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Research article

**When drugs plasticize film coatings: Unusual formulation effects observed with
metoprolol and Eudragit RS**

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Abstract

Metoprolol tartrate and metoprolol free base loaded pellet starter cores were coated with Eudragit RS, plasticized with 25 % triethyl citrate (TEC). The initial drug loading and coating level were varied from 10 to 40 and 0 to 20 %, respectively. Drug release was measured in 0.1 N HCl and phosphate buffer pH 7.4. The water uptake and swelling kinetics, mechanical properties and TEC leaching of/from coated pellets and/or thin, free films of identical composition as the film coatings were monitored. The following unusual tendencies were observed: (i) the relative drug release rate from coated pellets increased with increasing initial drug content, and (ii) drug release from pellets was much faster for metoprolol free base compared to metoprolol tartrate, despite its much lower solubility (factor > 70). These phenomena could be explained by plasticizing effects of the drug for the polymeric film coatings. In particular: 1) Metoprolol free base is a much more potent plasticizer for Eudragit RS than the tartrate, leading to higher film permeability and overcompensating the pronounced differences in drug solubility. Also, Raman imaging revealed that substantial amounts of the free base migrated into the film coatings, whereas this was not the case for the tartrate. 2) The plasticizing effects of the drug for the film coating overcompensated potential increasing limited solubility effects when increasing the initial drug loading from 10 to 40 %. In summary, this study clearly demonstrates how important the plasticization of polymeric controlled release film coatings by drugs can be, leading to unexpected formulation effects.

Keywords: Controlled drug delivery; coated pellet; Eudragit RS; metoprolol; Raman-microscopy.

1. Introduction

Film coated dosage forms are frequently used to control the resulting drug release rates from solid oral dosage forms (Maroni et al., 2013a,b; Palugan et al., 2015; Macchi et al., 2015; Lopez et al., 2017). Often polymers are used to form the barrier membranes surrounding drug loaded cores (Andersson et al., 2016; Kazlauske et al., 2017a). Different types of macromolecules can be used for this purpose, e.g. ethylcellulose (Siepmann et al., 2007; Gauno et al., 2013), hydroxypropyl methylcellulose (Maroni et al., 2016) polymethacrylates (Nollenberger and Albers, 2013; Varum et al., 2013; Dodoo et al., 2017) and polyvinylacetate (Kolter et al., 2013). Also, blending different types of polymers might offer an interesting option to achieve desired film coating properties and drug release kinetics (Siepmann et al., 2008). Furthermore, often plasticizers are added to the polymeric film coatings to provide adequate mechanical properties and drug permeability. It has to be pointed out that in some cases the incorporated drug might act as a plasticizer for the controlled release polymeric film coating (Wu and McGinity, 1999; Siepmann et al., 2006). For example, Glaessl et al. (2009, 2010b) reported on the plasticizing activity of metoprolol for Eudragit RS.

Eudragit RS is a poly(ethylacrylate methylmethacrylate trimethylammonioethylmethacrylate chloride) (1:2:0.1) copolymer, which can be applied from organic solutions or aqueous dispersions. In this study, an aqueous dispersion (available under the trade name Eudragit RS) was used to coat starter cores consisting of 90 to 60 % microcrystalline cellulose (MCC) and 10 to 40 % drug (metoprolol free base or metoprolol tartrate). Importantly, the macromolecules in Eudragit RS contain quaternary ammonium groups and are, thus, permanently positively charged. Charge neutrality is achieved by chloride counter ions. However, once exposed to the release medium, these counter ions might be exchanged by other anions coming from the surrounding bulk fluid, resulting in potentially important changes in the film coatings' properties (Narisawa et al., 1994, 1996).

Different types of physico-chemical processes can be involved in the control of drug

release from a coated dosage form. Upon exposure to aqueous body fluids, water penetrates into the system, dissolving the drug and potentially other system components. Once dissolved, the drug diffuses out into the surrounding environment, due to concentrations gradients. The drug might diffuse through an intact polymeric network, and/or through water filled cracks. The latter might be created due to the pressure built up within the core of the dosage form, resulting from the penetration of water into the system. Also, it has recently been proposed that the formation of air bubbles might play a decisive role for crack formation in controlled release film coatings (Fahier et al. 2016). Furthermore, depending on the type of drug and initial drug loading, limited solubility effects might be of major importance: Eventually the amount of liquid available in the core of the formulation (e.g., tablet, pellet or capsule) might not be able to dissolve immediately the entire drug amount. In these cases, dissolved and non-dissolved drug co-exist during certain time periods. It has to be pointed out that only dissolved drug is available for diffusion. In addition, the leaching of water-soluble plasticizers from the film coating into the release medium might alter the key properties of the polymeric barriers over time. Depending on the exact composition and manufacturing procedure of the coated dosage forms, the underlying mass transport mechanisms controlling drug release might be more or less complex (Marucci et al., 2010; Kaunisto et al., 2011; Cuppok et al., 2011; Kazlauske et al., 2017b).

Furthermore, drugs might act as efficient plasticizers for polymeric film coatings. For example, McGinity et al. reported the plasticization of Eudragit RS by ibuprofen (Wu and McGinity, 1999). Siepmann et al. (2006) showed that metoprolol tartrate, chlorpheniramine maleate as well as ibuprofen plasticize Eudragit RS films. Also, Glaessl et al. (2009, 2010a,b) studied the plasticizing effects of metoprolol free base, metoprolol tartrate and tartaric acid on thin Eudragit RL and Eudragit RS films in the dry and wet state. And Gasmi et al. (2015a,b) demonstrated the plasticizing effects of ketoprofen and prilocaine free base on poly(lactic-co-glycolic acid) (PLGA).

Despite the great practical importance of polymeric controlled release film coatings and the potential impact of drugs acting as plasticizers for the macromolecular barriers, yet surprisingly little is known on: (i) the potential *impact of such plasticizing effects* on the resulting drug release kinetics, and on (ii) the *effects of the device design* on drug release in these cases. The aim of this study was to monitor the impact of Eudragit RS plasticization by metoprolol free base and metoprolol tartrate on drug release from coated pellets. The initial drug loading was varied from 10 to 40 %, and the coating level from 0 to 20 %. Drug release was measured in 0.1 N HCl and phosphate buffer pH 7.4. In order to better understand the observed tendencies, the key properties of the coated pellets (and of thin, free films of identical composition as the film coatings) were monitored before and after exposure to the release media.

2. Materials and methods

2.1. Materials

Metoprolol tartrate, metoprolol succinate and ethyl acetate (Sigma Aldrich, Saint-Quentin Fallavier, France); microcrystalline cellulose (MCC, Avicel PH 101; FMC Biopolymer, Brussels, Belgium); Eudragit RS 30 D [an aqueous dispersion of poly(ethylacrylate methylmethacrylate trimethylammonioethylmethacrylate chloride) (1:2:0.1) copolymers] and hydrophobic fumed silica (Aerosil R 972) (Evonik, Darmstadt, Germany); triethyl citrate (TEC; Vertellus Performance Materials Greensboro, USA); talc (Luzenac val Chisone, Porte, Italy); 1 M aqueous sodium hydroxide solution and water-free magnesium sulfate (Acros Organics, Geel, Belgium).

Metoprolol free base was obtained as follows: 100 g metoprolol succinate were dissolved in 700 mL 1 M aqueous sodium hydroxide solution. The free base was extracted into

125 mL ethyl acetate (three times), followed by drying of the organic phase with water-free magnesium sulfate. The ethyl acetate was evaporated at 32 °C in a rotary evaporator connected to a vacuum pump (140 rpm; Rotavapor R 205, Buechi Labortechnik, Flawil, Switzerland). The resulting yellowish liquid was cooled down over night to 4-7 °C, inducing crystallization of metoprolol free base in the form of white, ice like crystals, which were subsequently gently ground in a mortar with a pestle.

2.2. Preparation of thin polymeric films

Eudragit RS 30 D was diluted with water to reach a polymer content of 15 % w/w, and plasticized with TEC (25 % w/w referred to the polymer content, overnight stirring). Thin films were prepared by spraying the plasticized dispersions onto Teflon plates (Bytac; Saint-Gobain Performance Plastics, Charny Oree de Puisaye, France). Talc (50 % w/w based on the polymer content) was added 5 min prior to spraying as an anti-tacking agent (dispersed with an Ultraturrax). A manual spray gun with standard gravity-feed cup was used (Pilot Mini; Walther Pilot, Wuppertal, Germany). The process parameters were as follows: spray rate = 0.8-1.5 g/min; atomization pressure = 1.6 bar; nozzle diameter = 1.8 mm. The films were dried in an oven for 24 h at 60 °C.

2.3. Film characterization

The thickness of the films was measured using a thickness gauge (Minitest 600; Erichsen, Hemer, Germany). The mean thickness of the films was in the range of 300-340 µm.

The water uptake kinetics of the free films were measured gravimetrically upon exposure to phosphate buffer pH 7.4 (USP 40), optionally containing 30 % w/w metoprolol tartrate or metoprolol free base. Pieces of 1.5 × 5 cm were placed into 50 mL plastic containers filled with 40 mL pre-heated medium, followed by horizontal shaking at 37 °C (80 rpm, GFL 3033; Gesellschaft fuer Labortechnik, Burgwedel, Germany). After 4 h, samples were

withdrawn, excess water gently removed with precision wipes (Goma-Camps, La Riba, Spain), the films accurately weighed (*wet mass*) and dried to constant weight at 60 °C (*dry mass*). The *water content (%)* was calculated as follows:

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

The mechanical properties of free films were determined with a texture analyzer (TAXT.Plus; Winopal Forschungsbedarf, Ahnsbeck, Germany) in the wet state at 37 °C after different exposure times to phosphate buffer pH 7.4 (USP 40), optionally containing 30 % w/w metoprolol tartrate or metoprolol free base. Film specimen were incubated in the media in a horizontal shaker at 37 °C (80 rpm, GFL 3033). At pre-determined time points, samples were withdrawn and mounted on a film holder (with cylindrical holes), which was placed in a plastic container filled with the respective medium (kept at 37 °C). The puncture probe (spherical end: 5 mm diameter) was fixed on the load cell (5 kg), and driven downwards with a cross-head speed of 0.1 mm/s to the middle of a film holder's hole. Load versus displacement curves were recorded until rupture of the film and used to determine the mechanical properties as follows:

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

Here, R denotes the radius of the film exposed in the cylindrical hole of the holder, and d the displacement at rupture. At each time point, six measurements were made, mean values +/- standard deviations are reported.

