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Research paper

pH-sensitive film coatings: Towards a better understanding and facilitated optimization

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Abstract

The major aims of this study were: (i) to prepare and characterize polymeric film coatings with pH-dependent properties for oral administration; and (ii) to better understand the underlying mass transport mechanisms upon exposure to simulated gastric and intestinal fluids. Propylene glycol alginate (containing free carboxylic groups) was chosen as a pH-sensitive film former, which was blended with different amounts of ethylcellulose (being water-insoluble throughout the gastro-intestinal tract). The water uptake kinetics of thin free films in 0.1 M HCl and phosphate buffer pH 7.4 were monitored gravimetrically and quantitatively described using an appropriate analytical solution of Fick's law of diffusion. Interestingly, the addition of only a low percentage (2.5–10%) of propylene glycol alginate to ethylcellulose significantly increased both, the rate and extent of the films' water uptake, irrespective of the pH of the release medium. Importantly, diffusion was found to be the pre-dominant mass transport mechanism for all system compositions and types of release media. The apparent water diffusivity in the polymeric films could quantitatively be determined as a function of the polymer blend ratio. It significantly increased with increasing pH of the release medium, due to the presence of the free carboxylic groups in propylene glycol alginate. Also the dry mass loss of the polymer networks was much more pronounced at high compared to low pH. The differences in both water uptake as well as dry mass loss resulted in a clear pH-dependence of the drug release kinetics from coated pellets. Importantly, desired pH-sensitive release rates can easily be adjusted by varying the propylene glycol alginate content.

Keywords: Solid dosage form; Polymeric drug delivery systems; Coating; Pellets; Controlled release; pH-sensitivity; Ethylcellulose; Release mechanism; Diffusion

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1. Introduction

Film coatings are frequently used to mask unpleasant tastes and odors, to protect drugs against moisture during storage and/or to control the rate at which a drug is released along the gastro-intestinal tract upon oral administration [1–4]. In the case of controlled release coatings, the pharmacokinetic and pharmacodynamic characteristics of the drug determine which release patterns from the dosage form are required to provide optimal therapeutic effects of the treatment. Different types of profiles can be desired, including monotonically increasing or decreasing release rates, pulsatile release patterns or zero order kinetics (constant release rates). In the latter case, a constant drug supply can aim to compensate the continuous elimination of the drug out of the human body, resulting in essentially constant drug concentrations at the site of action over prolonged periods of time. If this type of release profile is targeted for a drug with pH-independent solubility, a polymeric film coating should be chosen, the properties of which do not change along the gastro-intestinal transit. In the ideal case, the drug concentration within the dosage form does not change during a long time period (e.g., a

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saturated drug solution is provided), sink conditions are maintained (due to continuous drug absorption) and the film coating controlling drug release is not altered.

However, certain drugs exhibit strongly pH-dependent solubility. For example, verapamil (being a weak base) is freely soluble at low pH (being protonated and, thus, positively charged), but poorly soluble at high pH (being de-protonated and neutral) (>150 mg/mL and 0.75 mg/mL in 0.1 M HCl and phosphate buffer pH 7.4 at 37 °C, respectively [5]). Consequently, the resulting drug release rates are high in the stomach (high drug concentration gradients) and significantly decrease in the intestine (low drug concentration gradients) when using conventional film coatings. To be able to compensate such pH-dependent drug solubility effects, film coatings with low permeability at low pH and high permeability at high pH can be used [6–9]. To provide such pH-sensitive permeability, film coatings can for instance contain polymers with free carboxylic or sulfate groups. At low pH, these groups are protonated and uncharged, whereas at high pH they are de-protonated, negatively charged and, thus, more hydrophilic. Examples of this type of polymer include methacrylic acid-methyl methacrylate copolymers, hydroxypropyl methylcellulose acetate succinate, hydroxypropyl methylcellulose acetate phthalate, cellulose acetate phthalate, carrageenans and alginates. However, little is yet known on the underlying mass transport mechanisms dominating in this type of film coating once it is exposed to low and high pH aqueous media. Thus, device optimization is based on series of time-consuming and cost-intensive trial-and-error experiments.

In this study, propylene glycol alginate (PG alginate, alginate which is partially esterified with 1,2-propandiol) has been chosen as pH-sensitive compound due to its good film forming properties and safety upon oral administration. However, the use of pure PG alginate as a rate controlling membrane is not feasible, because pure PG alginate is water-soluble. Thus, a second component needs to be added, preferably one that is water-insoluble throughout the gastro-intestinal tract. Ethylcellulose (which is widely used in oral pharmaceutical formulations and generally regarded as nontoxic, non allergenic and nonirritant) has been chosen as second film compound. It has recently been shown to form pH-*in*sensitive film coatings when blended with a poly(vinyl alcohol)-poly(ethylene glycol) graft copolymer [10]. The idea in the present study is to hinder the dissolution of PG alginate by the presence of ethylcellulose at low pH, and to provide pH-sensitive film coating properties due to the presence of free carboxylic groups in the polymeric systems.

In addition to the composition of the film coatings the type of coating technique (using aqueous dispersions or organic solutions) can tremendously affect the properties of the resulting polymeric membranes, including their permeability for water and drug, mechanical resistance and dissolution behavior [11–16]. As the use of aqueous polymer dispersions is advantageous not only from a toxicological point of view (avoidance of residual organic solvents), but also with respect to ease of processing (formulations with higher solid contents can be used [17]) and environmental concerns (reduced pollution), an aqueous ethylcellulose dispersion was used in this study. That is why particular attention has been paid to the effects of the curing conditions on the resulting drug release patterns: If the polymer particles are not fully coalesced, structural changes during long term storage are likely, resulting in altered drug release rates.

