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RESEARCH PAPER

Basic Coating Polymers for the Colon-Specific Drug Delivery in Inflammatory Bowel Disease

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ABSTRACT

During acute attacks of inflammatory bowel disease, the luminal pH of the colon decreases significantly. This drop in pH can be exploited by developing coated dosage forms with acid-soluble coating polymers to achieve topical drug delivery to the colon. Two batches of minitablets, a conventional and a swellable formulation, were prepared by direct compression and coated with different amounts of either Eudragit® E or AEA® in a small coating pan. The release of the model drug dexamethasone from the coated tablets was measured spectrophotometrically at pH 2.0, 4.0, 5.0, and 6.8 and different stirring rates (100–200 rpm) to simulate the influence of pH and hydrodynamic stress on drug release. In general, lag times of drug release, determined as the time points of a 5% drug release, were longer with AEA-coated cores compared to those coated with Eudragit E, resulting from a lower polymer dissolution rate and water permeability of this film. In low pH media, drug release was dependent on the stirring rate because the onset of drug release is determined by the time required for dissolution of the basic polymer films. At pH 6.8, lag times from nonswelling tablets coated with Eudragit E, for which drug release only begins after complete erosion of the polymer film, are not significantly affected by hydrodynamic stress. Drug release from AEA-coated cores is determined by the slow drug diffusion through the polymer film. Lag times from tablets with swelling properties, for which drug release is induced by disruption of the basic polymer films due to water penetration and subsequent core swelling, are not sig-

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nificantly affected by hydrodynamic stress. Additional coating layers such as an intermediate hydroxypropylcellulose (HPC) layer and an enteric outer layer do not influence the lag times of drug release, nor does a 2-hr pretreatment of the entire dosage form in acidic media.
Key Words: *Colon-specific drug delivery; Inflammatory bowel disease; Lag time; pH-controlled drug release.*

INTRODUCTION

Topical treatment of colonic disorders is desirable to lower the drug dose and to reduce side effects. There are currently four approaches to achieve colon specificity with coated dosage forms (1): pH-controlled drug release, for which coating polymers with a pH-dependent solubility that relies on the difference in pH between the small and the distal large intestine are used; time-controlled drug release, which takes advantage of the relatively constant small intestinal transit time with coating polymers that exhibit a slow or pH-dependent rate of swelling, dissolution, or erosion; enzyme-controlled drug release, which is based on coating polymers that are degradable by microbial enzymes in the colon; and pressure-controlled drug release, with coating polymers that form firm layers destroyed by an increase of the luminal pressure in the colon due to peristaltic waves.

Under physiological conditions, the pH difference between the small and the large intestine is not very pronounced (2). It has been found not to be significant enough to allow reproducible drug delivery to the colon with enteric coating polymers that dissolve above pH 6 or 7 (3–5). During acute attacks of inflammatory bowel disease, a significant decrease in colonic pH from normally 6.4–7 to values between 2.3 and 4.7 may be observed (6–9). This drop in pH has been attributed to a failure of bicarbonate secretion and a reduction of carbonic anhydrase I in colonic mucosa rather than excessive bacterial fermentation (6,10).

In a recent study, the basic aminoalkyl methacrylate copolymer Eudragit® E was evaluated with regard to its ability to allow drug delivery from coated minitablets only in the acidic environment of the inflamed colon (11). It was found that the mechanism of delivery of the poorly water soluble corticosteroid dexamethasone depends on the pH of the release medium, the tablet core composition, and the thickness of the applied polymer film. The objective of this study was to investigate another basic polymer, polyvinylacetal diethylaminoacetate (AEA®), as film-coating material and to compare drug release data from minitablets coated with this polymer to data obtained with the tablets coated with Eudragit E. Furthermore, it was examined whether drug release profiles from a conventional and a swellable tablet formulation coated with basic polymers are susceptible to hydrodynamic stress.

