Drug Development and Industrial Pharmacy, 2009; 35(10): 1190–1200

informa
healthcare

ORIGINAL ARTICLE

Characterization of ethylcellulose: starch-based film coatings for colon targeting

Youness Karrout[1], Christel Neut[2], Daniel Wils[3], Florence Siepmann[1], Laetitia Deremaux[3], Pierre Desreumaux[4] and Juergen Siepmann[1]

[1]College of Pharmacy, University of Lille, Lille, France, [2]College of Pharmacy, Clinical Bacteriology, University of Lille, Lille, France, [3]Roquette, Biology and Nutrition Department, Lestrem, France and [4]School of Medicine, Gastroenterology, University of Lille, Lille, France

Abstract

Background: The site-specific delivery of drugs to the colon can be highly advantageous for various applications, including the local treatment of inflammatory bowel diseases. The aim of this study was to provide efficient tools that can be used to easily adjust the key properties of novel polymeric film coatings allowing for colon targeting. *Methods*: Free films based on blends of ethylcellulose and different types of starch derivatives (partially being pregelatinized, acetylated, and/or hydroxypropylated) were prepared and characterized. *Results*: The key properties of the polymeric systems can effectively be adjusted by varying the polymer blend ratio and type of starch derivative. This includes the water uptake and dry mass loss kinetics as well as the mechanical properties of the films before and upon exposure to aqueous media simulating the contents of the upper GIT. *Conclusion*: Broad ranges of film coating properties can easily be provided, being adapted to the needs of the respective drug treatment.

Key words: *Colon targeting; controlled release; ethylcellulose; film coating; starch*

Introduction

The site-specific delivery of drugs to the colon can be highly advantageous for various applications, including: (i) the local treatment of inflammatory bowel diseases and (ii) the oral administration of protein drugs, which are to be absorbed into the bloodstream[1]. In the first case, premature drug release in the stomach is likely to lead to complete and rapid drug absorption into the systemic circulation. Thus, the risk of undesired side effects can be considerable, and, at the same time, the resulting drug concentrations at the site of action (in the colon) are low, leading to poor therapeutic efficacies[2]. In the second case, fragile protein drugs need to be effectively protected against the low pH and enzymatic degradation within the upper gastrointestinal tract (GIT). Thus, in both cases, premature release into the contents of the stomach and small intestine must be avoided. In contrast, once the colon is reached, the drug should be released (in a time-controlled manner) to allow for local drug action in the case of inflammatory bowel diseases or to allow for drug absorption into the bloodstream in the case of protein drugs with systemic effects[3].

Several strategies have been proposed in order to provide such site-specific drug delivery to the colon[4–6]. Most of them are based on the incorporation of the drug within a polymeric matrix or on the coating of a drug reservoir (e.g., pellet starter core, tablet, or capsule) with a polymeric film[7–9]. In both cases, the macromolecular networks should be poorly permeable for the drug in the upper GIT, but become permeable once the colon is reached. To provide this change in drug permeability, the delivery system might: (i) be sensitive to the changes in the pH along the GIT, (ii) be preferentially degraded by enzymes, which are located in the colon, or (iii) undergo significant structural changes, for example, crack formation in poorly permeable coatings or erosion in matrix systems once the colon is reached. Alternatively,

Address for correspondence: Professor Juergen Siepmann, College of Pharmacy, JE 2491, University of Lille, 3 rue du Professeur Laguesse, 59006 Lille, France. Tel: +33 3 20964708, Fax: +33 3 20964942. E-mail: juergen.siepmann@univ-lille2.fr

(Received 28 Oct 2008; accepted 1 Mar 2009)

ISSN 0363-9045 print/ISSN 1520-5762 online © Informa UK, Ltd.
DOI: 10.1080/03639040902858868

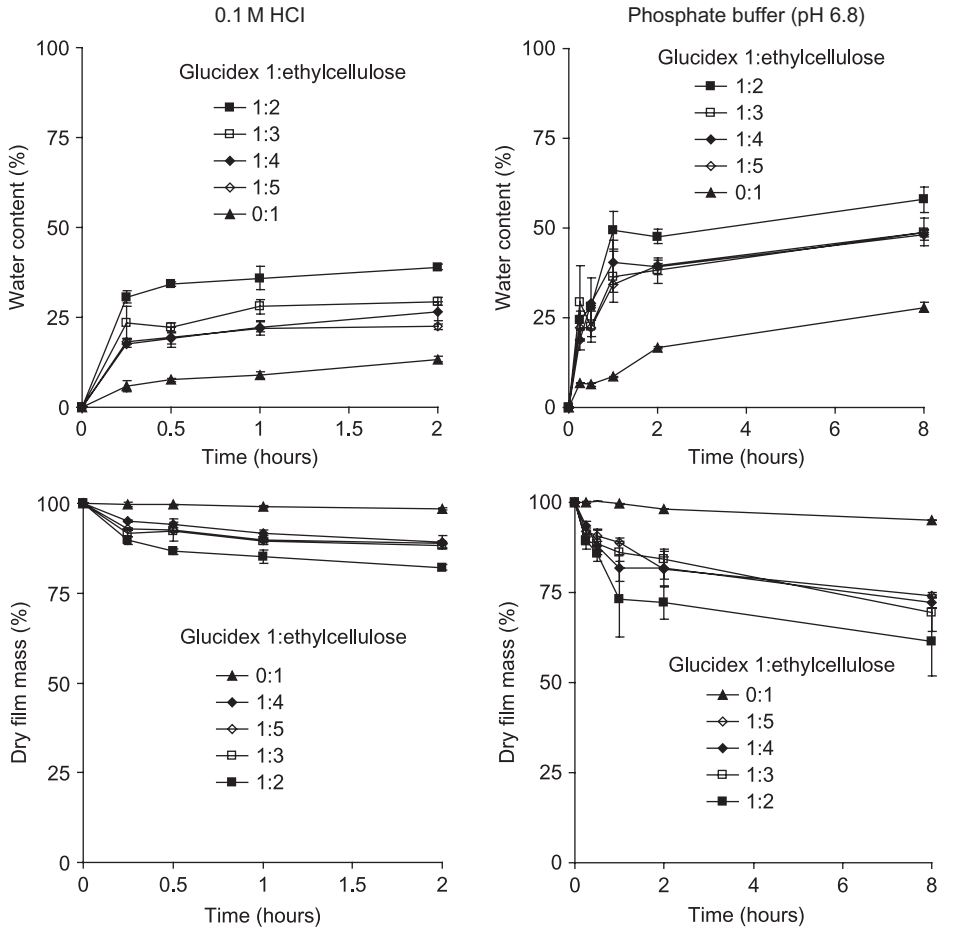

Figure 1. Water uptake and dry mass loss of thin films consisting of Glucidex 1:ethylcellulose blends upon exposure to 0.1 M HCl and phosphate buffer (pH 6.8), respectively. The polymer blend ratio is indicated in the figures. For reasons of comparison also the behavior of pure (plasticized) ethylcellulose films is shown.

