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Research paper

Dynamic and static curing of ethylcellulose:PVA–PEG graft copolymer film coatings

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ABSTRACT

When using aqueous polymer dispersions for the preparation of controlled-release film coatings, instability during long-term storage can be a crucial concern. Generally, a thermal after treatment is required to assure sufficient polymer particle coalescence. This curing step is often performed under static conditions in an oven, which is a time-consuming and rather cumbersome process. Dynamic curing in the fluidized bed presents an attractive alternative. However, yet little is known on the required conditions, in particular: temperature, time, and relative humidity, to provide stable film structures. The aim of this study was to better understand the importance of these key factors and to evaluate the potential of dynamic curing compared with that of static curing. Recently proposed ethylcellulose:poly(vinyl alcohol)–poly(ethylene glycol) graft copolymer (PVA–PEG graft copolymer) dispersions were coated on theophylline and metoprolol succinate-loaded starter cores, exhibiting different osmotic activity. Importantly, processing times as short as 2 h were found to be sufficient to provide long-term stable films, even upon open storage under stress conditions. For instance, 2-h dynamic curing at 57 °C and 15% relative humidity are assuring stable film structures in the case of theophylline matrix cores coated with 15% ethylcellulose:PVA–PEG graft copolymer 85:15. Importantly, the approach is also applicable to other types of drugs and starter cores, and the underlying drug release mechanisms remain unaltered.

1. Introduction

Polymeric film coatings can efficiently control the release rate of a drug out of a pharmaceutical dosage form [1–3]. They can be applied either from organic solutions or from aqueous dispersions [4–7]. Water offers the advantage of being non-toxic, non-explosive, and environmentally friendly. However, the film formation mechanisms are different when using aqueous- versus organic-coating formulations, and eventually, the underlying drug release mechanisms from the final dosage forms can significantly differ [8]. One particular challenge when using aqueous polymer dispersions for the preparation of controlled-release film coatings is the assurance of long-term stable systems. If the polymer particles do not completely fuse during coating, further coalescence might occur during storage, resulting in denser film structures and less permeable barriers. Consequently, the resulting drug release rate might significantly decrease upon storage [9–11]. To overcome this restriction, a thermal after treatment ("curing") can be applied [12,13]. Obviously, the curing temperature, time, and relative humidity can have a major impact on the resulting polymeric structures: With increasing temperature, the mobility of the macromolecules increases, facilitating polymer particle coalescence. Also, increasing relative humidity enhances film formation, since water is an efficient plasticizer for many polymers (including ethylcellulose) [14].

Curing can be performed either under static conditions, e.g., on trays in an oven, or under dynamic conditions, e.g., in a fluidized bed. The major disadvantage of static curing is that it is generally cumbersome to realize, necessitating the transfer of the coated dosage forms into an oven and often requiring prolonged curing times. To be able to control the relative humidity during static curing, also special equipment is needed. An interesting alternative is dynamic curing, performed in the same equipment as the coating process. Thus, transfer steps are avoided and the relative humidity in the curing chamber can generally be easily controlled by spraying water at appropriate rates. However, yet little is known on the impact of the key factors, namely: time, temperature, and relative humidity during dynamic curing on the resulting drug release patterns from the coated dosage forms and on the long-term stability of the systems.

It was the aim of this study to better understand the impact of the curing conditions during static as well as dynamic curing on the resulting drug release rates and storage stability of different

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types of coated pellets. In particular, the importance of the curing time, temperature, and relative humidity was to be investigated. Recently proposed aqueous ethylcellulose:poly(vinyl alcohol)–poly(ethylene glycol) graft copolymer (PVA–PEG graft copolymer) dispersions [15–19] were used for film coating. Two types of beads were studied: (i) theophylline matrix cores and (ii) sugar cores layered with metoprolol succinate. Thus, pellet cores exhibiting very different osmotic activity were investigated and also drugs with very different solubility.

2. Materials and methods

2.1. Materials

Theophylline matrix pellets (70% drug content, diameter: 0.71–1.25 mm; FMC BioPolymer, Philadelphia, USA); sugar cores (sugar spheres NF, diameter: 0.71–0.85 mm; NP Pharm, Bazainville, France); metoprolol succinate (Salutas, Barleben, Germany); hydroxypropyl methylcellulose (HPMC, Methocel E 5; Colorcon, Dartford, UK); Ethylcellulose Aqueous Dispersion NF (Aquacoat ECD; FMC Biopolymer, Philadelphia, USA); poly(vinyl alcohol)–poly(ethylene glycol) graft copolymer (PVA–PEG graft copolymer, Kollicoat IR; BASF, Ludwigshafen, Germany); triethyl citrate (TEC; Morflex, Greensboro, USA).

2.2. Preparation of drug-layered starter cores

Sugar starter cores were coated with an aqueous solution of metoprolol succinate (18.2% w/w) and HPMC (0.9% w/w) in a fluidized bed coater (Strea 1, Wurster insert; Niro; Aeromatic-Fielder, Bubendorf, Switzerland). The process parameters were as follows: batch size = 500 g, inlet temperature = 40 °C, product temperature = 40 ± 2 °C, spray rate = 1–3 g/min, atomization pressure = 1.2 bar, nozzle diameter = 1.2 mm, air flow rate = 100 m^3/h. The final drug loading was 10% w/w.

