Peas Starch-Based Film Coatings for Site-Specific Drug Delivery to the Colon

Y. Karrout,[1,2] C. Neut,[1,3] D. Wils,[4] F. Siepmann,[1,2] L. Deremaux,[4] M. P. Flament,[1,2] L. Dubreuil,[1,3] P. Desreumaux,[3,5] J. Siepmann[1,2]

[1]*University Lille Nord de France, College of Pharmacy, Department of Pharmaceutical Technology, Lille 59006, France*
[2]*INSERM U 1008, Controlled Drug Delivery Systems and Biomaterials, Lille 59006, France*
[3]*INSERM U 995, Inflammatory Bowel Diseases, Lille 59006, France*
[4]*Roquette, Biology and Nutrition Department, Lestrem 62080, France*
[5]*University Lille Nord de France, School of Medicine, Department of Gastroenterology, Lille 59006, France*

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ABSTRACT: Peas starch : ethylcellulose-based film coatings are proposed allowing for site-specific drug delivery to the colon of inflammatory bowel disease patients. The film coatings are poorly permeable for 5-aminosalicylic acid in media simulating the contents of the stomach and small intestine. Thus, they can minimize premature drug release in the upper gastrointestinal tract and subsequent absorption into the blood stream. However, once the colon is reached, drug release sets on and is time controlled. This can be attributed to the partial degradation of the peas starch by enzymes secreted by bacteria, which are preferentially present in the colon. Thus, the drug is released at the site of action, which is likely to minimize undesired side effects in the healthy part of the human body and to optimize the therapeutic efficacy of the treatment. A blend ratio of 1 : 4 peas starch : ethylcellulose and a coating level of 15% (w/w) seem to be optimal for pellet coating. Importantly, the polymeric films can be expected to withstand the mechanical stress encountered *in vivo* because of the motility of the stomach and small intestine. Furthermore, the systems are long-term stable: drug release from coated pellets remains unaltered during 1-year open storage. © 2010 Wiley Periodicals, Inc. J Appl Polym Sci 119: 1176–1184, 2011

Key words: polysaccharides; drug delivery systems; biodegradable; thin films; mechanical properties

INTRODUCTION

Polymeric drug delivery systems can be very useful to optimize the therapeutic effects of a drug treatment.[1–3] Because of the presence of specific macromolecules, drug release might be time controlled and/or site controlled (drug targeting). Pharmaceutical dosage forms that are able to deliver a drug specifically to the colon can be highly beneficial for the local treatment of inflammatory bowel diseases (e.g., Crohn's disease and ulcerative colitis).[4,5] The idea is to suppress drug release within the stomach and small intestine to avoid premature release and subsequent drug absorption into the blood stream. Consequently, the resulting drug concentrations in the healthy part of the human body can be limited and undesired side effects be minimized. However, once the dosage form reaches the colon, drug release should set on and ideally be time controlled. Hence, the drug is directly released at the target site, and the resulting concentrations are elevated, leading to optimized therapeutic effects.

Correspondence to: J. Siepmann (juergen.siepmann@univ-lille2.fr).

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Different approaches have been proposed in the literature to provide such site-specific drug delivery to the colon.[6–8] Generally, the drug is embedded in a polymeric matrix or a drug reservoir is surrounded by a polymeric film.[9,10] In both cases, the macromolecular barriers are poorly permeable for the drug in the upper gastrointestinal tract, but become permeable as soon as the target site is reached.[11] This onset of drug release might be caused by:

i. a change in pH of the surrounding bulk fluid (the pH of the contents of the gastrointestinal tract continuously changes from the mouth to the rectum),[12,13]
ii. a rupturing of the film coating after a predetermined lag time (e.g., because of the creation of a hydrostatic pressure inside the system acting against the film coating),[14,15] or
iii. a degradation of the macromolecules by enzymes that are particularly concentrated in the colon, for instance enzymes that are secreted by bacteria of the colonic microflora.[16,17]

However, great care must be taken, because the conditions in an inflamed colon of a patient suffering from Crohn's disease or ulcerative colitis might

be very different from the conditions in a healthy subject.[18,19] In particular, the pH at the target site might be much lower than expected,[20] the transit times in the various gastrointestinal tract sections might be significantly shortened,[18] and the quality and quantity of the colonic microflora (and secreted enzymes) might be significantly altered.[21] Consequently, the *in vivo* performance of the respective drug delivery systems might significantly vary from patient to patient and from day to day. To minimize this inter- and intravariability, drug release should ideally be induced in the colon under the pathophysiological conditions of the disease.

It has recently been shown that certain starch derivatives are degraded by enzymes that are present in the colon of inflammatory bowel disease patients.[22] However, as these starch derivatives are soluble/highly swellable in water, an additional, water-insoluble/poorly swellable compound must be added to avoid undesired film dissolution/drug release in the upper gastrointestinal tract. In this study, peas starch has been combined with ethylcellulose at different ratios. The aim was to evaluate the potential of this type of polymeric films to allow for site-specific drug delivery to the colon of patients suffering from Crohn's disease and ulcerative colitis. 5-Aminosalicylic acid (5-ASA) was chosen as drug, because it is frequently used for the local treatment of this type of diseases. The drug was incorporated into spherical beads (0.7–1 mm in diameter), also called pellets. The latter were surrounded by peas starch : ethylcellulose films of different composition and thickness, and drug release was measured in media simulating the contents of the entire gastrointestinal tract.

