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Research paper

Characterisation of quaternary polymethacrylate films containing tartaric acid, metoprolol free base or metoprolol tartrate

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ABSTRACT

The aim of this study was to better understand the interactions between metoprolol tartrate and quaternary polymethacrylate (Eudragit RL and Eudragit RS) films. For reasons of comparison, polymeric films containing the free base metoprolol or free tartaric acid were also prepared. Systems containing various amounts of the free base, free acid and the salt were characterised using polarising light microscopy, X-ray powder diffraction, differential scanning calorimetry and mechanical analysis (puncture test). The free base is the most efficient plasticiser of the three species for Eudragit RL and Eudragit RS, but with limited solubility in the polymers. Due to its hydrophobicity, it can interact with the hydrophobic polymer backbones. In contrast, in salt containing films, ionic interactions between the positively charged quaternary ammonium groups and the negatively charged tartrate anions apparently occur, this being suggested by the different effects on Eudragit RL versus RS, which have different contents of quaternary ammonium groups. Importantly, the combination of acid and base as a salt avoids drug precipitation at higher metoprolol contents. The obtained new insight into the occurring drug–polymer interactions can help to facilitate the development/optimisation of this type of dosage forms.

1. Introduction

For the coating of oral controlled drug delivery systems, acrylic resins in the form of methacrylic ester copolymers with quaternary ammonium groups are frequently used, and are available under the trade names Eudragit RL and Eudragit RS. These polymers form water-insoluble, but swellable film coatings [1,2]. Eudragit RS and Eudragit RL [poly(ethylacrylate-methylmethacrylate-trimethylammonioethylmethacrylate chloride) 1:2:0.1 and 1:2:0.2, respectively] are cationic polymers containing quaternary ammonium groups with Cl^- as counter ions. Since Eudragit RL contains double the level of these functional groups compared to Eudragit RS (10% versus 5% w/w), it is more hydrophilic.

To improve the properties of a polymeric film coating and to allow for film formation from aqueous polymer dispersions, different types of excipients are frequently added to the polymer solution or dispersion, including plasticisers, pigments, pore formers and glidants [3]. Plasticisers are primarily used for improved processability (facilitated polymer particle coalescence), increased permeability and/or higher flexibility of the polymer by modifying its thermal and mechanical properties [4], i.e. increase the toughness, strength, tear resistance and impact resistance [5]. Many plasticisers are applied in the chemical industry, but due to environmental and/or health concerns, only a few are approved for pharmaceutical applications [5]. Drugs can also act as plasticisers for polymers used in the pharmaceutical field, potentially allowing for a reduction of the required amount of conventional plasticisers. For instance, Jenquin and McGinity [6] detected the plasticising effect of salicylic acid and chlorpheniramine maleate on the polymethacrylates Eudragit RL and Eudragit RS. The drug–polymer interactions were reported to involve the quaternary ammonium groups of the Eudragits (acting like ion exchange resins). Furthermore, Holgado et al. [7] described complex formation between carteolol and Eudragit L in a controlled release dosage form, and Lin et al. [8] monitored an interaction of piroxicam with Eudragit E. The latter had a significant effect on the mechanical properties of piroxicam-loaded Eudragit E films (e.g. decrease in adhesion strength), as well as on drug release. Siepmann et al. [9] investigated the plasticising capacity of ibuprofen, chlorpheniramine maleate and metoprolol tartrate in Eudragit RS-based systems and reported a significant decrease in the glass transition temperature with increasing drug content, whereas the film flexibility and drug release rate increased. The results showed that these drugs are efficient plasticisers for this polymer.

Although the number of drug–polymer interactions described in the literature is increasing, an investigation of the interaction

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mechanism is often beyond the scope of these studies or the methods applied do not allow firm conclusions. For a better understanding of drug–polymer interactions in controlled drug delivery systems, the mechanical and thermal properties of the systems can be measured [4,5,8,10,11]. For instance, Lin et al. [8] determined the tensile strength and elongation at break of different piroxicam-containing Eudragit E films. The observed changes in these properties were attributed to drug–polymer interactions via hydrogen bonding. Wu and McGinity [5] showed that the flexibility of Eudragit RS films increased with increasing ibuprofen content. Lecomte et al. [10] monitored changes in the puncture strength, elongation at break and energy at break of thin films based on different types of plasticised polymer blends. Ethylcellulose:Eudragit L films showed deviations from the theoretically expected energy at break values at blend ratios of 75:25 and 50:50 (w/w). The observed relative maximum in the energy at break and puncture strength of films prepared from aqueous dispersions at the blend ratio 50:50 might at least partially be attributed to improved particle packing during film formation and significant polymer–polymer interactions.

