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Drug release mechanisms from Kollicoat SR:Eudragit NE coated pellets

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ABSTRACT

Thin, free films based on Kollicoat SR:Eudragit NE blends were prepared by casting or spraying aqueous dispersions of these polymers, and were thoroughly characterized with respect to their water uptake behavior, water permeability, dry mass loss kinetics, mechanical properties and drug release patterns. A mechanistic mathematical model based on Fick's law of diffusion was used to quantify the experimentally measured release of metoprolol succinate from various types of systems. With increasing Eudragit NE content the films became more hydrophobic, resulting in decreased water permeability as well as water uptake rates and extents. In addition, the dry mass loss upon exposure to the release medium decreased. Consequently, the films' permeability for the drug decreased. Importantly, metoprolol succinate release from thin films was mainly controlled by pure diffusion, allowing for the determination of the apparent diffusion coefficient of the drug in the different polymeric systems. Knowing these values, drug release from coated pellets could be quantitatively predicted, assuming intact film coatings throughout the observation period. Comparison with independent experimental results showed that crack formation set on very rapidly in the polymeric membranes upon exposure to the release medium in the case of sugar starter cores, irrespective of the polymer:polymer blend ratio and investigated coating level. In contrast, the onset of crack formation was delayed as a function of the blend ratio and coating thickness in the case of microcrystalline cellulose starter cores, attracting less water into the pellets core. The obtained new insight into the underlying drug release mechanisms can be very helpful during device optimization and improve the safety of this type of advanced drug delivery systems.

1. Introduction

Polymeric film coatings are highly suitable to control drug release from pharmaceutical dosage forms (Ghebre-Sellassie, 1994; McGinity and Felton, 2008). Several types of polymers used for this purpose are commercially available and well known, e.g. Eudragit L (methacrylic acid copolymer), Eudragit RS (acrylate:methacrylate copolymer), Kollicoat SR (polyvinyl acetate), Aquacoat ECD (an aqueous dispersion of ethylcellulose). In order to adjust a specific, desired drug release profile for a given application, different formulation parameters can be varied, including the coating level as well as the addition of varying amounts and types of plasticizers (Frohoff-Huelsmann et al., 1999; Struebing et al., 2007; Ye et al., 2007; Ho et al., 2009). However, too thin or too thick, too brittle or too sticky film coatings must be avoided. Thus, it is eventually highly challenging to provide a specific release profile for a given drug and drug dose. The synthesis of *novel* types of polymers exhibiting new properties (e.g., a specific permeability for a given drug) might help overcoming this restriction. However, in these cases time- and cost-intensive studies are required, including toxicity tests. An interesting alternative option is to use blends of different types of well-known polymers: by simply varying the polymer:polymer blend ratio very different film coating properties can eventually be obtained, allowing to provide broad spectra of drug release patterns (Amighi and Moes, 1995; Lecomte et al., 2003; Siepmann et al., 2008; Ensslin et al., 2008, 2009a). However, yet relatively little is known on how these systems work and the underlying drug release mechanisms are still poorly understood for many of these more complex film coatings (Siepmann and Siepmann, 2008; Ensslin et al., 2009b).

The aim of this study was to blend: (i) a highly flexible, more hydrophobic polymer:poly(ethyl acrylate-co-methyl methacrylate) 2:1, commercially available as an aqueous dispersion under the trade name "Eudragit NE", with (ii) a more hydrophilic and more

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brittle polymer:poly(vinyl acetate), commercially available as an aqueous dispersion under the trade name "Kollicoat SR". In order to better understand the underlying drug release mechanisms from pellets coated with these polymer blends, thin, free films of identical composition as the film coatings were prepared by casting or spraying and thoroughly characterized with respect to their: (i) water uptake behavior, (ii) water permeability, (iii) dry mass loss kinetics, (iv) in vitro drug release patterns, and (v) mechanical properties. Furthermore, mechanistic mathematical theories were identified and used to quantify the resulting drug release kinetics from thin, free films as well as from coated pellets, taking into account the given initial and boundary conditions (Crank, 1975; Cussler, 1984; Fan and Singh, 1989). Comparison with experimental results allowed for a better understanding of the involved mass transport phenomena in the investigated systems, in particular with respect to the importance of drug diffusion through the intact polymeric film coatings versus drug diffusion and/or convection through water-filled cracks. The obtained new insight on how the coated dosage forms control drug release can be very helpful during device optimization and improve the safety of the respective medical treatments.

2. Materials and methods

2.1. Materials

Metoprolol succinate (Hexal, Holzkirchen, Germany); an aqueous dispersion of poly(vinyl acetate) [Kollicoat SR 30D, also containing small amounts of poly(vinyl pyrrolidone) and sodium lauryl sulfate; BASF, Ludwigshafen, Germany]; an aqueous dispersion of poly(ethyl acrylate-co-methyl methacrylate) 2:1 (Eudragit NE 30D; Evonik, Darmstadt, Germany).

2.2. Preparation of thin, polymeric films

Cast films: The aqueous dispersions Kollicoat SR 30D and Eudragit NE 30D were blended at different ratios (as indicated) and subsequently diluted with demineralized water so that a dry mass content of 15% was achieved. These blends were cast onto Teflon plates and subsequently dried in an oven at 60 °C for 48 h. In case of *drug loaded* films, metoprolol succinate was dissolved in the added demineralized water. The final drug content of the films was 1% (w/w). Unless otherwise stated, cast films were used in this study.

Sprayed films: Kollicoat SR 30D:Eudragit NE 30D blends were sprayed onto a rotating drum. The latter was filled with hot water (initial temperature = 60 °C, end temperature = 40 °C). After spraying, the films were peeled off the drum and kept in a desiccator.

