Polymer Blends Used for the Coating of Multiparticulates: Comparison of Aqueous and Organic Coating Techniques

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Purpose. The purpose of this study was to use polymer blends for the coating of pellets and to study the effects of the type of coating technique (aqueous vs. organic) on drug release.

Methods. Propranolol HCl–loaded pellets were coated with blends of a water-insoluble and an enteric polymer (ethyl cellulose and Eudragit L). Drug release from the pellets as well as the mechanical properties, water uptake, and dry weight loss behavior of thin polymeric films were determined in 0.1 M HCl and phosphate buffer, pH 7.4.

Results. Drug release strongly depended on the type of coating technique. Interestingly, not only the slope, but also the shape of the release curves was affected, indicating changes in the underlying drug release mechanisms. The observed effects could be explained by the higher mobility of the macromolecules in organic solutions compared to aqueous dispersions, resulting in higher degrees of polymer-polymer interpenetration and, thus, tougher and less permeable film coatings. The physicochemical properties of the latter were of major importance for the control of drug release, which was governed by diffusion through the intact polymeric films and/or water-filled cracks.

Conclusions. The type of coating technique strongly affects the film microstructure and, thus, the release mechanism and rate from pellets coated with polymer blends.

KEY WORDS: coating; controlled release; pellet; polymer blend; release mechanism.

INTRODUCTION

The use of aqueous polymer dispersions instead of organic polymer solutions for the coating of solid dosage forms offers various advantages, such as reduced toxicity and shortened processing times (1,2). The latter can be decreased because much higher polymer concentrations can be used in the coating formulations, exhibiting relatively low viscosities compared to the respective organic solvent-based coating solutions. However, the coating process with aqueous polymer dispersions can be sensitive to different factors, such as temperature, pH, addition of electrolytes and other polymers, potentially resulting in the coagulation of the dispersions. The film formation process is fundamentally different for the two coating techniques: In organic solvent–based systems, the polymer solutions undergo sol to gel transitions upon solvent evaporation to finally form the polymeric films. Upon spraying aqueous polymer dispersions, the polymer particles are deposited on the surfaces of the solid dosage forms. The colloidal particles come into direct contact with each other and form close-packed arrays due to water evaporation and the interfacial tension between water and polymer. Capillary forces then drive the particles to coalesce together (3). Often, the addition of a plasticizer is required to reduce the minimum film formation temperature (MFT), softening the polymer particles and facilitating their coalescence.

Various studies have been reported in the literature comparing organic and aqueous coating techniques (4–9). For example, Iyer *et al.* (7) investigated the performance of three ethyl cellulose (EC)-based film coatings (one prepared from organic solution, two from commercially available aqueous dispersions). Three different drug release profiles were obtained, indicating the importance of the physicochemical properties and microstructure of the film coatings.

The use of polymer blends for the coating of solid dosage forms presents a powerful tool to provide broad varieties of drug release patterns in different release media (10). Adjusting the polymer blend ratio, desired film coating properties can be obtained and used to control the release rate of an incorporated drug. For example, Amighi *et al.* (11) provided constant and complete release of a weakly basic drug along the gastrointestinal tract with blends of two acrylic polymers as coating material. Fan *et al.* (12) developed coated tablets exhibiting pulsatile drug release patterns using organic polymer solutions of blends of EC and Eudragit L.

However, limited knowledge is yet available on the importance of the type of coating technique (aqueous vs. organic) when using polymer blends for the coating of solid dosage forms. In contrast to films comprising only one polymer, the effects of the film formation mechanism on the resulting coating structure (and, thus, release mechanisms and drug release rates) can be expected to be much more pronounced (13–17). Boczar *et al.* (16) investigated the influence of the latex particle size and polymer compatibility on the rate and extent of interparticle diffusion in blends of aqueous dispersions of amyl methacrylate and butyl methacrylate.

The mechanisms controlling drug release from coated dosage forms are complex and strongly depend on the design of the delivery systems. Rekhi *et al.* (18) reported that propranolol HCl release from pellets coated with aqueous EC dispersions was primarily diffusion-controlled. Nesbitt *et al.* (19) studied water-soluble drug-containing pellets coated with Aquacoat ECD and showed that these devices worked like mini-osmotic pumps, releasing the drug through water-filled channels. Hjärtstam *et al.* (20,21) used organic solutions of blends of EC and hydroxypropyl methylcellulose (HPMC) to coat metoprolol succinate–loaded pellets. The amount of HPMC in the coating was found to regulate its water permeability. The imbibition of aqueous media created elevated hydrostatic pressures within the cores and, consequently, enlarged micropores in the film coatings.

The major objectives of the current study were i) to investigate the effects of the type of coating technique (aqueous vs. organic) on the drug release patterns from pellets coated with blends of EC and Eudragit L (a water-insoluble and an enteric polymer) at low as well as at high pH; and ii) to understand the observed phenomena based on the physicochemical properties of the systems.

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MATERIALS AND METHODS

Materials

Materials used were propranolol hydrochloride (propranolol HCl, Abbott, Ludwigshafen, Germany), Eudragit L100-55 (methacrylic acid-ethyl acrylate copolymer 1:1) and an aqueous dispersion thereof (Eudragit L30D-55) (Röhm, Darmstadt, Germany), ethyl cellulose (EC, Ethocel Standard 10 Premium, Dow Chemical Company, Midland, MI, USA), Aquacoat ECD30 (an aqueous EC dispersion, FMC c/o Interorgana, Köln, Germany), triethyl citrate (TEC, Morflex, Greensboro, NC, USA), talc (Merck, Darmstadt, Germany), non-pareils (Suglets sugar spheres NF, NP Pharm S.A., Bazainville, France), hydroxypropyl methylcellulose (HPMC, Methocel E5, Colorcon, Orpington, UK), and polyethylene glycol 4000 (PEG 4000, BASF, Ludwigshafen, Germany).

