Carrageenan as an Efficient Drug Release Modifier for Ethylcellulose-Coated Pharmaceutical Dosage Forms

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Introduction

Pharmaceutical dosage forms (e.g., tablets, capsules) are frequently coated with polymeric films for various reasons such as to facilitate swallowing, to protect the drug during storage against moisture or oxygen, to protect the stomach from the drug, or to control the resulting drug release kinetics. In the latter case, the aim is to optimize the drug concentration-time profile at the site of action in the human body: Each drug has a characteristic "minimum effective concentration" (below which no therapeutic effects occur) and a "minimum toxic concentration" (above which toxic side effects occur). The range in between is called the therapeutic window. If the drug is administered using a conventional immediate release dosage form (e.g., standard tablet), the entire dose may be rapidly dissolved within the stomach. On absorption into the blood stream, a high maximum plasma concentration (peak) results, with the risk of toxic side effects for drugs with a narrow therapeutic window. Subsequent elimination of the drug reduces the plasma concentration, limiting the time periods with therapeutic concentrations. To overcome these restrictions, the time course of drug release from the dosage form can be controlled, using for instance polymeric drug delivery systems.[1–7] The drug can either be directly embedded within a polymeric matrix (monolithic systems),[8] or a drug depot is surrounded by a rate-limiting polymeric shell (reservoir systems).[9] Different physicochemical processes may be involved in the control of the resulting drug release rate, e.g., dissolution, diffusion, crack formation within the polymeric shell (coating), osmotic effects, and polymer swelling.[10,11]

For the preferred oral route of administration, water-insoluble film coatings are frequently used to control drug release within the gastrointestinal tract. Common water-insoluble polymers are either synthetic acrylate derivatives, such as poly(ethyl acrylate-comethyl methacrylate-cotrimethylammonioethyl methacrylate chloride) and poly(ethyl acrylate-comethyl methacrylate),[9] or ethylcellulose (a partial ester of the biomacromolecule cellulose), which is a good film former and generally regarded as nontoxic, nonallergenic, and nonirritant.[12] Ethylcellulose-based films can either be applied from organic solutions or aqueous dispersions.[13] The use of aqueous systems is advantageous because of: (i) environmental concerns, (ii) the risk of toxicity of organic solvent residues for the patient, and (iii) the reduced processing times (aqueous dispersions generally contain higher polymer amounts than organic solutions for film coating because their viscosity is lower; the formulations need to be sprayable). However, if pharmaceutical dosage forms are surrounded by a continuous ethylcellulose film, the resulting drug release rates may be too low to allow sufficient drug release within the gastrointestinal transit time.

To overcome this restriction, the addition of hydroxypropyl methylcellulose (HPMC) to the film coatings has been proposed.[14,15] However, HPMC destabilizes colloidal ethylcel-

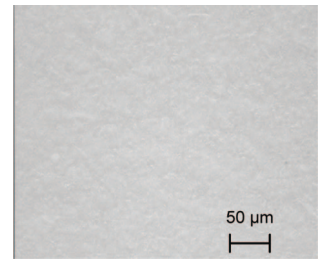

Figure 1. Microscopic picture of a 90:10 Aquacoat ECD (a colloidal aqueous ethylcellulose dispersion):carrageenan blend after 24 h stirring at room temperature.

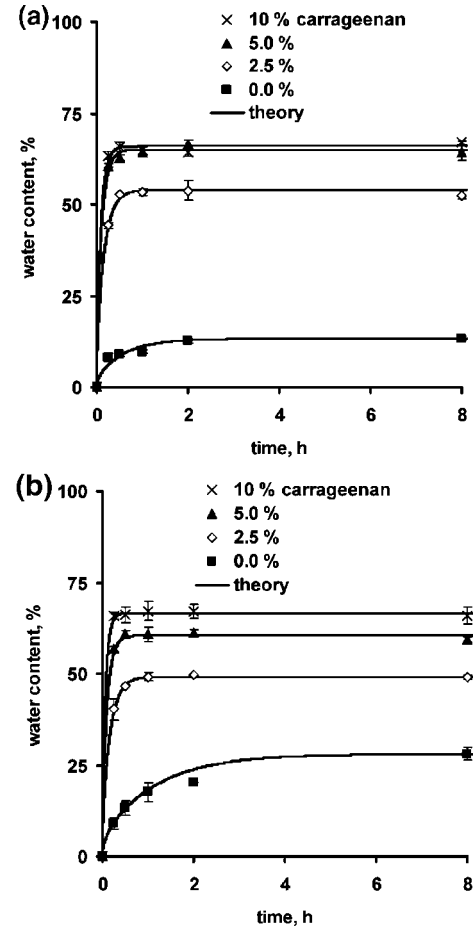

Figure 2. Water uptake behavior of ethylcellulose-based films containing different amounts of carrageenan (indicated in the figures) upon exposure to: (a) 0.1 M HCl; (b) phosphate buffer pH 7.4. The symbols represent the experimentally measured values, the curves the fitted theory (eq 6).