2.3. Water uptake and dry mass loss studies

Thin, polymeric films were cut into pieces of 3.5 cm × 3.5 cm, which were placed into 100 mL plastic containers filled with 100 mL pre-heated, demineralized water, followed by horizontal shaking (37 °C, 80 rpm; GFL 3033, Gesellschaft fuer Labortechnik, Burgwedel, Germany; $n = 3$). At pre-determined time points, samples were withdrawn, accurately weighed [wet mass (t)] and dried to constant mass at 60 °C [dry mass (t)]. The water content (%) and dry film mass (%) at time t were calculated as follows:

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

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

2.4. Water permeability measurements

Water permeability measurements were performed using a side-by-side diffusion cell, according to a procedure described in detail elsewhere (Hjaertstam and Hjertberg, 1999). Briefly, the two chambers of the cell were separated by the film of interest (which was prepared by spraying), and the system was thermostatted with a water jacket at 37 °C. The area of the film available for diffusion was 0.48 cm^2. The chambers were filled at the same time with 15 mL demineralized water (37 °C). The water diffusion experiment started when a small amount of tritiated water (10 mL, 400 kBq) was added to the donor compartment. The solutions in the donor and receiver compartments were well stirred with paddles. Samples of 500 μL were removed from the receiver compartment at regular intervals and replaced by the same amount of demineralized water. The samples were weighed and analyzed in a liquid scintillator counter (1414 LSC, Win Spectral, Wallac, Waltham, MA, USA). A sample of 500 μL was taken from the donor compartment 1 min after the diffusion experiment had been started to determine the tritium activity in this compartment. From the tritium activity measurements it was possible to calculate the amount of water that had diffused through the film at different times, and thus the water permeability of the film. The films were either initially dry or soaked overnight in water prior to the measurement (as indicated).

2.5. In vitro drug release measurements

From thin films: Drug release from thin, free films was measured by placing 3.5 cm × 3.5 cm specimen into 100 mL plastic flasks filled with 100 mL pre-heated demineralized water, followed by horizontal shaking for 48 h (37 °C, 80 rpm; GFL 3033; $n = 3$). To avoid film folding and floating during the experiments (resulting in potential variations of the surface area exposed to the release medium), the films were fixed within the plastic flasks. At pre-determined time intervals, 3 mL samples were withdrawn (replaced with fresh medium) and analyzed UV-spectrophotometrically ($\lambda = 222$ nm; UV-1650PC; Shimadzu, Champs-sur-Marne, France).

From ensembles of pellets: Drug release from *ensembles* of pellets was measured in pre-heated demineralized water using the USP 30 paddle apparatus (AT 7; Sotax, Basel, Switzerland) (900 mL, 37 °C, 100 rpm; $n = 3$). At pre-determined time intervals, 3 mL samples were withdrawn and analyzed by UV-spectrophotometry ($\lambda = 222$ nm; UV-1650PC). If not otherwise stated, drug release from ensembles of pellets is shown.

From single pellets: Drug release from *single* pellets was measured using an absorbance microplate reader (SpectraMax M2, Molecular Devices, Sunnyvale, CA, USA) set at an absorbance wavelength of 274 nm. For each pellet a release medium initially consisting of 300 μL of pure water was used. The release medium was refilled with 100 μL of pure water every 6–7 h to compensate for the amount of evaporated water. The absorbance of the release medium is proportional to the height of the release medium multiplied by the drug concentration. As the absorbance was kept in the region where the dependency between the concentration and the absorbance is linear, the evaporation and the refilling did not effect the measurements. The system was continuously agitated and thermostatted at 37 °C. Measurements were made over time. For each of the batches investigated, twelve pellets randomly chosen were studied.

2.6. Determination of the partition coefficient

The partition coefficient of the drug between the polymeric films and the release medium at 37 °C was determined by placing film pieces of 3.5 cm × 3.5 cm in 100 mL plastic flasks filled with 100 mL pre-heated demineralized water, saturated with metoprolol suc-

cinate and containing a large excess of this drug (fine powder, as received). The flasks were horizontally shaken at 80 rpm and kept at 37 °C (GFL 3033). At predetermined time points, samples of the aqueous phase and film samples were withdrawn and analyzed for their drug content. The drug content of the aqueous samples was determined as described in Section 2.5. In vitro *drug release measurements.* The drug content of the film samples was determined UV-spectrophotometrically upon film dissolution in ethanol (λ = 222 nm, UV-1650PC). The partition coefficient was calculated from the plateau concentrations reached in the aqueous phase and in the films at equilibrium. All experiments were conducted in triplicate.

2.7. Determination of the mechanical properties

The mechanical properties of the films (puncture strength, percent elongation and energy at break) in the dry and wet state were measured using the puncture test and a texture analyzer (TAXT.Plus, Swantech, Villeneuve la Garenne, France). Film specimen were mounted on a film holder (n = 6). 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 (diameter: 10 mm). Load versus displacement curves were recorded until rupture of the film and used to determine the mechanical properties as follows:

$$\text{puncture strength} = \frac{F}{A} \quad (3)$$

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

$$\%\ \text{elongation at break} = \frac{\sqrt{R^2 + d^2} - R}{R} \times 100\,\% \quad (4)$$

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

$$\text{energy at break per unit volume} = \frac{\text{AUC}}{V} \quad (5)$$

where AUC is the area under the load versus displacement curve and V the volume of the film located in the die cavity of the film holder (the energy at break is normalized to the film's volume).