Preparation of Polymeric Films

Thin films were prepared by casting ethanolic polymer solutions or aqueous polymer dispersions onto Teflon plates and subsequent controlled drying. TEC was added, acting as a plasticizer for both polymers [25% w/w (based on the total polymer mass) (aqueous polymer dispersions) or 10% w/w (based on the total polymer mass) (organic polymer solutions), unless otherwise stated]. Aqueous polymer dispersions were plasticized overnight prior to casting. The drying process in the case of ethanolic polymer solutions was as follows: 1 day at room temperature, 1 day at 60°C, and 1 day at room temperature, whereas cast aqueous polymer dispersions were immediately placed in an oven at 60°C for 1 day, followed by 1 day at room temperature.

Water Uptake of Polymeric Films

Thin, polymeric films were cut into pieces of 8 × 8 cm, which were placed into 500 ml plastic containers filled with 200 ml 0.1 M HCl or phosphate buffer pH 7.4 (USP XXV) (n = 3, separate film preparation, error bars in the figures indicate ± 1 standard deviation), followed by horizontal shaking for 8 h (37°C, 75 rpm; GFL 3033, Gesellschaft für Labortechnik, Burgwedel, Germany). At predetermined time intervals, samples were withdrawn, accurately weighed [wet weight (t)], and dried to constant weight at 60°C [dry weight (t)]. The water content (%) at time t was calculated as follows:

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

Mechanical Properties of Polymeric Films

The mechanical properties 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 were mounted on a film holder (n = 6, separate film preparation, error bars in the figures indicate ±1 standard deviation). The puncture probe (spherical end: 5 mm diameter) was fixed on the load cell (5 kg) and driven downward with a cross-head 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:

$$\text{puncture strength} = \frac{F}{A} \quad (2)$$

where F is the load required to puncture the film and A the cross-sectional area of the edge of the film located in the path.

$$\text{\% elongation at break} = \frac{\sqrt{R^2 + D^2} - R}{R} \cdot 100\% \quad (3)$$

Here, R denotes the radius of the film exposed in the cylindrical hole of the holder and D the displacement to puncture.

$$\text{energy at break per unit volume} = \frac{AUC}{V} \quad (4)$$

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

Preparation of Coated Pellets

Propranolol HCl–loaded pellets (10% w/w drug loading) were prepared by layering a drug-binder solution (21.7% w/w propranolol HCl, 1.0% w/w hydroxypropyl methylcellulose, 0.1% w/w polyethylene glycol, 40.8% w/w ethanol, 36.4% w/w water) onto non-pareils in a ball coater (Kugelcoater UNILAB-05, Hüttlin, Steinen, Germany). The drug-loaded pellets were coated with ethanolic solutions of EC, Eudragit L100-55 and blends thereof, or with the respective aqueous polymer dispersions. The ethanolic polymer solutions contained 10% TEC (w/w, based on the total polymer mass) and talc was added as anti-tacking agent (50% w/w, based on the mass of Eudragit L). The aqueous polymer dispersions were plasticized overnight with 25% w/w TEC (w/w, based on the total polymer mass) and adjusted to 15% w/w polymer content prior to coating. The following EC:Eudragit L blend ratios were investigated: 0:100, 25:75, 50:50, 75:25, 100:0 (w/w). The coating formulations were sprayed onto a mixture of drug-loaded pellets and non-pareils (1:4 w/w, 500 g) to achieve a polymer weight gain of 20% (w/w). The process parameters were as follows: product temperature = 25 ± 2°C (ethanolic solutions) or 37 ± 2°C (aqueous dispersions), spray rate = 2 to 3 g/min, atomization pressure = 0.4 bar, pressure of microclimate = 0.2 bar, nozzle diameter = 0.8 mm. Subsequent to coating, the pellets were further fluidized for 15 min to minimize the residual solvents' content, and—in the case of aqueous polymer dispersions—cured for 24 h at 60°C.

In vitro Drug Release from Coated Pellets

Drug release in 0.1 M HCl and phosphate buffer pH 7.4 was determined using the USP XXV paddle apparatus at 37°C [100 rpm, n = 3 (separate release studies, same batch of coated pellets), error bars in the figures indicate ±1 standard deviation]. At predetermined time intervals, 3 ml samples were withdrawn and analyzed UV-spectrophotometrically (λ = 290 nm; UV-2101 PC, Shimadzu Scientific Instruments, Columbia, MD, USA).

RESULTS AND DISCUSSION

Drug Release from Coated Pellets

Broad ranges of propranolol HCl release patterns were obtained at low as well as at high pH by varying the polymer blend ratio (Fig. 1). Pellets coated with organic solutions and aqueous dispersions showed substantial differences. Importantly, not only the slope, but also the shape of the release curves strongly depended on the type of coating technique.