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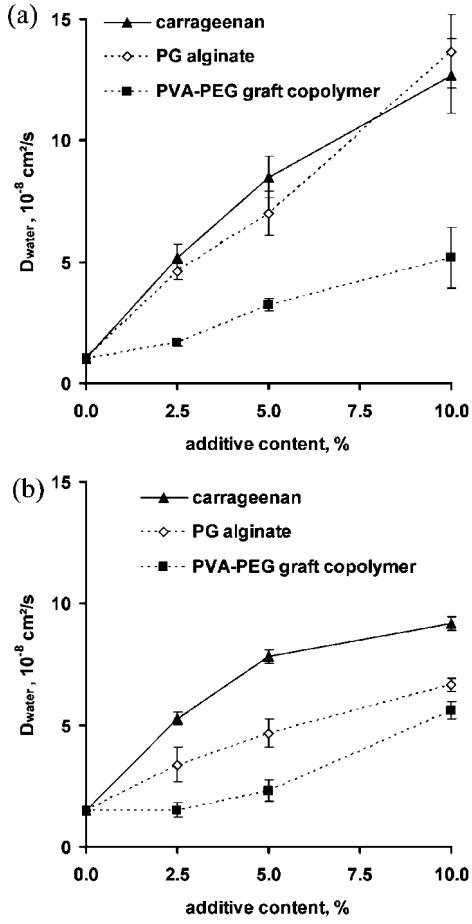

Figure 3. Water diffusivity in ethylcellulose-based films upon exposure to: (a) 0.1 M HCl; (b) phosphate buffer pH 7.4. Effects of the type and amount of additive (the results obtained with PG alginate and PVA-PEG graft copolymer are reproduced from refs 18, 19 for reasons of comparison).

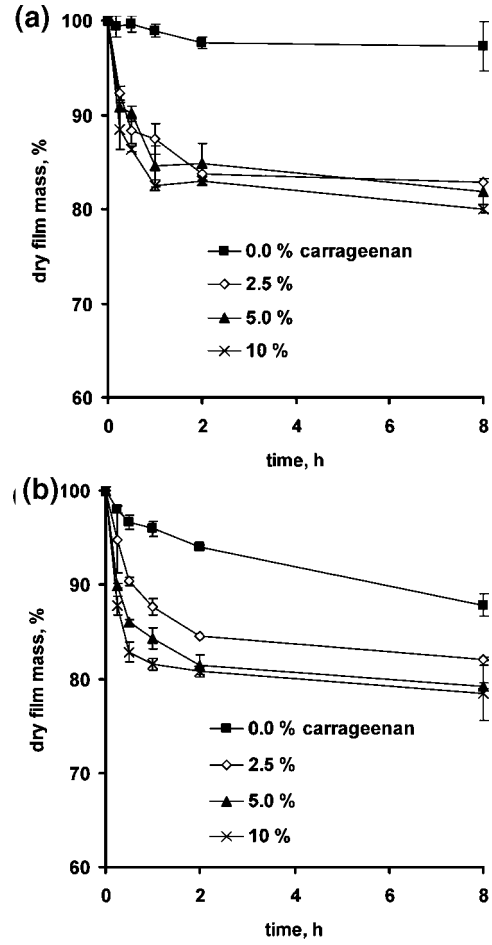

Figure 4. Effects of the addition of small amounts of carrageenan (indicated in the figures) on the dry mass loss of ethylcellulose-based films upon exposure to: (a) 0.1 M HCl; (b) phosphate buffer pH 7.4.

lulose dispersions,[16,17] resulting in flocculation and inhomogeneous film formation. It has recently been shown that synthetic poly(vinylalcohol)-poly(ethyleneglycol) graft copolymer is an efficient drug release modifier for ethylcellulose-based film coatings, which does not cause flocculation in the coating formulations.[18] But this is a synthetic polymer. Also, propylene glycol alginate has been shown to be suitable, but with pH-dependent drug release kinetics.[19] Thus, the drug release rate depends on the location within the gastrointestinal tract.

The aim of the present study was to identify a biomacromolecule that allows effective pH-independent modification of drug release from ethylcellulose-coated pharmaceutical dosage forms without causing flocculation of the coating dispersion.

Experimental Section

Materials. Theophylline anhydrous (BASF, Ludwigshafen, Germany), theophylline pellets (70% drug content; FMC, Philadelphia, PA), aqueous ethylcellulose dispersion (Aquacoat ECD; FMC), λ carrageenan (Viscarin GP 209; FMC), propylene glycol alginate (PG alginate, Protanal ester SD-LB; FMC), poly(vinyl alcohol)-poly(ethylene glycol) graft copolymer (PVA-PEG graft copolymer, Kollicoat IR; BASF, Ludwigshafen, Germany), triethyl citrate (TEC; Morflex, Greensboro, NC).

Preparation of Thin, Free Films. Thin, polymeric films were prepared by casting aqueous dispersions of ethylcellulose (Aquacoat ECD), plasticized with 25% w/w (based on the polymer mass) triethyl citrate (being listed in the Food Chemical Codex and included in the FDA Inactive Ingredients Guide). The systems were stirred overnight to allow for plasticization (magnetic stirrer, 600 rpm, room temperature). Optionally, carrageenan was added (as aqueous solution; the blended systems were stirred for 30 min prior to casting). The respective aqueous dispersions were cast onto Teflon plates and subsequently dried in an oven (for 24 h at 60 °C). The following ethylcellulose:carrageenan blend ratios were investigated: 90:10, 95:5, 97.5:2.5, and 100:0 (w/w). Drug-containing films were prepared similarly by adding theophylline to the aqueous dispersions. In all cases, the drug loading (0.25% w/w, based on the total dry polymer mass) was below the solubility of theophylline within the polymeric systems (clear films, monolithic solutions). The thickness of the films (around 200 μm) was measured using a thickness gauge (Minitest 600; Erichsen, Hemer, Germany).

Evaluation of the Stability of the Aqueous Dispersions. The stability of the aqueous dispersions was evaluated after 24 h stirring (magnetic stirrer, 600 rpm, room temperature) by visual observation with a light microscope (Nikon Eclipse E400; Elvetec, Templemars, France) equipped with a Sony camera (Hyper HAD model SSC-DC38DP; Elvetec, Templemars, France) and the Optimas 6.0 software (Media Cybernetics, Silver Spring, MD).

