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Improved long term stability of aqueous ethylcellulose film coatings: Importance of the type of drug and starter core

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ABSTRACT

Instability during long term storage due to further gradual coalescence of the film remains one of the major challenges when using aqueous polymer dispersions for controlled release coatings. It has recently been shown that the addition of small amounts of poly(vinyl acetate)–poly(ethylene glycol)-graft-copolymer (PVA–PEG-graft-copolymer) to aqueous ethylcellulose dispersion provides long term stable drug release patterns even upon open storage under stress conditions in the case of theophylline matrix cores. However, the transferability of this approach to other types of drugs and starter cores exhibiting different osmotic activity is yet unknown. The aim of this study was to evaluate whether this novel approach is also applicable to freely water-soluble drugs and osmotically active sugar starter cores. Importantly, long term stable drug release profiles from coated diltiazem HCl-layered sugar cores could be achieved even upon open storage for 1 year under stress conditions (40 °C and 75% relative humidity). However, to provide desired drug release profiles the amount of added PVA–PEG-graft-copolymer must be adjusted. A minimal critical content of 10% (w/w) of this hydrophilic additive was identified, under which further polymer particle coalescence upon long term storage under stress conditions cannot be excluded. Potentially too rapid drug release can effectively be slowed down by increasing the coating level. Thus, adapting the polymer blend ratio and coating thickness desired and long term stable drug release profiles (even under stress conditions and open storage) can be provided for very different types of drugs and starter cores by the addition of small amounts of PVA–PEG-graft-copolymer to aqueous ethylcellulose dispersion.

1. Introduction

Ethylcellulose is a highly suitable polymer for film coating (Wallace, 1990; Iyer et al., 1993; Ye et al., 2007). It is nontoxic, nonallergenic, nonirritant and a good film former (Wade and Weller, 1994; Naelpäa et al., 2007). For many years this polymer has been widely used in oral pharmaceutical formulations for various purposes, including moisture protection, taste masking (DeMerlis et al., 2005) and controlled release.

Ethylcellulose-based film coatings can be applied either from organic solutions or from aqueous dispersions (McGinity, 1997). The use of *aqueous* polymer dispersions instead of *organic* polymer solutions offers various major advantages, including reduced processing times (due to the higher solids' contents that can be used in the coating formulations, as a result of the comparatively low viscosity of aqueous polymer dispersions versus organic polymer solutions), avoidance of potential product toxicity due to residual organic solvents and reduced environmental concerns (Fukumori, 1997; McGinity, 1997). But care needs to be taken, because the underlying film formation mechanisms are fundamentally different. In organic polymer solutions the individual macromolecules are highly mobile. Upon solvent evaporation the polymer chains approach each other and finally form a continuous homogenous network with a high degree of polymer chain entanglement (Banker, 1966). In contrast, in the case of aqueous polymer dispersions the polymer is initially deposited as polymer spheres, which must fuse or coalesce to form a continuous homogenous network. Failure to achieve full coalescence gives film coatings with significantly different microstructure (Lecomte et al., 2004). Upon water evaporation the polymer particles approach each other and form densely packed arrays (Chevalier et al., 1992; Wheatley and Steuernagel, 1997). Under appropriate conditions (in particular at an appropriate temperature and water content) the individual particles fuse together. The presence of water during this process has two major impacts: (i) it acts as a plasticizer for many polymers (including ethylcellulose), increasing the macromolec-

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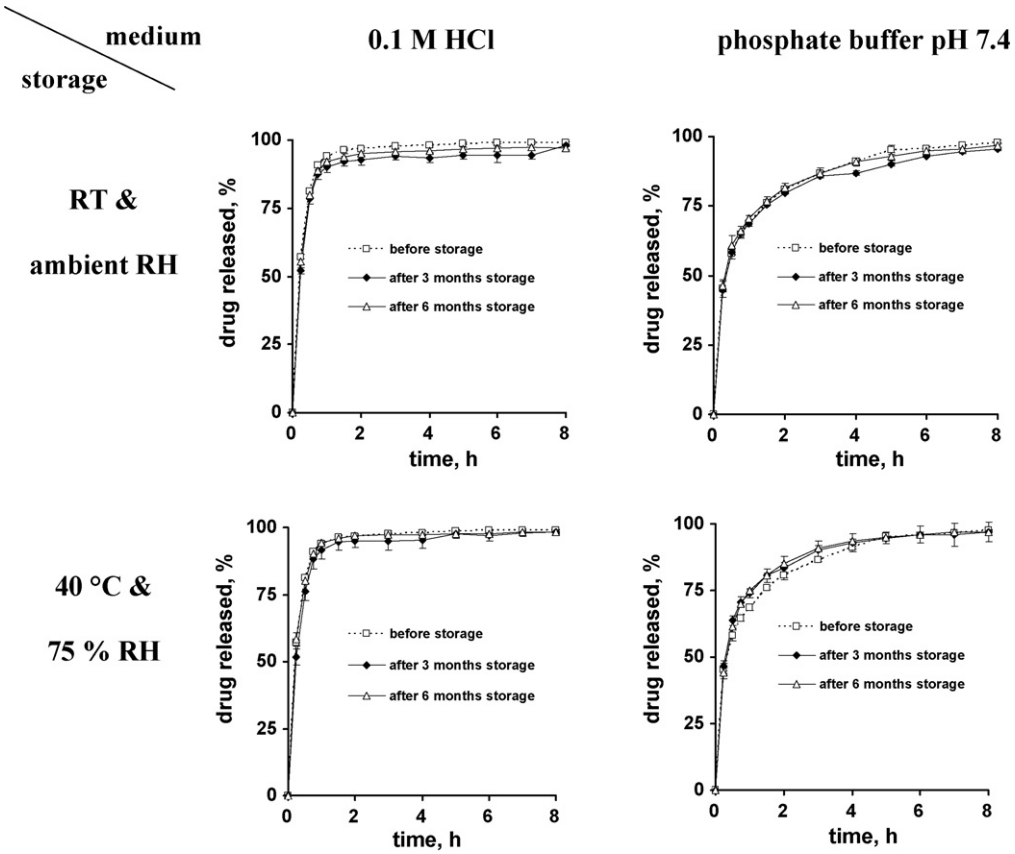