2.3. Preparation of coated pellets

Metoprolol succinate-layered sugar cores as well as theophylline matrix cores were coated with aqueous ethylcellulose dispersion containing small amounts of PVA–PEG graft copolymer in a fluidized bed coater (Strea 1, Wurster insert). The coating dispersions were prepared as follows: The aqueous ethylcellulose dispersion was plasticized overnight with triethyl citrate (25% w/w, based on the ethylcellulose content) under magnetic stirring. Aqueous PVA–PEG graft copolymer solution (3.7% w/w in the case of metoprolol succinate-layered sugar cores and 6.0% w/w in the case of theophylline matrix cores) was added so that a final solids' content of 15% w/w was obtained in both cases. The respective blends were stirred for 30 min prior to coating. The coating parameters were as follows: batch size = 500 g, inlet temperature = 38 °C, product temperature = 38 ± 2 °C, spray rate = 1–3 g/min, atomization pressure = 1.2 bar, nozzle diameter = 1.2 mm, air flow rate = 100 m^3/h.

2.4. Pellet curing

Static curing: The pellets were further fluidized in the coater for 10 min and subsequently cured for 2–48 h at 40–60 °C (as indicated) in an oven.

Dynamic curing: The pellets were further fluidized in the coater for 0.5–3 h at 45–57 °C and 15–28% relative humidity (as indicated). During curing, water was atomized at a spray rate of 5.0, 5.2, and 5.5 g/min (at 45, 50 and 57 °C). The temperature and relative humidity were monitored using a "High Accuracy Humidity and Temperature Data Logger" (EL-USB-2; Lascar Electronics, Salisbury, UK).

2.5. Drug release measurements

Drug release from pellets was measured in 0.1 M HCl and phosphate buffer pH 7.4 (USP 33) using the USP 33 paddle apparatus (Sotax, Basel, Switzerland) (900 mL; 37 °C, 100 rpm; $n = 3$). At predetermined time intervals, 3 mL samples were withdrawn and analyzed UV-spectrophotometrically ($\lambda = 270.4$ nm in 0.1 N HCl and $\lambda = 272.2$ nm in phosphate buffer pH 7.4; UV-1650PC, Shimadzu, Champs-sur-Marne, France).

2.6. Storage stability

Coated pellets were stored in *open* glass vials at room temperature (25 ± 2 °C)/ambient RH (60 ± 5%) as well as under stress conditions: 40 °C/75% RH. Drug release was measured before and after storage as described in Section 2.5.

3. Results and discussion

3.1. Static curing

Fig. 1 shows drug release from theophylline matrix cores coated with 15% ethylcellulose:PVA–PEG graft copolymer 85:15 in:

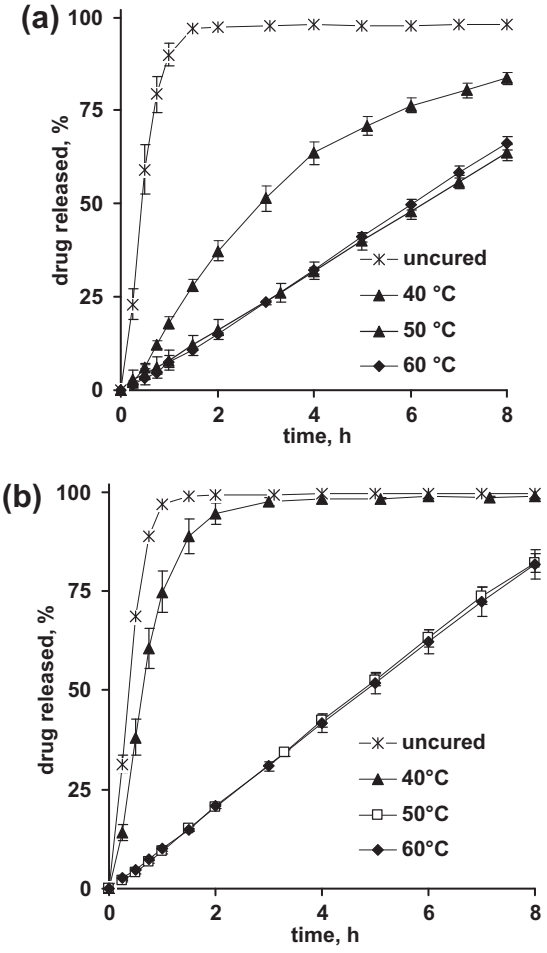

Fig. 1. Effects of the curing temperature during static curing in an oven on drug release from theophylline matrix cores coated with ethylcellulose:PVA–PEG graft copolymer 85:15 in: (a) 0.1 N HCl and (b) phosphate buffer pH 7.4 (curing time: 24 h).