Water Uptake and Dry Mass Loss of Thin, Free Films. Thin, polymeric films were cut into pieces of 2 cm × 2 cm, which were placed into 50 mL plastic flasks filled with 40 mL of preheated 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 predetermined time intervals, samples were withdrawn, accurately weighed [wet mass (t)] and dried

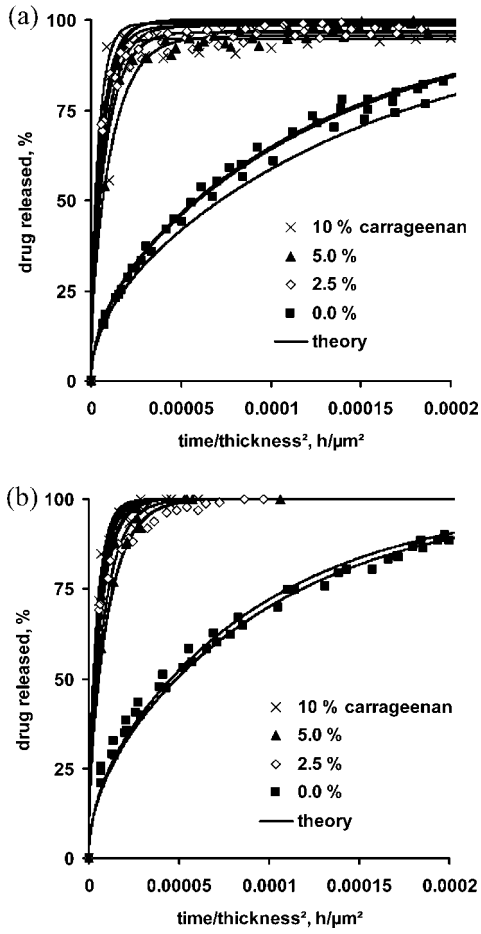

Figure 5. Theophylline release from ethylcellulose-based films upon exposure to: (a) 0.1 M HCl; (b) phosphate buffer pH 7.4. Effects of the addition of small amounts of carrageenan (indicated in the figures). The results are normalized to the films' thickness. The symbols represent the experimentally measured values, the curves the fitted theory (eq 6).

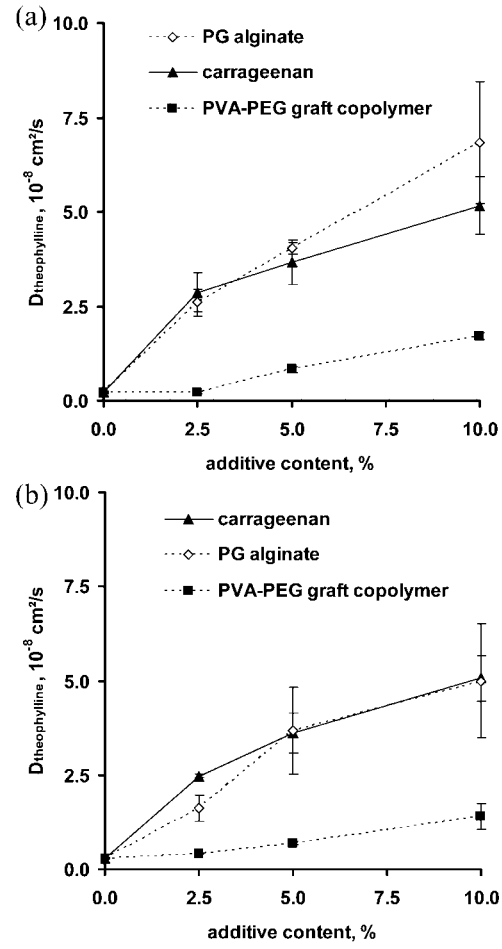

Figure 6. Apparent diffusion coefficient of theophylline in ethylcellulose-based films upon exposure to (a) 0.1 M HCl; (b) phosphate buffer pH 7.4. Effects of the type and amount of additive (the results obtained with PVA-PEG graft copolymer are reproduced from ref 18 for reasons of comparison).

to constant mass at 60 °C [dry mass (t)]. The water content (%) and dry film mass (%) at time t were calculated as follows:

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

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

Drug Release from Thin, Free Films. Drug release from thin, drug-containing films was measured by placing film pieces (2 cm × 2 cm) into 50 mL plastic flasks filled with 40 mL of preheated 0.1 M HCl or phosphate buffer pH 7.4 (USP XXIX), followed by horizontal shaking for 80 h (37 °C, 80 rpm; GFL 3033; $n = 3$). To avoid film folding and/or floating during the experiments (resulting in potential variations of the surface area exposed to the release medium), the films were fixed within the plastic flasks. At predetermined time intervals, 3 mL samples were withdrawn (replaced with fresh medium) and analyzed UV spectrophotometrically ($\lambda = 271$ nm; Anthelie Advanced; Secomam, Domont, France).

Preparation of Coated Pellets. Theophylline pellets (70% w/w drug loading) were coated with aqueous ethylcellulose dispersion (Aquacoat ECD) containing various levels of carrageenan (for details on the preparation procedure, see Preparation of Thin, Free Films) in a fluidized bed coater equipped with a Wurster insert (Strea 1; Niro Inc., Aeromatic-Fielder AG, Bubendorf, Switzerland). 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 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).

Drug Release from Coated Pellets. Theophylline release from the pellets was measured in 0.1 M HCl 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 predetermined time intervals, 3 mL samples were withdrawn and analyzed UV spectrophotometrically ($\lambda = 271$ nm; Anthelie Advanced).

