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Research paper

Aqueous HPMCAS coatings: Effects of formulation and processing parameters on drug release and mass transport mechanisms

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Abstract

The major aim of the present work was to study the effects of various formulation and processing parameters on the resulting drug release kinetics from theophylline matrix pellets coated with aqueous hydroxypropyl methylcellulose acetate succinate (HPMCAS) dispersions. The plasticizer content, coating level and curing conditions significantly affected the release patterns in 0.1 M HCl, whereas no major effects were observed in phosphate buffer, pH 7.4. Due to the significant size of the HPMCAS particles (being in the micrometer range), their coalescence was particularly crucial and not complete upon coating. Consequently, at low coating levels continuous water-filled channels connected the bead cores with the release medium through which the drug could rapidly diffuse, resulting in high release rates even at low pH. In contrast, at high coating levels such continuous connections did not exist (due to the increased number of polymer particle layers), and drug release was controlled by diffusion through the macromolecular network resulting in much lower release rates in 0.1 M HCl. Importantly, pellet curing at elevated temperature and ambient relative humidity or exposure to elevated relative humidity at room temperature did not significantly alter the microstructure of the coatings, leading to only slightly decreased drug release rates. In contrast, pellet curing at elevated temperature combined with elevated relative humidity induced significant further polymer particle coalescence, resulting in a change of the underlying drug release mechanism and significantly reduced drug release rates.

Keywords: HPMCAS; Aqueous coating; Curing; Pellets; Enteric coating

1. Introduction

The use of aqueous polymer dispersions instead of organic polymer solutions for the coating of solid dosage forms offers various advantages, such as reduced toxicity and shortened processing times. However, the film formation process is fundamentally different and the coalescence of the polymer particles is a critical step. To avoid incomplete film formation and instability during storage, the type and amount of added plasticizer as well as the curing conditions must be carefully selected [1–4]. For example, Amighi and Moes [2] showed that theophylline release from pellets coated with aqueous Eudragit® RS dispersions decreased upon storage. This could be attributed to further gradual coalescence of the latex particles. Importantly, film formation during coating and curing could significantly be enhanced by increasing the plasticizer level. Liu and Williams III [5–8] studied the effects of different formulation and processing parameters of aqueous cellulose acetate phthalate-based coatings on the resulting film properties and drug release kinetics. Adequate curing was shown to be a very efficient tool to induce further film formation and, thus, improve storage stability.

The size of the polymer particles in the aqueous coating dispersions is known to be of major importance for the film

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formation process. With increasing particle dimension coalescence becomes more and more difficult [9–11]. For example, Eckersley and Rudin [10] found a significant increase in the minimum film formation temperature (MFT) of methyl methacrylate/butyl acrylate copolymers with increasing particle size. Thoma and Bechtold [12] studied pancreatin release from pellets coated with aqueous hydroxypropyl methylcellulose phthalate dispersions. The film formation was found to be enhanced with decreasing polymer particle size. Consequently, lower coating levels were required to provide enteric properties when using aqueous dispersions containing small particles. Nakagami et al. [13] compared aqueous ethyl cellulose latexes with aqueous dispersions of micronized ethyl cellulose powder (particle size in the nano- versus micrometer range). Much less plasticizer was required to assure film formation with the latexes.

Hydroxypropyl methylcellulose acetate succinate (HPMCAS) is an enteric polymer which can be used for the preparation of matrix tablets as well as for film coating. Aqoat® is a commercially available, redispersible HPMCAS powder with a relatively large particle size (being in the micrometer range). Thus, the formulation and processing parameters of Aqoat®-based coatings can be expected to be particularly crucial for film formation, drug release and storage stability. However, very limited knowledge is yet available on the resulting film coating structures and underlying drug release mechanisms.

The major objectives of the present study were: (i) to coat theophylline matrix pellets with aqueous HPMCAS (Aqoat®) dispersions; (ii) to investigate the effects of the plasticizer level, curing conditions (including temperature, relative humidity and time) and coating level on the resulting drug release kinetics; and (iii) to explain the observed phenomena based on the physicochemical properties of the film coatings and underlying drug release mechanisms.

2. Materials and methods

2.1. Materials

Theophylline (Boehringer Ingelheim, Ingelheim, Germany), theophylline pellets (710–850 μm, 94% drug content; Klinge Pharma GmbH, Munich, Germany), hydroxypropyl methylcellulose acetate succinate (HPMCAS; Aqoat® grade AS-MF; ShinEtsu c/o Syntapharm, Mühlheim an der Ruhr, Germany), triethyl citrate (TEC; Morflex, Greensboro, NC, USA) and sodium dodecyl sulfate (SDS; Merck, Darmstadt, Germany) were used as received.

