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Deeper insight into the drug release mechanisms in Eudragit RL-based delivery systems

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ABSTRACT

Tartaric acid, metoprolol free base and metoprolol tartrate act as plasticisers for Eudragit RL, in the dry but also in the wet state. Fitting analytical solutions of Fick's second law of diffusion allowed for the determination of the apparent diffusivities of water and of tartaric acid, metoprolol free base and metoprolol tartrate upon exposure of thin films to 0.1 M HCl, phosphate buffer pH 7.4 and distilled water. Based on these calculations, it could be shown that water penetration into the systems is predominantly controlled by pure diffusion, irrespective of the type of bulk fluid. Interestingly, the plasticising effect of metoprolol tartrate was much more pronounced than that of tartaric acid, resulting in monotonically increasing diffusion coefficients with increasing initial drug content. In contrast, the plasticising activity of metoprolol free base was very limited in the wet state, due to drug precipitation in aqueous environments. Partially observed film shrinking (after an initial system swelling) could be attributed to the leaching of the plasticising compound into the release medium, resulting in less flexible polymeric networks and squeezing out of water. Also the release of tartaric acid, metoprolol free base and metoprolol tartrate into the investigated bulk fluids was predominantly diffusion controlled. However, the precipitation of the free base in wet films rendered the mass transport mechanisms more complex, at moderate and high initial drug loadings. The obtained new insight into the underlying drug release mechanisms in Eudragit RL networks can help to facilitate the optimisation of this type of dosage forms.

1. Introduction

Drug delivery systems based on poly(acrylic acid) derivatives are highly suitable in order to provide time-, and/or position-controlled drug delivery within the gastro intestinal tract (Semdé et al., 2000; Moustafine et al., 2005; Goole et al., 2008; Albers et al., 2009; Sauer et al., 2009). This type of polymers can be used either as a matrix former, or for controlled release film coatings (Lecomte et al., 2003; Schilling et al., 2008). However, despite of the significant practical importance of this type of advanced pharmaceutical dosage forms, the underlying mass transport phenomena are not yet fully understood (Jenquin and McGinity, 1994; Siepmann and Siepmann, 2008) and device optimisation is often based on time- and cost-intensive series of trial-and-error experiments.

In order to better understand the underlying drug release mechanisms in a particular dosage form, the latter should be thoroughly characterised before and upon exposure to different release media (Siepmann and Peppas, 2001; Siepmann and Goepferich, 2001). This includes the determination of the water uptake kinetics as well as of the mechanical properties of the systems and changes thereof upon exposure to different types of release media at 37 °C. Importantly, the presence of water can fundamentally alter key features of the dosage form (Bodmeier and Paeratakul, 1993, 1994; Siepmann et al., 2008). For instance, Eudragit L films are very brittle in the dry state, but become highly flexible in the wet state, because water acts as a potent plasticiser for this polymer (Lecomte et al., 2004). The lowering of the glass transition temperature (T_g) also affects other crucial system properties, including the mobility of the macromolecules and, thus, the free volume available for the diffusion of incorporated drug molecules/ions. Furthermore, the type of release medium might significantly affect the resulting properties of the dosage forms, in particular in the case of poly(acrylic acid) derivatives (Knop, 1996; Wagner and McGinity, 2002). Consequently, the polymeric systems should be characterised upon exposure to different types of bulk fluids, exhibiting different pH values (if the dosage forms are intended for oral administration). Based on the obtained experimental results, appropriate mathematical theories should be identified and applied. These theories should consider the given initial and boundary conditions, including the geometry of the systems, degree of homogeneity of the initial drug distribution, the "initial drug concentration:drug solubility" ratio as well as the maintenance or absence of perfect sink conditions. Such

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calculations allow for the determination of system-specific parameters. For instance, the apparent diffusion coefficient of the drug within a polymeric network can be quantified. Knowing these values, the dominant mass transport phenomena in the investigated drug delivery systems can be identified.

It has recently been shown that tartaric acid, metoprolol free base and metoprolol tartrate act as plasticisers for Eudragit RL-based networks in the dry state (Glaessl et al., 2009). However, the impact of the presence of water on the interactions of these compounds with the polymer is yet unknown. It was the aim of this study to experimentally monitor the effects of the system composition on the water uptake kinetics, tartaric acid, metoprolol free base and metoprolol tartrate release kinetics as well as on the mechanical properties of Eudragit RL films. Based on these results, appropriate mathematical theories were to be identified and system-specific parameters to be determined in order to better understand the underlying drug release mechanisms.

2. Materials and methods

2.1. Materials

The following chemicals were used as received: tartaric acid (Acros Organics, Halluin, France), metoprolol tartrate (Novartis, Barleben, Germany) and Eudragit RL PO [poly(ethylacrylate-methylmethacrylate-trimethylammonioethylmethacrylate chloride) 1:2:0.2, Evonik Roehm, Darmstadt, Germany]. The metoprolol free base was obtained from metoprolol succinate (Novartis, Barleben, Germany) by first dissolving the salt in a sodium hydroxide solution, and subsequent extraction with dichloromethane, followed by drying with water-free sodium sulphate. For further water elimination, the resulting oily liquid was dried at 80 °C in a rotary evaporator (Buechi Rotavapor model R110, Buechi, Flawil, Switzerland), connected to a vacuum pump. The resulting yellowish liquid was cooled down to 4–7 °C, inducing crystallisation of the free base in the form of white crystals, which were subsequently gently ground with a mortar and pestle. The chemical structures of tartaric acid, metoprolol free base, metoprolol tartrate as well as of Eudragit RL are shown in Fig. 1.

