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Novel polymeric film coatings for colon targeting: How to adjust desired membrane properties

Youness Karrout[a], Christel Neut[b], Daniel Wils[c], Florence Siepmann[a], Laetitia Deremaux[c], Pierre Desreumaux[d], Jürgen Siepmann[a,*]

[a] College of Pharmacy, JE 2491, University of Lille, 3 rue du Professeur Laguesse, 59006 Lille, France
[b] College of Pharmacy, Clinical Bacteriology, University of Lille, 3 rue du Professeur Laguesse, 59006 Lille, France
[c] Roquette, Biology and Nutrition Department, 62080 Lestrem, France
[d] School of Medicine, Gastroenterology, INSERM U795, University of Lille, Rue Michel Polonovski, 59006 Lille, France

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ABSTRACT

The major aim of this work was to optimize the properties of novel polymeric films based on blends of ethylcellulose and Nutriose (a water-soluble, branched dextrin). Such blends were recently shown to be highly promising for the site-specific delivery of drugs to the colon in patients suffering from inflammatory bowel diseases, in particular Crohn's disease and ulcerative colitis. Importantly, and in contrast to various other colon targeting approaches, the system is adapted to the pathophysiological conditions in the disease state. However, it is yet unknown how desired membrane properties, especially water uptake and dry mass loss kinetics as well as mechanical stability can be adjusted to the specific needs of particular drug treatments. Different highly efficient and easy to apply tools were identified altering the membrane's properties, in particular their mechanical resistance required to withstand the shear forces resulting from the motility of the upper GIT and the hydrostatic pressure built up within the devices upon contact with aqueous media. This includes the variation of the Nutriose:ethylcellulose blend ratio and initial plasticizer content. Importantly, Nutriose also exhibits significant pre-biotic activity, normalizing the microflora in the patients' colon, which is of major clinical benefit in the case of inflammatory bowel diseases.

1. Introduction

The appropriate delivery of a drug for the local treatment of inflammatory bowel diseases, such as Crohn's disease (CD) and ulcerative colitis (UC) is highly challenging, because the release needs to be suppressed in the *upper* gastro intestinal tract (GIT) and time-controlled within the colon (Rubinstein et al., 1993; Klotz and Schwab, 2005). When a conventional dosage form is used, the entire drug dose is rapidly released within the contents of the stomach and the drug most likely absorbed into the blood stream. Thus, significant systemic drug concentrations result, leading to potentially severe side effects. At the same time, the drug concentrations at the site of action in the colon are low, leading to poor therapeutic efficacy (Bondesen, 1997; Qureshi and Cohen, 2005; Fedorak and Bistritz, 2005). To overcome these restrictions, different types of advanced drug delivery systems have been proposed (Yang et al., 2002). Generally, the drug is embedded within a polymeric matrix former, or a drug depot (e.g., tablet or pellet) is surrounded by a polymeric film (Milojevic et al., 1996a,b; Leong et al., 2002; Siew et al., 2000a,b; Basit et al., 2004). The type of polymer is chosen in such a way that the permeability of the macromolecular network is low in the contents of the stomach and small intestine, but becomes considerable once the colon is reached. This change in drug permeability might be triggered, by (a) the change in the pH of the contents of the GIT, (ii) degradation via enzymes that are preferentially located in the colon, or (iii) time-dependent structural changes in the dosage form, e.g., crack formation within a poorly permeable film coating occurring after a pre-determined lag-time (Gazzaniga et al., 1994a,b, 2006; Sangalli et al., 2001). Alternatively, drug release might already start at the beginning of the GIT transit, but at a rate that is sufficiently low to assure that drug release is still continued in the colon.

However, great caution must be paid when using such colon targeting approaches, because the *pathophysiological* conditions in the GIT of a patient suffering from Crohn's disease or ulcerative colitis might lead to system failure, because (i) the pH is not as required, (ii) the concentrations and types of enzymes present in the colon are significantly altered, e.g., due to changes in the quality and quantity of the (enzyme secreting) microflora, and/or (iii) the

* Corresponding author. Tel.: +33 3 20964708; fax: +33 3 20964942.
E-mail address: juergen.siepmann@univ-lille2.fr (J. Siepmann).