2.2. Methods

2.2.1. Preparation and characterization of thin, polymeric films

Commercially available (micronized) HPMCAS powder was dispersed into a cold aqueous 0.3% w/w SDS solution (ice bath), containing 25 or 30% w/w TEC (as indicated; based on the dry polymer mass). To avoid polymer coagulation, the HPMCAS dispersions were kept cool throughout the experiments. The suspensions were stirred overnight to allow polymer plasticization. Thin films were prepared by spraying the aqueous dispersions onto Teflon® plates (heated with an IR lamp to 35 °C) and subsequent curing (as indicated) at defined temperature (room temperature, 40 or 60 °C) and relative humidity (RH) (ambient RH or 75% RH) with or without an additional drying step (for 24 h at 60 °C and ambient RH).

The mechanical properties of the films were measured using the puncture test and a texture analyzer (TAXT Plus; Winopal Forschungsbedarf GmbH, Ahnsbeck, Germany). Film specimens were mounted on a film holder. 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 % elongation at break as follows:

$$\text{elongation at break } (\%) = \frac{\sqrt{R^2 + D^2} - R}{R} \cdot 100\%, \qquad (1)$$

where R denotes the radius of the film exposed in the cylindrical hole of the holder and D the displacement to puncture.

To monitor potential changes in the mechanical properties upon 2 h exposure to the release medium, film pieces (5 × 5 cm) were placed into 50 ml plastic containers filled with 40 ml pre-heated 0.1 M HCl, followed by horizontal shaking (37 °C, 75 rpm; GFL 3033; Gesellschaft für Labortechnik, Burgwedel, Germany). After 2 h exposure time, samples were withdrawn and analyzed as described above.

2.2.2. Preparation and characterization of coated pellets

Theophylline matrix pellets (94% w/w drug loading) were coated with aqueous HPMCAS dispersions in a ball coater (Kugelcoater UNILAB-05, Hüttlin, Steinen, Germany). The aqueous polymer dispersions were prepared as described in Section 2.2.1. All dispersions were adjusted to 10% (w/w) polymer content with purified water prior to coating. The coating dispersions were sprayed onto a mixture of theophylline pellets and non-pareils (1:4 w/w, 500 g) until a weight gain of 10% or 20% (w/w) was achieved (as indicated). The process parameters were as follows: product temperature = 35 ± 2 °C, spray rate = 4–5 g/min, atomization pressure = 0.4 bar, pressure of microclimate = 0.2 bar, nozzle diameter = 0.8 mm. After coating the pellets were further fluidized for 15 min and subsequently cured (as indicated) at defined temperature (room temperature, 40 or 60 °C) and relative humidity (RH) (ambient RH or 75% RH) with or without an additional drying step (for 24 h at 60 °C and ambient RH).

In vitro drug release from the coated pellets was studied in 0.1 M HCl using the USP XXV paddle apparatus (37 °C, 100 rpm, $n = 3$; VK 7000 dissolution tester, Varian,

Darmstadt, Germany). At pre-determined time intervals, 3 ml samples were withdrawn and analyzed UV-spectrophotometrically ($\lambda = 271$ nm; UV-2101 PC; Shimadzu Scientific Instruments, Columbia, MD, USA).

3. Results and discussion

In phosphate buffer, pH 7.4, theophylline release from the investigated HPMCAS-coated pellets was very rapid, irrespective of the coating formulation and curing conditions (complete drug release within less than 10 min, data not shown). This can be explained by the rapid dissolution of the enteric polymer at high pH and perfect sink conditions provided throughout the experiments. In the following, only drug release at low pH (in 0.1 M HCl) will be discussed.

3.1. Overall drug release kinetics and mechanisms

As it can be seen in Figs. 1, 2, 4–6, theophylline release from the investigated pellets followed zero order kinetics (at least over major parts of the release period), irrespective of the coating formulation and curing conditions. This clearly indicates that theophylline release is primarily controlled by diffusion through the film coatings (via the macromolecular network and/or via water-filled channels located within the coatings). In the pellet cores, a saturated drug solution is provided (theophylline solubility at 37 °C in 0.1 M HCl: 15.4 mg/ml [14]), whereas outside the beads perfect sink conditions are maintained throughout the experiments. Thus, the drug concentration gradients (being the driving forces for diffusion) are about constant (until the excess of theophylline within the pellets is exhausted), resulting in constant drug release rates. The structure and composition of the coatings (e.g., degree of polymer particle coalescence and plasticizer level) determine the resulting apparent film permeability and, thus, drug release rate. The observed significant differences between the theophylline release patterns from the investigated pellets (Figs. 1, 2, 4–6) indicate that the selected formulation and processing parameters can be expected to have distinct effects on the resulting film structure and permeability.