The thermal properties of thin polymer films can be measured using differential scanning calorimetry (DSC). Even though the exact nature of an interaction cannot easily be revealed solely by DSC thermograms, these measurements can give valuable information on potential drug–polymer interactions, resulting, for example, in changes of the glass transition temperature (T_g) of the polymer. If conventional DSC is not sensitive enough to identify the T_g of a specific polymer, modulated temperature DSC (MTDSC) may be used, offering a higher resolution and the possibility to separate different thermal events [12–14]. Changes in the T_g of a polymer essentially depend on the degree of interaction between the drug and the macromolecule [15,16]. Addition of a drug might lead to one of the following effects: (i) The T_g of the polymer might *increase* in the case of a very strong interaction (reduction in polymer chain mobility and subsequent stiffening of the polymer, so-called antiplasticising action of the drug). (ii) The T_g of the polymer might *decrease* due to the mere physical presence of the drug molecules being located between the polymer chains, which increases the segmental mobility and the free volume of the polymer (plasticising action). When the strength of the interaction is weak, the drug simply acts as an additive and usually induces a rise in the polymer chain mobility and hence a reduction in the T_g value. (iii) The T_g of the polymer might remain *unaltered* due to a balance between antiplasticising and plasticising actions. All three effects were observed by Holgado et al. [7] in Eudragit L-based systems containing carteolol (antiplasticising effect), ephedrine (plasticising effect) or morphine (no effect).

The aim of this study was to better understand the interactions between a drug salt, metoprolol tartrate and quaternary polymethacrylate-based systems. Films containing tartaric acid and metoprolol free base were also prepared to assess the degree of participation of the acidic and basic part of the salt on any interaction. The different Eudragit RL and Eudragit RS films were characterised visually, and by using polarising light microscopy, X-ray powder diffraction, MTDSC and mechanical analysis.

2. Materials and methods

2.1. Materials

The following chemicals were used as received: tartaric acid (Acros Organics, Halluin, France), metoprolol tartrate (Novartis, Barleben, Germany), Eudragit RL PO and Eudragit RS PO (Evonik, Darmstadt, Germany). All other substances used were of pharmaceutical grade. The free metoprolol base was extracted from metoprolol succinate (Novartis, Barleben, Germany) by first dissolving the salt in a sodium hydroxide solution, and subsequent extraction with dichloromethane followed by drying with water-free sodium sulphate. For further water elimination, the resulting oily liquid was dried at 80 °C in a rotary evaporator (Büchi Rotavapor model R110, Büchi, Flawil, Switzerland) connected to a vacuum pump. The yellowish liquid was cooled down to 4–7 °C, inducing crystallisation of the free base in the form of white, ice like crystals, which were subsequently gently ground in a mortar with a pestle. The chemical structures of tartaric acid, metoprolol free base, metoprolol tartrate as well as of Eudragit RL and RS are shown in Fig. 1.

2.2. Film preparation

Thin films were prepared with a casting knife (Multicator 411, Erichsen, Hemer, Germany) from ethanolic polymer solutions, optionally containing tartaric acid, metoprolol free base or metoprolol tartrate (5.0–30.0% w/w, based on the polymer mass). The films were dried for 3 days at room temperature and 1 day at 50 °C. The thickness of the films was measured using a thickness gauge (Minitest 600, Erichsen, Hemer, Germany).

2.3. Microscopic analysis

Tartaric acid, metoprolol free base and metoprolol tartrate-containing Eudragit RL and Eudragit RS films were analysed by polarising light microscopy (PLM) at a magnification of 100× (Axioskop; Carl Zeiss, Jena, Germany). The microscope was equipped with an imaging system (EasyMeasure; INTEQ Informationstechnik, Berlin, Germany).