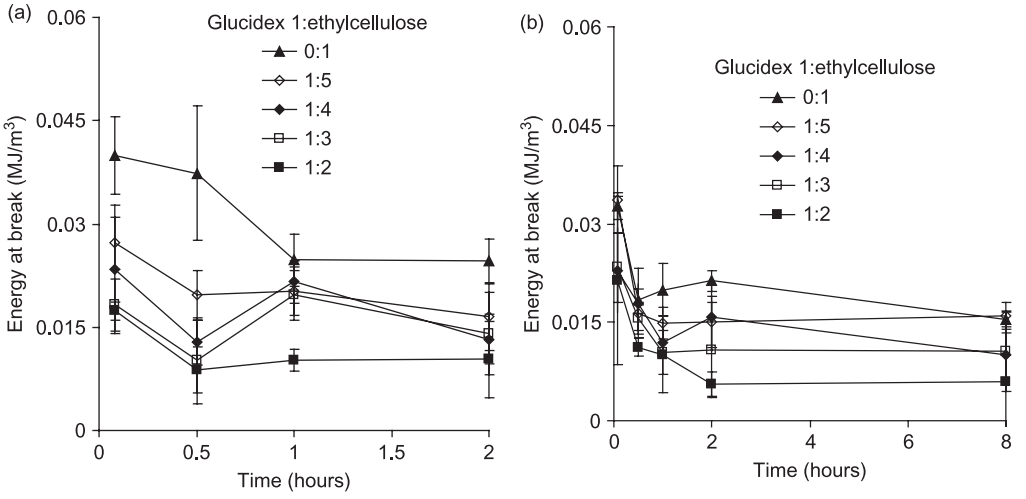

Figure 2. Changes in the energy at break of thin Glucidex 1:ethylcellulose films upon exposure to: (a) 0.1 M HCl and (b) phosphate buffer (pH 6.8). The polymer blend ratio is indicated in the figures. For reasons of comparison also the results obtained with pure (plasticized) ethylcellulose films are shown.

Table 1. Effects of the type of starch derivative blended with ethylcellulose and of the starch derivative:ethylcellulose blend ratio on the mechanical properties of thin films in the dry state at room temperature.

	Blend ratio	Puncture strength ± (s), MPa	Elongation at break ± (s), %	Energy at break ± (s), MJ/m^3
Glucidex 1	1:2	0.34 ± (0.05)	0.43 ± (0.08)	0.012 ± (0.005)
	1:3	0.36 ± (0.09)	0.57 ± (0.05)	0.014 ± (0.006)
	1:4	0.43 ± (0.07)	0.53 ± (0.04)	0.011 ± (0.003)
	1:5	0.42 ± (0.11)	0.58 ± (0.07)	0.015 ± (0.009)
Lycoat RS 780	1:2	0.45 ± (0.04)	0.55 ± (0.09)	0.016 ± (0.008)
	1:3	0.40 ± (0.03)	0.53 ± (0.07)	0.012 ± (0.007)
	1:4	0.42 ± (0.09)	0.60 ± (0.09)	0.016 ± (0.008)
	1:5	0.50 ± (0.08)	0.60 ± (0.05)	0.020 ± (0.004)
Eurylon 7 A-PG	1:2	0.78 ± (0.09)	0.63 ± (0.02)	0.061 ± (0.005)
	1:3	0.84 ± (0.05)	0.67 ± (0.08)	0.065 ± (0.009)
	1:4	0.85 ± (0.04)	0.66 ± (0.07)	0.070 ± (0.011)
	1:5	0.87 ± (0.05)	0.75 ± (0.02)	0.073 ± (0.006)
Eurylon 6 A-PG	1:2	0.60 ± (0.01)	0.50 ± (0.07)	0.052 ± (0.002)
	1:3	0.52 ± (0.05)	0.75 ± (0.10)	0.068 ± (0.008)
	1:4	0.76 ± (0.02)	0.82 ± (0.04)	0.077 ± (0.006)
	1:5	0.77 ± (0.03)	0.81 ± (0.06)	0.075 ± (0.010)
Eurylon 6 HP-PG	1:2	0.53 ± (0.07)	0.72 ± (0.05)	0.053 ± (0.010)
	1:3	0.64 ± (0.03)	0.81 ± (0.07)	0.066 ± (0.009)
	1:4	0.63 ± (0.02)	0.82 ± (0.07)	0.062 ± (0.009)
	1:5	0.87 ± (0.03)	0.77 ± (0.05)	0.070 ± (0.010)

the dosage form might release the drug right from the beginning (in the stomach), but at a rate that is sufficiently low to allow for drug release throughout the GIT, including the colon[10–13]. However, great caution must be paid, because the conditions in a patient's colon might significantly differ from those in the physiological state[14]. For instance, it is well known that the pH and transit times in the various GIT segments as well as the types and concentrations of enzymes in the colon of patients suffering from Crohn's disease and ulcerative colitis can fundamentally vary from those in a healthy subject[15–18]. Thus, a dosage form might reliably deliver the drug to the target site in a healthy subject, but fail in a patient. Furthermore, considerable inter- and intra-individual variability in the therapeutic efficacy might be observed. To avoid these major disadvantages, the drug delivery system should be adapted to the disease state of the patient. For instance, if the onset of drug release in the colon is induced by enzymatic degradation, the responsible enzymes must be present in the colon of the patients in sufficient quantities.

Recently, novel types of polymeric films consisting of blends of different types of starch derivatives and ethylcellulose were identified as promising coating materials allowing for site-specific drug delivery to the colon[19]. Such starch derivatives include Lycoat RS 780 (a pregelatinized modified starch), Glucidex 1 (a maltodextrin), Eurylon 7 A-PG (an acetylated and pregelatinized high amylose starch), Eurylon 6 A-PG (an acetylated and pregelatinized high amylose starch) and Eurylon 6 HP-PG (a hydroxypropylated and pregelatinized high amylose starch). Ethylcellulose is water insoluble and avoids premature film dissolution in the upper GIT[20]. The starch derivative is water soluble and preferentially degraded by enzymes secreted by the microflora present in the colon of Crohn's disease and ulcerative colitis patients.

However, it is yet unclear how the key properties of these novel film coatings (water uptake, dry mass loss, and mechanical resistance upon exposure to media simulating the contents of the upper GIT and the colon) allowing for colon targeting in the disease state can be adjusted to the specific needs of a particular drug treatment, for example, the hydrostatic pressure developed within the core formulation upon water penetration into the system and the administered drug dose. Ideally, the film coatings should take up no (or only small amounts of) water, lose no (or only minor amounts of) dry mass, and remain stable within the contents of the upper GIT in order to prevent premature drug release. However, once the colon is reached, the water uptake and dry mass loss should become significant to allow for controlled drug delivery at the target site. The major aim of this study was to identify efficient tools that can be used to easily adjust the crucial film coating properties.

