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Research Paper

pH-Sensitive Polymer Blends Used as Coating Materials to Control Drug Release from Spherical Beads: Elucidation of the Underlying Mass Transport Mechanisms

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Purpose. To elucidate the drug release mechanisms from pellets coated with pH-sensitive polymer blends.
Methods. Verapamil hydrochloride-loaded beads were coated with various blends of a water-insoluble and an enteric polymer, ethylcellulose:Eudragit L and Eudragit NE:Eudragit L, respectively. Both experimental and theoretical techniques were used to characterize the systems before and upon exposure to 0.1 M HCl and phosphate buffer (pH 7.4).
Results. Using analytical solutions of Fick's second law of diffusion, optical and scanning electron microscopy, and mechanical and gravimetric analysis, new insight into the underlying drug release mechanisms could be gained. More importantly, the latter can be effectively altered by varying the type of polymer blend and blend ratio. For example, at low pH drug release is primarily controlled by diffusion through the intact film coatings in Eudragit NE:Eudragit L blends, whereas crack formation is of major importance in ethylcellulose:Eudragit L-coated systems. At high pH, the (partial) leaching of the enteric polymer out of the coatings plays an important role. In all cases, the observed drug release profiles could be explained based on the occurring mass transport processes.
Conclusions. The obtained new knowledge can be used to effectively adjust desired drug release mechanisms and, thus, release patterns.

KEY WORDS: controlled drug release; pellets; polymer blend; polymer coatings; release mechanism.

INTRODUCTION

Due to their versatility polymer blends are frequently used as excipients in controlled drug delivery systems. For example, they serve as matrix formers in tablets (1–3) and micro- and nanoparticles (4–6) or as coating materials for solid dosage forms (7,8). The idea is to combine two polymers with different properties such as permeability for water and drugs, pH, temperature sensitivity, and biodegradability (e.g., enzymatically driven or not). By simply varying the polymer blend ratio, broad ranges of system characteristics and, thus, drug release patterns can be provided.

Blends of enteric and gastrointestinal tract (GIT)-insoluble polymers are particularly interesting for the coating of solid dosage forms because they can be used to provide large ranges of drug release profiles at low and at high pH, as previously shown (8–10). In contrast to pH-insensitive polymer blends, the properties of this type of coatings are triggered by the pH of the surrounding environment. In the stomach (at low pH), both polymers are insoluble, whereas in the intestine (at high pH), the enteric polymer is soluble and might leach out of the coatings. This can lead to significant, dynamic changes in the physicochemical properties of the films during GIT transit (e.g., increased permeability) and, thus, to altered drug release kinetics.

An interesting application of this type of pH-sensitive coating materials is the possibility to render the release of weakly basic drugs exhibiting strongly pH-dependent solubility pH independent. The idea is to be able to compensate for the decrease in drug solubility along the GIT (high solubility in the stomach, low solubility in the intestine) by a simultaneous increase in drug permeability of the film coating. For example, Amighi *et al.* (11) used blends of aqueous dispersions of the water-insoluble polymer Eudragit NE30D (ethyl acrylate:methyl methacrylate copolymer) and the enteric polymer Eudragit L30D (methacrylic acid:ethyl acrylate copolymer 1:1) to achieve pH-independent release of a weakly basic model drug (ucb 11056). In that study, classical approaches based on hydrophilic matrices and pellets coated with only one single polymer failed to provide pH-independent drug release (the release rate being too slow at high pH). In contrast, 70:30 Eudragit NE:Eudragit L blends used as coating materials for drug-loaded pellets provided almost

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pH-independent release patterns in the pH range 1–7. Dashevsky *et al.* (12) blended Kollicoat SR and Kollicoat MAE [aqueous dispersions of poly(vinyl acetate) and methacrylic acid:ethyl acrylate copolymer 1:1] for the coating of verapamil hydrochloride-layered sugar cores. The pH-dependent solubility of the weakly basic drug was successfully masked and pH-independent drug release was provided at a polymer blend ratio of 90:10 (Kollicoat SR:Kollicoat MAE) and a coating level of 10%.

Furthermore, blends of enteric and GIT-insoluble polymers can be used to provide adequate mechanical properties of the film coatings. For example, most enteric polymers are brittle in the dry state. Thus, when compressing coated pellets into tablets, the film coatings can be severely damaged and the enteric properties can get lost. To overcome this restriction, highly flexible, GIT-insoluble polymers can be added to the film coatings (13–15). Beckert *et al.* (13) used 50:50 blends of the enteric polymer Eudragit L30D (which is brittle in the dry state) and the highly flexible, GIT-insoluble polymer Eudragit NE30D to coat bisacodyl-containing pellets. The film damage occurring during tabletting could significantly be reduced. Zheng and McGinity (16) added small amounts of Eudragit L to reduce the tackiness of Eudragit NE films. An 85:15 Eudragit NE30D:Eudragit L30D-55 blend effectively prevented agglomeration of phenylpropanolamine hydrochloride-loaded pellets during coating and storage. In addition, the curing time required to provide the formation of a stable film decreased in the presence of Eudragit L. Fan *et al.* (17) used blends of organic solutions of ethylcellulose (EC) and Eudragit L for the coating of diltiazem hydrochloride-containing tablets. The aim of their study was to provide pulsatile drug delivery. More importantly, the plasma concentration–time curves of eight volunteers showed that the desired release patterns could be achieved *in vivo*. Wu and McGinity (18) added different amounts of the enteric polymer Eudragit L100-55 to an aqueous dispersion of the GIT-insoluble polymer Eudragit RS (ammonio methacrylate copolymer). Theophylline release from pellets coated with such blends was studied. Interestingly, the presence of Eudragit L significantly increased the storage stability of the system.

The mechanisms involved in the control of drug release from coated dosage forms are complex and not yet fully understood (19–23). Upon contact with aqueous human body fluids, water diffuses into the systems (due to concentration gradients) and dissolves the drug. The latter subsequently diffuses out of the dosage forms through the film coatings (which can control the overall drug release rate). In addition, due to the imbibing water, significant hydrostatic pressures can be created within the bead cores. These hydrostatic pressures can lead to the formation of cracks within the polymeric films and, thus, to significant changes in drug permeability. When pH-sensitive polymer blends are used as coating materials instead of one single polymer, the occurring mass transport processes become even more complex. Yet, very little knowledge is available on the underlying drug release mechanisms in this type of delivery system and the development and optimization of the latter is generally trial-and-error based.

The major objectives of the present study were (1) to prepare and physicochemically characterize pellets coated with different types of pH-sensitive polymer blends and (2) to elucidate the underlying drug release mechanisms based on the experimental results and adequate mathematical theories.

MATERIALS AND METHODS

Materials

Verapamil hydrochloride (BASF, Ludwigshafen, Germany), hydroxypropyl methylcellulose (HPMC, Methocel E5, Colorcon, Orpington, UK), methacrylic acid:ethyl acrylate copolymer 1:1 (Eudragit L100-55, Röhm, Darmstadt, Germany) and an aqueous dispersion thereof (Eudragit L30D-55; Röhm), an aqueous dispersion of ethyl acrylate: methyl methacrylate copolymer (Eudragit NE30D; Röhm), ethylcellulose (EC, Ethocel Standard 10 Premium, Dow Chemical Company, Midland, MI, USA) and an aqueous dispersion thereof (Aquacoat ECD30, FMC, c/o Interorgana, Köln, Germany), triethyl citrate (Morflex, Greensboro, NC, USA), sugar beads (Suglets sugar spheres NF, 710 to 850 μm, NP Pharm S.A., Bazainville, France), polyoxyethylene sorbitan monooleate (Tween 80, Sigma-Aldrich Chemie GmbH, Steinheim, Germany), glycerol monostearate (Cutina GMS, Cognis, Düsseldorf, Germany), and talc (Merck, Darmstadt, Germany) were used as received.