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transit times within the various GIT segments are fundamentally altered (Friend, 2005). Consequently, the inter- and intra-variability of the resulting drug concentration time profiles at the site of action can be considerable and devices that reliably delivery the drug to the colon under physiological conditions fail in *patients*. To properly address this fundamental aspect, the use of fecal samples from Crohn's disease and ulcerative colitis patients has recently been suggested for the identification of novel polymeric film coatings allowing for colon targeting in the disease state (Karrout et al., submitted for publication). Different types of polymeric blends have been investigated and a combination of Nutriose (a water-soluble, branched dextrin with high fiber contents obtained from wheat starch) with ethylcellulose was shown to be particularly promising. The presence of ethylcellulose avoids premature film dissolution within the *upper* GIT (Nutriose being water-soluble). The role of the starch derivative is to provide the ability for colon targeting in the disease state. Due to the presence of α-1,6 linkages and non-digestible glycoside linkages (e.g., α-1,2 and α-1,3), Nutriose is only incompletely hydrolyzed and absorbed in the small intestine (approximately 10–15%). But this starch derivative is progressively fermented to about 85% in the colon. Importantly, it was also shown that Nutriose serves as a substrate also for the colonic microflora of inflammatory bowel disease *patients* (Karrout et al., submitted for publication). Furthermore, Nutriose is known to exhibit a significant pre-biotic activity, normalizing the microflora and enzyme patterns in the colon of the patients (van den Heuvel et al., 2004, 2005; Pasman et al., 2006; Lefranc-Millot et al., 2006). This is of major clinical benefit for this type of GIT diseases (Velazquez and Rombeau, 1997; Wachtershauser and Stein, 2000; Cummings et al., 2001; Macfarlane et al., 2006). Nutriose is a glucose polysaccharide produced by the chromatographic separation of a dextrin fraction derived from maize, wheat or other edible starches in the food industry (Wils et al., 2008). The investigated Nutriose type in this study is "Nutriose FB", which is prepared by roasting wheat starch under controlled conditions (essentially with respect to acidity, moisture, time and temperature). Upon purification with activated carbon and anionic and cationic resins, the hydrolyzed dextrin is subjected to a chromatographic separation, removing glucose and lower molecular weight oligosaccharides. The final product – Nutriose FB – is a blend of glucose polymers with a relatively narrow range of molecular weight (number average molecular weight, Mn = 2000–4000 Da; weight average molecular weight, Mw = 4000–6000 Da). The degree of polymerization is in the range of 12–25.

However, yet it is unclear whether Nutriose:ethylcellulose films provide sufficient mechanical stability to withstand the shear stress they are exposed to in the *upper* GIT (due to the gastro intestinal motility) and to withstand the potentially significant hydrostatic pressure developed within the dosage forms due to water penetration into the systems upon contact with aqueous media. Accidental crack formation can result in premature drug release through water-filled channels (Lecomte et al., 2004a,b). Furthermore, the effects of the polymer:polymer blend ratio and of the plasticizer content on the film coatings' properties are unknown. It was the aim of this study to elucidate these aspects and to be able to easily adapt the film coatings' properties to the specific needs of a particular type of drug treatment (e.g., osmotic activity of the drug and administered dose).

2. Materials and methods

2.1. Materials

Nutriose FB 06 (Nutriose, a water-soluble, branched dextrin with high fiber contents obtained from wheat starch; Roquette Freres, Lestrem, France); aqueous ethylcellulose dispersion (Aquacoat ECD 30; FMC Biopolymer, Philadelphia, USA); triethylcitrate (TEC; Morflex, Greensboro, USA).

2.2. Preparation of thin, polymeric films

Thin polymeric films were prepared by casting blends of different types of polysaccharides and aqueous ethylcellulose dispersion into Teflon moulds and subsequent drying for 1 day at 60 °C. Nutriose was dissolved in purified water (5%, w/w), blended with plasticized aqueous ethylcellulose dispersion (25.0, 27.5 or 30.0% TEC, overnight stirring; 15% (w/w) polymer content) at a ratio of 1:2, 1:3, 1:4, 1:5 (polymer:polymer w/w), as indicated. The mixtures were stirred for 6 h prior to casting.