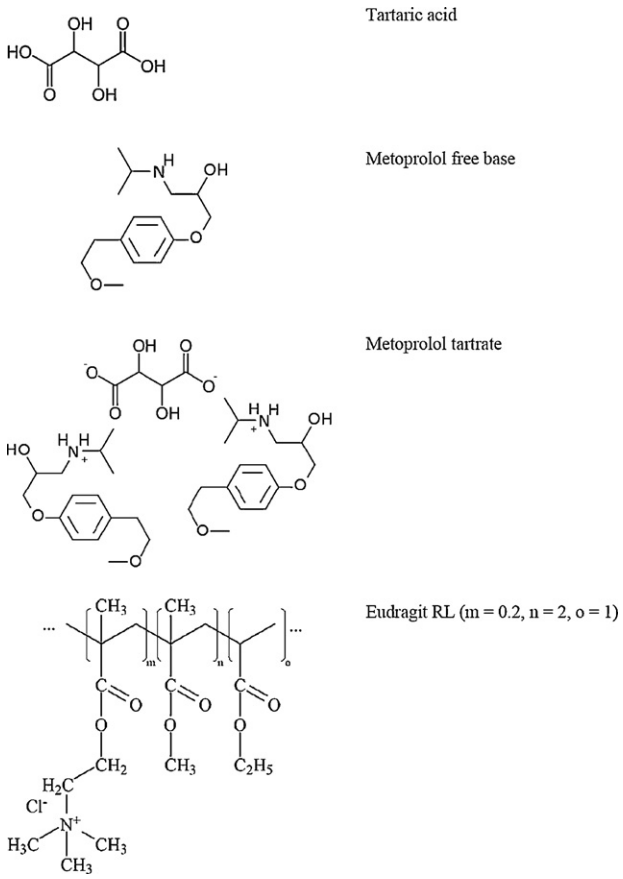

Fig. 1. Chemical structures of tartaric acid, metoprolol free base, metoprolol tartrate and Eudragit RL.

2.2. Film preparation

Thin Eudragit RL films were prepared with a casting knife (Multicator 411, Erichsen, Hemer, Germany) and a PTFE plate from ethanolic polymer solutions, optionally containing tartaric acid, metoprolol free base or metoprolol tartrate (0–20%, w/w, based on the polymer mass). The films were dried for 3 d at room temperature, followed by 1 d at 50 °C. The thickness of the films was measured using a thickness gauge (Minitest 600, Erichsen, Hemer, Germany).

2.3. Water uptake of thin, polymeric films

Thin compound free and compound containing polymeric films were cut into pieces of approximately 4 cm × 4 cm, and placed into plastic flasks filled with pre-heated release medium [0.1 M HCl, phosphate buffer pH 7.4 (USP 32) or distilled water], followed by horizontal shaking for 8 h (37 °C, 80 rpm; GFL 3033, Gesellschaft fuer Labortechnik, Burgwedel, Germany). The films were weighed before exposure to the media [dry weight ($t = 0$), m_{dry}] (about 300–400 mg, accuracy of the balance: 0.1 mg). At pre-determined time points, the films were withdrawn from the media, carefully dried from adhering water and accurately weighed [wet weight (t)]. The water uptake (%) at time t was calculated as follows:

$$\text{water uptake } (t)\,(\%) = \frac{m_{wet}(t) - m_{dry}}{m_{dry}} \cdot 100\ (\%) \qquad (1)$$

All experiments were conducted in triplicate.

The following analytical solution of Fick's second law of diffusion considering the given initial and boundary conditions (initial homogeneous film structure, excess amounts of water at the film surfaces, negligible edge effects) was fitted to the experimentally determined water uptake kinetics:

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2 \cdot \pi^2} \cdot \exp\left(-\frac{(2n+1)^2 \cdot \pi^2}{4 \cdot L^2} \cdot D \cdot t\right) \qquad (2)$$

Here, M_t and M_∞ denote the absolute cumulative amounts of water taken up at time t and $t = \infty$, respectively (in the case of shrinking films, the relative maxima of the water contents were considered as M∞ values); D represents the apparent diffusion coefficient of water within the system and L the half-thickness of the film.

2.4. In vitro release from thin, polymeric films

The release of tartaric acid, metoprolol free base and metoprolol tartrate from thin films was measured by placing film pieces into plastic flasks filled with pre-heated release medium [0.1 M HCl, phosphate buffer pH 7.4 (USP 32) or distilled water], followed by horizontal shaking for 8 h (37 °C, 80 rpm, GFL 3033) ($n = 3$). At pre-determined time points, samples of 3 mL were withdrawn and replaced with fresh, pre-heated medium. The respective compound was detected UV-spectrophotometrically (UV-1650; Shimadzu, Champs sur Marne, France) (λ = 212.0/204.3/220.0,

274.7/275.0/274.7, and 274.7/274.7/274.7 nm for tartaric acid/metoprolol free base/metoprolol tartrate in 0.1 M HCl, phosphate buffer pH 7.4 and distilled water, respectively), except for tartaric acid released in distilled water, which was quantified by isocratic HPLC analysis [HPLC ProStar 230 (Varian, Paris, France), equipped with a ProStar 230 pump, a Prostar 410 autosampler and a Prostar 325 UV–vis detector]. The reverse-phase column (Synergi 4u Hydro-RP 80A, 250 mm × 4.6 mm, Phenomenex, Auckland, New Zealand) was kept at 30 °C. The flow rate of the mobile phase [20 mM potassium phosphate buffer pH 2.9 (Phenomenex)] was 0.7 mL/min. Fifty μL samples were injected and the drug detected at λ = 220 nm. Data was analysed using the Galaxie software (Varian). Tartaric acid standard solutions containing 400, 300, 200, 150, 100 and 50 μg/mL were used for calibration (linear standard curve in the range of 50–400 μg/mL, correlation coefficient $R^2 > 0.999$. Intra-day and inter-day variability as well as assay precision and accuracy were satisfactory (data not shown).

The apparent diffusion coefficients of the compounds within the polymeric systems were determined by fitting an appropriate analytical solution of Fick's second law of diffusion to the experimentally determined release kinetics from thin polymeric films, in which the compounds were molecularly dispersed (monolithic solutions). As the surface of the films was very large compared to their thickness, edge effects were negligible and the mathematical analysis could be restricted to one dimension. Hence, the release kinetics can be described by Fick's second law of diffusion in a plane sheet (Crank, 1975):

$$\frac{\partial c}{\partial t} = D \cdot \frac{\partial^2 c}{\partial x^2} \tag{3}$$

where c denotes the concentration of the compound within the polymeric system, as a function of time (t) and position (x). The initial condition for this partial differential equation is as follows, expressing the fact that the compounds are uniformly distributed throughout the film at the beginning of the experiment:

$$t = 0 \quad c = c_{ini} \quad -L \le x \le +L \tag{4}$$

Here, c_{ini} represents the initial tartaric acid, metoprolol free base or metoprolol tartrate concentration in the system, L is the half-thickness of the film. The concentration of the compounds far away from the surface of the film are assumed to be constant and equal to zero because the release medium is well stirred and perfect sink conditions are maintained during the experiments. Adjacent to the surface of the film an unstirred liquid layer is considered (even in well-agitated systems thin unstirred layers exist, leading to an additional mass transfer resistance). As there is no accumulation of any of the compounds on the surface of the films, the rates at which they are transported to the surface by diffusion through the film are always equal to the rates at which they leave the film. These rates, per unit area, are proportional to the differences of the actual concentrations on the surface, c_{sur}, and the concentrations required maintaining equilibrium with the surrounding environment, c_∞. The proportionality constant is called the mass transfer coefficient in the boundary layer (h). As the thickness of the boundary layer essentially depends on the rate of stirring, h is a function of the stirring rate. This boundary condition is mathematically expressed as:

$$t > 0 \quad -D \cdot \left| \frac{\partial c}{\partial x} \right|_{x=\pm L} = h(c_{sur} - c_\infty) \tag{5}$$

This initial value problem (Eqs. (3)–(5)) can be solved using a Laplace transformation, leading to (Carslaw and Jaeger, 1959; Vergnaud, 1993):

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=1}^{\infty} \frac{2 \cdot G^2}{\beta_n^2 \cdot (\beta_n^2 + G^2 + G)} \cdot \exp\left(-\frac{\beta_n^2}{L^2} \cdot D \cdot t\right) \tag{6}$$

where β_n is the positive root of:

$$\beta \cdot \tan\ \beta = G \tag{7}$$

with

$$G = \frac{L \cdot h}{D} \tag{8}$$

Here, M_t and M_∞ are the cumulative amounts of tartaric acid, metoprolol free base or metoprolol tartrate released at time t and $t = \infty$, respectively; G denotes a dimensionless constant. The diffusion coefficients of the compounds, D, were determined by fitting Eqs. (6)–(8) to experimentally measured in vitro release kinetics.

2.5. Solubility measurements

The solubility of tartaric acid, metoprolol free base and metoprolol tartrate in 0.1 M HCl, phosphate buffer pH 7.4 (USP 32) and distilled water at 37 °C was determined as follows: a known excess amount of the respective compound was exposed to 1 mL of the media in a horizontal shaker (GFL 3033; 37 °C, 80 rpm). Every 24 h, 20 μL pre-heated medium was added, until all drug excess was dissolved.

2.6. Mechanical properties of wet polymeric films

The mechanical properties of the films were determined by a puncture test using a texture analyser (TA.XT Plus; Swantech, Gennevilliers, France). Film specimens (7 cm × 7 cm) were mounted on a film holder, which was placed into a flask filled with release medium (37 °C). The puncture probe (spherical end: 5 mm diameter) was fixed on the load cell (5 kg) and driven downwards with a cross-head speed of 0.1 mm/s to the centre of the film holder's hole. Load versus displacement curves were recorded until rupture of the films occurred and used to determine the energy at break (J/m^3) as follows:

$$\text{Energy at break} = \frac{AUC}{V_c} \tag{9}$$

where AUC is the area under the load versus displacement curve and V_c is the volume of the film located in the die cavity of the film holder (the energy at break is normalised to the volume of the film). Average values from nine measurements are reported.

3. Results and discussion

3.1. Water uptake kinetics

The symbols in Fig. 2 show the experimentally determined water uptake kinetics of thin, free Eudragit RL-based films containing 0–20% tartaric acid, metoprolol free base or metoprolol tartrate upon exposure to 0.1 M HCl, phosphate buffer pH 7.4 or distilled water at 37 °C. As can be seen, the water uptake of tartaric acid-loaded films is almost unaffected by the initial content of this compound. In contrast, metoprolol free base and metoprolol tartrate containing films showed significantly increasing water uptake rates and extents with increasing initial concentrations of these substances. This can probably be attributed to the considerable plasticising effects of the two compounds on Eudragit RL, which have recently been demonstrated in the *dry* state (Glaessl et al., 2009). In contrast, tartaric acid has been shown to have only minor plasticising effects on this polymer in the dry state. It has