EXPERIMENTAL

Materials

Micronized dexamethasone was a gift from MSD Sharp and Dohme GmbH, Haar, Germany. Microcrystalline cellulose (Avicel® PH-101) and the mucoadhesive polymer carbomer 934 (Carbopol® 934) were provided by Lehmann and Voss and Company (Hamburg, Germany) and B. F. Goodrich Company (Cleveland, OH), respectively. Lactose (Tablettose® 80) was obtained from Meggle GmbH (Wasserburg, Germany), and Povidone 25 (Kollidon® 25) was donated by BASF AG (Ludwigshafen, Germany). Eudragit E was a gift from Röhm GmbH (Darmstadt, Germany) and AEA was provided by Sankyo Company, Limited (Tokyo, Japan). Low-viscosity hydroxypropylcellulose (HPC) (Klucel®, type LF) and HPMC-AS (hydroxypropylmethyl cellulose acetate succinate) (Aqoat®, type LF) were provided by Hercules, Incorporated (Wilmington, DE) and Shin-Etsu Chemical Company, Limited (Tokyo, Japan), respectively. Gelatin DAB was obtained from Deutsche Gelatine-Fabriken Stoess and Company GmbH (Eberbach, Germany). All other chemicals and solvents were high purity or analytical grade and were used as received.

Coated Minitablets

Two batches of minitablets, a conventional and a swellable formulation, were prepared according to the formulas shown in Table 1 by direct compression with a single-punch excenter press (OA, Ed. Frogerais, Vitry sur Seine, France). The swellable polymer carbomer 934 had to be used in its neutralized form to prevent dissolution of the basic polymer films from the core side after water penetration. Tablets had a diameter of 3 mm, a height of 2.5 mm, and an average weight of 20 mg. To avoid sharp tablet edges, concave punches (radius 2 mm) were used.

The coating process was performed in a spherical

Table 1

Overview of the Tablet Formulas

Formula PAA/MC		Formula Lac/St	
Dexamethasone	20%	Dexamethasone	20%
Microcrystalline cellulose	39.5%	Potato starch	37%
Carbomer 934 (neutralized)	39.5%	Lactose	37%
Magnesium stearate/silicon dioxide	1%	Povidone 25	5%
		Magnesium stearate/silicon dioxide	1%

coating pan (ø 8 cm) with a precision spray gun (Sata Minijet, Sata Farbspritztechnik, Ludwigsburg, Germany) as described previously (11). A fluidized bed was obtained by passing pressurized air into the core bed through silicone tubing.

Four different amounts of 6% (w/v) polymer solutions in methylene chloride of either Eudragit E (80, 120, 160, and 200 ml) or AEA (20, 40, 60, and 80 ml) were applied to batch sizes of 300 tablet cores. After the coating process, tablets were stored in a desiccator for 2 days to allow for complete evaporation of the solvent from the applied films. As the friability of the cores was low (0.5% w/w), film thickness levels were calculated from the increase in tablet diameter, measured with a micrometer (Micromaster, Tesa, Renens, Switzerland) (11). They amounted to 143, 221, 281, and 356 μm for cores coated with Eudragit E and 28, 53, 79, and 106 μm for AEA-coated cores. Additional coating layers, such as low-viscosity HPC (1.25% w/v in methylene chloride) as an intermediate layer (30 μm) and HPMC-AS (4% w/v in acetone containing 1% triethyl citrate) as an enteric coating (35 μm), were applied to the coated tablets in the same manner.