3. Results and discussion

3.1. Water uptake, permeability and dry mass loss of thin films

The water uptake kinetics of cast, free Kollidon SR:Eudragit NE films upon exposure to demineralized water at 37 °C are shown in Fig. 1. The polymer:polymer blend ratio was varied as follows: 100:0, 90:10, 80:20, 70:30, 50:50, and 0:100. Clearly, the *rate* as well as the *extent* of the water uptake significantly decreased with increasing Eudragit NE content. This can be attributed to the fact that Eudragit NE is less hydrophilic than Kollicoat SR. The experimentally measured *water permeability* of films of identical composition prepared by spraying is illustrated in Fig. 2. Side-by-side diffusion cells were used for these measurements and the transport of tritiated water across the films monitored. The latter were either initially dry (open diamonds in Fig. 2), or had been exposed to demineralized water at 37 °C overnight prior to the experiment (filled diamonds in Fig. 2). As it can be seen, the permeability of the Kollidon SR:Eudragit NE films for water significantly decreased with increasing Eudragit NE content. This is consistent with the observed water uptake kinetics of the respective cast films (Fig. 1) and can be explained by the more hydrophobic nature of Eudragit NE compared to Kollicoat SR. Thus, dosage forms coated

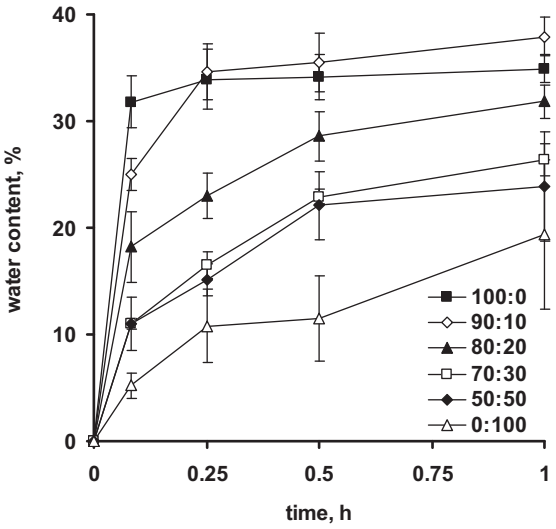

Fig. 1. Impact of the Kollicoat SR:Eudragit NE blend ratio (indicated in the diagram) on the water uptake kinetics of thin, free films prepared by casting upon exposure to demineralized water at 37 °C.

with Eudragit NE-rich films can be expected to limit water penetration into the device more efficiently than Kollicoat SR-rich film coatings. Furthermore, it can be seen that the overnight exposure of the films to water at 37 °C prior to the measurements did not substantially affect the measured water permeability (filled versus open diamonds in Fig. 2).

Fig. 3 shows the experimentally measured changes in the dry mass of thin, free Kollidon SR:Eudragit NE films (prepared by casting) upon exposure to demineralized water at 37 °C. Again, the polymer:polymer blend ratio was varied from 0:100 to 100:0. Clearly, pure Eudragit NE films showed virtually no mass loss. In contrast, pure Kollicoat SR films rapidly lost approximately 7% of their initial dry mass upon exposure to water. This can at least partially be attributed to the leaching of the water-soluble compounds poly(vinyl pyrrolidone) and sodium lauryl sulfate, which are present in small amounts in Kollicoat SR 30D. The dry mass loss of the films based on polymer:polymer *blends* increased (as expected) with increasing Kollicoat SR content (Fig. 3).

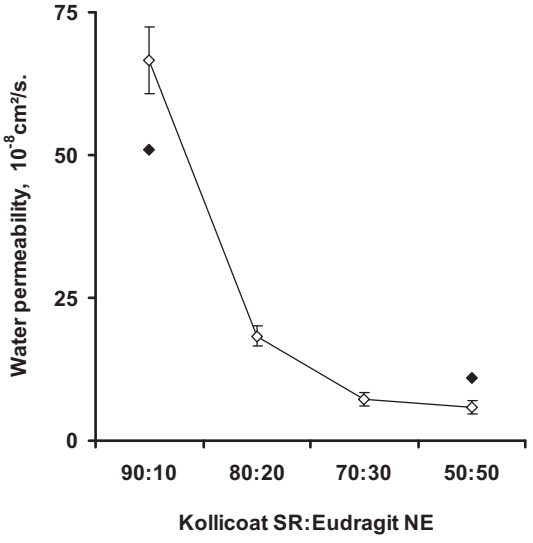

Fig. 2. Water permeability of sprayed Kollicoat SR:Eudragit NE films at 37 °C. ♦: films were soaked overnight in water prior to the measurement. ◊: dry films were used for the experiment.

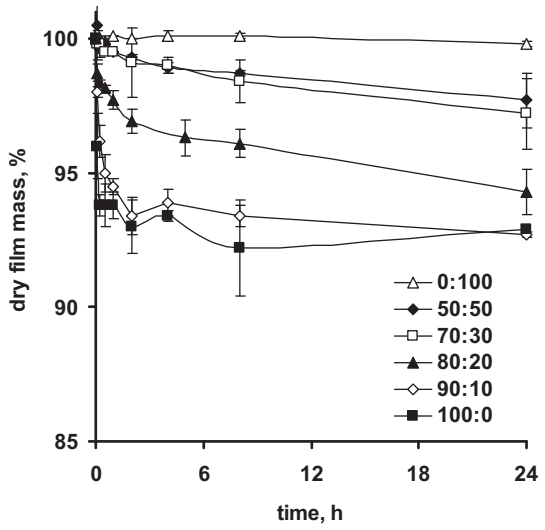

Fig. 3. Impact of the Kollicoat SR:Eudragit NE blend ratio (indicated in the diagram) on the dry mass loss kinetics of thin films prepared by casting upon exposure to demineralized water at 37 °C.

Thus, based on the experimentally measured water uptake and dry mass loss kinetics of thin free films as well as on their water permeabilities, it can be expected that the film coatings containing high amounts of Kollicoat SR are more permeable for many drugs (especially freely water-soluble, low molecular weight drugs) than film coatings, which are rich in Eudragit NE.