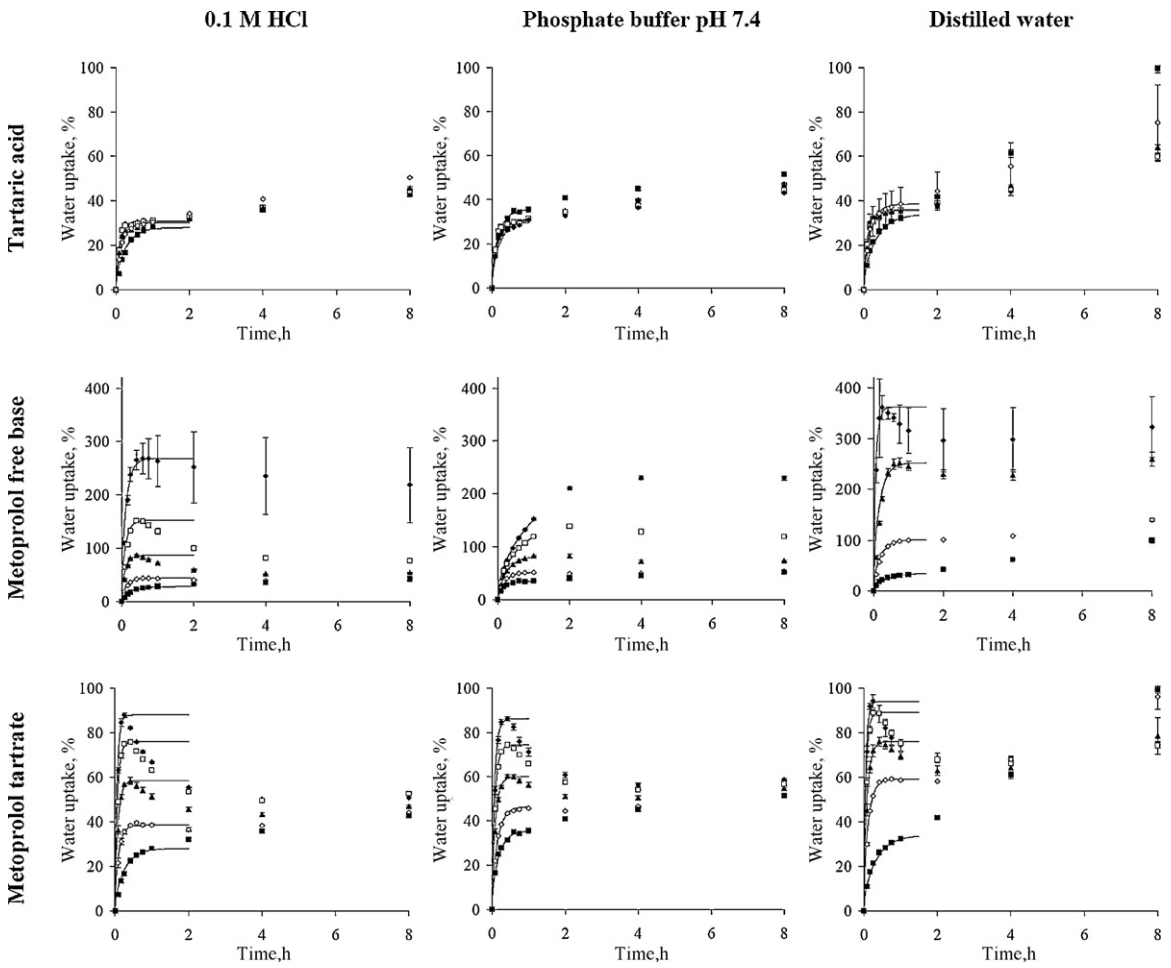

Fig. 2. Water uptake kinetics of thin Eudragit RL films containing 0% (closed squares), 5% (open diamonds), 10% (closed triangles), 15% (open squares), or 20% (closed diamonds) tartaric acid, metoprolol free base or metoprolol tartrate (as indicated) upon exposure to 0.1 M HCl, phosphate buffer pH 7.4 or water (left, middle and right column) at 37 °C. The symbols indicate the experimentally determined results, the curves the fitted theory (Eq. (2)). Note the different scaling of the *y*-axes.

to be pointed out that the presence of water can significantly alter the properties of a macromolecular network, acting as a plasticiser for many polymers. However, the results shown in Fig. 2 indicate that the plasticising activity of tartaric acid, metoprolol free base and metoprolol tartrate on Eudragit RL follow similar trends as in the dry state. The plasticising activity of metoprolol free base on Eudragit RL can probably be attributed to drug interactions with the polymer backbone, whereas also ionic interactions with the quaternary ammonium groups of the macromolecules are involved in the case of metoprolol tartrate. The more rapid uptake of water into metoprolol tartrate containing films compared to metoprolol free base containing films can be explained by the more hydrophilic nature of the salt compared to the free base. However, it should be noted that the extents of water uptake are higher in the case of metoprolol free base containing films compared to those loaded with metoprolol tartrate.

The observed initial increase and subsequent partial decrease in the water contents of the films containing metoprolol free base and metoprolol tartrate (Fig. 2, middle and bottom row) can be explained as follows: metoprolol free base and metoprolol tartrate act as plasticisers for the polymer and assure very flexible polymer networks at early time points, which allow for significant initial water penetration into the systems. However, due to the given drug concentration gradients, these compounds diffuse out of the polymeric systems into the bulk fluids. Thus, the plasticiser content decreases with time, resulting in reduced film flexibility and subsequent water squeezing out of the systems. Similar tendencies have been reported on Eudragit NE:Eudragit L blends upon exposure to phosphate buffer pH 7.4 (Lecomte et al., 2005).

Comparing the left, middle and right column in Fig. 2, it becomes obvious that the type of bulk fluid (0.1 M HCl, phosphate buffer pH 7.4, distilled water) does not fundamentally affect the water uptake kinetics of the polymeric systems (irrespective of the type of compound), with one exception: the shrinkage phenomenon of metoprolol free base containing films is less pronounced upon exposure to phosphate buffer pH 7.4 compared to 0.1 M HCl and distilled water. This can be explained by partial drug precipitation in these films, a phenomenon which has been shown previously in the dry state (Glaessl et al., 2009). Metoprolol free base precipitation slows down drug release and, thus, the loss of the plasticiser (Fig. 3).

The curves shown in Fig. 2 show the theoretically calculated (Eq. (2)) water uptake kinetics of tartaric acid, metoprolol free base and metoprolol tartrate containing Eudragit RL films upon exposure to 0.1 M HCl, phosphate buffer pH 7.4 and distilled water, respectively. The theory is based on Fick's second law of diffusion and considers the given initial and boundary conditions (e.g., homogenous initial film composition and excess amount of water at the films' surface). As it can be seen, good agreement between theory and experiment is obtained in all cases at early time points. This indicates that water penetration into the systems is predominantly controlled by pure diffusion (at least at the beginning). In the case of partially shrinking films, the relative maxima of the water contents were considered to be the M_∞ values in Eq. (2). In the case of tartaric acid-loaded films,