EXPERIMENTAL

Materials

Peas starch N-735 (peas starch; Roquette Freres, Lestrem, France); Aquacoat ECD 30 (aqueous ethylcellulose dispersion; FMC Biopolymer, Brussels, Belgium); triethyl citrate (TEC; Morflex, Greensboro, NC); 5-aminosalicylic acid (Sigma-Aldrich, Isle d'Abeau Chesnes, France); microcrystalline cellulose (Avicel PH 101; FMC Biopolymer); bentonite and polyvinylpyrrolidone (PVP, Povidone K 30) (Coopertation Pharmaceutique Francaise, Melun, France); pancreatin (from mammalian pancreas = mixture of amylase, protease, and lipase); and pepsin (Fisher Bioblock, Illkirch, France); extracts from beef and yeast as well as tryptone (pancreatic digest of casein) (Becton, Dickinson and Company, Franklin Lakes, NJ); L-cysteine hydrochloride hydrate (Acros Organics, Geel, Belgium); and cysteinated Ringer solution (Merck, Darmstadt, Germany).

Preparation of free films

Thin, free films were prepared by casting blends of peas starch and aqueous ethylcellulose dispersion (plasticized with 25% TEC) into Teflon moulds and subsequent controlled drying (1 day at 60°C). Peas starch was dispersed in purified water at 65–75°C (5% w/w). Aqueous ethylcellulose dispersion (15% w/w solids content) was plasticized for 24 h with 25% TEC (w/w, referred to the solids content of the dispersion). The peas starch and ethylcellulose dispersions were blended at room temperature at the following ratios: 1 : 2, 1 : 3, 1 : 4, and 1 : 5 (polymer : polymer, w:w). The mixtures were stirred for 6 h before casting.

Characterization of free films

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: (i) simulated gastric fluid (0.1*M* HCl) and (ii) simulated intestinal fluid [phosphate buffer pH 6.8 (United States Pharmacopeia, USP, 32)] at 37°C as follows: pieces of 1.5 cm × 5 cm were placed into 120-mL plastic containers filled with 100-mL preheated 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, and the films were 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 were determined using a texture analyzer (TAXT.Plus; Winopal Forschungsbedarf, Ahnsbeck, Germany) and the puncture test in the dry state as well as upon exposure to 0.1*M* HCl and phosphate buffer pH 6.8 (in the wet state). 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:

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

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 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.

Preparation of coated pellets

Drug (5-ASA)-loaded pellet starter cores (diameter: 0.7–1.0 mm; 60% 5-ASA, 32% microcrystalline cellulose, 4% bentonite, and 4% PVP) were prepared by extrusion and subsequent spheronization as follows: the respective powders were blended in a high-speed granulator (Gral 10; Collette, Antwerp, Belgium), and purified water was added until a homogeneous mass was obtained (41 g of water for 100 g of powder blend). The wetted mixture was passed through a cylinder extruder (SK M/R, holes: 1 mm diameter, 3 mm thickness, rotation speed: 96 rpm; Alexanderwerk, Remscheid, Germany). The extrudates were subsequently spheronized at 520 rpm for 2 min (Spheroniser Model 15; Calveva, Dorset, UK) and dried in a fluidized bed (ST 15; Aeromatic, Muttenz, Switzerland) at 40°C for 30 min. The size fraction 0.7–1.0 mm was obtained by sieving. These drug-loaded starter cores were then coated in a fluidized bed (Wurster insert, Strea 1; Aeromatic-Fielder, Bubendorf, Switzerland) with different peas starch : ethylcellulose blends until a weight gain of 5, 10, 15, or 20% (w/w) was achieved. The coating formulations were prepared in the same way as the dispersions used for film casting (as described in section Preparation of free films). The process parameters were as follows: inlet temperature = 39°C ± 2°C, product temperature = 40°C ± 2°C, spray rat = 1.5–3 g/min, atomization pressure = 1.2 bar, nozzle diameter = 1.2 mm. Afterward, the pellets were further fluidized for 10 min and subsequently cured in an oven for 24 h at 60°C.

Drug release from coated pellets

Drug release from coated pellets was measured in media simulating the conditions in the upper gastrointestinal tract and entire gastrointestinal tract.

Upper gastrointestinal tract

Pellets were placed into 120-mL plastic containers and filled with 100 mL dissolution medium: 0.1*M* HCl (optionally containing 0.32% pepsin) during the first 2 h and phosphate buffer, pH 6.8 (USP 32) (optionally containing 1% pancreatin), during the subsequent 9 h. The flasks were agitated in a horizontal shaker (80 rpm; GFL 3033). At predetermined time points, 3 mL samples were withdrawn and analyzed UV spectrophotometrically for their drug content (λ = 302.6 nm in 0.1*M* HCl; λ = 330.6 nm in phosphate buffer pH 6.8) (UV-1650; Shimadzu, Champs sur Marne, France). In the presence of enzymes, the samples were centrifuged for 15 min at 11,000 rpm and subsequently filtered (0.2 μm) before UV measurements. Each experiment was conducted in triplicate.