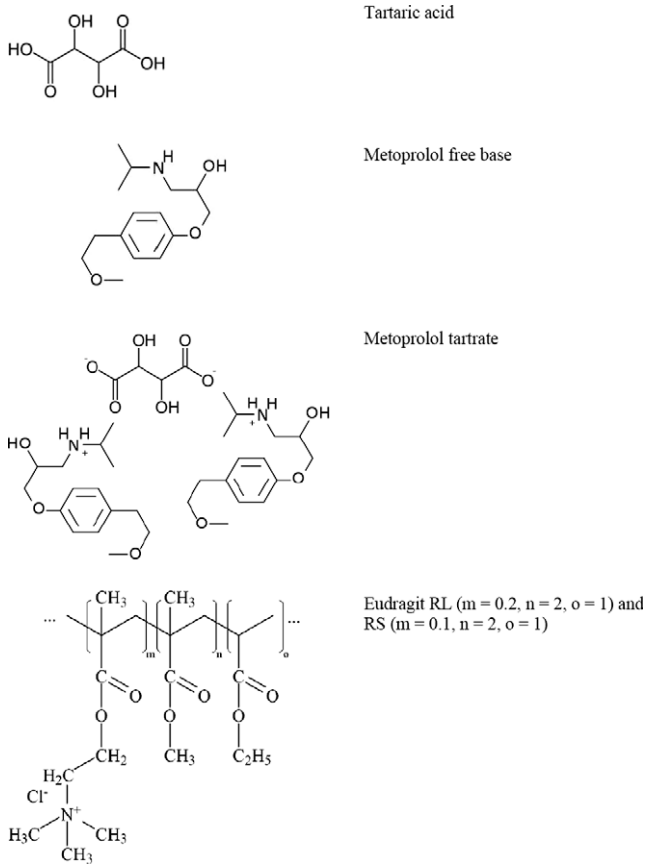

Fig. 1. Chemical structures of the investigated compounds.

2.4. X-ray powder diffraction (XRPD)

XRPD analysis was performed using an X'Pert PRO X-ray diffractometer (MPD PW3040/60 XRD; CuKα anode; $\lambda = 1.541$ Å; PANalytical, Almelo, The Netherlands). Powdered material was gently consolidated in an aluminium holder, while thin films were directly placed into the measuring chamber of the diffractometer and scanned at 40 kV and 30 mA from 5 to 35° 2θ using a scanning speed of 0.1285°/min and a step size of 0.0084°. The diffraction patterns were analysed using X'Pert High Score software (version 2.2.0). For the preparation of quench-cooled metoprolol free base and metoprolol tartrate, the latter were firstly molten at a temperature slightly above their respective melting points and subsequently doused with liquid nitrogen to prevent recrystallisation. The quench-cooled drugs were stored in a vacuum oven at room temperature and investigated by XRPD within 24 h.

2.5. Mechanical properties of the polymeric films

The films were characterised using the puncture test with a texture analyser (TA.XT Plus; Swantech, Gennevilliers, France). Film specimens were mounted on a film holder. The puncture probe (spherical end: 5 mm diameter) was fixed on the load cell (5 kg) and driven downward with a cross-head speed of 0.1 mm/s to the centre of the film holder. Load versus displacement curves were recorded until rupture of the films and used to determine the elongation at break (%) and energy at break (J/m^3) as follows:

$$\text{Elongation at break } (\%) = \frac{\sqrt{R^2 + d^2} - R}{R} \cdot 100 \quad (1)$$

where R denotes the radius of the film exposed in the cylindrical hole of the holder and d is the displacement at rupture.

$$\text{Energy at break} = \frac{\text{AUC}}{V_c} \quad (2)$$

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

For tartaric acid and metoprolol tartrate-containing films, three individual films were prepared for each drug loading. In the case of metoprolol free base-containing films, one film was prepared of each formulation. All films (7 × 7 cm) were subjected to the puncture test at nine different positions, and average values are reported.

2.6. Modulated temperature differential scanning calorimetry (MTDSC)

MTDSC was used to determine the glass transition temperature (T_g) of the investigated films. The measurements (sample weight: 7–8 mg crimped in a standard aluminium pan) were carried out using a DSC1 (Mettler-Toledo SAS, Viroflay, France) at a heating rate of 1 K/min from −30 to 100 °C (tartaric acid and metoprolol tartrate-containing films) or −65 to 100 °C (metoprolol free base-containing films) under a nitrogen gas flow. The modulation amplitude was 0.5 °C, and the period was chosen stochastically by the DSC software between 30 and 60 s. Temperature and enthalpy calibration were performed using indium as a standard. All experiments were conducted in triplicate (except for metoprolol free base-containing samples: $n = 1$). The T_gs of tartaric acid, metoprolol free base, metoprolol tartrate and of the two polymers were also determined in order to allow for the calculation of the theoretical T_g in the investigated two-component systems (acid, base or salt plus Eudragit RL or Eudragit RS) using the Gordon–Taylor equation:

$$T_g(\text{GT}) = \frac{w(\text{drug}) \cdot T_g(\text{drug}) + \frac{\rho(\text{drug})}{\rho(\text{polymer})} \cdot T_g(\text{polymer}) \cdot w(\text{polymer})}{w(\text{drug}) + \frac{\rho(\text{drug})}{\rho(\text{polymer})} \cdot w(\text{polymer})} \quad (3)$$

where w denotes the weight fraction of either drug or polymer, T_g is the experimentally determined value of the glass transition temperature of the pure substances and ρ is the true density of the amorphous materials measured by helium pycnometry (AccuPyc 1330 Gas Pycnometer, Micromeritics Instruments, Norcross, GA). The true density of the amorphous material was only assessable for metoprolol tartrate and the polymers; hence, for tartaric acid and metoprolol free base, the true density of the crystalline polymorph was used as an approximation.

3. Results and discussion

3.1. Macro- and microscopic investigation of the films

Films consisting of Eudragit RL or Eudragit RS and containing different amounts of tartaric acid, metoprolol free base or metoprolol tartrate were assessed visually and by polarising light microscopy (PLM, Fig. 2). Systems in which a compound precipitated showed crystalline regions (birefringence in the PLM micrographs). No evidence for tartaric acid precipitation was visible in Eudragit RL films up to 15% (w/w) and in Eudragit RS films up to 10% (w/w). The free base metoprolol precipitated at an initial concentration above 20% (w/w), irrespective of the type of Eudragit. In contrast, metoprolol tartrate appeared to be completely dissolved in both polymers at all investigated concentrations. In general, the Eudragit RL films were slightly opaque when compared to the clear Eudragit RS films. As previously described in the literature, this is a characteristic of Eudragit RL itself [17].

3.2. X-ray powder diffraction

The type of compound distribution within the polymeric films was further investigated by X-ray powder diffraction (XRPD). The respective substances can either be present in the form of individual molecules or ions (monolithic solutions), or in the form of amorphous drug particles or crystals (monolithic dispersions). Note that very small crystals do not necessarily show X-ray diffraction peaks. Thus, XRPD should not be used solely to characterise the physical state of a compound within a polymeric system. In this study, this technique was combined with polarising light microscopy, the determination of mechanical film properties as well as with MTDSC measurements.

Fig. 3 shows the diffraction patterns obtained with Eudragit RL and Eudragit RS films containing metoprolol free base or metoprolol tartrate. For reasons of comparison, also the diffractograms of the respective crystalline drug powders and quench-cooled drugs were determined. Quench-cooled metoprolol tartrate exhibited only the typical halo of an amorphous substance. In contrast, metoprolol free base recrystallised during quench cooling. Crystalline metoprolol free base was also detectable in Eudragit RL and Eudragit RS-based films above about 20% drug content. In contrast, no diffraction peaks were detectable in metoprolol tartrate-containing films, irrespective of the type of Eudragit. Since metoprolol tartrate is able to form a somewhat stable amorphous polymorph, it may be more likely to form an amorphous mixture with the Eudragits. In contrast, the free base does not exist easily in an amorphous form and as such may be more likely to recrystallise in the films.