The major aims of this work included: (i) to prepare and physico-chemically characterize thin free PG alginate/ethylcellulose films; (ii) to study the potential of these films to control drug release in simulated gastric and intestinal fluids; and (iii) to better understand the underlying mass transport phenomena, in order to facilitate the optimization of this type of controlled drug delivery system.

2. Materials and methods

2.1. Materials

Theophylline anhydrous (BASF, Ludwigshafen, Germany), theophylline pellets (average diameter = 1 mm, 70% drug content; FMC, Princeton, NJ), Aqueous Ethylcellulose Dispersion NF [Aquacoat ECD, containing residual sodium dodecyl sulfate (SDS) used as emulsifier during manufacture, FMC, Philadelphia, PA], propylene glycol alginate (PG alginate, Protanal ester SD-LB; FMC), triethyl citrate (TEC; Morflex, Greensboro, NC).

2.2. Preparation of thin free films

Thin, polymeric films were prepared by casting aqueous dispersions of ethylcellulose (Aquacoat ECD, plasticized with 25% w/w TEC, based on the polymer mass) and/or PG alginate onto Teflon plates and subsequent controlled drying (for 24 h at 60 °C in an oven). The following ethylcellulose/PG alginate blend ratios were investigated: 90:10, 95:5, 97.5:2.5 and 100:0 (w/w). The thickness of the films (around 200 μm) was measured using a thickness gauge (Minitest 600; Erichsen, Hemer, Germany).

2.3. Morphology of thin free films

The morphology of the investigated ethylcellulose/PG alginate-based films was studied using an optical imaging system (Nikon SMZ-U; Nikon, Tokyo, Japan) equipped with a Sony camera (Hyper HAD model SSC-DC38DP; Elvetec, Templemars, France) and the Optimas 6.0 software (Media Cybernetics, Silver Spring, MD).

2.4. Water uptake and dry mass loss of thin free films

Thin, polymeric films were cut into pieces of 2 × 2 cm, which were placed into 50 mL plastic flasks filled with 40 mL pre-heated 0.1 M HCl or phosphate buffer pH 7.4

(USP XXIX), followed by horizontal shaking for 8 h (37 °C, 80 rpm; GFL 3033; Gesellschaft fuer Labortechnik, Burgwedel, Germany). At pre-determined time intervals, samples were withdrawn, accurately weighed [wet mass (*t*)] and dried to constant mass at 60 °C [dry mass (*t*)]. The water content (%) and dry film mass (%) at time *t* were calculated as follows:

$$\text{water content (\%)}\ (t) = \frac{\text{wet mass}\ (t) - \text{dry mass}\ (t)}{\text{wet mass}\ (t)} \cdot 100\% \qquad (1)$$

$$\text{dry film mass (\%)}\ (t) = \frac{\text{dry mass}\ (t)}{\text{dry mass}\ (0)} \cdot 100\% \qquad (2)$$

2.5. Preparation of coated pellets

Theophylline pellets (70% w/w drug loading) were coated with blends of ethylcellulose and PG alginate in a fluidized bed coater equipped with a Wurster insert (Strea 1; Niro Inc., Aeromatic-Fielder AG, Bubendorf, Switzerland). All dispersions were plasticized overnight with triethyl citrate (25% w/w based on the ethylcellulose mass). The following ethylcellulose/PG alginate blend ratios were investigated: 90:10, 95:5, 97.5:2.5 and 100:0 (w/w). The coating dispersions were sprayed onto theophylline pellets until a weight gain of 5, 10, 15 and 20% (w/w) was achieved. The process parameters were as follows: inlet temperature = 40 °C, product temperature = 38 ± 2 °C, spray rate = 3–4 g/min, atomization pressure = 1.2 bar, air volume = 100 m^3/h, nozzle diameter = 1.2 mm. After coating the pellets were further fluidized for 10 min and subsequently cured for 24/48 h at 60 °C and ambient relative humidity (RH) or for 24/48 h at 40 °C and 75% RH (followed by an additional drying step of 24 h at 60 °C and ambient RH).

2.6. Drug release from coated pellets

Theophylline release from the pellets was measured in 0.1 M HCl (optionally containing 10, 25 or 50 mmol/L calcium chloride) and phosphate buffer pH 7.4 (USP XXIX) using the paddle apparatus (USP XXIX; Sotax, Basel, Switzerland) (900 mL; 37 °C, 100 rpm; $n = 3$). At pre-determined time intervals, 3 mL samples were withdrawn and analyzed UV-spectrophotometrically ($\lambda = 271$ nm; Anthelie Advanced; Secomam, Domont, France).

3. Results and discussion

3.1. Morphology of thin free films

When using polymer blends for film coating, it is important to evaluate the morphology of the resulting polymeric membranes. Fig. 1 shows an optical photomicrograph of a thin ethylcellulose film containing 10% (w/w) PG alginate. Importantly, no phase separation is visible. This was true also for the other investigated blend ratios (data not shown). All films were transparent and had a smooth surface. The morphology of the films does not indicate any incompatibility of the two polymers. This is important, because in the case of polymer–polymer incompatibility, the risk of structural changes within the film coatings during long term storage (resulting in changes in the drug permeability and, thus, release patterns) would be considerable.