Entire gastrointestinal tract

Pellets were exposed to 0.1*M* HCl for 2 h and subsequently to phosphate buffer pH 6.8 (USP 32) for 9 h in a USP Apparatus 3 (Bio-Dis; Varian, Paris, France) (dipping speed = 10 dpm). Afterward, the pellets were transferred into 120-mL flasks filled with: (i) 100 mL culture medium inoculated with fresh feces from inflammatory bowel disease patients, (ii) culture medium inoculated with *Bifidobacterium*, or (iii) sterile culture medium for reasons of comparison. The samples were agitated (50 rpm) at 37°C under anaerobic conditions (5% CO_2, 10% H_2, 85% N_2). Culture medium was prepared by dissolving 1.5 g beef extract, 3 g yeast extract, 5 g tryptone, 2.5 g NaCl, and 0.3 g L-cysteine hydrochloride hydrate in 1 L distilled water (pH 7.0 ± 0.2) and subsequent sterilization in an autoclave. Feces of patients suffering from Crohn's disease or ulcerative colitis were diluted 1 : 200 with cysteinated Ringer solution; 2.5 mL of this suspension was diluted with culture medium to 100 mL. At predetermined time points, 2 mL samples were withdrawn, centrifuged at 13,000 rpm for 5 min, filtered (0.22 μm), and analyzed by HPLC for their drug content (ProStar 230; Varian). The mobile phase consisted of 10% methanol and 90% aqueous acetic acid solution (1% w/v). Samples were injected into a Pursuit C18 column (150 mm × 4.6 mm; 5 μm), and the flow rate was 1.5 mL/min.

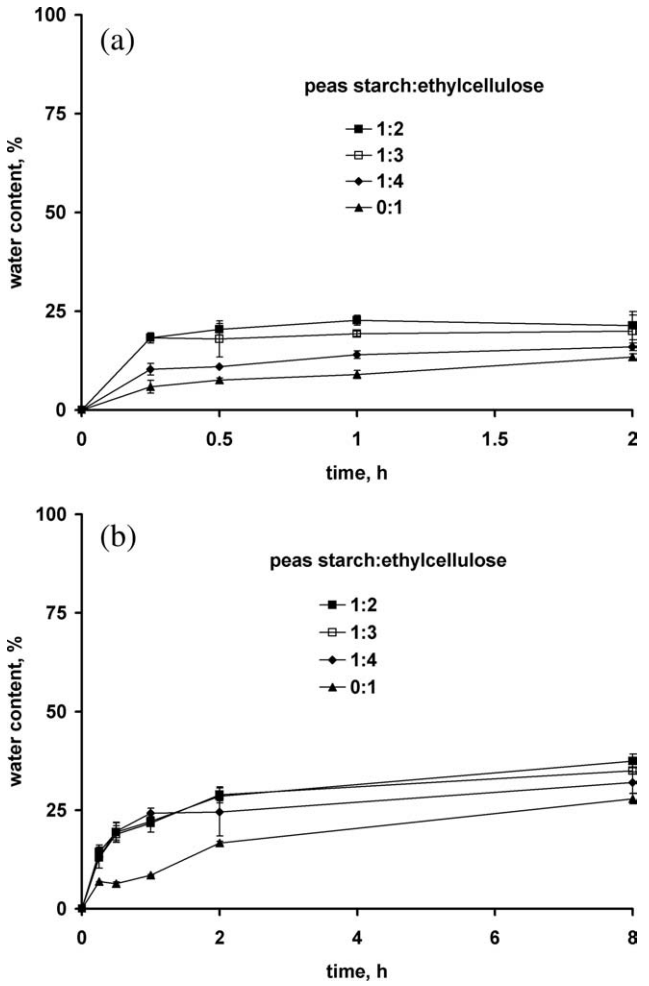

Figure 1 Water uptake kinetics of thin peas starch : ethylcellulose films upon exposure to: (a) 0.1*M* HCl and (b) phosphate buffer pH 6.8. The polymer : polymer blend ratio (w:w) is indicated in the diagrams.

The drug was detected UV spectrophotometrically at $\lambda = 300$ nm.

Drug release was measured from freshly prepared pellets (if not otherwise stated) as well as from pellets stored for 1 year at room temperature (23°C ± 2°C) and ambient relative humidity (55% ± 5 %) in open glass vials (no packaging material).

RESULTS AND DISCUSSION

Water uptake and dry mass loss of thin films

Ideally, a polymeric film coating allowing for site-specific drug delivery to the colon should effectively suppress drug release in the upper part of the gastrointestinal tract: the stomach and the small intestine. Thus, the film coating (which surrounds the drug reservoir) should be poorly permeable for the drug upon exposure to media simulating the contents of these organs (to avoid premature drug release and subsequent absorption into the blood stream). If a polymeric film coating takes up significant amounts of water or loses considerable amounts of dry mass upon exposure to a bulk fluid, its permeability for drug molecules can be expected to remarkably increase.[23] For this reason, the water uptake and dry mass loss kinetics of thin peas starch : ethylcellulose films were monitored upon exposure to: (a) 0.1*M* HCl (simulating the contents of the stomach) for 2 h and (b) phosphate buffer pH 6.8 (simulating the contents of the small intestine) for 8 h. Figure 1 shows the experimentally determined water contents of the films as a function of time. The peas starch : ethylcellulose blend ratio was varied from 1 : 2 to 1 : 4, as indicated. For reasons of comparison, also films consisting only of (plasticized) ethylcellulose were studied (filled triangles). As it can be seen, the water uptake rates and extents increased with increasing peas starch contents, because of the hydrophilic nature of this polymer. Importantly, the water uptake remained limited in all cases (below 30%). The slightly higher water uptake rates and extents at pH 6.8 compared with pH 1.2 [Fig. 1(b) vs. 1(a)] can probably be attributed to the presence of sodium dodecyl sulfate (SDS), which is present in the aqueous ethylcellulose dispersion used for film preparation, serving as a stabilizer of this dispersion. At low pH, SDS is protonated and noncharged, whereas at pH 6.8 it is deprotonated and, thus, negatively charged. Hence, its hydrophilicity is increased, and water penetration into the films is facilitated.[24]