Drug Release

Dexamethasone release from the coated tablets was measured at 37°C in a USP 23 dissolution apparatus 2 (5 tablets per vessel) under sink conditions at 150 rpm and also at 100 and 200 rpm for the investigation of the effect of hydrodynamic stress on drug release. Drug concentrations were recorded spectrophotometrically (Lambda 2, Perkin-Elmer, Überlingen, Germany) in 1-cm quartz cells over time at 242 nm in the following four release media: 0.1 M potassium chloride/hydrochloric acid buffer pH 2.0 and 0.1 M phosphate buffers pH 4.0, 5.0, and 6.8. The potential effect of hydrodynamic stress on drug release was investigated only at pH 4.0 and 6.8. All release profiles were measured in triplicate. From the ultraviolet absorption data, the amounts of drug released were calculated as percentage of the total drug amount in the 5 tablets. Lag times of drug release t_{lag} were determined as the time required for a 5% release of the drug as described by Ueda et al. (12).

Pretreatment of the entire dosage form, including all three coating layers (Fig. 1) at 37°C in 0.1 M HCl and in 0.1 M phosphate buffer solution pH 4.0, respectively, was also done in the USP dissolution apparatus. Tablets were transferred into the vessel with the final release medium (0.1 M phosphate buffer solution pH 6.8) after the 2-hr pretreatment period.

Water Vapor Permeability of Polymer Films

To investigate the water vapor transmission (WVT) of isolated Eudragit E and AEA films, the method developed by Frömder and Lippold (13) for gravimetric measurement of the WVT of lipophilic liquids was adopted. Briefly, polymer solutions in methylene chloride (Eudragit E 10–20%, AEA 3–6% w/v) were poured onto the surface of 100 g of a 10% gelatin hydrogel (pH 6.8) in a cylindrical stainless steel container with a diameter of 14.09 cm, corresponding to an area of diffusion of 156 cm^2. The solvent was allowed to evaporate for 10 hr at 37°C, and the WVT was determined gravimetrically in an incubator with gentle air circulation under standardized

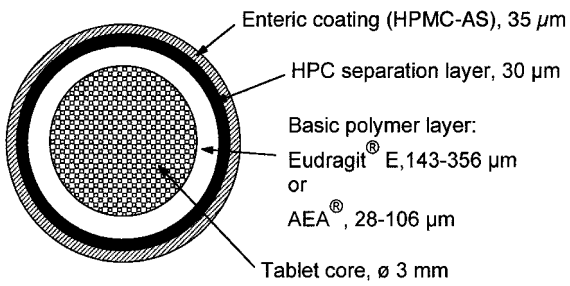

Figure 1. Design of the colonic dosage form.

climatic conditions (37°C ± 0.5°C, relative humidity [RH] < 5%) every 10 min for another 10 hr. Measurements were done with four different film thicknesses (Eudragit E 220–420 μm, AEA 50–125 μm).

The WVT is defined as follows:

$$\mathrm{WVT} = (P \cdot \Delta c)/d = m/(t \cdot A) \quad (1)$$

where P represents the water permeability of the polymer films with a thickness d, Δc is the water concentration gradient in the films, m is the mass of water evaporated, and A is the area of water vapor diffusion.

Δc may be expressed as

$$\Delta c = c_D - c_A = c_D \qquad c_A \approx 0 \quad (2)$$

where c_D and c_A are the water concentrations in the donor (gelatin gel) and acceptor (air) compartments, respectively.

The water vapor permeability may then be written as

$$P = (\mathrm{WVT} \cdot d)/(c_D - c_A) \quad (3)$$

Under the experimental conditions, the concentration gradient $c_D - c_A$ was assumed to be 1 g/ml.

As the permeabilities P calculated from the WVT data do not depend on the film thickness, permeabilities were determined as average values from four experiments to obtain one average P value for each polymer.