Preparation of Coated Beads

Verapamil hydrochloride-loaded beads (10% w/w drug loading) were prepared by layering an aqueous drug-binder solution (6.7% w/w verapamil hydrochloride, 0.7% w/w HPMC, 3.4% w/w talc) onto drug-free sugar beads in a fluidized bed coater (Kugelcoater UNILAB-05, Hüttlin, Steinen, Germany). The drug-loaded beads were coated with a water-insoluble polymer (Aquacoat ECD or Eudragit NE30D), a pH-sensitive polymer (Eudragit L30D-55, water soluble at pH >5.5), or blends thereof (Kugelcoater UNILAB-05). The aqueous polymer dispersions were plasticized with 25% triethyl citrate (w/w, based on the total dry polymer weight, for EC:Eudragit L blends) or 10% triethyl citrate (w/w, based on the dry Eudragit L weight, for Eudragit NE:Eudragit L blends). Due to the sticking tendency of Eudragit NE, glycerol monostearate (5% w/w, based on the dry Eudragit NE30D weight) was added as antitacking agent (in the form of a 2% w/w emulsion in an aqueous 0.08% w/w Tween 80 solution). The polymer content was adjusted to 15% (w/w) with purified water. The following polymer blend ratios were investigated: 0:100, 25:75, 50:50, 75:25, and 100:0 (w/w). The coating dispersions were sprayed onto a mixture of drug-loaded spherical beads and drug-free sugar beads (1:4 w/w, 500 g) until a weight gain of 20% (w/w) was achieved. The process parameters were as follows: product temperature = (30–37) ± 2°C (depending on the type of polymer), spray rate = 3–4 g/min, atomization pressure = 0.4 bar, pressure of microclimate = 0.2 bar, nozzle diameter = 0.8 mm. After coating, the beads were further fluidized for 15 min (Kugelcoater UNILAB-05) and then cured in an oven (without ventilation; T 6120, Heraeus, Hanau, Germany) for 24 h at 60°C (EC:Eudragit L blends) or 24 h at 40°C (Eudragit NE:Eudragit L blends) as indicated.

Preparation of Thin Polymeric Films

Thin, drug-free films of identical composition as the pellet coatings were prepared by spraying aqueous dispersions of Aquacoat ECD, Eudragit NE30D or Eudragit L30D-55 and blends thereof onto Teflon plates and subsequent curing in an oven (without ventilation; T 6120) (as described for coated beads). The thickness of the films was measured using a thickness gauge (Minitest 600, Erichsen, Hemer, Germany). Thin, drug-containing films were prepared by casting acetone drug/polymer solutions (10% w/w verapamil hydrochloride, based on the dry polymer weight) using a casting knife (Multicator 411, Erichsen). The subsequent drying process was standardized as follows: 1 day at room temperature, 1 day at 40°C in an oven (without ventilation; T 6120), and 1 day at room temperature. Identical amounts of plasticizers and antitacking agent as used for the pellet coatings were added.

Water Uptake and Dry Weight Loss of Thin Polymeric Films

Thin polymeric films were cut into pieces of 5 × 5 cm, which were placed into 50-mL plastic containers filled with 40 mL 0.1 M HCl or phosphate buffer (pH 7.4, USP XXVII), followed by horizontal shaking for 8 h (37°C, 75 rpm, $n = 3$; GFL 3033, Gesellschaft für Labortechnik, Burgwedel, Germany; one film per container). To avoid film folding and floating during the experiment (resulting in potential variations of the surface area exposed to the release medium), the films were fixed within the plastic containers. At predetermined time intervals, samples were withdrawn and gently blotted with precision wipes to remove excess amounts of water at the surface of the films. The latter were weighed [wet weight (t)], and dried to constant weight at 60°C in an oven (without ventilation; T 6120) [dry weight (t)]. The water content (%) and dry film weight (%) at time t were calculated as follows:

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

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

Dry weight (0) denotes the dry weight of the films before exposure to the release medium.

Changes in the Surface Area of Thin Polymeric Films

Thin polymeric films were cut into pieces of 3 × 3 cm, which were placed into 50-mL plastic containers filled with 40 mL phosphate buffer (pH 7.4, USP XXVII), followed by horizontal shaking for 2 h (37°C, 75 rpm, films were fixed; GFL 3033). At predetermined intervals, samples were withdrawn and their surface area measured with an optical imaging system (EasyMeasure, INTEQ Informationstechnik GmbH, Berlin, Germany).

Mechanical Properties of Thin Polymeric Films

The mechanical properties (percent elongation and energy at break) of thin polymeric films in the dry and wet state were measured using the puncture test and a texture analyzer (TAXT Plus, Winopal Forschungsbedarf GmbH, Ahnsbeck, Germany). Film specimens (7 × 9 cm) were mounted on a film holder. The puncture probe (spherical end, 5 mm diameter) was fixed on the load cell (5 kg) and driven downward with a crosshead speed of 0.1 mm/s to the center of the film holder's hole. Load *vs.* displacement curves were recorded until rupture of the film and used to determine the mechanical properties as follows:

$$\text{Elongation at break (\%)} = \frac{\sqrt{R^2 + d^2} - R}{R} \times 100\% \quad (3)$$

Here, R denotes the radius of the film exposed in the cylindrical hole of the holder (0.5 cm in the present study) and d is the displacement to puncture.

$$\text{Energy at break} = \frac{\text{AUC}}{V} \quad (4)$$

where AUC is the area under the load *vs.* displacement curve and V is the volume of the film located in the die cavity of the film holder.

Increase in Bead Diameter

Single beads were placed into small vials filled with 0.1 M HCl, followed by horizontal shaking for 8 h (37°C, 75 rpm; GFL 3033). At predetermined intervals, the beads' diameter was measured using an optical imaging system (EasyMeasure, INTEQ) ($n = 10$). The increase in bead diameter (%) at time t was calculated as follows:

$$\text{Increase in bead diameter (\%) } (t) = \frac{\text{diameter } (t) - \text{diameter } (0)}{\text{diameter } (0)} \times 100\% \quad (5)$$

Drug Release from Coated Beads and Thin, Drug-Containing Films

Drug release from coated beads was determined using the USP XXVII paddle apparatus in 0.1 M HCl and phosphate buffer (pH 7.4, 37°C, 100 rpm, $n = 3$). At predetermined time intervals, 3-ml samples were withdrawn and analyzed with UV spectrophotometry ($\lambda = 278$ nm; UV-2101 PC, Shimadzu Scientific Instruments, Columbia, MD, USA). Drug release from thin, drug-containing films was measured by placing film pieces (5 × 5 cm) into 50-ml plastic containers filled with 40 ml 0.1 M HCl, followed by horizontal shaking for 48 h (37°C, 75 rpm, GFL 3033, $n = 3$). To avoid film folding and floating during the experiment (resulting in potential variations of the surface area exposed to the release medium), the films were fixed within the plastic containers. At predetermined time intervals, 3-ml samples were with-

drawn (replaced with fresh medium) and analyzed by UV spectrophotometry (λ = 278 nm, UV-2101 PC).

Morphology of Coated Beads

The morphology of surfaces and cross sections of coated beads was examined by scanning electron microscopy before and upon exposure to the release media (treating the beads as described for the drug release studies). Samples were coated with a 10-nm-thick gold layer under argon atmosphere (SCD 040, Bal-tec GmbH, Witten, Germany) and observed with a Hitachi S-4000 high-resolution field-emission scanning electron microscope (Hitachi High-Technologies Europe GmbH, Krefeld, Germany) operating at 20 kV.