Results and Discussion

Compatibility of the Coating Components. When adding a new compound to an aqueous colloidal polymer dispersion used for film coating, the stability of the novel system needs to be evaluated. For instance, bridging effects can lead to polymer particle agglomeration and thus unstable coating formulations. In practice, this can lead to inconsistent or inhomogeneous film formation, resulting in poorly reproducible drug release profiles. Figure 1 shows an optical microscopy picture of a 90:10 blends of Aquacoat ECD (an aqueous ethylcellulose dispersion) and carrageenan after 24 h stirring at room temperature. Clearly, no signs of polymer particle agglomeration or other incompatibilities are visible. This is true for all the investigated blends

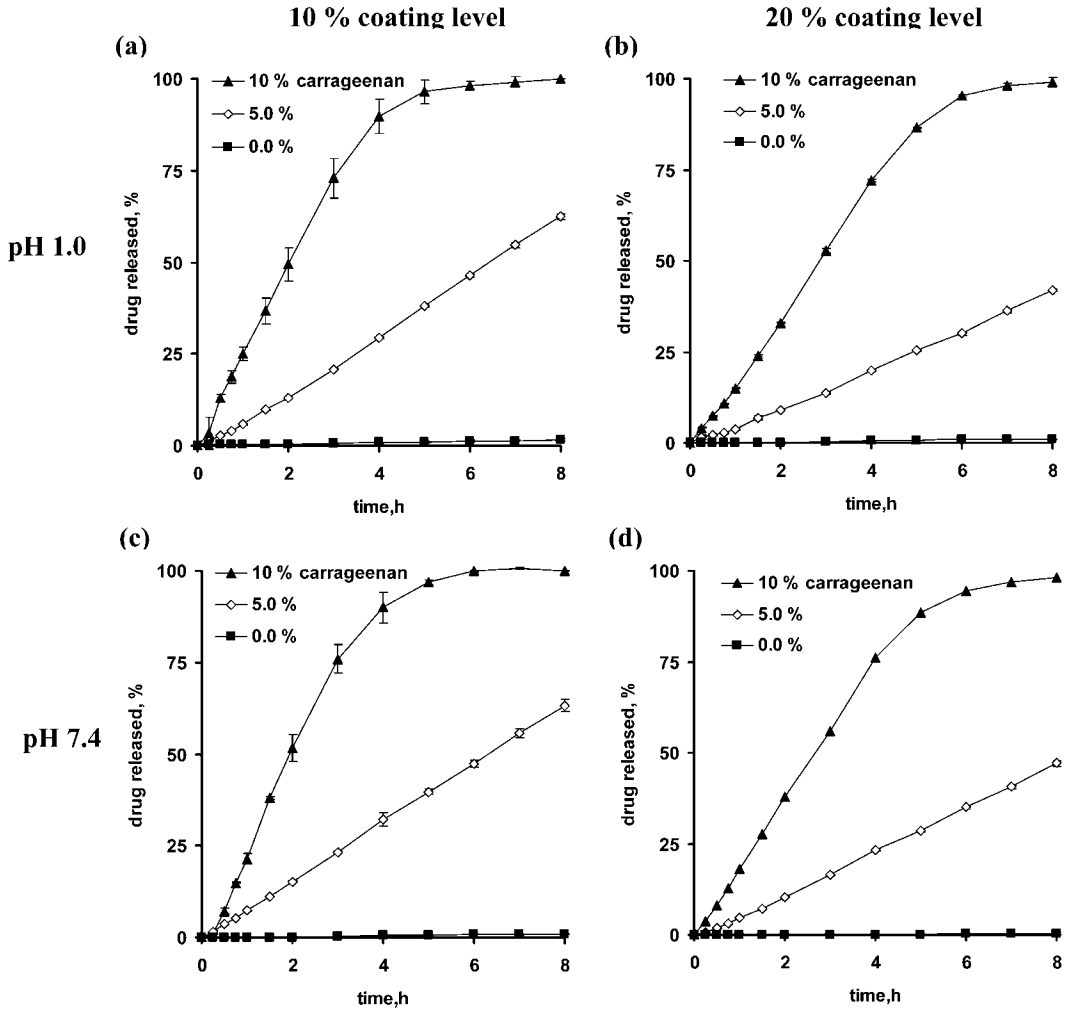

Figure 7. Theophylline release from pellets coated with ethylcellulose containing small amounts of carrageenan (indicated in the figures) upon exposure to: (a) 0.1 M HCl, 10% coating level; (b) 0.1 M HCl, 20% coating level; (c) phosphate buffer pH 7.4, 10% coating level; (d) phosphate buffer pH 7.4, 20% coating level (curing = 1 d at 60 °C and ambient RH).

ratios (data not shown). Importantly, derivatives of other biomacromolecules (e.g., hydroxypropyl methylcellulose) lead to significant flocculation.[16,17] Thus, carrageenan fulfills the first prerequisite for an efficient release modifier for ethylcellulose film coatings: It is compatible with the aqueous coating formulation. Next, it is important to see whether small amounts of carrageenan are able to effectively alter the physicochemical properties of ethylcellulose films.

Water Uptake of Thin, Free Films. As it can be seen in Figure 2, the rate and extent of water uptake in pure (plasticized) ethylcellulose films (filled squares) is limited in simulated gastric as well as in simulated intestinal fluids (0.1 M HCl and phosphate buffer pH 7.4, respectively). This can at least partially explain why ethylcellulose is poorly permeable for many drugs: with increasing water content the mobility of the macromolecules increases and thus the free volume available for drug diffusion increases. Importantly, both the rate and extent of water uptake in these films tremendously increases with only a few percent of carrageenan, irrespective of the type of release medium (Figure 2). This clearly indicates the ability of this biomacromolecule to significantly alter the properties of ethylcellulose film coatings. For instance, the addition of only 5% (w/w) carrageenan results in a water content of around 65% (instead of 13%) upon film swelling in 0.1 M HCl. Thus, more than half of the film consists of water. This can be expected to significantly affect the mobility of drug molecules in these polymeric networks and thus the resulting drug release kinetics from coated pharmaceutical dosage forms.

