European Journal of Pharmaceutics and Biopharmaceutics 74 (2010) 362–370

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Curing of aqueous polymeric film coatings: Importance of the coating level and type of plasticizer

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ARTICLE INFO

Article history:
Received 24 June 2009
Accepted in revised form 30 October 2009
Available online 4 November 2009

Keywords:
Coating
Pellets
Plasticizer
Aqueous ethylcellulose dispersion
Curing

ABSTRACT

The aim of this study was to better understand the effects of the curing conditions on the resulting drug release patterns from pellets coated with aqueous polymer dispersions. Diltiazem HCl was used as model drug, ethylcellulose as polymer, triethyl citrate (TEC), dibutyl sebacate (DBS), and distilled acetylated monoglycerides (Myvacet) as plasticizers. Interestingly, the effects of the curing conditions strongly depended on the coating level and the type of plasticizer: in the case of TEC, the drug release rate monotonically decreased with increasing harshness of the curing conditions (time, temperature, and relative humidity), irrespective of the coating level. In contrast, in the case of DBS and Myvacet, this type of relationship was only observed at low coating levels (5%). At intermediate coating levels (around 7.5%), the curing conditions had virtually no effect on drug release. At high coating levels ($\geqslant$10%), the release rate initially increased and then decreased with increasing harshness of the curing conditions. This more complex behavior might be attributable to the superposition of two competing phenomena: improved film formation and drug migration into the polymeric membrane. Furthermore, it could be shown that the type of plasticizer had a major effect on drug release in not fully coalesced and equilibrated film coatings, whereas the release profiles were similar for all plasticizers in the case of completely formed and equilibrated film coatings. Importantly, the latter systems were stable for long term even during storage under stress conditions.

1. Introduction

Polymeric film coatings exhibit a great potential for the control of drug release from oral dosage forms [21,28,3,7] . They can be applied from organic solutions or aqueous dispersions [9,5,16]. The latter are of steadily increasing importance due to safety, economical, and environmental concerns related to the use of organic solvents [5,17]. However, the underlying film formation mechanisms are fundamentally different, and one of the major remaining challenges associated with aqueous polymer dispersions is to provide long-term stability. In not fully coalesced films, polymer particle fusion can continue during storage, resulting in less permeable film coatings and decreasing drug release rates [26,30].

Once sprayed onto the dosage forms' surface, the droplets of the aqueous polymer dispersion form a thin aqueous film. Due to water evaporation, the dispersed polymer particles approach each other and become closely packed. Upon further water evaporation, the (softened) particles deform due to capillary pressure effects (air–water surface tension) and coalesce to form a continuous film [5,12,19,11]. However, in practice, it is often difficult to assure complete film formation during coating. This is why generally a thermal post-treatment (curing step) is required to enhance the degree of polymer particle coalescence [6,26]. Crucial parameters in this processing step include the temperature, relative humidity, and time, which need to be optimized. With increasing temperature, the mobility of the macromolecules increases, facilitating polymer particle coalescence. The relative humidity during curing determines the water content of the system, water being mandatory for the capillary forces driving the particles together and acting as a plasticizer for many polymers [13]. To sufficiently soften the polymer particles, often plasticizers are added, decreasing the glass transition temperature of the polymeric system and, thus, increasing the mobility of the macromolecules [20,26]. Several studies have been reported in the literature addressing the importance of the curing step for the resulting drug release rate and storage stability [1,12]. However, so far the importance of the *coating level* for the impact of the curing conditions has been generally ignored, and

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doi:10.1016/j.ejpb.2009.10.007

no study has been described taking this parameter systematically into account. Furthermore, the relationships between the type of plasticizer, curing conditions, coating level, and drug release kinetics are often not well understood, and process optimization is based on time- and cost-intensive series of trial and error studies.

The major aims of this study were: (i) to monitor the effects of the curing time and relative humidity on the resulting drug release kinetics from pellets coated with aqueous ethylcellulose dispersion, plasticized with hydrophilic and lipophilic plasticizers when cured at 60 °C, (ii) to systematically vary the coating level, (iii) to monitor long-term stability under stress conditions, and (iv) to better understand the underlying mechanisms. Ethylcellulose was used as polymer, because it offers a great potential for controlled release coatings and is widely used in the pharmaceutical industry [10]. It is generally recognized as safe, odourless, tasteless, nontoxic, nonirritant, and approved for use in food and pharmaceutical products [4]. Aquacoat ECD is a commercially available aqueous ethylcellulose dispersion containing 29–32% solids. Sodium lauryl sulfate and cetyl alcohol are included as emulsifiers and stabilizers (concentration ranges: 0.9–1.7% and 1.7–3.3%, respectively) [4]. Triethyl citrate (TEC), dibutyl sebacate (DBS), and distilled acetylated monoglycerides (Myvacet) were used as plasticizers, and diltiazem HCl as model drug.

2. Materials and methods

2.1. Materials

Diltiazem HCl-layered sugar spheres (76% w/w drug loading; Ethypharm, Grand-Quevilly, France); aqueous ethylcellulose dispersion (Aquacoat ECD; FMC, Philadelphia, PA, USA); dibutyl sebacate (DBS; Morflex, Greensboro, NC, USA); distilled acetylated monoglycerides (Myvacet 9–45; Kerry, Tralee, Ireland); triethyl citrate (TEC; Morflex); fumed silica (Aerosil R972; Evonik, Essen, Germany).