3.2. Mechanical properties of thin films

When studying the drug release mechanisms from polymer coated dosage forms, it is decisive to know how flexible the release rate controlling membranes are: upon contact with aqueous body fluids, water penetrates into the system (due to concentration gradients), potentially generating significant hydrostatic pressure in the device (Marucci et al., 2008, 2009, 2010). This pressure acts against the film coating from the inside of the dosage form. This is particularly true if the core of the device contains high amounts of freely water-soluble compounds (drugs and/or excipients). If the film coating cannot withstand this pressure, crack formation sets on. From this time point, drug is also released via diffusion and convection through the newly created water-filled channels (and not only through the intact film coating). Generally, drug transport through water-filled pores is much more rapid than drug transport through an intact polymeric membrane. Eventually, the hydrostatic pressure built up within the dosage form's core is so high that significant amounts of the drug are "pushed out" into the surrounding bulk fluid as soon as crack formation sets on (resulting in "pulsatile" drug release). Fig. 4 shows the experimentally measured puncture strength, percent elongation at break and energy required to break thin, free Kollicoat SR:Eudragit NE films (prepared by casting) in the dry state at room temperature (left hand side) and in the wet state at 37 °C (upon exposure to demineralized water for different time periods, right hand side). The polymer:polymer blend ratio was varied from 90:10 to 70:30 to 50:50, as indicated. Note that caution has to be paid when directly comparing the results obtained in the dry versus wet state, since the temperature during these measurements was different (room temperature versus 37 °C). An increase in temperature generally leads to increased polymer molecular mobility and, thus, to more flexible films. As it can be seen, an increase in the Eudragit NE content of the films resulted in more flexible and mechanically more stable films in the dry state as well as in the wet state (irrespective of the exposure time to water). This can be explained by the higher elasticity of Eudragit NE networks compared to Kollicoat SR networks. The partially observed initial increase in film flexibility upon exposure to the aqueous phase can probably be attributed to the plasticizing effect of water on these polymeric systems. The (subsequent) decrease in mechanical stability with increasing exposure time is likely to be caused by the leaching of water-soluble compounds into the surrounding bulk fluid (Fig. 3).

3.3. Drug release from thin films

The experimentally measured metoprolol succinate release from thin, free films into demineralized water at 37 °C is illustrated in Fig. 5 (symbols). The systems were prepared by casting (open circles) or spraying (filled squares). The Kollicoat SR:Eudragit NE blend ratio was 90:10. For each type of system drug release from three single films of identical composition is shown. In order to quantitatively describe these results, the following mathematical theory was applied: the model is based on Fick's second law of diffusion and considers that the drug is initially homogeneously and molecularly distributed within the polymeric films (monolithic solutions). The latter were transparent in all cases and did not show any evidence for the presence of drug crystals or amorphous particles. Furthermore, the theory takes into account that the release medium is well stirred and that perfect sink conditions are provided throughout the experiments. Considering these initial and boundary conditions and assuming constant drug diffusivities, the following analytical solution of Fick's second law of diffusion can be derived using the method of Laplace transformation (Crank, 1975):

$$\frac{M_t}{M_\infty} = 1 - \frac{8}{\pi^2}\sum_{n=0}^{\infty}\frac{1}{(2n+1)^2}\exp\left(\frac{-D(2n+1)^2\pi^2 t}{L^2}\right) \quad (6)$$

where M_t and M_∞ denote the absolute cumulative amounts of drug released at time t and infinity, respectively; n is a dummy variable, D the diffusion coefficient of the drug within the polymeric system, L is the thickness of the film.

The *curves* in Fig. 5 show the fittings of this equation to the sets of experimentally measured drug release kinetics. As it can be seen, good to rather good agreement between theory and experiment was obtained in all cases. This was true for all the investigated Kollicoat SR:Eudragit NE blend ratios (data not shown). Thus, drug diffusion through the polymeric networks is likely to be the dominant mass transport mechanism. Note that the *x*-axis in Fig. 5 is normalized to the film thickness in order to account for slight variations in this parameter from sample to sample. This normalization is made according to Eq. (6). Importantly, based on these calculations, the apparent diffusion coefficient of metoprolol succinate in the different types of films could be determined (Fig. 6). Clearly, the mobility of the drug significantly decreased with increasing Eudragit NE content, irrespective of the type of preparation technique of the film. This can at least partially be attributed to the decreasing water uptake rate and extent (Fig. 1), decreasing water permeability (Fig. 2) and decreasing dry mass loss of the systems upon exposure to the release medium (Fig. 3) with increasing Eudragit NE content. Based on these results, it can be expected that Kollicoat SR-rich film coatings release the drug more rapidly than Eudragit NE-rich films.

Furthermore, Fig. 5 shows that metoprolol succinate release from cast films was much more rapid than from sprayed films. This might be due to phase separation occurring during film formation: the polymer nanoparticles are highly mobile in the aqueous dispersions and have time to sediment more or less rapidly. In contrast, in the case of spraying, such effects can be expected to be minimized due to rapid water evaporation. Thus, the nano- and micro-structure of the films prepared by casting might be different