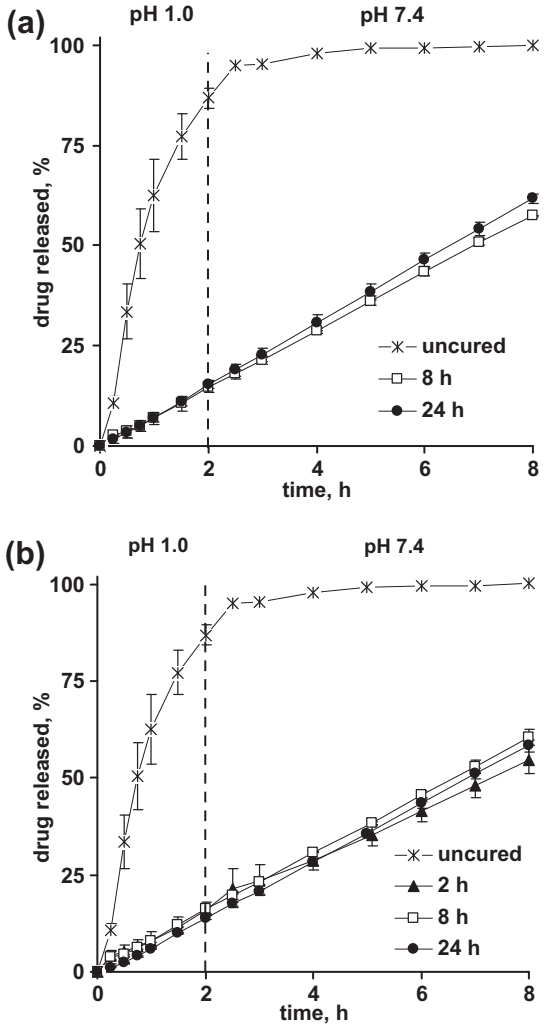

Fig. 2. Effects of the curing time during static curing in an oven at (a) 50 °C, (b) 60 °C on drug release from theophylline matrix cores coated with ethylcellulose:PVA–PEG graft copolymer 85:15 in 0.1 N HCl, and phosphate buffer pH 7.4 (medium change after 2 h).

(a) 0.1 M HCl and (b) phosphate buffer pH 7.4. The pellets were cured in an oven for 24 h at 40, 50, and 60 °C, as indicated. For reasons of comparison, also drug release from uncured pellets is shown. Clearly, drug release was most rapid from uncured pellets, irrespective of the type of release medium. This indicates that film formation was not complete under the given coating conditions. Twenty-four-hour curing at 40 °C led to decreased drug release rates in both cases, indicating improved polymer particle coalescence. The increase in temperature leads to increased macromolecular mobility and thus facilitated film formation. Increasing the curing temperature to 50 °C resulted in a further pronounced decrease in the release rates (Fig. 1). Importantly, the release patterns from pellets cured at 60 °C were virtually overlapping with those from pellets cured at 50 °C, in 0.1 M HCl as well as in phosphate buffer pH 7.4. Thus, a stable system is likely to be obtained under these conditions. Comparing Fig. 1a and b, it becomes obvious that drug release is faster in phosphate buffer pH 7.4 than in 0.1 M HCl in the case of not fully coalesced film coatings (upon curing at 40 °C). This can at least partially be attributed to the presence of the stabilizer sodium dodecyl sulfate (SDS) in the aqueous ethylcellulose dispersion: At low pH, SDS is protonated and neutral, whereas at pH 7.4 it is de-protonated and negatively charged. Thus, SDS located in channels in only partially coalesced film coatings