Materials and methods

Materials

Lycoat RS 780 (a pregelatinized hydroxypropyl pea starch), Glucidex 1 (a maltodextrin), Eurylon 7 A-PG (an acetylated and pregelatinized high amylose starch), Eurylon 6 A-PG (an acetylated and pregelatinized high amylose starch), and Eurylon 6 HP-PG (a hydroxypropylated and pregelatinized high amylose starch; (Roquette Freres, Lestrem, France); aqueous ethylcellulose dispersion (Aquacoat ECD 30; FMC Biopolymer, Philadelphia, PA, USA); triethylcitrate (TEC; Morflex, Greensboro, NC, USA).

Preparation of thin, polymeric films

Thin polymeric films were prepared by casting blends of different types of polysaccharides and aqueous ethylcellulose dispersion into Teflon molds and subsequent drying for 1 day at 60°C. The water-soluble polysaccharide was dissolved in purified water [5% (w/w), in the case of Eurylon 7 A-PG, Eurylon 6 A-PG, and Eurylon 6 HP-PG in hot water], blended with plasticized aqueous ethylcellulose dispersion [25% (w/w) TEC, referred to the ethylcellulose content, overnight stirring] at a ratio of 1:2, 1:3, 1:4, 1:5 (polymer:polymer, w/w). The mixtures were stirred for 6 hours prior to casting.

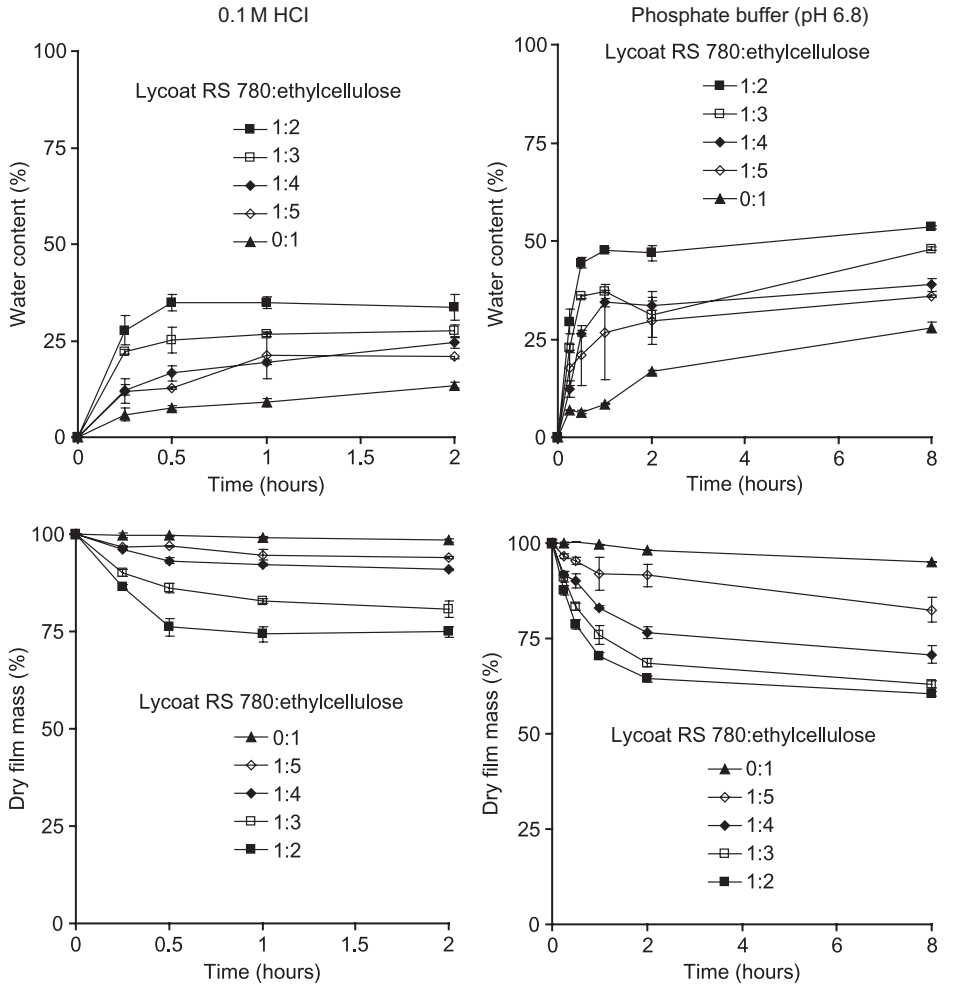

Figure 3. Water uptake and dry mass loss of thin films consisting of Lycoat RS 780:ethylcellulose blends upon exposure to 0.1 M HCl and phosphate buffer (pH 6.8), respectively. The polymer blend ratio is indicated in the figures. For reasons of comparison also the behavior of pure (plasticized) ethylcellulose films is shown.

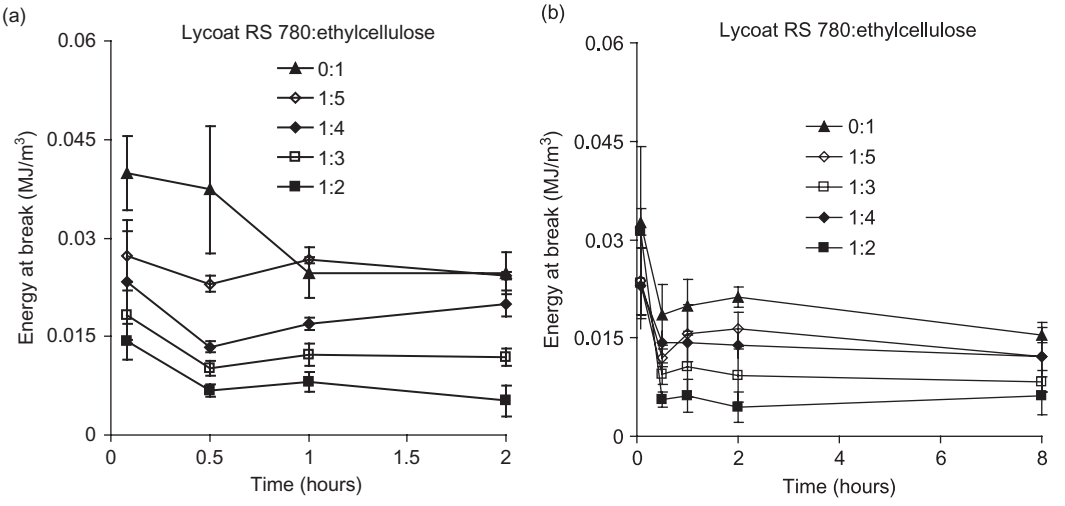

Figure 4. Changes in the energy at break of thin Lycoat RS 780:ethylcellulose films upon exposure to: (a) 0.1 M HCl and (b) phosphate buffer (pH 6.8). The polymer blend ratio is indicated in the figures. For reasons of comparison also the results obtained with pure (plasticized) ethylcellulose films are shown.