2.2. Preparation of aqueous polymer dispersions

Aqueous ethylcellulose dispersion was plasticized overnight (16 h magnetic stirring) with 24% (w/w, based on the dry mass of the aqueous dispersion) water-insoluble (DBS or Myvacet 9–45) or water-soluble (TEC) plasticizers and adjusted to 15% (w/w) dry substance content with purified water prior to use. A plasticization time of 16 h was considered to be sufficient in all cases, according to the literature [2,22].

2.3. Preparation of thin films

Free films were prepared by casting aqueous ethylcellulose dispersions onto Teflon moulds and subsequent controlled drying in an oven (for 24 h at 60 °C and 75% relative humidity). The thickness of the films was in the range of 300–600 μm (measured using a thickness comparator; Mitutoyo, Roissy, France).

2.4. Water uptake and dry mass loss studies

Free films were cut into pieces of 18 mm × 22 mm, which were placed into the baskets of an USP basket apparatus (AT7, Sotax, Basel, Switzerland) (500 mL 0.1 N HCl, 37 °C, 50 rpm, $n = 3$). At pre-determined time points, samples were withdrawn, accurately weighed (wet mass (t)) and dried to constant mass at 40 °C (dry mass (t)). The water content (%) and dry film mass (%) at time t were calculated as follows:

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

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

2.5. Preparation of coated pellets

Diltiazem HCl-layered sugar spheres (76% drug loading, 1 mm diameter) were coated in a fluidized bed coater (Ohlmann K, Markt Erlbach, Germany), equipped with a Wurster column (bottom spray). The process conditions were as follows: inlet air temperature = 41–44 °C; product temperature = 34–35 °C; spray rate = 3–4 g/min; atomization pressure = 1.2 bar; nozzle diameter = 1.2 mm; air flow velocity = 60 m^3/h. The coating dispersions (of identical composition as those used for the preparation of cast free films) were sprayed onto the diltiazem HCl-layered sugar spheres until a weight gain of 5–18% (w/w) was achieved (batch size = 900 g). The coating efficiency was 99 ± 1% (w/w), and the total yield was 96–99% (w/w). After coating, the pellets were further fluidized for 10 min and then sieved (710–1180 μm). The pellets were blended with 0.5% (w/w) fumed silica as external anti-tacking agent and subsequently cured in an oven for 1 or 24 h at 60 °C and ambient or 75% relative humidity (as indicated). According to FMC BioPolymer [4], the glass transition temperature of Aquacoat ECD films plasticized with 24% TEC, DBS, and Myvacet is equal to 32–33, 40–41, and 44–45 °C, respectively. The minimum film formation temperature (MFT) of the investigated coating dispersions was ⩽ room temperature (20 °C) and, thus, well below the product temperature during coating.

2.6. In vitro drug release studies

Diltiazem HCl release from the pellets was measured using the USP paddle apparatus (Sotax SMART or AT7, Sotax) in 900 mL

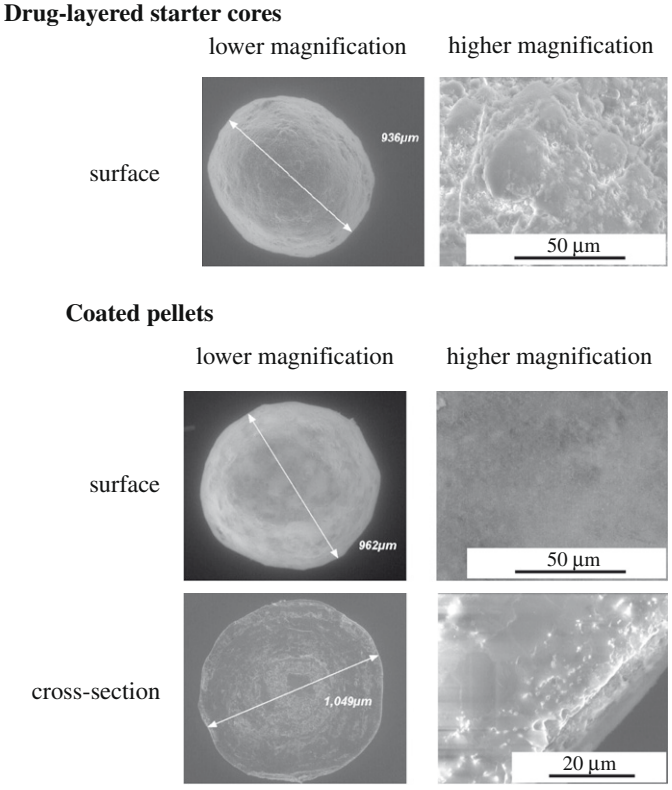

Fig. 1. SEM pictures of surfaces and cross-sections of diltiazem HCl-layered starter cores and coated pellets (coating level = 5%, plasticizer = TEC, curing conditions = 1 h at 60 °C).

0.1 N HCl at 37 °C (100 rpm, $n = 3$). At pre-determined time points, samples were withdrawn, and their drug content were determined by UV spectrophotometry (Uvikon; Kontron, Milan, Italy) at $\lambda = 237$ nm. The analytical equipment was qualified, and the method was validated [ICH Q2 (R1)].

2.7. Long-term storage stability

Coated pellets were stored in closed high-density polyethylene bottles (Duma Twist-Off Cap; Gerresheimer Plastic Packaging, Vaerloese, Denmark) under accelerated stability conditions (40 °C and 75% RH). Drug release from the pellets was measured before and after 6 months of storage, as described in Section 2.6.

2.8. Mathematical analysis

The similarity of drug release profiles was evaluated using the f_2 factor [18,8]:

$$f_2 = 50 \log \left(\left[1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} \times 100 \right) \quad (3)$$

where n is the number of observations, R_t denotes the percentage of drug released from the reference formulation, and T_t the percentage of drug released from the test formulation. Drug release profiles are similar, if the f_2 factor is close to 100 (generally, greater than 50).

