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RESEARCH PAPER

Mechanisms Controlling Theophylline Release from Ethanol-Resistant Coated Pellets

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ABSTRACT

Purpose To elucidate the mass transport mechanisms controlling drug release from recently proposed, ethanol-resistant, polymeric film coatings.

Methods Theophylline matrix pellets were coated with ethylcellulose: guar gum blends. Drug release from single pellets and ensembles of pellets was measured in various release media. Changes in the systems' morphology, composition and mechanical properties were monitored using SEM, gravimetrical analysis and a texture analyzer. Based on the obtained experimental results a mechanistically realistic mathematical model was identified and used to quantitatively predict drug release from coated pellets in ethanol-free and ethanol-containing bulk fluids.

Results Drug diffusion though the intact polymeric film coatings is likely to be the dominant mass transport mechanism in the investigated systems, irrespective of the ethanol content in the surrounding environment. An appropriate solution of Fick's law could be used to quantitatively predict theophylline release from pellets coated with different ethylcellulose:guar gum blends at different coating levels. Importantly, independent experiments confirmed the theoretical predictions.

Conclusions *In silico* simulations can help facilitating the optimization of the novel ethanol-resistant polymeric film coatings, avoiding time-consuming and cost-intensive series of trial-and-error experiments. The presence/absence of ethanol does not affect the underlying drug release mechanisms.

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INTRODUCTION

Recently, a novel type of ethanol-resistant polymeric film coating to control drug release has been proposed (1). Blends of ethylcellulose and guar gum were shown to provide controlled drug release, which was not significantly affected by the addition of 40% ethanol to the release medium. This type of advanced drug delivery system offers the potential to avoid a crucial risk associated with many oral controlled release dosage forms containing highly potent drugs: If water-insoluble, but ethanol-soluble polymers are used to control drug release, the co-consumption of alcoholic beverages can result in undesired dissolution of these polymers. Consequently, the capacity of the delivery system to sustain drug release might no longer be guaranteed, leading to "dose dumping" (accidental release of the entire dose in a short period of time). The resulting side effects might eventually be fatal for the patient. For these reasons, the marketing of the hydromorphone HCl containing, controlled release product "Palladone" was suspended. In this system the release of the opioid drug is controlled from pellets comprising ethylcellulose, ammonia methacrylate copolymer type B and stearyl alcohol (2). A clinical trial with healthy subjects revealed that the co-consumption of 240 mL of 40% alcohol together with a 12-mg Palladone capsule (containing the controlled release pellets) resulted in an average peak hydromorphone concentration, about 6 times greater than when the product was administered with water (3). One individual showed a 16-fold increase in the maximal plasma concentration. Furthermore, Walden *et al.* (4) demonstrated the ethanol sensitivity of Palladone SR capsules *in vitro*. In addition to the risk of potentially severe side effects due to dose dumping, also the intended therapeutic effect is no longer assured during the envisaged time period.

The potentially significant impact of the consumption of alcoholic beverages on the drug release kinetics from oral controlled release dosage forms was also demonstrated by various other research groups (5–10). For instance, Fadda *et al.* (2) showed that the addition of up to 40% ethanol to the surrounding bulk fluid considerably altered the release of 5-aminosalicylic acid from three commercially available controlled drug delivery products (Pentasa, Asacol, and Salofalk). One strategy to reduce the risk of dose dumping resulting from co-consumption of alcoholic beverages is the use of clearly visible warning labels on the drug product. Unfortunately, this option was shown to be unsuccessful in practice: Booker *et al.* (11) reported that heavy drinkers suffering from chronic low back pain did not reduce their opiate use, despite such warning labels. Furthermore, according to the Behavioral Risk Factor Surveillance System, 1 of 3 drinkers in the U.S. are "binge drinking", consuming 4/5 drinks (women/men) in a short period of time (12).

For these reasons the recently proposed, novel polymeric film coatings providing drug release, which is not affected by the presence of even high concentrations of ethanol (40%), offer a great potential to improve the safety and efficacy of many drug treatments. The film coatings comprise a blend of the water-insoluble polymer ethylcellulose and the ethanol-insoluble polymer guar gum. The basic idea is that the presence of ethylcellulose avoids undesired dissolution of guar gum in water-rich media and that the presence of guar gum avoids undesired dissolution of ethylcellulose in ethanol-rich media. However, so far, the mass transport mechanisms controlling drug release from dosage forms coated with these novel ethanol-resistant polymer blends is unknown and the potential impact of the presence of ethanol in the surrounding bulk fluid on the drug release mechanism is unclear.

Different types of mass transport mechanisms can be involved in the control of drug release from coated dosage forms (13–16), such as water penetration into the system, polymer swelling, drug dissolution, drug diffusion through the polymeric network and/or through water-filled pores/cracks, polymer dissolution, limited drug solubility and so on, to mention just a few (17–19). Appropriate mathematical equations can be used to quantitatively describe these physicochemical phenomena (20–22). Fitting such models to sets of experimentally determined drug release kinetics and other key features of the dosage form (*e.g.* water uptake behavior and changes in the mechanical strength upon exposure to aqueous media) can allow determination of system-specific parameters, such as the apparent diffusion coefficient of the drug within the film coating. Knowing these values, the importance of the involved mass transport phenomena in the respective type of drug delivery system can be estimated and the dominant release mechanism can be identified. In addition, mechanistically realistic mathematical theories allow for the quantitative prediction of the effects of the device design (*e.g.* composition, geometry and dimensions) on the resulting drug release kinetics (23–26).