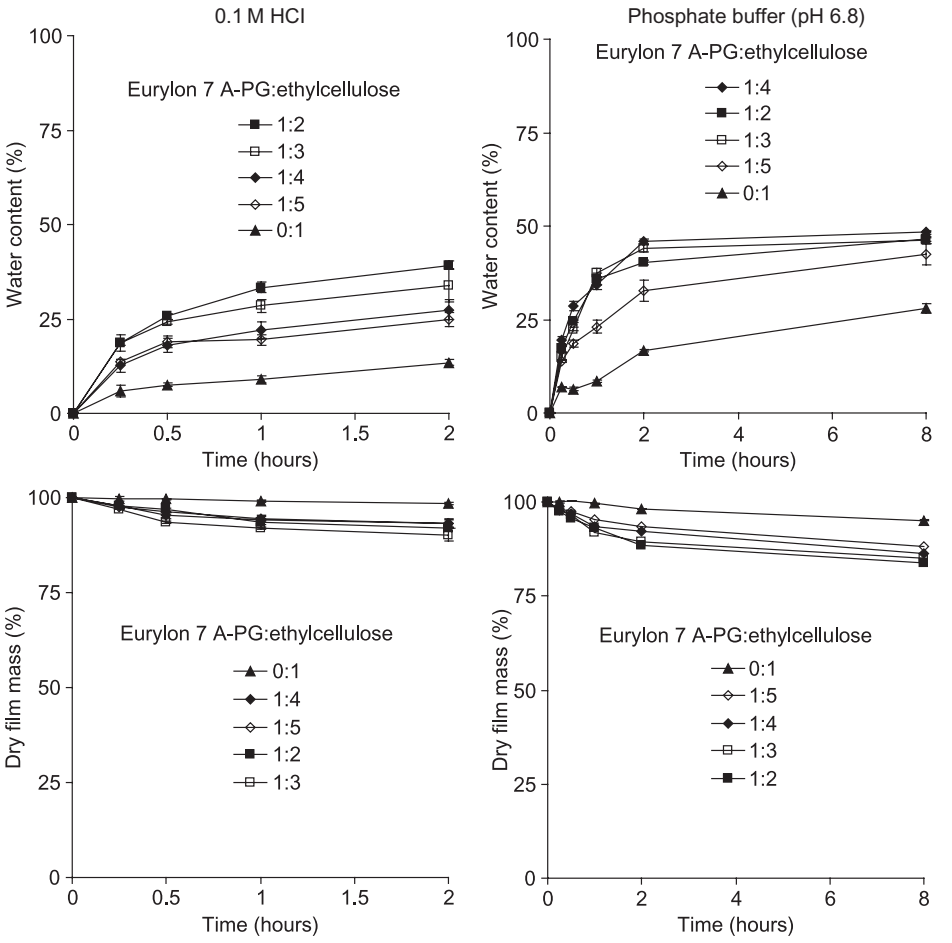

Figure 5. Water uptake and dry mass loss of thin films consisting of Eurylon 7 A-PG:ethylcellulose blends upon exposure to 0.1 M HCl and phosphate buffer (pH 6.8), respectively. The polymer blend ratio is indicated in the figures. For reasons of comparison also the behavior of pure (plasticized) ethylcellulose films is shown.

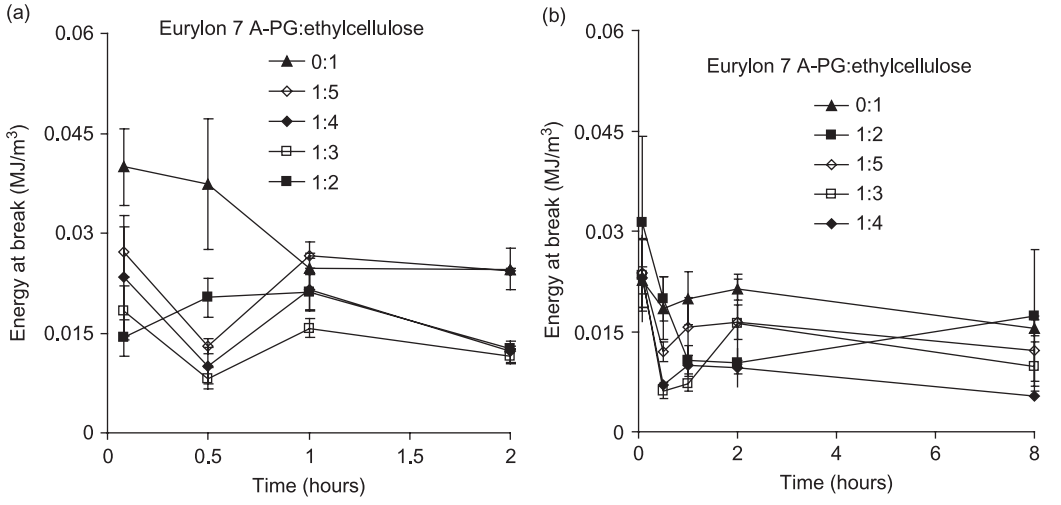

Figure 6. Changes in the energy at break of thin Eurylon 7 A-PG:ethylcellulose films upon exposure to: (a) 0.1 M HCl and (b) phosphate buffer (pH 6.8). The polymer blend ratio is indicated in the figures. For reasons of comparison also the results obtained with pure (plasticized) ethylcellulose films are shown.