2.3. 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 cm × 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 pre-determined 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:

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

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

2.4. Mechanical properties of thin films

The mechanical properties of free films in the dry and wet state were determined with a texture analyzer (TAXT.Plus, Winopal Forschungsbedarf, Ahnsbeck, Germany). 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:

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

where F is the load required to puncture the film and A is 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 the volume of the film located in the die cavity of the film holder.

3. Results and discussion

3.1. Water uptake and dry mass loss of thin films

The permeability of a polymeric film coating strongly depends on its water content (Siepmann and Peppas, 2000). In a dry system, the diffusion coefficients approach zero. With increasing water content, the mobility of the macromolecules increases and, thus, also the mobility of incorporated drug molecules. Fig. 1a and b shows the gravimetrically measured water uptake of thin, polymeric films based on different Nutriose:ethylcellulose blends upon exposure to 0.1 M HCl and phosphate buffer pH 6.8 at 37 °C. Clearly, the polymer blend ratio significantly affected the resulting water penetration *rates* and *extents*. With increasing Nutriose content the amount of water taken up as well as the rate of this mass transport step increased. This phenomenon can be attributed to the more hydrophobic nature of ethylcellulose compared to the water-soluble starch derivative Nutriose. Thus, it can be expected that the mobility of a drug within this type of polymeric films significantly increases with increasing Nutriose contents. Interestingly, the water uptake rates and extents of the investigated films were higher in phosphate buffer pH 6.8 than in 0.1N HCl (Fig. 1b versus Fig. 1a). This can be attributed to the presence of the emulsifier sodium dodecyl sulfate (SDS) in the aqueous ethylcellulose dispersion Aquacoat ECD. At low pH, SDS is protonated and neutral, whereas at pH 6.8 it is de-protonated and negatively charged. Thus, the ability to decrease interfacial surface tensions is more pronounced at pH 6.8, resulting in facilitated water penetration into the system. Importantly, even the highest water uptake rates and extents of the investigated systems (up to a blend ratio of 1:2 Nutriose:ethylcellulose) are relatively low (Fig. 1). Thus, premature drug release within the upper GIT can be expected to be limited with this type of polymeric films, irrespective of the polymer:polymer blend ratio in the investigated range.

In addition to the water uptake kinetics, also the *dry mass loss* behavior of thin polymeric films offers important insight into the latter's ability to suppress or allow drug release. The effects of the Nutriose:ethylcellulose blend ratio on the resulting dry mass loss of thin films upon exposure to 0.1 M HCl and phosphate buffer pH 6.8 are illustrated in Fig. 2a and b, respectively. Clearly, both, the rate and the extent of the dry mass loss increased with increasing Nutriose contents. This can at least partially be attributed to the leaching of this water-soluble compound out into the bulk fluids. However, also the diffusion of the water-soluble plasticizer