Drug release from the coated pellets was quantitatively described using Fick's first law of diffusion, assuming that:

(i) Drug diffusion is the dominant mass transport step.
(ii) The initial drug concentration is below drug solubility within the pellets.
(iii) Perfect sink conditions are maintained throughout the experiment.
(iv) The film coatings' properties are time independent.

Under these conditions, the following equation can be derived:

$$M_t = M_\infty (1 - e^{-k(t - t_0)}) \quad (4)$$

where M_t and M_∞ represent the cumulative amounts of drug released at time t and $t = \infty$, respectively; k is a constant (being a function of the surface area available for diffusion, the diffusion coefficient of the drug within the membrane and the thickness of the film coating); and t_0 denotes the lag time prior to drug release.

2.9. Pellet morphology

The morphology of surfaces and cross-sections of coated and noncoated pellets was studied by scanning electron microscopy (SEM) using an Environmental Secondary Electron Detector (ESED) (S-3000 N; Hitachi Ltd., Tokyo, Japan). Cross-sections of pellets were obtained using a cutter blade.

3. Results and discussion

3.1. External and internal morphology

The upper raw in Fig. 1 shows SEM pictures of the surfaces of diltiazem HCl-layered starter cores at lower and higher magnification. Below this raw, SEM pictures of surfaces and cross-sections of

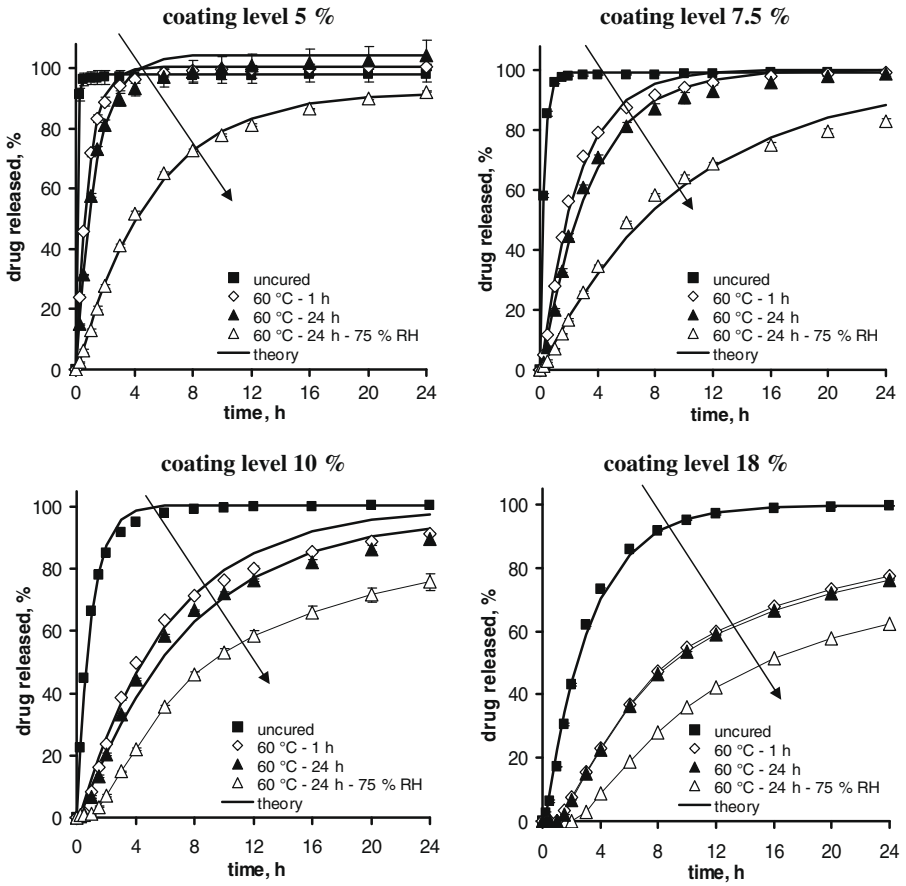

Fig. 2. Effects of the coating level and curing conditions on drug release from diltiazem HCl-layered sugar cores coated with aqueous ethylcellulose dispersion plasticized with TEC (symbols and thin curves: experiments; thick curves: theory).

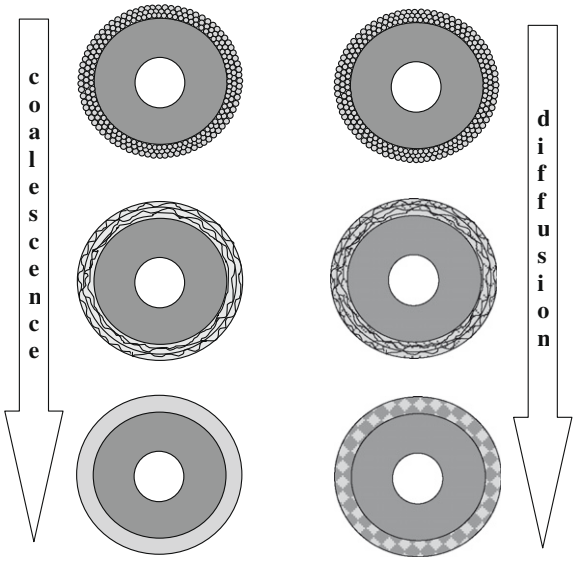

Fig. 3. Schematic representation of the structural changes occurring within the polymeric film coatings during curing: improved polymer particle coalescence and drug migration.

coated pellets are illustrated at different magnifications. Exemplarily, pellets coated with 5% ethylcellulose, plasticized with TEC, and cured for 1 h at 60 °C are shown. The outer and inner morphology of all other investigated pellets was similar (data not shown). The starter cores as well as all coated pellets were spherical in shape. The surface of the starter cores was rough than that of coated pellets. Cross-sections allowed for a distinction between the sugar starter core, the drug layer, and the polymer coating (Fig. 1, bottom row).