Figure 2 shows the experimentally measured dry mass loss kinetics of various peas starch : ethylcellulose films upon exposure to: (a) 0.1*M* HCl and (b) phosphate buffer pH 6.8. As it can be seen, the dry mass loss rates and extents slightly increased with increasing peas starch content, because this polysaccharide significantly swells upon contact with water and, thus, facilitates the leaching of water-soluble film compounds (e.g., of the water-soluble plasticizer TEC)[25] into the surrounding bulk fluid. The lowest mass loss was observed with peas starch-free films, irrespective of the type of medium. This can be attributed to the fact that ethylcellulose is poorly swellable and permeable upon contact with aqueous media. It effectively hinders the leaching of water-soluble compounds.

Thus, the observed water uptake and dry mass loss kinetics of peas starch : ethylcellulose films are very promising with respect to the potential use of these films as barrier membranes hindering drug release in stomach and small intestine. If required, the film thickness and/or ethylcellulose contents might be increased. However, care should be taken that sufficient amounts of peas starch are present in the coatings, because this compound is intended to induce the onset of drug release in the colon (being

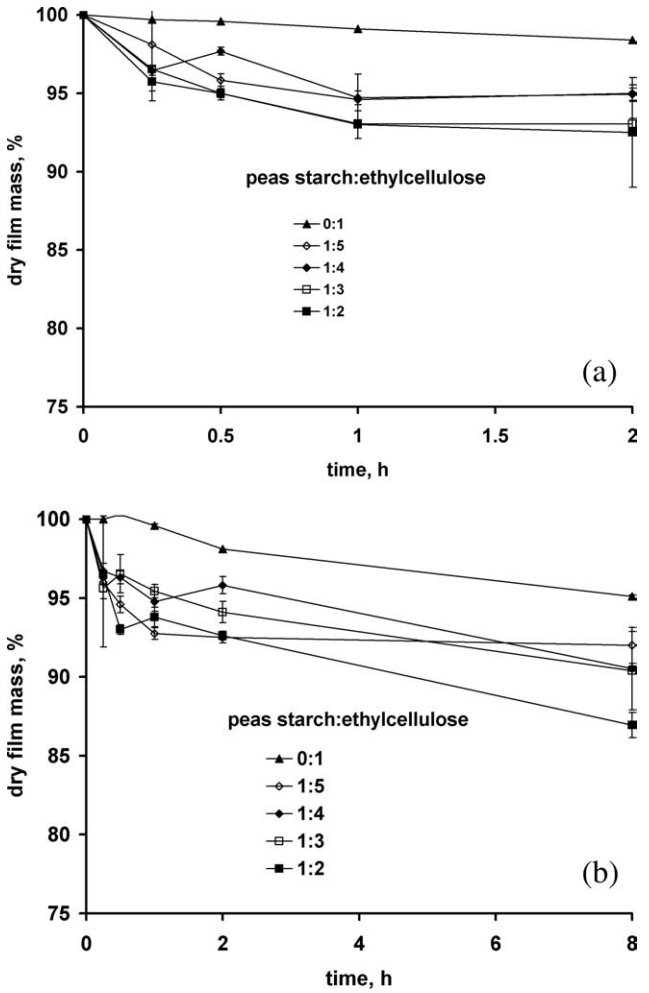

Figure 2 Dry mass loss kinetics of thin peas starch : ethylcellulose films upon exposure to: (a) 0.1*M* HCl and (b) phosphate buffer pH 6.8. The polymer : polymer blend ratio (w:w) is indicated in the diagrams.

degraded by enzymes secreted from colonic bacteria).[22]

Mechanical properties of thin films

In addition to limited water uptake and dry mass loss, polymeric film coatings aiming at site-specific drug delivery to the colon should provide a sufficient mechanical stability. Because of the motility of the stomach and small intestine, mechanical stress is exerted onto the coated dosage forms. If the film coatings are fragile, crack formation occurs and the drug is rapidly released through water-filled channels. To evaluate the mechanical stability of the investigated peas starch : ethylcellulose blends, a texture analyzer and the puncture test were used. Figure 3 shows the: (a) puncture strength at break, (b) % elongation at break, and (c) energy required to break thin polymeric films in the dry state. Clearly, the mechanical stability of the films significantly increased with increasing ethylcellulose content. Interestingly, all values are relatively high, suggesting that film coatings with an appropriate thickness

