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Research paper

Drug release mechanisms from ethylcellulose: PVA-PEG graft copolymer-coated pellets

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ABSTRACT

The aim of this study was to better understand the underlying drug release mechanisms from aqueous ethylcellulose-coated pellets containing different types of drugs and starter cores. Theophylline, paracetamol, metoprolol succinate, diltiazem HCl and metoprolol tartrate were used as model drugs exhibiting significantly different solubilities (e.g. 14, 19, 284, 662 and 800 mg/mL at 37 °C in 0.1 N HCl). The pellet core consisted of a drug matrix, drug-layered sugar bead or drug-layered microcrystalline cellulose (MCC) bead, generating different osmotic driving forces upon contact with aqueous media. Importantly, the addition of small amounts of poly(vinyl alcohol)-poly(ethylene glycol) graft copolymer (PVA-PEG graft copolymer) to the ethylcellulose coatings allowed for controlled drug release within 8–12 h, irrespective of the type of drug and composition of the pellet core. Drug release was found to be controlled by diffusion through the *intact* polymeric membranes, irrespective of the drug solubility and type of core formulation. The ethylcellulose coating was dominant for the control of drug release, minimizing potential effects of the type of pellet core and nature of the surrounding bulk fluid, e.g. osmolality. Thus, this type of controlled drug delivery system can be used for very different drugs and is robust.

1. Introduction

Polymer-coated pellets offer various important advantages as oral controlled drug delivery systems [1–3]. In contrast to single unit dosage forms, they allow to avoid the "all-or-nothing" effect and provide less variable transit times within the gastro intestinal tract (GIT). In addition, the drug dose is more homogeneously spread throughout the contents of the digestive tract. Different types of polymers can be used for pellet coating, for example, cellulose derivatives, poly(vinyl acetate), poly(vinyl pyrrolidone) and polymethacrylates [3–6]. Ethylcellulose is particularly suitable, because it is a good film former, nontoxic, nonallergenic and nonirritant [7]. It can be applied either from *organic* solutions or from *aqueous* dispersions [8–10]. The use of *aqueous* dispersions offers the advantage to minimize toxicity and environmental concerns and to shorten processing times. However, long-term stable drug release patterns might be difficult to achieve if the film is not fully coalesced. Further gradual coalescence during storage results in decreasing drug permeability and, thus, decreasing release rates [11–13].

It has recently been shown that the addition of small amounts of poly(vinyl alcohol)-poly(ethylene glycol) graft copolymer (PVA-PEG graft copolymer) to aqueous ethylcellulose dispersion can significantly improve the film formation during coating and/or curing allowing for long-term stable drug release profiles, even upon *open* storage under stress conditions for 6 months [14,15]. This can probably be attributed to the fact that PVA-PEG graft copolymer traps water within the system, water acting as a plasticizer for ethylcellulose and being mandatory for the capillary force needed to drive the particles together [13,16,17]. In contrast to hydroxypropyl methylcellulose (HPMC), PVA-PEG graft copolymer does not cause flocculation of aqueous ethylcellulose dispersion [14].

However, as yet knowledge on the applicability of this approach to different types of drugs and different types of starter cores is very limited. Importantly, the composition of the inner pellet core can significantly affect the resulting drug release patterns from polymer-coated pellets [10,18]. For instance, osmotically active sugar cores or drug matrix cores consisting of a freely water-soluble drug can lead to significant water influx into the system upon contact with aqueous media. This water influx can have two major consequences: (i) it presents a potential hindrance for drug diffusion out of the pellets (convective water influx versus countercurrent drug diffusion), and (ii) significant hydrostatic pressure can built up within the pellet core and stress the coating. This phenomenon might lead to crack formation at a given time point (when the

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mechanical stability of the polymeric membrane is insufficient to withstand the pressure), and rapid drug release through water-filled channels might result [19–21]. So far, it is unclear whether such osmotic effects (including crack formation in the film coatings) are of importance for the control of drug release from ethylcellulose:PVA-PEG graft copolymer-coated pellets. It has to be pointed out that the underlying drug release mechanisms from polymer-coated pellets can be very straightforward (e.g., diffusion through the *intact* polymeric film coatings), but also highly complex [22–24]. Surprisingly, little is yet known on the mass transport mechanisms governing drug release from polymer-coated pellets and the importance of the type of drug and starter core composition, despite the significant practical importance of this type of advanced drug delivery systems. Furthermore, there is a significant need for appropriate experimental measurement techniques allowing for deeper insight into the involved physico-chemical phenomena [25–27].

The major aims of this study were (i) to better understand the relative importance of the film coating and of the pellet core for the control of drug release from ethylcellulose-coated multiparticulates, and (ii) to evaluate the applicability of the approach of adding small amounts of PVA-PEG graft copolymer as the film formation/permeability enhancer to very different types of drugs and pellet starter cores.

