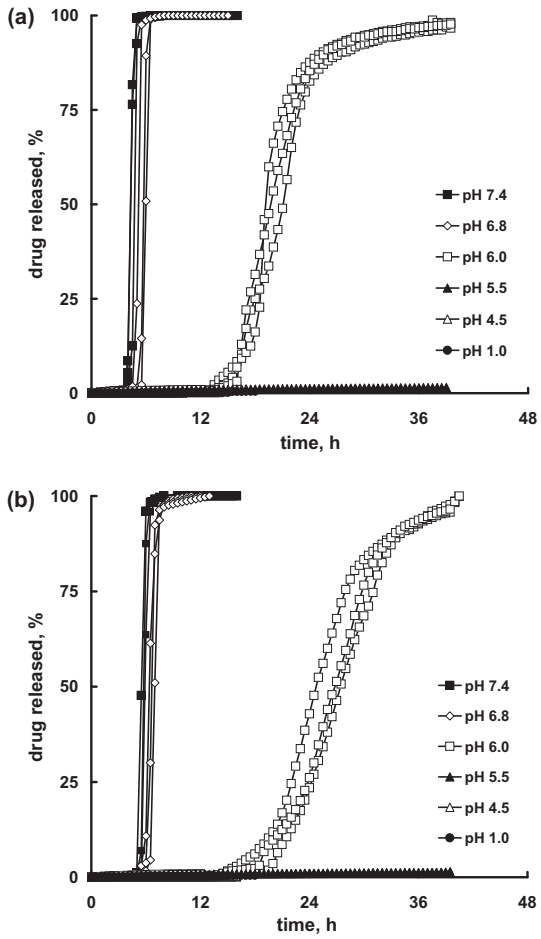

Fig. 5. Effect of pH of the release medium on the chlorpheniramine maleate release from compression-coated tablets (core:coat, 1:2, 6 mm tablet cores in 9 mm compression-coated tablets, 25 kN compression force): (a) Eudragit L:ethylcellulose, 95:5; (b) Eudragit L: ethylcellulose, 90:10 ($n = 3$, individual release profiles shown).

reproducibility of the compression-coating process. This initial study proofed the potential of erosion-controlled Eudragit L compression-coated tablets for the delivery of drugs of varying solubility to the lower intestine. Chlorpheniramine maleate, the drug with the highest water solubility and thus the most challenging one to retard, was selected for further studies.

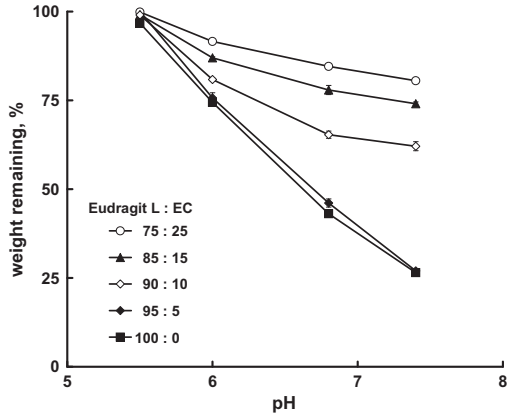

Fig. 6. Effect of pH of release medium on the weight remaining (reflecting erosion) of drug-free Eudragit L:ethylcellulose (EC) tablets (300 mg, 9 mm diameter, 25 kN compression force) after 4 h ($n = 3$).

Ethylcellulose, a water-insoluble and directly compressible fine polymer powder, was added to the enteric Eudragit L to decrease the release of chlorpheniramine maleate at low pH. Surprisingly, the addition of only 2.5% ethylcellulose prolonged the gastric resistance beyond 18 h (Fig. 2a); 5–25% ethylcellulose resulted in no release in 0.1 N HCl. This was attributed to the decrease in acid uptake with increasing ethylcellulose content (Fig. 2b). Tablets containing 10% ethylcellulose had only 8.5% weight increase (acid uptake) in 0.1 N HCl after 18 h, when compared to more than 80% uptake with pure Eudragit L compression-coated tablets. Ethylcellulose FP grade is a micronized powder (6.1 μm mean diameter) [16] and thus was very effective in inhibiting rapid penetration of the dissolution medium when compared to the larger sized Eudragit L powder ($\geqslant$95% smaller than 250 μm) [21]. In addition, a comparison of the tapped densities of Eudragit L and ethylcellulose (0.55 and 0.33 g/ml, respectively) also explained a higher volume- than mass-fraction of ethylcellulose in the Eudragit L:ethylcellulose compression-coat (80:20 w/w vs. a volume ratio of 70:30 v/v).