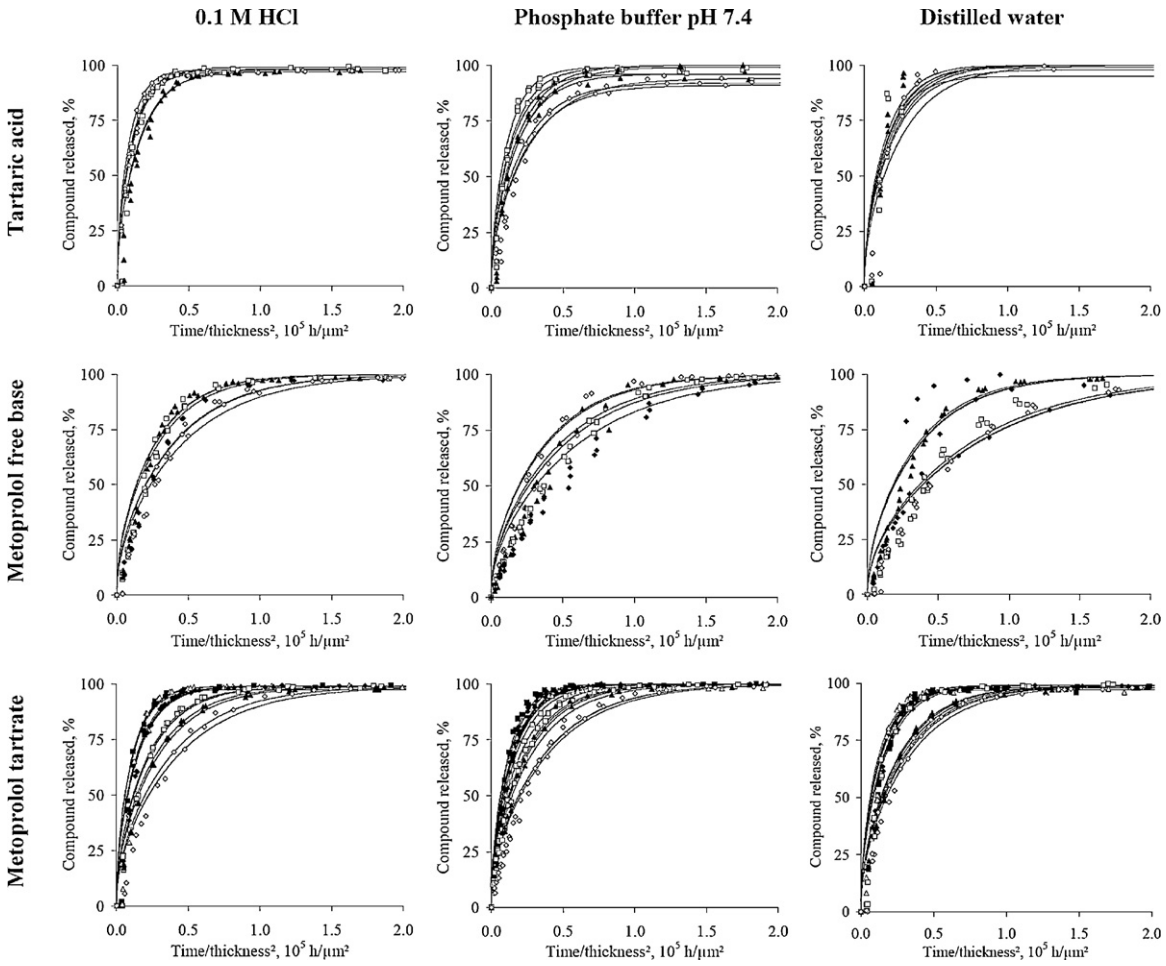

Fig. 3. Release kinetics of tartaric acid, metoprolol free base and metoprolol tartrate from thin Eudragit RL films initially containing 5% (open diamonds), 10% (closed triangles), 15% (open squares), 20% (closed diamonds), 25% (open triangles), or 30% (closed squares) of this compound upon exposure to 0.1 M HCl, phosphate buffer pH 7.4 or water (left, middle and right column) at 37 °C (normalised to the film thickness). The symbols indicate the experimentally determined results, the curves the fitted theory (Eqs. (6)–(8)).

the plateaus obtained after 1–2 h were considered as M_∞ values. Based on these calculations, the apparent diffusion coefficients of water within the polymeric systems could be determined.

As can be seen in Fig. 4, the water diffusivity only slightly increased with increasing initial tartaric acid content and significantly increased with increasing metoprolol tartrate content, irrespective of the type of bulk fluid (white, grey and black bars). This indicates that metoprolol tartrate is a potent plasticiser for Eudragit RL, also in the wet state, whereas the plasticising activity of tartaric acid is only limited (as in the dry state). In the case of metoprolol free base containing films, the water diffusivity: (i) first increased and then decreased again with increasing initial drug content upon exposure to 0.1 M HCl (white bars), (ii) monotonically decreased with increasing initial drug content upon exposure to phosphate buffer pH 7.4 (grey bars), and (iii) monotonically increased with increasing initial drug content upon exposure to distilled water (black bars). The monotonic decrease in the case of phosphate buffer pH 7.4 might be attributable to the low solubility of metoprolol free base in this medium (Table 1). Although this drug is soluble up to 20% in Eudragit RL films in the dry state (Glaessl et al., 2009), once significant amounts of water have penetrated into the system (Fig. 2), the nature of the polymeric network fundamentally changes (becoming more hydrophilic) and the free base is likely to precipitate. Visual observation confirmed that the respective films became turbid within a few minutes upon exposure to phosphate buffer pH 7.4. Thus, the absolute amount of dissolved plasticiser does not increase with increasing initial metoprolol free base content, whereas the presence of increasing amounts of precipitated free base is likely to render the films more hydrophobic and less permeable for water. In the case of 0.1 M HCl, the solubility of the drug is almost twice as high as in phosphate buffer pH 7.4 (Table 1). Thus, metoprolol free base precipitation occurs only at higher initial drug contents. This leads to initially increasing water diffusivities with increasing initial drug contents (metoprolol free base acting as a plasticiser for this polymer). However, as soon as drug precipitation in the wet films occurs, the water diffusion coefficients decrease again (Fig. 4). In the case of film exposure to distilled water, the water diffusivity surprisingly monotonically increased with increasing initial metoprolol free base content throughout the investigated range (despite of the low solubility of the drug in this medium, Table 1). This phenomenon is yet not fully understood but might be attributed

Table 1
Solubility of tartaric acid, metoprolol free base and metoprolol tartrate in the investigated release media at 37 °C, in g/100 mL. Note that the pH in the saturated solution does not necessarily correspond to the initial pH of the bulk fluid.