To better understand which mass transport phenomena (e.g., diffusion, polymer chain relaxation, dissolution) are of importance once the polymeric films are exposed to the release media, the experimentally measured water uptake kinetics (symbols in Figure 2) were analyzed using an appropriate analytical solution of Fick's second law. The mathematical model quantifies diffusional mass transport in one dimension into a plane sheet:[20]

$$\frac{\partial c}{\partial t} = D \cdot \frac{\partial^2 c}{\partial x^2} \qquad (3)$$

where c denotes the water concentration within the polymeric system, being a function of time t and position x; D represents the apparent diffusion coefficient of water.

The model takes into account that the films are initially dry:

$$t = 0 \qquad c = 0 \qquad -L \le x \le +L \qquad (4)$$

(with L being the half-thickness of the films) and that edge effects are negligible (because the films' surface is very large in relation their thickness: ~8 cm^2 versus ~200 μm). Furthermore, the theory considers that the water concentration in the

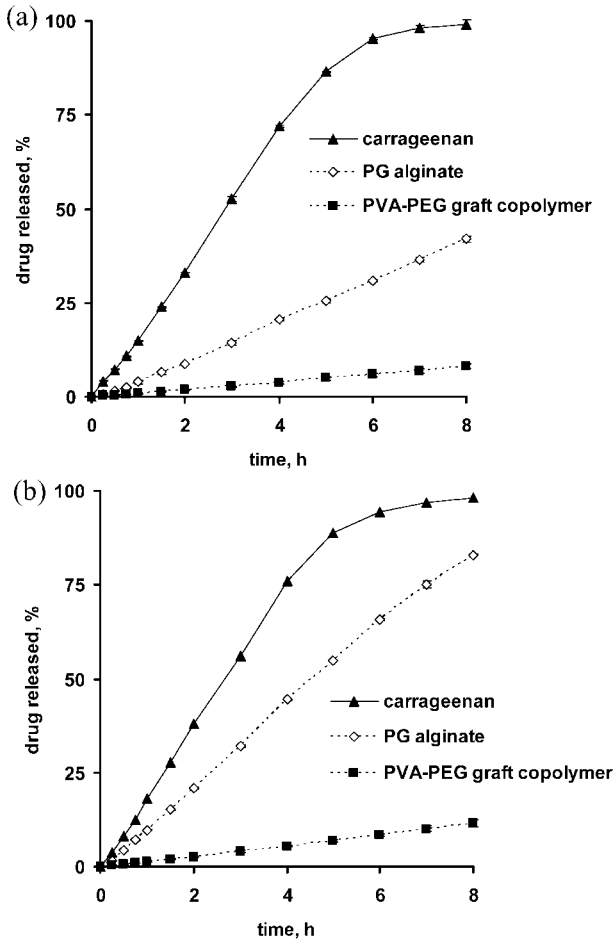

Figure 8. Importance of the type of additive (indicated in the figures) on theophylline release from pellets coated with ethylcellulose containing 10% carrageenan, PG alginate, or PVA-PEG graft copolymer upon exposure to: (a) 0.1 M HCl; (b) phosphate buffer pH 7.4 (20% coating level; curing = 1 d at 60 °C and ambient RH) (the results obtained with PVA-PEG graft copolymer and PG alginate are reproduced from refs 18, 19 for reasons of comparison).

bulk fluids (0.1 M HCl or phosphate buffer pH 7.4) remains constant throughout the experiments:

$$t > 0 \qquad c = \text{constant} \qquad x = +/-L \qquad (5)$$

This initial value problem (eqs 3−5) can be solved using the method of Laplace transform, leading to:[21,22]

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

where M_t and M_∞ are the absolute cumulative amounts of water taken up at time t and $t = \infty$, respectively, and n is a dummy variable running from 0 to ∞.

As it can be seen in Figure 2, fitting this equation to the experimentally measured water uptake kinetics results in good agreement between theory (curves) and experiment (symbols) in all cases. This clearly indicates that the water influx into the film coatings is predominantly controlled by pure diffusion. Importantly, the addition of small amounts of carrageenan (leading to a significant increase in the rates and extents of water uptake) does not alter the relative importance of the involved mass transport phenomena. If polymer chain relaxation was the dominant mass transport mechanism, zero-order uptake kinetics would have been observed under the given experimental conditions. If both polymer chain relaxation and water diffusion simultaneously governed the water influx kinetics, significant deviations between theory and experiment would have been observed in Figure 2.

On the basis of these calculations the apparent diffusion coefficient of water in the polymeric film coatings can be determined. Figure 3 shows the water diffusivity in ethylcellulose films upon exposure to simulated gastric and intestinal fluids as a function of the carrageenan content (filled triangles). Clearly, the water permeability significantly increases upon addition of only 2.5–10% (w/w) carrageenan. This can be explained by the high hydrophilicity of this biomacromolecule. For comparison, the results obtained with two other polymers, poly(vinyl alcohol)-poly(ethylene glycol) graft copolymer (PVA-PEG graft copolymer) and propylene glycol alginate (PG alginate) are also shown in Figure 3 (filled squares and open diamonds, respectively). Importantly, the synthetic copolymer was much less efficient in altering the ethylcellulose film properties than the two biomacromolecules. Thus, much smaller amounts of the latter are necessary to achieve equivalent effects. In contrast to PG alginate, carrageenan-containing films have relatively pH-independent properties, e.g., drug permeabilities.[19] pH changes within the human gastrointestinal tract can be expected to lead to significant alterations in release from pH-dependent film coatings. Such "environmentally triggered" coating properties can be advantageous for certain types of drugs. However, for the large majority of therapeutic treatments, dosage forms with pH-independent drug release kinetics are desirable. Thus, on the basis of the water diffusivities shown in Figure 3, carrageenan can be expected to be the most efficient pH-independent drug release modifier for ethylcellulose film coatings.