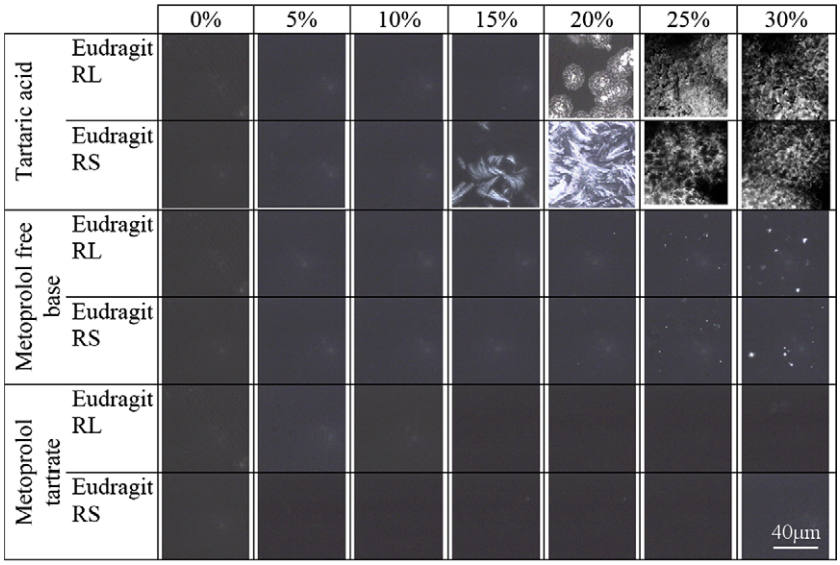

Fig. 2. Polarising light microscopic images of Eudragit RL and Eudragit RS films containing different amounts of tartaric acid, metoprolol free base or metoprolol tartrate. The concentrations of these compounds are indicated on the top. All percentages (w/w) are based on the dry polymer mass.

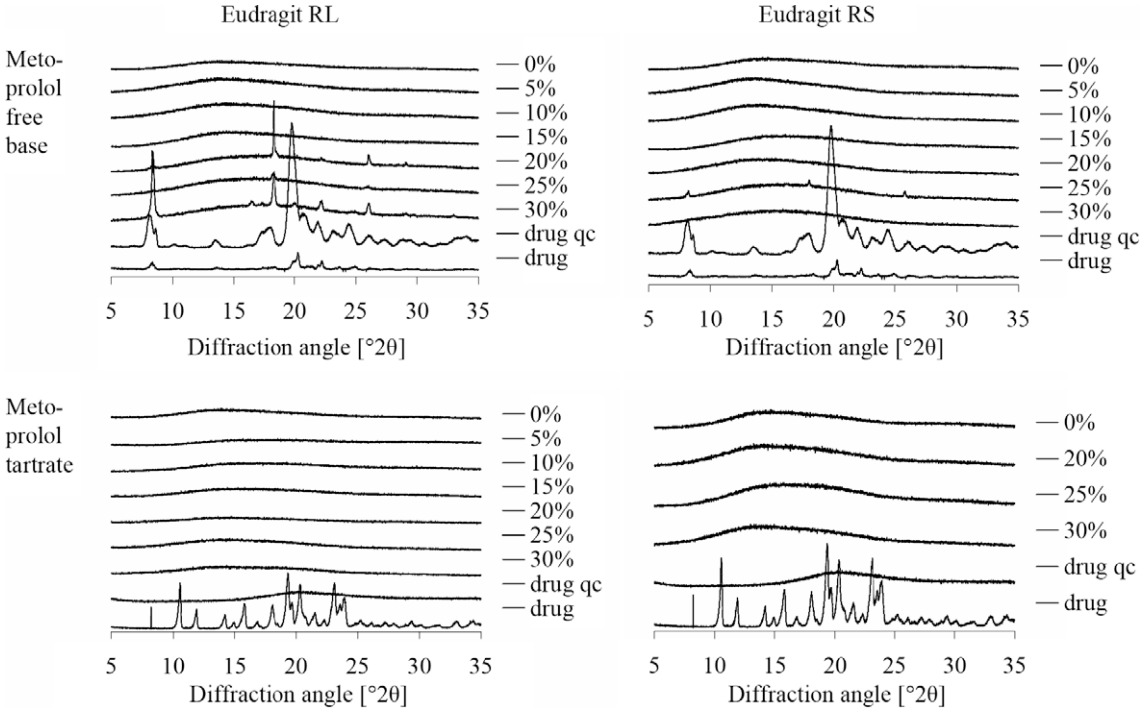

Fig. 3. XRPD patterns of metoprolol free base and metoprolol tartrate-containing Eudragit RL and Eudragit RS films. The drug contents are indicated in the diagrams (based on dry polymer mass). For reasons of comparison, the diffractograms of the respective drug powders and quench-cooled (qc) drugs are shown. All percentages (w/w) are based on the dry polymer mass.

3.3. Mechanical properties of polymer films

The presence of an external plasticiser within a polymeric system decreases the attractive forces between the macromolecules, resulting in an increased macromolecular mobility and increased film flexibility [18,19]. The elongation at break of Eudragit RL and Eudragit RS films containing increasing amounts of tartaric acid, metoprolol free base or metoprolol tartrate are shown in Fig. 4. The respective values for films consisting of the pure polymers were equal to 2.6 ± 1.0% for Eudragit RL and 0.3 ± 0.3% for Eudragit RS. Since tartaric acid is not very soluble in Eudragit RS and Eudragit RL (Fig. 2), films containing lower amounts of this compound (2.5%, 7.5% and 12.5%) were included in this study. Films containing 25.0% and 30.0% tartaric acid (showing significant precipitation) were not included.