	0.1 M HCl	Phosphate buffer pH 7.4	Distilled water
Tartaric acid	137	137	137
Metoprolol free base	4.8	2.5	1.8
Metoprolol tartrate	368	356	363

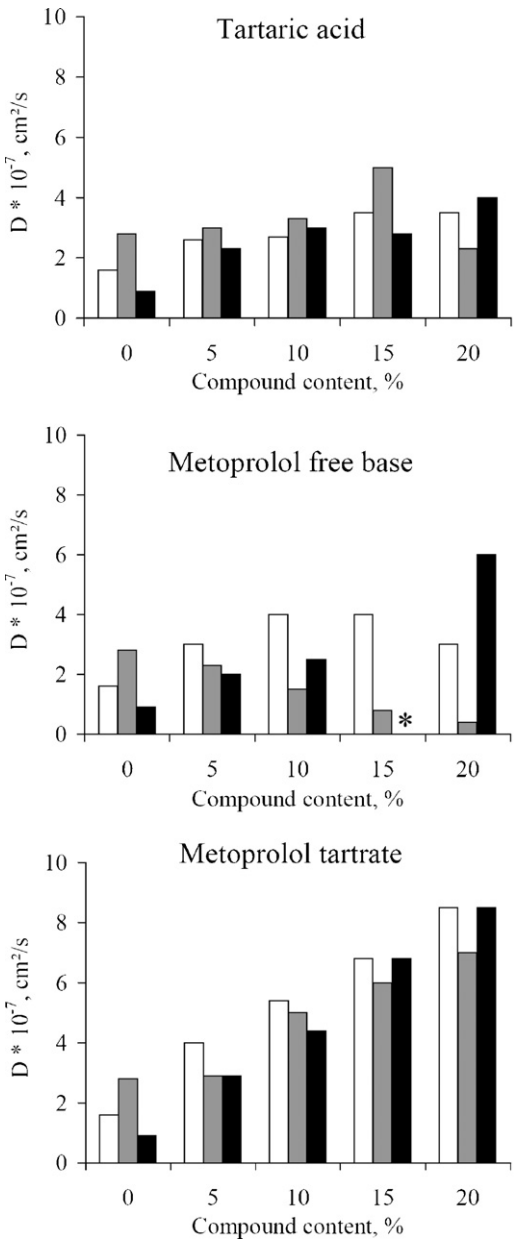

Fig. 4. Apparent diffusion coefficient of water in thin Eudragit RL films containing 0, 5, 10, 15, or 20% tartaric acid, metoprolol free base or metoprolol tartrate (as indicated) upon exposure to 0.1 M HCl (white bars), phosphate buffer pH 7.4 (grey bars) or water (black bars) at 37 °C (determined by fitting Eq. (2) to the experimentally measured water uptake kinetics shown in Fig. 2). An asterisk indicates that Eq. (2) is not applicable.

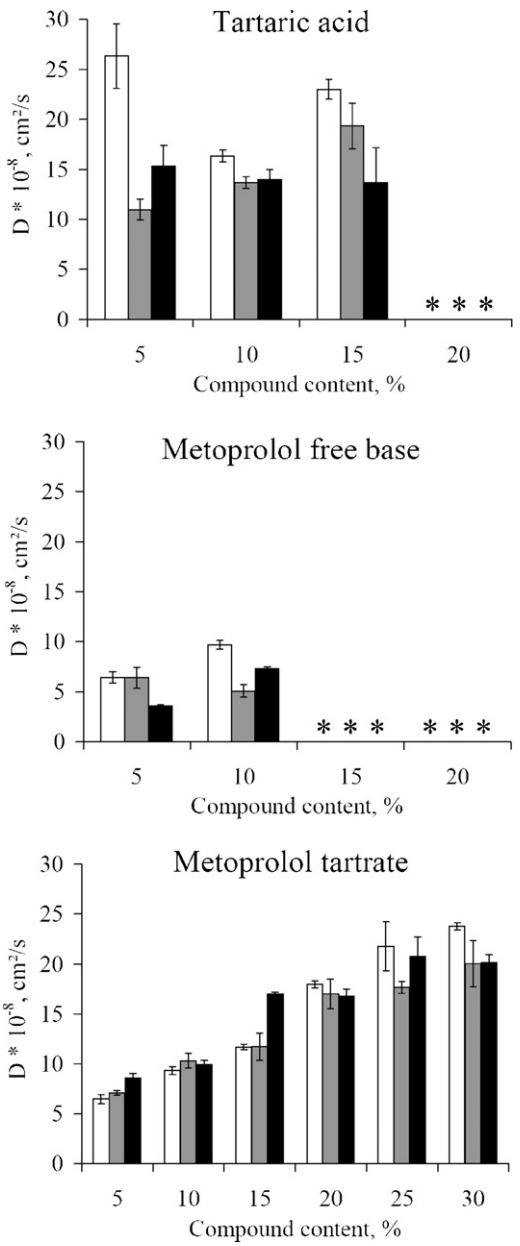

Fig. 5. Apparent diffusion coefficient of tartaric acid, metoprolol free base and metoprolol tartrate in thin Eudragit RL films initially containing 0, 5, 10, 15, 20, 25, or 30% of this compound (as indicated) upon exposure to 0.1 M HCl (white bars), phosphate buffer pH 7.4 (grey bars), or water (black bars) at 37 °C (determined by fitting Eqs. (6)–(8) to the experimentally measured compound release kinetics shown in Fig. 3). An asterisk indicates that Eqs. (6)–(8) are not applicable.

to the creation of super-saturated drug solutions under the given micro-environmental conditions in the polymeric network.

3.2. Compound release kinetics

The symbols in Fig. 3 show the experimentally determined release kinetics of tartaric acid (top row), metoprolol free base (middle row) and metoprolol tartrate (bottom row) upon exposure to 0.1 M HCl (left column), phosphate buffer pH 7.4 (middle column) and distilled water (right column), respectively. The initial compound concentration was varied from 5 to 15% in the case of tartaric acid, from 5 to 20% in the case of metoprolol free base [because it has recently been shown that above these concentrations, compound precipitation occurred in the dry state (Glaessl et al., 2009)] and 5–30% in the case of metoprolol tartrate. The curves in Fig. 3 show the theoretically calculated compound release kinetics. The theory considers an initial homogeneous and molecular distribution of tartaric acid, metoprolol free base and metoprolol tartrate within the thin films and the maintenance of perfect sink conditions throughout the experiments. Under these conditions and taking into account the additional mass transfer resistance due to the presence of liquid, unstirred boundary layers on both sides of the films, Eqs. (6)–(8) can be derived (see Section 2.4). Good agreement between theory (curves) and experiment (symbols) was obtained in most cases (except for films with moderate to high initial metoprolol free base contents and high initial tartaric acid contents). Interestingly, the mass transfer resistance within