Dry Mass Loss of Thin, Free Films. In addition to water uptake, the kinetics of dry mass loss of polymeric film coatings are also of fundamental importance to control drug release from pharmaceutical dosage forms. If major parts of the films are water-soluble and leach into the surrounding bulk fluid, the density of the polymeric network decreases, thereby reducing the barrier to drug diffusion. Figure 4 illustrates the experimentally determined dry mass loss of pure (plasticized) ethylcellulose films (filled squares) as well as of ethylcellulose: carrageenan films (open diamonds, filled triangles, and crosses) upon exposure to simulated gastric and intestinal fluids. Clearly, the dry mass loss of pure (plasticized) ethylcellulose films is limited due to the water-insolubility of this compound. The observed slight mass loss is due to leaching of the water-soluble plasticizer triethyl citrate, which is limited by the water-insoluble polymer [the films contain 25% (w/w) water-soluble plasticizer referred to the ethylcellulose mass, thus the dry mass could theoretically decrease down to 80%, referred to the total film mass]. The significant increase in the dry mass loss upon addition of as little as 2.5% (w/w) water-soluble carrageenan can be attributed to the facilitated leaching of the water-soluble plasticizer. As shown in Figure 2, the carrageenan-containing films are composed of at least 50% water upon swelling. This high water content facilitates the diffusion of water-soluble substances within the polymeric networks. Importantly, the increase in dry mass loss upon carrageenan addition is similar to that observed with PG alginate[19] and much more pronounced than that observed with (the synthetic) PVA-PEG graft copolymer.[18]

Both phenomena, the significant increase in the rate and extent of water uptake as well as the increase in the dry mass loss CDV

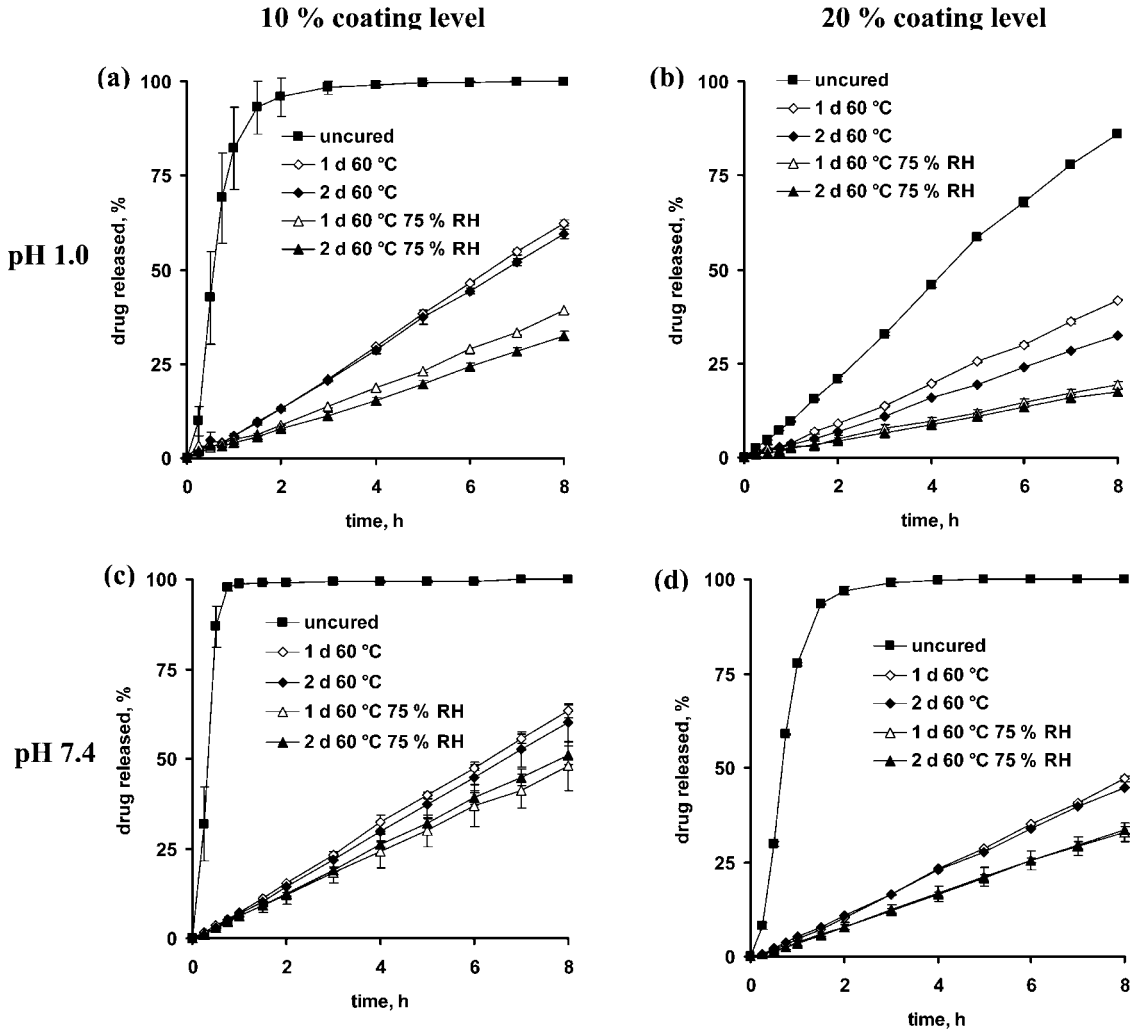

Figure 9. Effects of the curing conditions (indicated in the figures) on theophylline release from pellets coated with ethylcellulose containing 5% carrageenan upon exposure to: (a) 0.1 M HCl, 10% coating level; (b) 0.1 M HCl, 20% coating level; (c) phosphate buffer pH 7.4, 10% coating level; (d) phosphate buffer pH 7.4, 20% coating level.

the polymeric films upon addition of only minor amounts of carrageenan to ethylcellulose films, indicate that this biomacromolecule is a very promising drug release modifier for pharmaceutical dosage forms.