RESULTS AND DISCUSSION

During an acute attack of inflammatory bowel disease, the pH of the colon lumen often decreases significantly (6–9), a fact that may be used to advantage to achieve topical drug delivery to the inflamed colon. Physiologically, a luminal pH of around 7 is maintained by exchange of bicarbonate for luminal chloride anions. Bacterial fatty acids resulting from the degradation of oligo- and polysaccharides in the proximal colon further stimulate the luminal appearance of bicarbonate. In ulcerative colitis, a diminished *n*-butyrate-stimulated bicarbonate output may be observed that supports the hypothesis of an inadequate oxidation of bacterial fatty acids by the inflamed mucosa in vivo (6). Furthermore, a reduction of carbonic anhydrase I activity found in the colonic mucosa of colitis patients may contribute to the pH decrease (10). This pathological drop in the luminal pH of the colon has led to the development of a coated dosage form with the acid-soluble coating film Eudragit E to achieve topical drug delivery in the colon (11).

Eudragit E, a copolymer consisting of dimethylaminoethyl methacrylate and neutral methacrylic acid esters, with a pK_a of 6.3, and polyvinylacetal diethylaminoacetate (AEA), with a pK_a of 5–6 depending on the ionic strength of the titration medium (14), are readily soluble only under acidic conditions at a pH below 5. In a neutral or alkaline environment, the water-permeable polymer films swell, and in the case of Eudragit E, the polymer film slowly erodes and dissolves. Due to these properties, both polymers appear to be suitable coating materials for drug release in an acidic environment.

The design of the complete dosage form is shown in Fig. 1. A colonic dosage form based on drug cores coated with Eudragit E or AEA requires an enteric coating to protect the acid-soluble polymers from dissolution in the stomach. Because of possible ionic interactions between the cationic polymers and the anionic enteric polymer HPMC-AS, an inert intermediate layer such as low-viscosity HPC has to be applied. In this study, most of the presented data were obtained with minitablets coated with only the basic polymer layer.

From the drug release profiles, the onsets of drug release t_{lag}, defined as the time points of a 5% drug release, were determined to characterize the release mechanism. As recently shown with tablets coated with Eudragit E, the shape of the drug release curves corresponds to that obtained with the uncoated cores, and 80% of the total drug amount is released within 30 min (11). An overview of the onsets of drug release t_{lag} as a function of the membrane thickness measured at four different pH values with tablet cores coated with both Eudragit E and AEA is shown in Fig. 2. Overall, drug release strongly depends on the pH of the release medium and on the thickness of the polymer film. At pH 2.0–5.0, lag times of drug release t_{lag} from the two coated tablet formulations are comparable, ranging from 5 to 50 min, depending on the coating level. Lag times t_{lag} increase in a linear manner with increasing coating thickness due to polymer dissolution and subsequent drug release in these low pH media. A tendency of increasing lag times with increasing pH may be observed because of decreasing solubilities and dissolution rates of the polymers with increasing pH. However, drug release in low pH media begins within less than 1 hr even at high coating levels. The slightly delayed drug release from the polyacrylic acid (PAA)/microcrystalline cellulose (MC) formula compared to the Lac/St (lactose/starch) formula may be a result of an interaction between the cationic coating polymers and the anionic polyacrylic acid.

A linear dependency of the lag time of drug release on the coating thickness has also been found with the colon-targeted delivery capsule (CTDC), a time-controlled dosage form consisting of enteric gelatin capsules