2. Materials and methods

2.1. Materials

Diltiazem hydrochloride (diltiazem HCl; VWR, Fontenay-sous-Bois, France); paracetamol, metoprolol succinate and metoprolol tartrate (Salutas, Barleben, Germany); theophylline (BASF, Ludwigshafen, Germany); theophylline matrix pellets (70% drug content, diameter: 0.71–1.25 mm; FMC, Philadelphia, PA, USA); sugar cores (sugar spheres NF, 710–850 μm; NP Pharm, Bazainville, France); microcrystalline cellulose cores (MCC cores, Celpheres CP-708, 710–850 μm; Asahi Kasei, Tokyo, Japan); microcrystalline cellulose (Avicel PH 101; Seppic, Paris, France); hydroxypropyl methylcellulose (HPMC, Methocel E 5; Colorcon, Dartford, UK); Ethylcellulose Aqueous Dispersion NF (Aquacoat ECD; FMC, Philadelphia, PA, USA); poly(vinyl alcohol)-poly(ethylene glycol) graft copolymer (PVA-PEG graft copolymer, Kollicoat IR; BASF, Ludwigshafen, Germany); triethyl citrate (TEC; Morflex, Greensboro, NC, USA); sodium chloride (NaCl; Fisher Bioblock Scientific, Illkirch, France).

2.2. Preparation of coated pellets

2.2.1. Drug-loaded matrix cores

Metoprolol tartrate and diltiazem HCl-loaded matrix pellets were prepared via extrusion–spheronization. The drug powders and microcrystalline cellulose were mixed with demineralized water in a planetary mixer (Kenwood Chef, Kenwood, Croydon, UK). The obtained wet masses (30% metoprolol tartrate, 49% MCC, 21% water, or 40% diltiazem HCl, 36.5% MCC, 23.5% water) were extruded using a cylinder extruder with two counter-rotating rollers (1 mm orifice, extrusion speed = 63 and 96 rpm for metoprolol tartrate and diltiazem HCl; Alexanderwerk GA 65; Alexanderwerk, Remscheid, Germany). The extrudates were subsequently spheronized (Caleva model 15; Caleva, Dorset, UK) for 150/180 s at 600/750 rpm in the case of metoprolol tartrate/diltiazem HCl. The obtained beads were dried for 24 h in an oven at 40 °C and sieved (fraction: 0.71–1.25 mm). Theophylline matrix cores (70% drug content, diameter: 0.71–1.25 mm) were used as received from the supplier.

2.2.2. Drug-layered starter cores

Sugar and MCC cores were coated with drug solutions or suspensions containing 0.9% (w/w) hydroxypropyl methylcellulose in a fluidized bed coater (Strea 1, Wurster insert; Niro; Aeromatic-Fielder, Bubendorf, Switzerland). Details on the composition of

Table 1
Coating formulations and final drug loadings of the investigated drug-layered sugar and MCC cores.

Type of drug	Type of starter core	Type of coating formulation (drug content)	Final drug loading (% w/w)
Theophylline	Sugar/MCC	Aqueous suspension (18.2% w/w)	7
Paracetamol	Sugar	Solution in ethanol:water (95:5) (15% w/w)	9
Diltiazem HCl	Sugar	Aqueous solution (18.2% w/w)	9
Metoprolol succinate	Sugar	Aqueous solution (18.2% w/w)	12