In 0.1 M HCl, drug release from pellets coated with organic solutions almost monotonically increased with increasing Eudragit L content. In contrast, when aqueous polymer dispersions were used, the release rate first decreased and then increased with increasing Eudragit L content. Furthermore, significant lag-times (3–4 h) were observed with 75:25 and 50:50 (EC: Eudragit L) blends in the case of aqueous dispersions, but not in the case of organic solutions. At high pH, the release rate monotonically increased with increasing Eudragit L content, irrespective of the type of coating technique. Interestingly, steep increases in the drug release rates were observed above critical Eudragit L contents. The respective threshold values strongly depended on the type of coating technique: 0–25% (aqueous dispersion) and 25–50% (organic solution). To better understand the observed effects, thin, polymeric films of identical composition as the pellet coatings were prepared and their physicochemical properties were determined as a function of the exposure time to the release media.

Water Uptake of Polymeric Films

Clearly, the polymer blend ratio strongly affected the rate and extent at which water diffused into the polymeric systems at low as well as at high pH, irrespective of the type of preparation technique (Fig. 2). In 0.1 M HCl, the water uptake rate and extent increased monotonically with increasing Eudragit L content, which can be attributed to the higher hydrophilicity of this polymer compared to EC. As shown previously, the increase in water uptake leads to an increase in drug diffusivity through the film coatings (10), which is in good agreement with the monotonic increase in the drug release rate from pellets coated with organic solutions (Fig. 1b). However, the monotonic increase in water uptake does not correlate with the observed initial decrease and subsequent increase in the release rate from pellets coated with aqueous polymer dispersions with increasing Eudragit L content (Fig. 1a). This clearly indicates that drug release from these sys-

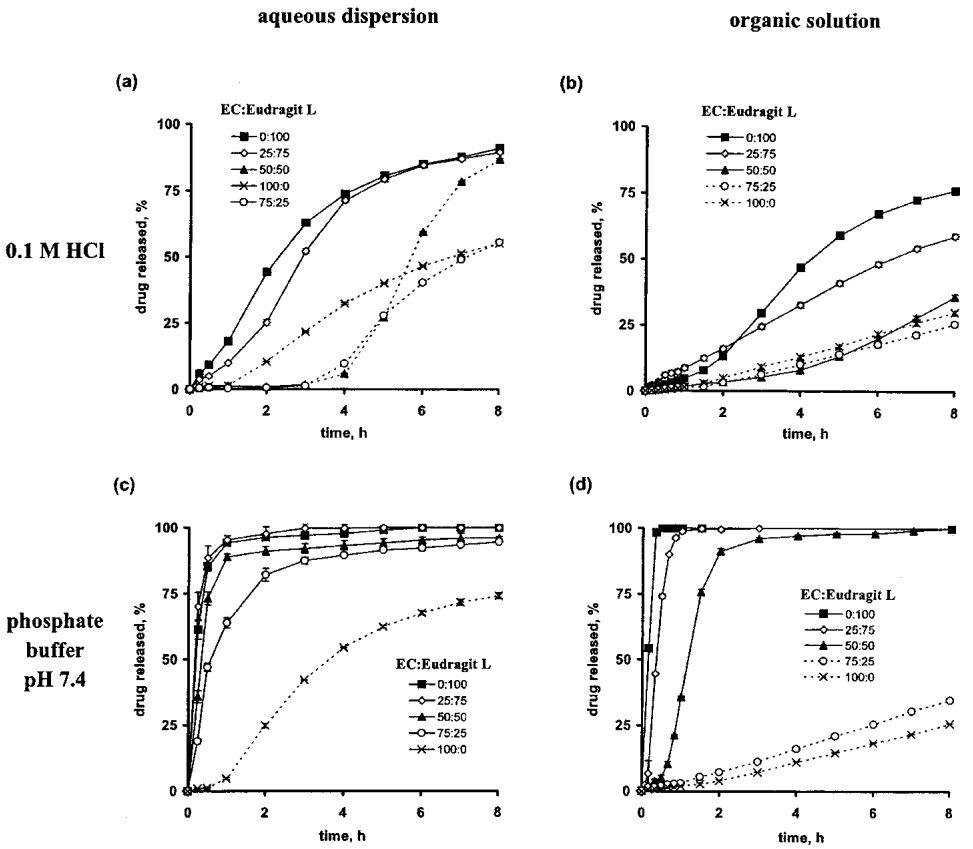

Fig. 1. Effect of the EC:Eudragit L blend ratio on propranolol HCl release from pellets coated with (a) aqueous polymer dispersions in 0.1 M HCl, (b) organic polymer solutions in 0.1 M HCl, (c) aqueous polymer dispersions in phosphate buffer pH 7.4, and (d) organic polymer solutions in phosphate buffer pH 7.4 (dotted curves: drug release predominantly controlled by drug diffusion through water-filled cracks; solid curves in 0.1 N HCl: drug release predominantly controlled by drug diffusion through intact film coatings; solid curves in phosphate buffer pH 7.4: drug release predominantly controlled by Eudragit L leaching/swelling) (the experimental results shown in Figs. 1b and 1d are reproduced from Ref. 10).