The aim of the present study was to elucidate the mass transport mechanisms controlling drug release from pellets coated with the novel ethanol-resistant polymeric film coatings. Being multiple unit dosage forms, pellets provide an additional advantage for this type of applications: In case accidental film damage and dose dumping would occur in a pellet, the overall release from the ensemble of pellets would hardly be affected. Based on a comprehensive experimental characterization of the devices before and after exposure to different release media, appropriate mathematical equations were to be identified and a mathematical model to be developed allowing for facilitated drug product optimization: *In silico* simulations should be able to predict the effects of formulation parameters on the resulting drug release kinetics.

MATERIALS AND METHODS

Materials

Theophylline matrix pellets (70% drug content, diameter: 0.71–1.25 mm; FMC BioPolymer, Philadelphia, PA, USA); Ethylcellulose Aqueous Dispersion NF (Aquacoat® ECD 30; FMC BioPolymer); dibutyl sebacate (DBS; Morflex, Greensboro, NC, USA); ethanol (Fisher Bioblock Scientific, Illkirch, France); *medium viscosity* guar gum (*medium* η guar gum, apparent viscosity of a 1% aqueous guar gum solution = 320 cPs; Polygum 240/80; Polygal Trading, Maerstetten, Switzerland); *high viscosity* guar gum (*high* η guar gum, apparent viscosity of a 1% aqueous guar gum solution in the range of 575–625 cPs; Guar HV 225; Alland & Robert, Port-Mort France, France). The apparent viscosities were measured using an AR2000Ex rheometer (TA Instruments, New Castle, DE, USA) at a shear rate of 50 s^{-1} in a 1% aqueous guar gum solution measured rotationally at 20°C after 1 min equilibration using a 6 cm acrylic cone (1°), wherein the shear was ramped up linearly from 1 to 50 s^{-1} in 25 steps over 29 s.

Preparation and Characterization of Thin Polymeric Films

Aquacoat® ECD 30 was plasticized for 1 day with 25% DBS (w/w; based on the ethylcellulose mass). Guar gum was dissolved in purified water at 65°C (2 h stirring) and cooled down to room temperature. The two liquids were blended and stirred for 30 min prior to use. Films were prepared by spraying (0.8 mm spray nozzle) or casting (as indicated) Aquacoat® ECD 30:guar gum blends onto Teflon plates and subsequent controlled drying for 24 h at 60°C.

The (water + ethanol) uptake and dry mass loss kinetics of the films were determined as follows: Pieces of 5 × 5 cm were

placed into 100 mL plastic flasks filled with 100 mL pre-heated release medium, followed by horizontal shaking (37°C, 80 rpm; GFL 3033, Gesellschaft fuer Labortechnik, Burgwedel, Germany). 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 + ethanol) content (%) and dry film mass (%) at time t were calculated as follows:

$$(water + ethanol)\ content\,(\%)\,(t) = \frac{wet\ \ mass\,(t) - dry\ \ mass\,(t)}{wet\ \ mass\,(t)} \cdot 100\% \quad (1)$$

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

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 specimens 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:

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

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.

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

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

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

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).

Pellet Coating

Theophylline matrix cores were coated with Aquacoat® ECD 30:guar gum 85:15 or 93:7 blends (as indicated). Aquacoat® ECD 30 was plasticized for 1 day with 25% DBS (w/w; based on the ethylcellulose mass). Guar gum (*medium* η guar gum, if not otherwise stated) was dissolved in purified water at 65°C (0.7% or 1% w/w, as indicated; 100% reference value = total coating formulation; 2 h stirring) and cooled down to room temperature. The two liquids were blended and stirred for 30 min prior to use. The coating dispersions were sprayed onto theophylline pellets using a fluidized bed coater (Strea 1, Wurster insert; Niro; Aeromatic-Fielder, Bubendorf, Switzerland). The process parameters were as follows: inlet temperature = 38°C, product temperature = 38 ± 2°C, spray rate = 2 g/min, atomization pressure = 1.2 bar, nozzle diameter = 1.2 mm, batch size = 500 g. After coating the pellets were further fluidized for 10 min and subsequently cured for 24 h at 60°C in an oven.

Drug Release Measurements

From Ensembles of Pellets

Theophylline release from coated pellets was measured in 0.1 M HCl or 0.1 M HCl: ethanol blends (optionally containing different amounts of NaCl), followed by phosphate buffer pH 7.4 (USP 36) using the USP 36 paddle apparatus (Sotax, Basel, Switzerland) (900 mL, complete medium change after 2 h; 37°C, 100 rpm, $n = 3$). At pre-determined time points, 3 mL samples were withdrawn and analyzed UV-spectrophotometrically [$\lambda = 270.4$ nm in 0.1 N HCl, $\lambda = 272.2$ nm in 0.1 M HCl:ethanol blends and phosphate buffer pH 7.4] (UV 1650 PC, Shimadzu, Champs-sur-Marne, France).

From Single Pellets

Single pellets (from the same batch) were placed into 100 mL plastic flasks filled with 100 mL pre-heated release medium (0.1 M HCl or 0.1 M HCl:ethanol 60:40 for 2 h, followed by phosphate buffer pH 7.4). The flasks were horizontally shaken at 37°C and 80 rpm (GFL 3033). At pre-determined time points, 3 mL samples were withdrawn and analyzed UV-spectrophotometrically as described above.

SEM Studies

The morphology of coated pellets was characterized using a cold field emission high resolution scanning electron microscope (S-4700 Field Emission Gun; Hitachi, Hitachi High-Technologies Europe, Krefeld, Germany). Samples were covered under vacuum with a carbon layer.

Diffusion Cell Studies

Drug permeation through thin, drug-free (sprayed) polymeric films was measured using vertical diffusion cells, which were placed in a horizontal shaker (37°C, 80 rpm; GFL 3033) (27). The film surface exposed to the medium was 1.8 cm^2. The donor compartment (at the top) was filled with an excess of dry theophylline powder (as received). The acceptor compartment (at the bottom) was filled with 350 mL 0.1 M HCl or 0.1 M HCl:ethanol 60:40. At pre-determined time intervals, 3 mL samples were withdrawn and analysed UV-spectrophotometrically as described above. All experiments were conducted in triplicate.