3.2. Effects of the coating level and curing conditions

Fig. 2 shows the effects of the curing conditions on diltiazem HCl release from pellets coated with 5%, 7.5%, 10%, and 18% ethylcellulose, respectively. The plasticizer was the water-soluble TEC, the curing conditions were as follows: (i) 60 °C for 1 h, (ii) 60 °C for 24 h, (iii) 60 °C and 75% relative humidity (RH) for 24 h, as well as "uncured" for reasons of comparison. Clearly, the resulting drug release rate decreased in all cases with increasing harshness of the curing conditions: increasing time, temperature, and relative humidity. This can be attributed to further polymer particle coalescence, rendering the polymeric membranes less permeable for the drug, as schematically illustrated on the left hand side of Fig. 3. An increase in temperature increases the mobility of the macromolecules and, thus, facilitates the fusion of neighboring polymer particles. An increase in the relative humidity increases the water content of the system during particle coalescence. Importantly, water is mandatory for the capillary

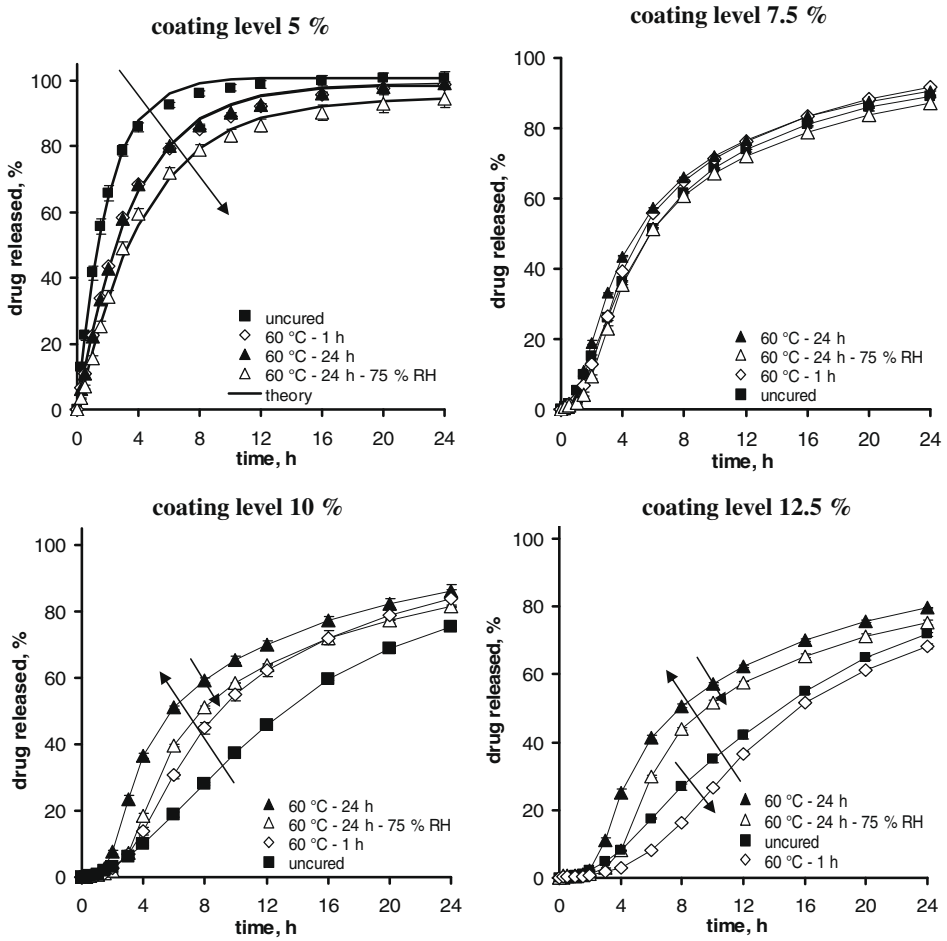

Fig. 4. Effects of the coating level and curing conditions on drug release from diltiazem HCl-layered sugar cores coated with aqueous ethylcellulose dispersion plasticized with DBS (symbols and thin curves: experiments; thick curves: theory).

forces driving the polymer particles together and acts as a plasticizer for ethylcellulose [23,27]. It has to be pointed out that this tendency "harshness of the curing conditions ⇑ → drug release rate ⇓" was observed at all the investigated coating levels.