THEORETICAL SECTION

Apparent drug diffusion coefficients within the polymeric systems were determined by fitting an analytical solution of Fick's second law of diffusion to experimentally determined drug release kinetics from thin films, in which the drug was molecularly dispersed (monolithic solution). As the surface of the films was very large compared to their thickness (approximately 50 cm^2 *vs.* 20 μm), edge effects were negligible and the mathematical analysis was restricted to one dimension. Hence, the release kinetics could be described by Fick's second law of diffusion in a plane sheet (24):

$$\frac{\partial c}{\partial t} = D \times \frac{\partial^2 c}{\partial x^2} \tag{6}$$

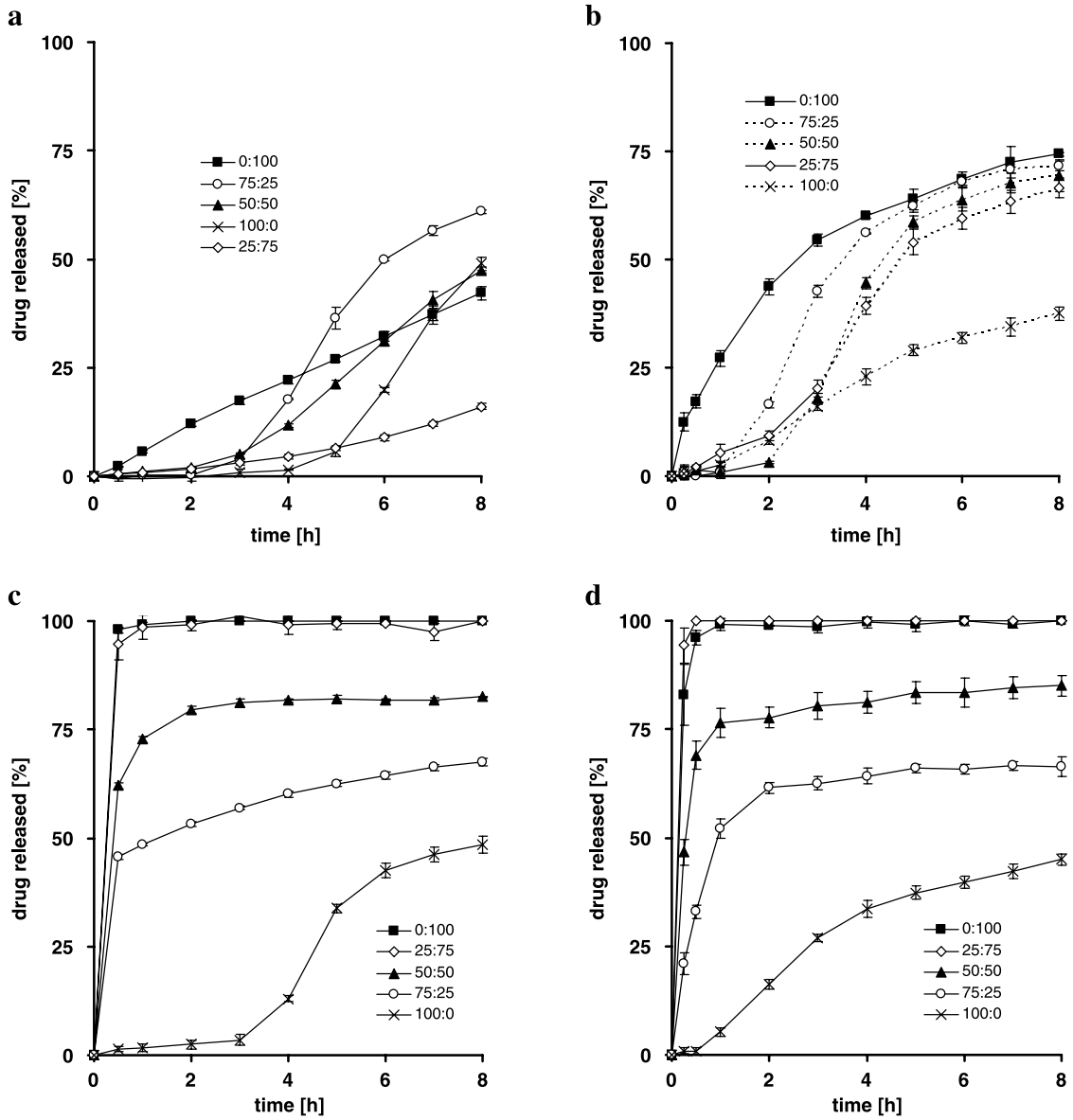

Fig. 1. Verapamil hydrochloride release from spherical beads coated with (a) Eudragit NE:Eudragit L blends in 0.1 M HCl; (b) EC:Eudragit L blends in 0.1 M HCl; (c) Eudragit NE:Eudragit L blends in phosphate buffer (pH 7.4); (d) EC:Eudragit L blends in phosphate buffer (pH 7.4) (mean ± SD, n = 3). The polymer blend ratio is indicated in the figures. For (a) and (b), solid curves indicate that drug release is primarily controlled by diffusion through the intact film coatings; dotted curves indicate that drug release is primarily controlled by diffusion through water-filled cracks.

where c denotes the concentration of the drug within the polymeric system, being a function of time t and position x; D represents the apparent diffusion coefficient of the drug.

The initial condition for this partial differential equation is as follows, expressing that the drug is uniformly distributed throughout the films at the beginning of the experiment:

$$t = 0 \quad c = c_{\text{ini}} \quad -L \leq x \leq +L \tag{7}$$

Here, c_{ini} represents the initial drug concentration in the system and L the half thickness of the film. The drug concentration far from the surface of the film is assumed constant and equal to zero because the release medium is well stirred and perfect sink conditions are maintained during the experiment. Near 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. Because there is no accumulation of the drug on the surface of the film, the rate at which the drug is transported to the surface by diffusion through the film is always equal to the rate at which it leaves the film. This rate per unit area is proportional to the difference of the actual concentration on the surface, c_{sur}, and the concentration required to maintain equilibrium with the surrounding environment, c_{∞}. The constant of proportionality is called the mass transfer coefficient in the boundary layer, k. As the thickness of the boundary layer depends essentially on the rate of stirring, k is a function of the stirring rate. This boundary condition is mathematically expressed as

$$t > 0 \quad -D \times \left|\frac{\partial c}{\partial x}\right|_{x = \pm L} = k \times (c_{\text{sur}} - c_{\infty}) \tag{8}$$