The incorporation of ethylcellulose prolonged the lag time in pH 7.4 from 2.5 h to approximately 5 h for 0–10% ethylcellulose followed by a big jump in lag time for ethylcellulose concentrations in excess of 15% (lag time >15 h) to no release within 18 h for >20% ethylcellulose (Fig. 2c–d). Ethylcellulose thus significantly retarded the erosion of the Eudragit L coating [15], especially in thick compression-coatings. The release profiles remained steep, indicating rapid, pulsatile release after the lag time.

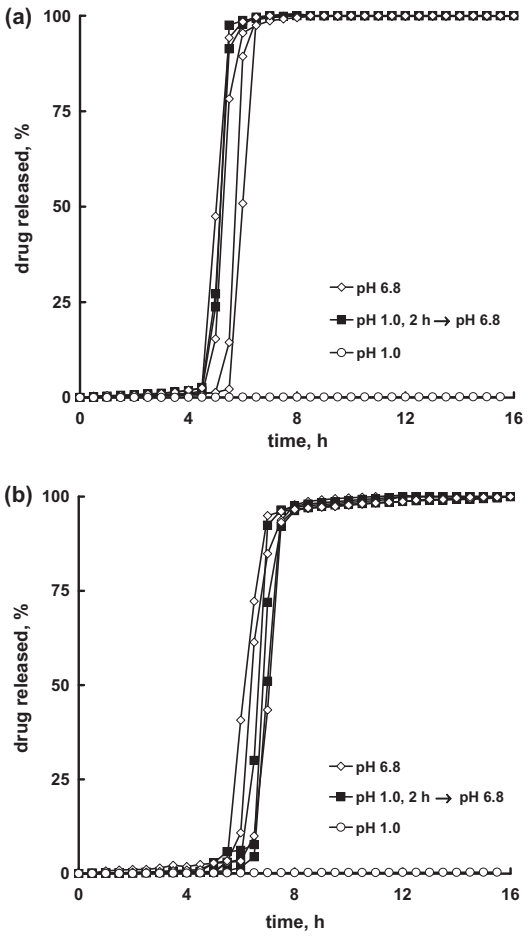

Fig. 7. Effect of pH-change of the dissolution medium on the chlorpheniramine maleate release from compression-coated tablets (core:coat, 1:2, 6 mm tablet cores in 9 mm compression-coated tablets, 25 kN compression force): (a) Eudragit L:ethylcellulose, 95:5; (b) Eudragit L:ethylcellulose, 90:10 ($n = 3$, individual release profiles shown).

The swelling and erosion behaviour of the Eudragit L:ethylcellulose matrix tablets were investigated in pH 1.0 and pH 7.4 in order to further clarify the influence of Eudragit L:ethylcellulose ratio on the drug release. Increasing the ethylcellulose amount decreased the weight increase (swelling) in 0.1 N HCl and decreased the weight loss and erosion (increased weight remaining) in pH 7.4 (Fig. 3a–b), thus paralleling the findings of drug release. Eudragit L matrix tablets containing 5% ethylcellulose had a 50% weight increase in 0.1 N HCl; this coating provided already full gastric protection (>18 h) (Fig. 2a). Eudragit L tablets with >10% ethylcellulose significantly decreased the weight increase to <10%. The weight loss studies in pH 7.4 confirmed the decrease in erosion with increasing ethylcellulose coating. In addition, the wettability of Eudragit L:ethylcellulose matrix tablets (0–25% ethylcellulose) with release medium decreased with increasing amount of ethylcellulose (Fig. 4). The contact angle of the media drops on Eudragit L:ethylcellulose matrix tablets increased with increasing ethylcellulose amount (0%, 5%, 10%, 15% and 25%) in pH 1.0 from 0° to 42°, 48°, 52° and 54° and in pH 7.4 from 14° to 43°, 50°, 52° and 53°. The contact angle remained fairly constant from 10% ethylcellulose onwards, this being consistent with the data shown in Fig. 2. The 0.1 N HCl drop penetrated quickly into Eudragit L-only tablets and was not visible after 6 min, while the 0.1 N HCl drop penetrated much slower into ethylcellulose-containing tablets. The visible drop of pH 7.4 buffer on Eudragit L-only tablets after 360 min was explained with the gradual dissolution of Eudragit L without swelling in this medium.