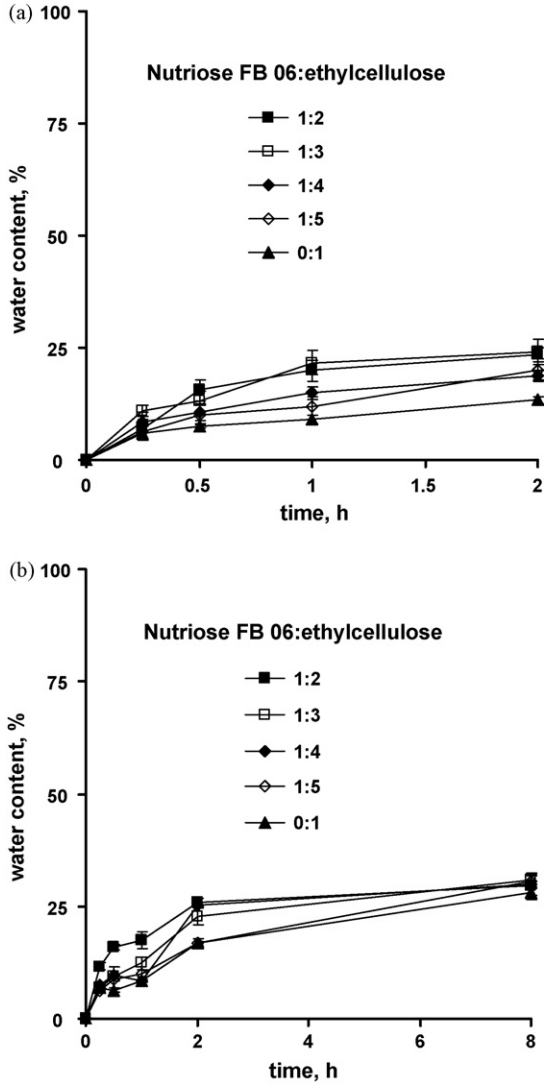

Fig. 1. Water uptake of thin films consisting of Nutriose:ethylcellulose blends (the ratio is indicated in the figures) upon exposure to (a) 0.1 M HCl and (b) phosphate buffer pH 6.8 (TEC content, referred to the ethylcellulose mass: 25%, w/w).

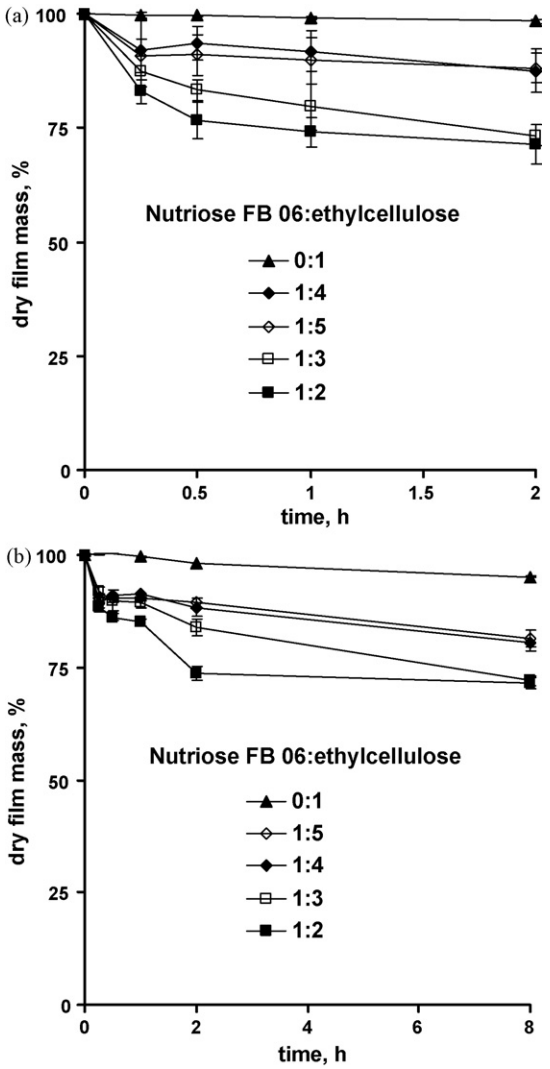

Fig. 2. Dry mass loss of thin films consisting of Nutriose:ethylcellulose (the ratio is indicated in the figures) upon exposure to (a) 0.1 M HCl and (b) phosphate buffer pH 6.8 (TEC content, referred to the ethylcellulose mass: 25%, w/w).

TEC (which is used to facilitate the fusion of the ethylcellulose nanoparticles during film formation) into the release media can be expected to be significantly facilitated: Due to the increasing water contents of the systems (Fig. 1), the mobility of the polymer chains increases and, thus, also the mobility of the low molecular weight plasticizer. Please note that the dry mass loss of pure (plasticized) ethylcellulose films can primarily be attributed to such TEC leaching and that a (slight) pH dependence of this phenomenon is observed (due to the SDS effect discussed above). Importantly, the dry mass loss is limited in all cases, and the presence of the water-insoluble ethylcellulose in the films effectively hinders the leaching of the water-soluble starch derivative into the bulk fluids. Again, premature drug release within the *upper* parts of the GIT is likely to be limited, irrespective of the polymer:polymer blend ratio in the investigated range (up to 1:2 Nutriose:ethylcellulose).