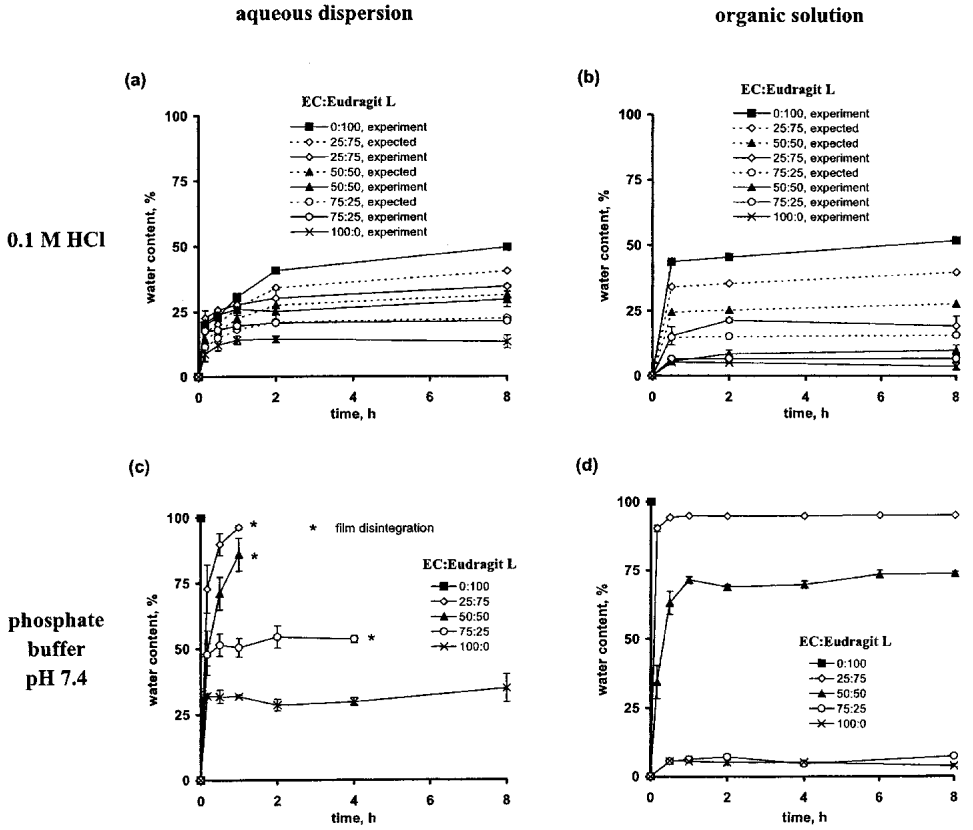

Fig. 2. Effect of the EC:Eudragit L blend ratio on the water uptake behavior of thin, polymeric films prepared from (a) aqueous polymer dispersions, in 0.1 M HCl, (b) organic polymer solutions, in 0.1 M HCl, (c) aqueous polymer dispersions, in phosphate buffer pH 7.4, and (d) organic polymer solutions, in phosphate buffer pH 7.4 [solid curves: experimentally measured values; dotted curves: calculated values (based on the behavior of the pure polymers); at high pH, pure Eudragit L films dissolved too rapidly to be accurately measurable, thus, the water uptake kinetics could not be calculated (based on the behavior of the pure polymers)] (the results shown in Fig. 2b are reproduced from Ref. 10).

tems is not only governed by diffusion through the intact polymer coating and/or swelling of the latter.

To evaluate the hindrance of Eudragit L swelling in 0.1 M HCl due to the presence of EC in the polymeric systems, the "expected" water imbibition kinetics into blended films was calculated based on the results obtained with the pure polymers (EC fraction × water uptake of pure EC + Eudragit L fraction × water uptake of pure Eudragit L) (Figs. 2a and 2b, dotted curves) and compared to the experimentally measured values (solid curves). Importantly, the Eudragit L swelling was much more effectively hindered in films prepared from organic solutions (significant differences between solid and dotted curves) compared to those prepared from aqueous dispersions (less important differences between solid and dotted curves).

This phenomenon can be explained based on the different film formation mechanisms, which are schematically illustrated in Fig. 3. For reasons of simplicity, differences in particle and molecule size were neglected and complete polymer-polymer miscibility was assumed. In organic polymer solutions, the two types of macromolecules are highly mobile (Fig. 3b, upper scheme). If the polymers are (partially) compatible/miscible, it can be expected that the different types of macromolecules are intimately blended and randomly distributed throughout the solution. Upon solvent evaporation, the polymer chains approach each other and finally form a film with a high degree of polymer-polymer-interpenetration (Fig. 3b, lower scheme). [It has to be pointed out that the miscibility/compatibility of the two polymers can vary with temperature and concentration. In the present case, all EC:Eudragit L solutions and films were clear and did not show any evidence for phase separation. Scanning electron microscopy pictures (not shown) indicated homogeneous film structures. Especially hydrogen bonds can be expected to promote the miscibility/compatibility of EC and Eudragit L.] In contrast, separated pure EC and pure Eudragit L domains exist at the beginning of the film formation process when aqueous polymer dispersions are used (Fig. 3a, upper scheme). Due to the restricted mobility of the macromolecules within the colloidal particles, the polymer chains cannot completely interdiffuse. Only in regions close to the particles' surfaces, more or less intimate polymer-polymer blending can be expected. Thus, upon water evaporation polymeric films with pure EC and pure Eudragit L domains are formed (Fig. 3a, lower scheme), and the resulting degree of polymer-polymer interpenetration is much lower than in the case of films prepared from organic solutions. These differences in the film microstructure strongly affect the swelling kinetics of Eudragit L within the polymeric films. In systems with high degrees of EC-Eudragit L chain entanglement, the enteric