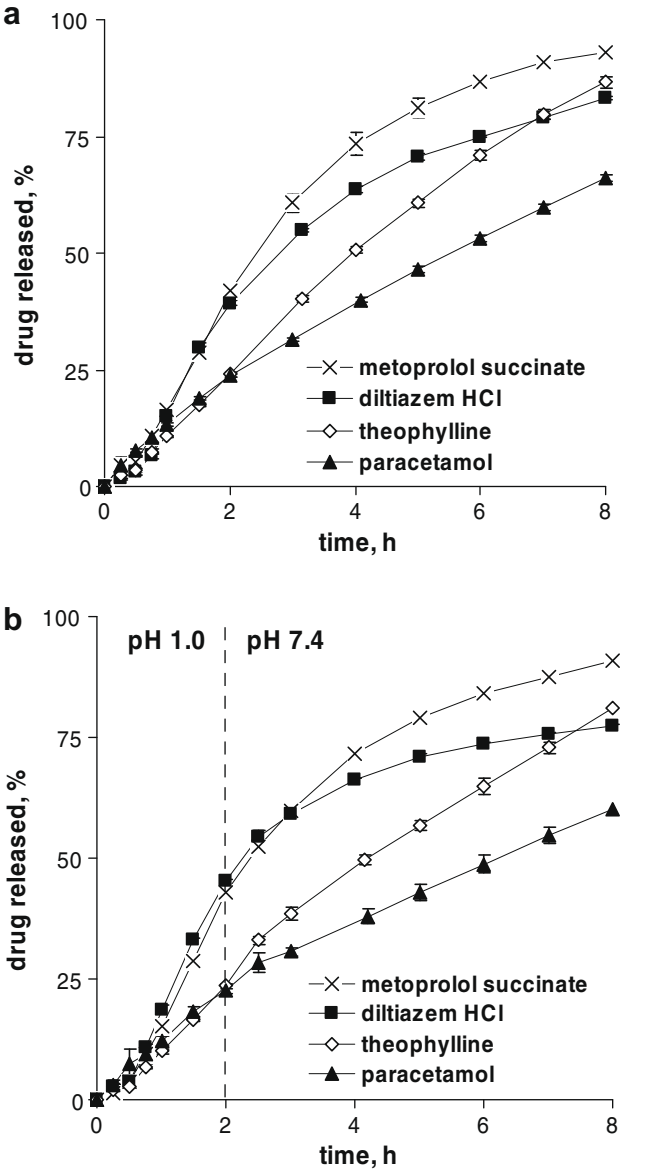

Fig. 1. Effects of the type of drug (indicated in the figures) on the release patterns from pellets coated with ethylcellulose:PVA-PEG graft copolymer 90:10 in: (a) 0.1 N HCl for 8 h, and (b) 0.1 N HCl for 2 h and subsequent complete medium change to phosphate buffer, pH 7.4 (coating level: 30%, drug-layered sugar cores).

the coating formulations and final drug loadings are given in Table 1. The process parameters were as follows: inlet temperature = 40 °C, product temperature = 40 ± 2 °C, spray rate = 1–3 g/min, atomization pressure = 1.2 bar, air flow rate = 100 m^3/h, batch size = 500 g, nozzle diameter = 1.2 mm.

2.2.3. Controlled release pellets

Drug matrix cores as well as drug-layered sugar and MCC 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). Aqueous PVA-PEG graft copolymer solution was added, and the blends were stirred for 30 min prior to coating. 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, air flow rate = 100 m^3/h, batch size = 500 g, nozzle diameter = 1.2 mm. After coating, the pellets were further fluidized for 10 min and subsequently cured for 24 h at 60 °C.

2.3. Drug release from coated pellets

Drug release from *ensembles* of pellets was measured in 0.1 N HCl and phosphate buffer, pH 7.4 (USP 30) using the USP 30 paddle apparatus (Sotax, Basel, Switzerland) (900 mL, 37 °C, 100 rpm; $n = 3$). Optionally, NaCl was added to adjust the osmotic pressure of the release media. Drug release from *single* pellets was measured in 6 mL 0.1 N HCl in agitated glass vials (80 rpm, horizontal shaker, GFL 3033; Gesellschaft fuer Labortechnik, Burgwedel, Germany) at 37 °C. At pre-determined time intervals, 3 mL (*ensembles* of pellets) or 2 mL (*single* pellets) samples were withdrawn and analyzed by UV-spectrophotometry (diltiazem HCl/theophylline/metoprolol succinate: λ = 236.9/270.4/222.8 nm in 0.1 N HCl and λ = 237.4/272.2/222.2 nm in phosphate buffer, pH 7.4; metoprolol tartrate/paracetamol: λ = 222.6/243.4 nm in both media; UV-1650PC, Shimadzu, Champs-sur-Marne, France).

2.4. Swelling behavior of single pellets

Single pellets were treated as described in Section 2.3, single pellet release studies. At pre-determined time intervals, pellet samples were withdrawn and their diameter was measured with an optical image analysis system (Nikon SMZ-U; Nikon, Tokyo, Japan) equipped with a Sony camera (Hyper HAD model SSC-DC38DP; Elvetec, Templemars, France).

2.5. Scanning electron microscopy

The morphology of the coated pellets before and after 2 h exposure to 0.1 N HCl (conditions as described for the in vitro drug release studies for single pellets in Section 2.3) was monitored using a scanning electron microscopy (S-4000; Hitachi High-Technologies Europe, Krefeld, Germany) after covering the samples under an argon atmosphere with a fine gold layer (10 nm; SCD 040; BAL-TEC, Witten, Germany).

2.6. Determination of the drug solubility

Excess drug amounts were placed in contact with 0.1 N HCl and phosphate buffer, pH 7.4 (USP 30) at 37 °C in a horizontal shaker (80 rpm, GFL 3033) for at least 48 h. Every 12 h, samples were withdrawn, filtered and analyzed for their drug content as described in Section 2.3, until equilibrium was reached.

3. Results and discussion

3.1. Importance of the type of drug

It has recently been shown that theophylline release from spherical drug matrix cores coated with aqueous ethylcellulose dispersion containing small amounts of poly(vinyl alcohol)-poly(ethylene glycol) graft copolymer (PVA-PEG graft copolymer) can effectively be controlled during the periods of 8–12 h [14]. In contrast to the frequently used pore former hydroxypropyl methylcellulose (HPMC), PVA-PEG graft copolymer does not cause flocculation of the coating dispersions. Furthermore, long-term stable drug release profiles can be provided, even upon *open* storage under stress conditions [15]. However, it is yet unclear, whether this approach is applicable also to other types of drugs and to pellet starter cores.