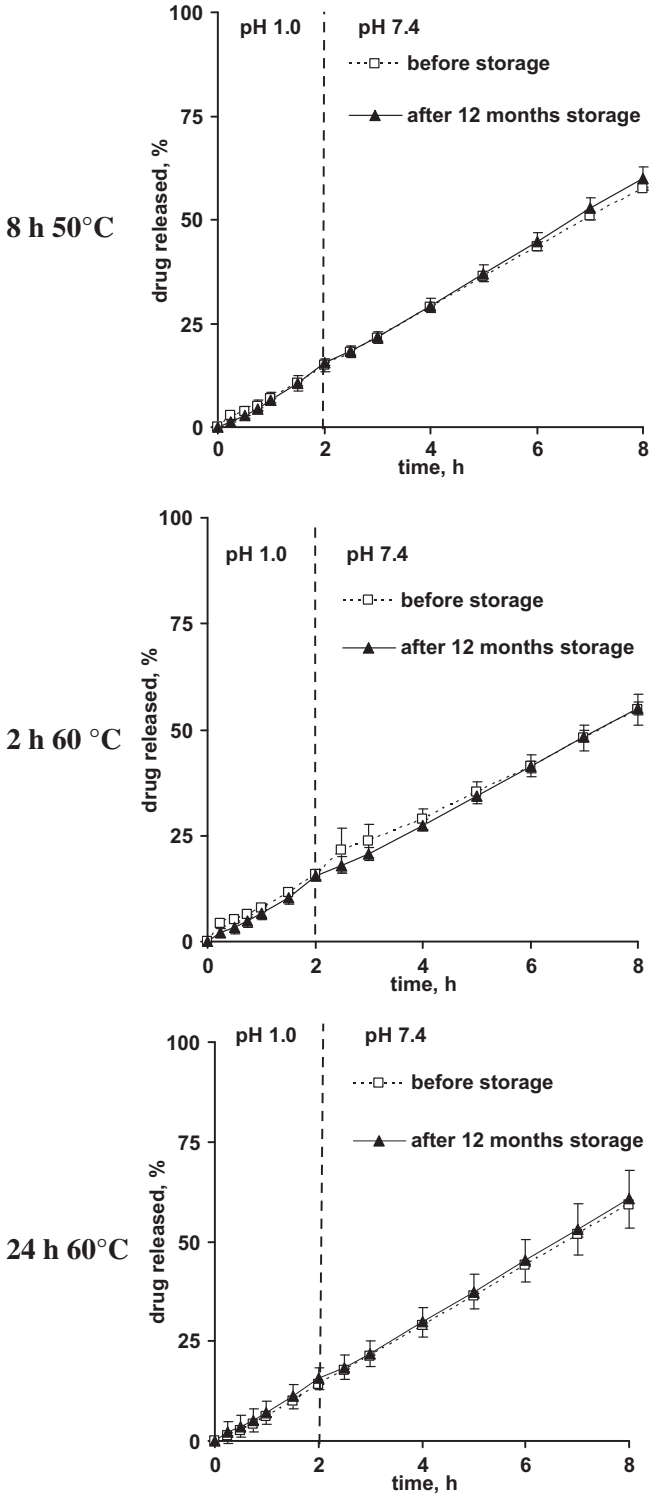

Fig. 3. Storage stability of ethylcellulose:PVA–PEG graft copolymer 85:15 coated theophylline matrix cores, cured in an oven for "8 h at 50 °C", "2 h at 60 °C", or "24 h at 60 °C" (as indicated) (storage under ambient conditions in open glass vials). The release medium was 0.1 N HCl during the first 2 h, followed by phosphate buffer pH 7.4.

can be expected to lower the surface tension more efficiently at pH 7.4, resulting in facilitated water penetration. The pH-dependent drug release cannot be attributed to a difference in drug solubility in the media: theophylline is even slightly better soluble in 0.1 M HCl than in phosphate buffer pH 7.4: 15.4 versus 12.0 mg/mL [20].