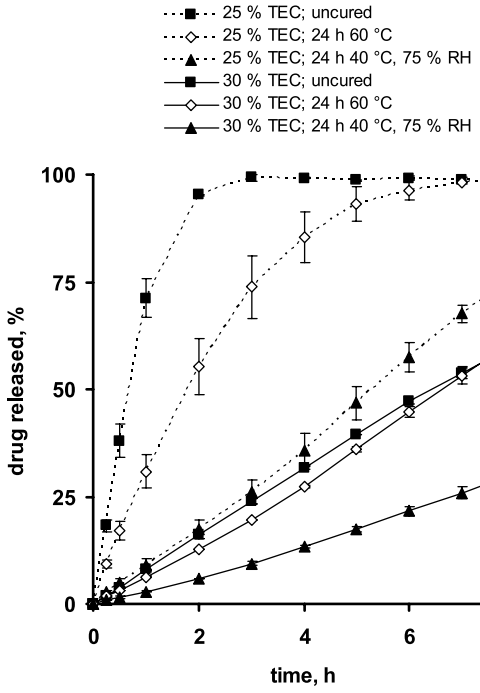

Fig. 1. Effects of the plasticizer level and curing conditions (indicated in the figure) on theophylline release from pellets coated with HPMCAS in 0.1 M HCl (20% coating level).

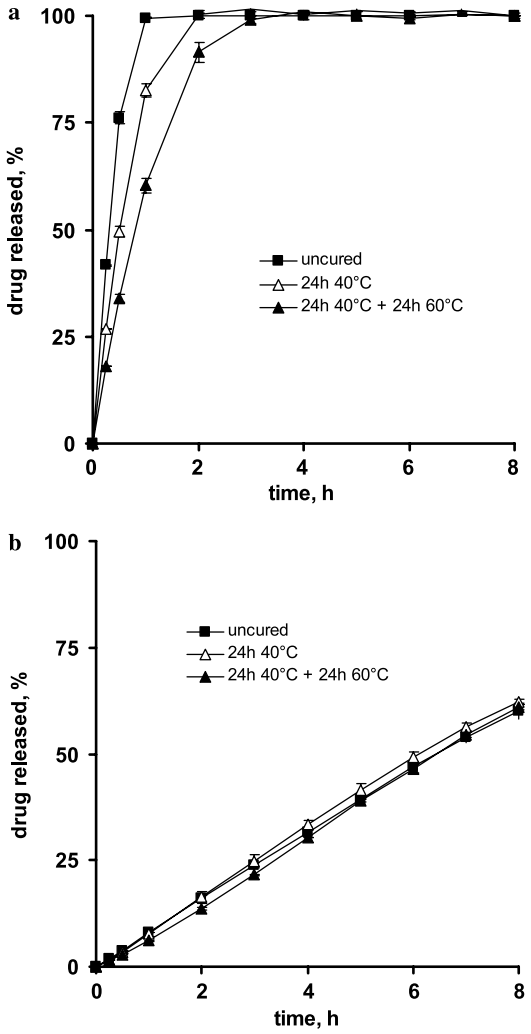

Fig. 2. Theophylline release from pellets coated with HPMCAS in 0.1 M HCl: effects of curing for 24 h at 40 °C and ambient RH, followed or not by 24 h at 60 °C and ambient RH: (a) 10% coating level; (b) 20% coating level (30% TEC).

3.2. Effects of the plasticizer level

Clearly, the plasticizer level fundamentally affected the resulting drug release rate, irrespective of the curing conditions (Fig. 1). Increasing the TEC content by only 5%

(from 25% to 30% w/w) led to a substantial decrease in the theophylline release rate. For example, the latter dropped from 72%/h to only 8%/h (thus, by a factor of 9.4) for uncured pellets. This effect can be attributed to the lowering of the glass transition temperature of HPMCAS in the presence of TEC, resulting in enhanced polymer particle coalescence and, thus, less permeable film coatings (the manufacturer of the investigated HPMCAS recommends to add 28% TEC). It has to be pointed out that the size of the HPMCAS particles is in the micrometer range (average diameter = 5 μm). This is in contrast to most commercially available coating dispersions (with polymer particle sizes in the nanometer range). As described by Steward et al. [9], the ability of polymer particles to fuse into a homogeneous film significantly decreases with increasing particle size. Thus, due to the considerable size of the HPMCAS particles, the film formation process in the investigated coatings can be expected to be particularly crucial.

3.3. Effects of the curing conditions and coating level

To better understand the film formation process in the investigated HPMCAS-based coatings, the effects of different curing conditions (including temperature, relative humidity and time) on theophylline release in 0.1 M HCl were studied at a constant plasticizer level (30% TEC). HPMCAS (being an ester) can hydrolytically be degraded during storage. Thus, it was important to study also the effects of a secondary drying step after curing (especially if the latter was performed at high RH).