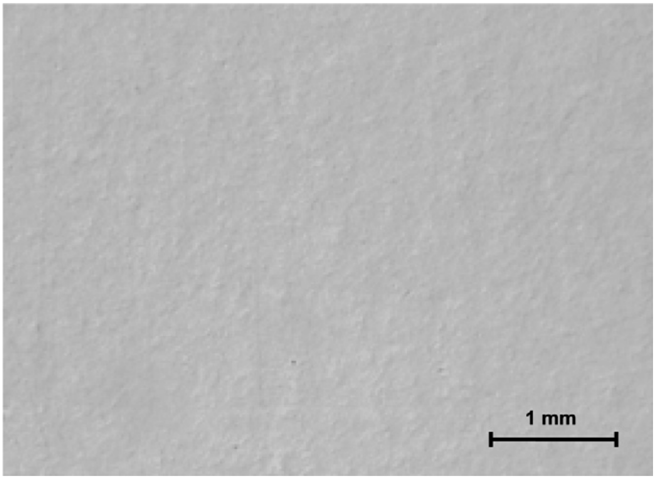

Fig. 1. Optical microscopy pictures of thin, polymeric films prepared from 90:10 ethylcellulose/PG alginate blends.

3.2. Water uptake of thin free films

The rate and extent to which a polymeric film takes up water strongly affects the resulting mobility of the macromolecules and, thus, the free volume available for drug diffusion. Generally, the permeability of polymeric networks significantly increases with increasing water content (water acting as a plasticizer). The filled squares in Fig. 2 illustrate the changes in the water content of thin free films consisting of pure (plasticized) ethylcellulose upon exposure to simulated gastric and intestinal fluids. Clearly, the limited rate and extent of the water uptake of these systems may at least partially explain why pure ethylcellulose films are poorly permeable for certain drugs. Comparing Figs. 2a and b, it can be seen that the extent of water uptake of pure (plasticized) ethylcellulose films is higher in phosphate buffer pH 7.4 than in 0.1 M HCl. This is consistent with the pH-dependent wetting effect of sodium dodecyl sulfate (SDS) in a partially coalesced ethylcellulose film [16]. SDS is used as an emulsifier in the manufacture of aqueous ethylcellulose dispersion. At low pH, the dodecyl sulfate groups are protonated, whereas they are de-protonated at high pH (and significantly facilitate the penetration of aqueous media). Importantly, the addition of only small amounts of PG alginate fundamentally increases both, the rate (the slope of the curves) as well as the extent (the plateau value) of the water uptake (diamonds, triangles and

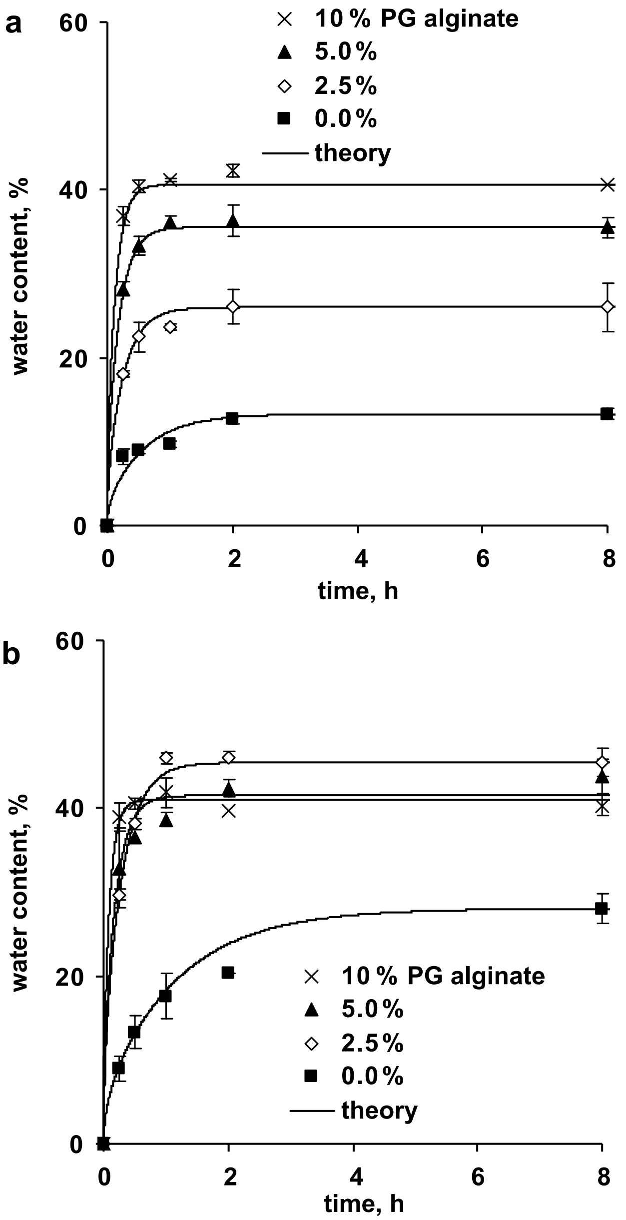

Fig. 2. Effects of the addition of small amounts of PG alginate (indicated in the figures) on the water uptake behavior of ethylcellulose-based films upon exposure to: (a) 0.1 M HCl; (b) phosphate buffer pH 7.4. The symbols represent the experimentally measured results, the curves the fitted theory (Eq. (6)).