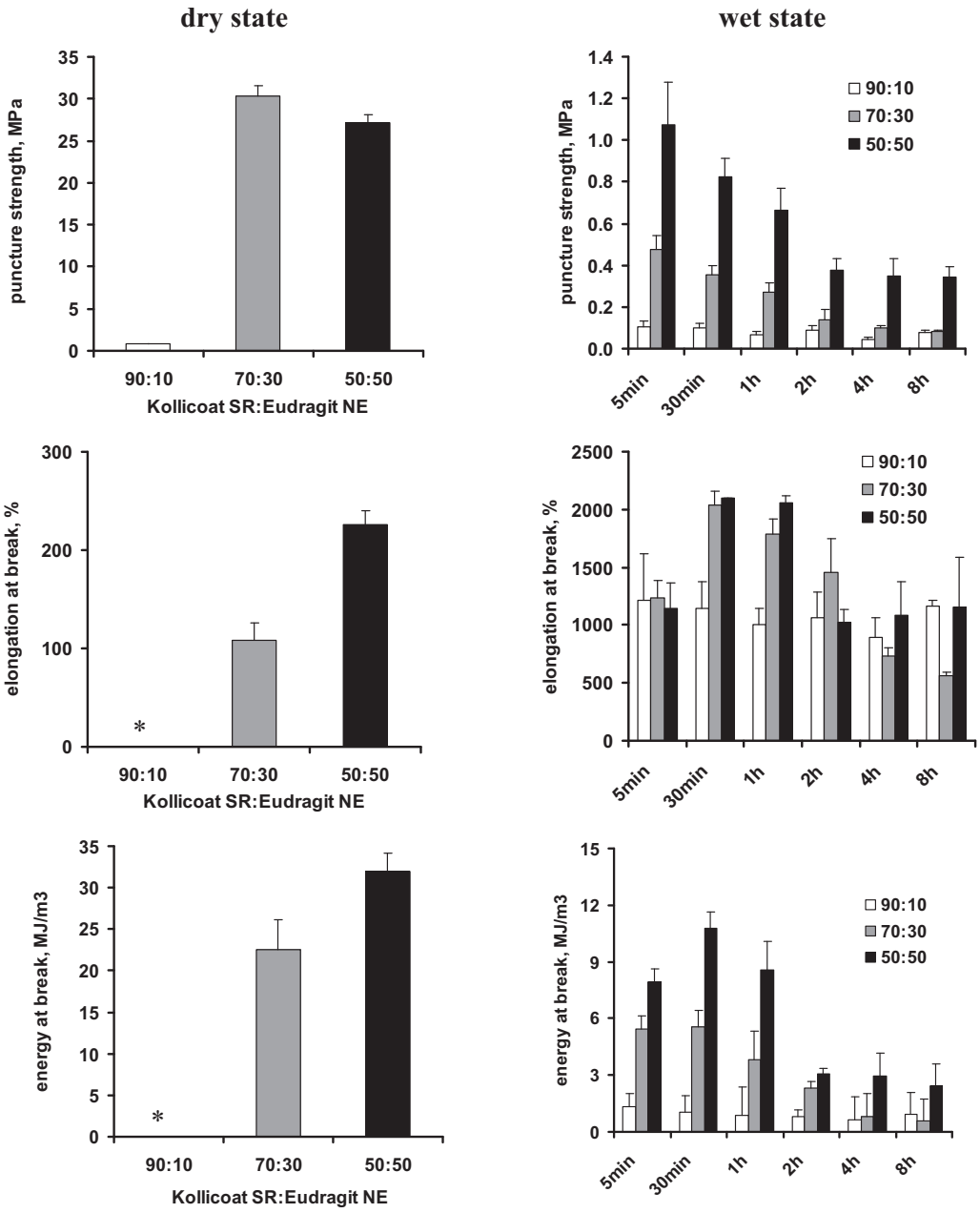

Fig. 4. Mechanical properties of Kollicoat SR:Eudragit NE films prepared by casting, measured with a texture analyzer in the dry state at room temperature as well as in the wet state after different exposure times to water at 37 °C. The stars indicate very small values, which are not visible with the given scaling of the *y*-axis.

from that of films prepared by spraying. These differences could be quantified using Eq. (6), allowing for the determination of the apparent diffusion coefficient of metoprolol succinate in the investigated systems. Fig. 6 clearly shows that the mobility of the drug in sprayed films was much lower than in cast films (gray versus black bars).

3.4. Drug release from coated pellets

Once knowing the diffusion coefficient of the drug within the film coating, an appropriate solution of Fick's second law can be used to theoretically *predict* the resulting drug release kinetics from coated dosage forms, assuming that drug diffusion through the intact film coating is the dominant mass transport process. Considering the spherical geometry of the investigated pellets as well as their initial drug loading, the drug solubility and the fact that perfect sink conditions are provided throughout the experiments, the following solution of Fick's law can be derived, allowing to quantify drug release from the coated pellets:

$$\frac{M_t}{M_\infty} = 1 - \exp\left(-\frac{3DKR_0t}{(R_o - R_i)^{\bullet}R_i^2}\right) \quad (7)$$

where M_t and M_∞ denote the absolute cumulative amounts of drug released at time t and infinity, respectively; D the diffusion coefficient of the drug within the membrane; K the partition coefficient of the drug between the membrane and the reservoir, R_i and R_o are the inner and outer radii of the coated pellet.