Determination of the Drug Solubility and of the Partition Coefficient of the Drug

Excess amounts of theophylline powder were exposed to 0.1 M HCl or 0.1 M HCl:ethanol 60:40 in flasks in a horizontal shaker (80 rpm, 37°C). At pre-determined time intervals, samples were withdrawn, filtered and analysed for their drug content (as described above) until equilibrium was reached.

Thin, initially drug free (sprayed) films were exposed to saturated theophylline solutions in 0.1 M HCl or 0.1 M HCl:ethanol 60:40 containing excess amounts of non-dissolved drug in flasks in a horizontal shaker (80 rpm, 37°C). At pre-determined time intervals, film samples were withdrawn, surface water removed and the films analyzed for their drug content. The latter was determined UV-spectrophotometrically upon film dissolution in ethanol. The partition coefficient was calculated from the plateau concentrations reached in the films and in the aqueous phase at equilibrium. All experiments were conducted in triplicate.

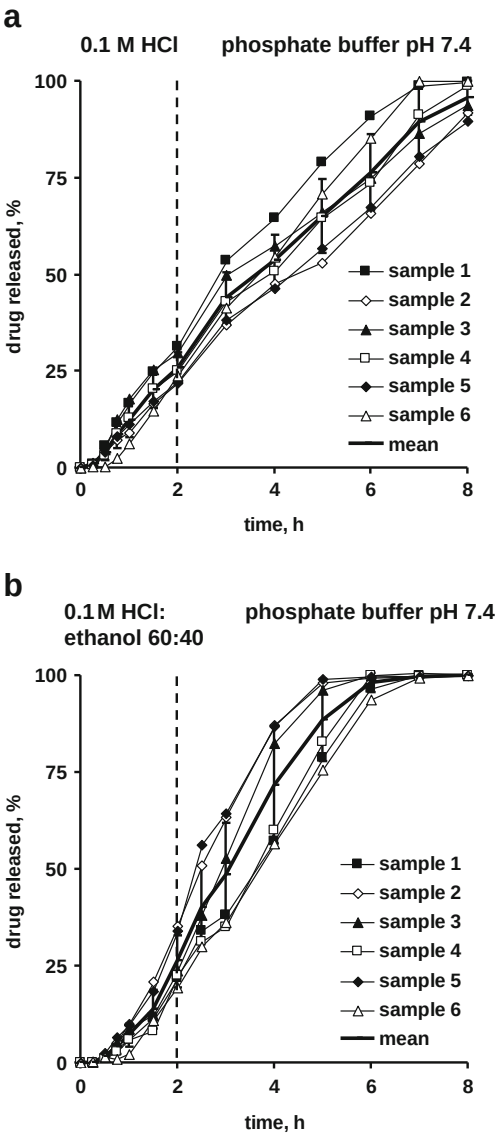

Fig. 1 Theophylline release from *single* pellets coated with 20% (w/w) ethylcellulose:guar gum 85:15 in. (**a**) 0.1 M HCl for 2 h, followed by phosphate buffer pH 7.4, or (**b**) 0.1 M HCl:ethanol 60:40 for 2 h, followed by phosphate buffer pH 7.4. The *thick curves* show the respective mean values, *error bars* indicate standard deviations. The guar gum concentration in the total dispersion was 0.7% w/w.

RESULTS AND DISCUSSION

Drug Release from Single Pellets

When elucidating the drug release mechanisms from multiple dosage forms, it is decisive to first of all clarify whether the single units release in a similar way, or whether the release profile observed with ensembles of multiple units is the sum of very different individual release profiles (28). For instance, in an extreme case, zero order release kinetics observed from an ensemble of hundreds of pellets might result from pulsatile drug release from individual pellets with highly variable lag-times, evenly distributed within the observation period.

Figure 1 shows the experimentally measured theophylline release kinetics from single pellets coated with 20% (w/w) 85:15 ethylcellulose:guar gum. The release medium was either 0.1 M HCl for 2 h (Fig. 1a), or 0.1 M HCl:ethanol 60:40 for 2 h (Fig. 1b), in both cases followed by 6 h phosphate buffer pH 7.4. The thick curves indicate the respective mean values, the error bars standard deviations. Clearly, the investigated single pellets behave similarly, irrespective of the type of release medium: About zero order release kinetics are observed in all cases. Thus, the underlying drug release mechanism seems to be the same for all single units. Slight variations in the film coatings' thickness are likely to be responsible for the observed differences in the individual release profiles (29). Importantly, the presence or absence of 40% ethanol in

the release medium does not seem to affect the underlying drug release mechanism.

Impact of the Osmolality of the Release Medium

Drug release from coated pharmaceutical dosage forms might be strongly affected by the osmolality of the release medium. In certain cases, osmotic effects play a major role for the control of drug release (17). Importantly, considerable variations in the osmolality of the release medium did not significantly affect the resulting drug release kinetics, irrespective of the ethylcellulose:guar gum blend ratio and the presence/absence of ethanol in the release medium. Figure 2a and b show for example the experimentally measured release of theophylline from pellets coated with 20% w/w ethylcellulose:guar gum 85:15 in 0.1 M HCl or 0.1 M HCl:ethanol 60:40 containing 0–5% NaCl for 2 h, followed in both cases by phosphate buffer pH 7.4 for 6 h. As it can be seen, there was only a limited impact on drug release, despite the important variations in the osmolality of the surrounding bulk fluid. Also, no general tendency was visible for any release medium. Based on these results, osmotic pumping as the dominant release mechanism can be excluded.