Fig. 1. Drug release from diltiazem HCl-layered sugar cores coated with ethylcellulose:PVA–PEG-graft-copolymer 85:15 before (dotted lines) and after 3 and 6 months storage (full lines, as indicated). The release media are shown at the top and the storage conditions on the left (coating level: 15%; plasticizer: TEC; drug loading of the diltiazem HCl-layered sugar cores: 10%).

ular mobility and, thus, facilitating polymer particle coalescence and (ii) it is mandatory for the capillary forces driving the polymer particles together. Often, complete polymer particle coalescence is difficult to be assured during the *coating* process. This is why generally a thermal after-treatment (curing step) is required (Bodmeier and Paeratakul, 1991; McGinity, 1997). The idea is to increase the temperature and, thus, the mobility of the polymer chains, facilitating further polymer particle coalescence. If the curing is performed at elevated relative humidity, significant amounts of water act as plasticizer and at the same time increase the capillary forces. However, in practice/in production curing is generally conducted only at ambient relative humidity and the acceptable curing times and temperatures are limited. Thus, even an additional curing step (feasible during production) cannot assure fully coalesced films in various cases, resulting in further polymer particle coalescence during long term storage. This often leads to decreasing drug permeability of the film coatings and, thus, to decreasing drug release rates (Amighi and Moes, 1996; Hamdani et al., 2006).

To overcome these restrictions the addition of small amounts of poly(vinyl acetate)–poly(ethylene glycol)-graft-copolymer (PVA–PEG-graft-copolymer) to aqueous ethylcellulose dispersion was recently proposed (Siepmann et al., 2007, 2008). The presence of this hydrophilic compound can be expected to trap water within the film coatings during *coating* and *curing*, thus, facilitating polymer particle coalescence. For theophylline matrix cores an ethylcellulose film coating containing 15% PVA–PEG-graft-copolymer was shown to provide long term stable drug release profiles even upon open storage under stress conditions (40 °C, 75% relative humidity). However, yet it is not clear whether this approach can also be applied to other types of drugs and other types of pellet starter cores, exhibiting different osmolarity.

The aim of this study was to evaluate whether this novel approach (allowing for significantly improved long term stability of aqueous polymeric coatings) is also applicable to freely water-soluble drugs and osmotically active sugar starter cores. Instability during long term storage remains one of the major challenges to be addressed when coating solid dosage forms with aqueous polymer dispersions.

2. Materials and methods

2.1. Materials

Sugar starter cores (sugar spheres NF, 710–850 μm; NP Pharm, Bazainville, France), diltiazem hydrochloride (diltiazem HCl; VWR, Fontenay-sous-Bois, France), ethylcellulose aqueous dispersion NF (Aquacoat ECD; FMC, Philadelphia, PA), poly(vinyl alcohol)–poly(ethylene glycol)-graft-copolymer (Kollicoat IR; BASF, Ludwigshafen, Germany), triethyl citrate (TEC; Morflex, Greensboro, NC, USA), dibutyl sebacate (DBS; Morflex).

2.2. Preparation of drug-layered starter cores

Sugar starter cores were coated with an aqueous solution of diltiazem HCl (18.2%, w/w) and hydroxypropyl methylcellulose (HPMC, Methocel E 5; Colorcon, Dartford, UK) (0.9%, w/w) in a fluidized bed coater (Strea 1, Wurster insert; Niro, Bubendorf, Switzerland). The process parameters were as follows: inlet temperature = 40 °C, product temperature = 40 ± 2 °C,