These results strongly support the excellent suitability of ethylcellulose as erosion-controlling (retarding) excipient in Eudragit L compression-coatings for colonic delivery.

Next, the effect of the pH of the dissolution medium on the drug release for Eudragit L:ethylcellulose (95:5 and 90:10) compression-coated tablets was investigated (Fig. 5a–b). The drug was not released below pH 6. The threshold pH for the dissolution of Eudragit L is above pH 5.5. A large decrease in lag time was seen from pH 6 to pH 6.8 or 7.4, which could be explained with the faster erosion of Eudragit L in higher pH media (Fig. 6). Importantly, the addition of ethylcellulose reduced the pH-dependency of the erosion process between pH 5.5 and 7.4 as indicated by a flatter curve (Fig. 6). Increasing the amount of ethylcellulose lead to an increase in lag time (Fig. 5b), as already seen before. The observed gastric resistance of the compression-coated tablets in the pH range of 1.0–5.5 could reduce inter- and intra-subject variability in vivo and ensure the release of drug in the lower intestinal tract.

The influence of pH-change of the dissolution medium on the drug release was investigated. Previously, a longer lag time after the acid treatment of HPMCAS compression-coated tablets has been reported. This was explained by a decrease in the microenvironmental pH due to the acid uptake of the swollen HPMCAS coat [19]. The swelling of HPMCAS matrix tablets in pH 1.0 after 2 h was high (80%) [22]. In our study, the pH-change had no influence on the drug release (Fig. 7) because of the low swelling or acid uptake of Eudragit L:ethylcellulose blends after 2 h in pH 1.0. This was due to the presence of ethylcellulose; the acid uptakes were 42% and 3% for Eudragit L:ethylcellulose blends of 95:5 and 90:10, respectively

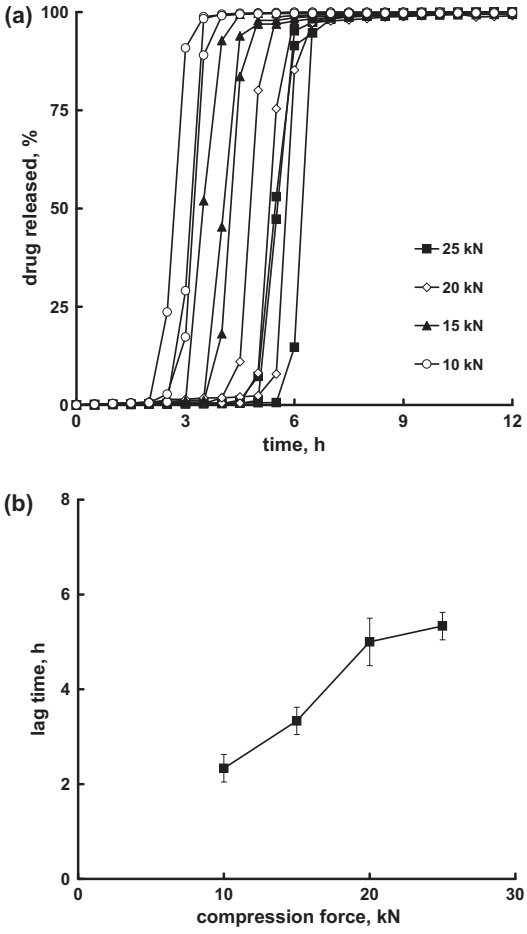

Fig. 8. Effect of compression force on chlorpheniramine maleate release from Eudragit L: ethylcellulose (90:10) compression-coated tablets (core:coat, 1:2, 6 mm tablet cores in 9 mm compression-coated tablets, 25 kN compression force): (a) drug release ($n = 3$, individual release profiles shown); (b) lag time.