Figs. 2a and b illustrate the effects of pellet curing at 40 °C and ambient RH for 24 h on the resulting theophylline release profiles in 0.1 M HCl at a coating level of 10% and 20%, respectively. As it can be seen, the thermal treatment decreased the release rate from pellets coated with 10% HPMCAS, whereas no significant effect was observed in the case of 20% HPMCAS coatings. A further decrease in the release rate was observed upon subsequent curing at 60 °C and ambient RH for 24 h of the pellets with 10% coating level, whereas the release rate remained unchanged in the case of 20% HPMCAS film coatings. This clearly indicates that the film formation process was not complete after coating and that the polymer particles further coalesced during curing.

Importantly, the resulting changes in the film structure led to a distinct decrease in the apparent drug permeability at a coating level of 10%, whereas the permeability was not significantly altered at a coating level of 20% (Figs. 2a vs. b). This can be explained by the difference in film coating thickness/number of involved polymer particle layers, as schematically illustrated in Fig. 3. In thin film coatings (with a low number of initial HPMCAS particle layers), incomplete coalescence results in high drug permeabilities, because the probability that continuous water-filled channels exist, connecting the bead core with the surrounding bulk fluid, is high. In contrast, in thicker films (with a higher number of initial HPMCAS particle layers), the same degree of (incomplete)

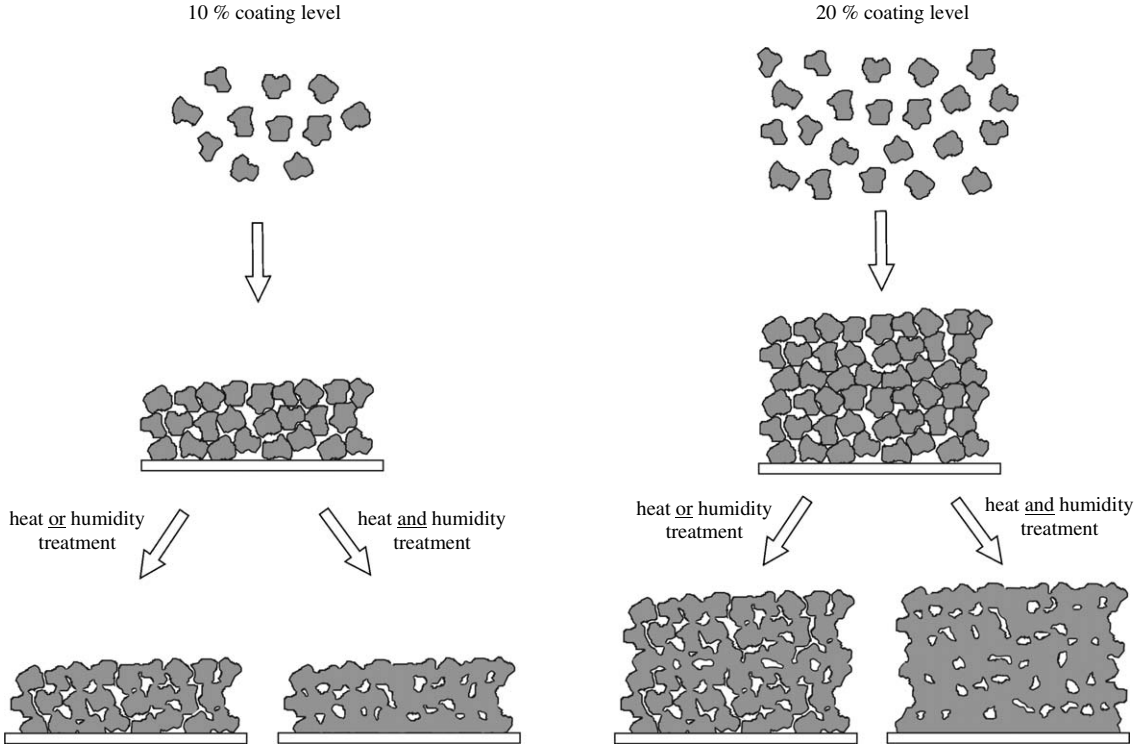

Fig. 3. Schematic illustration (not up to scale) of the film structure in the investigated HPMCAS-based coatings depending on the coating level and curing conditions.

polymer particle coalescence results in a much lower probability for the existence of continuous water-filled channels directly connecting the inner and outer surfaces of the film coatings [15]. Thus, depending on the coating level, theophylline release can be expected to be primarily controlled by diffusion through water-filled channels (thin films) or by diffusion through the macromolecular network (thick films). Further polymer particle coalescence during curing leads to the closure of parts of the water-filled channels. Clearly, this has a stronger impact on drug release in the case of thin film coatings (the water-filled channels representing the preferred diffusion pathways for the drug), whereas the consequences at high coating levels are much less significant (drug release being primarily controlled by diffusion through the polymeric network).