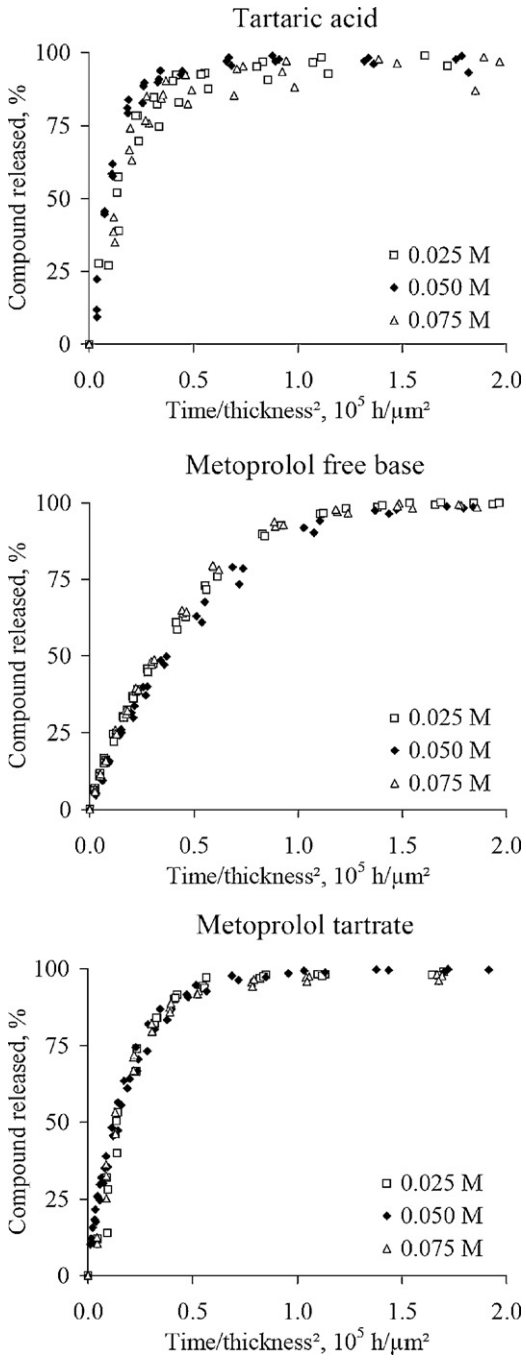

Fig. 6. Effects of the molality of the phosphate buffer pH 7.4 (indicated in the diagrams) on the release of tartaric acid, metoprolol free base and metoprolol tartrate from thin Eudragit RL films initially containing 15% of the respective compound.

the liquid unstirred boundary layers at the surfaces of the films was found to be negligible compared to the mass transfer resistance within the polymeric networks (high dimensionless number $G = L \times h/D > 100$) in all cases, in which the theory was applicable (Siepmann et al., 1999). This indicates that diffusional mass transport through the polymeric networks is predominant for the control of the release of tartaric acid, metoprolol tartrate and metoprolol free base (in the latter case at low initial concentrations) from Eudragit RL films, irrespective of the type of bulk fluid. To account for slight differences in the film thickness (each experiment was conducted in triplicate), the compound release kinetics shown in Fig. 3 were normalised with respect to the length of the diffusion pathways ("time/thickness^2" is plotted on the *x*-axes). Based on these calculations, the apparent diffusion coefficients of the investigated compounds in Eudragit RL films upon exposure to 0.1 M HCl, phosphate buffer pH 7.4 and distilled water could be determined (Fig. 5).

The relative release rate of metoprolol tartrate monotonically increased with increasing initial content of this compound (Fig. 3, bottom row), corresponding to monotonically increasing drug diffusion coefficients (Fig. 5). This can predominantly be attributed to the considerable plasticising effect of metoprolol tartrate on Eudragit RL. This phenomenon was independent of the type of release medium (left, middle and right column in Fig. 3), and the apparent drug diffusivities were very similar in all media (white, grey and black bars in Fig. 5). In contrast, in the case of tartaric acid containing films, the increase in the relative release rate with increasing initial content of this compound was limited (Fig. 3, top row), irrespective of the type of bulk fluid. This corresponds to non-systemic (arbitrary) variations in the determined apparent diffusion coefficients (Fig. 5). Note that the applied theory (Eqs. (6)–(8)) is not applicable to films initially containing 20% tartaric acid. This can be attributed to the limited solubility of this compound in Eudragit RL, as it has recently been shown in the dry state (Glaessl et al., 2009). Also, visual observation of the wet films showed that the systems became turbid upon exposure to the release media. In the case of metoprolol free base containing films, the presented theory (Eqs. (6)–(8), based on Fick's law) was only applicable to systems with an initial drug concentration of 5 and 10% (middle row in Fig. 3). At higher concentrations, the free base precipitated in the wet films (visual observation), a phenomenon which is not considered in the theory. Thus, only at low initial drug contents, the apparent diffusivities could be determined (Fig. 5).

The observed increase in the diffusion coefficient of metoprolol tartrate in the Eudragit RL films with increasing initial drug content might also partially be attributable to the increased porosity of the systems upon drug leaching. However, the importance of this effect is likely to be limited, because the diffusivity of tartaric acid was not very much affected by the initial compound content.

In order to evaluate the importance of the osmolality of the release medium on drug release from the investigated films, the molality of the phosphate buffer pH 7.4 was varied from 0.025 to 0.075 M and the release of tartaric acid, metoprolol free base and metoprolol tartrate was measured from films initially containing 15% of these compounds (Fig. 6). The resulting compound release kinetics was very similar in all cases for the investigated osmolalities of the phosphate buffer. Thus, ion exchange processes with the buffer ions do not appear to play a crucial role in these systems.

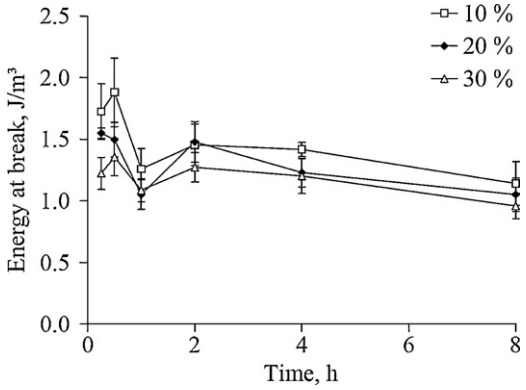

Fig. 7. Changes in the energy at break of thin Eudragit RL films initially containing 10, 20 and 30% metoprolol tartrate (as indicated) upon exposure to phosphate buffer pH 7.4 at 37 °C.