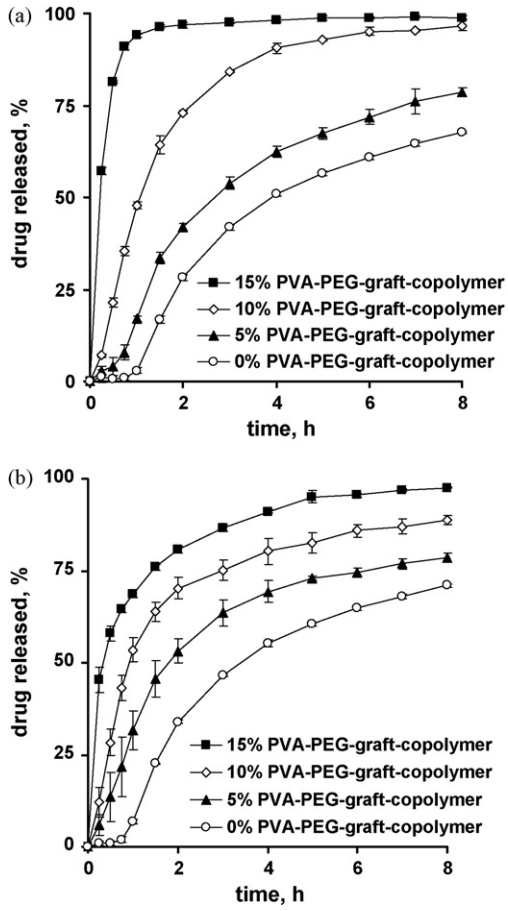

Fig. 2. Effects of the PVA–PEG-graft-copolymer content (indicated in the diagrams) in the ethylcellulose-based film coatings on drug release in: (a) 0.1N HCl and (b) phosphate buffer pH 7.4 (coating level: 15%; plasticizer: TEC; drug loading of the diltiazem HCl-layered sugar cores: 10%).

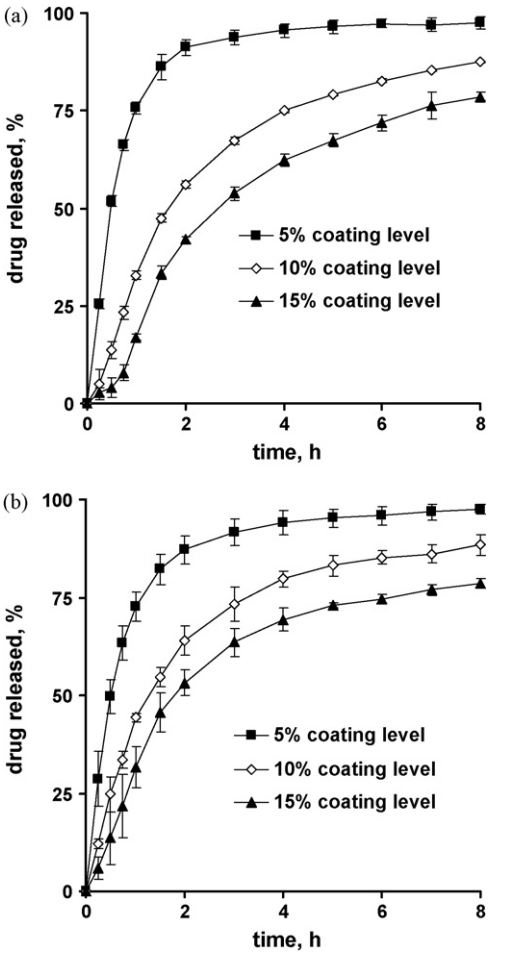

Fig. 3. Effects of the coating level (indicated in the diagrams) on drug release from ethylcellulose:PVA–PEG-graft-copolymer 95:05 coated diltiazem HCl-layered sugar cores in: (a) 0.1N HCl and (b) phosphate buffer pH 7.4 (plasticizer: TEC; drug loading of the diltiazem HCl-layered sugar cores: 10%).

spray rate = 1–3 g/min, atomization pressure = 1.2 bar, nozzle diameter = 1.2 mm. The final drug loading of the diltiazem HCl-layered sugar cores was 10% and 20% (w/w), respectively.

2.3. Preparation of polymer-coated pellets

The drug-layered sugar cores were coated with aqueous ethylcellulose dispersion (Aquacoat ECD) containing small amounts of PVA–PEG-graft-copolymer in a fluidized bed coater (Strea 1, Wurster insert). All dispersions were plasticized overnight with TEC or DBS (25%, w/w, based on the ethylcellulose content), respectively. The following ethylcellulose:PVA–PEG-graft-copolymer blend ratios were investigated: 85:15, 90:10, and 95:5 (w/w). The coating dispersions were sprayed onto the diltiazem HCl-layered sugar cores until a weight gain of 5–30% (w/w) was achieved (as indicated). The process parameters were as follows: inlet temperature = 38 °C, product temperature = 38 ± 2 °C, spray rate = 2–3 g/min, atomization pressure = 1.2 bar, and nozzle diameter = 1.2 mm. After coating the pellets were further fluidized for 10 min and subsequently cured for 24 h at 60 °C at ambient relative humidity.

2.4. Drug release studies

Diltiazem HCl release from the pellets was measured in 0.1N HCl and phosphate buffer pH 7.4 (USP 30) using the paddle apparatus (USP 30; Sotax, Basel, Switzerland) (900 ml, 37 °C, 100 rpm; $n = 3$). At pre-determined time intervals, 3 ml samples were withdrawn and analyzed UV-spectrophotometrically ($\lambda = 236.9$ nm in 0.1N HCl and $\lambda = 237.4$ nm in phosphate buffer pH 7.4; UV-1650PC, Shimadzu, Champs-sur-Marne, France). In all cases, perfect sink conditions were provided.