Interestingly, the elongations at break of films containing identical amounts of *tartaric acid* were very similar for Eudragit RL and Eudragit RS (Fig. 4a, dark versus light bars). Most likely, this is due to the presence of the free acid in the unionised form, not allowing for *ionic* interaction with the quaternary ammonium groups of the polymers. Thus, tartaric acid–Eudragit RL and tartaric acid–Eudragit RS interactions occur primarily via the *polymer backbone*. A

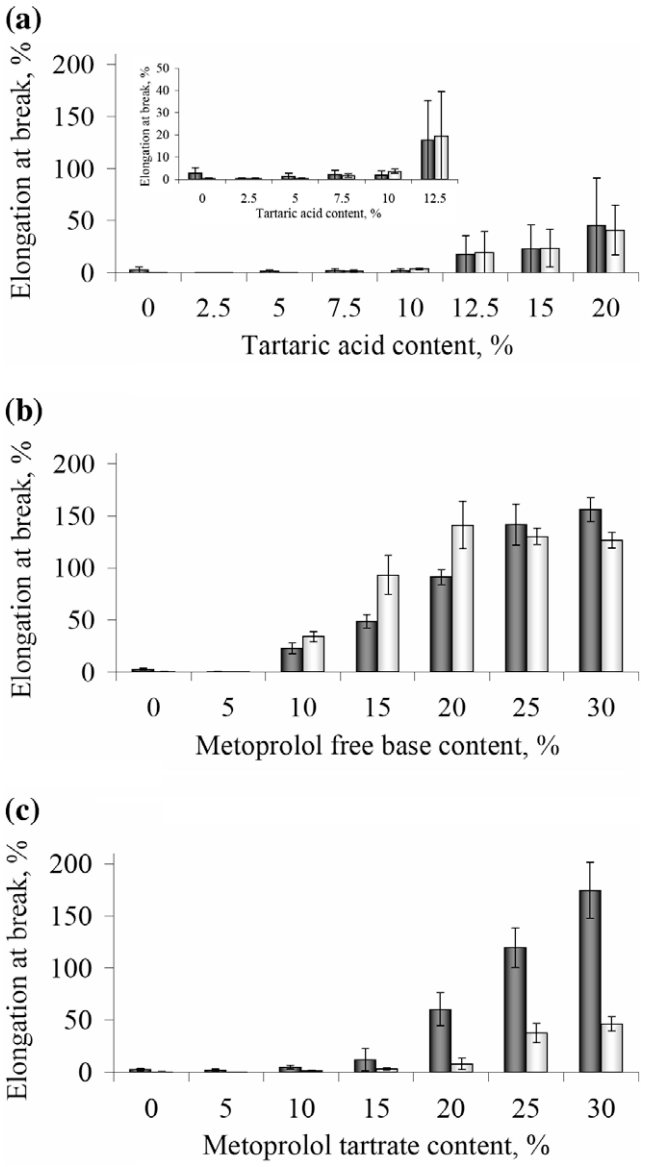

Fig. 4. Elongation at break (%) of Eudragit RL (dark bars) and Eudragit RS (light bars)-based films containing different amounts of: (a) tartaric acid, (b) metoprolol free base and (c) metoprolol tartrate. All percentages (w/w) are based on the dry polymer mass.

strong increase in the elongation at break value was noticed at 12.5% tartaric acid in both polymer species, which might be due to the amount of tartaric acid molecules now being sufficiently high for the molecules to arrange themselves between the polymer chains, independent of the amount of quaternary ammonium groups in the polymer.

Also, for *metoprolol free base* films, no systematic difference was detected between the two Eudragit types (Fig. 4b, dark grey versus light grey bars). As in the case of the unionised free acid, the free base as a hydrophobic molecule is likely to interact with the hydrophobic *polymer backbone*, resulting in similar absolute elongation at break values for both Eudragit types. This is in good agreement with the results from the microscopic investigations (Fig. 2). The fact that the elongation at break of metoprolol free base-containing films levelled off above 20–25% drug content can be attributed to the precipitation of excess free base, as observed by polarising light microscopy (Fig. 2).