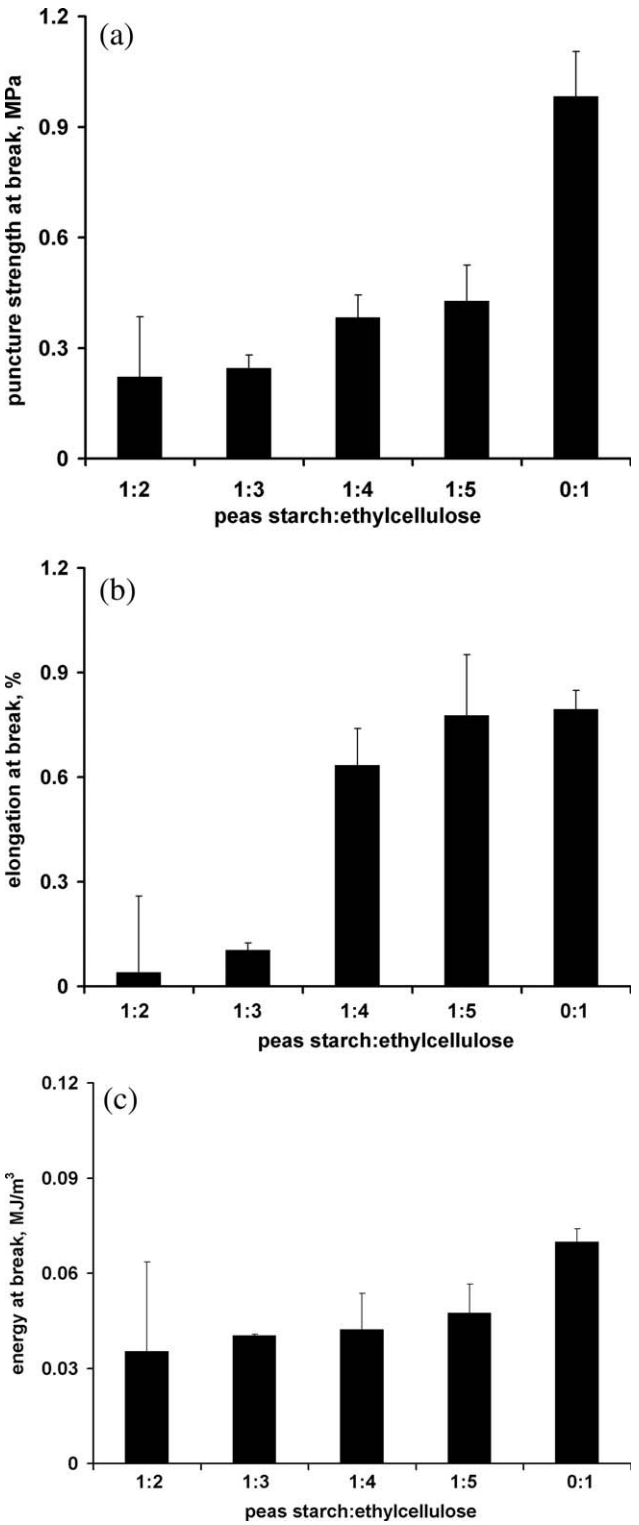

Figure 3 Mechanical properties of thin peas starch : ethylcellulose films in the dry state: (a) puncture strength at break, (b) % elongation at break, and (c) energy at break. The polymer : polymer blend ratio (w:w) is indicated on the *x* axes.

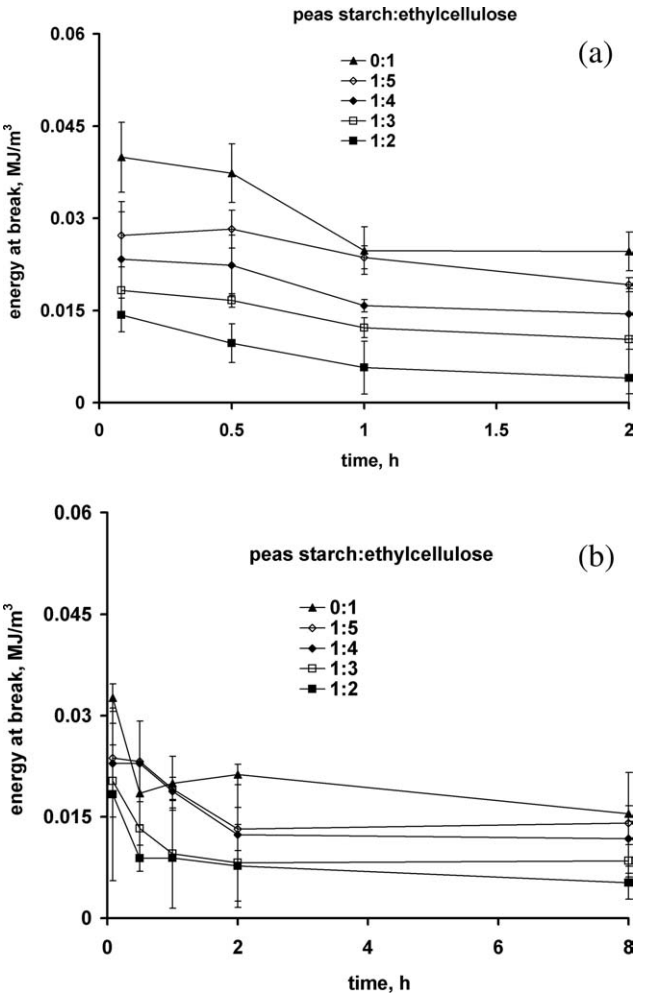

Figure 4 Changes in the energy at break of thin peas starch : ethylcellulose films upon exposure to: (a) 0.1*M* HCl (for up to 2 h) or (b) phosphate buffer pH 6.8 (for up to 8 h) at 37°C. The polymer : polymer blend ratio (w:w) is indicated in the diagrams.

can withstand the mechanical stress experienced within the gastrointestinal tract *in vivo*.