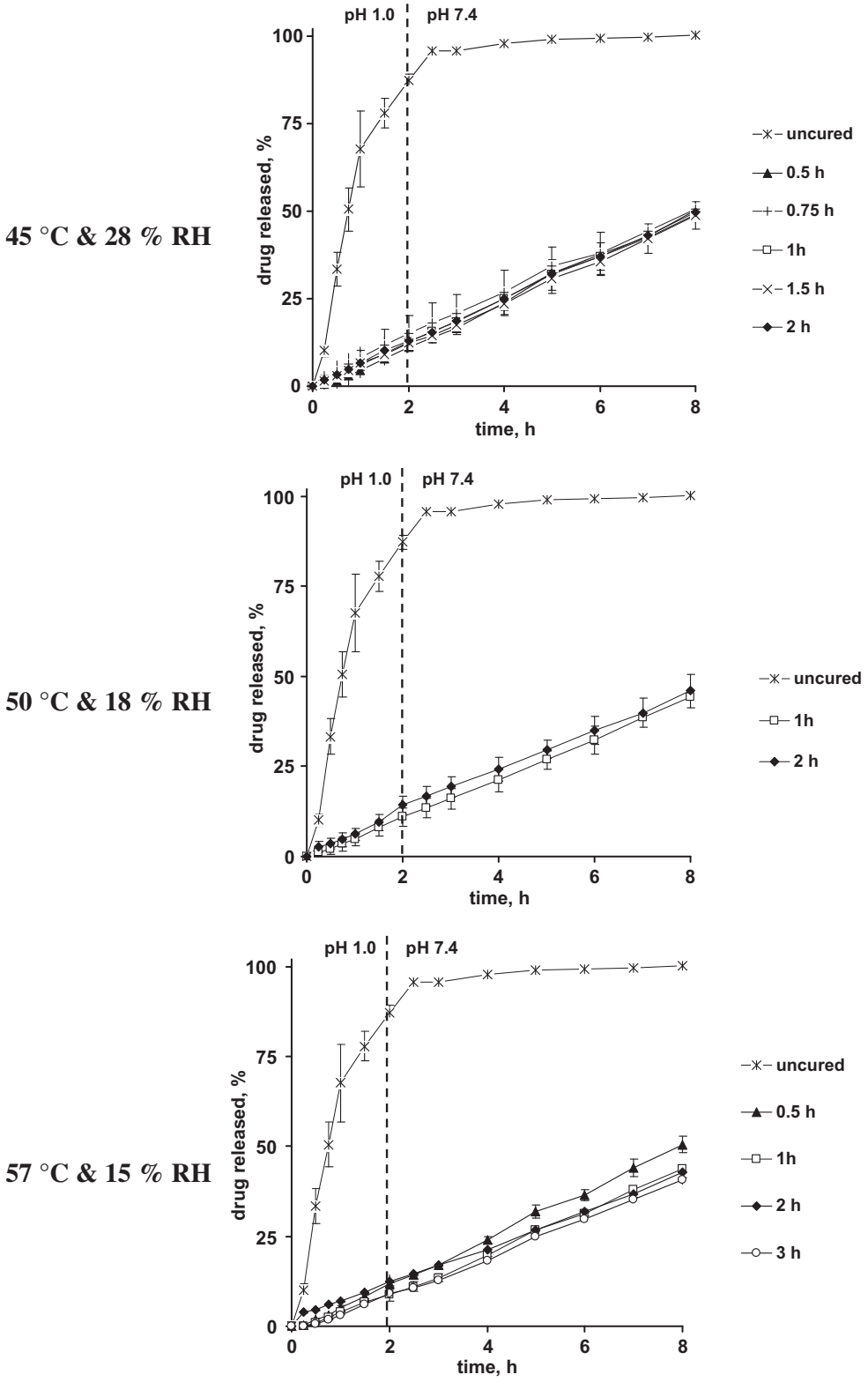

Fig. 4. Effects of the curing time on theophylline release from ethylcellulose:PVA–PEG graft copolymer 85:15 coated drug matrix cores, cured in a fluidized bed at "45 °C & 28% RH", "50 °C & 18% RH", or "57 °C & 15% RH" (as indicated).

The impact of the curing *time* of static curing in an oven on drug release from theophylline matrix cores coated with 15% ethylcellulose:PVA–PEG graft copolymer 85:15 is illustrated in Fig. 2. The release medium was 0.1 M HCl during the first 2 h, which was completely replaced by phosphate buffer pH 7.4 for the subsequent 6 h. The curing temperature was 50 or 60 °C (Fig. 2a and b). The curing time was varied from 0 to 24 h. Importantly, virtually overlapping drug release profiles were obtained in the case of 8 and 24 h curing at 50 °C and in the case of 2, 8, and 24 h curing at 60 °C. Thus, stable film coatings seem to be achieved already after

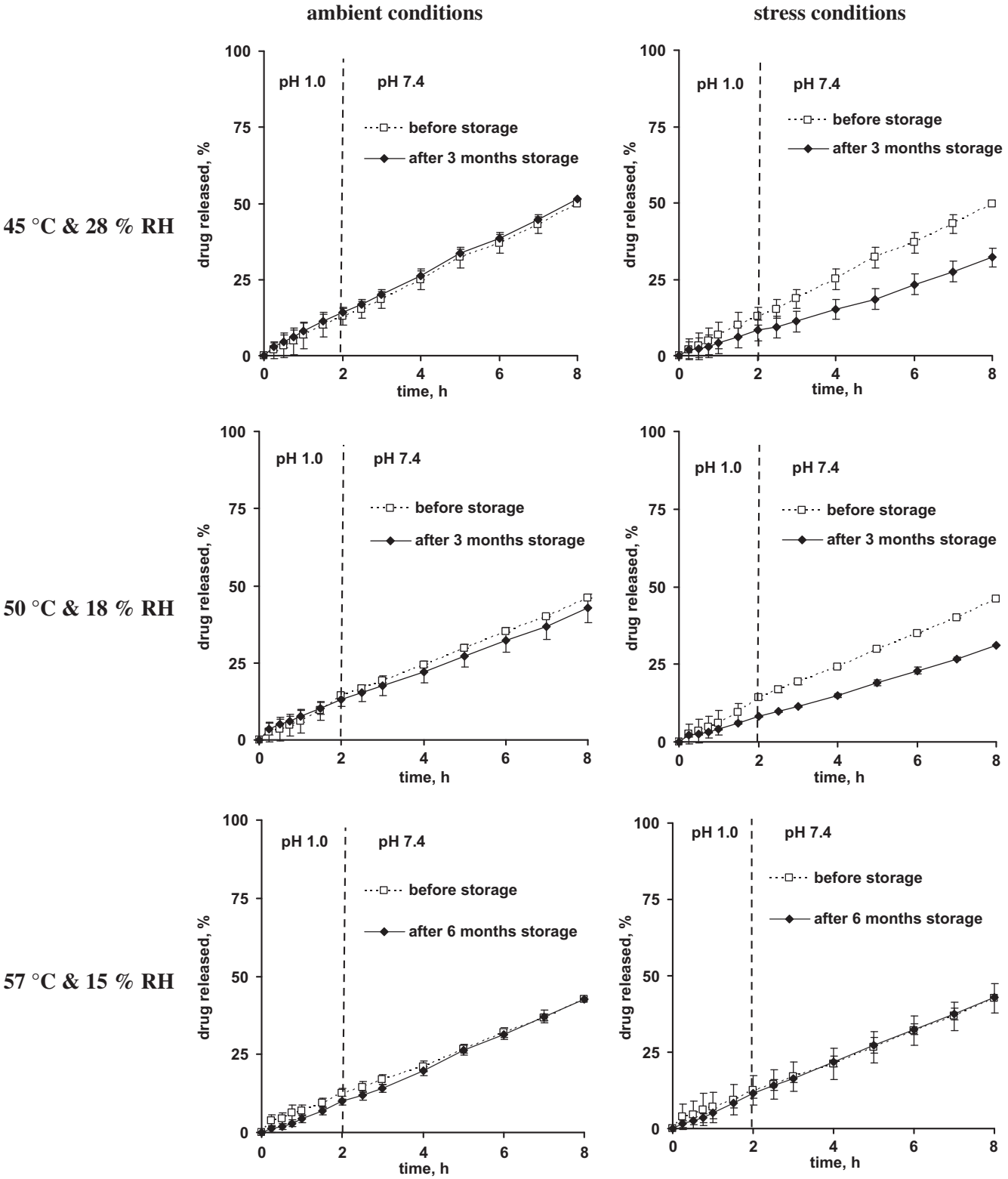

Fig. 5. Storage stability of ethylcellulose:PVA–PEG graft copolymer 85:15 coated theophylline matrix cores cured for 2 h in a fluidized bed at "45 °C & 28% RH", "50 °C & 18% RH", or "57 °C & 15% RH" under ambient (left column) and stress (right column) conditions. The release medium was 0.1 N HCl during the first 2 h, followed by phosphate buffer pH 7.4.

these curing times at these temperatures. This is of significant practical importance during production.