Triethyl citrate leaching from the films was monitored using side-by-side diffusion cells (PermeGear, Bechenheim, Germany) (surface exposed to the media: 28.26 cm² on each side). The donor and acceptor compartments were filled with a 1 % metoprolol tartrate or metoprolol free base solution in 0.1 N HCl. The diffusion cells were placed in a horizontal shaker (GFL

3033, 80 rpm) and kept at 37 °C. At pre-determined time points, 2 mL samples were withdrawn from both compartments, filtered (0.45 µm) and analyzed by HPLC for their drug content (ProStar 230; Varian, Paris, France), using a method previously reported by Bodmeier and Paeratakul (1991). Briefly, the mobile phase consisted of 70 % methanol and 30 % water (v/v). Samples (20 µL) were injected into a Pursuit C18 column (150 × 4.6 mm; 5 µm) (Phenomenex, Paris, France), the flow rate was 0.8 mL/min. The plasticizer was detected UV-spectrophotometrically at $\lambda = 220$ nm.

The partition coefficient of metoprolol free base between the films and 0.1 N HCl was determined at 37 °C by placing film pieces of 1.5 × 1.5 cm² in 100 mL plastic flasks, filled with 100 mL pre-heated release medium. The latter was saturated with the drug and contained a large excess of non-dissolved metoprolol free base. The flasks were horizontally shaken at 80 rpm (GFL 3033). At predetermined time points, samples of the aqueous phase as well as film samples were withdrawn and analyzed for their drug contents. The metoprolol content of the liquid samples was determined by UV-spectrophotometry ($\lambda = 274$ nm; Shimadzu UV-1650, Champs sur Marne, France). The drug content of the films was determined UV-spectrophotometrically upon sample dissolution in ethanol 95 % ($\lambda = 274$ nm, Shimadzu UV-1650). 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.

2.4. Preparation of coated pellets

Pellet starter cores containing different amounts of metoprolol tartrate or metoprolol free base (10, 20, 30, 40 % w/w) and MCC were prepared by extrusion-spheronization. The powders were blended in a high speed granulator (M5R; Loedige, Paderborn, Germany) and purified water was added until a homogeneous mass was obtained. The wetted mixture was passed through a cylinder extruder (SK M/R, holes: 1 mm diameter, 3 mm thickness, rotation speed: 63 rpm; Alexanderwerk GA 65, Remscheid, Germany). The extrudates were

subsequently spheronised at 939 rpm for 10 min (Spheroniser Model 15; Calveva, Dorset, UK) and dried in a fluidized bed (ST 15; Aeromatic, Muttenz, Switzerland) at 40 °C for 30 min. The size fraction 0.7-1.0 mm was obtained by sieving.

Drug loaded pellet starter cores were coated with an aqueous dispersion of Eudragit RS 30 D, plasticized with 25 % w/w TEC (referred to the polymer content). The coating formulations were prepared as described in section 2.2. *Preparation of thin polymeric films* (including dilution to 15 % polymer content and 50 % talc addition prior to use). Pellets were coated in a fluidized bed coater, equipped with a Wurster insert (Strea 1; Aeromatic-Fielder, Bubendorf, Switzerland) until a weight gain of 5, 10, 15 or 20 % (w/w) was achieved. The process parameters were as follows: inlet temperature = 40 ± 2 °C, product temperature = 38 ± 2 °C, spray rate = 1.5-3 g/min, atomization pressure = 1.2 bar, nozzle diameter = 1.2 mm. Afterwards, the pellets were further fluidized for 10 min (without spraying any liquid) and subsequently cured in an oven for 24 h at 60 °C.

2.5. Pellet characterization

The in vitro release of metoprolol tartrate and of the free base from ensembles of coated pellets (approximately 80 mg) was measured under sink conditions upon exposure to 0.1 M HCl or phosphate buffer pH 7.4 (USP 40) at 37 °C as follows: Pellets were placed into 120 mL plastic containers, filled with 100 mL pre-heated release medium. The flasks were agitated in a horizontal shaker (80 rpm; GFL 3033). At pre-determined time points, 3 mL samples were withdrawn and analyzed by UV-spectrophotometry for their drug content ($\lambda = 274$ nm in 0.1 M HCl & phosphate buffer pH 7.4) (Shimadzu UV-1650). Each experiment was conducted in triplicate.

The water uptake of pellets was monitored gravimetrically. At pre-determined time point, ensembles of pellets (which were treated as for in vitro release studies) were withdrawn and their water content was determined as the water content of free films (described in section

2.3. *Film characterization*). Each experiment was conducted in triplicate.

The swelling behavior of pellets was monitored as follows: Pellets were placed into 2 mL vials (one pellet per vial), filled with pre-heated release medium, followed by horizontal shaking at 37°C (80 rpm; GFL 3033). At predetermined time points, pellets were withdrawn (excess of water was gently removed with precision wipes) and their diameter was measured in the wet state [*diameter (t)*] using an optical image analysis system (Nikon SMZ-U, Nikon, Tokyo, Japan), equipped with a Sony camera (Hyper HAD model SSC-DC38DP; Elvetec, Templemars, France). The increase in *pellet diameter (%)* at time *t* was calculated as follows:

$$\text{increase in pellet diameter } (\%) (t) = \frac{\text{diameter } (t) - \text{diameter } (0)}{\text{diameter } (0)} \cdot 100 \% \quad (3)$$

where *diameter (0)* is the pellet's diameter at time *t* = 0. Each experiment was conducted six times.

The distribution of the drug and plasticized polymer in the film coatings was monitored using a Renishaw InVia Raman spectrometer (Wotton-under-Edge Gloucestershire, UK), comprising a single-grating spectrograph coupled to an optical Leica microscope (DM 2500M, Leica, Wetzlar, Germany). The spectra of pure metoprolol free base, metoprolol tartrate, aqueous Eudragit RS 30 D dispersion and TEC were separately recorded in back scattering geometry, with a resolution of 2 cm⁻¹ in the 600 – 3800 cm⁻¹ frequency range with the acquisition time of 30 s. The 785 nm line of a Renishaw diode laser was used for the analysis of cross-sections of pellets, which were obtained by cutting with a scalpel. A “×100 objective” was applied, the analyzed volume was about 40 μm³ (maximum width ~ 1.4 μm, Δz ~ 25 μm). The direct classical least-squares (DCLS) method was used to find linear combinations of the spectra of the drug and the plasticized polymer that most closely matched the Raman spectra collected during the mapping of the pellet's cross-sections. Surfaces of 5 cross-sections of each sample type were analyzed using the hyper rapid streamline technology. About 4000 spectra

were collected by mapping, line by line with a step size of 1.1 μm . Typically, $70 \times 60 \mu\text{m}^2$ areas were scanned during about 3 h.

3. Results and discussion

3.1. Drug release from coated pellets

Figure 1 shows the experimentally determined drug release kinetics from pellets coated with 5-20 % Eudragit RS (plasticized with 25 % TEC). The release medium was 0.1 N HCl or phosphate buffer pH 7.4, as indicated. The starter cores were based on 90 % MCC and 10 % metoprolol tartrate (green curves) or metoprolol free base (black curves). For reasons of comparison, also drug release from uncoated pellets is shown. As expected, the release rate decreased with increasing coating level in all cases. Interestingly, also the following two unusual tendencies were observed:

1. Drug release was faster in the case of starter cores loaded with the free base compared to starter cores loaded with the tartrate, irrespective of the type of release medium and coating level. This is unexpected in the light of the solubility of the two drug forms in these media: Metoprolol tartrate is much more soluble than metoprolol free base in 0.1 N HCl and phosphate buffer pH 7.4: 368 vs. 4.8 g/100 mL and 356 vs. 2.5 g/100 mL (at 37 °C) (Glaessl et al. 2010a). These differences in drug solubility are remarkable and it could have been expected that the much higher solubility of the metoprolol tartrate in both media results in more rapid drug release compared to the free base. The observed opposite tendency can serve as a first indication that plasticizing effects of the drugs for the film coatings likely play an important role in these systems, overcompensating potential drug solubility effects: Metoprolol free base has been reported to be a more potent plasticizer for Eudragit RS than metoprolol tartrate (Glaessl et al., 2009).

2. Comparing the two diagrams in Figure 1, it becomes obvious that metoprolol release was faster in phosphate buffer pH 7.4 than in 0.1 N HCl, irrespective of the drug form (tartrate or free base) and coating level. Again, this contradicts the expectation in the light of the drug solubility at 37 °C: 2.5 vs. 4.8 g/100 mL for the free base in phosphate buffer pH 7.4 and 0.1 N HCl, and 356 vs. 368 g/100 mL for the free base in phosphate buffer pH 7.4 and 0.1 N HCl, respectively. Thus, again, other phenomena must play an important role and overcompensate potential drug solubility effects (please note that the latter were likely much less pronounced than those discussed above). This might include differences in the interactions of the Eudragit RS with the ions in the release media (Narisawa et al., 1994, 1996).