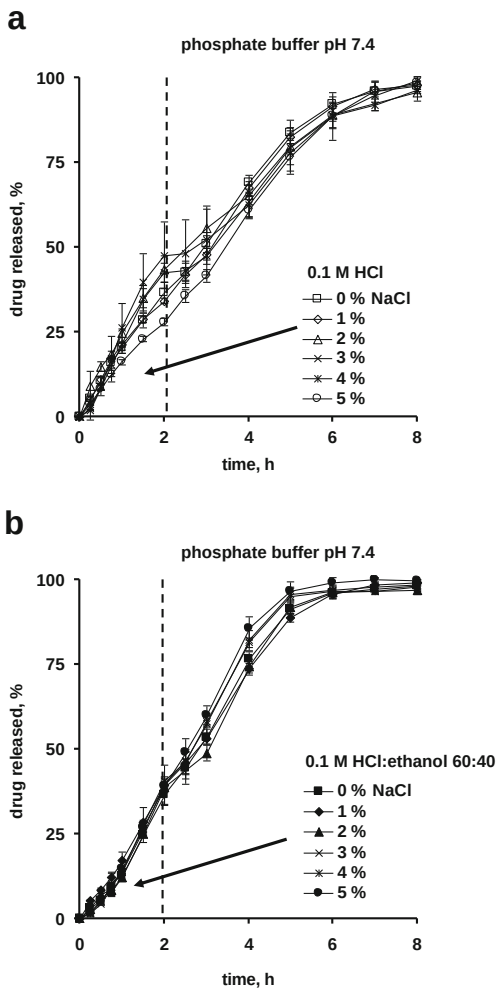

Fig. 2 Impact of the osmolality of the bulk fluid: theophylline release from pellets coated with 20% w/w ethylcellulose:guar gum 85:15 in. (**a**) 0.1 M HCl containing different amounts of NaCl for 2 h, followed by phosphate buffer pH 7.4, or (**b**) 0.1 M HCl:ethanol 60:40 containing different amounts of NaCl for 2 h, followed by phosphate buffer pH 7.4. The guar gum concentration in the total dispersion was 0.7% w/w.

Morphology and Mechanical Properties of the Film Coatings

Drug release from polymer coated solid dosage forms can either occur through the continuous macromolecular network, or through water-filled cracks or pores (potentially created upon water penetration into the system) (30). Often, drug transport through water-filled pores/cracks is much faster than drug transport through a continuous polymeric network (31). In order to know whether water-filled channels exist in the investigated ethylcellulose:guar gum coated pellets, the latters' morphology was studied using Scanning Electron Microscopy before and after exposure to 0.1 M HCl, or 0.1 M HCl:ethanol 60:40 for 2 h. As it can be seen in Fig. 3, no signs for the presence of pores or cracks are visible before exposure to the release media. The same was true after 2 h contact with the bulk fluids, irrespective of the presence of high ethanol concentrations (data not shown). However, it must be pointed out that the pellets had to be dried after exposure to the release media and that eventually created pores/cracks might have been closed during this drying step. In addition, nano-sized pores would not necessarily be visible (*e.g.*, being hidden by the carbon layer or due to the limited resolution). Thus, caution has to be paid when drawing conclusions from this type of measurements. Nevertheless, the absence of visible macro-sized pores under the given conditions is interesting information. In other studies on different polymeric film coatings such pores could clearly be seen in SEM pictures (13).

Obviously, the mechanical strength of the polymeric film coatings is decisive for the potential creation of cracks upon

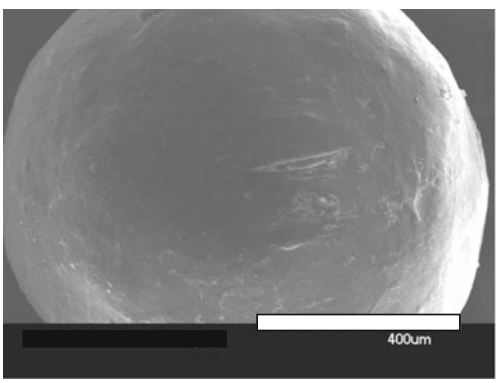

Fig. 3 SEM picture of the surface of a pellet coated with 20% w/w ethylcellulose:guar gum 85:15 before exposure to the release medium. The guar gum concentration in the total dispersion was 0.7% w/w.

water penetration into the systems. Water entering the pellet core builds up a hydrostatic pressure, which acts against the macromolecular membrane. If the latter is fragile, the onset of crack formation is likely after a system-specific lag-time. In contrast, if the film coating is mechanically sufficiently stable and withstands the generated hydrostatic pressure, drug release might be controlled by diffusion through the intact polymeric network. Table I shows the puncture strength, percent elongation at break and energy required to break thin, free films based on different ethylcellulose:guar gum blends in the dry state (before exposure to the release medium). As it can be seen, the mechanical stability of the films increases with increasing guar gum content. This might at least partially be attributable to the fact that an aqueous *dispersion* of ethylcellulose nanoparticles and an aqueous *solution* of guar gum were used for film preparation (as this is the case for the film coatings). Thus, the underlying film formation mechanism is fundamentally different for the two polymers and a much higher degree of polymer–polymer chain entanglement can be expected in the case of guar gum (32).