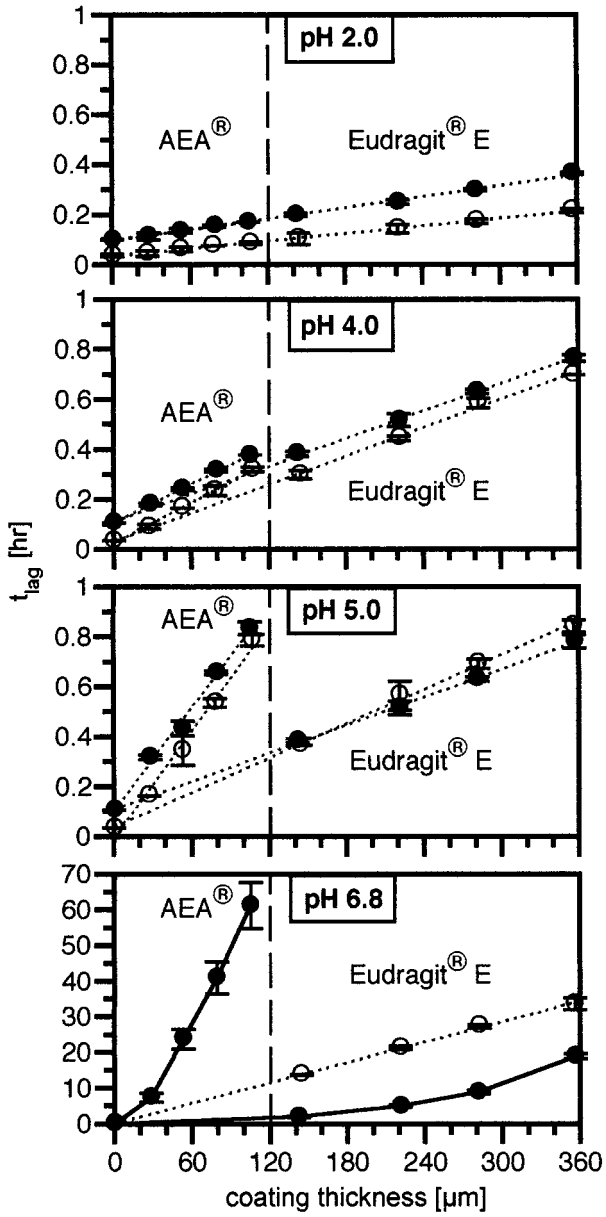

Figure 2. Lag times of drug release t_{lag} as a function of the coating thickness for minitablets coated with AEA and Eudragit E (○ Lac/St, ● PAA/MC) at different pH values and 150 rpm. Dotted lines are regression lines. Error bars are SD ($n = 3$). ○ Drug release at pH 6.8 < 1% in 48 hr.

coated with Eudragit E that contain a solid organic acid, which induces dissolution of the basic Eudragit E film and thus drug release after water penetration into the inside of the capsule (15).

Another colon-specific drug formulation relying on the dissolution of Eudragit E under acidic conditions has been developed by Watanabe et al. (16) and is available on the market as Codes®. Drug release from the drug cores after dissolution of the outer enteric coat is induced by microbial degradation of a lactulose layer to short-chain fatty acids by the colonic microflora with subsequent dissolution of the underlying Eudragit E film.

At pH 6.8, the onsets of drug release are much longer compared to those obtained in low pH media. The release of the poorly water soluble drug dexamethasone from the Lac/St cores coated with Eudragit E starts only after complete erosion of the polymer film from the cores, which is a slow process and again leads to a linear relationship between the lag time of drug release and the coating thickness. The poor water solubility and low drug permeability of the AEA film at this higher pH explains the very slow drug release, less than 1% in 48 hr, from AEA-coated Lac/St tablets. Drug release from coated PAA/MC cores at pH 6.8 starts earlier compared to the Lac/St tablets, and an overproportionate increase of the lag times of drug release with increasing coating thickness may be observed. This overproportionate increase of the lag times of drug release is a result of substantial core swelling after water penetration into the PAA/MC cores, which causes rupture of the applied basic polymer film (11). The difference in onsets of drug release between PAA/MC cores coated with Eudragit E and AEA may be interpreted as the result of different water permeabilities of the coating films. Water vapor permeabilities P of Eudragit E and AEA films calculated from the WVT data according to Eq. 3 amounted to $35.8 \pm 1.3 \times 10^{-9}$ and $6.8 \pm 0.7 \times 10^{-9}$ cm^2/s, respectively. Accordingly, significantly faster water penetration into the tablet cores with tablets coated with Eudragit E and thus shorter lag times t_{lag} have to be expected.