Note that in the case of *uncoated* pellets, no noteworthy differences were observed with respect to the type of release medium or drug form: In all cases, metoprolol release was rapid. This can be explained by the facts: (i) that sink conditions were provided throughout the experiments, and (ii) that the drug particles were in contact with very high amounts of water in these cases. To better understand the reasons for the above described unusual tendencies, the key properties of the coated pellets as well as of thin, free films of identical composition as the film coatings were determined, and dynamic changes thereof monitored upon exposure to the release media.

3.2. Water uptake and swelling kinetics of coated pellets and thin, free films

Figure 2a shows the water uptake kinetics of *ensembles* of pellets coated with 15 % Eudragit RS (plasticized with 25 % TEC) upon exposure to 0.1 N HCl or phosphate buffer pH 7.4. The pellet cores contained 10 % metoprolol tartrate or free base. As it can be seen, there were no fundamental differences in the water uptake rates: In all cases, an initial rapid uptake was observed, followed by a phase with an about constant uptake rate during at least 8 h, irrespective of the drug form (tartrate or free base) and release medium. The shape of these profiles might be explained as follows: Initially, the film coatings are dry, so they can take up

relatively high amounts of water. Once the polymeric membranes are wetted, the subsequent water penetration into the systems is determined by a high water excess outside (in the surrounding bulk fluid) and partially remaining dry material within the pellets' cores. These conditions likely remain unchanged during the observation period, leading to about constant water uptake rates.

Figure 2b shows the changes in the diameter of the pellets upon exposure to 0.1 N HCL and phosphate buffer pH 7.4, respectively. Again, the pellet cores contained 10 % metoprolol tartrate or free base, and the coating level was 15 %. As it can be seen, there were no fundamental differences between the systems, which is consistent with the above discussed water uptake kinetics. Also, no indications for crack formation were observed (like sudden leveling off of swelling profiles of *single* pellets, data not shown). Consequently, potential differences in the water uptake and swelling kinetics of the coated pellets can probably be ruled out as possible explanation for the above described pronounced effects of the drug form (tartrate vs. free base) and type of release medium on metoprolol release.

3.3. Mechanical properties, water uptake and TEC leaching of/from thin free films

Figure 3a shows the “% elongation at break” of thin films of identical composition as the film coatings surrounding the drug loaded pellet starter cores as a function of the exposure time to phosphate buffer pH 7.4, optionally containing 30 % metoprolol tartrate or free base. Please note that the experiments were conducted at 37 °C and that the films were in the wet state (to mimic the conditions encountered during drug release). Clearly, in all cases an initial increase in film flexibility was observed, followed by a decline after about 0.5-1 h, and plateaus were attained after about 2-4 h. The initial increase in film flexibility can be explained by the fact that water acts as an efficient plasticizer for Eudragit RS (Glaessl et al. 2010b) (and that high amounts of water are taken up at early time points, Figure 2a). The subsequent decrease in film flexibility can be explained by the fact that the water soluble plasticizer TEC at least

partially leaches out into the release medium: Figure 4 shows for instance the TEC loss of Eudragit RS films plasticized with 25 % TEC upon exposure to 0.1 N HCl containing 1 % metoprolol free base or tartrate. As it can be seen, at least half of the TEC content was lost into the medium after only 2 h. Please note that these TEC leaching experiments were conducted in diffusion cells with free films exhibiting a thickness of about 300 μm . Since these films were much thicker than those surrounding the pellet starter cores, TEC leaching can be expected to be even faster from the coated pellets. This plasticizer loss can explain the decrease in film flexibility observed after 1-2 h upon exposure to the release medium (Figure 3a).

Once the plasticizer loss levelled off (Figure 4), the film composition remained about constant, and the “% elongation values at break” reached plateau values (Figure 3a). The differences in these plateau values might be explained as follows: In the case of metoprolol free base, the plasticizing effect of the drug is highest: It has previously been shown that metoprolol free base more efficiently plasticizes Eudragit RS than metoprolol tartrate, probably because of important interactions with the polymer backbone (Glaessl et al. 2010a,b). The fact that the Eudragit RS films were least flexible upon exposure to phosphate buffer pH 7.4 containing 30 % metoprolol tartrate can likely be attributed to the fact that these films exhibited the lowest water contents: Figure 3b shows for instance the water contents of Eudragit RS films (initially containing 25 % TEC) after 4 h exposure to phosphate buffer pH 7.4, optionally containing 30 % metoprolol free base or tartrate. As it can be seen, the water content is lowest in the case of the tartrate, eventually at least partially due to the highest osmolality of this release medium (slowing down water penetration into the films). Comparing Figures 3a and 3b, it seems that the flexibility of the Eudragit RS films in the plateau phases is primarily determined by their water contents. Since metoprolol free base is an efficient plasticizer for Eudragit RS, the respective polymeric networks are most easily expandable and can take up the highest amounts of water. Furthermore, the observation that *during the first hour* the flexibility of Eudragit RS films was higher upon exposure to phosphate buffer pH 7.4 free of drug compared to phosphate

buffer pH 7.4 containing 30 % metoprolol free base (grey versus black curve in Figure 3a) can probably be explained by the fact that the films were initially drug free and it took some time for the free base to diffuse into the polymeric membranes under the given experimental conditions.

The results obtained with these film flexibility and water uptake studies (performed with thin, free films of identical composition as the film coatings) can, thus, very much help to better understand the unexpected drug release tendencies observed with coated pellets in the light of the drug's solubility: The fact that metoprolol free base is a much more potent plasticizer for Eudragit RS results in more flexible films with higher water contents and higher drug permeability.

3.4. Impact of the initial drug content on metoprolol release from pellets

If the above described plasticizing effects are of fundamental importance for the control of drug release, also the impact of the initial drug loading on the resulting drug release rates might eventually be unusual: Often, increasing initial drug loadings of polymer coated pellets lead to decreasing relative drug release rates. This is because the amount of water available within the pellet cores might not be sufficient to immediately dissolve the entire drug dose (at least at early time points). Consequently, dissolved drug and non-dissolved drug co-exist during a certain time period. Importantly, only dissolved drug is available for diffusion (Siepmann and Siepmann, 2008, 2012). Hence, an increase in the initial drug loading does not increase the resulting concentration gradient of *dissolved* drug (the driving force for drug diffusion), leading to about constant absolute drug release rates. But the 100 % reference value increases. Consequently, the *relative* drug release rate generally decreases with increasing initial drug content. Figure 5 shows that the opposite trend was observed in the present study: The drug release rates from Eudragit RS coated pellets loaded with 10 to 40 % metoprolol tartrate or metoprolol free base in 0.1 N HCl and phosphate buffer pH 7.4 are shown. In all cases, the

relative drug release rate increased with increasing drug loading. This clearly indicates the tremendous importance of plasticizing effects in the investigated systems: For both drug forms (metoprolol free base and metoprolol tartrate) the above described potential limited drug solubility effects are overcompensated by the fact that metoprolol is an efficient plasticizer for Eudragit RS: The higher the drug loading, the more pronounced the plasticization of the film coating, resulting in increased drug permeability and increased absolute and relative drug release rates. Please note that the importance of the increase in the relative drug release rate with increasing initial drug content is roughly similar for metoprolol tartrate and the free base, although the free base is a much more potent plasticizer for the polymer compared to the tartrate. This can be explained by the fact that the limited solubility effects can be expected to be much more important in the case of the free base compared to the tartrate [which is much more soluble: 368 vs. 4.8 g/100 mL and 356 vs. 2.5 g/100 mL (at 37 °C) in 0.1 N HCl and phosphate buffer pH 7.4, respectively (Glaessl et al. 2010a)].

3.5. Importance of diffusional mass transport

Due to the considerable flexibility of the investigated Eudragit RS film coatings, plasticized by TEC, water and the drug, diffusional mass transport through *intact* film coatings likely plays a major role for the control of metoprolol release from the investigated systems (Siepmann and Siepmann, 2012). Also, as discussed above, the pellet swelling studies did not reveal any sign for crack formation in the film coatings upon exposure to the release media. Hence, an appropriate solution of Fick's second law of diffusion should be able to describe the experimentally observed drug release kinetics in a quantitative manner (Siepmann and Siepmann, 2008, 2012). In the present case, the delivery system is spherical in shape, and a drug reservoir is surrounded by a release rate controlling membrane. Furthermore, sink conditions were maintained throughout the experiments.

The importance of limited drug solubility effects within the core depends on the initial drug loading and drug solubility in the core. Considering for example the case of metoprolol

free base, a drug loading of 10 % and 0.1 N HCl as release medium, the drug solubility in the pellet's core might be *very roughly* estimated to be in the same order of magnitude as the solubility in the release medium at 37 °C. Please note that this is a *simplification*, because the composition of the liquid in the pellet's core is not identical to the composition of the release medium. Furthermore, other compounds (e.g., TEC) are co-dissolved and might eventually alter the drug's solubility. Unfortunately, it is generally very difficult to precisely measure the exact solubility of the drug in the system's core, and this solubility might also change with time (due to changes in the core's composition). In this example, the solubility of the free base in 0.1 N HCl at 37 °C is 4.8 g/100 mL (Glaessl et al., 2010a). Thus, the solubility is *very roughly* in the same order of magnitude as the considered initial drug loading (10 %). Hence, it might be assumed that all drug is rapidly dissolved in this case *to keep the mathematical treatment simple*. Under these conditions/assumptions, the following equation can be derived from Fick's second law of diffusion, quantifying drug release from this type of coated pellets (Siepmann and Siepmann, 2012):

$$M_t = M_\infty \cdot \left[1 - \exp\left(-\frac{ADKt}{Vl}\right) \right] \quad (4)$$

where M_t denotes the absolute cumulative amount of drug released from a pellet at time t ; $M_{infinity}$ is the total drug amount released at infinity time; A represents the total surface area of the pellet, D the *apparent* diffusion coefficient of the drug in the polymeric film coating, K the partition coefficient of the drug between the film coating and the bulk fluid (considering the simplification that the liquid in the pellet's core was similar to the release medium), V is the volume of the pellet's core, and l the thickness of the film coating.