2.5. Long term storage stability

Coated pellets were stored in open glass vials at room temperature and ambient relative humidity (RH) as well as under stress conditions (40 °C and 75% RH). Diltiazem HCl release from the pellets was measured before and after 3, 6 or 12 months storage as described in Section 2.4.

2.6. Determination of the drug solubility

Excess diltiazem HCl was placed in contact with 0.1N HCl and phosphate buffer pH 7.4 (USP 30) at 37 °C in a horizontal shaker (80 rpm, GFL 3033; Gesellschaft fuer Labortechnik, Burgwedel, Germany) for at least 48 h. Every 12 h, samples were withdrawn, filtered and analyzed for their drug content as described in Section 2.4 until equilibrium was reached.

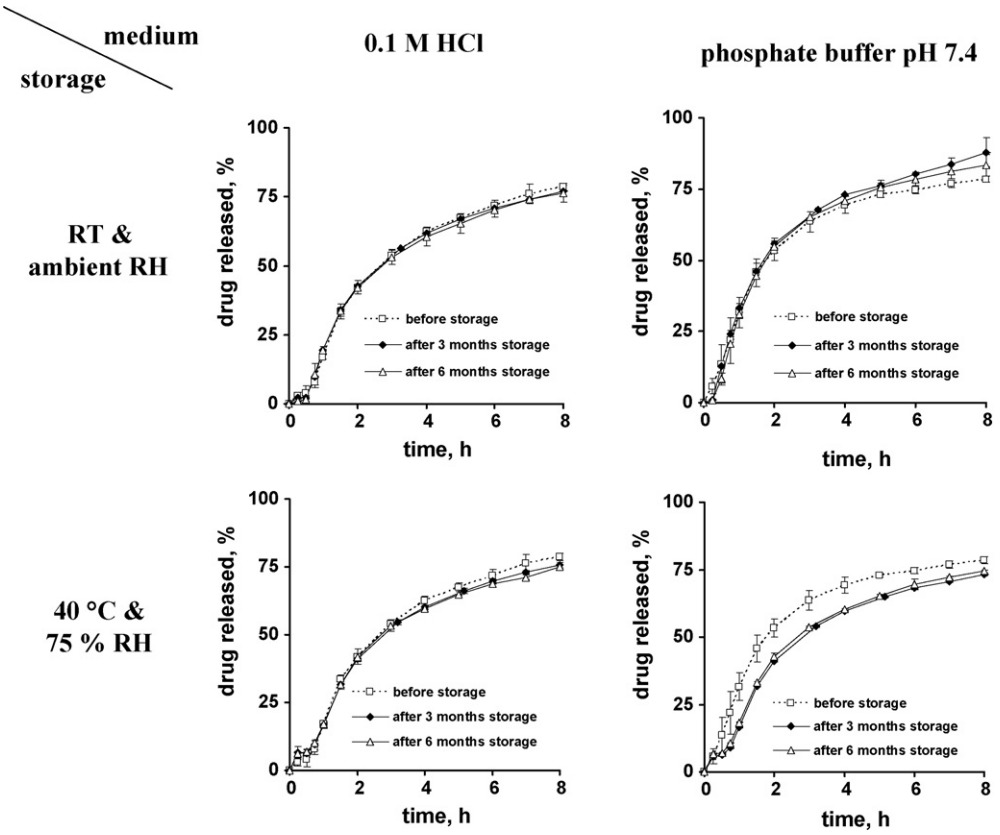

Fig. 4. Drug release from diltiazem HCl-layered sugar cores coated with ethylcellulose:PVA–PEG-graft-copolymer 95:5 before (dotted lines) and after 3 and 6 months storage (full lines, as indicated). The release media are shown at the top, the storage conditions on the left (coating level: 15%; plasticizer: TEC; drug loading of the diltiazem HCl-layered sugar cores: 10%).

3. Results and discussion

3.1. Ethylcellulose:PVA–PEG-graft-copolymer 85:15 blends

Recently, long term stable and constant drug release rates during 8–12 h were reported for theophylline matrix cores coated with ethylcellulose:PVA–PEG-graft-copolymer 85:15 blends at a coating level of 15% (Siepmann et al., 2008). In contrast to those pellets containing poorly water-soluble theophylline, in the present case very rapid drug release was observed when using this type of film coating at the same coating level and similarly sized diltiazem HCl-layered sugar cores, irrespective of the type of release medium (Fig. 1, dotted curves). This significant difference can at least partially be attributed to the much higher aqueous solubility of diltiazem HCl compared to theophylline: 662 mg/ml versus 15.4 mg/ml in 0.1N HCl at 37 °C, and 581 mg/ml versus 12.0 mg/ml in phosphate buffer pH 7.4 at 37 °C, respectively (values in phosphate buffer have been reported by Bodmeier and Chen, 1989). Furthermore, the presence of the sugar core can be expected to result in more pronounced water penetration into the pellet (driven by osmosis) upon contact with the release media, resulting in an increased hydrostatic pressure acting against the film coating (Lecomte et al., 2005). Importantly, as in the case of theophylline matrix cores, diltiazem HCl release from the pellets coated with ethylcellulose:PVA–PEG-graft-copolymer 85:15 blends was stable during open storage for 3 and 6 months under ambient as well as under stress conditions (40 °C and 75% RH), irrespective of the type of release medium (Fig. 1, solid curves).