However, it has to be pointed out that the results shown in Figure 3 were obtained with dry films. Upon contact with aqueous body fluids, the mechanical properties of a polymeric film coating can significantly change, for instance because of compound leaching into the surrounding bulk fluid and/or the plasticizing effect of water.[23,24] For these reasons, the mechanical properties of the investigated peas starch : ethylcellulose films were also measured upon up to 2-h exposure to 0.1*M* HCl and up to 8-h exposure to phosphate buffer pH 6.8. Figure 4(a,b) shows the respective energies required to break the wet films of different composition. Clearly, the mechanical strength of all films decreased with increasing exposure time, irrespective of the type of bulk fluid. This can at least partially be attributed to the leaching of the water-soluble plasticizer TEC into the bulk fluids.[25] As expected, an increase in the ethylcellulose content resulted in increased energies required to break the films in both media. Importantly, the observed values suggest that all film coatings are likely to withstand the mechanical stress encountered *in vivo* within the gastrointestinal tract, also in the wet state (at appropriate coating levels).

Drug release in the upper gastrointestinal tract

Ideally, no or very little drug should be released from the dosage form in the stomach and small intestine. The solid curves in Figure 5 show the experimentally determined drug release kinetics from pellets coated with peas starch : ethylcellulose 1 : 2 at a coating level of 0, 5, 10, 15, and 20% (w/w) into 0.1*M* HCl (for 2 h), followed by phosphate buffer pH 6.8 (for 9 h) at 37°C. As it can be seen, 5-ASA was rapidly released from uncoated pellets as well as from pellets coated with only 5% peas starch : ethylcellulose 1 : 2. This can at least partially be attributed to the water uptake and dry mass loss of these film coatings upon exposure to the release media (Figs. 1 and 2), in combination with an insufficient thickness of the polymeric barrier. Importantly, at coating levels equal to and above 10% (w/w), drug release was effectively slowed down (probably because of the increase in the length of the diffusion pathways and increased mechanical stability of the film coatings).

However, it has to be pointed out that the presence of enzymes within the gastrointestinal tract *in vivo* might significantly affect the film coating properties, e.g., due to partial polymer degradation. For this reason, drug release from the coated pellets was also measured in: (i) 0.1*M* HCl containing 0.32% pepsin (for 2 h) and (ii) phosphate buffer pH 6.8

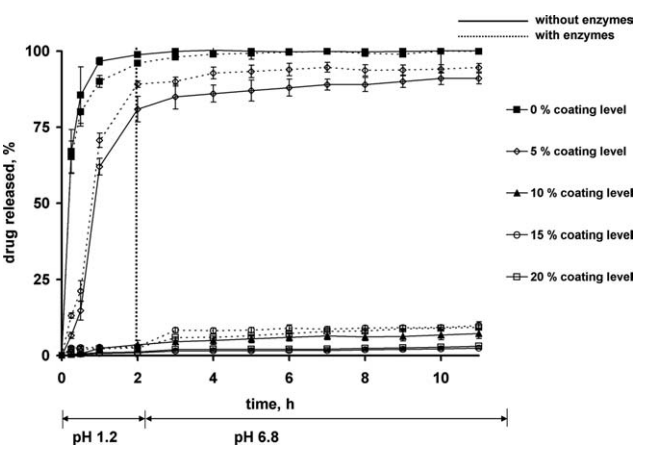

Figure 5 Drug release from pellets coated with peas starch : ethylcellulose 1 : 2 under conditions simulating the transit through the upper gastrointestinal tract: 2-h exposure to 0.1*M* HCl, followed by 9-h exposure to phosphate buffer pH 6.8. The coating level is indicated in the diagram as well as the absence (solid curves) and presence (dotted curves) of enzymes (0.32% pepsin at low pH, 1% pancreatin at neutral pH).