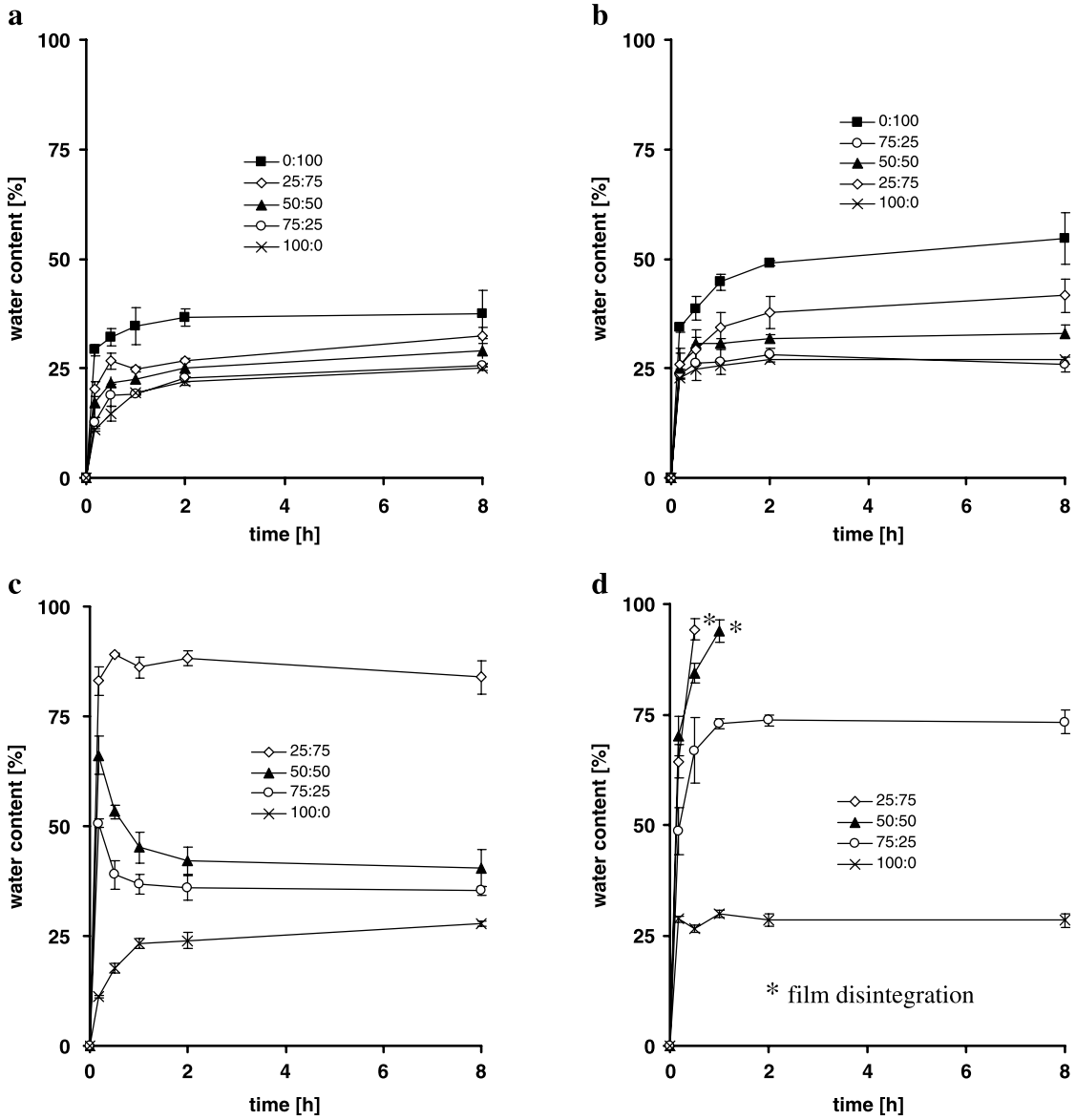

Fig. 2. Water contents of thin polymeric films consisting of (a) Eudragit NE:Eudragit L blends upon exposure to 0.1 M HCl; (b) EC:Eudragit L blends upon exposure to 0.1 M HCl; (c) Eudragit NE:Eudragit L blends upon exposure to phosphate buffer (pH 7.4); (d) EC:Eudragit L blends upon exposure to phosphate buffer (pH 7.4) (mean ± SD, n = 3). The polymer blend ratio is indicated in the figures. At pH 7.4, pure Eudragit L films dissolved too rapidly to allow accurate measurements of the water content.

This initial value problem [Eqs. (6)–(8)] can be solved using Laplace transform, leading to (25,26)

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=1}^{\infty} \frac{2 \times G^2}{\beta_n^2\left(\beta_n^2 + G^2 + G\right)} \times \exp\left(-\frac{\beta_n^2}{L^2} \times D \times t\right) \quad (9)$$

where the $\beta_n s$ are the positive roots of

$$\beta \times \tan\beta = G \quad (10)$$

with

$$G = \frac{L \times k}{D} \quad (11)$$

Here, M_t and M_∞ are the cumulative amounts of drug released at time t and $t = \infty$, respectively, and G denotes a dimensionless constant.

The diffusion coefficient of the drug, D, and the mass transfer coefficient in the boundary layer, k, are simultaneously determined by fitting this set of equations [Eqs. (9)–(11)] to experimentally measured cumulative *in vitro* drug release kinetics.

RESULTS AND DISCUSSION

Drug Release from Coated Pellets

Broad ranges of drug release patterns can be achieved from verapamil hydrochloride-loaded beads coated with Eudragit NE:Eudragit L and EC:Eudragit L blends in both simulated gastric and intestinal fluids (Fig. 1). Interestingly, the type of polymer blend significantly affected the resulting drug release kinetics in 0.1 M HCl, whereas in phosphate buffer (pH 7.4) rather similar profiles were observed. At low pH, drug release was generally slower in the case of Eudragit NE:Eudragit L blends compared to EC:Eudragit L blends. In particular, the initial periods without significant drug release (lag times) were much more pronounced. This can be attributed to the different physicochemical properties of Eudragit NE and EC and (at least partially) to the different plasticizer levels (10 *vs.* 25%) required to assure adequate film formation in both types of polymer blends: higher plasticizer levels in Eudragit NE:Eudragit L blends led to intense sticking; lower plasticizer levels in EC:Eudragit L blends led to poor film formation.

In phosphate buffer (pH 7.4), drug release was much faster than at low pH. Interestingly, verapamil hydrochloride release was very rapid at the beginning (except for pure EC and pure Eudragit NE coatings) and then leveled off. The higher release rates can be attributed to the leaching of the pH-sensitive polymer out of the film coatings at this pH, resulting in increased drug permeabilities. Furthermore, acidic microclimates can be expected in the bead cores at early time points (due to the dissolution of verapamil hydrochloride), leading to high drug solubilities and, thus, high concentration gradients (being the driving forces for diffusion). However, once buffer ions from the release medium neutralize the acids within the bead cores, the solubility of the drug drastically decreases (27). Consequently, the concentration gradients and drug release rates decrease. As can be seen, increasing Eudragit L contents led to decreasing amounts of "entrapped" drug, which can (at least partially) be attributed to increased Eudragit L leaching and, thus, accelerated drug diffusion at early time points.

Obviously, the effects of the type of polymer blend and polymer blend ratio on the resulting drug release kinetics are not straightforward. To better understand the underlying mass transport mechanisms, the physicochemical properties of thin polymeric films of identical composition as the film coatings and dynamic changes thereof upon exposure to the release media were studied.

Water Uptake and Dry Weight Loss Behavior of Thin Polymeric Films

Changes in the water contents of Eudragit NE:Eudragit L and EC:Eudragit L films upon exposure to 0.1 M HCl and phosphate buffer (pH 7.4) are illustrated in Fig. 2. Increasing Eudragit L contents led to increasing water uptake rates and extents, irrespective of the type of water-insoluble polymer. This can be explained by the higher hydrophilicity and swelling capacity of this polymer compared to EC and Eudragit NE as well as to its leaching out of the films at high pH (being replaced by imbibing water). The (slightly) higher water uptake rates and extents of EC:Eudragit L blends compared to Eudragit NE:Eudragit L in 0.1 M HCl can (at least partially) be attributed to the higher plasticizer contents (25 *vs.* 10% triethyl citrate).

In phosphate buffer (pH 7.4), the water uptake rates and extents were much higher than in 0.1 M HCl (except for pure EC films). This can be explained by the dissolution of the pH-sensitive polymers (being replaced by imbibing water) and the electrostatic repulsion of the COO^- groups, leading to higher swelling degrees. These higher water contents agree

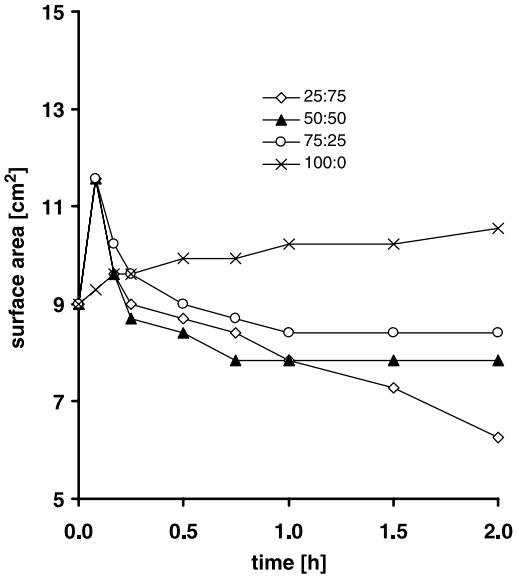

Fig. 3. Changes in the surface area of Eudragit NE:Eudragit L films upon exposure to phosphate buffer (pH 7.4). The polymer blend ratio is indicated in the figure.

very well with the observed drug release profiles: The coatings become more permeable for the drug; thus, the release rate increases (Fig. 1). Interestingly, the shape of the water uptake profiles of 50:50 and 75:25 Eudragit NE:Eudragit L blends is highly unusual at pH 7.4: Whereas all other films monotonically take up water until they disintegrate or plateau values are reached, these films initially take up 51–66% water and then partially "squeeze" the latter out before attaining plateau values around 35–40% (Fig. 2c). This behavior can be explained as follows. Initially, the films contain significant amounts of the hydrophilic polymer Eudragit L, leading to high water uptake rates and extents. Once in contact with phosphate buffer (pH 7.4), this hydrophilic component leaches out of the systems (water imbibition is much faster than polymer leaching because of the considerably smaller size of the water molecules compared to that of the macromolecules). Due to the loss of Eudragit L the films become less hydrophilic and squeeze out water. An important prerequisite for this squeezing out phenomenon is sufficient elasticity of the remaining polymeric structure: The Eudragit NE network is very flexible (conserving the deformation energy from the initial swelling process), whereas the EC network is not (retaining the shape of the swollen state).