The different diffusion pathways also explain the tremendous effect of the coating level on the theophylline release rate from the investigated pellets (Figs. 2a vs. b). Clearly, the release rate of the drug was reduced by a factor >2 when increasing the coating level from 10% to 20% (and, hence, about doubling the film thickness). According to Fick's law of diffusion, the resulting drug concentration gradients within the coatings in the steady state (saturated drug solutions inside the pellets, perfect sink conditions outside) are expected to decrease only by 50% under these conditions. Thus, if the apparent diffusivity of the drug remains unaltered, the drug release rates should also only decrease by 50%. However, the experimentally measured decrease was much more pronounced, for instance in the case of uncured pellets the release rate dropped from 155%/h to 8%/h (thus, by a factor of 19). This is in good agreement with the hypothesized coating structure and change in the underlying drug release mechanism (Fig. 3).

Importantly, even at a coating level of 20% the USP requirements for enteric drug release (cumulative relative amount of drug released after 2 h exposure to simulated gastric fluid <10%) were not fulfilled. Also an increase in the curing temperature from 40 to 60 °C (for 24 h at ambient RH) did not lead to enteric properties (Fig. 4). Comparing Figs. 2 and 4, a slight decrease in the theophylline release rate from pellets coated with 10% HPMCAS can be seen, whereas the release rate remained unchanged from pellets coated with 20% HPMCAS (due to the reasons explained above). Interestingly, an increase in curing time (from 24 to 48 h) did not affect the resulting drug release at a coating level of 10% (Fig. 4a). Thus, further polymer particle coalescence is unlikely under these conditions. [It has to be pointed out that the manufacturer of the investigated HPMCAS recommends the addition of 30% talc to the coating dispersion. The presence of this additive can be expected to affect the resulting film permeability and drug release kinetics. However, this phenomenon was not the topic of the present study.]

Another important processing parameter, which can affect the coalescence of polymer particles during film formation, is relative humidity. As an increase in curing temperature and time revealed to be insufficient to provide

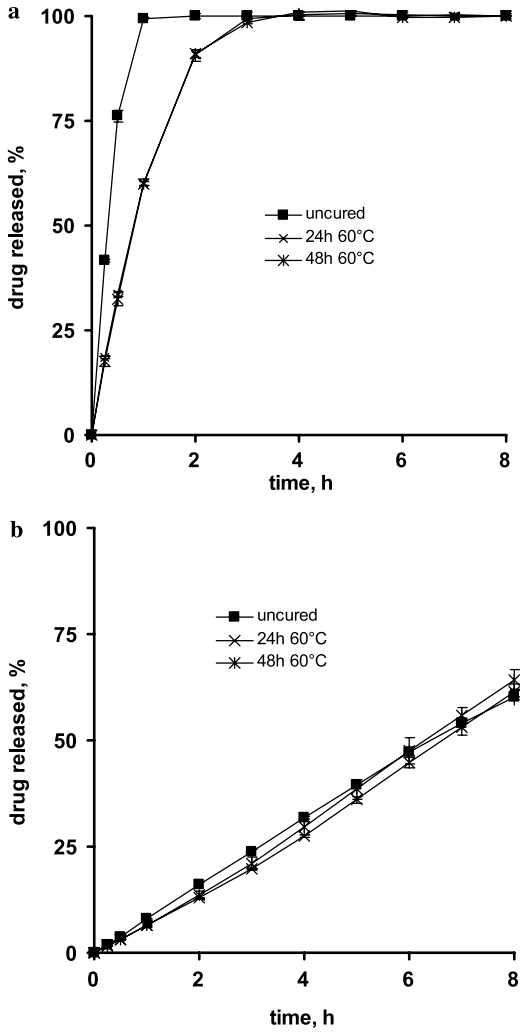

Fig. 4. Theophylline release from pellets coated with HPMCAS in 0.1 M HCl: effects of the curing time at 60 °C and ambient RH: (a) 10% coating level; (b) 20% coating level (30% TEC).

enteric drug release from the investigated pellets, also the relative humidity during curing was increased. Figs. 5a and b show the drug release profiles from HPMCAS-coated pellets cured for 24 h at 40 °C and 75% RH with and without subsequent drying (for 24 h at 60 °C) at a coating level of 10% and 20%, respectively. Clearly, the increase in relative humidity during curing resulted in a significant decrease in the resulting drug release rate, irrespective of the coating level. This can be attributed to the plasticizing effect of water, reducing the minimum film formation temperature of HPMCAS and, thus, enhancing polymer particle coalescence (Fig. 3). As expected, this effect was particularly pronounced in thin film coatings. However, even at a coating level of 20% the release rate was reduced by a factor of 2. This clearly indicates the significance of the changes in the inner film structure. Importantly, enteric drug release could be achieved with these curing conditions at a coating level of 20% (even in the absence of 30% talc). The subsequent drying step did not significantly affect the