crosses in Fig. 2). At only 10% (w/w) initial PG alginate content, 40% of the film consists of pure water upon swelling. This can be expected to tremendously alter the conditions for drug diffusion through the polymeric networks. Interestingly, the effects are more pronounced in phosphate buffer pH 7.4 than in 0.1 M HCl (Fig. 2b vs. 2a). This can be attributed to the free carboxylic groups present in PG alginate: At low pH they are protonated, whereas at high pH they are de-protonated (rendering the polymeric films more hydrophilic). Importantly, the presence of 90.0–97.5% ethylcellulose does not mask the pH-dependent properties of PG alginate.

To better understand, which mass transport phenomena are dominating once the polymeric films are exposed to the release media, an appropriate analytical solution of Fick's law of diffusion was fitted to the experimentally determined water uptake kinetics (curves in Fig. 2). The model considers:

(1) The geometry of the thin polymeric films.
(2) The fact that the systems are initially dry (at $t = 0$).
(3) Constant water concentrations at the surfaces of the films throughout the experiments.
(4) Diffusional mass transport in one dimension (edge effects are negligible, as the surfaces of the films are much larger in relation to their thickness: approximately 8 cm^2 versus 200 μm).

The initial value problem is as follows [18]:

$$\frac{\partial c}{\partial t} = D \cdot \frac{\partial^2 c}{\partial x^2} \tag{3}$$

$$t = 0, \quad c = 0, \quad -L \leqslant x \leqslant +L \tag{4}$$

$$t > 0, \quad c = \text{constant}, \quad x = +/-L \tag{5}$$

where c denotes the water concentration within the polymeric films, being a function of time t and position x; D is the apparent diffusion coefficient of water and L is the half-thickness of the film. Using the method of Laplace transform, this set of equations can be solved leading to [19,20]:

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2 \cdot n + 1)^2 \cdot \pi^2} \cdot \exp\left(-\frac{(2 \cdot n + 1)^2 \cdot \pi^2}{4 \cdot L^2} \cdot D \cdot t \right) \tag{6}$$

with M_t and M_∞ denoting the absolute cumulative amounts of water taken up at time t and $t = \infty$, respectively.

As it can be seen in Fig. 2, the agreement between experiment (symbols) and theory (curves) is good in all cases. This clearly indicates that water diffusion through the polymeric networks is the pre-dominant mass transport mechanism. Importantly, the addition of small amounts of PG alginate does not alter the relative importance of the involved physico-chemical phenomena: Water diffusion remains rate-limiting. Based on these calculations, the apparent diffusion coefficient of water in the ethylcellulose films containing 0–10% PG alginate could quantitatively be determined. Fig. 3 shows the results obtained in 0.1 M HCl and phosphate buffer pH 7.4, respectively. Clearly, the water permeability significantly increases with increasing PG alginate content. Furthermore, the water diffusion coefficients are much higher in simulated intestinal fluid than in simulated gastric fluid (at the same PG alginate contents). The difference increases with increasing PG alginate content. This can be attributed to the presence of the free carboxylic groups and clearly indicates that

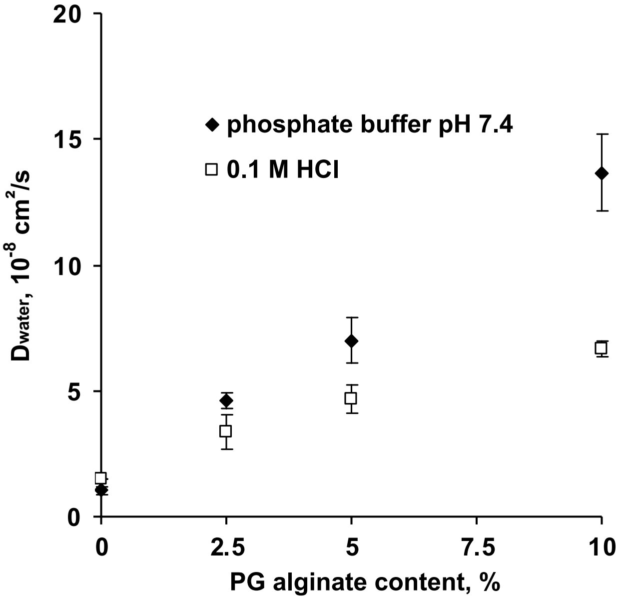

Fig. 3. Diffusion coefficient of water in ethylcellulose-based films as a function of the PG alginate content upon exposure to 0.1 M HCl and phosphate buffer pH 7.4, respectively.

ethylcellulose/PG alginate blends offer an interesting potential for pH-sensitive film coatings.

3.3. Dry mass loss of thin free films

In addition to the water uptake behavior of a polymeric film coating its dry mass loss kinetics upon exposure to the release media are also of major importance for its ability to control drug release. With increasing amounts of film components leaching out into the bulk fluid, the films become more and more permeable (because the remaining polymer network becomes less dense). As it can be seen in Fig. 4, the dry mass loss of pure (plasticized) ethylcellulose films is limited (filled squares). This can be explained by the water insolubility of ethylcellulose. It has to be pointed out that 20% (w/w) of the films consist of the water-soluble plasticizer triethyl citrate. Thus, theoretically the dry film mass can decrease down to 80% (upon complete plasticizer leaching). Looking at Fig. 4 it becomes obvious that ethylcellulose is able to effectively hinder this process. Comparing Figs. 4b and a, it can be seen that the decrease in dry film mass of pure (plasticized) ethylcellulose films is more pronounced in phosphate buffer pH 7.4 than in 0.1 M HCl. This is consistent with the pH-dependent wetting effect of sodium dodecyl sulfate (SDS) in a partially coalesced ethylcellulose film [16], as discussed above.