Fig. 1 shows that this strategy can successfully be applied to drugs exhibiting very different solubility, irrespective of the type of release medium. In these cases, the drugs are layered onto sugar cores. Interestingly, the rank order of drug solubility did not correlate with the rank order of the observed release rates. The experimentally measured drug solubility at 37 °C increased as follows: theophylline < paracetamol < metoprolol succinate < diltiazem HCl (14 < 19 < 284 < 662 mg/mL and 11 < 18 < 251 < 582 mg/mL in 0.1 N HCl and phosphate buffer, pH 7.4, respectively). Thus, the permeability of the dissolved drug molecules/ions in the wetted polymeric networks plays a major role for the control of drug release (in addition to drug solubility). Once dissolved, the drug molecules/ions diffuse through the film coatings. Due to their different sizes and interactions with the macromolecules, this mass transport step is more or less hindered.

Fig. 2 illustrates that ethylcellulose:PVA-PEG graft copolymer blends can also effectively be used to control drug release from different types of coated *drug matrix cores*. The relative release rate of diltiazem HCl, metoprolol tartrate and theophylline from the coated pellets in 0.1 N HCl and phosphate buffer, pH 7.4, is shown. Importantly, there is no major impact of the pH of the release medium on the resulting drug release rate in any case (dashed versus solid curves).

To better understand the underlying drug release mechanisms from these various types of coated pellets, the effects of the osmolality of the release medium on the resulting release rate of theophylline, diltiazem HCl and metoprolol succinate from the drug-layered sugar cores coated with ethylcellulose:PVA-PEG graft copolymer 90:10 (coating level = 30% w/w) were monitored

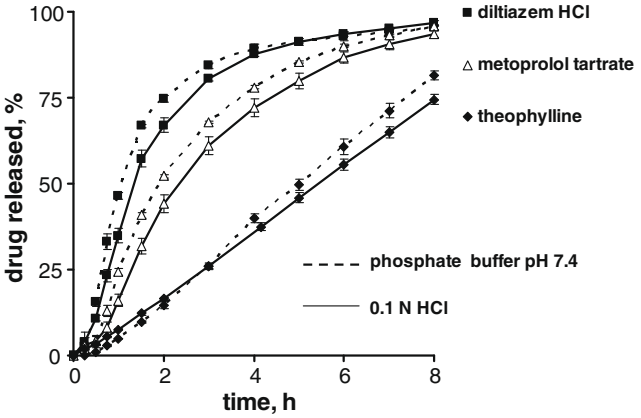

Fig. 2. Effects of the type of release medium (indicated in the figure) on drug release from ethylcellulose:PVA-PEG graft copolymer-coated pellets (matrix cores) (diltiazem HCl/metoprolol tartrate/theophylline: polymer:polymer blend ratio = 90:10/90:10/85:15 and coating level = 25/30/15%).