However, it is well known that the composition of polymeric film coatings can significantly change upon exposure to the release medium (33). For instance, water penetrating into the film coating can act as a plasticizer for a polymeric component. On the other hand, water soluble film compounds (*e.g.* guar gum) might at least partially leach out of the film into the bulk fluid. Also, plasticizers (such as dibutyl sebacate) might be partially lost into the surrounding medium. Due to these changes in the film coatings' composition, the latters' mechanical properties might be significantly altered. Figure 4 shows the dynamic changes in the puncture strength, percent elongation at break and energy required to break thin films based on 93:7, 90:10, or 85:15 ethylcellulose blends upon exposure to 0.1 M HCl:ethanol 60:40 (37°C) for different time periods. As it can be seen, the mechanical stability of the systems: (i) decreases with time in the case of 85:15 ethylcellulose:guar gum blends, (ii) generally only slightly, and more or less arbitrarily varies with time in the case of the other two blends. In most cases, the energy required to break the films increases with increasing guar gum content, irrespective of the exposure time to the release medium (for the reasons discussed above).

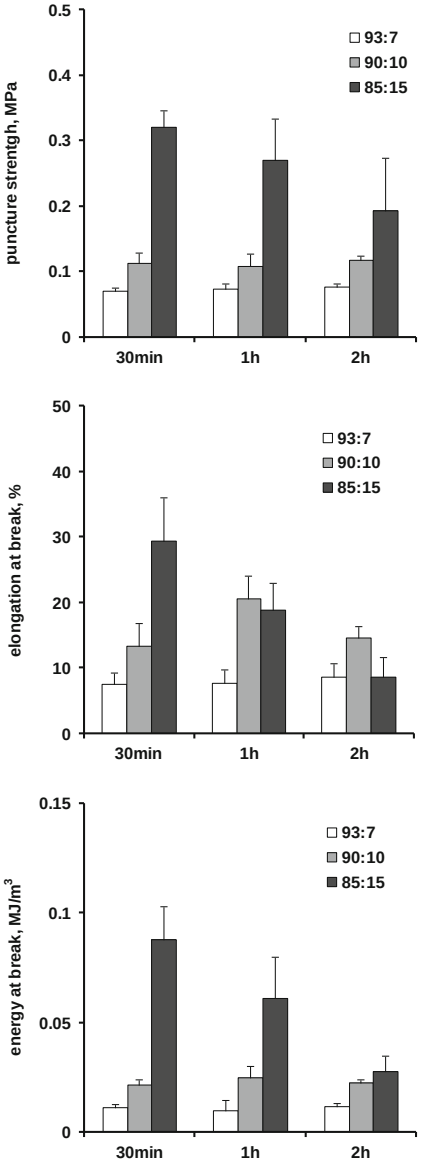

Fig. 4 Dynamic changes in the mechanical properties of free ethylcellulose:guar gum (cast) films upon exposure to 0.1 M HCl:ethanol 60:40 (37°C) for different time periods. The ethylcellulose:guar gum blend ratio (w/w) is indicated in the diagrams. The guar gum concentration in the total dispersion was 0.7% w/w.

Table I Impact of the Ethylcellulose:Guar Gum Blend Ratio (w/w) on the Mechanical Properties (Puncture Strength, Percent Elongation at Break and Energy at Break) of Free (Cast) Films in the Dry State (Mean Values ± Standard Deviation)

	Ethylcellulose:guar gum blend ratio				
	100:0	93:7	90:10	85:15	0:100
Puncture strength, MPa	0.2 ± 0.0	0.4 ± 0.0	0.5 ± 0.0	0.6 ± 0.1	11.6 ± 4.4
Elongation at break, %	1.1 ± 0.2	1.2 ± 0.2	1.1 ± 0.1	0.8 ± 0.1	0.6 ± 0.3
Energy at break, J/m^3	11 ± 0.2	18 ± 0.2	19 ± 2	22 ± 5	323 ± 185

Drug Mobility Within the Film Coatings

Based on the experimentally observed drug release kinetics from single pellets, the very limited impact of changes in the osmolality of the release medium on drug release, the morphology of the pellets' surface before and after exposure to the release medium as well as the mechanical properties of the

polymeric films and dynamic changes thereof upon contact with the bulk fluids, one hypothesis can be that drug release is eventually controlled primarily by diffusion through the intact polymeric film coatings. In order to evaluate the validity of this assumption, the apparent diffusion coefficient of theophylline in thin, free films of identical composition as the investigated film coatings was experimentally determined using vertical diffusion cells. Knowing these values and using an appropriate solution of Fick's law of diffusion the resulting drug release kinetics from coated pellets can be quantitatively predicted (based on the hypothesis of purely diffusion controlled drug release). Comparison of these theoretical predictions with independent experimental results should allow evaluating the validity of the hypothesized release mechanism.

The symbols in Fig. 5 show the experimentally measured permeation of theophylline through thin ethylcellulose:guar gum 85:15 films. Vertical diffusion cells were used, the films were initially drug-free, the donor compartment contained theophylline powder, the acceptor compartment either 0.1 M HCl (filled symbols), or 0.1 M HCl:ethanol 60:40 (open symbols) (37°C), in order to mimic the conditions in initially dry pellets exposed to the release medium. Importantly, about straight lines were observed right from the beginning. Thus, water penetration into and through the films was rapid compared to drug diffusion through the polymeric barrier: Very soon, a steady-state was established, with a saturated drug solution in the donor compartment and perfect sink conditions in the acceptor compartment. Hence, also the dissolution of the theophylline particles was much more rapid than the subsequent diffusion through the thin films. The thickness of the latter was in the range of 17 to 23 μm (thus, in a similar range as the film coatings of the investigated pellets). Furthermore, no major difference was observed when using 0.1 M HCl *versus* 0.1 M HCl:ethanol 60:40 as bulk fluids. Fitting the following solution of Fick's law of diffusion to the experimentally determined drug permeation kinetics allowed determining the apparent diffusion coefficient of the drug in these polymeric films (34):