Interestingly, the addition of only 2.5–10% PG alginate fundamentally increases both, the rate as well as the extent of the dry mass loss of ethylcellulose films (Fig. 4). This can partially be explained by the leaching of this water-soluble compound into the bulk fluids and partially to an increased leaching of the water-soluble plasticizer into the release media: The presence of PG alginate in the polymeric films significantly increases the water uptake of the systems (Fig. 2) (for instance, some of the films consist of 40% water upon swelling). Under these conditions, triethyl citrate can much more easily diffuse out into the bulk fluids, resulting in higher dry mass loss rates and extents (Fig. 4) (Remark: It was beyond the scope of this study to distinguish between plasticizer and PG alginate leaching). Importantly, the effects of the presence of PG alginate on the dry mass loss of the polymeric films were much more pronounced at high pH than at low pH. This can again be explained by the free carboxylic groups of the hydrophilic polymer (being protonated in 0.1 M HCl and de-protonated in phosphate buffer pH 7.4).

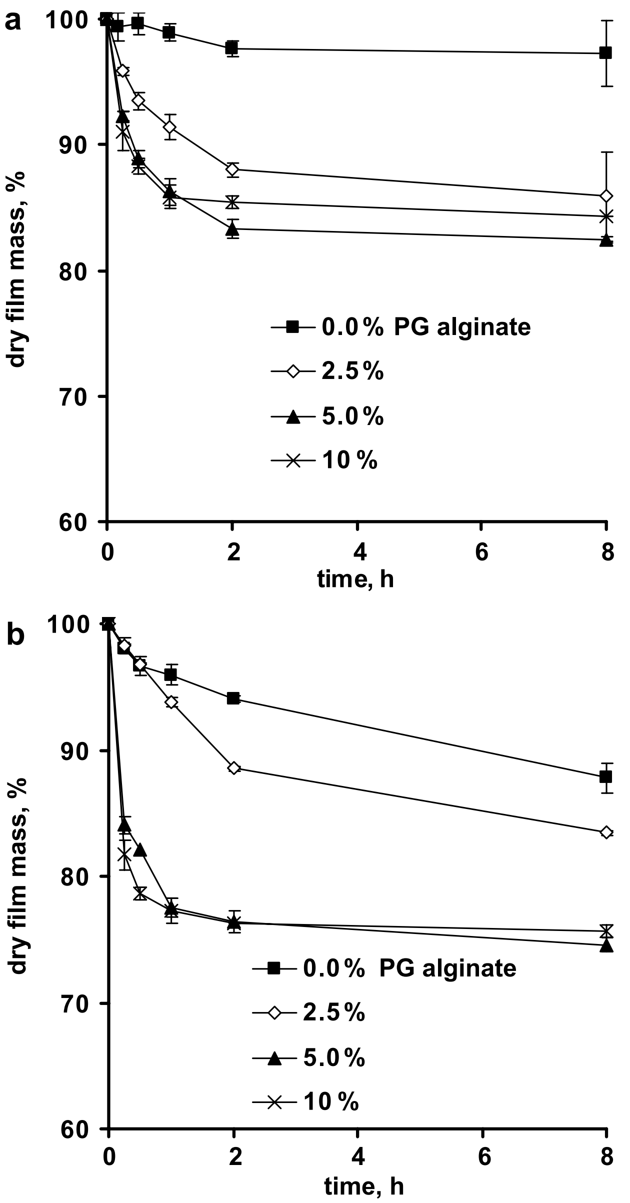

Fig. 4. Effects of the addition of small amounts of PG alginate (indicated in the figures) on the dry mass loss of ethylcellulose-based films upon exposure to: (a) 0.1 M HCl; (b) phosphate buffer pH 7.4.

Based on the water uptake and dry mass loss kinetics of the free, polymeric films (Figs. 2 and 4), it can be expected that the addition of a low percentage of PG alginate to ethylcellulose-based coatings can significantly accelerate the resulting drug release kinetics from coated dosage forms, e.g. pellets.

3.4. Drug release from coated pellets

Theophylline release from pellets coated with pure (plasticized) ethylcellulose (squares) and ethylcellulose/PG alginate blends (diamonds, triangles and crosses) in 0.1 M HCl as well as in phosphate buffer pH 7.4 at 10% and 20% coating level (w/w) is illustrated in Fig. 5 (curing: 2 d 60 °C). Clearly, the addition of only small amounts of PG alginate significantly accelerates drug release, irrespective of the coating level and type of release medium. This can be attributed to the significantly increased water contents and decreased dry masses of the polymeric film coatings, offering less resistance for theophylline diffusion. From a practical point of view, desired drug release rates can easily be adjusted by varying the amount of added PG alginate. Comparing Figs. 5a and c with b,d it becomes obvious that also the variation