Thus, the overall approach to add small amounts of PVA–PEG-graft-copolymer to aqueous ethylcellulose dispersion to provide long term stability even under stress conditions is applicable also to other types of drugs than theophylline and to osmotically active starter cores. However, the exact thickness and composition of the film coatings suitable to achieve controlled drug release during 8–12 h need to be adjusted. In order to slow down diltiazem HCl release from the investigated pellets, two strategies were followed: the percentage of the water-soluble PVA–PEG-graft-copolymer was decreased and the coating level was increased.

3.2. Effects of the PVA–PEG-graft-copolymer content on drug release

As it can be seen in Fig. 2, the lowering of the PVA–PEG-graft-copolymer content in the film coating from 15% to 0% was very efficient to slow down drug release from the coated diltiazem HCl-layered sugar cores, irrespective of the type of release medium. This can be explained by the water-insolubility and lower permeability of ethylcellulose compared to PVA–PEG-graft-copolymer (Siepmann et al., 2007). In contrast to theophylline matrix cores coated with this type of polymer blend, no zero-order release kinetics were observed. This can be attributed to the significantly higher water-solubility of diltiazem HCl compared to theophylline. The entire drug dose is rapidly dissolved upon water penetration into the pellets, and drug molecules that leave the system are not replaced by dissolving drug excess. Thus, the drug concentration gradients (inside–outside the polymeric membranes) decrease with time, resulting in decreasing absolute and relative drug release rates, irrespective of the type of release medium and PVA–PEG-graft-copolymer content (Fig. 2).

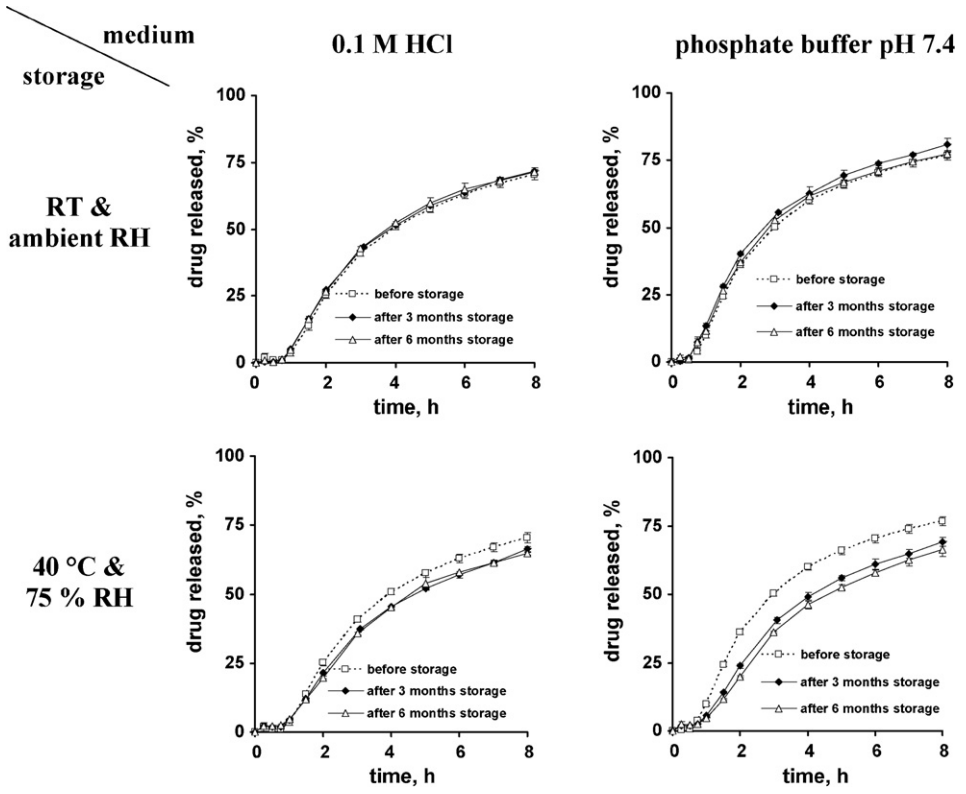

Fig. 5. Drug release from diltiazem HCl-layered sugar cores coated with ethylcellulose:PVA–PEG-graft-copolymer 95:5 before (dotted lines) and after 3 and 6 months storage (full lines, as indicated). The release media are shown at the top, the storage conditions on the left (coating level: 15%; plasticizer: TEC; drug loading of the diltiazem HCl-layered sugar cores: 20%).