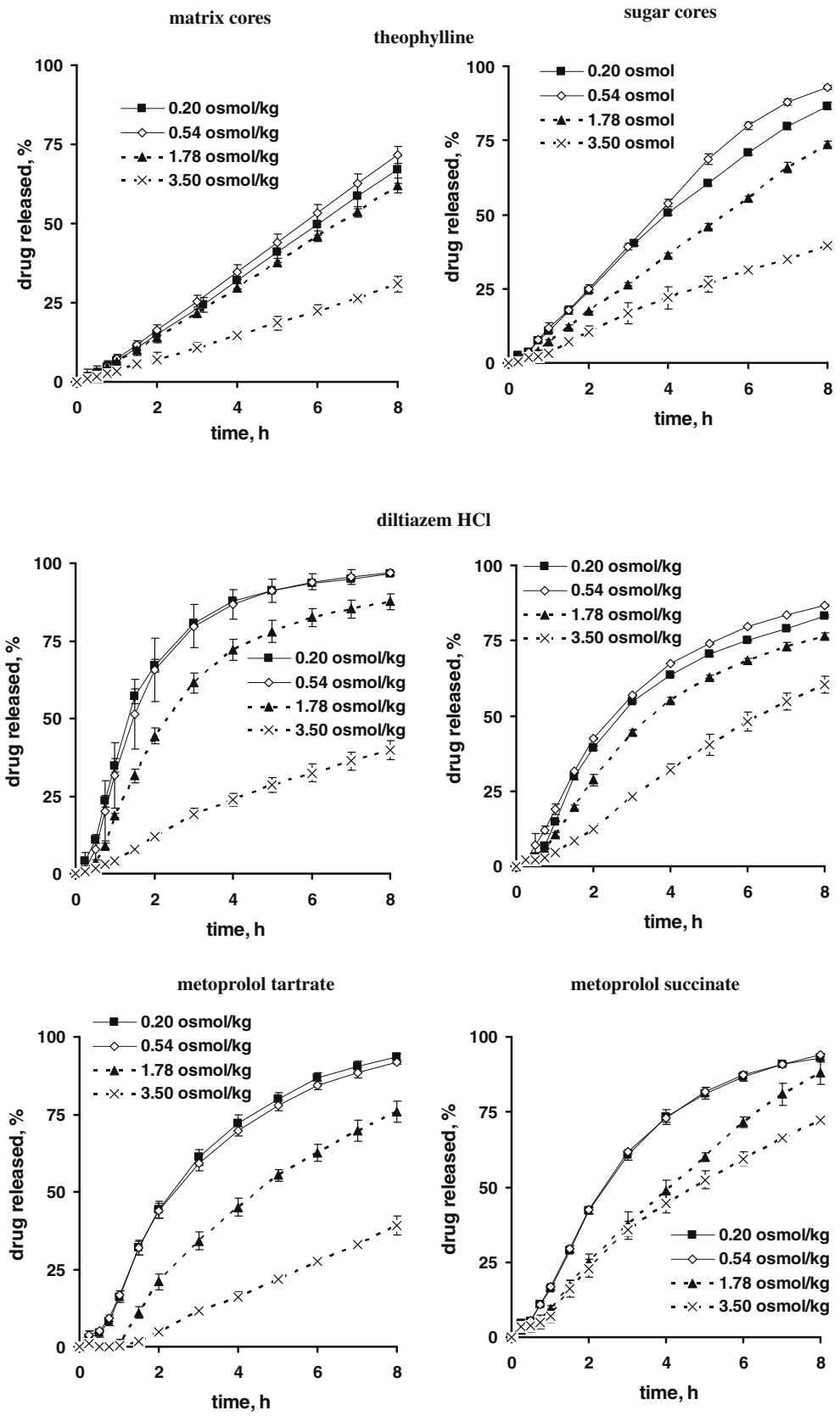

Fig. 3. Importance of the osmotic pressure of the release medium for drug release from pellets coated with ethylcellulose:PVA-PEG graft copolymer containing different types of cores (as indicated on the top) loaded with different types of drugs in 0.1 N HCl containing different amounts of NaCl (dotted curves indicate non-physiological conditions). Matrix cores loaded with: theophylline/diltiazem HCl/metoprolol tartrate: polymer:polymer blend ratio = 85:15/90:10/90:10 and coating level = 15/25/30%; sugar cores layered with: theophylline/diltiazem HCl/metoprolol succinate: polymer:polymer blend ratio = 90:10 and coating level = 30%.

(Fig. 3). Please note that the osmolalities of 1.78 and 3.50 osmol/kg are not within the physiological range [28,29]. They are only used in this study to get deeper insight into the underlying drug release mechanisms. Interestingly, the resulting release rate was very similar for the physiologically relevant osmolalities of 0.20 and 0.54 osmol/kg, irrespective of the type of drug. This indicates that significant variations in the drug release rates *in vivo*, due to alterations in the osmotic pressure of the surrounding bulk fluid within the gastro intestinal tract are unlikely. This is very important from a practical point of view, because such changes in the osmolality (for instance caused by the type of ingested food) might fundamentally change the underlying drug release mechanism and release rate from coated solid dosage forms: With decreasing osmolality of the bulk fluid, the water penetration rate into the system increases, resulting in increasing amounts of water available for drug dissolution and a more pronounced/accelerated increase in the hydrostatic pressure acting against the polymeric coatings from inside the system. If the film coatings are not sufficiently (mechanically) stable, crack formation is induced, and subsequent drug release is primarily controlled via diffusion through water-

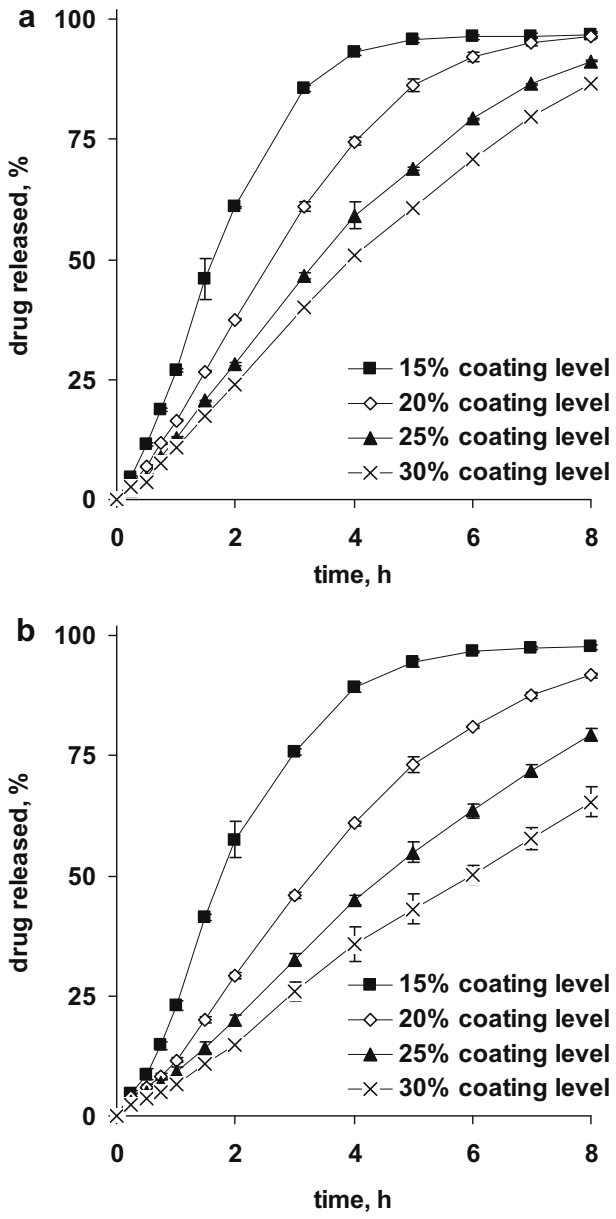

Fig. 4. Effects of the coating level on theophylline release in 0.1 N HCl from pellets coated with ethylcellulose:PVA-PEG graft copolymer 90:10, containing: (a) drug-layered sugar cores, and (b) drug-layered MCC cores.