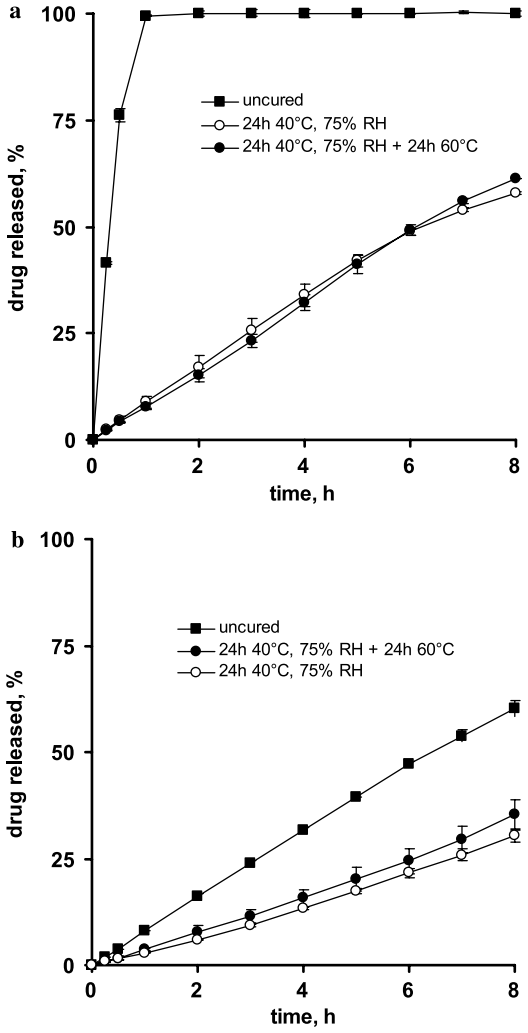

Fig. 5. Theophylline release from pellets coated with HPMCAS in 0.1 M HCl: effects of curing at 40 °C/75% RH with or without subsequent drying at 60 °C/ambient RH: (a) 10% coating level; (b) 20% coating level (30% TEC).

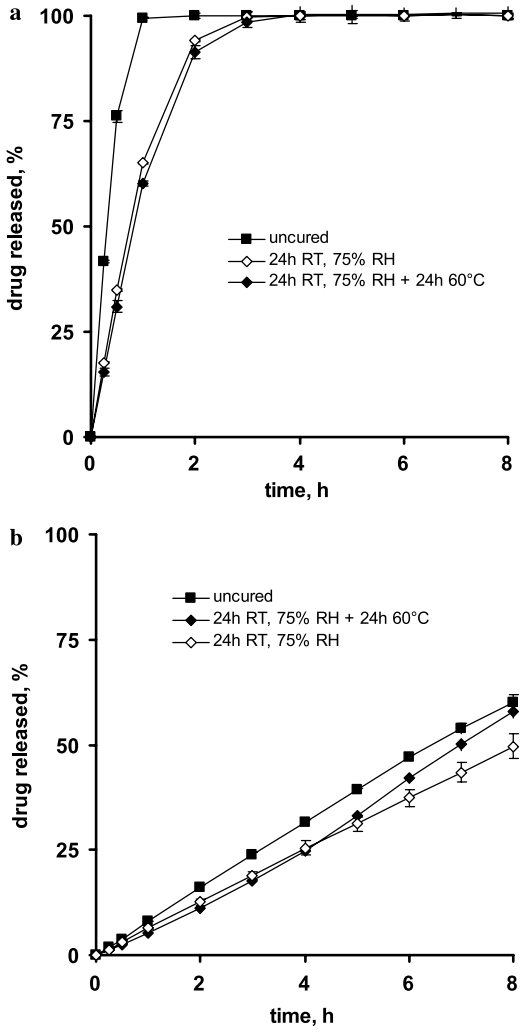

Fig. 6. Theophylline release from pellets coated with HPMCAS in 0.1 M HCl: effects of curing at room temperature/75% RH with or without subsequent drying at 60 °C/ambient RH: (a) 10% coating level; (b) 20% coating level (30% TEC).

theophylline release rate, irrespective of the coating thickness. Thus, the degree of polymer particle coalescence can be expected to remain almost unaltered during drying.