The partition coefficient of metoprolol succinate between the film coating and the bulk fluid varied between 0.60 and 1.00, depending on the Kollicoat SR:Eudragit NE blend ratio. Using Eq. (7), the diffusion coefficient determined with sprayed films and assuming that metoprolol succinate diffusion through the intact

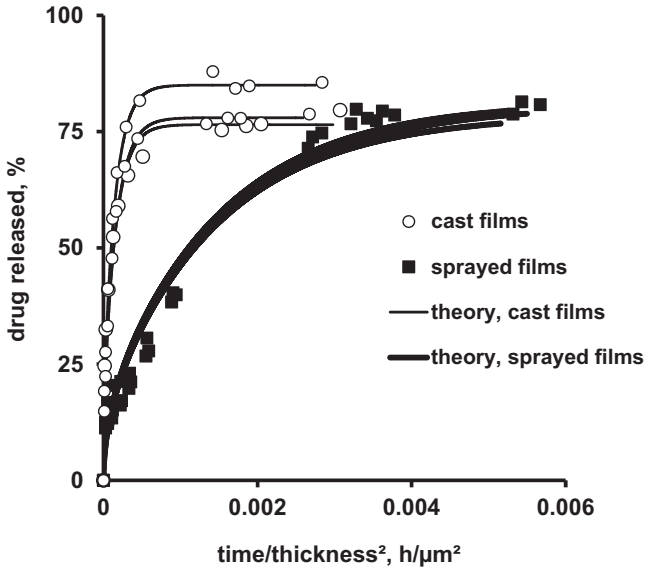

Fig. 5. Drug release from thin, free films prepared by casting or spraying (as indicated), based on Kollicoat SR:Eudragit NE 90:10 in demineralized water at 37 °C. The symbols represent the experimental results, the curves the fitted theory (Eq. (6)).

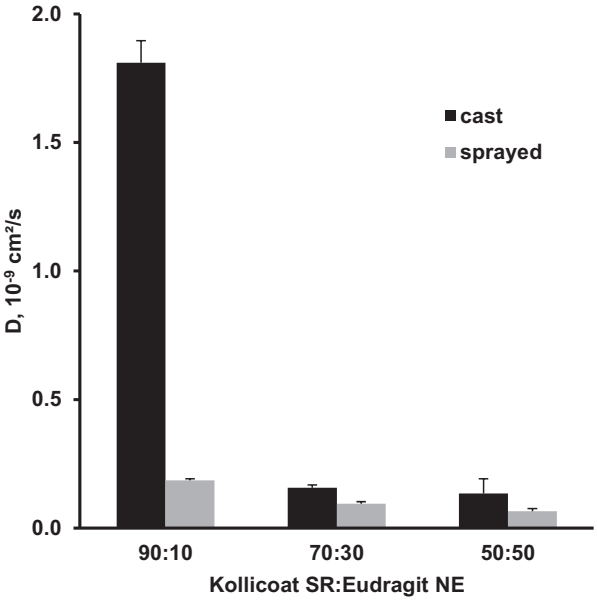

Fig. 6. Dependence of the apparent diffusion coefficient of metoprolol succinate in thin Kollicoat SR:Eudragit NE films upon exposure to demineralized water at 37 °C on the polymer:polymer blend ratio and type of preparation technique.

film coatings is the dominant mass transport process, the dashed curves in Fig. 7 could be calculated, considering different polymer:polymer blend ratios and coating levels. Clearly, the resulting release rate decreased with increasing Eudragit NE content, due to the lower mobility of the drug in these films. Also, the release rate decreased with increasing coating level, due to the increasing length of the diffusion pathways to be overcome.

In order to verify these theoretical predictions, metoprolol succinate layered *sugar cores* were coated with 10 and 20% Kollicoat