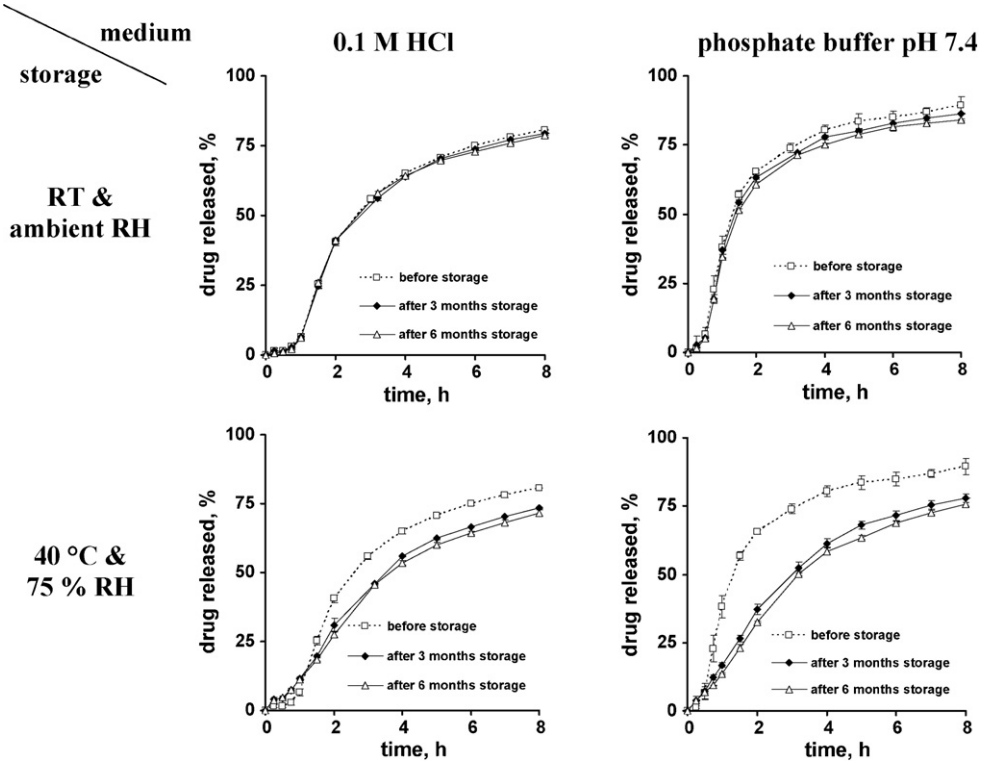

Fig. 6. Drug release from diltiazem HCl-layered sugar cores coated with ethylcellulose:PVA–PEG-graft-copolymer 95:5, plasticized with DBS, before (dotted lines) and after 3 and 6 months storage (full lines, as indicated). The release media are shown at the top, the storage conditions on the left (coating level: 15%; drug loading of the diltiazem HCl-layered sugar cores: 10%).

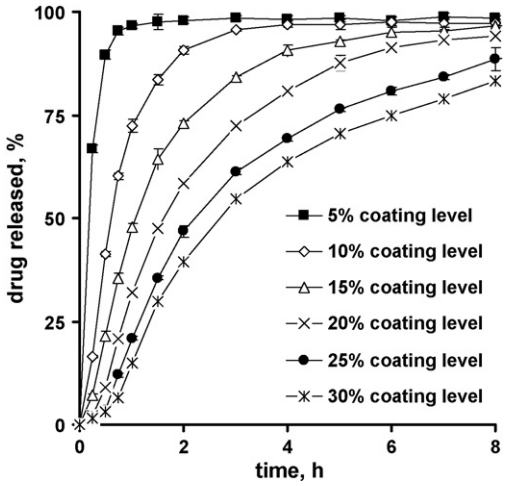

Fig. 7. Importance of the coating level (indicated in the diagram) on drug release from diltiazem HCl-layered sugar cores coated with ethylcellulose:PVA–PEG-graft-copolymer 90:10 in 0.1N HCl (plasticizer: TEC; drug loading of the diltiazem HCl-layered sugar cores: 10%).

Based on these findings, ethylcellulose:PVA–PEG-graft-copolymer 95:5 blends were selected for further studies, allowing for intermediate drug release rates.

3.3. Ethylcellulose:PVA–PEG-graft-copolymer 95:5 blends

In addition to the variation of the PVA–PEG-graft-copolymer content also the variation of the coating level is an efficient tool to adjust desired release patterns from the investigated systems (Fig. 3). An increase in the coating level from 5% to 15% (w/w) resulted in a significant decrease in the absolute and relative release rates, irrespective of the type of release medium. Importantly, the drug release patterns from these pellets did not significantly change upon open storage for 3 and 6 months under *ambient* conditions (irrespective of the type of release medium) and under *stress* conditions in 0.1N HCl (Fig. 4). However, the release rate decreased upon open long term storage under *stress* conditions in *phosphate buffer pH 7.4*. This phenomenon can probably be attributed to further polymer particle coalescence. The effect is more pronounced under stress conditions than under ambient conditions, because the mobility of the ethylcellulose chains significantly increases with increasing temperature and because water acts as a plasticizer for ethylcellulose and is mandatory for the capillary forces driving the particles together. The effect is also more pronounced at pH 7.4 than at pH 1.0, because Aquacoat ECD contains the anionic surfactant sodium dodecyl sulphate (SDS). In only partially coalesced films, the wettability of the film coatings and their permeability depend on the charge of this surfactant. At low pH, SDS is protonated and, thus, neutral, whereas at pH 7.4 it is deprotonated and, thus, negatively charged. The negatively charged SDS more effectively lowers the surface tension and facilitates water penetration into the partially coalesced film (Wesseling and Bodmeier, 1999).