Drug Release from Thin, Free Films. Figure 5 shows the experimentally measured release of the model drug theophylline from thin ethylcellulose films (filled squares). To account for slight differences in the films' thickness ($2L$) (all films were prepared in triplicate), the time (t) has been normalized with respect to this parameter: t was divided by L^2. This type of normalization is possible because the release of the drug can quantitatively be described by the same analytical solution of Fick's law of diffusion as used for the description of the water uptake kinetics (eq 6). But in this case, the direction of the mass transport is reversed: out of the films into the bulk fluid. Here, M_t and M_∞ represent the absolute cumulative amounts of drug released at time t and $t = \infty$, respectively; D denotes the apparent diffusion coefficient of the drug in the polymeric system. The initial condition takes into account that the drug is homogeneously and molecularly dispersed within the device (clear films). The boundary conditions are based on negligible edge effects (large surface area with respect to the films' thickness) and perfect sink conditions (the drug concentration within the release media remains below 10% of its solubility and thus does not hinder further drug release by saturation effects). The fittings of this theory to the experimentally measured drug release kinetics are shown in Figure 5 (curves). Clearly, good agreement between theory and experiment was obtained, indicating that theophylline diffusion with the ethylcellulose films is the dominant mass transport phenomenon.

Importantly, the addition of only 2.5–10% (w/w) carrageenan to the ethylcellulose films tremendously accelerates drug release, irrespective of the type of release medium (Figure 5). This can be attributed to the increase in the water content and decrease in the dry mass of the films (Figures 2 and 4), resulting in increased macromolecular mobilities and thus increased free volumes available for drug diffusion.

Interestingly, the presence of the hydrophilic biomacromolecule carrageenan does not alter the dominant mass transport mechanism: The good agreement between theory (curves) and experiment (symbols) in all cases indicates that theophylline diffusion remains the rate-limiting step, irrespective of the films' composition and type of release medium. On the basis of these calculations, the apparent diffusivity of the drug within the polymeric systems could quantitatively be determined for all carrageenan contents (Figure 6, filled triangles). Clearly, the diffusivity of theophylline in the films significantly increases when adding only small amounts of carrageenan. Importantly, this biomacromolecule is a much more efficient drug release modifier than the synthetic PVA-PEG graft copolymer (filled squares). The ability of carrageenan to alter the drug perm