The parameters M_t , A , K , V and l were directly measurable (or could be easily calculated). But the apparent diffusion coefficient of the drug in the film coating, D , was initially unknown. However, it could be determined by *fitting* Equation 4 to a set of

experimentally measured drug release kinetics from pellets loaded with 10 % metoprolol free base, coated with 5 % Eudragit RS (plasticized with 25 % TEC) in 0.1 N HCl (in this case K was equal to 6.36). The upper curve in Figure 6 shows this fitting, the respective experimental results are represented by the open squares. As it can be seen, good agreement between theory and experiment was obtained, but please note that this is not a real proof for the validity of the above described simplified hypotheses, since one model parameter was adjusted to minimize deviations. Based on these calculations, the following value was determined for the apparent diffusion coefficient of metoprolol free base in Eudragit RS film coatings (plasticized with 25 % TEC) upon exposure to 0.1 N HCl: $D = 6.7 \times 10^{-10} \text{ cm}^2/\text{s}$. It has to be pointed out that this parameter was determined with an initial drug content of 10 % in the pellet's core. It is likely that it depends on the initial drug content in this case (please see discussion above). Once this parameter was known, Equation 4 could be used to predict the impact of different formulation parameters (e.g., of the coating level) on the resulting drug release kinetics. However, in the present case, an additional phenomenon was of importance, which is not taken into account by Equation 4: At higher coating levels, drug release leveled off below 100 % (symbols in Fig. 6). This might be due to significant drug - polymer interactions. With increasing coating level, more polymer is present, increasing the importance of this effect. For this reason, the plateau values were experimentally determined as a function of the coating level. Knowing the D and M_{∞} values, Equation 4 was used to theoretically predict the resulting metoprolol release kinetics from pellets containing 10 % free base, coated with 10, 15 or 20 % Eudragit RS (plasticized with 25 % TEC) in 0.1 N HCl. These theoretical predictions are illustrated by the three lower curves in Figure 6. As it can be seen, rather good agreement was obtained between the theoretical predictions (curves) and the experiments (symbols) in all cases. However, it has again to be emphasized that the plateau values for drug release were determined experimentally as a function of the coating level.

It has to be pointed out that the above discussed plasticizing effects of the drug for the film coating do not change the fundamental underlying drug release mechanism (it remains diffusion), but these plasticizing effects strongly alter the permeability of the film coatings. In other words, the conditions for drug diffusion through the polymeric barrier are affected by the drug itself. These strong plasticizing effects even overcompensated well known drug solubility effects, as discussed above. Please note that an exact mathematical analysis should take into account the plasticizing effects of the drug on the film coating, TEC leaching into the bulk fluid, potential limited drug solubility effects as well as system swelling. But such an analysis was beyond the scope of this study.

3.6. Drug concentration profiles in the film coatings

To further evaluate the importance of the plasticizing effects of the drug for the film coatings, Raman imaging was used to get deeper insight into the inner structure of the polymeric barriers, in particular addressing the question whether metoprolol might potentially be able to migrate into the Eudragit RS membranes to a noteworthy extent before exposure to the release medium (during production and/or storage).

Raman images of cross-sections through film coatings based on Eudragit RS (plasticized with 25 % TEC) were obtained using a Renishaw InVia Raman spectrometer (before exposure to the release medium). The Raman spectra of the raw materials (metoprolol free base, metoprolol tartrate, Eudragit RS 30 D aqueous dispersion and TEC) are shown in Figure 7. Please note that the spectra of metoprolol free base and metoprolol tartrate are superimposed in the investigated range. Importantly, the drug on the one hand side, and the polymer & plasticizer on the other hand side, showed unambiguous, preponderant and separate contributions in the 1500-1800 cm^{-1} region. Consequently, during the Raman mapping of the cross-sections of the pellets this spectral range was used, allowing to distinguish between “metoprolol” and “Eudragit RS-TEC”. Figure 8 shows two examples for Raman images

obtained with parts of the cross-sections of pellets coated with 20 % Eudragit RS (plasticized with 25 % TEC): The picture at the top shows a pellet loaded with metoprolol free base, the picture at the bottom a pellet loaded with metoprolol tartrate. The blue color indicates domains, which were rich in Eudragit RS-TEC, the red color indicates domains rich in drug. The white frames are located at the pellets' surfaces. As it can be seen, the thickness of the coatings varied, which is consistent with results obtained using other imaging techniques (e.g., Terahertz pulsed imaging) and other types of coated pellets (Haaser et al., 2013a,b). It confirms that polymeric film coatings surrounding drug loaded cores, obtained using commonly used manufacturing techniques, are not very homogeneous with respect of their thickness. Importantly, comparing the two images in Figure 8, it can be seen that the interface “film coating – pellet core” seems to be much sharper in the case of metoprolol tartrate compared to metoprolol free base.

To be able to plot *drug concentration – distance profiles* across the film coatings, the relative contributions of metoprolol and Eudragit RS-TEC were estimated in $5 \times 5 \mu\text{m}^2$ squares, as schematically illustrated by the white frames in Figure 8. A series of such squares was measured along the dashed arrows indicated in the images, going from the pellets' surfaces to the pellets' cores. Using the DCLS method the “drug/Eudragit RS-TEC” concentration ratios were estimated. Figure 9 shows the obtained results as a function of the distance from the pellets' surfaces. Clearly, a steep concentration gradient was observed in the case of metoprolol tartrate loaded pellets at a distance of about 20-30 μm from the surface (green symbols). This is the interface “film coating - pellet core”. Within the polymeric coating (at distances below 20 μm from the surface), the drug levels were close to zero. In other words: The Eudragit RS membrane was almost free of drug. In contrast, an about linear drug concentration gradient across the entire film coating was observed in the case of metoprolol free base (black symbols). Thus, important amounts of the free base migrated into the film coating. This reflects the high affinity of metoprolol free base to Eudragit RS, which is consistent with the high potency of this drug to act as a plasticizer for this polymer (as discussed above).

Please note that the coating thicknesses were different in the investigated regions of the cross-sections: In the case of metoprolol tartrate loaded pellets, the coating was thinner than in the case of metoprolol free base loaded pellets in Figure 9. This is also visible in the Raman images in Figure 8 (the concentration - distance profiles were obtained along the white arrows). Furthermore, the linearity of the drug concentration - distance profile across the film coating in the case of metoprolol free base suggests that drug migration probably occurred mainly during production (and not during storage), when the aqueous Eudragit RS dispersion was sprayed onto the pellets' surfaces: Initially, higher amounts of drug could dissolve (since the water of the coating dispersion was directly in contact with the drug in the starter core) and diffuse into the coating (which was not yet dry). But with time an increasingly thicker polymeric film separated the aqueous formulation (that was continuously sprayed onto the pellets' surfaces) from the drug loaded core, and the distance between the new surface of the coating to the drug reservoir increased. Hence, the amount of drug that could dissolve in the water decreased, and the length of the diffusion pathways to be overcome by drug migrating from the core to the "newly added" outer layers of the film coating increased. Both effects result in decreasing drug concentrations towards the surface. Also, note that if the observed drug migration into the coating would have occurred *during storage*, a different type of drug concentration distance profile would be expected: a curve shaped profile before equilibrium is reached, and a plateau (homogeneously saturated polymeric membrane) once equilibrium is reached (Crank, 1975).

In summary, Raman imaging clearly revealed that metoprolol free base substantially migrated into the polymeric film coating, whereas metoprolol tartrate did not. This is due to the different affinities of the two drug forms to Eudragit RS and consistent with the above described differences in their potency to plasticize the polymeric barriers.

4. Conclusions

If drugs act as plasticizers for controlled release polymeric films coatings, unusual tendencies might be observed, such as increasing relative drug release rates when increasing the initial drug loading. Also, substantial differences in the drug's solubility in the release medium might be overcompensated by such plasticizing effects, resulting in unexpected effects of formulation parameters on drug release. Furthermore, important amounts of the drug might migrate into the polymeric barriers during manufacturing. These unusual behaviors should be taken into account during product optimization.

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References

- Andersson, H., Haebel, H., Olsson, A., Sandhagen, S., Von Corswant, C., Hjaertstam, J., Persson, M., Stading, M., Larsson A., 2016. The influence of the molecular weight of the water-soluble polymer on phase-separated films for controlled release. *Int. J. Pharmaceut.* 511, 223-235.
- Bodmeier, R., Paeratakul, O., 1991. Determination of plasticizers commonly used in pharmaceutical dosage forms by high performance liquid chromatography. *J. Liq. Chromatogr.* 14, 365-375.
- Crank, J. (Ed.), 1975. *The Mathematics of Diffusion*. Clarendon Press, Oxford.
- Cuppok, Y., Muschert, S., Marucci, M., Hjaertstam, J., Siepmann, F., Axelsson, A., Siepmann J., 2011. Drug release mechanisms from Kollicoat SR:Eudragit NE coated pellets. *Int. J. Pharmaceut.* 409, 30-37.
- Dodoo, C.C., Wang, J., Basit, A.W., Stapleton, P., Gaisford, S., 2017. Targeted delivery of probiotics to enhance gastrointestinal stability and intestinal colonization. *Int. J. Pharmaceut.* 530, 224-229.
- Fahier, J., Muschert, S., Fayard, B., Velghe C., Byrne, G., Doucet, J., Siepmann, F., Siepmann J., 2016. Importance of air bubbles in the core of coated pellets: Synchrotron X-ray microtomography allows for new insights. *J. Controlled Release* 237, 125-137.
- Gasmi, H., Danede, F., Siepmann, J., Siepmann, F., 2015a. Does PLGA microparticle swelling control drug release? New insight based on single particle swelling studies. *J. Controlled Release* 213, 120-127.
- Gasmi, H., Willart, J.F., Danede, F., Hamoudi, M.C., Siepmann, J., Siepmann, F., 2015b. Importance of PLGA microparticle swelling for the control of prilocaine release. *J. Drug Deliv. Sci. Technol.* 30, 123-132.
- Gauno, M.H., Vilhelmsen, T., Larsen, C.C., Boetker, J.P., Wittendorff, J., Rantanen, J., Ostergaard, J., 2013. Real-time in vitro dissolution of 5-aminosalicylic acid from single