The unusual water uptake and squeezing out behavior of 50:50 and 75:25 Eudragit NE:Eudragit L films was confirmed by the measurement of changes in the films' surface area (Fig. 3): The latter initially increased and then decreased again (the films shrank). [Remark: In addition, 25:75 Eudragit NE:Eudragit L films showed a clear initial increase

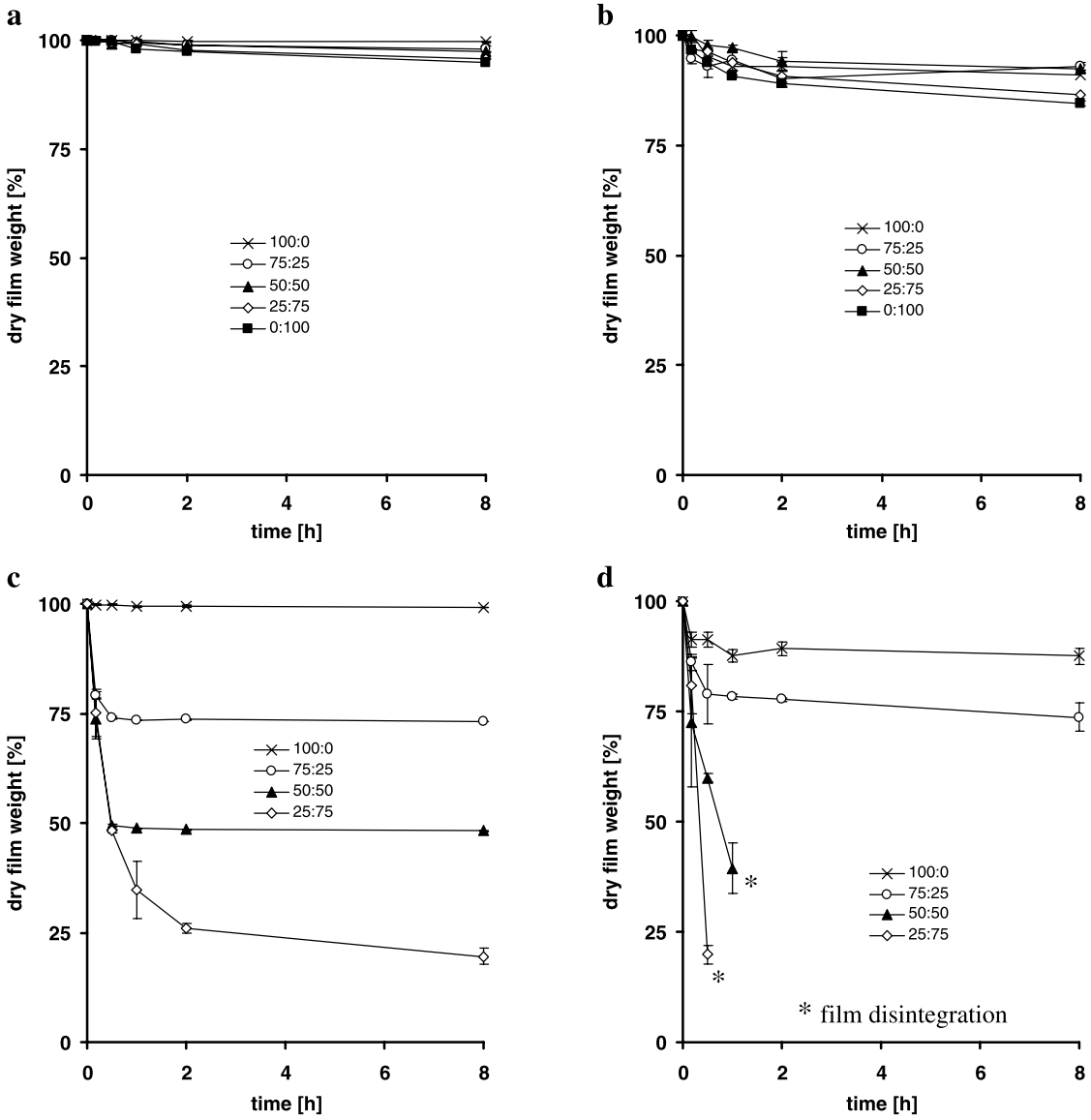

Fig. 4. Dry weight loss of thin, polymeric films consisting of (a) Eudragit NE:Eudragit L blends upon exposure to 0.1 M HCl; (b) EC:Eudragit L blends upon exposure to 0.1 M HCl; (c) Eudragit NE:Eudragit L blends upon exposure to phosphate buffer (pH 7.4); (d) EC:Eudragit L blends upon exposure to phosphate buffer (pH 7.4) (mean ± SD, $n = 3$). The polymer blend ratio is indicated in the figures. At pH 7.4, pure Eudragit L films dissolved too rapidly to allow accurate measurements of the dry weight.

and subsequent decrease in surface area, indicating film shrinkage. However, this phenomenon was not visible from the water content *vs.* time profiles (Fig. 2c). This can be explained by the significant leaching of the enteric polymer out of these films at pH 7.4 (Fig. 4c), compensating for the reduced film volume effect.] Pure Eudragit NE did not show any decrease in surface area (Fig. 3), which is in good agreement with the observed monotonic increase in the water contents of these films (Fig. 2c).

The difference in flexibility between the remaining Eudragit NE and EC networks also explains why all Eudragit NE:Eudragit L films remained intact upon exposure to phosphate buffer (pH 7.4), whereas EC:Eudragit L films with high Eudragit L content disintegrated after 0.5–1 h (Fig. 2). [Remark: Although films consisting of 50:50 EC:Eudragit L blends disintegrated after approximately 1 h, drug release from the respectively coated pellets was controlled for at least 8 h (Fig. 1d). This is because both surfaces were exposed to the release medium in the case of free films, whereas only one surface was exposed to the bulk fluid in the case of coated pellets (resulting in different enteric polymer leaching kinetics). Furthermore, the hydrodynamic conditions in the plastic containers and USP vessels were not identical.]

Nevertheless, a comparison of Figs. 1 and 2 shows that the water uptake kinetics of the polymeric coatings alone cannot fully explain the observed *in vitro* drug release kinetics and that other phenomena must be involved in the control of drug release. For example, the observed rank order of the release rates in 0.1 M HCl does not correspond to the rank order of the water uptake rates and extents in this medium.

The dry weight loss kinetics of thin EC:Eudragit L and Eudragit NE:Eudragit L films upon exposure to 0.1 M HCl and phosphate buffer (pH 7.4) is illustrated in Fig. 4. At low pH, none of the polymers is soluble, and the observed weight loss can be attributed to the (partial) leaching of the water-soluble plasticizer triethyl citrate into the aqueous medium. Because EC:Eudragit L blends initially contain more plasticizer than Eudragit NE:Eudragit L blends (25 *vs.* 10%), their dry weight loss is more pronounced. At high pH, the decrease in dry weight is much more substantial than at low pH because the pH-sensitive polymer is water soluble under these conditions and (partially) leaches out of the systems. More importantly, this leaching is rather rapid, explaining the high initial drug release rates observed in phosphate buffer (pH 7.4) (Fig. 1). As expected, increasing Eudragit L contents led to increased dry weight losses (Fig. 4). This is in good agreement with the drug release rates, which increased with increasing Eudragit L content (Fig. 1). Interestingly, Eudragit NE:Eudragit L and EC:Eudragit L films showed similar Eudragit L leaching kinetics at high pH (Fig. 4), explaining the similar drug release profiles observed in phosphate buffer (Fig. 1).