$$M_t = 2 \cdot A \cdot L \cdot K \cdot c_s \cdot \left[\frac{D \cdot t}{4 \cdot L^2} - \frac{1}{6} - \frac{2}{\pi^2} \cdot \sum_{n=1}^{\infty} \frac{(-1)^n}{n^2} \cdot \exp\left(\frac{-D \cdot n^2 \cdot \pi^2 \cdot t}{4 \cdot L^2} \right) \right] \quad (6)$$

where M_t is the cumulative absolute amount of drug in the acceptor compartment at time t; A denotes the surface area of the film available for diffusion, L the half-thickness of the film, and c_s the solubility of the drug in the medium; K is the partition coefficient of the drug between the film and the bulk fluid. The solubility of theophylline in 0.1 M HCl and 0.1 M HCl:ethanol 60:40 at 37°C was experimentally measured and found to be equal to 12.7 ± 0.5 and 30.2 ± 1.0 mg/mL, respectively. The partition coefficient, K, of this drug between the investigated ethylcellulose:guar gum films and 0.1 M HCl or 0.1 M HCl:ethanol 60:40 was determined to be equal to 1.8 and 0.5 (for both polymer:polymer blend ratios: 85:15 and 93:7).

As it can be seen in Fig. 5, good agreement was obtained when fitting Eq. 6 (curves) to the experimentally determined drug permeation kinetics through the polymeric films (symbols). Based on these calculations, the following apparent diffusion coefficients of theophylline in ethylcellulose:guar gum 85:15 based films could be determined: $D = 3.2 \pm 0.5$ and $5.0 \pm 0.4 \times 10^{-8}$ cm^2/s upon exposure to 0.1 M HCl and 0.1 M HCl:ethanol 60:40, respectively. In the case of ethylcellulose:guar gum 93:7 blends, the D values were equal to 2.1 ± 0.4 and $2.6 \pm 0.7 \times 10^{-8}$ cm^2/s, respectively. Thus, the presence of 40% ethanol in the bulk fluid had only a limited impact on drug mobility within the polymeric films. As expected, the theophylline mobility increased with increasing guar gum content, which can probably be attributed to increased water uptake of the films (guar gum being more hydrophilic than ethylcellulose) and/or partial leaching of this compound into the bulk fluid (leading to less dense polymeric networks).

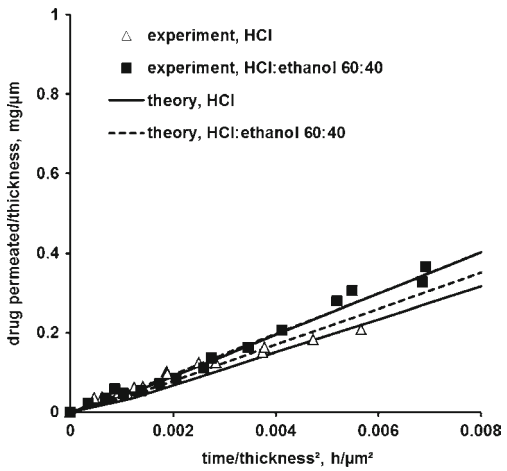

Fig. 5 Drug permeation through sprayed thin ethylcellulose:guar gum 85:15 films (measured in vertical diffusion cells): the donor compartment initially contained dry theophylline powder, the acceptor compartment pre-heated (37°C) 0.1 M HCl or 0.1 M HCl:ethanol 60:40 (as indicated). The *symbols* represent the experimentally measured results, the *curves* the fitted theory (Eq. 6). Note that "time/thickness^2" is plotted on the x-axis, and "drug permeated/thickness" is plotted on the y-axis to account for slight variations in the film thickness from sample to sample. This type of normalization is possible, according to Eq. 6. The guar gum concentration in the total dispersion was 0.7% w/w.

Mathematical Modeling of Drug Release

Based on this knowledge and on the hypothesis that theophylline release is predominantly controlled by drug diffusion through the intact polymeric film coatings (no crack formation), the following solution of Fick's second law of diffusion

can be used to quantitatively predict the resulting drug release kinetics from coated pellets exhibiting an initial excess of drug (drug loading > drug solubility) (35):

$$M_t = \frac{4 \cdot \pi \cdot D \cdot K \cdot c_s \cdot R_o \cdot R_i}{R_o - R_i} \cdot t \qquad (7)$$

where M_t denotes the cumulative amount of drug released at time t; D is the apparent diffusion coefficient of the drug within the film coating; K is the partition coefficient of the drug between the film coating and the bulk fluid; c_s is the solubility of the drug in the core, and R_i and R_o are the inner and outer radii of the device.

Knowing the values on the right hand side of Eq. 7, the resulting drug release kinetics could be quantitatively predicted for arbitrary coating levels. The straight lines in Fig. 6 show some examples: The dashed lines illustrate the theoretically predicted theophylline release kinetics in 0.1 M HCl from pellets coated with 10, 15, or 20% ethylcellulose:guar gum 85:15 (as indicated). The solid lines illustrate the respective release kinetics in 0.1 M HCl:ethanol 60:40. As it can be seen, very similar theophylline release rates are expected in the presence and absence of ethanol in the release medium. Thus, the slightly increased apparent diffusion coefficient of the drug and the increased drug solubility in the presence of 40% ethanol is compensated by the decreased partition coefficient between the film coating and the bulk fluid. In order to evaluate the validity of these theoretical predictions, the respective pellets were prepared (only after the predictions were made) and the resulting drug release kinetics were measured experimentally. Looking at Fig. 6, it can clearly be seen that the theoretical predictions (lines) and independent experiments (symbols) were in good agreement in all cases: irrespective of the presence/absence of ethanol in the release medium and of the coating level. Thus, theophylline diffusion through the intact polymeric film coatings seems to be indeed the dominant mass transport mechanism controlling drug release from these dosage forms. Figure 7 shows that this was also true for 93:7 ethylcellulose:guar gum blends. The dashed and solid lines show the theoretically predicted theophylline release kinetics from pellets (coating level = 15%) in 0.1 M HCl or 0.1 M HCl:ethanol 60:40, respectively. The symbols illustrate the independent experimental results. The