- ethyl cellulose coated extrudates studied by UV imaging. *J. Pharm. Biomedical. Analysis* 83, 49-56.
- Glaessl, B., Siepmann, F., Tucker, I., Siepmann, J., Rades, T., 2009. Characterisation of quaternary polymethacrylate films containing tartaric acid, metoprolol free base or metoprolol tartrate. *Eur. J. Pharm. Biopharm.* 73, 366-372.
- Glaessl, B., Siepmann, F., Tucker, I., Rades, T., Siepmann, J., 2010a. Deeper insight into the drug release mechanisms in Eudragit RL-based delivery systems. *Int. J. Pharmaceut.* 389, 139-146.
- Glaessl, B., Siepmann, F., Tucker, I., Rades, T., Siepmann, J., 2010b. Mathematical modeling of drug release from Eudragit RS-based delivery systems. *J. Drug Deliv. Sci. Technol.* 20, 127-133.
- Haaser, M., Gordon, K.C., Strachan, C.J. Rades, T. 2013a. Terahertz pulsed imaging as an advanced characterisation tool for film coatings- A review. *Int. J. Pharmaceut.* 457, 510-520.
- Haaser, M., Karrout, Y., Velghe, C., Cuppok, Y., Gordon, K.C., Pepper, M., Siepmann, J., Rades, T., Taday, P.F., Strachan, C.J., 2013b. Application of terahertz pulsed imaging to analyse film coating characteristics of sustained-release coated pellets. *Int. J. Pharmaceut.* 457, 521-526.
- Kaunisto, E., Marucci, M., Borgquist, P., Axelsson, A., 2011. Mechanistic modelling of drug release from polymer-coated and swelling and dissolving polymer matrix systems. *Int. J. Pharmaceut.* 418, 54-77.
- Kazlauske, J., Gardebjer, S., Almer, S., Larsson, A., 2017a. The importance of the molecular weight of ethyl cellulose on the properties of aqueous-based controlled release coatings. *Int. J. Pharmaceut.* 519, 157-164.

- Kazlauske, J., Cafaro, M.M., Caccavo, D., Marucci, M., Lamberti, G., Barba, A.A., Larsson, A., 2017b. Determination of the release mechanism of Theophylline from pellets coated with Surelease- A water dispersion of ethyl cellulose. *Int. J. Pharmaceut.*, 528, 345-353.
- Kolter, K., Dashevsky, A., Irfan, M., Bodmeier, R., 2013. Polyvinyl acetate-based film coatings. *Int. J. Pharmaceut.* 457, 470-479.
- Lopez, E.V., Alvarez, A.L., Méndez, J.B., Otero Espinar, F.J., 2017. Cellulose-polysaccharide film-coating of cyclodextrin based pellets for controlled drug release. *J. Drug Deliv. Sci. Technol.* 42, 273-283.
- Macchi, E., Zema, L., Maroni, A., Gazzaniga, A., Felton L.A., 2015. Enteric-coating of pulsatile-release HPC capsules prepared by injection molding. *Eur. J. Pharm. Sci.* 70, 1-11.
- Maroni, A., Zema, L., Loreti, G., Palugan, L., Gazzaniga, A., 2013a. Film coatings for oral pulsatile release. *Int. J. Pharmaceut.* 457, 362-371.
- Maroni, A., Dorly Del Curto, M., Zema, L., Foppoli, A., Gazzaniga, A., 2013b. Film coatings for oral colon delivery. *Int. J. Pharmaceut.* 457, 372-394.
- Maroni, A., Zema, L., Cerea, M., Foppoli, A., Palugan, L., Gazzaniga A., 2016. Erodible drug delivery systems for time-controlled release into the gastrointestinal tract. *J. Drug Deliv. Sci. Technol.* 32, 229-235.
- Marucci, M., Ragnarsson, G., Nilsson, B., Axelsson, A., 2010. Osmotic pumping release from ethyl-hydroxypropyl-cellulose-coated pellets: A new mechanistic model. *J. Controlled Release* 142, 53-60.
- Narisawa, S., Nagata, M., Danyoshi, C., Yoshino, H., Murata, K., Hirakawa, Y., Noda. K., 1994. An organic acid-induced sigmoidal release system for oral controlled-release preparations. *Pharm. Res.* 11, 111-6.
- Narisawa, S., Nagata, M., Hirakawa, Y., Kobayashi, M., Yoshino, H., 1996. An organic acid-induced sigmoidal release system for oral controlled-release preparations. 2.

- Permeability enhancement of Eudragit RS coating led by the physicochemical interactions with organic acid. *J. Pharm. Sci.* 85, 184-8.
- Nollenberger, K., Albers, J., 2013. Poly(meth)acrylate-based coatings. *Int. J. Pharmaceut.* 457, 461-469.
- Palugan, L., Cerea, M., Zema, L., Gazzaniga, A., Maroni, A., 2015. Coated pellets for oral colon delivery. *J. Drug Deliv. Sci. Technol.* 25, 1-15.
- Siepmann, F., Le Brun, V., Siepmann, J., 2006. Drugs acting as a plasticizers in polymeric systems: A quantitative treatment. *J. Controlled Release* 115, 298-306.
- Siepmann, F., Hoffmann, A., Leclercq, B., Carlin, B., Siepmann, J., 2007. How to adjust desired drug release patterns from ethylcellulose-coated dosage forms. *J. Controlled Release* 119, 182-189.
- Siepmann, F., Siepmann, J., Walther, M., MacRae, R.J., Bodmeier, R., 2008. Polymer blends for controlled release coatings. *J. Controlled Release* 125, 1-15.
- Siepmann, J. and Siepmann, F., 2008. Mathematical modeling of drug delivery. *Int. J. Pharmaceut.* 364, 328-343.
- Siepmann, J., Siepmann, F., 2012. Modeling of diffusion controlled drug delivery. *J. Controlled Release* 161, 351-362.
- Varum, F.J.O., Hatton, G.B., Freire, A.C., Basit A.W., 2013. A novel coating concept for ileo-colonic drug targeting: Proof of concept in humans using scintigraphy. *Eur. J. Pharm. Biopharm.* 84, 573-577.
- Wu, C., McGinity, J. W., 1999. Non-traditional plasticization of polymeric films. *Int. J. Pharmaceut.* 177, 15-27.

Figure captions

Fig. 1: Release kinetics of metoprolol free base (black curves) and metoprolol tartrate (green curves) from Eudragit RS coated pellets in 0.1 N HCl and phosphate buffer pH 7.4 (10 % initial drug loading, coating levels are indicated in the diagram) (n = 3).

Fig. 2: Pellet swelling upon exposure to 0.1 N HCl or phosphate buffer pH 7.4: (a) Water uptake kinetics (n = 3), and (b) dynamic changes in the pellets' diameter (n = 6). The pellets were loaded with metoprolol tartrate (green curves) or metoprolol free base (black curves), and coated with 15 % Eudragit RS (10 % initial drug loading).

Fig. 3: (a) Dynamic changes in the elongation at break (%) of thin, free Eudragit RS films in the wet state at 37 °C upon exposure to phosphate buffer pH 7.4, optionally containing 30 % metoprolol tartrate or metoprolol free base. The first time point was 10 s. (b) Water content of the films after 4 h exposure to the bulk fluids.

Fig. 4: Triethyl citrate leaching from Eudragit RS films into 0.1 M HCl (37 °C) containing 1 % metoprolol tartrate or metoprolol free base.

Fig. 5: Impact of the initial metoprolol loading (tartrate or free base; indicated in the diagrams) on drug release from pellets coated with 20 % Eudragit RS in 0.1 N HCl and phosphate buffer pH 7.4.

Fig. 6: Experiment (symbols) and theory (curves, Equation 4): Release kinetics of metoprolol (free base) from pellets coated with 5-20 % Eudragit RS in 0.1 N HCl (the coating level is indicated in the diagram; 10% initial drug loading).

Fig. 7: Raman spectra of the drug (solid black curve), Eudragit RS (dashed black curve) and TEC (solid grey curve). The spectra of metoprolol tartrate and of the free base were superimposed. The rectangles highlight the Raman bands used to generate the images in Figure 8, and the drug concentration distance profiles in Figure 9.

Fig. 8: Raman images of parts of the cross-sections of pellets loaded with metoprolol free base or metoprolol tartrate, and coated with 20 % Eudragit RS (plasticized with 25 % TEC). The images were obtained using the DCLS (Direct Classical Least-Squares) method, which was applied to spectra collected by mapping the cross-sections. The frames represent the domain sizes, in which relative drug concentrations were estimated (along the dashed arrows). The blue color indicates domains, which were rich in Eudragit RS-TEC, the red color indicates domains rich in drug.

Fig. 9: Drug concentration - distance profiles across the investigated Eudragit RS coatings (plasticized with TEC) surrounding starter cores loaded with metoprolol tartrate or metoprolol free base. The results were obtained based on a quantitative assessment of $5 \times 5 \mu\text{m}^2$ squares along the arrows shown in the Raman images in Figure 8.