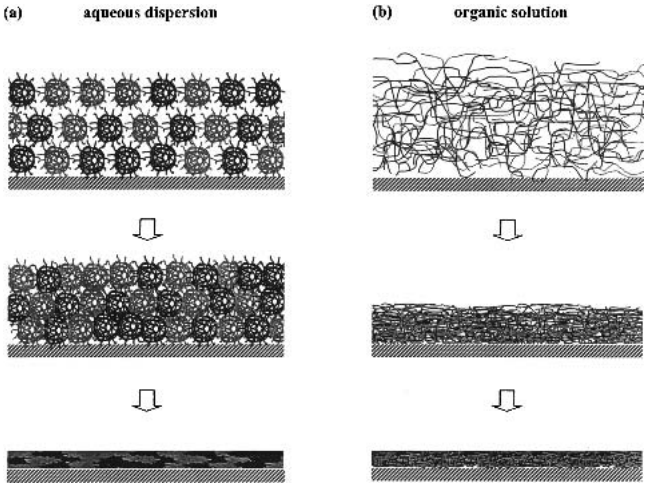

Fig. 3. Schematic presentation (not up to scale) of the film formation mechanisms in systems containing two types of polymers, prepared from (a) aqueous polymer dispersions, and (b) organic polymer solutions; black and gray lines represent EC and Eudragit L molecules, respectively (for reasons of simplicity differences in particle and molecule size were neglected and complete polymer-polymer miscibility was assumed).

polymer is more effectively hindered to take up water compared to systems in which pure Eudragit L domains exist (Fig. 2).

In phosphate buffer pH 7.4, the water content of the polymeric films increased much more rapidly and to a higher extent than in 0.1 M HCl, irrespective of the type of coating technique (Fig. 2). This can be attributed to the leaching of the enteric polymer Eudragit L at high pH into the bulk fluid, being replaced by imbibing water and to a higher degree of swelling of still entrapped Eudragit L (due to the repulsion of negatively charged COO^--ions). As expected, the increase in water content monotonically increased with increasing Eudragit L content, irrespective of the type of coating technique. This behavior correlates very well with the observed drug release kinetics (Figs. 1c and 1d). Interestingly, the steep increases in drug release between 0 and 25% Eudragit L in the case of aqueous polymer dispersions, and between 25% and 50% Eudragit L in the case of organic polymer solutions agree well with the observed steep increases in the water contents of the polymeric films (Figs. 2c and 2d). Increasing water contents lead to increased mobilities of the drug molecules and, thus, to increased diffusivities and release rates.

Importantly, Eudragit L swelling was almost completely suppressed at high pH in films containing 75% EC, when prepared from organic solutions (Fig. 2d), resulting in low drug release rates (Fig. 1d). In contrast, Eudragit L swelling was significant at this polymer blend ratio, when the films were prepared from aqueous dispersions (Fig. 2c), resulting in much higher drug release rates (Fig. 1c). As discussed above, this fundamental difference can be explained by the underlying film formation mechanisms and resulting microstructures of the polymeric systems.

Dry Weight Loss and Disintegration Behavior of Polymeric Films

A further consequence of the different degrees of polymer-polymer interpenetration in the film coatings prepared from organic solutions and aqueous dispersions affecting the resulting drug release kinetics is the different dry weight loss and disintegration behavior of the films at high pH (Fig. 4). The leaching of the enteric polymer into the bulk fluid was much more substantial when the systems were prepared from aqueous dispersions, resulting in much shorter disintegration times. Thus, not only Eudragit L swelling, but also Eudragit L leaching out of the films was strongly hindered at high degrees of polymer-polymer interpenetration. This is in good agreement with the observed drug release profiles from coated pellets (Figs. 1c and 1d). [It has to be pointed out that Eudragit L is negatively and the drug positively charged at pH 7.4. Thus, ionic polymer-drug-interactions might contribute to the control of drug release. However, in the present case, drug release at high pH seems to be primarily controlled by Eudragit L leaching (and swelling).]

In 0.1 M HCl, only a slight loss in dry film mass was

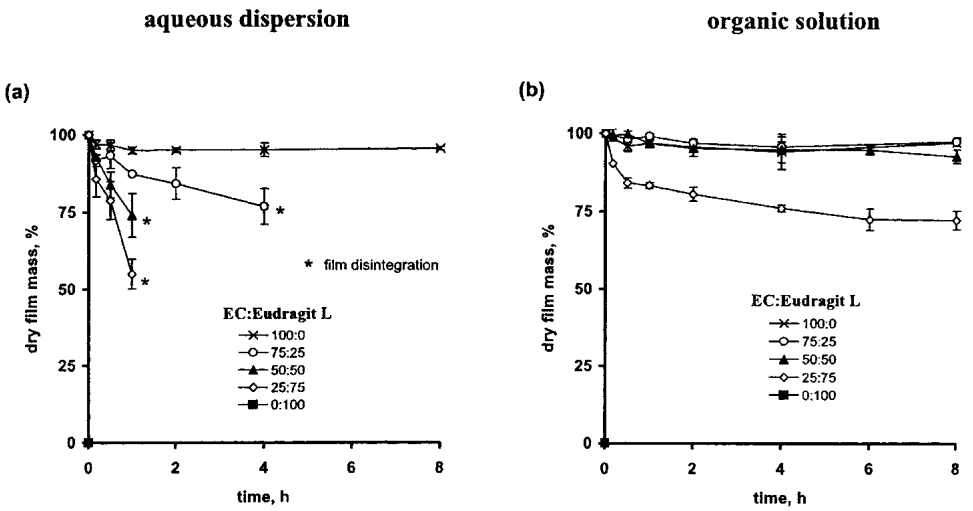

Fig. 4. Effect of the EC:Eudragit L blend ratio on the dry weight loss and disintegration behavior of thin, polymeric films prepared from (a) aqueous polymer dispersions, (b) organic polymer solutions, in phosphate buffer pH 7.4 (the results shown in Fig. 4b are reproduced from Ref. 10).

observed, because none of the polymers was soluble under these conditions, irrespective of the type of coating technique and polymer blend ratio (data not shown). This slight weight loss can be attributed to the leaching of the water-soluble plasticizer TEC into the bulk fluid (1).