3.2. Mechanical properties of thin films

In addition to limited water uptake and dry mass loss in the upper GIT, a polymeric film coating providing site-specific drug delivery to the colon must be sufficiently (mechanically) stable in order to avoid accidental crack formation due to the shear stress encountered in the stomach and small intestine *in vivo*. In addition, significant hydrostatic pressure might be built up within a coated dosage form due to the penetration of water into the system upon contact with aqueous body fluids. The presence/absence of osmotically active drugs and/or excipients in the core formulation can strongly affect the importance of this phenomenon. Fragile film coatings are likely to rupture because of such shear forces from *outside* (caused by the motility of the GIT) and hydrostatic pressures from *inside* (caused by water penetration) they are exposed to. In order to be able to estimate the risk of such accidental crack formation, the energy required to break the investigated Nutriose:ethylcellulose films was measured using a texture analyzer and the puncture test before and upon exposure to 0.1N HCl and phosphate buffer pH 6.8, respectively. The white bars in Fig. 3 indicate the mechanical stability of thin Nutriose:ethylcellulose films (plasticized with 25% (w/w) TEC, referred to the ethylcellulose content) in the *dry* state at room temperature as a function of the polymer blend ratio. Clearly, the energy at break of the films significantly increased with increasing ethylcellulose content, indicating that this compound mainly contributes to the mechanical stability of the system under these conditions. Importantly, all the investigated films showed a mechanical stability that is likely to be sufficient to withstand the shear stress and hydrostatic pressure they are exposed to within the *upper* GIT at appropriate coating levels. This was confirmed by the experimentally determined puncture strength and % elongation at break of the films (data not shown). However, it must be pointed out that the penetration of water into the polymeric systems significantly changes the composition of the films (Figs. 1 and 2) and, thus, most likely their mechanical properties. In particular the fact that water acts as a plasticizer for many polymers and that the water-soluble TEC and starch derivative (at least partially) leach out of the polymeric networks can be expected to lead to time-dependent changes in the mechanical stability of the films. In addition, the results shown in Fig. 3 were obtained at room temperature, and not at 37 °C body temperature. It is well known that the temperature of a polymeric network can strongly affect its mechanical properties, e.g., due to glassy-to-rubbery phase transitions.

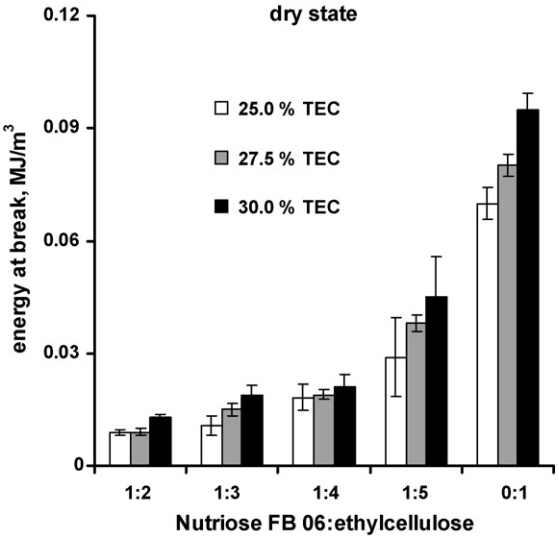

Fig. 3. Effects of the Nutriose:ethylcellulose blend ratio and initial plasticizer content on the energy required to break thin, polymeric films in the *dry* state at room temperature.