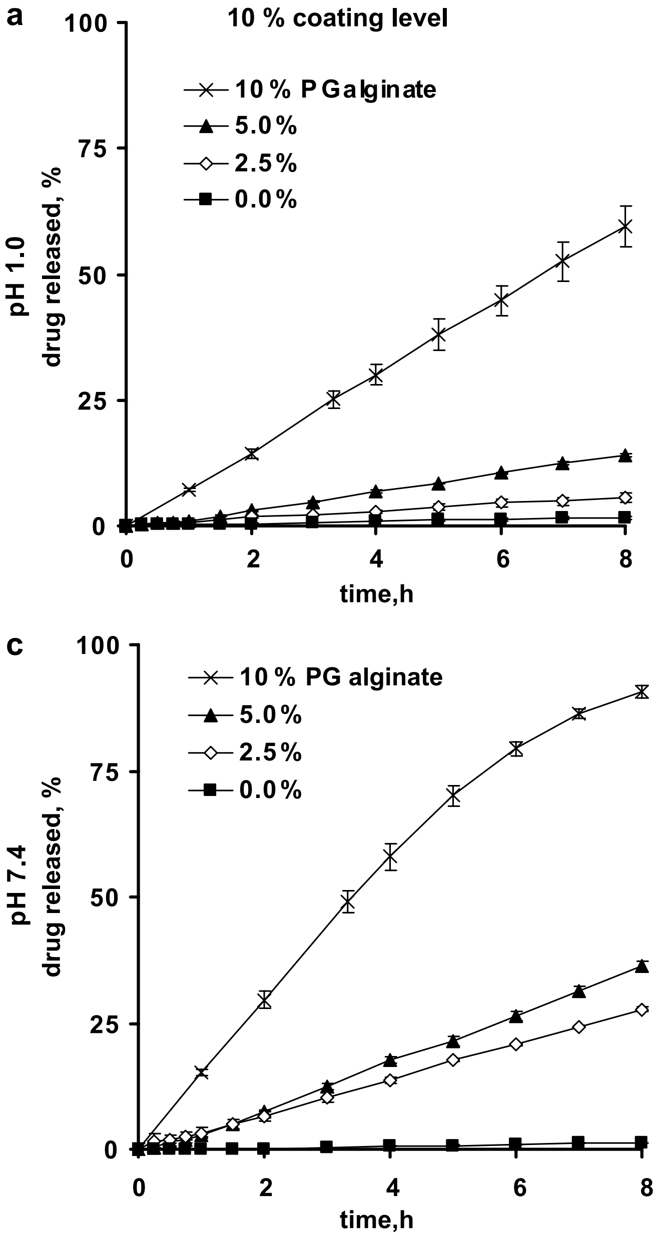

Fig. 5. Theophylline release from pellets coated with ethylcellulose containing small amounts of PG alginate (indicated in the figures) upon exposure to: (a) 0.1 M HCl, 10% coating level; (b) 0.1 M HCl, 20% coating level; (c) phosphate buffer pH 7.4, 10% coating level; (d) phosphate buffer pH 7.4, 20% coating level (curing: 2 d 60 °C).

of the coating level can be used to alter the resulting drug release patterns. As expected, the drug release rates decrease with increasing coating thickness (due to the increasing length of the diffusion pathways). In all cases, the theophylline release rate remains essentially constant during the observation period (zero order kinetics). This can be explained by the presence of an excess of drug within the core (assuring saturated theophylline solutions) and perfect sink conditions: The resulting drug concentration gradients, being the driving force for diffusion, are time-independent.

Importantly, theophylline release in phosphate buffer pH 7.4 is significantly higher than in 0.1 M HCl from all pellets coated with ethylcellulose/PG alginate blends, irrespective of the coating level (Figs. 5 and 6). Fig. 6 shows a direct comparison of theophylline release from pellets coated with 90:10 ethylcellulose/PG alginate blends at 10% and 20% coating levels (curing: 1 d 60 °C and 75% RH). The pronounced pH-dependent drug release can be attributed to the carboxylic groups in PG alginate. This type of pH-sensitive polymer coatings can be very advantageous for certain types of drugs, e.g. weak bases with pH dependent solubility: Acid burst effects can be suppressed and the decreased drug solubility after gastric emptying, due to the increase in pH, can be compensated by a simultaneous increase in the permeability of the film coatings, assuring pH-independent drug release kinetics.

3.5. Importance of curing conditions

When using aqueous polymer dispersions for film coating the selection of appropriate curing conditions is crucial: If the films are not completely formed, further polymer particle coalescence during long term storage is likely, resulting in decreasing drug release rates. Fig. 7 shows the effects of 1 and 2 d curing at 60 °C and ambient relative humidity (RH) as well as of 1 and 2 d curing at 60 °C and 75% RH (followed by 1 d at 60 °C and ambient RH for drying) on theophylline release from pellets coated with ethylcellulose films containing 10% PG alginate in 0.1 M HCl as well as in phosphate buffer pH 7.4 at 10% and 20% coating levels, respectively. Clearly, the release rate significantly decreases in all cases upon curing, indicating that the film formation is not complete right after coating. Interestingly, two "levels" of film formation seem to be reached, depending on the relative humidity the pellets were exposed to during curing (but independent of the curing time): In most cases, theophylline release was slightly slower when the curing was performed at 75% RH instead of ambient RH. This can be explained by the fact that water acts as a plasticizer for the two polymers, thus, facilitating polymer particle coalescence during curing. It indicates possible overdrying during coating which can yield partially coalesced thermostable but moisture-sensitive release profiles. The increased release profiles at higher pH are consistent with ionization of the PG alginate. At the 10% coating level, the release profiles from pellets cured at ambient and elevated RH in phosphate buffer pH 7.4 are overlapping. This can be attributed to the reduced film coating thickness (resulting in higher drug release rates than at 20% coating level) as well as to the effects of sodium dodecyl sulfate (SDS) in partially coalesced films, and the free carboxylic groups in PG alginate (resulting in higher drug release rates than in 0.1 M HCl). Under these conditions, the effect of the difference in the degree of polymer particle coalescence is outweighed by the higher permeability associated with the thinner film containing ionizable SDS and PG alginate.