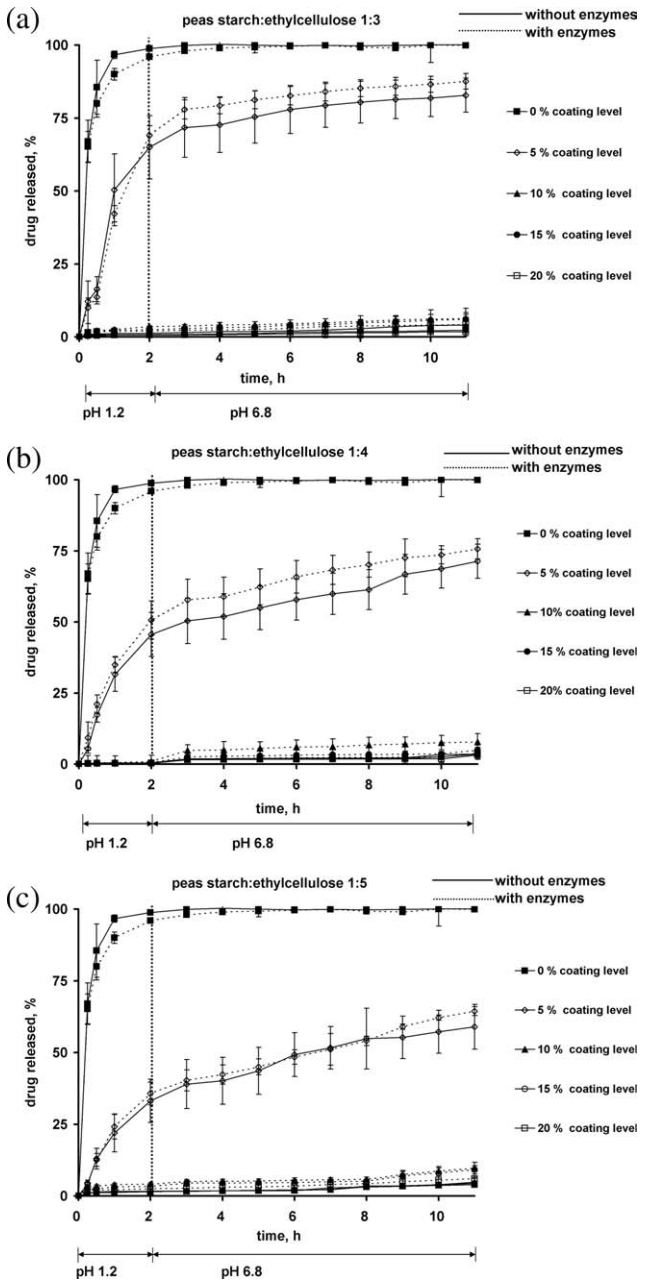

Figure 6 Effects of the peas starch : ethylcellulose blend ratio (w:w) and coating level (indicated in the diagrams) on drug release from coated pellets under conditions simulating the transit through the upper gastrointestinal tract: 2-h exposure to 0.1*M* HCl, followed by 9-h exposure to phosphate buffer pH 6.8. Solid/dotted curves indicate the absence/presence of enzymes (0.32% pepsin at low pH, 1% pancreatin at neutral pH).

containing 1% pancreatin (for 9 h). The respective results are indicated by the dotted curves in Figure 5. Clearly, in all cases, the drug release rate only slightly increased. Thus, the importance of such enzymatic degradation *in vivo* is likely to be limited.

As an increase in the relative ethylcellulose content of the films resulted in decreased water uptake and dry mass loss rates and extents (Figs. 1 and 2) as well as in increased mechanical stability of the films in the dry and wet state (Figs. 3 and 4), drug release was also measured from pellets coated with peas starch : ethylcellulose 1 : 3, 1 : 4, and 1 : 5 blends at different coating levels (Fig. 6). Interestingly, in these cases, even a film coating of only 5% (w/w) is able to slow down drug release. However, coating levels of 10% or more are more appropriate, because drug release is almost completely suppressed within the observation period.

Based on the obtained results (Figs. 1–6), pellets coated with peas starch : ethylcellulose 1 : 2 at a coating level of 15 and 20% have been selected for further studies. The relatively high content of peas starch can be expected to allow for an efficient onset of drug release at the target site.

Drug release in the entire gastrointestinal tract

Once the dosage form reaches the colon, the film coating should become permeable for the drug and release the latter in a time-controlled manner. Figure 7(a) shows the experimentally measured release of 5-ASA from pellets coated with peas starch : ethylcellulose 1 : 2 at a coating level of 15 and 20% (w/w) into: (i) 0.1*M* HCl for 2 h, (ii) phosphate buffer pH 6.8 for 9 h, and (c) culture medium inoculated with fecal samples from inflammatory bowel disease patients for 10 h (solid curves). For reasons of comparison, also drug release upon exposure to culture medium free of feces is illustrated (dotted curves). Clearly, the release set on as soon as the pellets came into contact with fecal samples. This can be attributed to the (at least partial) degradation of peas starch by the enzymes secreted by the bacteria present in the colon of the patients.[22] The decrease in polymer molecular weight and subsequent diffusion of degradation products into the surrounding bulk fluids renders the remaining macromolecular network more mobile. Consequently, also the mobility of the drug molecules within the film coating increases, and thus the release rate increases. In contrast, the drug release rate remained low upon exposure to culture medium free of feces [dotted curves in Fig. 7(a)]. This confirms that drug release is triggered by the enzymes present in the colon of inflammatory bowel disease patients. From a practical point of view, a coating level of 15% seems to be preferable to a coating level of 20% (potentially resulting in too slow drug release in the colon).

As a regular supply with fresh fecal samples from inflammatory bowel disease patients is difficult to assure (and as the samples cannot be deep-frozen or freeze-dried without significant damage of the microflora), it is highly desirable to provide an alternative type of release medium, simulating the conditions in the colon of a patient. For drug delivery

systems, which are sensitive to the presence of bacterial enzymes, caution has to be paid that the bulk fluid contains the crucial types and amounts of bacteria. In this study, culture medium inoculated with *Bifidobacterium* has been tested as potential alternative to culture medium inoculated with fresh fecal samples. Figure 7(b) shows the observed drug release rate from the same types of pellets as shown in Figure 7(a) upon exposure to: 0.1*M* HCl (for 2 h), phosphate buffer pH 6.8 (for 9 h), and culture medium inoculated with *Bifidobacterium* (for 10 h). Comparing Figures 7(a) and 7(b), it becomes obvious that culture medium inoculated with *Bifidobacterium* shows a promising potential as substitute for fresh fecal samples from inflammatory bowel disease patients, in particular for routine applications (such as quality controls during large-scale production).