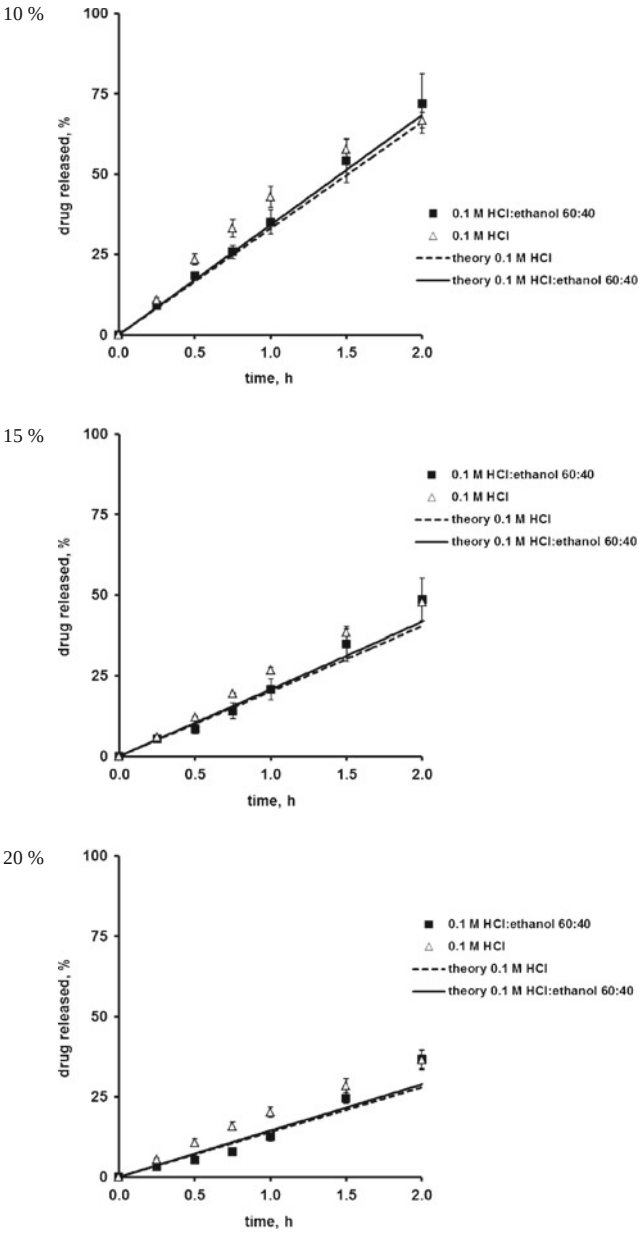

Fig. 6 Theoretical prediction (*straight lines*, Eq. 7) and independent experimental verification (*symbols*): theophylline release from pellets coated with 10, 15 or 20% ethylcellulose:guar gum 85:15 in 0.1 M HCl, or 0.1 M HCl:ethanol 60:40 (as indicated). The guar gum concentration in the total dispersion was 0.7% w/w.

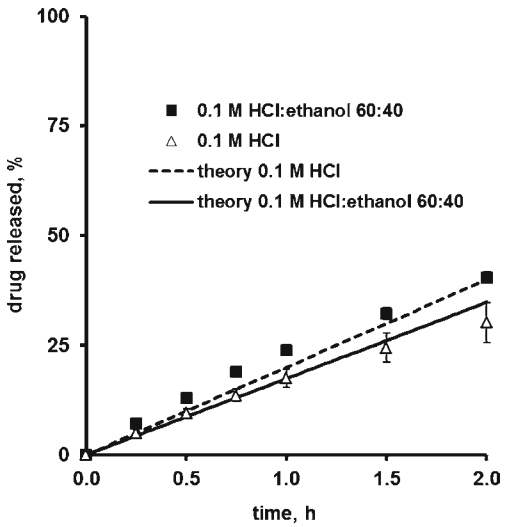

Fig. 7 Theoretical prediction (straight lines, Eq. 7) and independent experimental verification (*symbols*): theophylline release from pellets coated with 15% ethylcellulose:guar gum 93:7 in 0.1 M HCl, or 0.1 M HCl:ethanol 60:40 (as indicated).