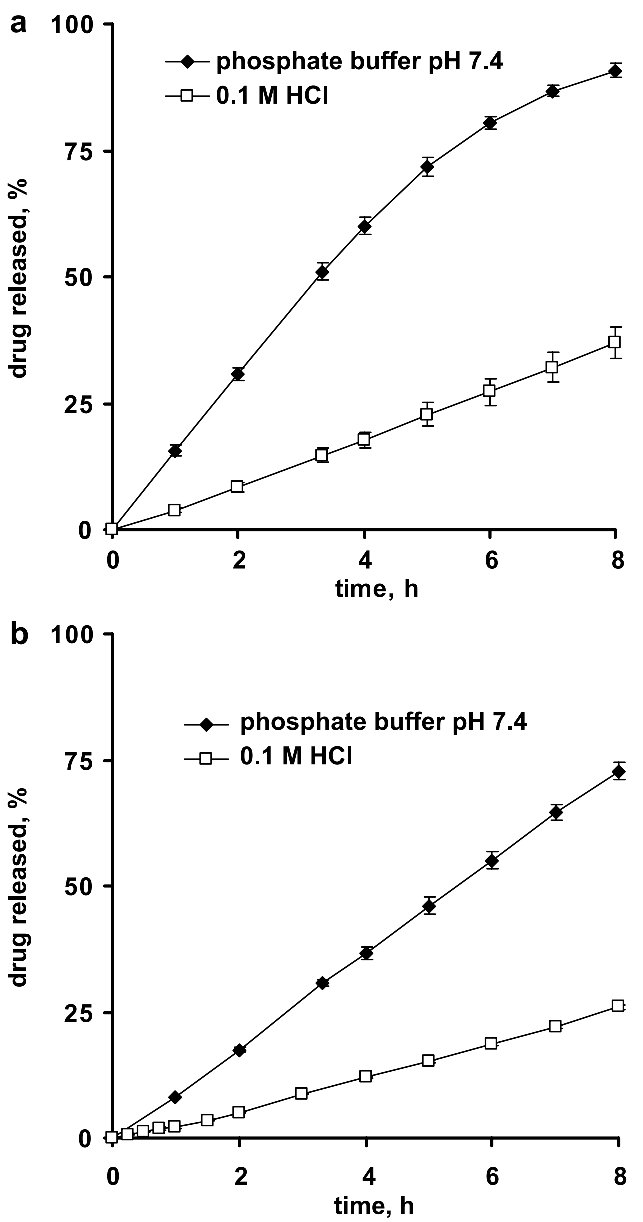

Fig. 6. Effects of the type of release medium (indicated in the figure) on theophylline release from pellets coated with ethylcellulose containing 10% PG alginate at: (a) 10% coating level; (b) 20% coating level (curing: 1 d 60 °C and 75% RH).