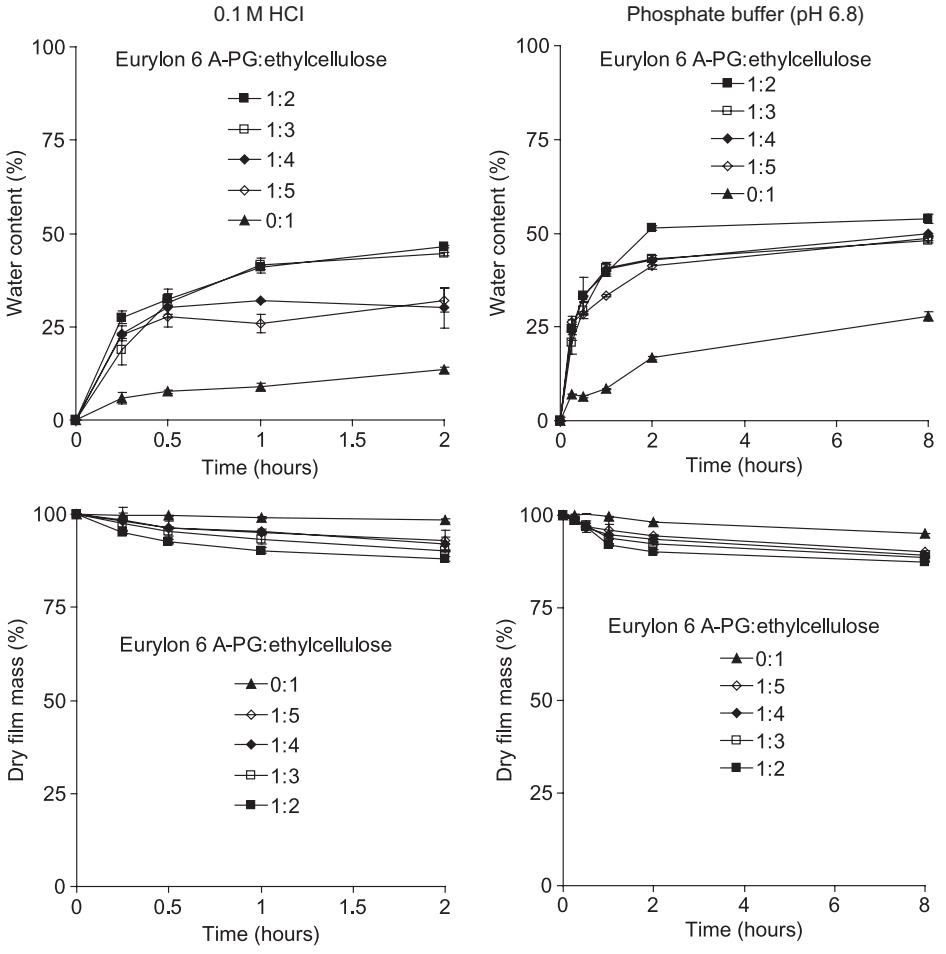

Figure 7. Water uptake and dry mass loss of thin films consisting of Eurylon 6 A-PG:ethylcellulose blends upon exposure to 0.1 M HCl and phosphate buffer pH 6.8, respectively. The polymer blend ratio is indicated in the figures. For reasons of comparison also the behavior of pure (plasticized) ethylcellulose films is shown.

Film characterization

The thickness of the films was measured using a thickness gauge (Minitest 600; Erichsen, Hemer, Germany). The mean thickness of all films was in the range of 300–340 µm. The water uptake and dry mass loss kinetics of the films were measured gravimetrically upon exposure to 0.1 M HCl and phosphate buffer (pH 6.8) (USP 30) as follows: Pieces of 1.5×5 cm were placed into 120 mL plastic containers filled with 100 mL pre-heated medium, followed by horizontal shaking at 37°C (80 rpm, GFL 3033, Gesellschaft fuer Labortechnik, Burgwedel, Germany). At predetermined time points, samples were withdrawn, excess water removed, the films accurately weighed (wet mass), and dried to constant weight at 60°C (dry mass). The water content (%) and dry film mass (%) at time t were calculated as follows:

$$\text{Water content}\,(\%)\,(t) = \frac{\text{wet mass}\,(t) - \text{dry mass}\,(t)}{\text{wet mass}\,(t)} \times 100\% \quad (1)$$

$$\text{Dry film mass}\,(\%)\,(t) = \frac{\text{dry mass}\,(t)}{\text{dry mass}\,(t=0)} \times 100\,\%. \quad (2)$$

The mechanical properties of the films in the dry and wet state were determined with a texture analyzer (TAXT.Plus, Winopal Forschungsbedarf, Ahnsbeck, Germany) and the puncture test. Film specimens were mounted on a film holder (n = 6). The puncture probe (spherical end: 5-mm diameter) was fixed on the load cell (5 kg) and driven downward with a cross-head speed of 0.1 mm/s to the center of the film holder's hole. Load versus displacement curves were recorded until rupture of the film and used to determine the mechanical properties as follows:

$$\text{Puncture strength} = \frac{F}{A}, \quad (3)$$

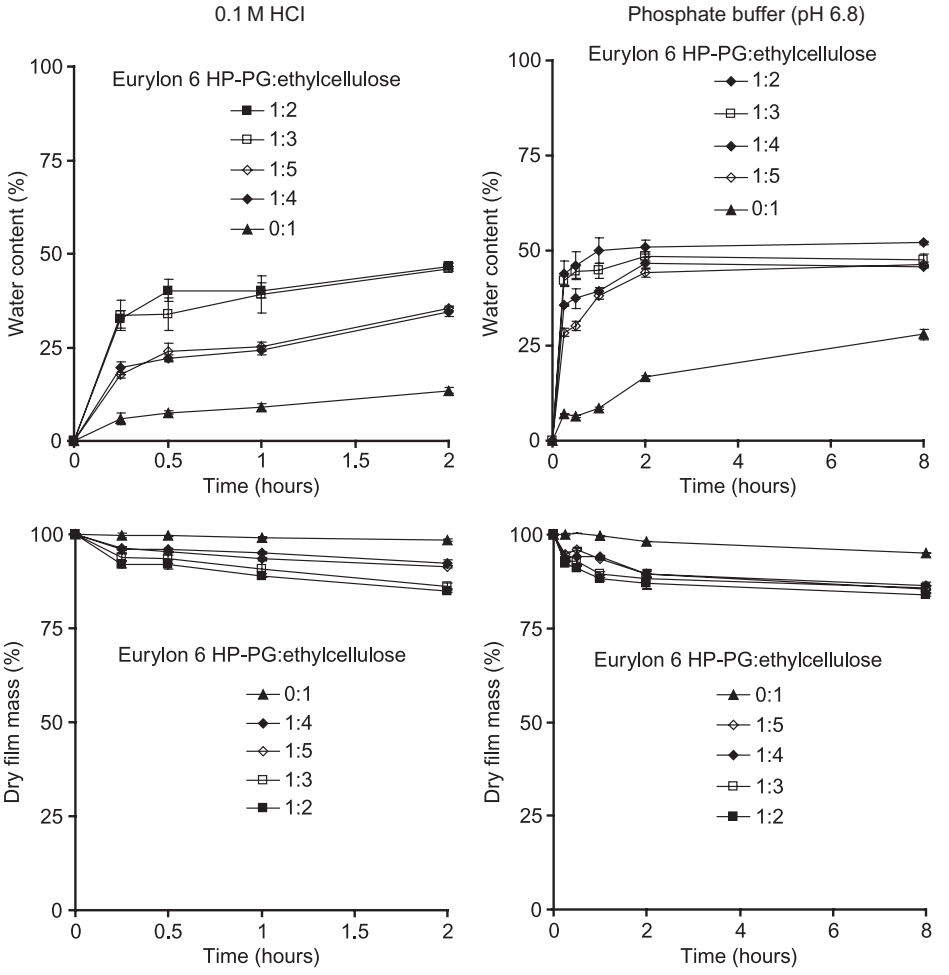

Figure 8. Water uptake and dry mass loss of thin films consisting of Eurylon 6 HP-PG:ethylcellulose blends upon exposure to 0.1 M HCl and phosphate buffer pH 6.8, respectively. The polymer blend ratio is indicated in the figures. For reasons of comparison also the behavior of pure (plasticized) ethylcellulose films is shown.