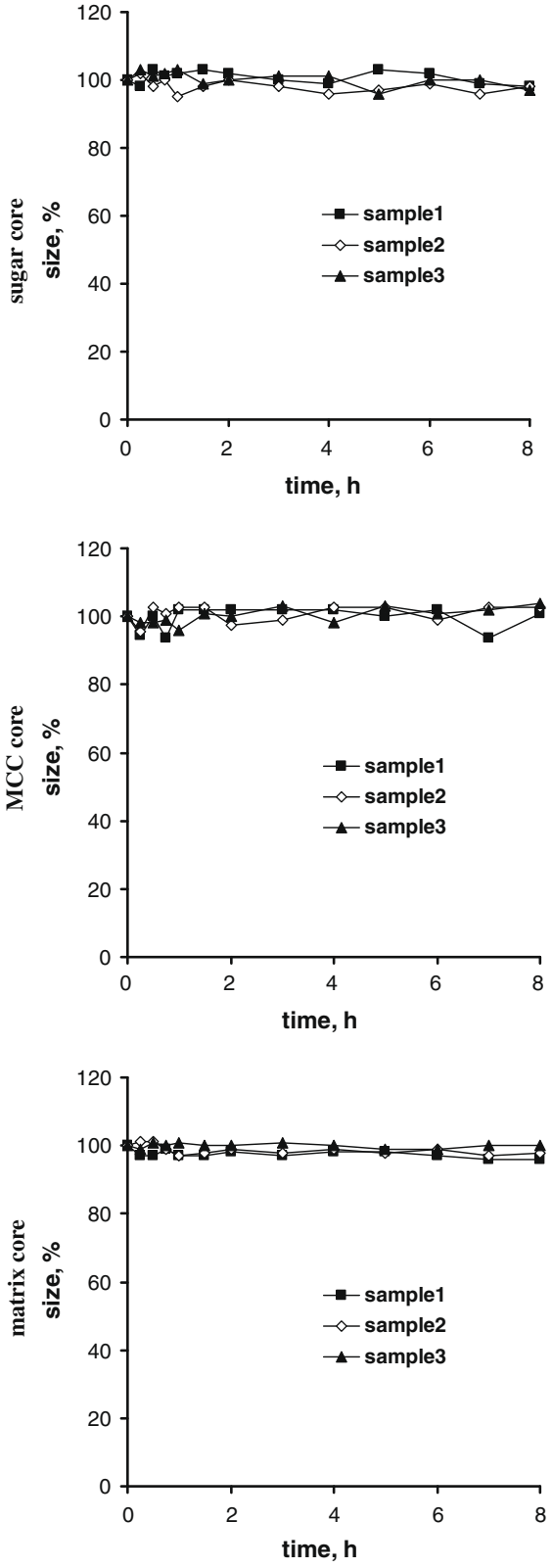

Fig. 5. Swelling behavior of theophylline-loaded pellets containing different types of starter cores (indicated in the figure), coated with ethylcellulose:PVA-PEG graft copolymer upon exposure to 0.1 N HCl (*sugar and MCC cores*: polymer polymer blend ratio = 90:10; *matrix cores*: polymer:polymer blend ratio = 85:15) (coating level = 30%, *single* pellets).

filled channels. The resulting release rates can be much higher than through the intact polymeric networks and drug release might be fundamentally faster. The fact that the experimentally measured release rates are very similar, irrespective of the osmolality of the release medium in the physiological range, clearly indicates that a change in the underlying drug release mechanism is highly unlikely *in vivo* due to this phenomenon. The observed decrease in the release rate of theophylline, diltiazem HCl and metoprolol succinate from the coated *layered-sugar cores* when increasing the osmolality of the bulk fluid up to (non-physiological) 3.50 osmol/kg can be explained by the decrease in the water penetration rate into the systems, water being required for drug dissolution and only dissolved drug being able to diffuse. The fact that the *shape* of the drug release curves does not fundamentally vary even under these very drastic conditions (e.g. pulsatile versus non-pulsatile release profile) indicates that the underlying drug release mechanism does not significantly change. Thus, these formulations are highly robust from a mechanistic point of view, even under non-physiological, extreme conditions. Fig. 3 also shows the release rates of theophylline, diltiazem HCl and metoprolol tartrate from ethylcellulose:PVA-PEG graft copolymer-coated *drug matrix cores* in 0.1 N HCl containing different amounts of NaCl. As in the case of drug-layered sugar cores, the resulting release patterns were very similar under physiological conditions, whereas an increase of the osmolality of the bulk fluid up to 3.50 osmol/kg led to a decrease in the release rate. Again, the shape of the respective drug release profiles remained similar, indicating the absence of changes in the underlying drug release mechanism.