Please note that *relative* drug release rates are plotted in Fig. 4. To minimize the importance of the decrease in the *relative* drug release rate observed upon open long term storage under stress conditions from the investigated pellets in phosphate buffer pH 7.4, the initial drug loading was increased from 10% to 20% (w/w) (referred to the drug-layered sugar core) (remark: in all experiments perfect

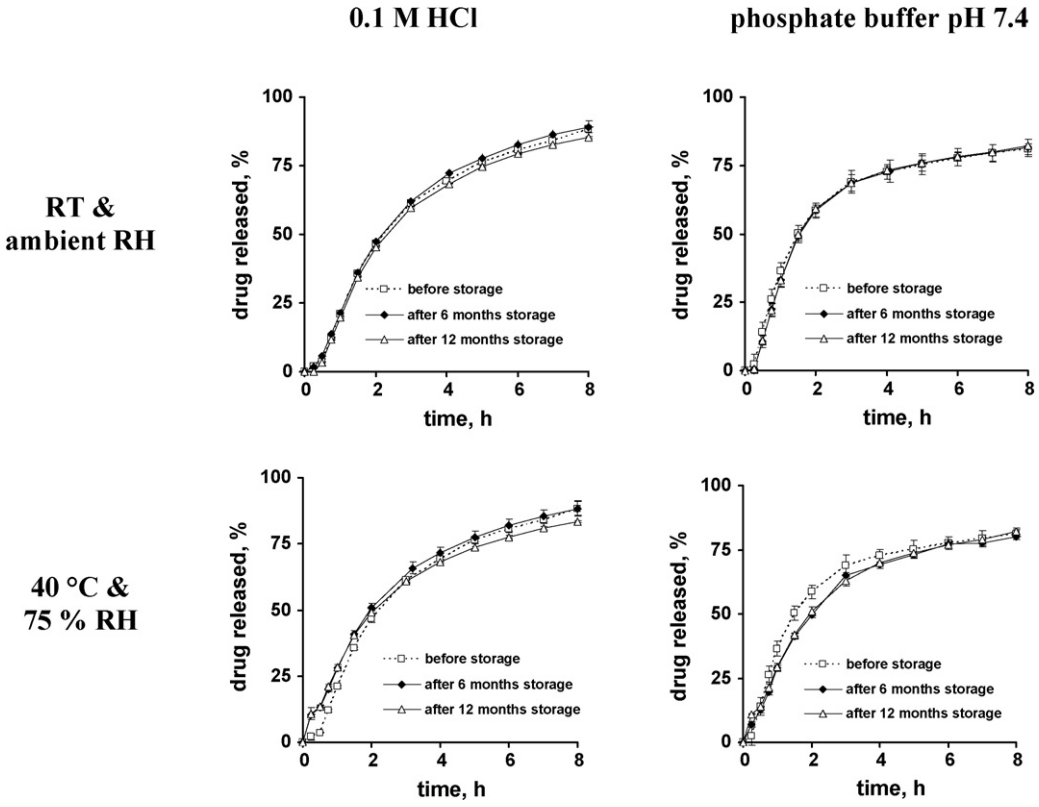

Fig. 8. Drug release from diltiazem HCl-layered sugar cores coated with ethylcellulose:PVA–PEG-graft-copolymer 90:10 before (dotted lines) and after 6 and 12 months storage (full lines, as indicated). The release media are shown at the top, the storage conditions on the left (plasticizer: TEC; coating level: 30%; drug loading of the diltiazem HCl-layered sugar cores: 10%).