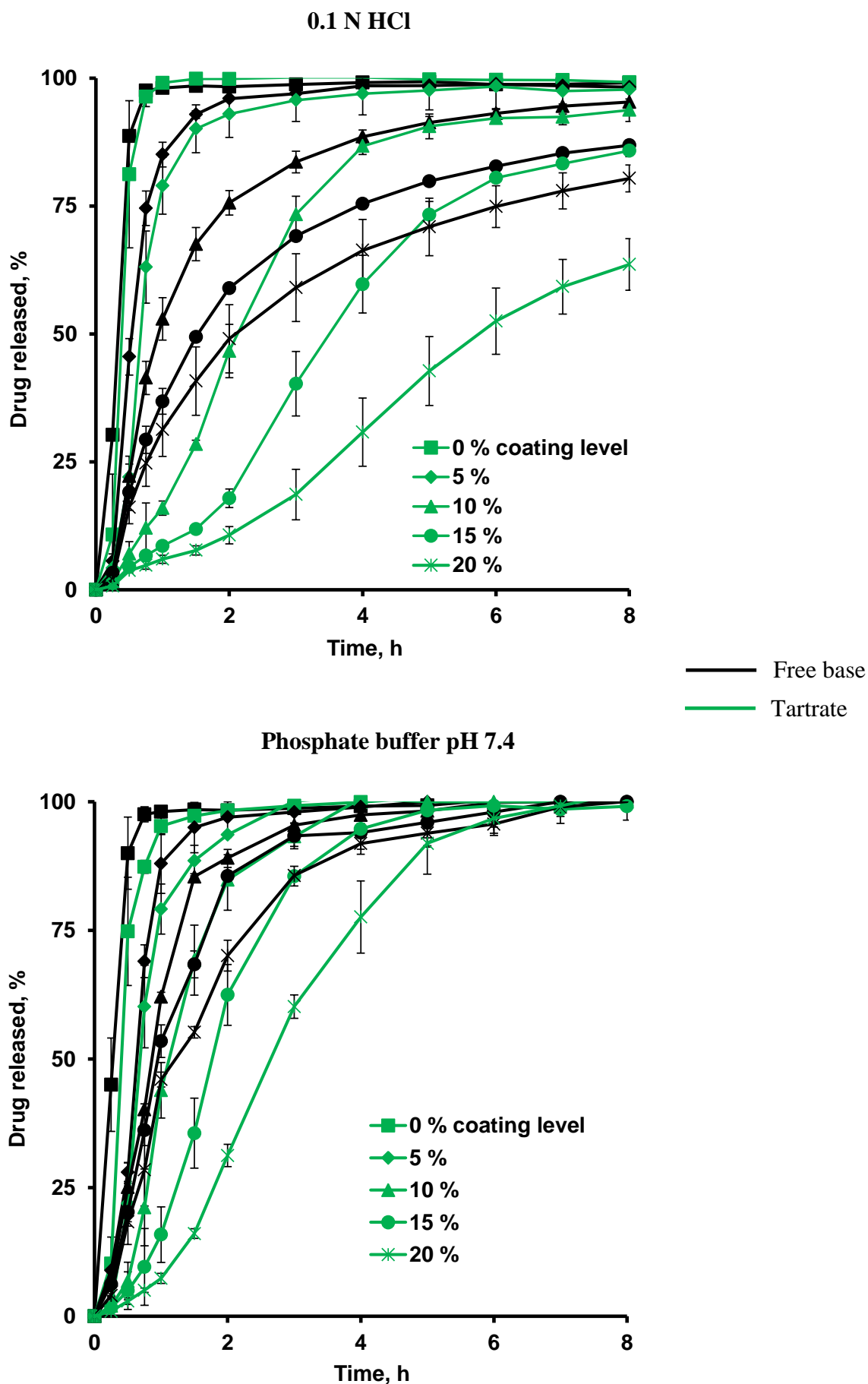


Figure 1

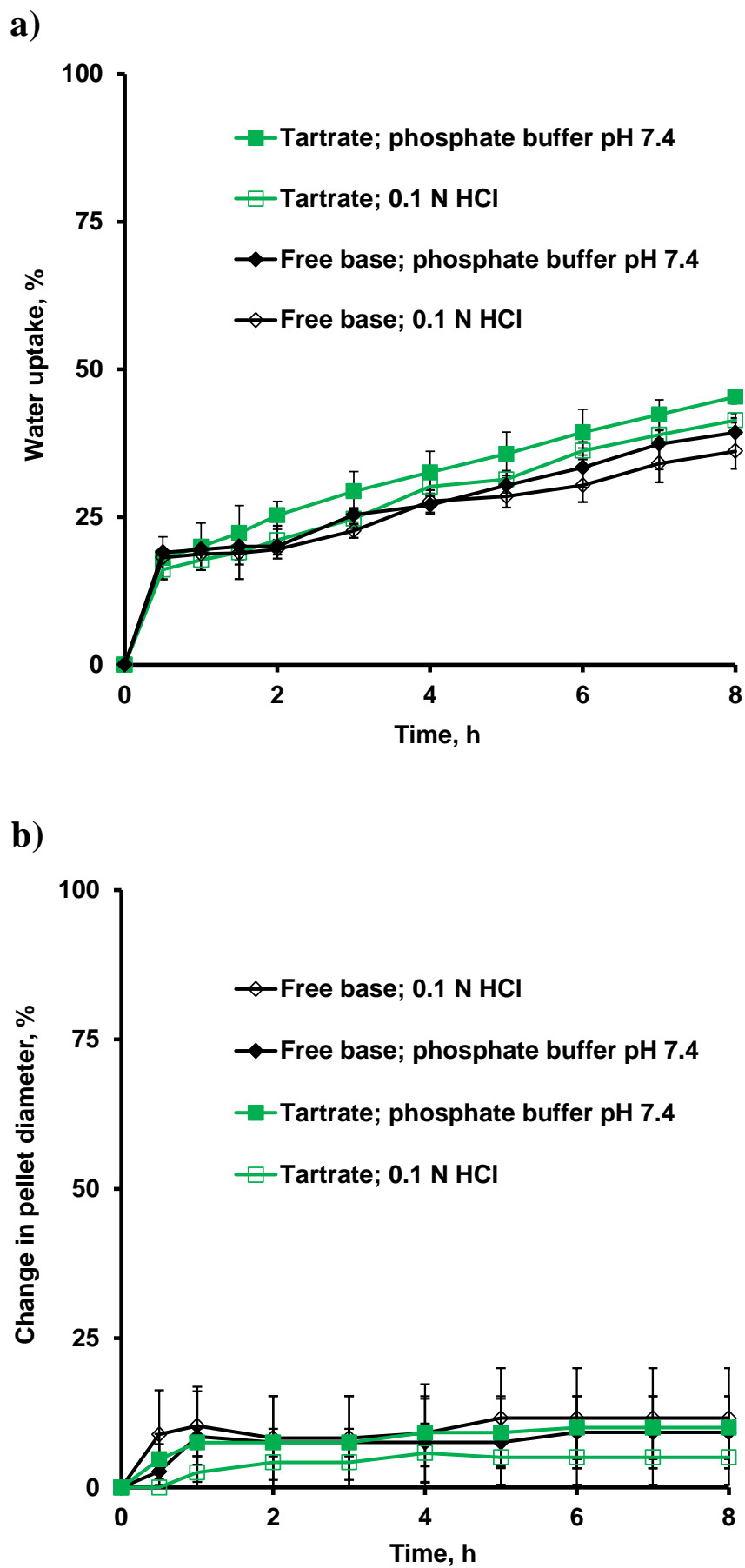


Figure 2

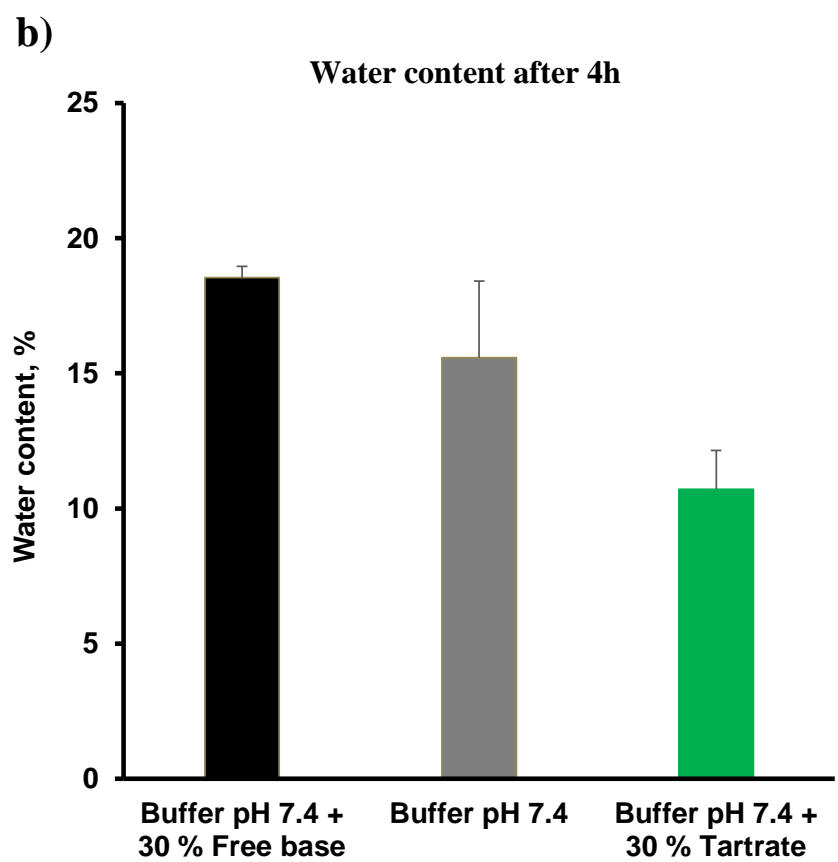
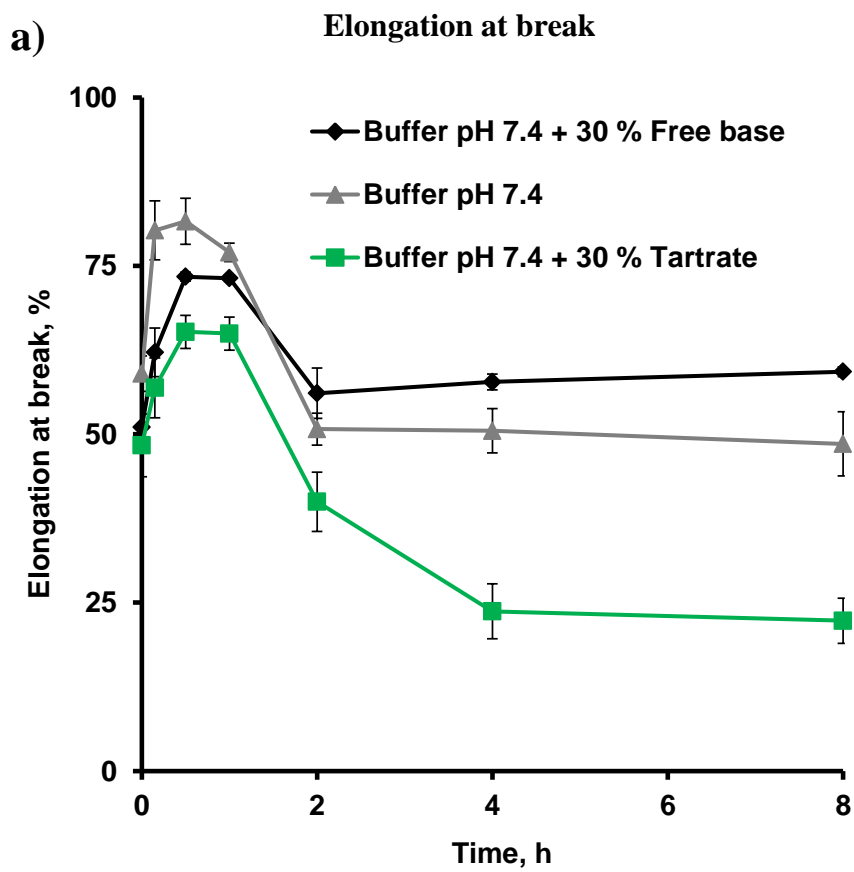