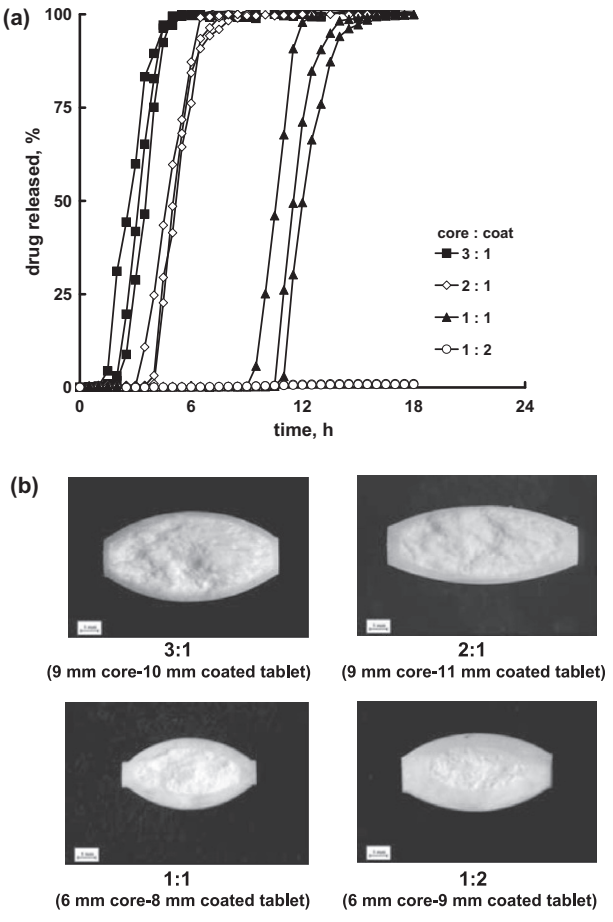

Fig. 9. Effect of tablet core:press-coat ratio on: (a) chlorpheniramine maleate release in pH 7.4 ($n = 3$, individual release profiles shown); (b) cross sections of compression-coated tablets (Eudragit L:ethylcellulose, 75:25, 25 kN compression force).

(Fig. 3a). This shows again the value of adding small amounts of ethylcellulose to the enteric polymer in order to get a more robust release.

As expected, the lag time increased with increasing compression force (10–25 kN) (Fig. 8a–b) because of a decreased porosity/higher density of the polymer compression-coating. The release phase after the lag time was still rapid and not affected by the compression force. Compression force is thus also a parameter to control the lag time. The porosity of the compression-coating could certainly also play a factor with the other formulation parameters investigated (e.g., Eudragit L:ethylcellulose ratio).

One potential disadvantage of compression-coated tablets is the limitation in maximum drug dose because of the relatively large amount of compression-coating. In order to maximize the potential drug loading, different tablet core:compression-coat ratios of 3:1 (9 mm core in 10 mm compression-coated tablet), of 2:1 (9 mm core in 11 mm compression-coated tablet), of 1:1 (6 mm core in 8 mm compression-coated tablet) and of 1:2 (6 mm core in 9 mm compression-coated tablet) were investigated. All formulations had no release in pH 1.0 for 20 h (data not shown) and a pulsatile release in pH 7.4 after a distinct lag time, which decreased with increasing core:coat ratio (Fig. 9a) because of the thinner compression-coating (Fig. 9b) and thus faster erosion.

4. Conclusions

In conclusion, tablets compression-coated with blends of Eudragit L and ethylcellulose were highly promising for potential targeting to the lower intestinal tract with no release in lower pH-media and rapid release after a controllable lag time in higher pH-media. The extended release polymer ethylcellulose significantly improved the desired release properties and release robustness of the enteric system.

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