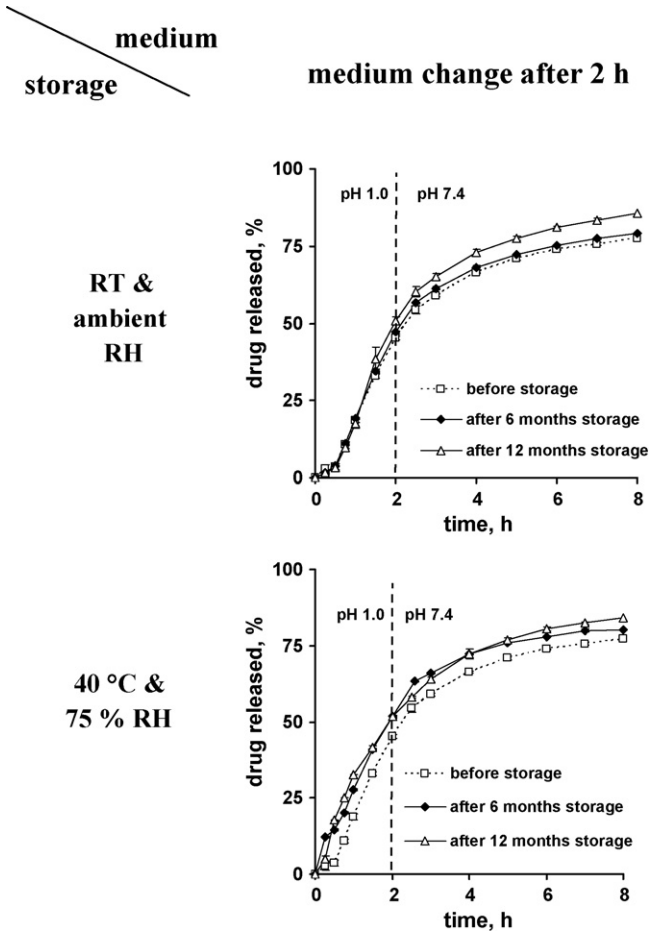

Fig. 9. Drug release from diltiazem HCl-layered sugar cores coated with ethylcellulose:PVA–PEG-graft-copolymer 90:10 before (dotted lines) and after 6 and 12 months storage (full lines, as indicated) in 0.1N HCl and phosphate buffer pH 7.4 (complete medium change after 2 h) (plasticizer: TEC; coating level: 30%; drug loading of the diltiazem HCl-layered sugar cores: 10%).

sink conditions were provided). The idea was that the *absolute* drug release rate might be unaffected from this change, and that due to the increase in the 100% reference value the extent of the decrease in the *relative* drug release is reduced. However, this strategy failed as it can be seen in Fig. 5. The decrease in the relative release rate in phosphate buffer pH 7.4 remained upon 3 and 6 months open storage under *stress* conditions (40 °C and 75% RH). As in the case of diltiazem HCl-layered sugar cores with 10% initial drug loading, storage under *ambient* conditions did not alter the release profiles, irrespective of the type of release medium.

Since the presence of plasticizer is essential for the mobility of the macromolecules, the type of plasticizer might affect the degree of polymer particle coalescence in the film coatings and/or the release profile. In an attempt to alter the film formation, the water-insoluble plasticizer dibutyl sebacate was used instead of the water-soluble plasticizer triethyl citrate. However, as it can be seen in Fig. 6, both, the storage *stability* under *ambient* conditions as well as the storage *instability* under *stress* conditions remained. Please note that the drug loading of the diltiazem HCl-layered sugar cores was again 10% for reasons of comparison. The decrease in the *relative* drug release rate upon 3 and 6 months storage under stress conditions was even more pronounced than in the case of the water-soluble plasticizer TEC (Fig. 6 versus Fig. 4). This phenomenon might be attributable to differences in the interactions between the plasticizers, the polymers and the drug. For instance, altered plasticizer distribution within the coating dispersions might lead to differences in the film properties, at least initially. A detailed analysis of this aspect was beyond the scope of this study.

Thus, it can be concluded that the presence of only 5% PVA–PEG-graft-copolymer is not sufficient to provide appropriate film formation during coating/curing and to avoid structural changes within the film coatings during storage, irrespective of the initial drug loading and type of plasticizer.

3.4. Ethylcellulose:PVA–PEG-graft-copolymer 90:10 blends

In order to sufficiently improve film formation during coating/curing and to stabilize the film coatings during storage, the PVA–PEG-graft-copolymer content was increased to 10% (w/w). As the resulting drug release rates were rather rapid at a coating level of 15% (Fig. 2), the sensitivity of the relative drug release rate to the coating level was determined under these conditions. As it can be seen in Fig. 7, a coating level of 30% was appropriate to allow for around 80% drug release within the first 8 h.

Importantly, the presence of 10% PVA–PEG-graft-copolymer proved to be sufficient to allow for appropriate film formation and stabilization even upon open long term storage under stress conditions. Fig. 8 shows the observed diltiazem HCl release profiles before and after 6 and 12 months storage under ambient and stress conditions upon exposure to 0.1N HCl and phosphate buffer pH 7.4, respectively. The release patterns observed upon 2 h exposure to 0.1N HCl and subsequent exposure for 6 h to phosphate buffer pH 7.4 were also stable (Fig. 9).

4. Conclusions

Adding small amounts of PVA–PEG-graft-copolymer to aqueous ethylcellulose dispersion to provide long term stability of drug release profiles from coated pellets, is applicable to a broad spectrum of starter cores. The latter can contain drugs of very different solubility and exhibit broad ranges of osmotic activity. To achieve desired drug release profiles the PVA–PEG-graft-copolymer content as well as the coating level can be adjusted. In the case of matrix cores consisting of poorly water-soluble drugs 15% PVA–PEG-graft-copolymer and a coating level of 15% are a good starting point, whereas in the case of freely water-soluble drugs layered onto osmotically active starter cores, 10% PVA–PEG-graft-copolymer and a coating level of 30% can be expected to result in controlled drug release during 8–12 h.

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