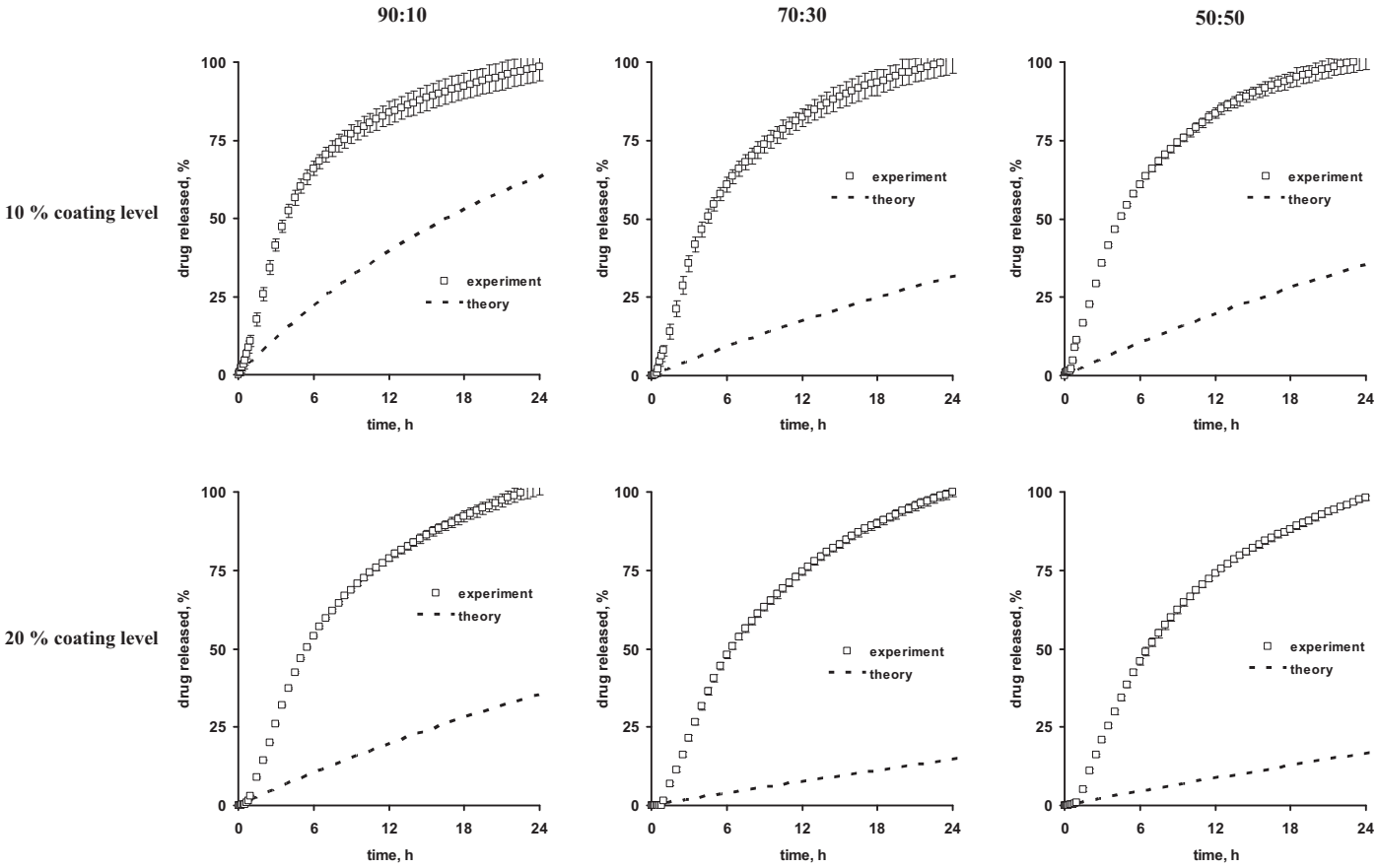

Fig. 7. Theoretical predictions (dashed curves) and independent experiments (symbols): metoprolol succinate release from drug-layered *sugar cores* coated with 10 or 20% Kollicoat SR:Eudragit NE 90:10, 70:30 or 50:50 (as indicated) in demineralized water at 37 °C. The predictions are calculated using Eq. (7) and the diffusion coefficients determined with thin sprayed films.

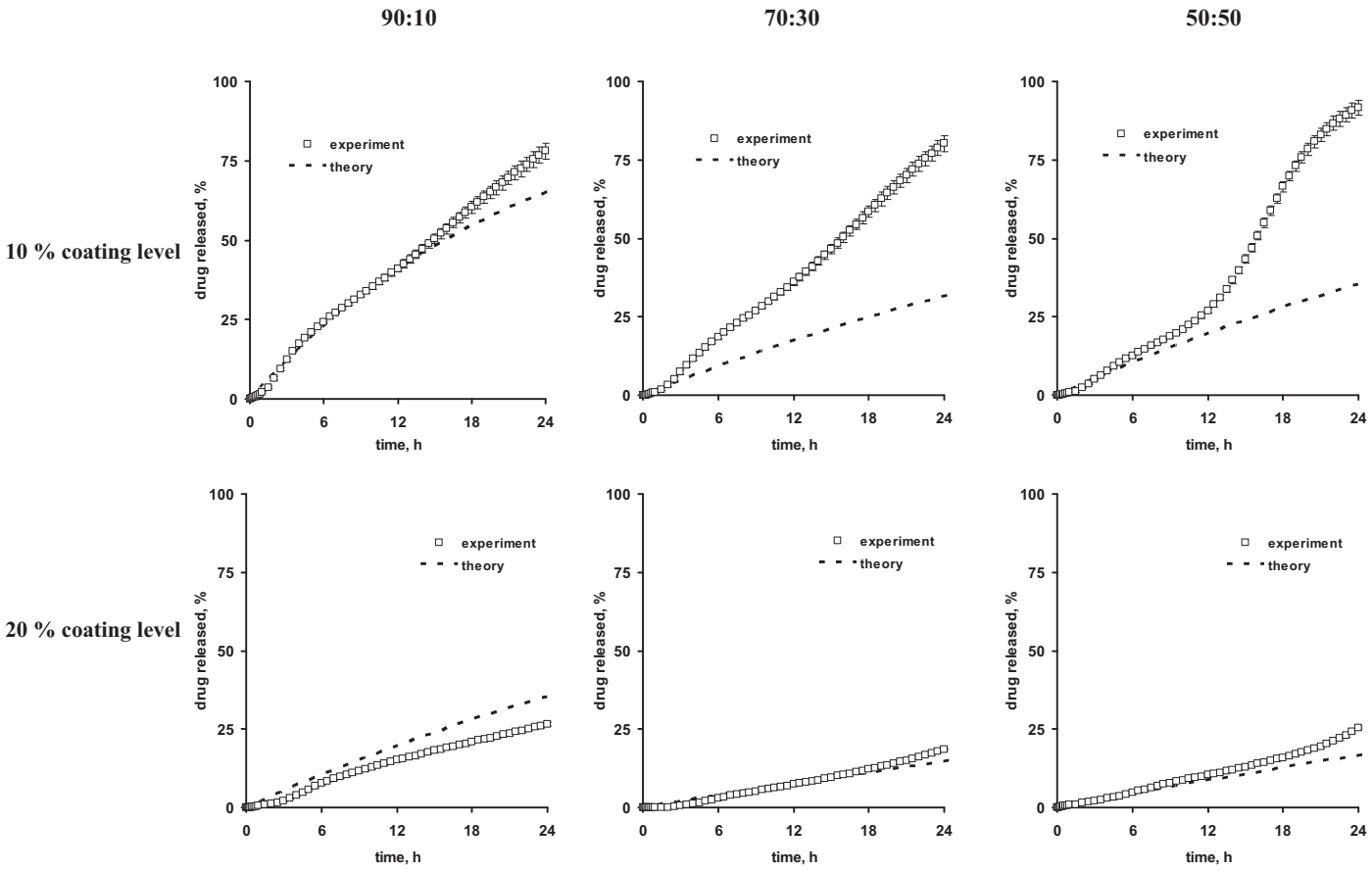

Fig. 8. Theoretical predictions (dashed curves) and independent experiments (symbols): metoprolol succinate release from drug-layered *MCC cores* coated with 10 or 20% Kollicoat SR:Eudragit NE 90:10, 70:30 or 50:50 (as indicated) in demineralized water at 37 °C. The predictions are calculated using Eq. (7) and the diffusion coefficients determined with thin sprayed films.