3.2. Drug release mechanisms

It has previously been shown that desired drug release patterns from theophylline matrix cores coated with ethylcellulose:PVA-PEG graft copolymer blends can easily be adjusted by varying the coating level [15]. Importantly, this is also true for other types of starter cores as it can be seen in Fig. 4a and b for theophylline-layered sugar and MCC cores. This indicates that it is the polymeric film coating that controls drug release, and not the type of starter core. By comparing Fig. 4a and b, it can be seen that the drug release is slightly faster from the investigated pellets containing sugar starter cores compared to MCC starter cores. This might be explained by the higher osmotic activity of sugar compared to MCC, driving more water into the system, water being mandatory for drug dissolution. The dominance of the film coating has further been confirmed when studying the drug release mechanisms of theophylline from drug matrix cores as well as from drug-layered sugar and MCC cores in more details. In order to distinguish between drug release occurring via diffusion through an intact polymeric coating versus diffusion through water-filled cracks, changes in the size of *single* pellets were monitored upon exposure to 0.1 N HCl (at 37 °C). As soon as the pellets come into contact with aqueous media, water diffuses into the systems, generating a monotonically increasing hydrostatic pressure inside the pellets, which acts against the film coating. If this hydrostatic pressure exceeds the mechanical stability of the film coating at a given time point, crack formation is induced and drug release will be greatly accelerated (because drug no longer has to diffuse through the polymer membrane). This type of phenomenon is often indicated by a steadily increasing pellet diameter, which suddenly levels off and even eventually decreases (since the pellet's content is pushed out of the system due to the pressure gradient) [10]. As it can be seen in Fig. 5, no such signs are visible in any case, irrespective of the type of starter core. Thus, drug release is likely to be controlled by diffusion through the intact ethylcellulose:PVA-PEG graft copolymer coatings in all cases. This hypothesis was further confirmed by scanning electron microscopy. Fig. 6 shows surfaces of pellets, which were exposed to 0.1 N HCl for 2 h. No sign of crack formation is visible in any case: theophylline matrix cores, theophylline-layered sugar and MCC cores, despite the significantly different osmotic activity of these starter cores.

When studying the underlying drug release mechanisms from coated multiparticulates, drug release should be investigated not only from *ensembles* of systems, but also from *single* dosage forms. For instance, an apparent zero order release kinetics observed with an ensemble of pellets might be the result of the summation of