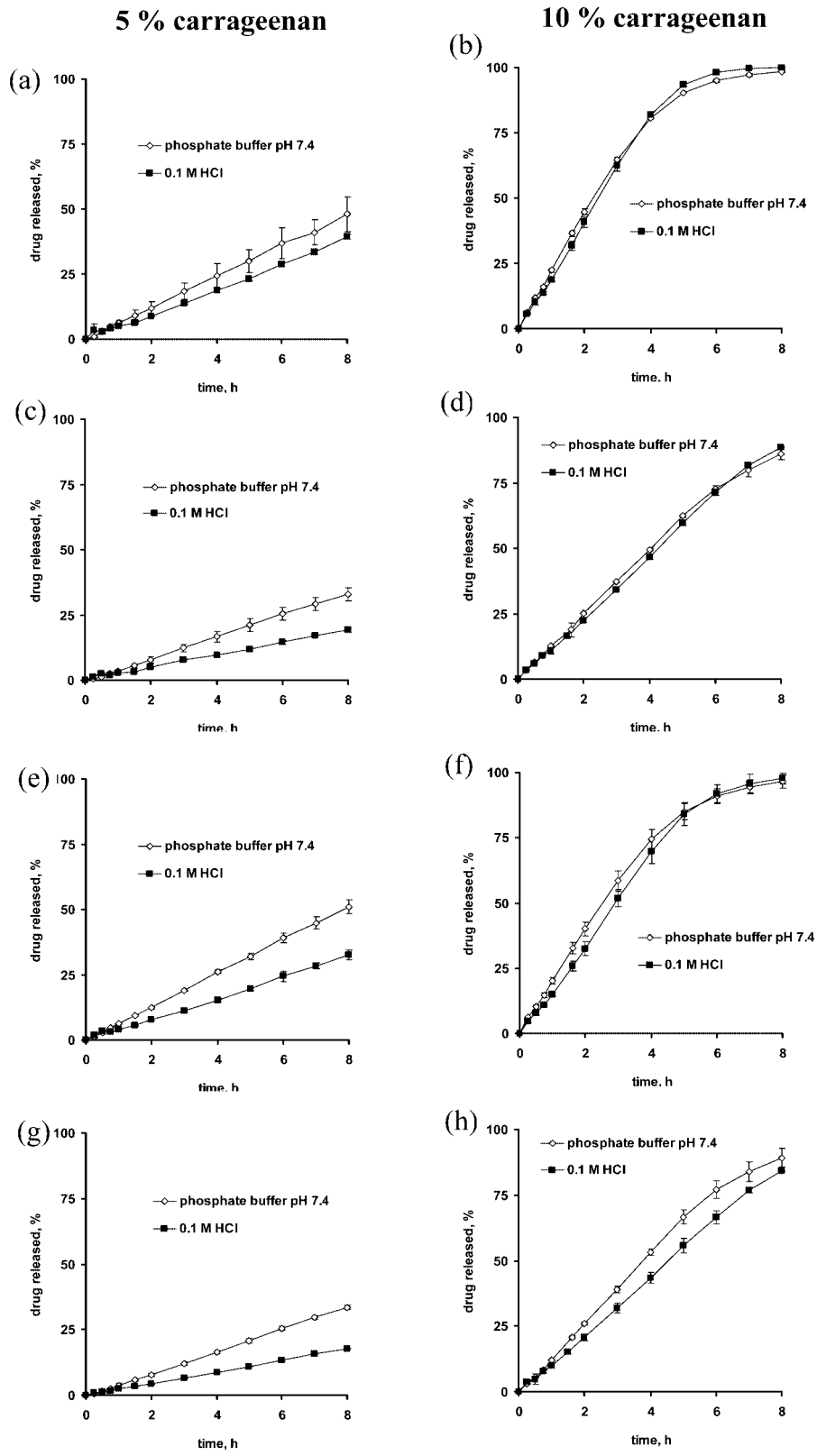

Figure 10. Effects of the type of the release medium on theophylline release from pellets coated with ethylcellulose containing 5 or 10% carrageenan (as indicated): (a,b) 10% coating level, curing = 1 d 60 °C and 75% RH; (c,d) 20% coating level, curing = 1 d 60 °C and 75% RH; (e,f) 10% coating level, curing = 2 d 60 °C and 75% RH; (g,h) 20% coating level, curing = 2 d 60 °C and 75% RH.

ability of ethylcellulose films is similar to that of PG alginate but pH-independent.[19]

On the basis of these results, it can be expected that carrageenan is a very potent biomacromolecule, allowing easy adjustment of drug release kinetics from ethylcellulose-coated pharmaceutical dosage forms.

Drug Release from Coated Pellets. Figure 7 illustrates the release of the model drug theophylline from pellets coated with pure (plasticized) ethylcellulose and with ethylcellulose:carrageenan blends in simulated gastric and intestinal fluids at 10 and 20% (w/w) coating level, respectively. Clearly, the presence of only small amounts of carrageenan effectively increases the

resulting drug release rates, irrespective of the type of release medium and coating level. In practice, desired release profiles (leading to optimal therapeutic effects) can easily be provided by adjusting the carrageenan content.

For reasons of comparison, theophylline release from pellets coated with 90% ethylcellulose and 10% carrageenan, PVA-PEG graft copolymer or PG alginate in 0.1 M HCl and phosphate buffer pH 7.4 is shown in Figure 8 (coating level = 20%). Clearly, carrageenan is the most efficient drug release modifier. This can be attributed to the more pronounced increase in the water uptake rate and extent and in the dry mass loss of the film coatings. Thus, to provide similar drug release rates, lower amounts of this additive are required.

For long-term stability during storage, it is decisive that there are no major structural changes within the polymeric film coatings. For example, if the film formation is not complete after coating, further polymer particle coalescence during storage can lead to decreased drug permeabilities and thus decreased drug release rates.[23] To avoid/minimize this phenomenon, a thermal treatment (called curing) is generally performed after coating. The idea is that, at elevated temperature, the mobility of the macromolecules is increased and thus particle coalescence facilitated. In some cases, curing is also conducted at elevated relative humidity (RH) to facilitate film formation: coalescence depends on the capillary pressure of the interstitial water,[24] and water also acts as a plasticizer for many coating polymers and thus decreases the glass transition temperature of the polymeric particles. This leads to an increased macromolecular mobility and, consequently, facilitated polymer particle coalescence. Figure 9 shows the release of the model drug theophylline from pellets coated with ethylcellulose containing 5% carrageenan, at 10 and 20% coating level, in simulated gastric and intestinal fluids, as a function of the curing conditions: 1 or 2 days at 60 °C and ambient RH, or 1 or 2 days at 60 °C and 75% RH (followed by 1 day at 60 °C and ambient RH for drying). Drug release from uncured pellets (filled squares) is illustrated for comparison. Clearly, a curing step is required in all cases to allow appropriate film formation (polymer particle coalescence). Interestingly, two types of release profiles were observed, dependent on whether curing was conducted at ambient or elevated RH. The lower drug release rates observed after curing at elevated RH suggest a higher degree of polymer particle coalescence. This may reflect potential overdrying of the pseudolatex during coating (which hinders coalescence by removing the driving force of capillary pressure of the interstitial water[24]). The absence of any change between samples cured at 60 °C and ambient RH for 1 and 2 days is a false stability end point if this release profile can be affected by elevated humidity storage. On the basis of these results, it can be concluded that curing must be validated with respect to the effects of both elevated temperature and humidity, not just elevated temperature alone.

Effects of pH on Drug Release. It is well-known that the pH−time profile experienced by a pharmaceutical dosage form within the different segments of the human gastrointestinal tract (e.g., stomach, small and large intestine) can significantly vary from patient to patient and even within the same patient (e.g., due to food effects or diseases that alter the motility of the gastrointestinal tract). The effects of the pH of the release medium on theophylline release from ethylcellulose:carrageenan coated pellets in simulated gastric and intestinal fluids (0.1 M HCl and phosphate buffer pH 7.4) are shown in Figure 10. As it can be seen, the release rates were higher in phosphate buffer for film coatings containing 5% (w/w) carrageenan, whereas there was no significant difference in the release rates at 10% carrageenan content, irrespective of the coating level and curing time. Wesseling and Bodmeier[25] reported a similar pH dependency for uncured Aquacoat ECD coatings, which they attributed to the pH-dependent charge of sodium dodecyl sulfate affecting the water penetration rate into a partially coalesced polymeric system. At the higher 10% carrageenan level, the film coating is sufficiently hydrophilic (Figure 2) to avoid this pH dependency.

Conclusions

The biomacromolecule carrageenan is a highly efficient release modifier for ethylcellulose-coated pharmaceutical dosage forms. The addition of only small amounts allows effective adjustment of drug release kinetics for optimal therapeutic effects. Importantly, carrageenan does not cause flocculation of the coating dispersions, and long-term stability during storage seems to be achievable upon appropriate curing.

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References and Notes

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