Achieving virtually overlapping drug release profiles at different temperatures and curing times is promising with respect to the systems' long-term stability, but it is not a proof of storage stability. Fig. 3 shows the release of theophylline from matrix pellets coated with 15% ethylcellulose:PVA–PEG graft copolymer 85:15 in 0.1 M HCl for the first 2 h, followed by phosphate buffer pH 7.4 for the subsequent 6 h. The dotted curves show drug release before storage, the solid curves drug release after 12 months storage

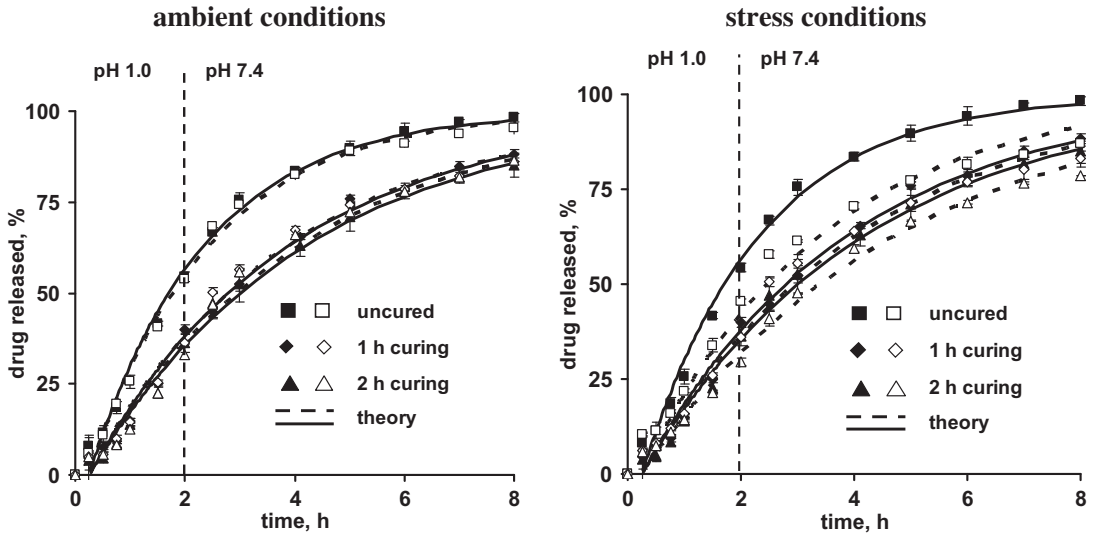

Fig. 6. Metoprolol succinate release from drug-layered sugar cores coated with 30% ethylcellulose:PVA–PEG graft copolymer 90:10, cured in a fluidized bed at 57 °C & 15% RH for 0, 1 or 2 h (as indicated): Experiments (symbols) and theory (curves, Eq. (1)). The closed symbols and solid curves show drug release prior to storage, and the open symbols and dotted curves show drug release after 10-month open storage under ambient or stress conditions.

under ambient conditions in open glass vials. The pellets were cured for 8 h at 50 °C or for 2 or 24 h at 60 °C. As it can be seen, the drug release patterns were stable, irrespective of the curing conditions and storage times. This confirms the hypothesis that the polymer particles coalesced to a sufficient degree during coating and curing to avoid any alterations during long-term storage.

3.2. Dynamic curing

In order to avoid transferring the pellets into an oven, the pellets were further fluidized in the coater after coating. The temperature was held at 45, 50, or 57 °C and the corresponding relative humidity at 28%, 18%, and 15% (by spraying water at 5.0, 5.2 and 5.5 g/min). The curing time was varied in the range of 0.5–3 h. Drug release from theophylline matrix cores coated with 15% ethylcellulose:PVA–PEG graft copolymer 85:15 was measured in 0.1 M HCl and phosphate buffer pH 7.4 (complete medium change after 2 h). Interestingly, the resulting release patterns were very similar upon dynamic curing at 45 °C & 28% RH for 0.5–2 h, at 50 °C & 18% RH for 1 and 2 h, and at 57 °C & 15% RH for 0.5–3 h (Fig. 4). This potentially indicates that stable film coatings were formed even after these short curing steps. However, caution must be paid, as it can be seen in Fig. 5 [illustrating the long-term (in)stability of the investigated systems]. Drug release was measured before and after 3 or 6 months open storage in glass vials under ambient and stress conditions (left and right column). Clearly, the release rate decreased in the case of pellets cured in the fluidized bed for 2 h at "45 °C & 28% RH" as well as at "50 °C & 18% RH" upon storage under stress conditions. This can probably be attributed to further polymer particle coalescence during long-term storage, resulting in reduced film coating permeability for the drug [21]. In contrast, pellets stored under ambient conditions showed stable drug release patterns. The instability under stress conditions can be attributed to the fact that water acts as a plasticizer for ethylcellulose and to the increased temperature: The mobility of the macromolecules is increased, resulting in facilitated polymer particle coalescence. Similar tendencies have been observed by Williams III and Liu with cellulose acetate phthalate (CAP) aqueous dispersion [22,23]. Importantly, the theophylline release rate was not altered upon long-term storage even under stress conditions, if the pellets were cured for 2 h at 57 °C & 15% RH in the fluidized bed (Fig. 5, bottom raw). Thus, long-term stable film coatings can be provided after only 2-h dynamic curing under appropriate conditions. This is of great practical importance.