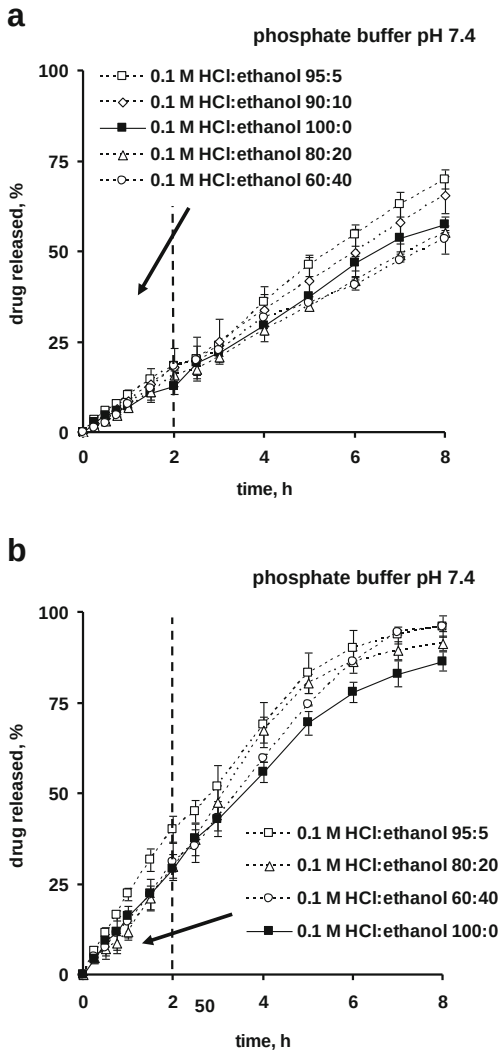

Fig. 8 Impact of intermediate ethanol concentrations in the release medium: theophylline release from pellets coated with 20%: (**a**) 93:7 ethylcellulose:*medium* η guar gum (guar gum concentration in the total dispersion = 1.0% w/w), or (**b**) 85:15 ethylcellulose:*high* η guar gum (guar gum concentration in the total dispersion = 0.7% w/w). The release medium was a 100:0, 95:5, 90:10, 80:20, or 60:40 blend of 0.1 M HCl and ethanol (V/V) (as indicated) for the first 2 h, followed by phosphate buffer pH 7.4 for the subsequent 6 h.

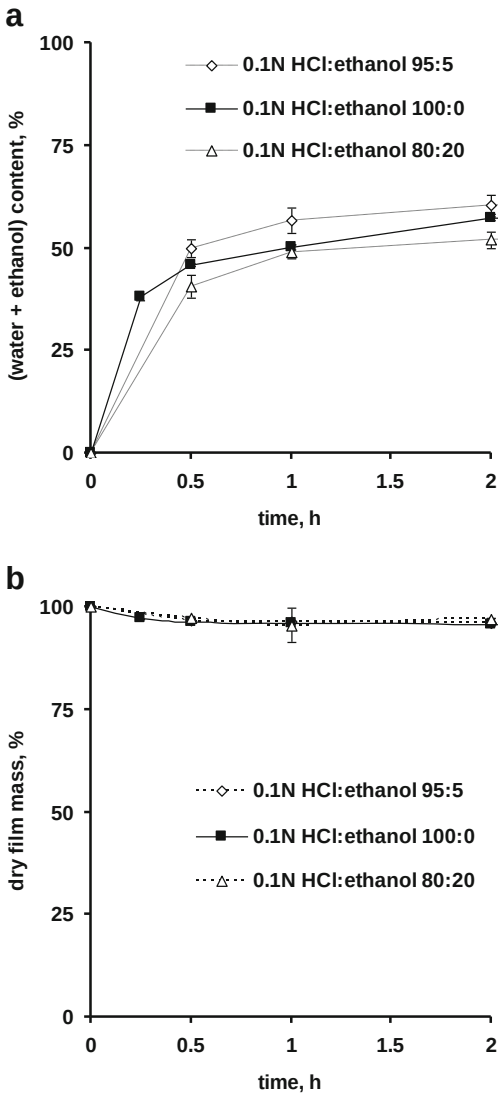

Fig. 9 Impact of intermediate ethanol concentrations in the release medium on changes in the (**a**) (water + ethanol) content, and (**b**) dry mass of thin, free (cast) 93:7 ethylcellulose:guar gum films upon exposure to a 100:0, 95:5, or 80:20 blend of 0.1 M HCl and ethanol (V/V) (as indicated).

observed good agreement further confirms the hypothesized drug release mechanism. These examples also demonstrate the great practical benefit of this type of mathematical modeling: *In silico* simulations offer the possibility to replace time-consuming and cost-intensive series of trial-and-error experiments during product optimization. The film composition and coating level required to achieve a specific, desired drug release profile can be theoretically predicted.

Intermediate Ethanol Concentrations

All results presented so far were obtained upon exposure to 0.1 M HCl, or 0.1 M HCl:ethanol 60:40, respectively. However, in practice the ethanol concentration in the contents of the gastro intestinal tract of a patient is more likely to be *in-between* 0 and 40% upon co-consumption of alcoholic beverages. Thus, it was important to see whether intermediate ethanol concentrations in the release medium might eventually affect the pellets' performance in a different way and/or alter the underlying drug release mechanism. Figure 8a and b show the experimentally measured theophylline release kinetics from pellets coated with 20% 93:7 ethylcellulose:*medium* η guar gum, or 85:15 ethylcellulose:*high* η guar gum, respectively. The release medium was a 100:0, 95:5, 90:10, 80:20, or 60:40 blend of 0.1 M HCl and ethanol (V/V) (as indicated) for the first 2 h, followed by phosphate buffer pH 7.4 for the subsequent 6 h. Clearly, the impact of varying the ethanol

concentration between 0 and 40% was limited in all cases, irrespective of the investigated ethylcellulose:guar gum blend ratio and guar gum viscosity. These results were consistent with the experimentally measured water and ethanol uptake kinetics of thin, free films of identical composition as the film coatings: Figure 9a and b show the limited impact of varying the ethanol concentrations in the release medium on the resulting changes in the "water + ethanol" content and dry mass of thin 93:7 ethylcellulose:guar gum films. In all cases, the presence of the guar gum effectively minimized undesired ethylcellulose dissolution (and *vice-versa*) and the "ethanol and water" uptake kinetics were similar. Hence, neither the ethanol-resistance, nor the underlying drug release mechanism was altered at intermediate ethanol concentrations (corresponding for instance to the co-consumption of beer or wine, instead of high amounts of hard liquors).

CONCLUSION

Drug diffusion through the intact polymeric film coatings seems to be the dominant mass transport mechanism controlling drug release from the recently proposed ethanol-resistant polymeric film coatings, based on ethylcellulose: guar gum blends. Hence, Fick's law of diffusion can be used to facilitate product optimization and to avoid time-consuming and cost-intensive series of trial-and-error experiments. Depending on the type of drug, eventually also other phenomena might have to be taken into account.

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