Figure 3

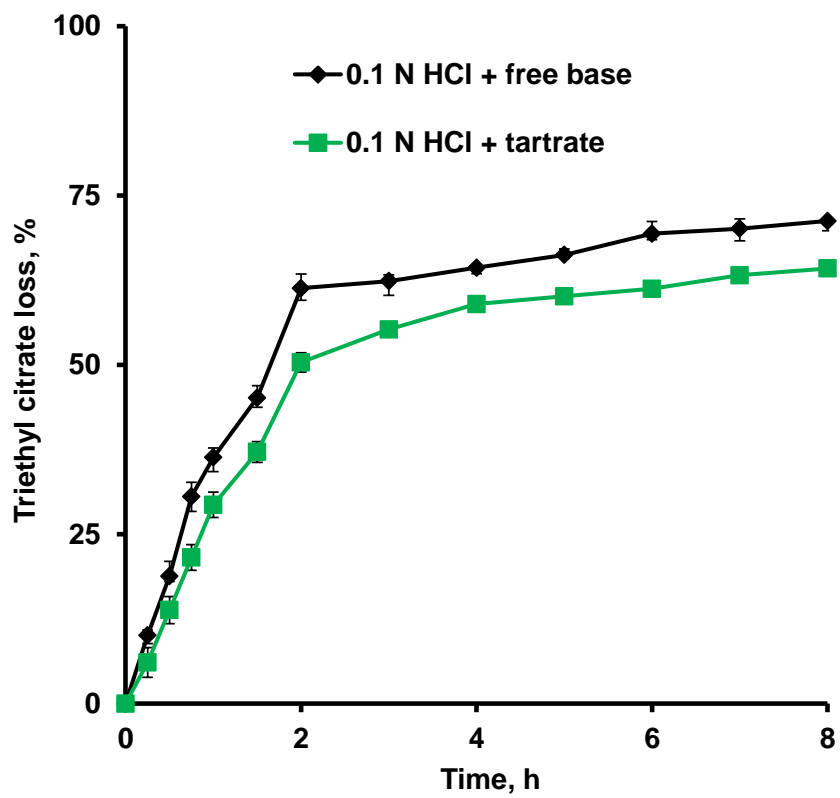


Figure 4

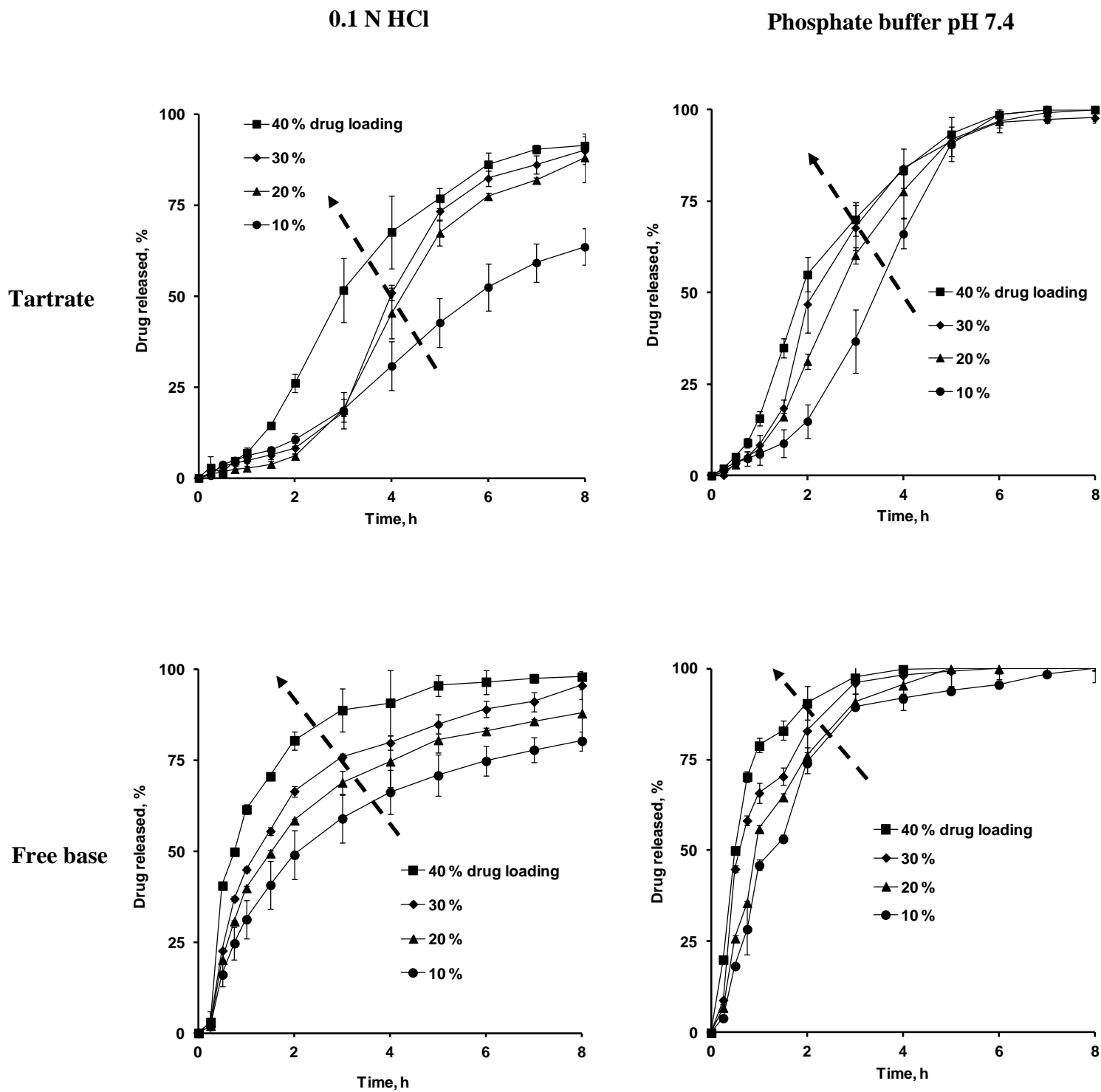


Figure 5

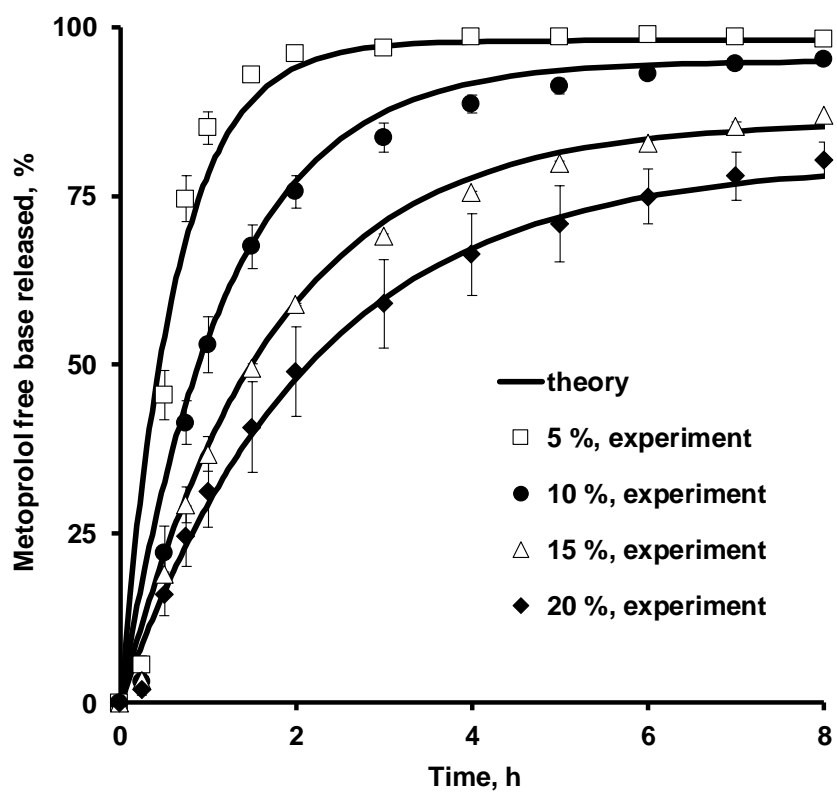


Figure 6