Mechanical Properties of Thin Polymeric Films in the Dry and Wet State

The effects of the type of polymer blend and polymer blend ratio on the percent elongation and energy at break of thin polymeric films in the dry state are illustrated in Fig. 5. As expected, Eudragit NE:Eudragit L blends were mechanically much more resistant than EC:Eudragit L blends, irrespective of the polymer blend ratio. This is because Eudragit NE is much more flexible than Eudragit L or EC.

As the composition of the investigated coatings fundamentally changes upon exposure to the release media (e.g., due to water imbibition and Eudragit L leaching; Figs. 2 and 4), it can be expected that also the mechanical properties of the films undergo significant changes during drug release. Thus, it was important to measure the percent elongation and energy at break as a function of the exposure time to the release media. Figure 6 shows, for example, the changes in the energy required to break Eudragit NE:Eudragit L and EC:Eudragit L films upon exposure to 0.1 M HCl. Clearly, the mechanical resistance of the systems significantly increased at early time points (except for high Eudragit NE contents) and then leveled off. This can be attributed to the water uptake kinetics of the films (Fig. 2), with water acting

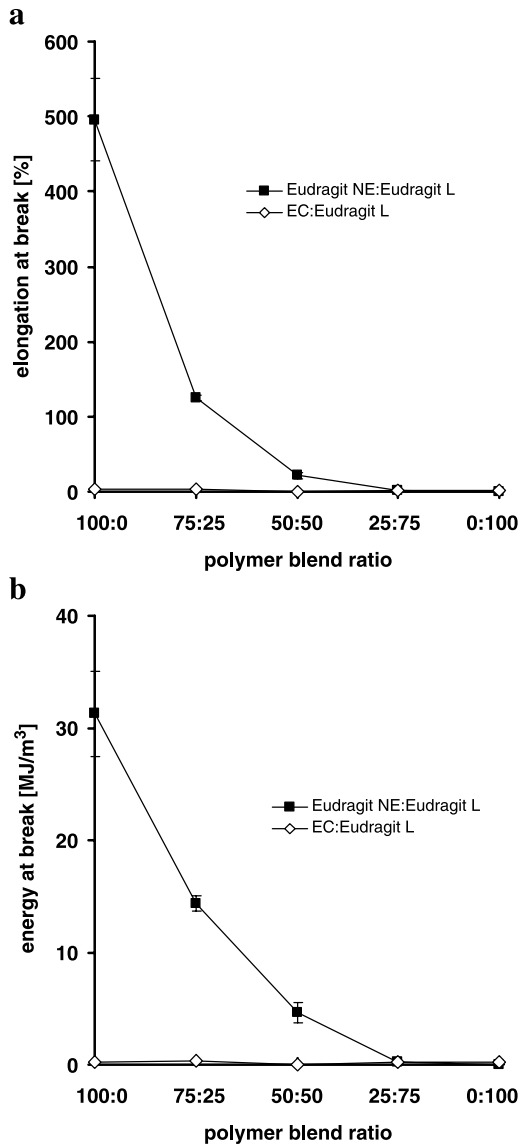

Fig. 5. Effects of the polymer blend ratio and type of polymer blend (indicated in the figure) on the mechanical properties of thin polymeric films in the dry state: (a) percent elongation at break; (b) energy at break (mean ± SD, $n = 6$).

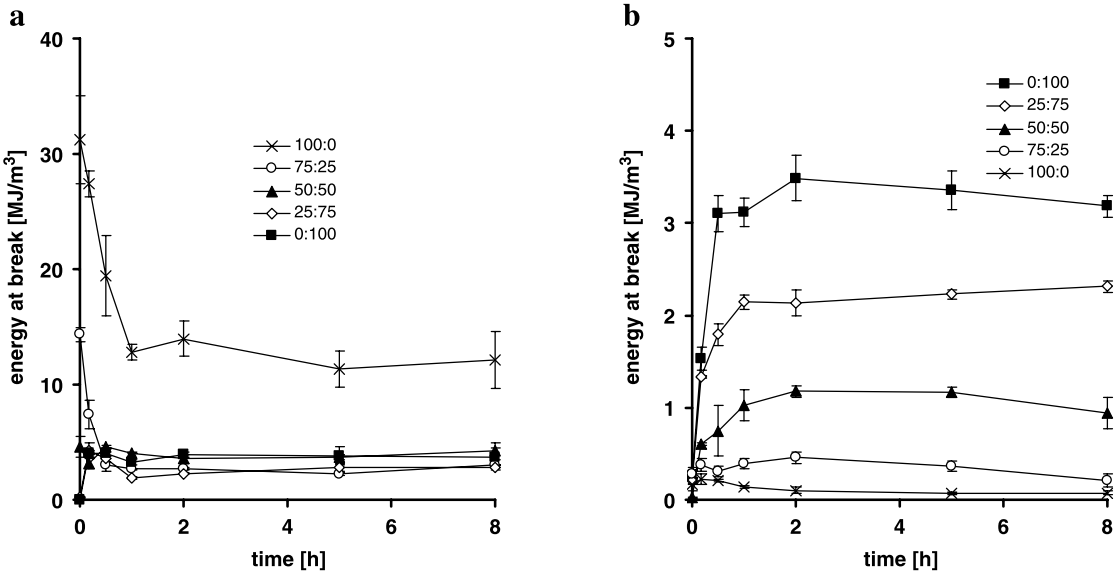

Fig. 6. Changes in the energy at break of thin polymeric films consisting of (a) Eudragit NE:Eudragit L blends; (b) EC:Eudragit L blends upon exposure to 0.1 M HCl (mean ± SD, n = 6). The polymer blend ratio is indicated in the figures.

as a plasticizer for the investigated polymers. The partially observed decrease in the energy at break can be attributed to the leaching of the water-soluble plasticizer triethyl citrate into the bulk fluid. More importantly, also in the wet state Eudragit NE:Eudragit L films were much tougher than EC:Eudragit L films (please note the different scaling of the y axes). The latter showed low mechanical resistance, except for high Eudragit L contents.

The mechanical properties of the film coatings can be decisive for the underlying drug release mechanisms: Upon contact with aqueous media, water diffuses into the beads, creating an elevated hydrostatic pressure within the cores (Fig. 7). This phenomenon is of particular importance when drug-layered sugar cores are used (as in the present study). Consequently, a steadily increasing force is exerted on the film coatings. If the latter are mechanically strong, they can withstand this mechanical stress, and drug release is primarily controlled by diffusion through the intact polymer coatings. On the other hand, if the film coatings are mechanically weak, they cannot withstand the mechanical stress and rupture at a certain time point. Cracks are formed (which are rapidly filled with water), and drug release is primarily controlled by diffusion through these water-filled cracks (offering much less hindrance than the polymeric networks). Based on the experimentally measured energies required to break the investigated polymeric films (Figs. 5 and 6), drug release can be expected to be controlled by diffusion through the intact coatings in the case of Eudragit NE:Eudragit L blends, whereas crack formation is likely in EC:Eudragit L-coated beads (Fig. 1).

To evaluate the hypothesized drug release mechanisms, the morphology of the polymeric coatings before and after exposure to the release media was monitored using scanning electron microscopy. Figure 8 shows exemplarily the surfaces of verapamil hydrochloride-layered sugar beads coated with 50:50 blends of Eudragit NE:Eudragit L and EC:Eudragit L after 6 h exposure to 0.1 M HCl. More importantly, the surface of Eudragit NE:Eudragit L-coated beads is free of cracks, whereas numerous defects are visible on the surface of EC:Eudragit L-coated systems.