In contrast, more complex behaviors were observed in the case of ethylcellulose coatings, which were plasticized with the more lipophilic dibutyl sebacate (DBS) (Fig. 4). The starter cores, coating levels, and curing conditions were the same as in the case of pellets plasticized with TEC (Fig. 2), only the type of plasticizer was altered. Interestingly, at 5% coating level, the same tendency as for the water-soluble TEC was observed at all coating levels: increasing the harshness of the curing conditions led to *decreased* drug release rates. However, at a coating level of 7.5%, the curing conditions did not significantly affect the resulting drug release rate ($68 < f_2 < 77$). This is of great practical importance. At a coating level of 10%, the release rate *in*creased when increasing the curing temperature to 60 °C and the curing time to 24 h. However, when increasing the relative humidity to 75% at 60 °C, the release rate *de*creased again. At a coating level of 12.5%, the release rate first decreased, then increased, and finally decreased again when increasing the curing temperature to 60 °C, the curing time to 24 h, and the relative humidity during curing to 75%. Also in the case of the more lipophilic plasticizer Myvacet, a more complex relationship between the harshness of the curing conditions, the coating level, and the resulting drug release rate was observed (Fig. 5). At low coating levels (5%), an increase in the harshness of the curing conditions led to *decreasing* drug release rates. At intermediate coating levels (7.5%), only slight curing effects were observed. At high coating levels (10%), the release rate first *in*creased and then *de*creased with increasing curing temperature, time, and relative humidity. Thus, the behavior of aqueous ethylcellulose coatings plasticized with Myvacet is similar to that of aqueous ethylcellulose coatings plasticized with DBS. These more complex behaviors (compared to the straightforward relationships observed with the water-soluble plasticizer TEC) might be explained as follows: two phenomena occur simultaneously, the relative importance of each phenomenon being a function of the coating level:

(i) As in the case of TEC, an increase in the curing temperature, time, and relative humidity facilitates polymer particle coalescence and, thus, improves film formation. This results in reduced permeability of the film coating for the drug: "Improved film formation effect". The type of plasticizer (TEC versus DBS versus Myvacet) can be expected to affect the degree of film formation under the various curing conditions [14].

(ii) The drug has a certain affinity to the film coating and migrates into the latter during curing [1]. The presence of the more lipophilic plasticizers DBS and Myvacet in the polymeric systems might favor this drug migration compared to the water-soluble plasticizer TEC: "Drug migration effect".

Both phenomena are schematically illustrated in Fig. 3. The fact that at *low* coating levels, the improved film formation effect is dominant (decreasing release rates with increasing harshness of the curing conditions; Figs. 4 and 5; 5% coating level) can be explained as follows: at low coating levels, the number of polymer particle layers is limited. Thus, the probability that a drug molecule can diffuse through water-filled pores/channels from the pellet core to the bulk fluid is relatively high. An improvement of film formation closes these continuous water-filled pathways and, thus, fundamentally alters the resistance for drug release and the resulting drug release [29,15]. In contrast, this effect is much less pronounced at *higher* coating levels, because the probability for the existence of continuous water-filled channels from the pellet core to the bulk fluid during drug release is low even prior to curing (due to the higher number of polymer particle layers). Thus, improved film formation does not fundamentally alter the type of diffusion pathway. Consequently, the relative importance of the "improved film formation effect" decreases with increasing coating level, whereas the importance of the "drug migration effect" does not. At intermediate coating levels (around 7.5%), both effects compensate each other, resulting in about unaltered drug release kinetics. At high coating levels (10% and more), the drug migration effects dominates, except for major improvements in film formation, such as upon increasing the relative humidity to 75% during

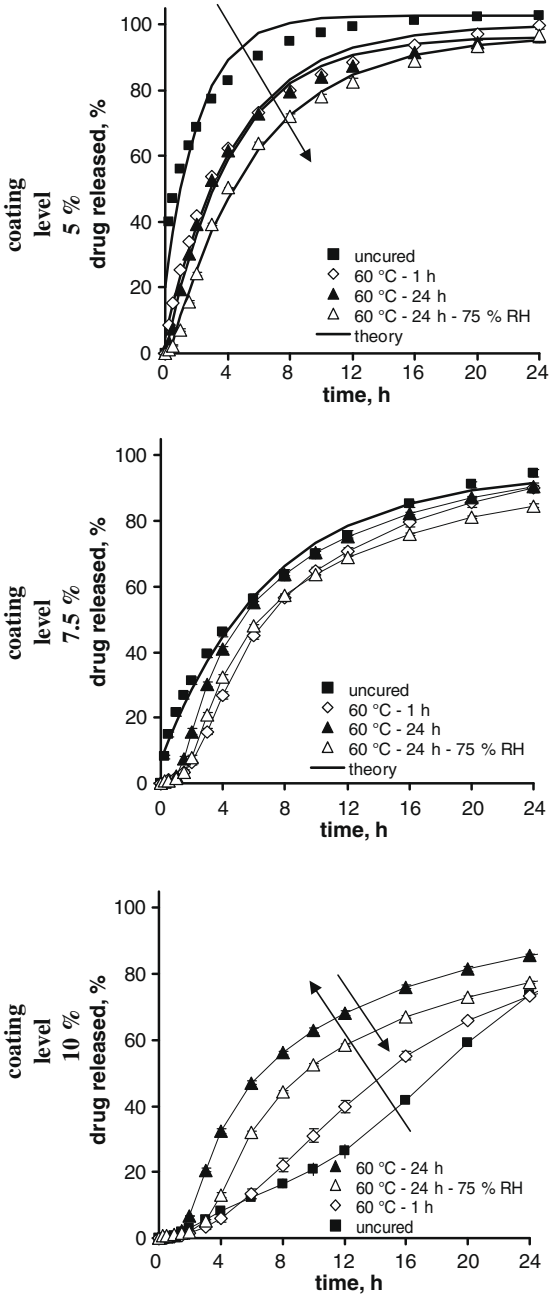

Fig. 5. Effects of the coating level and curing conditions on drug release from diltiazem HCl-layered sugar cores coated with aqueous ethylcellulose dispersion plasticized with Myvacet (symbols and thin curves: experiments; thick curves: theory).