3.3. Mechanical properties

The mechanical properties of thin Eudragit RL films initially containing 10, 20 or 30% metoprolol tartrate were determined using a texture analyser and the puncture test upon exposure to phosphate buffer pH 7.4 at 37 °C. It can be seen in Fig. 7 that the energy required to break the films decreased with time, irrespective of the initial drug concentration. This can be explained by the leaching of metoprolol tartrate into the bulk fluid (Fig. 3), the drug acting as a plasticiser for this polymer. Interestingly, this effect was not compensated (or overcompensated) by the penetration of water into the polymeric networks (Fig. 2). Water is known to be an effective plasticiser for many polymers. Thus, the backbone and ionic interactions of metoprolol tartrate with Eudragit RL are likely to be more important than water–Eudragit RL interactions.

4. Conclusion

The importance of drug–polymer interactions in controlled drug delivery systems is often underestimated and poorly understood. The impact of the presence of water further complicates the involved physical phenomena and the effects of formulation parameters on the resulting drug release kinetics can be surprising. The present study can help to better understand the importance of drug precipitation, drug–polymer interactions and the role of water and drug diffusion and/or drug dissolution in Eudragit RL-based drug delivery systems. Thus, the optimisation of this type of dosage forms can be facilitated, product development accelerated and trouble shooting during production becomes more efficient.

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References

Albers, J., Alles, R., Matthee, K., Knop, K., Schulze Nahrup, J., Kleinebudde, P., 2009. Mechanism of drug release from polymethacrylate-based extrudates and milled strands prepared by hot-melt extrusion. Eur. J. Pharm. Biopharm. 71, 387–394.

Bodmeier, R., Paeratakul, O., 1993. Dry and wet strengths of polymeric films prepared from an aqueous colloidal polymer dispersion, Eudragit RS30D. Int. J. Pharm. 96, 129–138.

Bodmeier, R., Paeratakul, O., 1994. Mechanical properties of dry and wet cellulosic and acrylic polymer films prepared from aqueous colloidal polymer dispersions. Pharm. Res. 11, 882–888.

Carslaw, H., Jaeger, J. (Eds.), 1959. Conduction of Heat in Solids. Clarendon Press, Oxford.

Crank, J. (Ed.), 1975. The Mathematics of Diffusion, 2nd edition. Clarendon Press, Oxford.

Glaessl, B., Siepmann, F., Tucker, I., Siepmann, J., Rades, T., 2009. Characterisation of quaternary polymethacrylate films containing tartaric acid, metoprolol free base or metoprolol tartrate. Eur. J. Pharm. Biopharm. 73, 366–372.

Goole, J., Deleuze, P., Vanderbist, F., Amighi, K., 2008. New levodopa sustained-release floating minitablets coated with insoluble acrylic polymer. Eur. J. Pharm. Biopharm. 68, 310–318.

Jenquin, M.R., McGinity, J.W., 1994. Characterization of acrylic resin matrix films and mechanisms of drug–polymer interactions. Int. J. Pharm. 101, 23–34.

Knop, K., 1996. Influence of buffer solution composition on drug release from pellets coated with neutral and quaternary acrylic polymers and on swelling of free polymer films. Eur. J. Pharm. Sci. 4, 293–300.

Lecomte, F., Siepmann, J., Walther, M., MacRae, R.J., Bodmeier, R., 2003. Blends of enteric and GIT-insoluble polymers used for film coating: physicochemical characterization and drug release patterns. J. Control. Rel. 89, 457–471.

Lecomte, F., Siepmann, J., Walther, M., MacRae, R.J., Bodmeier, R., 2004. Polymer blends used for the coating of multiparticulates: comparison of aqueous and organic coating techniques. Pharm. Res. 21, 882–890.

Lecomte, F., Siepmann, J., Walther, M., MacRae, R.J., Bodmeier, R., 2005. pH-sensitive polymer blends used as coating materials to control drug release from spherical beads: elucidation of the underlying mass transport mechanisms. Pharm. Res. 22, 1129–1141.

Moustafine, R.I., Kemenova, V.A., Van den Mooter, G., 2005. Characteristics of interpolyelectrolyte complexes of Eudragit E 100 with sodium alginate. Int. J. Pharm. 294, 113–120.

Sauer, D., Watts, A.B., Coots, L.B., Zheng, W.C., McGinity, J.W., 2009. Influence of polymeric subcoats on the drug release properties of tablets powder-coated with pre-plasticized Eudragit L 100-55. Int. J. Pharm. 367, 20–28.

Schilling, S.U., Bruce, C.D., Shah, N.H., Malick, A.W., McGinity, J.W., 2008. Citric acid monohydrate as a release-modifying agent in melt extruded matrix tablets. Int. J. Pharm. 361, 158–168.

Semdé, R., Amighi, K., Devleeschouwer, M.J., Moës, A.J., 2000. Studies of pectin HM/Eudragit RL/Eudragit NE film-coating formulations intended for colonic drug delivery. Int. J. Pharm. 197, 181–192.

Siepmann, J., Lecomte, F., Bodmeier, R., 1999. Diffusion-controlled drug delivery systems: calculation of the required composition to achieve desired release profiles. J. Control. Rel. 60, 379–389.

Siepmann, J., Goepferich, A., 2001. Mathematical modeling of bioerodible, polymeric drug delivery systems. Adv. Drug Deliv. Rev. 48, 229–247.

Siepmann, J., Peppas, N.A., 2001. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Adv. Drug Deliv. Rev. 48, 139–157.

Siepmann, J., Siepmann, F., 2008. Mathematical modeling of drug delivery. Int. J. Pharm. 364, 328–343.

Siepmann, F., Siepmann, J., Walther, M., MacRae, R.J., Bodmeier, R., 2008. Polymer blends for controlled release coatings. J. Control. Rel. 125, 1–15.

Vergnaud, J., 1993. Controlled Drug Release of Oral Dosage Forms. Ellis Horwood, Chichester.

Wagner, K.G., McGinity, J.W., 2002. Influence of chloride ion exchange on the permeability and drug release of Eudragit RS 30 D films. J. Control. Rel. 82, 385–397.