As elevated relative humidity during curing was identified to be a key factor inducing further film formation at 40 °C, it was interesting to study whether the exposure of the pellets to 75% RH at room temperature showed similar effects. As it can be seen in Fig. 6, the elevated relative humidity treatment led to a decrease in the drug release rate even at ambient temperature, irrespective of the coating level. However, this effect was much less pronounced than that at 40 °C (Fig. 5). Thus, to induce significant further polymer particle coalescence, the plasticizing effect of water must be combined with a simultaneous increase in temperature. Otherwise (if the elevated relative humidity treatment is followed by the thermal treatment), the release rate does not decrease more than in the case of an elevated relative humidity or temperature treatment alone, irrespective of the coating level (Fig. 5).

Importantly, the effects of elevated temperature and elevated relative humidity were not only additive, but synergistic. Compared to uncured pellets, the theophylline release rate at 10% coating level was reduced by a factor of 1.9 upon curing for 24 at 40 °C and ambient RH, and by a factor of 2.4 upon exposure to 75% RH for 24 h at room temperature. The combination of both parameters (curing at 40 °C and 75% RH for 24 h) resulted in a reduction of the release rate by a factor of 17 [Remark: A further increase in curing temperature to 60 °C at 75% RH led to intense sticking of the pellets].

The relative cumulative amounts of theophylline released after 2 h exposure to 0.1 M HCl from the investigated pellets are compared in Fig. 7. Clearly, the most substantial decrease in release rate was achieved by increasing the coating level from 10% to 20% (white vs. gray bars). This can be explained by the above-described change in the underlying drug release mechanism (altered diffusion pathway of the drug). At a coating level of 20%, theophyl-

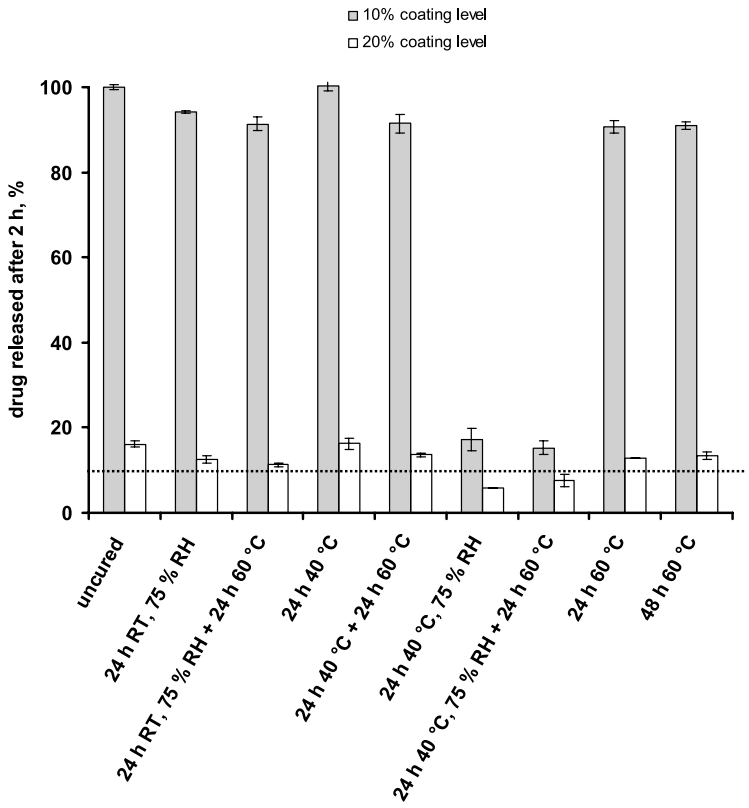

Fig. 7. Effects of the curing conditions and coating level on the relative amount of theophylline released from HPMCAS-coated pellets after 2 h exposure to 0.1 M HCl (30% TEC; the dotted line indicates the USP specification for enteric drug release) ("+24 h 60 °C" indicates a subsequent drying step for 24 h at 60 °C and ambient relative humidity).

line release is primarily controlled by diffusion through the polymeric network, whereas at a coating level of 10% diffusion through water-filled channels generally predominates. However, this is not true for pellets with 10% coating level after curing at elevated relative humidity and elevated temperature. In this case, further polymer particle coalescence during curing closed the continuous water-filled channels connecting the inner pellet core with the bulk fluid, and drug release was as well controlled by diffusion through the polymeric network. This change in the microstructure of the film coatings is in good agreement with the observed effect of the coating level on theophylline release (Figs. 5a vs. b). According to Fick's law of diffusion an increase in the coating level from 10% to 20% should lead to a decrease in the release rate in the steady state by a factor of 2 (if the apparent diffusivity of the drug remains unaltered, which can be expected in the case of films cured at 40 °C and 75% relative humidity). Importantly, this was experimentally confirmed: the release rate dropped from 8%/h to 4%/h.