Table 1
Dependence of the system-specific parameters characterizing diltiazem HCl release from the investigated pellets on the coating level, curing conditions, type of plasticizer, and storage time (obtained by fitting Eq. (4) to the experimental results shown in Figs. 2, 4, 5 and 8).

Coating level	Curing conditions	Aquacoat-TEC		Aquacoat-DBS		Aquacoat-Myvacet	
		k (h^{-1})	t_0 (h)	k (h^{-1})	t_0 (h)	k (h^{-1})	t_0 (h)
5%	Uncured	10.5	0	0.51	0	0.45	n.a.
	60 °C – 1 h	1.2	0	0.28	0	0.22	n.a.
	60 °C – 24 h	0.74	0	0.28	0.02	0.24	0.03
	60 °C – 24 h – 75%RH	0.20	0.11	0.23	0.09	0.18	0.3
	After storage* (all conditions)	0.17 (±0.00)	0 (±0)	0.20 (±0.00)	0 (±0.00)	0.19 (±0.03)	0.16 (±0.03)
7.5%	Uncured	3.7	0	n.a.	n.a.	0.14	n.a.
	60 °C – 1 h	0.39	0.08	n.a.	n.a.	n.a.	n.a.
	60 °C – 24 h	0.29	0.11	n.a.	n.a.	n.a.	n.a.
	60 °C – 24 h – 75%RH	0.10	0.02	n.a.	n.a.	n.a.	n.a.
	After storage* (all conditions)	0.11 (±0.00)	0.06 (±0.06)	n.a.	n.a.	n.a.	n.a.
10%	Uncured	1.0	0	n.a.	n.a.	n.a.	n.a.
	60 °C – 1 h	0.16	0.18	n.a.	n.a.	n.a.	n.a.
	60 °C – 24 h	0.14	0.20	n.a.	n.a.	n.a.	n.a.
	60 °C – 24 h – 75% RH	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	After storage* (all conditions)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
18%	Uncured	0.32	0.19	–	–	–	–

n.a.: Not applicable (the model is also not applicable at a coating level of 12.5% in the case of Aquacoat-DBS and at a coating level of 18% in the case of Aquacoat-TEC, except for uncured pellets).
–: Drug release not measured.
* Mean values of the parameters obtained for uncured and all types of cured pellets (± standard deviation).

curing (Figs. 4 and 5).

The experimentally measured drug release kinetics from pellets coated with aqueous ethylcellulose dispersion, plasticized with TEC, DBS, and Myvacet (symbols in Figs. 2, 4 and 5) were also analyzed theoretically. A solution of Fick's law of diffusion (Eq. (4)) was fitted to the various data sets (curves in Figs. 2, 4 and 5). The model considers that drug diffusion is the dominant mass transport step, that the initial drug concentration is below drug solubility within the pellets, that perfect sink conditions are maintained throughout the experiments, and that the film coatings' properties are time independent. At low coating levels, good agreement between theory and experiment was obtained, indicating that drug diffusion is the predominant mass transport step. In contrast, at intermediate and higher coating levels, systematic deviations between the fittings (Eq. (4)) and the experimental results were observed in most cases. If applicable, the model fitting allowed for the determination of the system-specific parameters listed in Table 1. Clearly, in the case of the less water-soluble plasticizers DBS and Myvacet, the deviations from the theory were more pronounced than in the case of the water-soluble plasticizer TEC at identical coating levels. Thus, the underlying drug release mechanisms are more complex. It has to be pointed out that the applied, simple mathematical model only takes into account purely diffusion-controlled drug release with constant diffusivities. Time-dependent changes in the film coatings' composition and, thus, properties are not considered. It was beyond the scope of this study to elucidate the underlying drug release mechanisms for all types of coated pellets in detail. Such an analysis must be based on a more comprehensive experimental characterization of the respective systems [25].

3.3. Effects of the type of plasticizer

Fig. 6 shows a direct comparison of the various drug release profiles of diltiazem HCl from pellets coated with aqueous ethylcellulose dispersion plasticized with TEC, DBS, and Myvacet. The coating level was varied from 5% to 10%, and two curing conditions were selected: (i) 1 h at 60 °C (left column) and (ii) 24 h at 60 °C and 75% relative humidity (right column). Clearly, the type of plasticizer strongly affected the resulting drug release patterns upon curing at 60 °C for 1 h. Under these conditions, it can be expected that film formation is not yet complete, and the polymeric membrane not yet in equilibrium (e.g., drug can still migrate into Myvacet films at a coating level of 10%). Fig. 7 shows a possible explanation for the observed ranking order in the drug release rates: Thin films of identical composition as the investigated film coatings were prepared and exposed to 0.1 N HCl (at 37 °C). Changes in their water content and dry mass were monitored gravimetrically. Clearly, TEC-containing films take up more water and more rapidly than DBS- and Myvacet-containing films. Also, the dry mass loss is more pronounced and more rapid in the case of TEC-containing systems compared to DBS- and Myvacet-based films. This can be explained by the higher water solubility of TEC compared to the more lipophilic DBS and Myvacet. A higher water content and dry mass loss can be expected to result in a higher permeability for the freely water-soluble drug diltiazem HCl. However, some caution needs to be paid when drawing conclusions based on these results, since the thickness and inner structure of the free films and of the films surrounding the pellets are not identical.