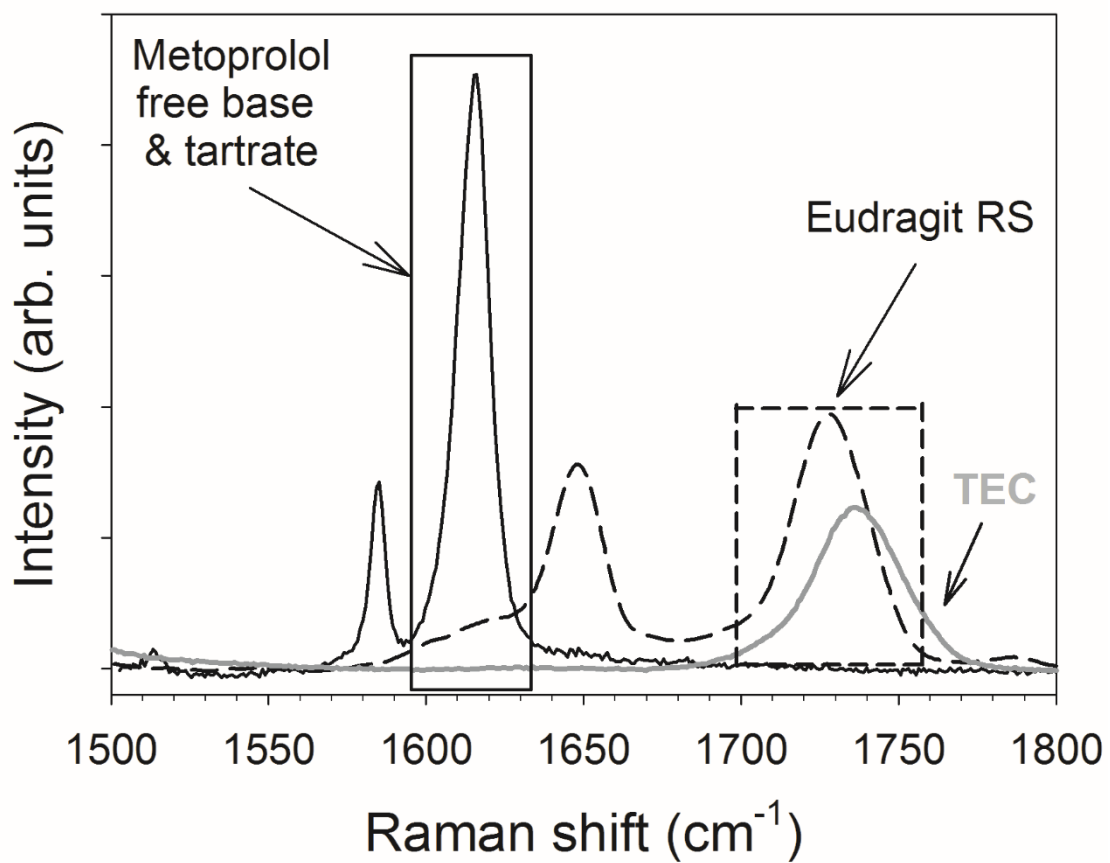


Figure 7

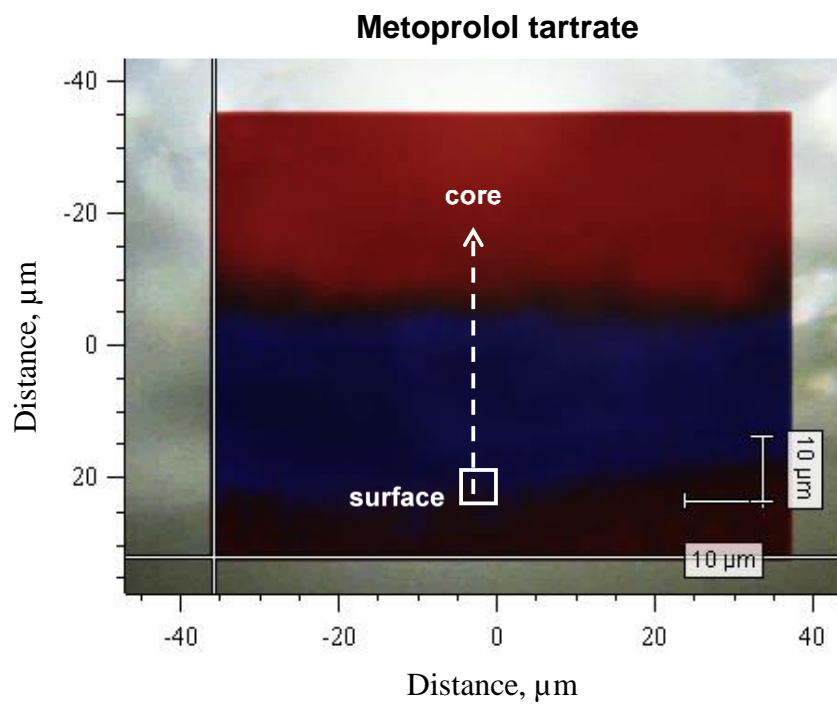
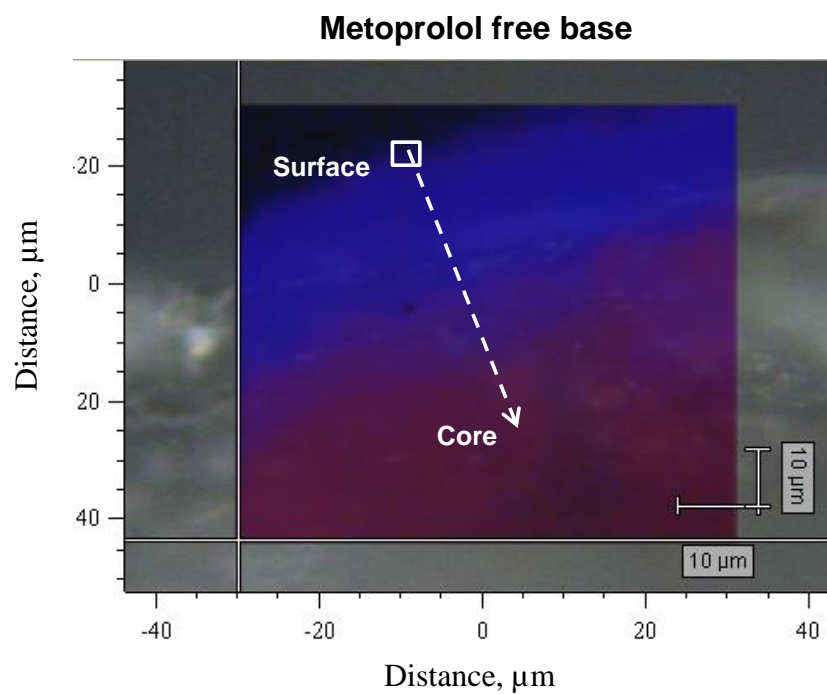


Figure 8

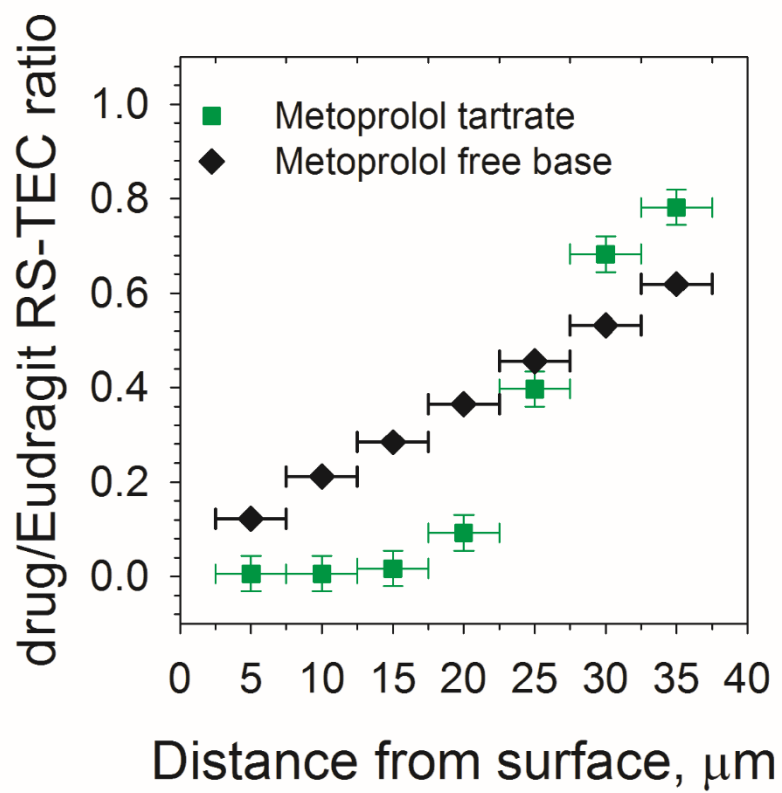


Figure 9