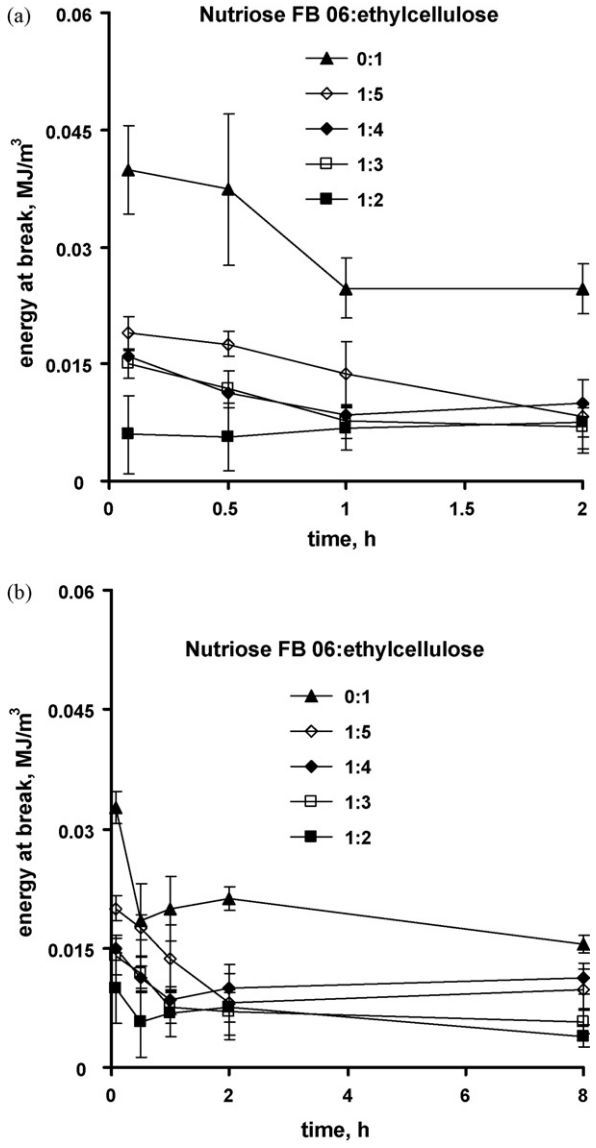

Fig. 4. Changes in the energy required to break thin Nutriose:ethylcellulose films (the blend ratio is indicated in the figures) upon exposure to (a) 0.1 M HCl and (b) phosphate buffer pH 6.8 at 37 °C (TEC content, referred to the ethylcellulose mass: 25%, w/w).

For these reasons the energy required to break the investigated Nurtiose:ethylcellulose films was also measured upon exposure to 0.1N HCl for up to 2 h and upon exposure to phosphate buffer pH 6.8 for up to 8 h at 37 °C (Fig. 4). As it can be seen, the mechanical stability of the polymeric networks decreased with time, irrespective of the polymer blend ratio and type of release medium. This can at least partially be attributed to the leaching of the water-soluble plasticizer TEC and of the starch derivative into the bulk fluids. Importantly, even the lowest observed values indicate that accidental crack formation due to external shear stress and/or internal hydrostatic pressure encountered *in vivo* is unlikely (at appropriate coating levels). Again, this was consistent with the experimentally determined puncture strength and % elongation of the films, irrespective of the polymer blend ratio, exposure time and type of release medium (data not shown).

3.3. Effects of the plasticizer content

It is well known that the plasticizer content can significantly affect the mechanical properties of polymeric films. In order to evaluate the importance of this phenomenon for the investigated Nutriose:ethylcellulose blends, the percentage of incorporated TEC was increased from 25 to 30% (w/w) (referred to the ethylcellulose content). TEC contents below 25% (w/w) would render the fusion of the ethylcellulose nanoparticles during film formation difficult, the mobility of the polymer chains being crucial for this step. TEC contents higher than 30% (w/w) significantly increase the sticking tendency during coating and curing and should, thus, be avoided. As it can be seen in Fig. 3, the mechanical stability of the Nutriose:ethylcellulose films significantly increased with increasing TEC content, irrespective of the polymer blend ratio. This was consistent with the experimentally determined puncture strength and % elongation of the films (data not shown). Thus, in case of osmotically highly active core formulations (resulting in significant hydrostatic pressure built up within the dosage forms upon water penetration), the required coating levels (avoiding accidental crack formation) can be decreased by increasing the TEC content. Again, it was important to monitor the effects of the time-dependent changes in the composition of the polymeric networks upon exposure to 0.1N HCl and phosphate buffer pH 6.8 as well as of the increase in temperature to 37 °C. As it can be seen in Fig. 5, the energy required to break the films decreased upon exposure to the release media for the reasons discussed above, irrespective of the polymer blend ratio, initial plasticizer content and type of release medium. Importantly, in all cases an increase in the initial TEC content from 25 to 30% (w/w) (referred to the ethylcellulose content) led to increased mechanical stability at all time points.