In contrast, there was no significant effect of the type of plasticizer, when the pellets were cured for 24 h at 60 °C and 75% RH (Fig. 6, right column, $f_2 \geqslant 56$). This is of major practical importance and indicates that the polymeric membranes are likely to be in an equilibrated state. Note that the water uptake and dry mass loss kinetics of the thin films shown in Fig. 7 were obtained with systems, which were much thicker than the polymeric coatings: 300–600 μm. Films of *comparable* thickness as the film coatings surrounding the pellets could not be used due to practical limitations (homogeneity of the films and gravimetric measurement errors). Furthermore, it has to be pointed out that the inner structure of the free films might be different from those of the film coatings surrounding the pellets, because of the different conditions during film formation (e.g., casting versus spraying).

When the pellets were cured for 24 h at 60 °C and at ambient relative humidity, the type of plasticizer also affected the resulting drug release patterns (data not shown), but to a lesser extent than

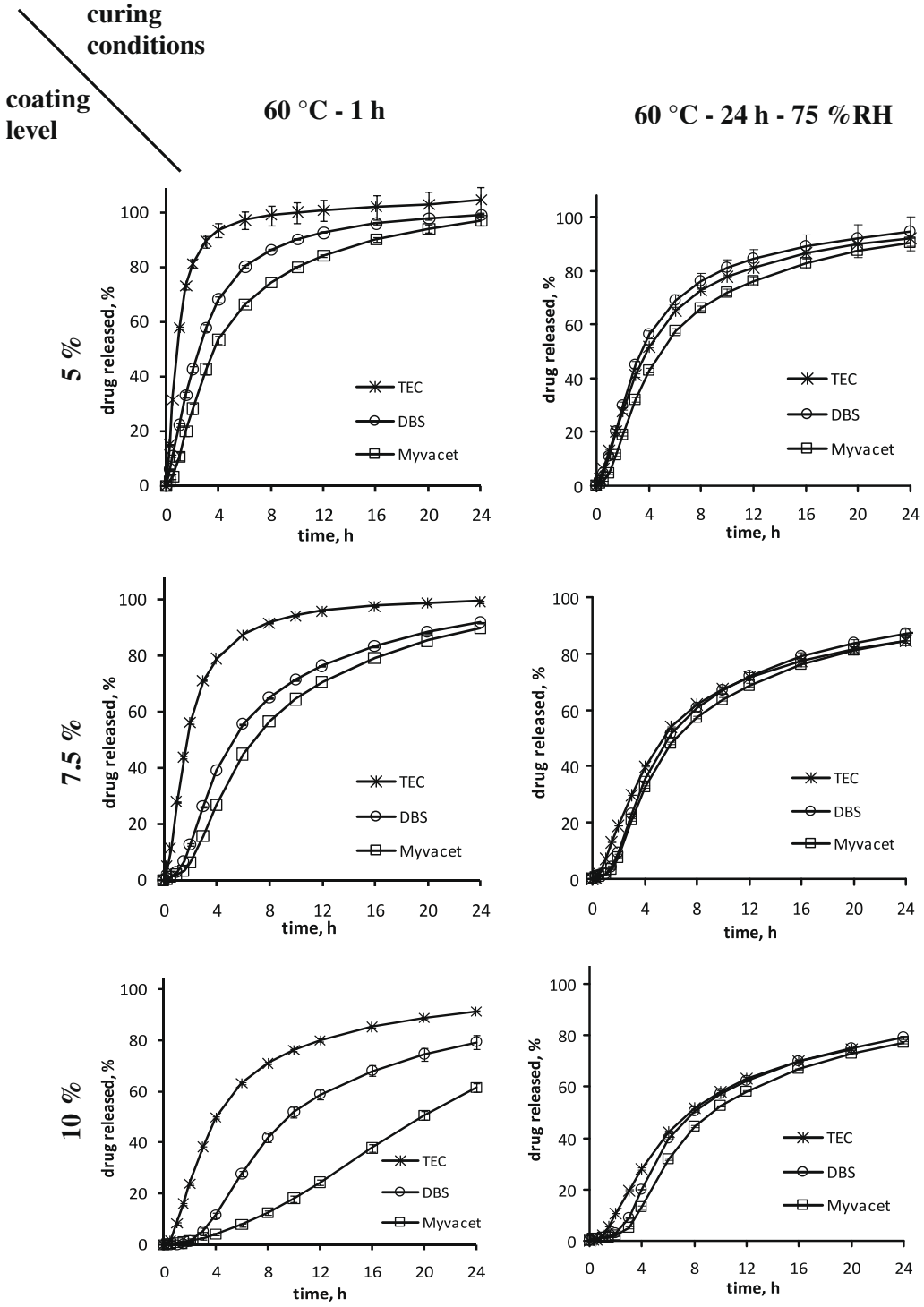

Fig. 6. Effects of the type of plasticizer on diltiazem HCl release from pellets coated with aqueous ethylcellulose dispersion. The coating level and curing conditions are indicated in the figure.

in the case of 1 h curing at 60 °C. Thus, also under these conditions, the equilibrium state is probably not reached.