The explosion-type drug release mechanism could be of potential use for the development of a time-controlled dosage form for drug delivery to the healthy colon. The time-controlled explosion system (TES) developed by Ueda et al. (12) consisting of a drug-containing core coated with an HPC swelling layer and an ethyl cellulose outer film represents a dosage form with a similar release mechanism.

Another explosion-type dosage form for colon-specific drug delivery based on tablet cores with a composition similar to that of the PAA/MC formula has been developed by Abramowitz et al. (17). Tablet cores with varying PAA:MC ratios were coated with the sustained-release coating material Eudragit RS 30 D and protected

by an outer enteric coating. Drug release after dissolution of the enteric coating film was pH dependent because of substantial carbomer swelling in the higher pH regions of the intestine (pH > 6.5), causing the sustained-release film to rupture.

In addition to their swelling properties, carbomers may act as mucoadhesive agents, intensifying and prolonging the contact between the dosage form and the site of absorption, thereby reducing the luminal diffusion pathway of the drug. The colon appears to be a suitable organ for mucoadhesive dosage forms because of the low mucus turnover rate in the lower part of the intestine, as shown in the rat (18). Under acidic conditions, the adhesion force of polycarbophil in the cecum and the colon of the rat is significantly stronger than in the stomach and the small intestine (18). However, in patients with ulcerative colitis, the mucin polymer content in colonic mucus gel is significantly decreased (19). Carbomer 934 has been shown to inhibit the mucolysis of porcine colonic mucin and to interact with mucin, as demonstrated by a marked synergistic increase in solution viscosity (20). Polyacrylates may therefore have therapeutic potential in inflammatory bowel disease.

The onsets of drug release from the coated tablet formulations in acidic release media and, in the case of Lac/St tablets coated with Eudragit E, also at pH 6.8 are determined by erosion and/or dissolution of the basic polymer layers. Theoretically, such an erosion/dissolution process should be dependent on hydrodynamic stress. Figure 3 shows the influence of hydrodynamic stress on the onset of drug release from coated minitablets as a function of core composition, coating thickness, and pH. As expected, onsets of drug release at pH 4.0 are significantly dependent on hydrodynamic stress in the release medium, which is most obvious at high coating levels. However, the decrease in t_{lag} of maximally 10 min with increasing stirring rate is not of practical relevance. At pH 6.8, no influence of hydrodynamic stress is observed with coated PAA/MC tablets because, at this pH, the drug is released from the dosage form after swelling of the cores due to water penetration (3.4-fold increase in volume) and subsequent rupture of the polymer membrane. In contrast, hydrodynamic stress may play a role in the case of drug release from the Lac/St cores coated with Eudragit E at pH 6.8 because these cores, with only a 1.4-fold increase in volume, do not swell extensively enough to cause a membrane disruption; drug release begins only after the slow erosion process of the Eudragit E layer. However, only a minor, statistically nonsignificant, effect of hydrodynamic stress could be detected.

The film coating strength of AEA films has been shown to be reduced at pH 5.0–5.8 due to film swelling (21). An increasing mechanical destructive force, as observed during gastrointestinal tract peristalsis, might therefore cause membrane rupture. However, at pH 6.8, swelling of AEA is decreased, and coating films should be sufficiently stable. The ionic strength of the release medium has also been shown to affect drug release from AEA-coated tablets with increasing ionic strength, leading to earlier onsets of drug release (14). The effect of increased ionic strength on drug release from tablets coated with Eudragit E and AEA is currently under investigation in our laboratory.

In Fig. 4, the effect of additional coating layers (HPC, HPMC-AS) and the pretreatment of the complete dosage form in acidic release media simulating the pH conditions in the fasted and nonfasted stomach on the lag times of drug release at pH 6.8 is shown. The uniform lag times with the untreated basic polymer-coated cores serving as reference suggest no significant effect of additional coating layers on drug release (i.e., no delay in drug release due to dissolution of these additional polymer layers). Moreover, during a 2-hr pretreatment period of the dosage form in acidic media, no premature drug release was observed, confirming the gastric resistance of the enteric coating. Pretreatment did not affect lag times of drug release at pH 6.8 (i.e., water penetration into the cores during the initial 2 hr is negligible).