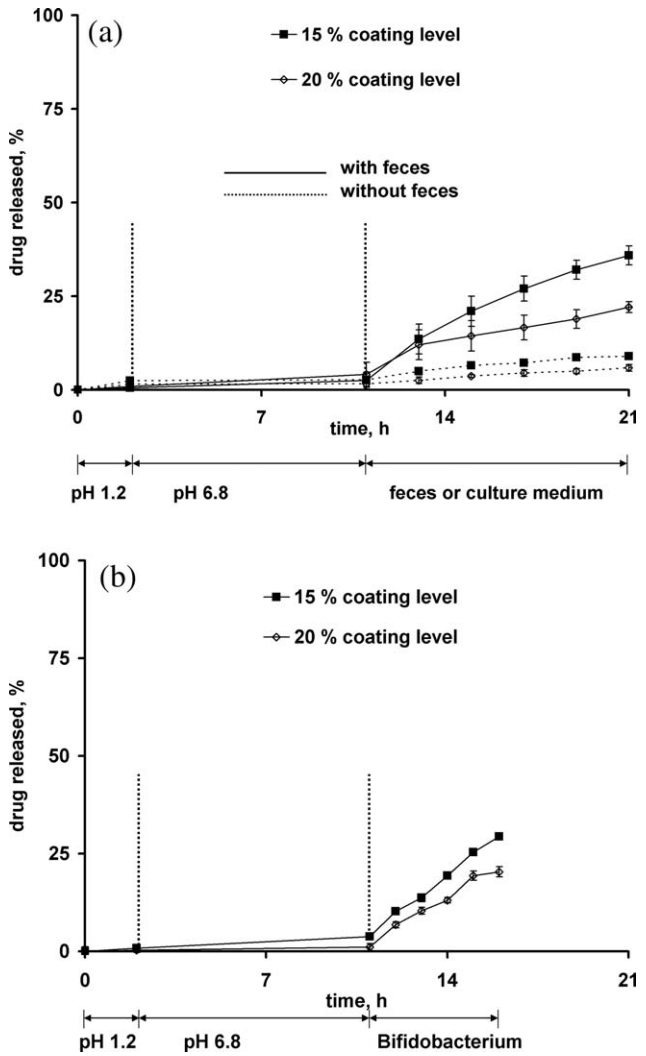

Figure 7 Drug release from pellets coated with peas starch : ethylcellulose 1 : 2 at a coating level of 15 or 20% (as indicated) under conditions simulating the transit through the entire gastrointestinal tract: 2-h exposure to 0.1*M* HCl, 9-h exposure to phosphate buffer pH 6.8, and 10-h exposure to: (a) culture medium inoculated with fresh fecal samples from inflammatory bowel disease patients (solid curves) or (b) culture medium inoculated with *Bifidobacterium* (solid curves). For reasons of comparison, also drug release upon exposure to sterile culture medium is shown in (a) (dotted curves).

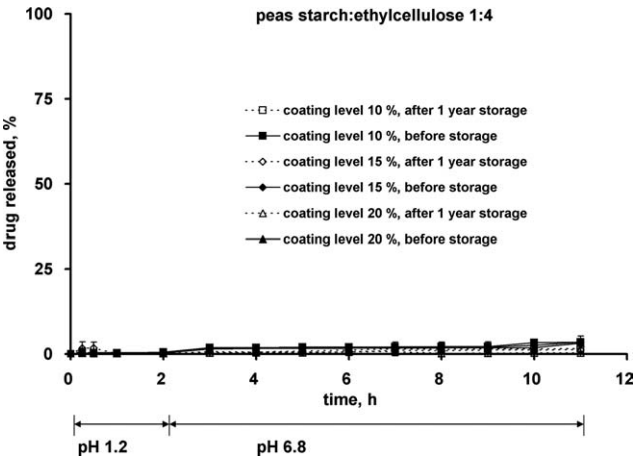

Figure 8 Storage stability of pellets coated with 10, 15, and 20% peas starch : ethylcellulose 1 : 4. Drug release in 0.1*M* HCl (for 2 h) and phosphate buffer pH 6.8 (for 9 h) before (solid curves) and after 1-year open storage (dotted curves).

Storage stability

A very important aspect from a practical point of view is the long-term stability of a controlled drug delivery system. Dosage forms should ideally be stable during at least 3 years. In the case of polymer-coated delivery systems, the resulting drug release rate might eventually increase with increasing storage time, e.g., because of drug migration into the film coating. Figure 8 shows the drug release kinetics from pellets coated with peas starch : ethylcellulose 1 : 4 at a coating level of 10, 15, and 15% (as indicated) before and after 1-year storage in open glass vials (solid and dotted curves). The systems were exposed to 0.1*M* HCl for 2 h and subsequently to phosphate buffer pH 6.8 for 9 h. As it can be seen, the release rate remained unaltered during long-term storage. The same was true for pellets coated with peas starch : ethylcellulose 1 : 2, 1 : 3, and 1 : 5 at a coating level of 10, 15, and 20% (data not shown). Thus, the proposed drug delivery systems are long-term stable.

CONCLUSIONS

Peas starch : ethylcellulose-based film coatings have been proposed with a highly promising potential for site-specific drug delivery to the colon: drug release from coated pellets can effectively be minimized in media simulating the contents of the stomach and small intestine. However, once the devices come into

contact with fecal samples, drug release sets on and is rate controlled, because of the partial degradation of the peas starch by enzymes secreted from bacteria present in the colon of inflammatory bowel disease patients. Thus, this type of advanced delivery systems allows avoiding premature drug release in the upper gastrointestinal tract (and subsequent absorption into the blood stream), while assuring that the drug is released at the site of action. Consequently, it can be expected that: (i) undesired side effects in the healthy part of the human body can be minimized, and (ii) the therapeutic effects of the treatment can be optimized.

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