However, when increasing the percentage of the water-soluble plasticizer TEC in the polymeric films, also the *rates and extents* of the systems' *water uptake* and *dry mass loss* upon exposure to aqueous media can be expected to increase. This might potentially lead to significantly increased drug permeability of the polymeric films, resulting in potential premature drug release within the *upper*

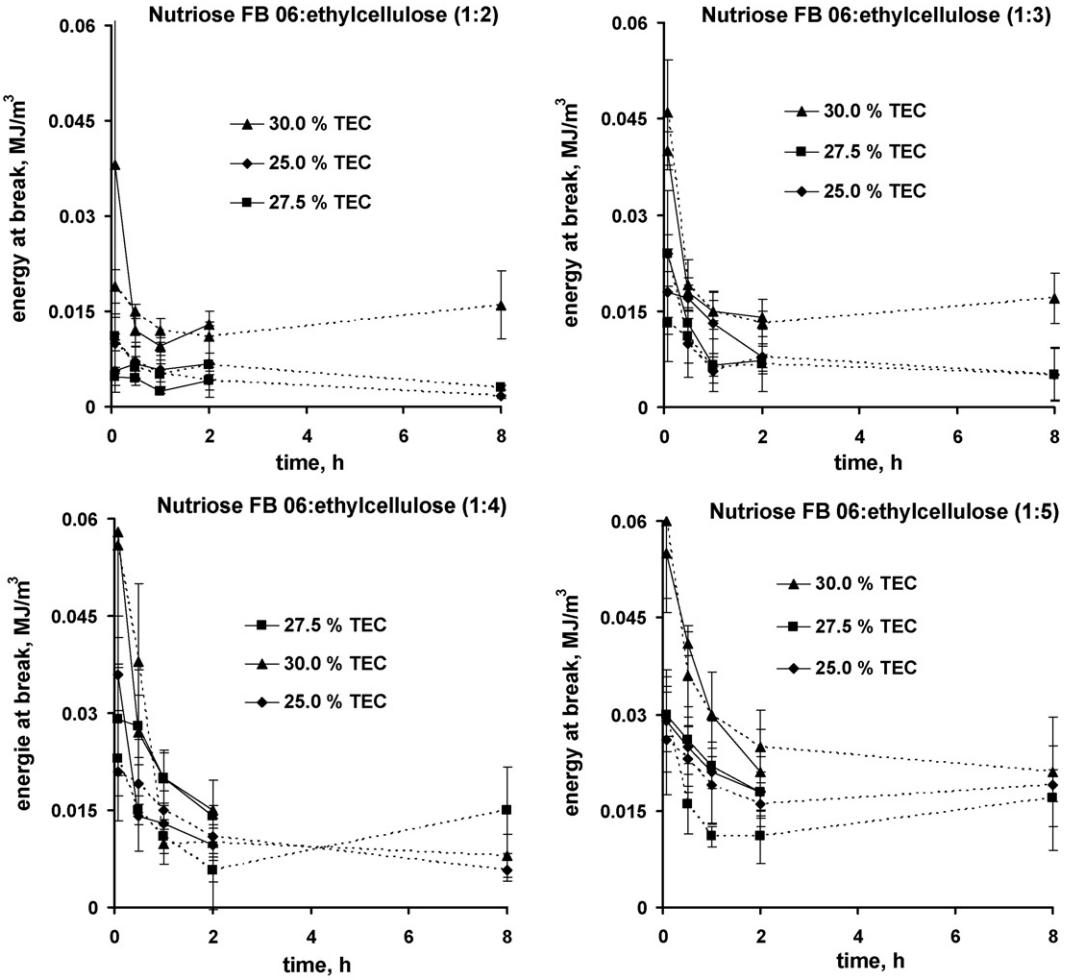

Fig. 5. Changes in the energy required to break thin films consisting of Nutriose:ethylcellulose (the blend ratio is indicated on the top of figures) plasticized with different amounts of TEC (the percentages refer to the ethylcellulose mass) upon exposure to 0.1 M HCl for 2 h (solid curves) and phosphate buffer pH 6.8 for 8 h at 37 °C (dotted curves).