It is obvious from the results of this study that one can distinguish between two mechanisms of drug release depending on the pH of the release medium and the composition of the cores: The linear relationship between the lag time of drug release and the coating thickness and the observed susceptibility to hydrodynamic stress at low pH values confirms that the onset of drug release occurs only after complete dissolution of the polymer film. At pH 6.8, drug release from the coated PAA/MC tablets is mainly caused by swelling of the cores and subsequent disruption of the basic polymer films, which leads to the typical overproportionate increase of the lag times of drug release with increasing coating thickness and explains the independency of drug release from hydrodynamic stress. Differences between the two polymers result from the different water permeabilities of the coating films. Drug release from the coated Lac/St cores at pH 6.8 either starts after complete erosion of the basic polymer film, a comparatively slow process that leads to a linear relationship between the lag time of drug release and the coating thickness (Eudragit E), or drug release is the result of slow drug diffusion through the polymer

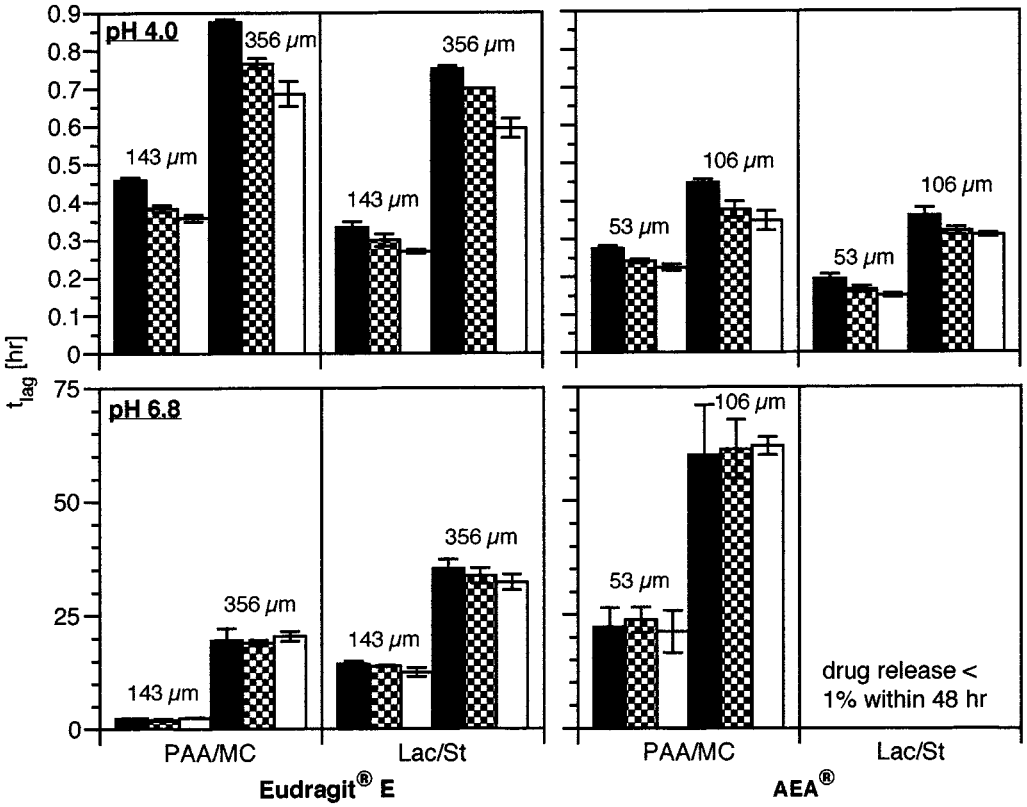

Figure 3. Lag times of drug release t_{lag} as a function of the stirring rate (■ 100 rpm, ▩ 150 rpm, □ 200 rpm) for conventional and swellable minitablet formulations coated with Eudragit E or AEA at two different coating levels and at pH 4.0 (upper panels) and 6.8 (lower panels). Error bars are SD (n = 3).