However, the mechanical resistance of the film coatings and the onset of crack formation cannot fully explain the

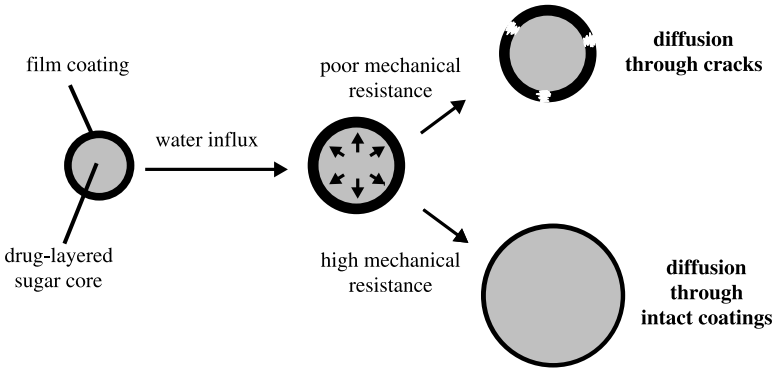

Fig. 7. Schematic presentation of the underlying drug release mechanisms from the investigated coated beads.

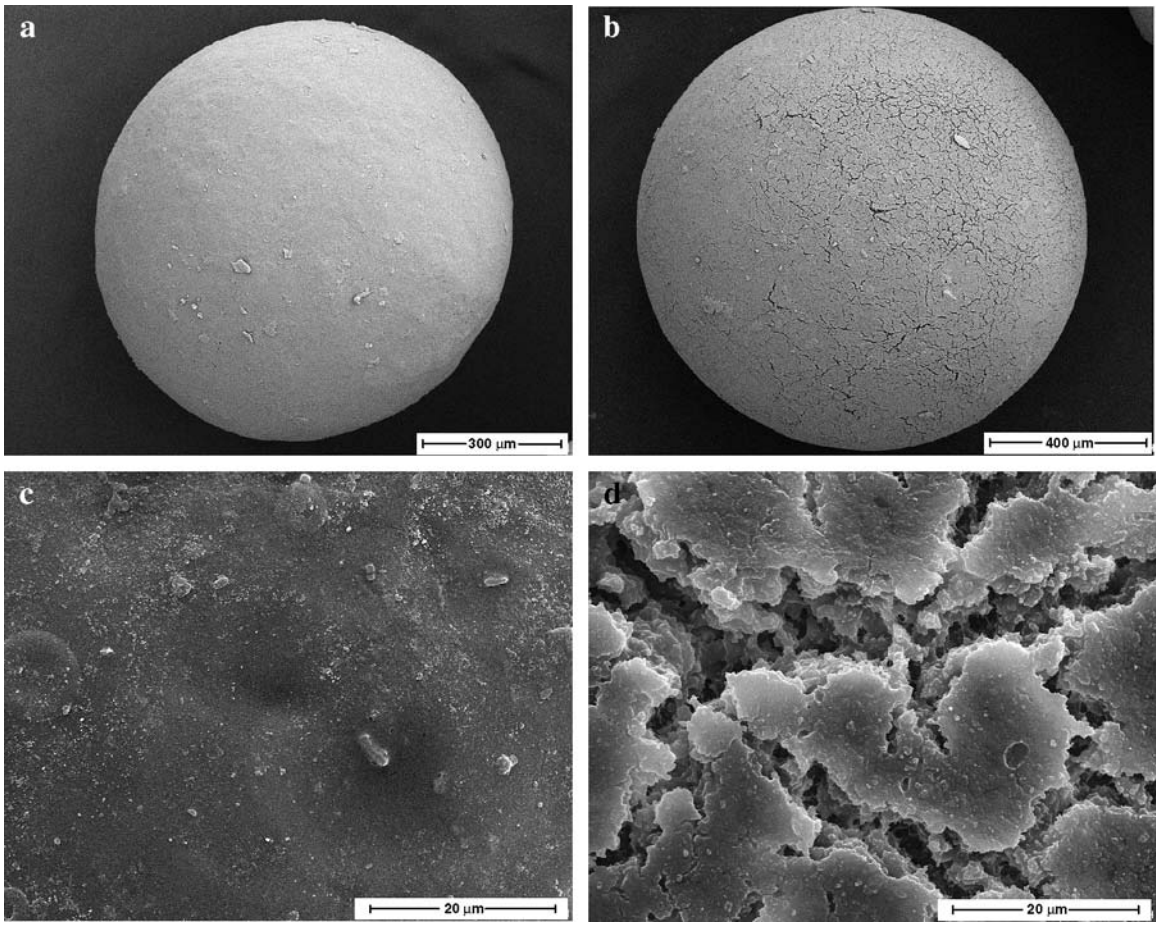

Fig. 8. Scanning electron microscopy pictures of verapamil hydrochloride-layered sugar beads coated with (a) Eudragit NE:Eudragit L blends (lower magnification); (b) EC:Eudragit L blends (lower magnification); (c) Eudragit NE:Eudragit L blends (higher magnification); (d) EC:Eudragit L blends (higher magnification) after 6 h exposure to 0.1 M HCl (polymer blend ratio 50:50).

observed drug release kinetics, in particular not the different slopes of the release curves in case of film coatings remaining intact during drug release (Fig. 1). To better understand the dominating transport mechanisms, the apparent diffusion coefficients of the drug in the polymeric systems were experimentally determined.

Drug Diffusivity Within the Polymeric Systems

The apparent diffusion coefficient of the drug within the investigated Eudragit NE:Eudragit L and EC:Eudragit L blends was determined by fitting Eqs. (9)–(11) to experimentally measured drug release kinetics from thin polymeric films. Figure 9 shows an example for such a fitting (verapamil hydrochloride release from 25:75 EC:Eudragit L films). Clearly, good agreement between theory and experiment was obtained [coefficient of determination (R^2) = 0.99], indicating the appropriateness of the applied mathematical model. Interestingly, the determined mass transfer coefficient in the boundary layer, k, was very high for all films ($>10^{-5}$ cm/s), resulting in high dimensionless numbers ($G > 100$). This indicates that the mass transfer resistance within the liquid boundary layer on the surface of the films is negligible compared to the mass transfer resistance within the

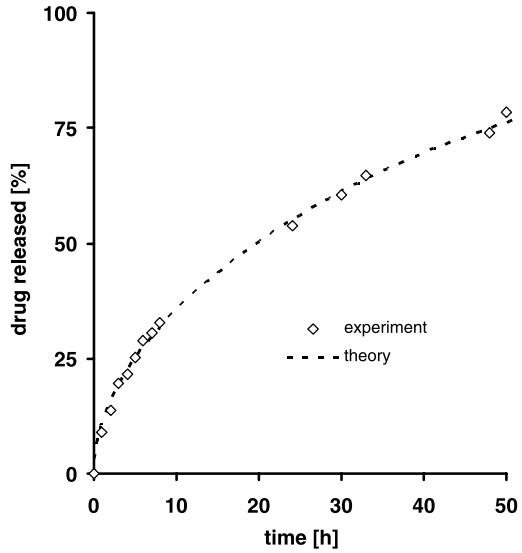

Fig. 9. Verapamil hydrochloride release from EC:Eudragit L 25:75 films in 0.1 M HCl: experiment (symbols) and theory (curve).