SR:Eudragit NE 90:10, 70:30 and 50:50 and drug release was measured in demineralized water at 37 °C (symbols in Fig. 7). As it can be seen, the experimentally measured drug release rates were much higher in all cases than theoretically predicted (symbols versus dashed curves in Fig. 7). Thus, crack formation is highly likely in these systems: the hydrostatic pressure built up within the pellets upon water penetration into the systems rapidly breaks the film coatings, resulting in additional drug release through water-filled channels (via diffusion and/or convection). This was true for all the investigated Kollicoat

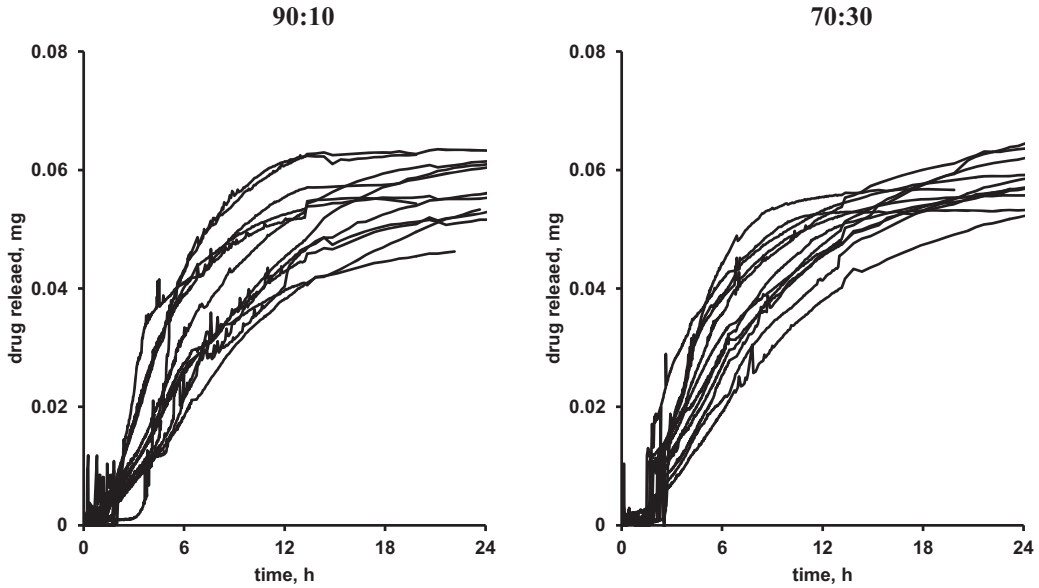

Fig. 9. Metoprolol succinate release from *single* pellets in demineralized water at 37 °C: the Kollicoat SR:Eudragit NE blend ratio was 90:10 or 70:30 (as indicated), the drug was layered onto sugar cores and the coating level was 20%.

SR:Eudragit NE blends and coating levels in the case of sugar starter cores.

Furthermore, metoprolol succinate layered *microcrystalline cellulose (MCC) cores* were coated with 10 and 20% Kollicoat SR:Eudragit NE 90:10, 70:30 and 50:50 and drug release was measured in demineralized water (symbols in Fig. 8). Note that the theoretical predictions for these systems (dashed curves in Fig. 8) are identical to those illustrated in Fig. 7, since Eq. (7) assumes that drug diffusion through the intact film coating is the dominant mass transport step and that the system's core acts as a well stirred drug reservoir. At a coating level of 10% (upper row in Fig. 8), the use of Eq. (7) again significantly underestimates the resulting drug release rate, indicating the formation of cracks in these film coatings. Interestingly, the onset of crack formation was not immediate (as in the case of drug layered sugar cores), but more or less delayed. This can be explained by the lower osmotic activity of MCC compared to sugar: the drug layered MCC cores attract less water into the core than drug layered sugar cores. Thus, the hydrostatic pressure acting against the film coatings increases less rapidly. In the case of 50:50 Kollicoat SR:Eudragit NE blends, crack formation starts only after about 12 h exposure time to the release medium. Interestingly, the pressure built up in these pellets pulls out parts of the drug rather rapidly upon crack formation, resulting in a partially "pulsatile" drug release profile.

Importantly, at a coating level of 20%, the polymeric membranes were mechanically sufficiently stable during major parts of the observation period to withstand the hydrostatic pressure built up within the systems: the agreement between theoretical predictions (dashed curves) and independent experiments (symbols) was good/rather good. Thus, crack formation (if occurring) is significantly delayed.

These hypothesized drug release mechanisms could further be confirmed by the experimental measurement of metoprolol succinate release from *single* pellets. Fig. 9 shows examples of drug release patterns from pellets coated with Kollicoat SR:Eudragit NE 90:10 or 70:30 blends, containing sugar cores, with a coating level of 20%. Clearly, in all cases drug release set on (rather) rapidly, probably due to the formation of cracks in the film coatings.

4. Conclusion

The drug release mechanisms from Kollicoat SR:Eudragit NE coated pellets are complex and strongly depend on the formulation parameters, including the film coating thickness, type of starter core and polymer:polymer blend ratio. In addition to drug diffusion through the intact film coatings, drug release through water-filled cracks is more or less important. Thus, variations in the systems' composition during device optimization can significantly affect the underlying drug release mechanisms and might result in unexpected changes in the resulting drug release patterns. Not only the slope of the curves, but also their shape can be affected. A mechanistic understanding of how this type of advanced drug delivery systems controls drug release can be very helpful, facilitating product development and improving product safety. In particular the knowledge whether or not crack formation in the film coating occurs and whether the drug is predominantly released through the intact film coating or through water-filled cracks is of importance.

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