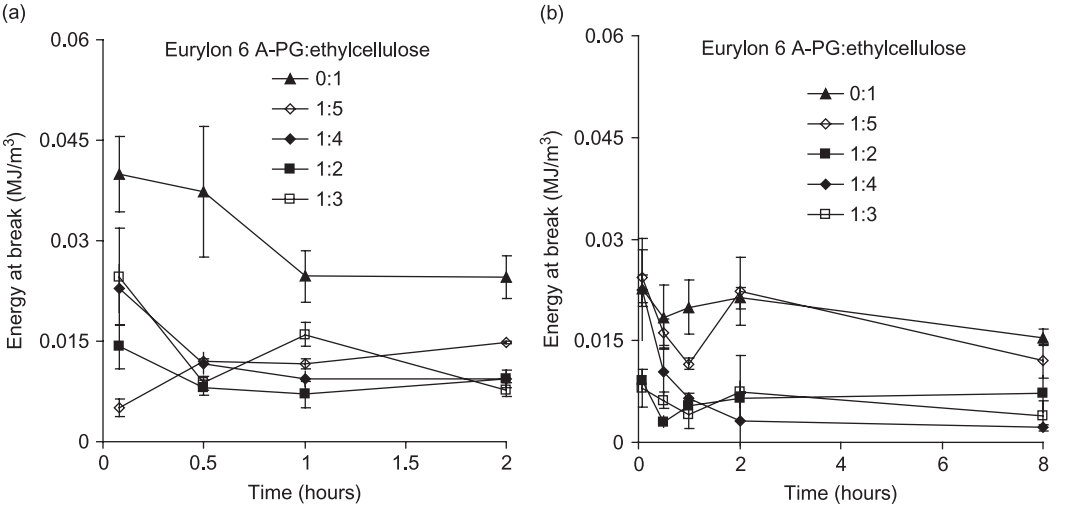

Figure 9. Changes in the energy at break of thin Eurylon 6 A-PG:ethylcellulose films upon exposure to: (a) 0.1 M HCl and (b) phosphate buffer pH 6.8. The polymer blend ratio is indicated in the figures. For reasons of comparison also the results obtained with pure (plasticized) ethylcellulose films are shown.

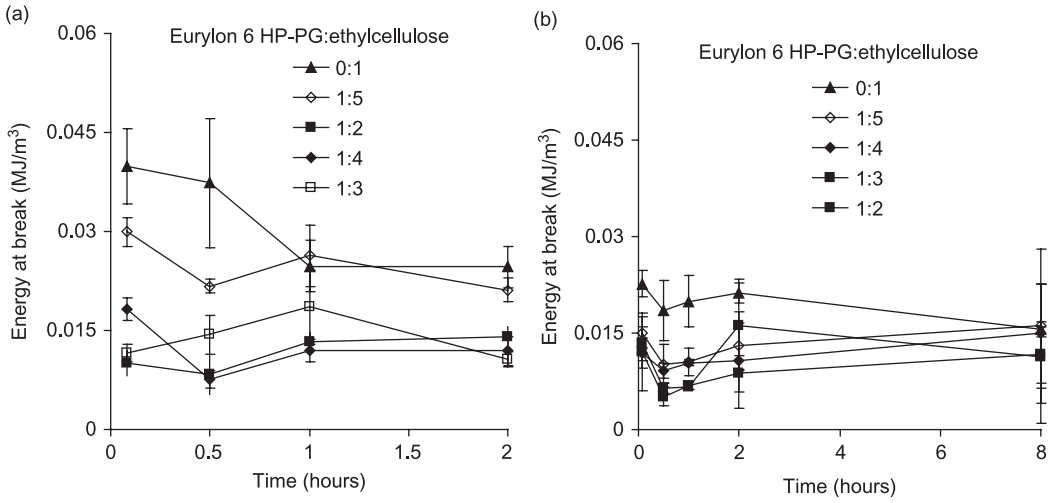

Figure 10. Changes in the energy at break of thin Eurylon 6 HP-PG:ethylcellulose films upon exposure to: (a) 0.1 M HCl and (b) phosphate buffer pH 6.8. The polymer blend ratio is indicated in the figures. For reasons of comparison also the results obtained with pure (plasticized) ethylcellulose films are shown.

where F is the load required to puncture the film and A the cross-sectional area of the edge of the film located in the path

$$\%\,\text{Elongation at break} = \frac{\sqrt{R^2 + D^2} - R}{R} \times 100\,\%. \quad (4)$$

Here, R denotes the radius of the film exposed in the cylindrical hole of the holder and D is the displacement.

$$\text{Energy at break per unit volume} = \frac{\text{AUC}}{V}, \quad (5)$$

where AUC is the area under the load versus displacement curve and V is the volume of the film located in the die cavity of the film holder.

Results and discussion

Glucidex 1:ethylcellulose blends

It was recently shown that blends of ethylcellulose and different types of starch derivatives (in particular Glucidex 1, Lycoat RS 780, Eurylon 7 A-PG, Eurylon 6 A-PG, and Eurylon 6 HP-PG) are promising to allow for site-specific drug delivery to the colon in order to improve the local treatment of inflammatory bowel diseases[19]. Importantly, such films serve as substrates for the microflora in the disease state of patients suffering from Crohn's disease and ulcerative colitis. However, it is yet unclear in how far the polymer:polymer blend ratio can affect the resulting systems' properties, in particular their water uptake and dry mass loss kinetics as well as their mechanical resistance to internal and external stress exhibited in vivo.

Figure 1 shows the effects of the composition of Glucidex 1:ethylcellulose films on the resulting water uptake kinetics and dry mass loss behavior upon exposure to 0.1 M HCl and phosphate buffer (pH 6.8), respectively. For reasons of comparison also the results obtained with pure (plasticized) ethylcellulose films are shown. Clearly, the water uptake rates and extents significantly increased when increasing the Glucidex 1:ethylcellulose blend ratio from 1:5 to 1:2. This can be attributed to the fact that Glucidex 1 is a maltodextrin and much more hydrophilic than ethylcellulose. At high initial Glucidex 1 contents the water uptake became significant, for example, about half of the films consisted of water in the case of 1:2 blends after 1-hour exposure to phosphate buffer (pH 6.8). This can be expected to render an efficient suppression of the release of freely water-soluble, low-molecular-weight drugs in the upper GIT challenging, because the mobility of the macromolecules significantly increases with increasing water content, resulting in increasing drug mobility. Elevated coating levels are likely to be required. However, the permeability for larger drug molecules (e.g., proteins) can be low in polymeric networks, even at elevated water contents. In this case, the mobility of the drug essentially depends on the ratio 'drug molecule size:average mesh-size of macromolecular network'. Advanced drug delivery systems with site-specific delivery to the colon might for instance be attractive to allow for the systemic delivery of proteins after oral administration: If the proteins are effectively protected against

the low pH and enzymatic degradation in the upper GIT, they might get absorbed upon release in the colon. Furthermore, the relative release rate of a poorly water-soluble drug might be very low, even if the film coating contains significant amounts of water, as long as the dosage form remains intact.

Interestingly, both the rates and the extents of water uptake were higher in phosphate buffer (pH 6.8) than in 0.1 M HCl, irrespective of the polymer blend ratio (Figure 1, top row). This can at least partially be attributed to the presence of sodium dodecyl sulfate (SDS) in the aqueous ethylcellulose dispersion (acting as a stabilizer) used for film preparation[21]. At low pH, this surfactant is protonated and neutral, whereas at pH 6.8 it is deprotonated and negatively charged. Thus, its ability to decrease interfacial tensions is increased, facilitating water penetration into the polymeric networks.