3.4. Storage stability

Long-term storage stability is a major challenge when using aqueous polymeric film coatings to control drug release [23,24]. Importantly, all formulations cured for 24 h at 60 °C and 75% relative humidity showed *unaltered* drug release upon 6-month storage under stress conditions (40 °C, 75% RH). Fig. 8 shows, for example, diltiazem HCl release from pellets coated with 7.5% ethylcellulose, plasticized with TEC, DBS, or Myvacet. The dotted curves show drug release from pellets before storage, the solid curves after storage. Additionally, the drug release profiles from uncured pellets as well

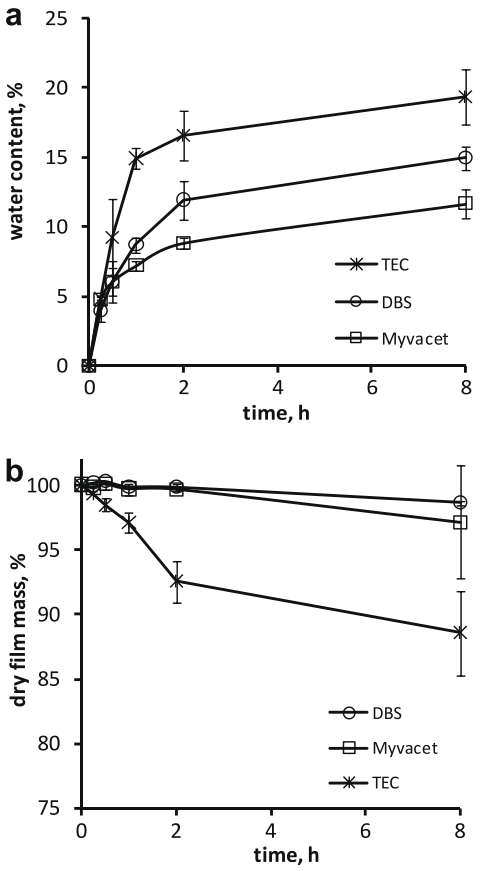

Fig. 7. Changes in the: (a) water content and (b) dry mass of free (cast) films containing different types of plasticizers (as indicated) upon exposure to 0.1 N HCl.

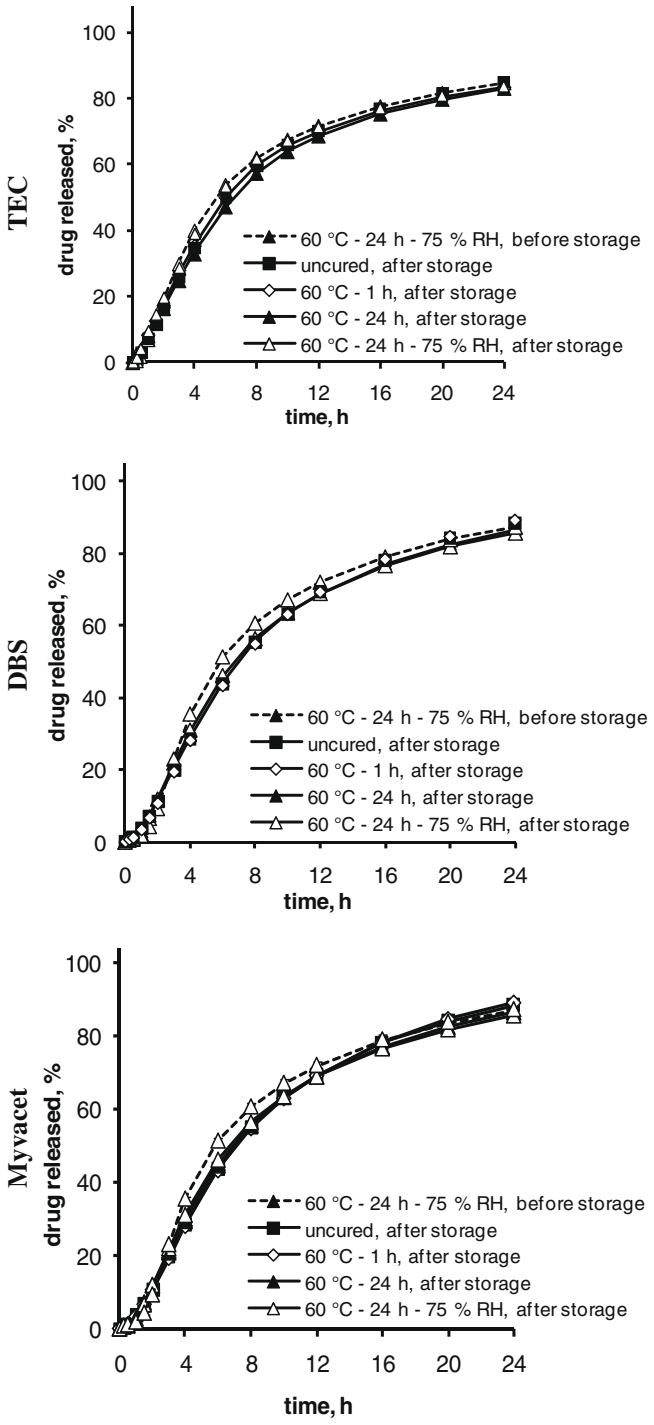

Fig. 8. Diltiazem HCl release from pellets coated with 7.5% Aquacoat, plasticized with TEC, DBS, or Myvacet (as indicated) before (dotted curve) and after 6 months of storage (solid curves) under stress conditions (40 °C and 75% relative humidity). The curing conditions are indicated in the diagrams.

as from pellets cured for 1 or 24 h at 60 °C are shown after 6-month storage under stress conditions. Interestingly, all curves are virtually overlapping ($55 < f_2 < 86$). This indicates that irrespective of the curing conditions after 6-month storage at 40 °C and 75% relative humidity, an equilibrium state seems to be reached for all types of systems. Similar tendencies were obtained for all the investigated coating levels (data not shown).

4. Conclusions

When using aqueous polymer dispersions for controlled release coatings, great care has to be taken when defining the curing conditions: time, temperature, and relative humidity. Importantly, the effects of these parameters on drug release can strongly depend on the type of plasticizer used and, to a great extent, on the coating level. This fact is often ignored.

Acknowledgement

The authors are grateful for the support of this work by the French Ministry ("Bourse CIFRE" for Ms. QiaoWen Yang).

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