In order to evaluate the transferability of the proposed dynamic curing to other types of drugs and other types of starter cores, also metoprolol succinate-layered sugar cores were coated with ethylcellulose:PVA–PEG graft copolymer. According to previously published results [17], ethylcellulose:PVA–PEG graft copolymer 90:10 blends and a coating level of 30% are a good starting point if 8–12 h controlled release is targeted for freely water-soluble drugs layered onto osmotically active starter cores. The closed symbols in Fig. 6 show the experimentally determined release kinetics of metoprolol succinate from drug-layered sugar cores coated with 30% ethylcellulose:PVA–PEG graft copolymer 90:10 prior to storage. The pellets were cured in the fluidized bed for 1 or 2 h at 57 °C & 15% RH. For reasons of comparison, also drug release from uncured pellets is illustrated. The release medium was 0.1 M HCl for the first 2 h, which was completely exchanged with phosphate buffer pH 7.4 for the subsequent 6 h. Importantly, the release patterns from pellets cured for 1 or 2 h are virtually overlapping, a promising observation with respect to long-term stability (although caution must be paid as discussed above).

In order to better understand the underlying drug release mechanisms, an appropriate mathematical model was used to quantitatively describe the experimentally measured metoprolol succinate release profiles [24]. The theory considers:

- The spherical geometry of the pellets.
- Perfect sink conditions (which were provided throughout the experiments).
- Diffusion through the polymeric film coating as the dominant mass transport step with constant diffusion coefficients.
- The initial amount of drug in the pellets, M_0.
- Drug partitioning from the pellet core into the polymeric film coatings.
- The dimensions of the system.

Under these conditions, the following analytical solution of Fick's law of diffusion can be derived:

$$M_t = M_0\left[1 - \exp\left(-\frac{ADKt}{Vl}\right)\right] \quad (1)$$

where A is the total surface area of a coated pellet; D denotes the apparent diffusion coefficient of the drug in the polymeric membrane; K represents the partition coefficient of the drug between the film coating and the pellet core; V is the volume of the pellet core and l the thickness of the film coating.

As it can be seen in Fig. 6, good agreement was obtained between the experimentally determined and theoretically calculated drug release patterns before storage (closed symbols and solid curves). This indicates that drug diffusion through the intact film coatings seems to be the dominant mass transport mechanism. Based on these calculations, the following "$D \times K$" (apparent diffusivity of metoprolol succinate in ethylcellulose:PVA–PEG graft copolymer 90:10 $\times$ partition coefficient of the drug between the coating and the release medium) values were determined: 4.7, 2.7, 2.5×10^{-9} cm^2/s for 0-, 1-, and 2-h dynamic curing.

The open symbols and dotted curves in Fig. 6 indicate the drug release patterns from the pellets after 10-month storage under ambient and stress conditions. Clearly, the drug release rate decreased upon long-term storage under stress conditions in the case of uncured pellets, but remained stable in all other cases. Thus, the approach of dynamic curing for short time periods is applicable to different types of drugs and starter cores. In all cases, the underlying drug release mechanisms remained the same (diffusion through the intact film coating being dominant). The following "$D \times K$" values were determined for metoprolol succinate-layered sugar cores coated with ethylcellulose:PVA–PEG graft copolymer 90:10 and cured for 0, 1, and 2 h at 57 °C & 15% RH after 10-month storage under ambient and stress conditions: 4.5, 2.7, 2.6×10^{-9} cm^2/s and 3.1, 2.6, 2.2×10^{-9} cm^2/s.

4. Conclusions

Long-term stable film coatings prepared from aqueous ethylcellulose dispersion containing small amounts of PVA–PEG graft copolymer can be obtained after only 8-h curing at 50 °C or 2-h static curing at 60 °C in an oven. Alternatively, also dynamic curing in the fluidized bed is possible under further water spraying for only 2 h. This is of significant practical importance since long-term stability of controlled release formulations prepared with aqueous polymer dispersions is critical.