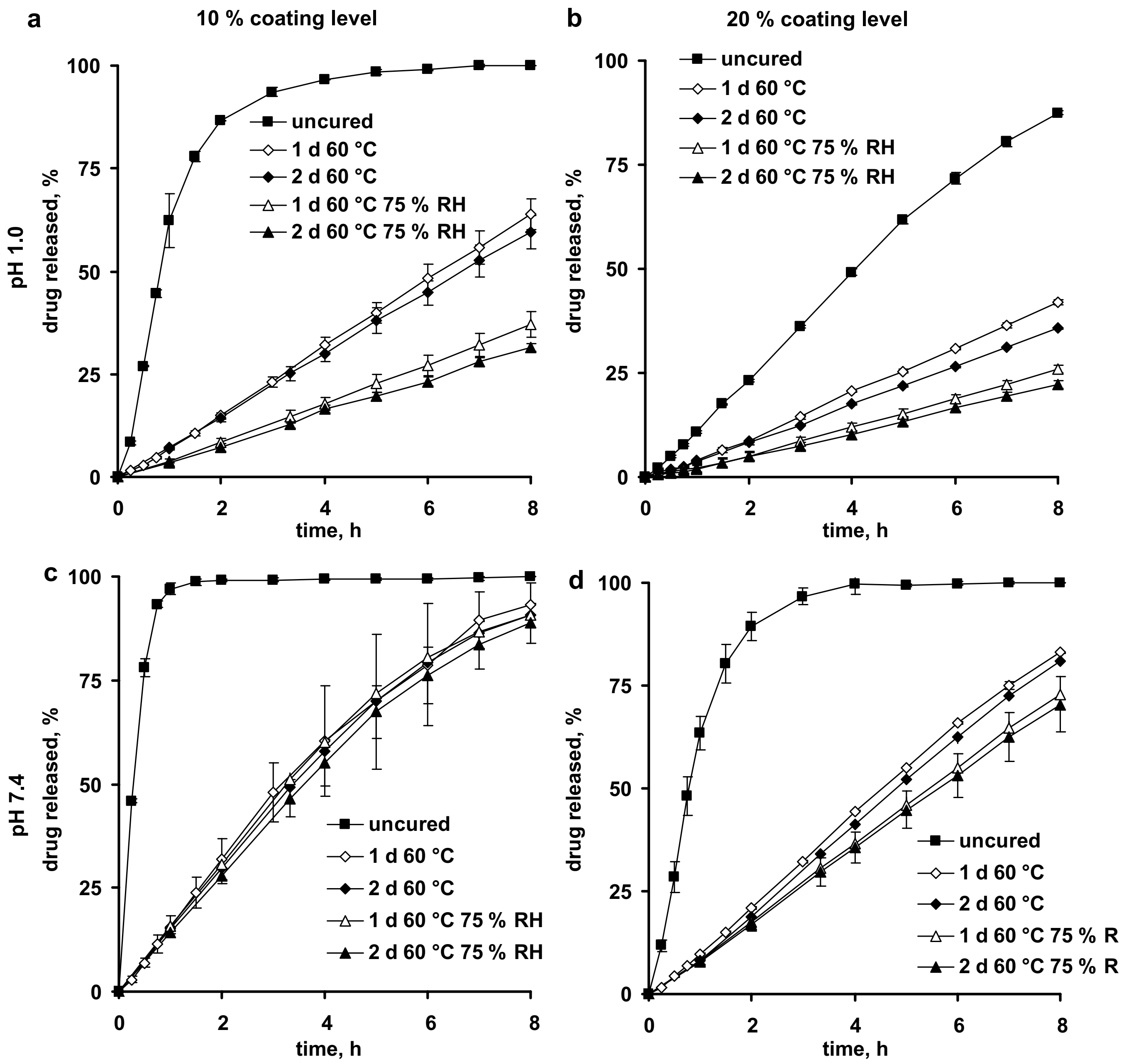

Fig. 7. Effects of the curing conditions (indicated in the figures) on theophylline release from pellets coated with ethylcellulose containing 10% PG alginate upon exposure to: (a) 0.1 M HCl, 10% coating level; (b) 0.1 M HCl, 20% coating level; (c) phosphate buffer pH 7.4, 10% coating level; (d) phosphate buffer pH 7.4, 20% coating level.

3.6. Calcium ion effects

As PG alginate contains free carboxylic groups, the permeability of polymeric films containing this polymer might be affected by the concentration of (bivalent) calcium ions in the release medium: Ca^{2+} and $–COO^-$ ions might form cross-links in the macromolecular networks, resulting in denser structures and, thus, decreased dug release rates. The Ca^{2+} ion concentration in the contents of the gastrointestinal tract can vary as a function of the food composition (e.g., milk is rich in calcium). For this reason it was interesting to see whether the addition of different amounts of Ca^{2+} ions affects the resulting drug release kinetics from ethylcellulose/PG alginate-coated pellets. As shown in Fig. 8, theophylline release in 0.1 M HCl was not altered when adding up to 50 mmol/L Ca^{2+} ions. Phosphate buffer pH 7.4 could not be used for this type of experiments, because calcium phosphate precipitates under these conditions. It has to be pointed out that most of the carboxylic groups are protonated in 0.1 M HCl. A more detailed analysis of potential calcium ion effects on drug release from this type of film coatings was beyond the scope of this study.

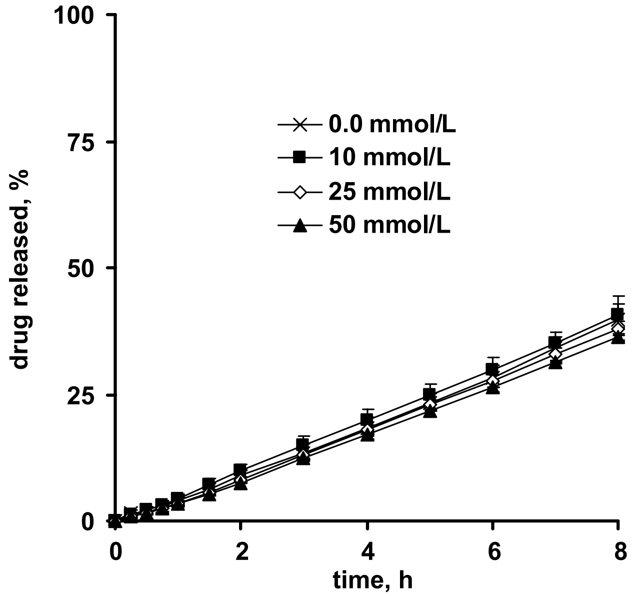

Fig. 8. Effects of the calcium ion concentration in the release medium (indicated in the diagram) on theophylline release from pellets coated with 90:10 ethylcellulose/PG alginate blends in 0.1 M HCl (20% coating level; curing = 1 d at 60 °C and ambient RH).

4. Conclusions

The obtained new knowledge can be used to facilitate the optimization of pH-sensitive film coatings for controlled drug release and to improve the safety and efficiency of the medications. Blends of PG alginate and ethylcellulose are promising coating materials, which can provide a large spectrum of coating permeabilities, triggered by the pH of the surrounding environment.

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