Furthermore, the rates and extents of the dry films' mass loss significantly increased with increasing Glucidex 1 content (Figure 1, bottom row). This can at least partially be explained by the leaching of this water-soluble maltodextrin into the bulk fluids. Furthermore, the (partial) leaching of the water-soluble plasticizer TEC into the release media is responsible for this phenomenon[22]. TEC is required for the plasticization of the ethylcellulose nanoparticles to allow for the film formation from aqueous dispersions. Even Glucidex 1 free films lose some dry mass, in particular at pH 6.8. The considerable water content of the polymeric systems containing high initial Glucidex 1 contents can be expected to facilitate the leaching of the low-molecular-weight, water-soluble plasticizer TEC. Again, the observed effects were more pronounced upon exposure to phosphate buffer (pH 6.8) than to 0.1 M HCl (Figure 1), because of the presence of SDS.

In addition to appropriate water uptake and dry mass loss kinetics, polymeric film coatings that are intended to allow for site-specific drug delivery to the colon must also provide sufficient mechanical stability in order to withstand the various mechanical stresses encountered in vivo. This concerns in particular: (i) the shear forces resulting from the motility of the upper GIT and (ii) the hydrostatic pressure acting against the film coating from the core of the dosage form, caused by the osmotically driven water influx into the system upon contact with aqueous body fluids. In order to estimate the capacity of the investigated Glucidex 1:ethylcellulose blends to withstand such external and internal stresses, the mechanical properties of thin films were measured with a texture analyzer and the puncture test. The puncture strength, percent elongation at break as well as the energy required to break the films in the dry state at room temperature are shown in Table 1. Clearly, the mechanical stability of the systems increased with increasing ethylcellulose content. Thus, the latter compound is the stabilizing agent in these polymeric networks. For reasons of comparison, the puncture strength, elongation at break, and energy at break of pure (plasticized) ethylcellulose films were equal to 0.98 ± (0.02) MPa, 0.85 ± (0.02)%, and 0.078 ± (0.002) MJ/m^3, respectively.

It has to be pointed out that the mechanical properties shown in Table 1 were obtained with dry films at room temperature. It is well known that water acts as a plasticizer for many polymers and as it can be seen in Figure 1, significant amounts of water penetrate into the films upon exposure to 0.1 M HCl and phosphate buffer (pH 6.8). Furthermore, the composition of the polymeric systems significantly changes upon contact with the release media due to (partial) Glucidex 1 and TEC leaching. In addition, the mechanical resistance of the polymeric films might significantly depend on the temperature. Polymers can for instance undergo glassy-to-rubbery phase transitions when increasing the temperature to 37°C. For these reasons, the mechanical properties of the investigated Glucidex 1:ethylcellulose blends were also determined following exposure to 0.1 M HCl for up to 2 hours and to phosphate buffer (pH 6.8) for up to 8 hours. As it can be seen in Figure 2, the mechanical stability of the polymeric films decreased with time due to partial Glucidex 1 and TEC leaching, irrespective of the polymer blend ratio and type of release medium. Importantly, appropriate mechanical stabilities can be adjusted effectively by varying the polymer:polymer blend ratio (and eventually by varying the coating thickness).

Lycoat RS 780:ethylcellulose blends

Figure 3 shows the gravimetrically determined water uptake and dry mass loss kinetics of thin films consisting of different types of Lycoat RS 780:ethylcellulose blends upon exposure to 0.1 M HCl and phosphate buffer (pH 6.8), respectively. Lycoat RS 780 is a pregelatinized modified starch. As in the case of Glucidex 1, the resulting extent and rate of the water penetration into the systems significantly increased when increasing the starch derivative:ethylcellulose ratio from 1:5 to 1:2 (Figure 1, top row). This can again be attributed to the higher hydrophilicity of the starch derivative compared to ethylcellulose. Appropriately elevated coating levels are likely to be required to suppress the premature release of freely water-soluble, small-molecular-weight drugs in the upper GIT at high initial Lycoat RS 780 contents. Also the rate and extent of the films' dry mass loss significantly increased with increasing Lycoat RS 780 contents due to partial TEC and starch derivative leaching. In all cases, the rates and extents of the water penetration and dry mass loss were higher in phosphate buffer (pH 6.8) compared to 0.1 M HCl, because of the pH-dependent ionization of SDS as discussed above.

As in the case of Glucidex 1:ethylcellulose blends, the mechanical stability of Lycoat RS 780:ethylcellulose films could effectively be adjusted by varying the initial ethylcellulose content. This was true for the puncture strength, % elongation at break, and energy at break in the dry state at room temperature (Table 1) as well as for the mechanical resistance in the wet state upon exposure to 0.1 M HCl and phosphate buffer (pH 6.8) (Figure 4). The decrease in the energy at break with time can again be attributed to partial plasticizer and starch derivative leaching into the bulk fluids, irrespective of the type of release medium.

Eurylon 7 A-PG:ethylcellulose blends

The water uptake and dry mass loss kinetics of thin films consisting of 1:2 to 0:1 Eurylon 7 A-PG:ethylcellulose blends in 0.1 M HCl and phosphate buffer (pH 6.8) are shown in Figure 5. Eurylon 7 A-PG is an acetylated and pregelatinized high amylose starch. As it can be seen, the same tendencies as with Glucidex 1:ethylcellulose and Lycoat RS 780:ethylcellulose blends were observed: (i) the water uptake rates and extents increased with decreasing ethylcellulose contents, (ii) the dry mass loss rates and extents increased with increasing starch derivative contents, and (iii) these effects were more pronounced in phosphate buffer (pH 6.8) than in 0.1 M HCl. Interestingly, the dry mass loss of thin films consisting of Eurylon 7 A-PG:ethylcellulose was much less pronounced than that of Glucidex 1:ethylcellulose and Lycoat RS 780:ethylcellulose films upon exposure to 0.1 M HCl and phosphate buffer (pH 6.8), respectively (bottom rows in Figures 1, 3, and 5). This was true for both the rates and the extents of the dry mass loss and for all the investigated polymer blend ratios. Importantly, the water contents of the Eurylon 7 A-PG:ethylcellulose films upon 2-hour exposure to phosphate were considerable: about 50% (w/w). Thus, also at high initial Eurylon 7 A-PG contents, elevated coating levels are likely to be required in order to suppress the premature release of freely water-soluble, low-molecular-weight drugs in the upper GIT. Importantly, the mechanical resistance of the Eurylon 7 A-PG:ethylcellulose-based films was significantly higher than that of films consisting of Glucidex 1:ethylcellulose and Lycoat RS 780:ethylcellulose blends in the dry state at room temperature (Table 1). However, these differences became minor when the films were exposed to 0.1 M HCl and phosphate buffer (pH 6.8), irrespective of the type of release medium (Figure 6). Importantly, the variation of the polymer blend ratio again allowed for an efficient adjustment of the mechanical stability of the films.