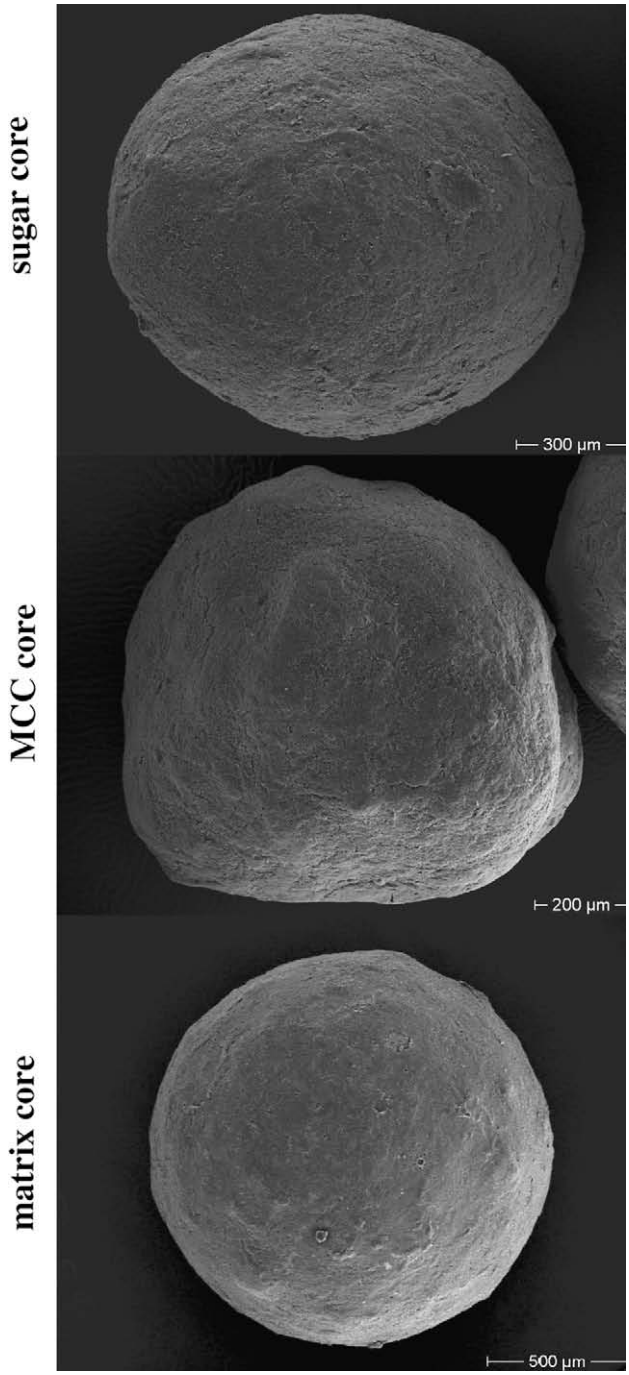

Fig. 6. Scanning electron microscopy pictures of theophylline-loaded pellets containing different types of starter cores (indicated in the figure), coated with ethylcellulose:PVA-PEG graft copolymer upon 2 h exposure to 0.1 N HCl (*sugar and MCC cores*: polymer polymer blend ratio = 90:10, coating level = 30%; *matrix cores*: polymer:polymer blend ratio = 85:15, coating level = 15%).

individual *pulsatile* drug release patterns with significantly different lag-times, which are homogeneously distributed throughout the observation period. As it can be seen in Fig. 7, theophylline release from the single pellets was very similar to that from the ensembles of pellets, irrespective of the type of starter core: drug matrix, sugar or MCC core. These findings are in good agreement with those previously reported on diltiazem HCl-layered sugar cores [30], and clearly indicate that the underlying drug release mechanism is uniform and that this type of controlled drug delivery system is very robust.

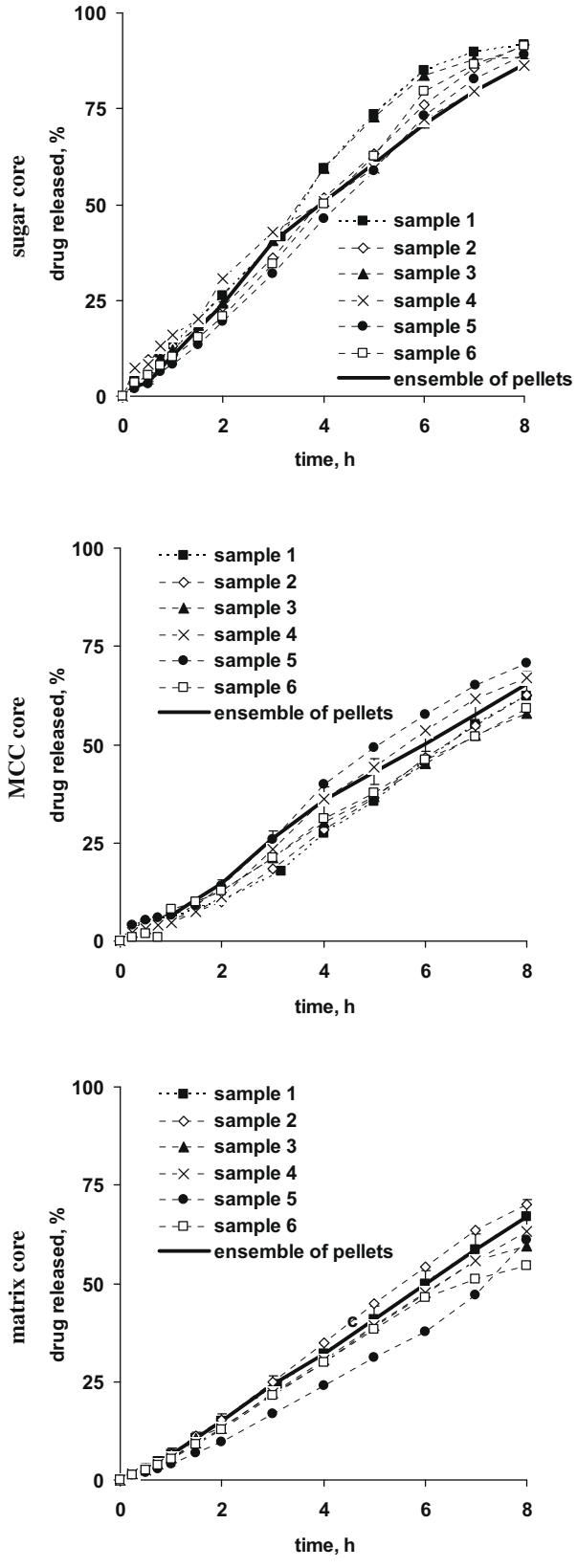

Fig. 7. Theophylline release from *single* pellets in 0.1 N HCl from drug-layered sugar and MCC cores, coated with ethylcellulose:PVA-PEG graft copolymer 90:10 (coating level: 30%) as well as from drug matrix cores, coated with ethylcellulose:PVA-PEG graft copolymer 85:15 (coating level: 15%). For reasons of comparison also drug release from *ensembles* of pellets is shown.

4. Conclusions

Drug release from the pellets coated with ethylcellulose containing small amounts of PVA-PEG graft copolymer as a release rate modifier and stabilizer is controlled by diffusion through the intact polymer membrane, irrespective of the type of drug and pellet starter core. The impact of the ethylcellulose coating is dominant, and the effects of the osmolality of the release medium (within the physiological range) and the nature of the starter core composition are negligible. Thus, this type of controlled drug delivery system can be used for very different drugs and is robust.

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