Mechanical Properties of Polymeric Films in the Dry State

The effects of the type of preparation method and polymer blend ratio on the mechanical properties of thin, polymeric films in the dry state are illustrated in Fig. 5. Clearly, the puncture strength and energy at break were much higher for blended films prepared from organic solutions compared to those prepared from aqueous dispersions. This can also be explained by the different degrees of polymer-polymer interpenetration resulting from the different film formation mechanisms. Higher degrees of entanglement of the two types of macromolecules lead to mechanically more resistant coatings.

Importantly, the mechanical properties of films prepared from organic solutions containing 25% TEC were similar to those containing 10% TEC (data not shown). Thus, the differences in the mechanical properties of films prepared from aqueous dispersions and organic solutions shown in Fig. 5 can primarily be attributed to the different film formation mechanisms and film structures, and not to the difference in the plasticizer content.

Mechanical Properties of Polymeric Films in the Wet State

Upon exposure to the release media, the composition of the polymeric films can significantly change. Water diffuses into the systems, whereas TEC and (at high pH) Eudragit L can/might leach out into the bulk fluid. These changes can strongly affect the mechanical properties of the coatings (Figs. 6 and 7). In 0.1 M HCl, the flexibility of all films initially increased, irrespective of the type of preparation method (Figs. 6a and 6b). This can be attributed to the significant water uptake at early time points (Fig. 2); water acting as a plasticizer for both polymers. Subsequently, the % elongation at break leveled off and slowly decreased, which can be explained by the leveling off of the water uptake (Fig. 2) and by the leaching of the water-soluble plasticizer TEC into the bulk fluid.

As the pellet cores in the current study consisted primarily of sucrose and propranolol HCl [solubility at 37°C: 220 mg/ml (0.1 M HCl); 254 mg/ml (phosphate buffer pH 7.4)], it can be expected that significant hydrostatic pressures are developed within the pellets upon water imbibition and sucrose and drug dissolution. As soon as the pressure within the cores

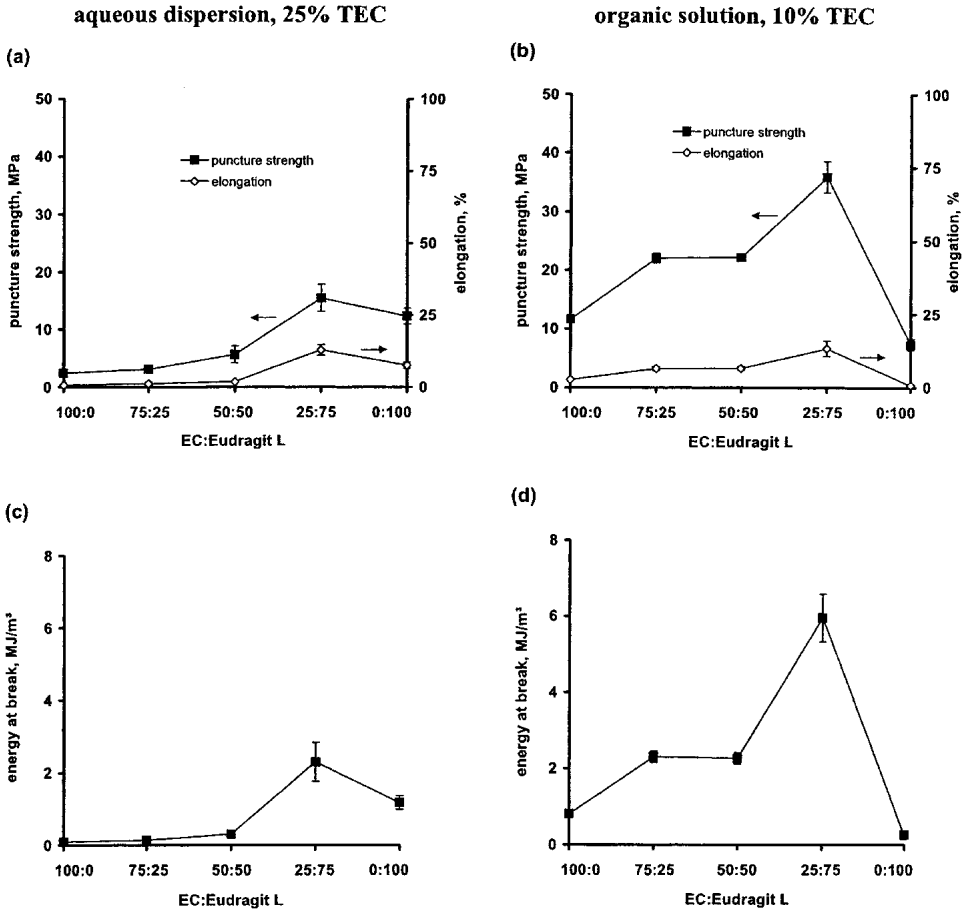

Fig. 5. Effect of the of the type of preparation technique (aqueous vs. organic) and EC:Eudragit L blend ratio on the mechanical properties of thin, polymeric films in the dry state: (a) puncture strength and % elongation at break, films prepared from aqueous polymer dispersions; (b) puncture strength and % elongation at break, films prepared from organic polymer solutions; (c) energy at break, films prepared from aqueous polymer dispersions; and (d) energy at break, films prepared from organic polymer solutions.