Eurylon 6 A-PG:ethylcellulose and Eurylon 6 HP-PG: ethylcellulose blends

Eurylon 6 A-PG is an acetylated and pregelatinized high amylose starch, and Eurylon 6 HP-PG is a hydroxypropylated and pregelatinized high amylose starch. Interestingly, the dry mass loss of thin films consisting of Eurylon 6 A-PG:ethylcellulose and Eurylon 6 HP-PG:ethylcellulose blends was limited upon exposure to 0.1 M HCl and phosphate buffer (pH 6.8), respectively (Figures 7 and 8, bottom rows). In contrast, the water uptake rates and extents of these films upon exposure to the different release media were considerable, reaching water contents of approximately 50% (w/w) after 1–2 hours exposure to phosphate buffer (pH 6.8) in the case of high initial starch derivative contents (Figures 7 and 8, top rows). Thus, also for Eurylon 6 A-PG:ethylcellulose and Eurylon 6 HP-PG:ethylcellulose blends elevated coating levels are likely to be required to suppress premature release of freely water-soluble, low-molecular-weight drugs in the upper GIT at low initial ethylcellulose contents. As it can be seen in Table 1, the mechanical properties of thin films consisting of these types of polymer blends in the dry state at room temperature are similar to those of Eurylon 7 A-PG:ethylcellulose blends at the same blend ratios. As in the case of the latter blends, exposure to 0.1 M HCl or phosphate buffer (pH 6.8) resulted in a decrease in the mechanical stability of the macromolecular networks, irrespective of the type of release medium and polymer blend ratio (Figures 9 and 10). Importantly, desired system stabilities can again effectively be adjusted by varying the polymer blend ratio.

Conclusion

The key properties of thin polymeric films consisting of starch derivative:ethylcellulose blends exhibiting an interesting potential to provide site-specific drug delivery to the colon (and being adapted to the pathophysiology of inflammatory bowel disease patients) can effectively be adjusted by varying the polymer blend ratio and type of starch derivative. This includes the water uptake and dry mass loss kinetics as well as the mechanical properties of the films before and upon exposure to aqueous media simulating the contents of the upper GIT. Thus, broad ranges of film coating properties can easily be provided, being adapted to the needs of the respective drug treatment (e.g., osmotic activity of the core formulation and administered dose).

Declaration of interest: The authors report no conflicts of interest.

References

1. Meissner Y, Lamprecht A. (2008). Alternative drug delivery approaches for the therapy of inflammatory bowel disease. J Pharm Sci, 97:2878–91.
2. Bondesen S. (1997). Intestinal fate of 5-aminosalicylic acid: Regional and systemic kinetic studies in relation to inflammatory bowel disease. Pharmacol Toxicol, 81(Suppl 2):1–28.
3. Haupt S, Rubinstein A. (2002). The colon as a possible target for orally administered peptides and proteins. Crit Rev Ther Drug Carrier Syst, 19:499–545.
4. Yang L, Chu JS, Fix JA. (2002). Colon-specific drug delivery: New approaches and in vitro/in vivo evaluation. Int J Pharm, 235:1–15.
5. Semde R, Moës AJ, Devleeschouwer MJ, Amighi K. (2003). Synthesis and enzymatic degradation of epichlorohydrin cross-linked pectins. Drug Dev Ind Pharm, 29:203–13.
6. Onishi H, Oosegi T, Machida Y, McGinity JW. (2005). Preparation and in vitro evaluation of chitosan microspheres containing prednisolone: Comparison of simple and conjugate microspheres. Drug Dev Ind Pharm, 31:597–605.
7. Cummings JH, Milojevic S, Harding M, Coward WA, Gibson GR, Botham RL, et al. (1996). In vivo studies of amylose- and ethylcellulose-coated [^{13}C] glucose microspheres as a model for drug delivery to the colon. J Control Release, 40:123–31.
8. Milojevic S, Newton JM, Cummings JH, Gibson GR, Botham RL, Ring SG, et al. (1996). Amylose as a coating for drug delivery to the colon: Preparation and in vitro evaluation using 5-aminosalicylic acid pellets. J Control Release, 38:75–84.
9. Milojevic S, Newton JM, Cummings JH, Gibson GR, Botham RL, Ring SG, et al. (1996). Amylose as a coating for drug delivery to the colon: Preparation and in vitro evaluation using glucose pellets. J Control Release, 38:85–94.
10. Gazzaniga A, Iamartino P, Maffione G, Sangalli ME. (1994). Oral delayed-release system for colonic specific delivery. Int J Pharm, 108:77–83.
11. Gazzaniga A, Sangalli ME, Giordano F. (1994). Oral Chronotropic drug delivery systems: Achievement of time and/or site specificity. Eur J Pharm Biopharm, 40:246–50.
12. Gazzaniga A, Maroni A, Sangalli ME, Zema L. (2006). Time-controlled oral delivery systems for colon targeting. Expert Opin Drug Deliv, 3:583–97.
13. Sangalli ME, Maroni A, Zema L, Busetti C, Giordano F, Gazzaniga A. (2001). In vitro and in vivo evaluation of an oral system for time and/or site-specific drug delivery. J Control Release, 73:103–10.
14. Siccardi D, Turner JR, Mrsny J. (2005). Regulation of intestinal epithelial function: A link between opportunities for macromolecular drug delivery and inflammatory bowel disease. Adv Drug Deliv Rev, 57:219–35.
15. El Yamani J, Mizon C, Capon C, Colombel JF, Fournet B, Cortot A, et al. (1992). Decreased fecal exoglycosidase activities identify a subset of patients with active Crohn's Disease. Clin Sci, 83:409–15.
16. Carrette O, Favier C, Mizon C, Neut C, Cortot A, Colombel JF, et al. (1995). Bacterial enzymes used for colon-specific drug delivery are decreased in active Crohn's Diseases. Dig Dis Sci, 40:2641–6.
17. Favier C, Neut C, Mizon C, Cortot A, Colombel JF, Mizon J. (1997). Fecal β-D-galactosidase production and bifidobacteria are decreased in Crohn's disease. Dig Dis Sci, 42:817–22.
18. Friend DR. (2005). New oral delivery systems for treatment of inflammatory bowel disease. Adv Drug Deliv Rev, 57:247–65.
19. Karrout Y, Neut C, Wils D, Siepmann F, Deremaux L, Dubreuil L, et al. (2009). Colon targeting with bacteria-sensitive films adapted to the disease state, submitted.
20. McConnell EL, Tutas J, Mohamed MAM, Banning D, Basit AW. (2007). Colonic drug delivery using amylose films: The role of aqueous ethylcellulose dispersions in controlling drug release. Cellulose, 14:25–34.
21. Wesseling M, Bodmeier R. (1999). Drug release from beads coated with an aqueous colloidal ethylcellulose dispersion, Aquacoat®, or an organic ethylcellulose solution. Eur J Pharm Biopharm, 47:33–8.
22. Siepmann F, Siepmann J, Walther M, MacRae RJ, Bodmeier R. (2005). Blends of aqueous polymer dispersions used for pellet coating: Importance of the particle size. J Control Release, 105:226–39.