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References

[1] Z.-W. Ye, P. Rombout, J.P. Remon, C. Vervaet, G. Van den Mooter, Correlation between the permeability of metoprolol tartrate through plasticized isolated ethylcellulose/hydroxypropyl methylcellulose films and drug release from reservoir pellets, Eur. J. Pharm. Biopharm. 67 (2007) 485–490.
[2] S. Ensslin, K.P. Moll, H. Metz, M. Otz, K. Mäder, Modulating pH-independent release from coated pellets: effect of coating composition on solubilization processes and drug release, Eur. J. Pharm. Biopharm. 72 (2009) 111–118.
[3] J. Goole, P. Deleuze, F. Vanderbist, K. Amighi, New levodopa sustained-release floating minitablets coated with insoluble acrylic polymer, Eur. J. Pharm. Biopharm. 68 (2008) 310–318.
[4] J.W. McGinity, Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms, second ed., Marcel Dekker, New York, NY, 1997.
[5] M. Wesseling, R. Bodmeier, Drug release from beads coated with an aqueous colloidal ethylcellulose dispersion, Aquacoat®, or an organic ethylcellulose solution, Eur. J. Pharm. Biopharm. 47 (1999) 33–38.
[6] F. Lecomte, J. Siepmann, M. Walther, R.J. MacRae, R. Bodmeier, Polymer blends used for the aqueous coating of solid dosage forms: importance of the type of plasticizer, J. Control. Release 99 (2004) 1–13.
[7] B.C. Lippold, R. Monells Pages, Film formation, reproducibility of production and curing with respect to release stability of functional coatings from aqueous polymer dispersions, Pharmazie 56 (2001) 5–17.
[8] F. Lecomte, J. Siepmann, M. Walther, R.J. MacRae, R. Bodmeier, Polymer blends used for the coating of multiparticulates: comparison of aqueous and organic coating techniques, Pharm. Res. 21 (2004) 882–890.
[9] W. Zheng, D. Sauer, J.W. McGinity, Influence of hydroxyethylcellulose on the drug release properties of theophylline pellets coated with Eudragit® RS 30D, Eur. J. Pharm. Biopharm. 59 (2005) 147–154.
[10] K. Amighi, A.J. Moes, Influence of plasticizer concentration and storage conditions on the drug release rate from Eudragit RS 30D film-coated sustained-release theophylline pellets, Eur. J. Pharm. Biopharm. (1996) 29–35.
[11] C. Wu, J.W. McGinity, Influence of relative humidity on the mechanical and drug release properties of theophylline pellets coated with an acrylic polymer containing methylparaben as a non-traditional plasticizer, Eur. J. Pharm. Biopharm. 50 (2000) 277–284.
[12] C.A. Gilligan, A. Li Wan Po, Factors affecting drug release from a pellet system coated with an aqueous colloidal dispersion, Int. J. Pharm. 73 (1991) 51–68.
[13] Q.W. Yang, M.P. Flament, F. Siepmann, V. Busignies, B. Leclerc, C. Herry, P. Tchoreloff, J. Siepmann, Curing of aqueous polymeric film coatings: importance of the coating level and type of plasticizer, Eur. J. Pharm. Biopharm. 74 (2010) 362–370.
[14] F. Lecomte, J. Siepmann, M. Walther, R.W. MacRae, R. Bodmeier, Blends of enteric and GIT-insoluble polymers used for film coating: physicochemical characterization and drug release patterns, J. Control. Release 89 (2003) 457–471.
[15] F. Siepmann, A. Hoffmann, B. Leclercq, B. Carlin, J. Siepmann, How to adjust desired drug release patterns from ethylcellulose-coated dosage forms, J. Control. Release 119 (2007) 182–189.
[16] F. Siepmann, S. Muschert, B. Leclercq, B. Carlin, J. Siepmann, How to improve the storage stability of aqueous polymeric film coatings, J. Control. Release 126 (2008) 26–33.
[17] S. Muschert, F. Siepmann, Y. Cuppok, B. Leclercq, B. Carlin, J. Siepmann, Improved long term stability of aqueous ethylcellulose film coatings: importance of the type of drug and starter core, Int. J. Pharm. 368 (2009) 138–145.
[18] S. Muschert, F. Siepmann, B. Leclercq, B. Carlin, J. Siepmann, Prediction of drug release from ethylcellulose coated pellets, J. Control. Release 135 (2009) 71–79.
[19] S. Muschert, F. Siepmann, B. Leclercq, B. Carlin, J. Siepmann, Drug release mechanisms from ethylcellulose:PVA–PEG graft copolymer coated pellets, Eur. J. Pharm. Biopharm. 72 (2009) 130–137.
[20] R. Bodmeier, H. Chen, Evaluation of biodegradable poly(lactide) pellets prepared by direct compression, J. Pharm. Sci. 78 (1989) 819–822.
[21] H. Kranz, S. Gutsche, Evaluation of the drug release patterns and long term stability of aqueous and organic coated pellets by using blends of enteric and gastrointestinal insoluble polymers, Int. J. Pharm. 380 (2009) 112–119.
[22] R.O. Williams III, J. Liu, Influence of processing and curing conditions on beads coated with an aqueous dispersion of cellulose acetate phthalate, Eur. J. Pharm. Biopharm. 49 (2000) 243–252.
[23] J. Lui, R.O. Williams III, Properties of heat-humidity cured cellulose acetate phthalate free films, Eur. J. Pharm. Sci. 17 (2002) 31–41.
[24] J. Siepmann, F. Siepmann, Mathematical modeling of drug delivery, Int. J. Pharm. 346 (2008) 328–343.