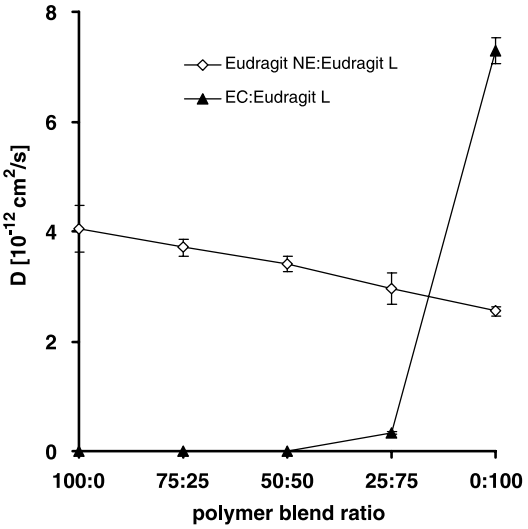

Fig. 10. Dependence of the apparent diffusion coefficient of verapamil hydrochloride within polymeric films on the type of polymer blend (indicated in the figure) and polymer blend ratio (release medium: 0.1 M HCl) (mean ± SD, $n = 3$).

polymeric systems (26). Consequently, the following simplified mathematical equation can be used to describe drug release from the investigated films under the given experimental conditions (and can be used to determine the drug diffusivities):

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2 \times n + 1)^2 \times \pi^2} \times \exp\left[-\frac{(2 \times n + 1)^2 \times \pi^2}{4 \times L^2} \times D \times t \right] \quad (12)$$

Furthermore, slight/moderate variations in the agitation speed of the plastic containers did not affect the observed drug release kinetics, which can serve as an experimental indication for negligible boundary layer effects in the present study.

The diffusion coefficient of the drug determined by the fitting shown in Fig. 9 was equal to 3.4×10^{-13} cm^2/s. However, this absolute value should be viewed with caution, because the free verapamil hydrochloride-containing films were prepared from organic solutions and not from aqueous dispersions as the bead coatings (due to flocculation it was not possible to prepare homogeneous drug-containing films with the investigated aqueous polymer dispersions). As the type of preparation method (via organic solutions *vs.* aqueous dispersions) can significantly affect the resulting microstructure of the macromolecular network (9), the absolute values of the drug diffusivities in the film coatings probably differ from those determined with the free films. However, general tendencies (e.g., effects of the type of polymer blend and polymer blend ratio) can be expected to be similar.

Figure 10 shows the dependence of the diffusion coefficient of verapamil hydrochloride on the type of polymer blend and polymer blend ratio. Clearly, the diffusivity decreased with increasing Eudragit L content in the case of Eudragit NE:Eudragit L blends, whereas it increased in the case of EC:Eudragit L blends. This is because Eudragit L is less permeable for the drug than Eudragit NE, but more permeable than EC. The difference in drug diffusivity for the two pure Eudragit L films (polymer blend ratio 0:100) can be explained by the different plasticizer levels (28). Importantly, the diffusion coefficient of verapamil hydrochloride was much higher in pure Eudragit L compared to all EC:Eudragit L blends. This can be attributed to the very low permeability of EC, and partially explains why drug release from purely Eudragit L-coated pellets was faster than from EC:Eudragit L-coated systems, although no cracks were formed (Fig. 1a). The decrease in drug diffusivity with increasing Eudragit L contents in Eudragit NE:Eudragit L blends corresponds very well with the experimentally measured drug release profiles (Fig. 1). Once drug release has started, the slope of the release curves (determined from the linear portions) decreased with increasing Eudragit L content: 17, 16, 9.7, and 5.0% per

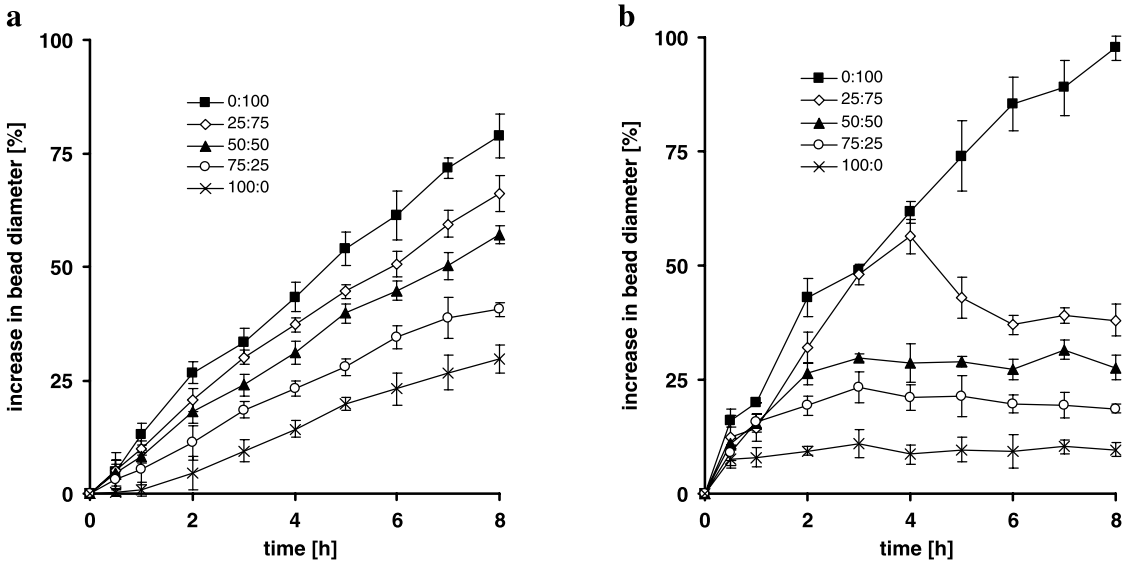

Fig. 11. Changes in the diameter of pellets coated with (a) Eudragit NE:Eudragit L blends and (b) EC:Eudragit L blends upon exposure to 0.1 M HCl (mean ± SD, $n = 10$) (the polymer blend ratio is indicated in the figures).

hour for 0, 25, 50, and 100% Eudragit L (for 75% Eudragit L the linear portion was not yet reached within the observation period). This confirms the hypothesis that drug release from these systems is primarily controlled by diffusion through the intact film coatings. The observed increasing lag times with increasing Eudragit NE content can be explained by the slower water uptake of the polymeric films (Fig. 2).

Changes in Bead Diameter During Drug Release

To further confirm the hypothesized drug release mechanisms, changes in the beads' diameters upon exposure to 0.1 M HCl were monitored (Fig. 11). As long as water imbibes into the systems and the film coatings do not rupture, the diameter monotonically increases. In contrast, if crack formation occurs, the diameter–time curve levels off, because the hydrostatic pressure developed within the bead cores pushes out aqueous drug–sugar solution into the bulk fluid. As can be seen in Fig. 11a, the diameter of Eudragit NE:Eudragit L-coated beads monotonically increased within the entire observation period, indicating the absence of crack formation. In contrast, the diameter–time curves of the EC-containing systems leveled off after 0.5 to 4 h (Fig. 11b), indicating the onset of crack formation at these time points (crack formation in 25:75 EC:Eudragit L coatings after approximately 4 h does not significantly accelerate drug release because the drug concentration within the bead cores is already low at this time point). Thus, these observations confirm the hypothesized drug release mechanisms from the investigated beads.

Furthermore, it can be seen in Fig. 11b that purely Eudragit L-coated pellets swell to a higher extent than all EC:Eudragit L-coated systems. This results in higher surface areas available for diffusion and in reduced coating thicknesses. Both effects, together with the increased permeability of the films for verapamil HCl (Fig. 10), explain why drug release from purely Eudragit L-coated pellets is faster than from EC:Eudragit L-coated systems despite the absence of crack formation.

CONCLUSIONS

pH-sensitive polymer blends are highly suitable to effectively vary the resulting drug release kinetics from coated pellets. More importantly, not only the slope but also the shape of the release profiles can be adjusted by simply varying the type of polymer blend and blend ratio. Based on the water uptake and dry weight loss kinetics, changes in morphology, mechanical properties, diffusion coefficients, and diameter of the investigated beads and free polymeric films the underlying release mechanisms could be elucidated. It has been shown that verapamil hydrochloride release in simulated gastric fluid is primarily controlled by diffusion through the intact film coatings in the case of Eudragit NE:Eudragit L blends, whereas crack formation is of major importance in EC:Eudragit L-coated systems. In simulated intestinal fluids, the pH-sensitive polymer (partially) leaches out of the coatings, resulting in significantly increased drug permeabilities and release rates. However, when the acidic microclimate within the bead cores is neutralized by imbibing bases from the release medium, the solubility of the drug significantly decreases and drug release levels off.

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