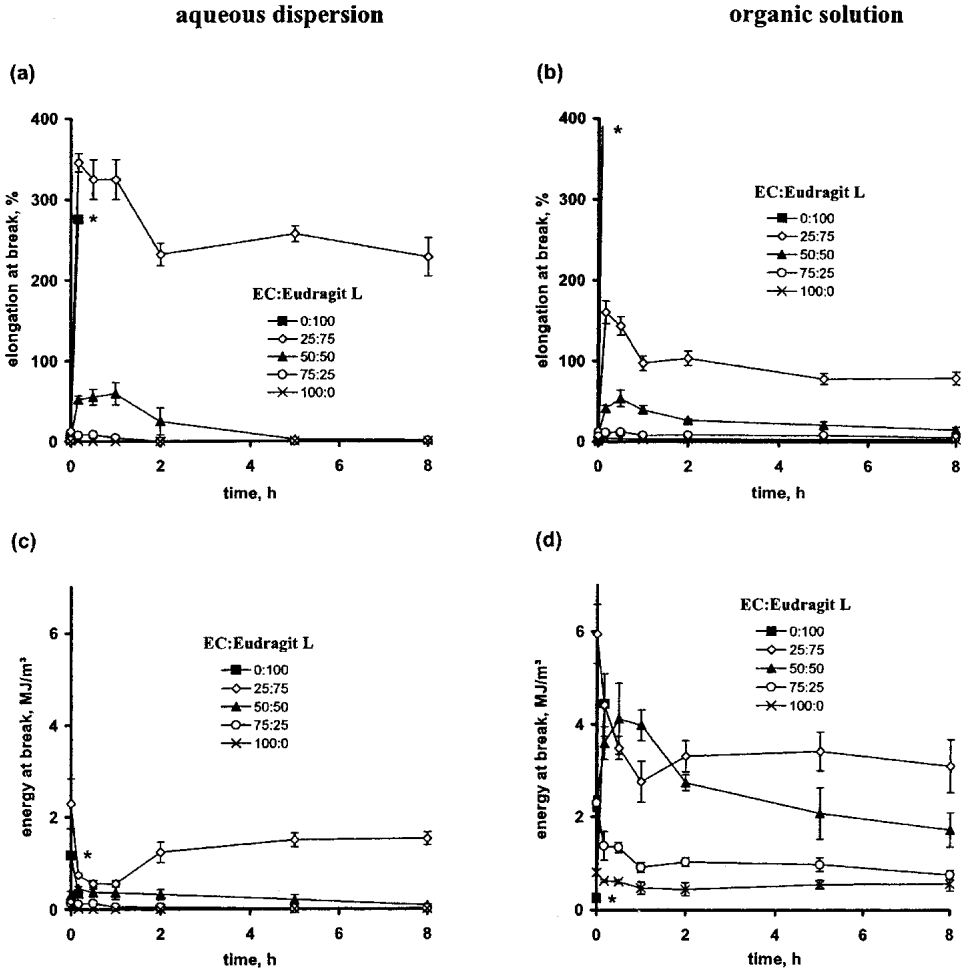

Fig. 6. Changes in the mechanical properties of thin, polymeric films upon exposure to 0.1 M HCl depending on the type of preparation technique and EC:Eudragit L blend ratio: (a) % elongation at break, films prepared from aqueous polymer dispersions; (b) % elongation at break, films prepared from organic polymer solutions; (c) energy at break, films prepared from aqueous polymer dispersions; and (d) energy at break, films prepared from organic polymer solutions (the asterix indicates that pure Eudragit L films became too elastic after 10 min to be accurately measurable with the experimental setup).

exceeds a critical value (which depends on the toughness of the film coatings), cracks start to be formed in the polymeric systems. As drug diffusion through water-filled cracks is much more rapid than through intact film coatings, the underlying release mechanism changes at that time point. Importantly, the experimentally measured energy at break of the films can serve as a measure for the easiness of crack formation in the coatings.

Upon exposure to 0.1 M HCl, the energy at break significantly increased with increasing Eudragit L content, irrespective of the type of preparation technique (Figs. 6c and 6d). Interestingly, steep increases in film toughness were observed when increasing the Eudragit L content from 50% to 75% (aqueous dispersions) and from 25% to 50% (organic solutions). These steep increases correlate very well with the observed drug release patterns (Figs. 1a and 1b). Film coatings prepared from aqueous polymer dispersions containing at least 75% Eudragit L were sufficiently tough to resist the hydrostatic pressure developed within the pellet cores (due to osmosis), and drug release predominantly occurred via diffusion through the intact film coatings. In contrast, films prepared from aqueous polymer dispersions containing ≤50% Eudragit L were not sufficiently tough to resist the hydrostatic pressure developed within the pellet cores upon exposure to 0.1 M HCl (Fig. 1a). Consequently, cracks were formed within the coatings after 1–3 h. As the drug diffusivities in these films are very low (10) (at least partially due to the low water uptake, Fig. 2), drug release was completely suppressed from the respective pellets until crack formation started. The dominating drug release mechanisms from pellets coated with EC:Eudragit L blends are illustrated in Fig. 1.