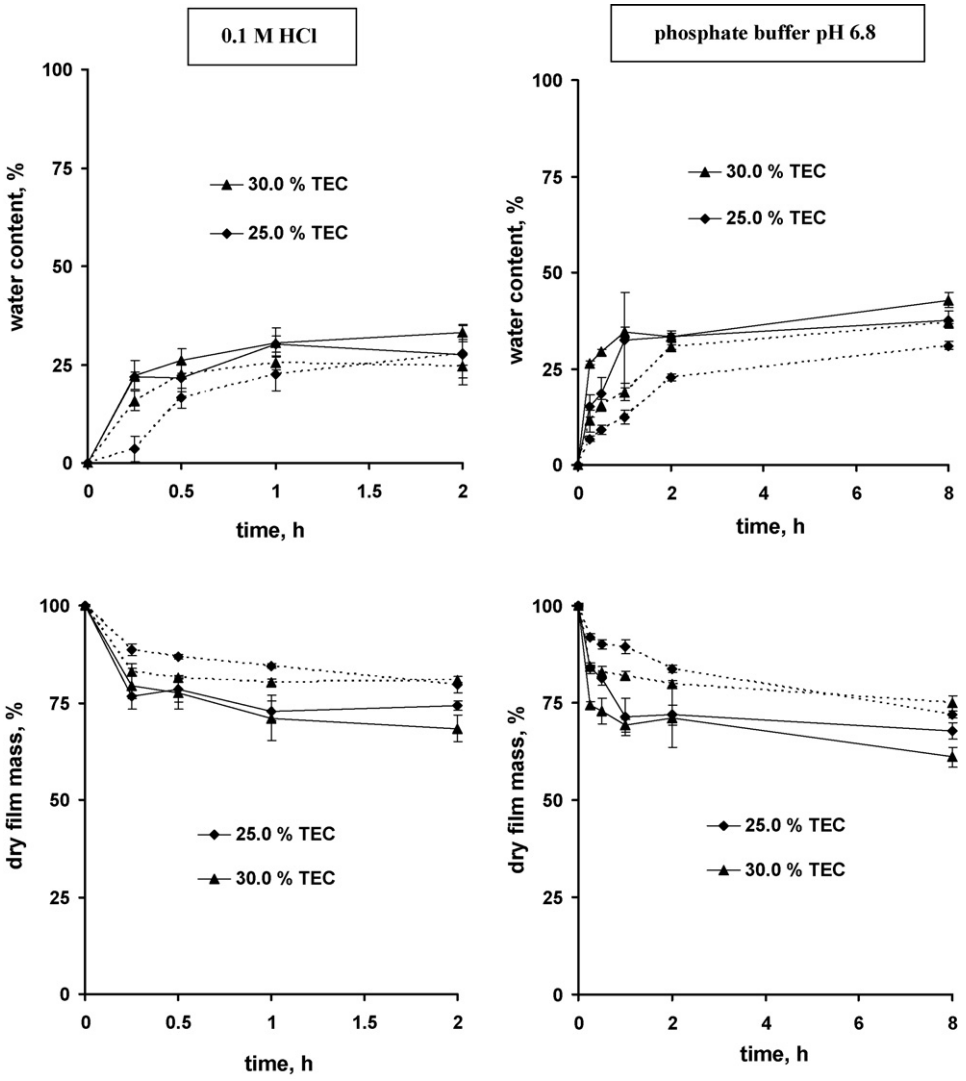

Fig. 6. Effects of the plasticizer content (indicated in the figures, referred to the ethylcellulose mass) on the water uptake and dry mass loss of Nutriose:ethylcellulose films upon exposure to 0.1 M HCl and phosphate buffer pH 6.8, respectively. The solid and dotted curves represent results obtained at the blend ratios 1:2 and 1:3.

GIT. To estimate the importance of these phenomena, the water uptake and dry mass loss kinetics of the investigated films were monitored upon exposure to 0.1N HCl for 2 h and upon exposure to phosphate buffer pH 6.8 for 8 h. The highest TEC content (30%) was selected as well as the two most critical Nutriose:ethylcellulose blend ratios: 1:2 and 1:3 (Fig. 6). Importantly, the resulting changes in the water uptake and dry mass loss kinetics were only minor when increasing the initial TEC content from 25 to 30%, irrespective of the polymer blend ratio and type of release medium. Thus, the mechanical stability of Nurtiose:ethylcellulose films can efficiently be improved by increasing the plasticizer level, without loosing the systems' capability to suppress drug release within the *upper* GIT.

4. Conclusion

Nutriose:ethylcellulose blends are highly promising film coating materials for advanced drug delivery systems allowing for colon targeting. Importantly, desired system properties, being adapted to the specific needs of a particular treatment (e.g., osmotic activity and dose of the drug) can easily be adjusted by varying the polymer:polymer blend ratio as well as the plasticizer content.

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