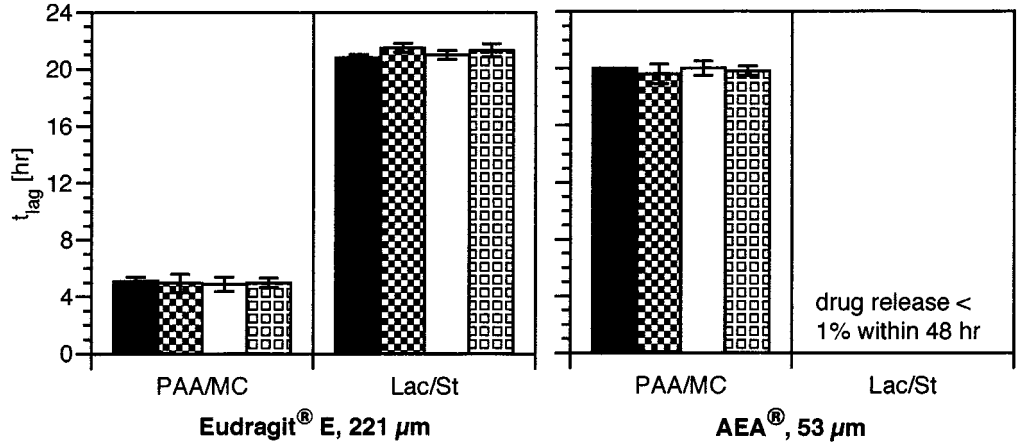

Figure 4. Influence of additional coating layers (HPC, HPMC-AS) and of a 2-hr pretreatment of the entire dosage form in acidic media on lag times of drug release t_{lag} at pH 6.8 (150 rpm), ■ entire dosage form, untreated; ▩ after 2 hr in 0.1 M HCl; □ after 2 hr at pH 4.0; ▦ coated with basic polymer only, untreated. Error bars are SD (n = 3).

membrane (AEA). In the case of the slow film erosion observed with Eudragit E, only a minor nonsignificant effect of hydrodynamic stress on drug release may be found.

CONCLUSION

From the presented results, it may be concluded that Eudragit E and AEA are suitable coating polymers for drug release under such acidic conditions as found in the colon of patients with inflammatory bowel disease. Coating thicknesses, and thus lag times of drug release, may be adjusted to achieve drug release only at the low pH values of the inflamed colon, but not in the healthy colon with a luminal pH of 6.5–7 and a transit time of 20–30 hr. Lag times of drug release from the presented dosage form strongly depend on the pH of the release medium, the thickness of the basic polymers layers, and the composition of the tablet cores. Furthermore, hydrodynamic stress and the water permeability of the polymer films may affect drug release. In acidic media, drug release from both coated tablet formulas occurs quickly due to the rapid dissolution of the basic polymers; it is therefore susceptible to hydrodynamic stress. With drug cores that swell only marginally (Lac/St), the onset of drug release at pH 6.8 in the case of tablets coated with Eudragit E is determined by a dissolution or a combined erosion/dissolution process of the polymer film, which may be influenced by hydrodynamic stress. Drug release from AEA-coated tablets is extremely slow due to the low solubility and drug permeability of the film at this pH. In contrast, with drug cores that strongly increase in volume due to swelling (PAA/MC), drug release at pH 6.8 is induced by disruption of the basic polymer layers, and lag times of drug release are independent of the hydrodynamic stress in the system. Differences in drug release between the two coating polymers are a result of the different pH-dependent dissolution behaviors as well as water permeabilities of the coating films. Additional coating layers in the complete dosage form do not affect lag times of drug release at pH 6.8.

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