Importantly, *metoprolol tartrate*-containing films showed a significantly different behaviour compared to free acid and free base-containing films (Fig. 4c versus a and b): The elongation at break values of Eudragit RL-based films were much higher than those of Eudragit RS-based films at the same drug contents (dark grey versus light grey bars). This indicates that the metoprolol tartrate–Eudragit RL and metoprolol tartrate–Eudragit RS interactions are at least partially attributable to *ionic interactions* between the negatively charged tartrate ions and the positively charged quaternary ammonium groups of the polymers. Since Eudragit RL contains twice as many quaternary ammonium groups than Eudragit RS, more tartrate ions can bind and hence have an effect on the mechanical properties of the polymer.

Comparing Fig. 4a–c, it becomes obvious that the free base is the most efficient plasticiser in the concentration range up to about 25% of added compound. The fact that metoprolol free base more intensively interacts with the hydrophobic polymer backbones than unionised tartaric acid can be explained by its more hydrophobic nature. The lower elongation at break values of metoprolol tartrate-loaded films compared to metoprolol free base-loaded films can be attributed to: (i) ionic interactions between ionised (protonated) base and deprotonated tartaric acid, and (ii) the lower molar content in metoprolol species.

The influence of the tartrate and metoprolol species on the mechanical properties of a metoprolol tartrate-containing film was further evaluated. Eudragit RL and RS films containing molar equivalents of the salt, the free acid and the free base were prepared. Films containing 15% metoprolol tartrate salt contain 3.29% of the acid and 11.71% of the base. Thus, for reasons of comparison, the energy required to break Eudragit RL and Eudragit RS films containing 3.29% of the acid, or 11.71% of the base was measured (Fig. 5). Importantly, the free base exhibited the highest impact on the mechanical properties of the films. This confirms the above described hypotheses.

3.4. Modulated temperature differential scanning calorimetry (MTDSC)

The results of the DSC measurements are shown in Fig. 6. The T_g values of the free acid, free base, salt and of the pure polymers were: tartaric acid, 17.8 °C; metoprolol free base, −67.0 °C; metoprolol tartrate, 13.2 °C; Eudragit RL, 56.1 °C; and Eudragit RS, 53.0 °C.

The type of polymer (Eudragit RL versus Eudragit RS) had little effect on the resulting T_g of all films, as the T_gs of the pure polymers were in the same range. To visualise a potential interaction between a specific compound and a particular polymer, the theoretical T_gs of the investigated binary mixtures (acid, base or salt plus

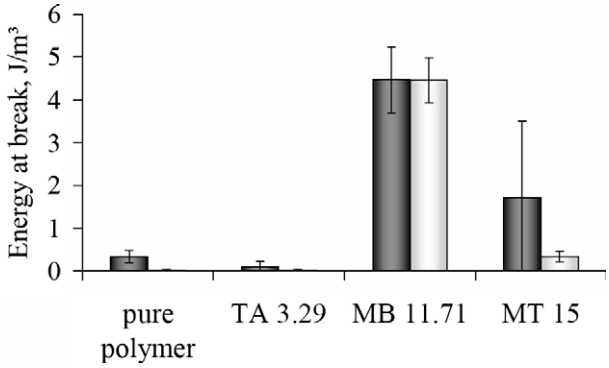

Fig. 5. Energy at break of Eudragit RL (dark grey bars) and Eudragit RS (light grey bars)-based films with an initial metoprolol tartrate (MT) content of 15% w/w. For reasons of comparison, also films containing equimolar amounts of tartaric acid (TA, 3.29% w/w) and metoprolol free base (MB, 11.71% w/w) are shown. All percentages (w/w) are based on the dry polymer mass.