As it can be seen in Fig. 7, the USP requirement for enteric drug release (indicated by the dotted line) was only fulfilled at a coating level of 20%, combined with a curing at elevated temperature and relative humidity.

In order to further confirm the hypothesized drug release mechanisms, thin polymeric films of identical composition as the pellet coatings were prepared and cured under the same conditions as the pellets. The mechanical properties of these films were determined before and upon exposure to 0.1 M HCl.

3.4. Mechanical properties of thin, polymeric films

The mechanical resistance of the pellet coatings can be of major importance for the underlying drug release mechanisms [16]. Brittle films tend to show crack formation during drug release, whereas tough films can withstand even considerable hydrostatic pressure developed within the bead cores. Furthermore, the mechanical properties of the polymeric films can allow getting deeper insight into the microstructure of the coatings, in particular with respect to the degree of polymer particle coalescence. Increasing degrees of coalescence can be expected to lead to increasing mechanical resistance.

Fig. 8a shows the experimentally measured percentage elongation at break of HPMCAS films (which have been cured under different conditions) in the dry state. Obviously, no clear correlation between the flexibility of the films and the observed in vitro drug release rates can be established. The films cured at elevated temperature and elevated humidity (black bar) showed intermediate flexibility, whereas drug release was most effectively slowed down with these curing conditions. However, these results were obtained with polymeric films in the dry state. It is well

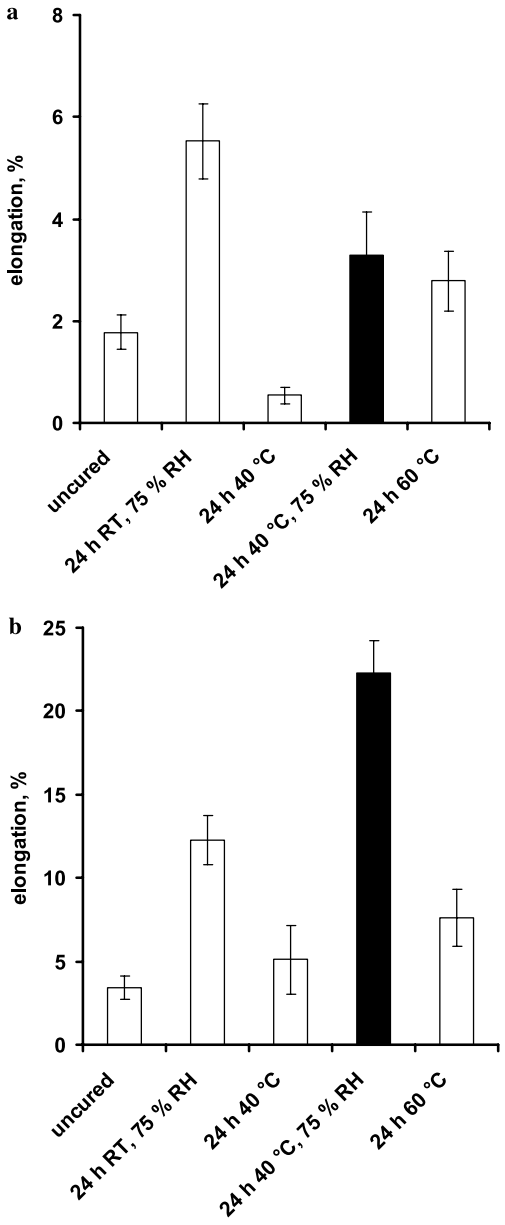

Fig. 8. Effects of the curing conditions (indicated in the figures) on the percentage elongation at break of HPMCAS films: (a) in the dry state; (b) after 2 h exposure to 0.1 M HCl (30% TEC).

known that the imbibition of water and leaching of the plasticizer can drastically alter the mechanical properties of polymeric coatings. Thus, it was important to measure the flexibility of the films also upon exposure to the release medium.

As it can be seen in Fig. 8b, the percentage elongation significantly increased upon 2 h exposure to 0.1 M HCl (please note the different scaling of the *y*-axis compared to Fig. 8a). This can be explained by the plasticizing effect of the water that diffused into the system. Importantly, the films cured at elevated temperature and elevated humidity (black bar) were much more flexible than all other films. This is a clear further indication for the enhanced polymer particle coalescence under these conditions, resulting in less permeable film coatings and, thus, reduced theophylline release rates. Hence, the mechanical properties of the wet films confirm the above-hypothesized coating microstructures and drug release mechanisms (Fig. 3).

4. Conclusions

The presented experimental results and the obtained new insight into the underlying drug release mechanisms clearly point out the importance of the preparation technique of aqueous-based HPMCAS film coatings to ensure enteric properties.

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