Similar tendencies were observed for systems prepared from organic solutions (Fig. 1b and Fig. 6d): Drug release from pellets coated with high Eudragit L contents (≥50%) was primarily governed by diffusion through the intact polymer coatings, whereas drug release from pellets coated with high EC contents predominantly occurred by diffusion through water-filled cracks. Interestingly, and in contrast to the respective systems coated from aqueous dispersions, crack formation in the film coatings consisting of 50:50 EC:Eudragit L blends did not occur within the first 8 h (Fig.

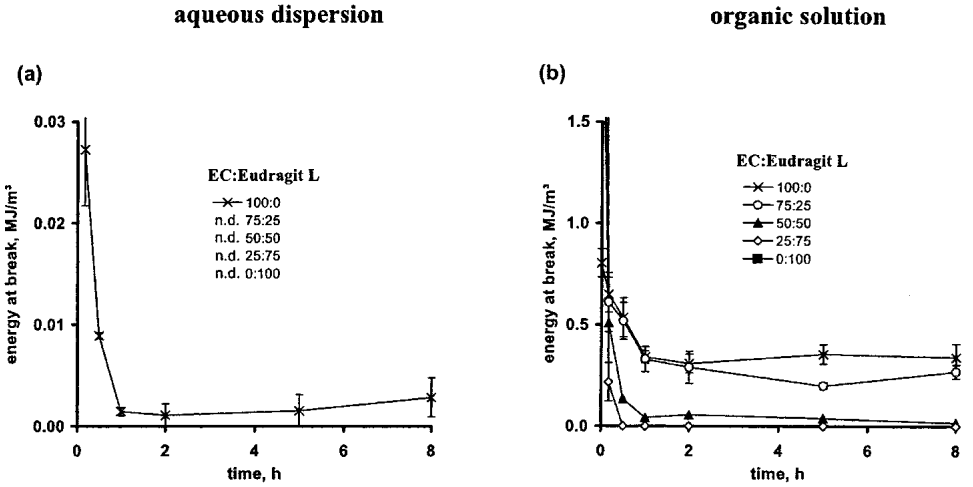

Fig. 7. Changes in the energy at break of thin, polymeric films upon exposure to phosphate buffer pH 7.4 depending on the type of preparation technique and EC:Eudragit L blend ratio: (a) films prepared from aqueous polymer dispersions, and (b) films prepared from organic polymer solutions (n.d.: not accurately detectable with the experimental setup; please note the different scaling of the y-axes).

1b vs. 1a). This can be explained by the higher degrees of polymer-polymer interpenetration in these films, resulting in higher energies required to break them (Fig. 6d vs. 6c).

As discussed above, the effect of the plasticizer level on the mechanical properties of the films was negligible compared to the effect of the type of preparation method. Furthermore, drug release from pellets coated with 50:50 EC:Eudragit L blends was similar for 25% and 10% TEC contents (data not shown). Also the mechanical properties of the films and changes thereof upon exposure to the release media were similar for these plasticizer levels (data not shown). Based on these results, it can be concluded that the observed differences in the drug release kinetics from coated pellets prepared from aqueous dispersions and organic solutions (Fig. 1) can primarily be attributed to the different film formation mechanisms, and not to the different plasticizer levels.

Changes in the mechanical properties of the films prepared from aqueous dispersions and organic solutions upon exposure to phosphate buffer pH 7.4 are illustrated in Fig. 7. Irrespective of the type of preparation method, the energy at break, puncture strength (not shown) and % elongation (not shown) decreased with increasing Eudragit L content. This can be attributed to the (partial) leaching of the enteric polymer out of the films at high pH. Interestingly, steep decreases in these parameters occurred when increasing the Eudragit L content from 0% to 25% (aqueous dispersions) and from 25% to 50% (organic solutions). These threshold values correlate very well with those observed with the drug release profiles from coated pellets (Figs. 1c and 1d). The effect of the type of preparation method on the critical Eudragit L content above which drug release steeply increases can again be explained by the different film formation mechanisms and the resulting degrees of polymer-polymer-interpenetration.

CONCLUSIONS

When using polymer blends for the coating of solid pharmaceutical dosage forms, the type of coating technique (aqueous vs. organic) strongly affects the resulting microstructure of the polymeric films. In organic solutions, the macromolecules are highly mobile and intimately blended. Mechanically strong films with high degrees of polymer-polymer interpenetration are formed upon solvent evaporation. Elevated hydrostatic pressures are required to cause crack formation within these coatings. In contrast, the mobility of the macromolecules is highly restricted in blends of aqueous polymer dispersions. Films with domains of the pure polymers result and the degree of polymer-polymer interpenetration is comparably low. Consequently, much lower hydrostatic pressures are sufficient to induce crack formation within these coatings. Based on the mechanical properties (puncture strength, % elongation, and energy at break), water uptake, dry weight loss, and disintegration behavior of thin, polymeric films in different release media, the effects of the type of coating technique (aqueous vs. organic) on the resulting drug release kinetics from propranolol HCl–loaded pellets could be elucidated.

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