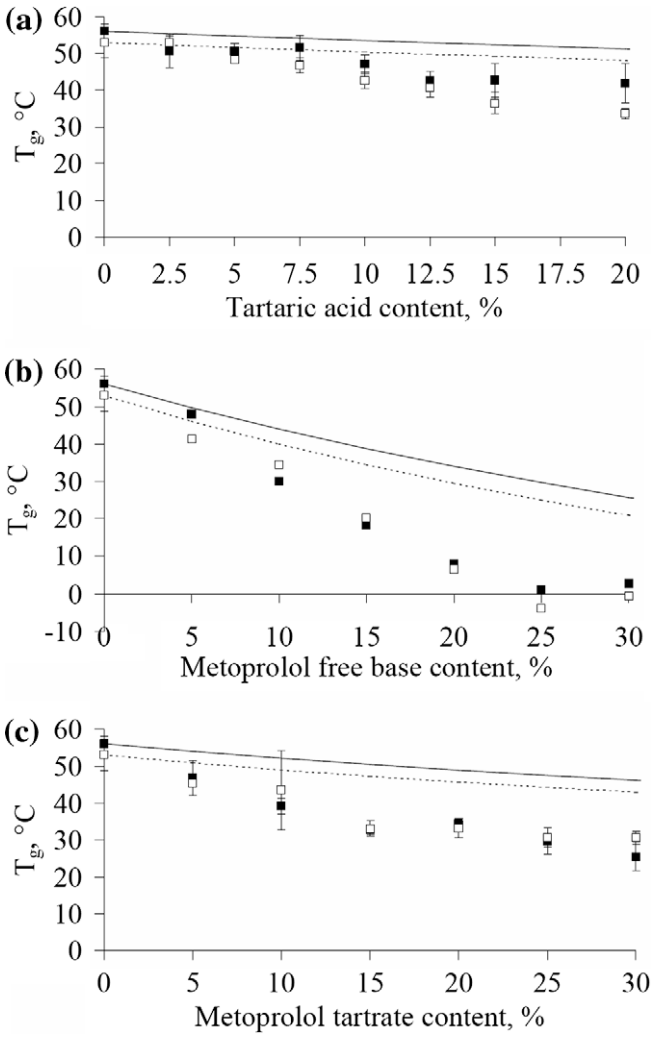

Fig. 6. Concentration-dependent changes in the glass transition temperature of: (a) tartaric acid, (b) metoprolol free base and (c) metoprolol tartrate-containing Eudragit RL films (closed symbols, solid curves) and Eudragit RS films (open symbols, dotted curves). Curves represent the theoretical values according to the Gordon–Taylor equation. All percentages (w/w) are based on the dry polymer mass.

Eudragit RL or Eudragit RS) were calculated according to the Gordon–Taylor equation. The latter predicts the T_g of an ideal amorphous one-phase system. When there are significant drug–polymer interactions, deviations from the predicted behaviour occur. For instance, if the drug acts as a plasticiser for the polymer, negative deviations from the theoretical T_g values are observed [20].

Increasing the amount of incorporated compound in the film resulted in increasing negative deviations from the predictions for all three substances (Fig. 6). The deviation was least pronounced for the tartaric acid-containing films (Fig. 6a). For up to 7.5% tartaric acid, the experimentally determined values deviated only slightly from the theoretical values. The metoprolol free base-containing films exhibited the strongest decrease in the T_g and the most pronounced deviation from the theoretical T_g values (Fig. 6b). The glass transition temperature decreased up to a drug content of approximately 25% and then levelled off, presumably, because the excess free base precipitated (Fig. 2). Also, the metoprolol tartrate-containing films showed significant plasticisation, becoming more pronounced with increasing drug loading (Fig. 6c). However, the effect was not as strong as for the free base-containing films. This confirms the lower plasticising efficacy of the salt compared to the free base.

Since the extent to which the T_g is lowered can be used as a measure for the efficiency of the plasticiser, the free base clearly is the most potent plasticiser for the investigated Eudragits. However, also tartaric acid and metoprolol tartrate significantly decreased the T_g with increasing drug loading. This again indicates that all three compounds act as plasticisers, but with different efficiencies for the acrylic polymers.

4. Conclusions

The interaction mechanism between metoprolol tartrate and the quaternary polymethacrylates Eudragit RL and Eudragit RS was investigated. For a better understanding of the interaction between the drug and the polymers, tartaric acid and metoprolol free base-containing films were also prepared. The main interaction, which has the most pronounced effect on the mechanical strength and the T_g of the polymeric network, appears to be a hydrophobic interaction between the metoprolol species and the polymeric backbones. Incorporation of metoprolol free base in polymeric films resulted in strong plasticisation of the latter. Metoprolol tartrate is assumed to be in the ionised form within the films; hence, ionic interactions with the polymer can take place. The combination of the acidic and basic species in the form of the salt metoprolol tartrate reduces the plasticising capacity of the base. This deeper insight into the drug–polymer interaction mechanism can help to facilitate the optimisation of this type of drug delivery system. Knowing which type of physicochemical phenomena is involved in the control of drug release avoids treating the delivery system as a "black box". Thus, the number of experiments required for device optimisation can be reduced and challenges encountered during product development and production can be more efficiently addressed.

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