**Release characteristics of polyurethane tablets containing dicarboxylic acids as release modifiers –
a case study with diprophylline**

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**Abstract**

The influence of several dicarboxylic acids on the release characteristics of polyurethane tablets with a high drug load was investigated. Mixtures of diprophylline (Dyph) and thermoplastic polyurethane (TPUR) (ratio: 50/50, 65/35 and 75/25 wt.%) were hot-melt extruded and injection molded with the addition of 1, 2.5, 5 and 10% wt.% dicarboxylic acid as release modifier. Incorporating malonic, succinic, maleic and glutaric acid in the TPUR matrices enhanced drug release, proportional to the dicarboxylic acid concentration in the formulation. No correlation was found between the water solubility, melting point, logP and pKa of the acids and their drug release modifying capacity. Succinic and maleic acid had the highest drug release modifying capacity which was linked to more intense molecular interactions with Dyph. A structural fit between the primary and secondary alcohol of Dyph and both carboxylic groups of the acids was at the origin of this enhanced interaction.

**Introduction**

Hot melt extrusion (HME) combined with injection molding (IM) as downstream processing step is a suitable technique to manufacture solid dosage forms with high dimensional precision (Claeys et al., 2013; Claeys et al., 2012; Quinten et al., 2009; Quinten et al., 2011). The use of polyurethanes as carrier for the production of sustained release formulations is favorable due to their highly elastomeric character, superior tensile strength, crack resistance and inherent lubricity. They have been successfully used for many years as drug release controlling polymers in vaginal rings (Clark et al., 2012; Gupta et al., 2008; Johnson et al., 2010), stents (Jansen et al., 1993), coatings (Sommer et al., 2010), implants (Bucky et al., 1994), and medical tubings (Randall and Lee, 2010). The inert, non-ionic and water-insoluble nature of polyurethanes enables them to release the incorporated API in a sustained manner, even at high drug loadings (>50wt.%) (Claeys et al.). However, depending on the properties of the drug the addition of a third component is required in the formulation to ensure complete drug release. The development of a polyurethane-based biomaterial, for instance, required the use of a pore former to alter the release characteristics of an antibacterial agent (cefadroxil) to prevent bacterial adhesion and growth on its surface. The highest release rate was observed when bovine serum albumin (BSA) was incorporated in the TPUR matrix, compared with polyethylene glycol (PEG 1450) and mannitol, possibly due to the different aqueous solubility of the pore formers although further investigation was necessary (Kim et al., 2000). In the development of an antifungal catheter, PEG 2000 and BSA were added to control the release of fluconazole in a water-swellable polyurethane matrix. The addition of PEG resulted in faster release profiles, whereas BSA was able to control the release over a longer period, which was attributed to its higher molecular weight (69 000 and 2000 g/mol for BSA and PEG, respectively) (Donelli et al., 2006). An oral TPUR application, containing mixtures of TPUR and diprophylline required the incorporation (2, 5 and 10%) of a pore former (PEG 4000) or a surfactant (Tween 80) to ensure complete drug release over a 24 h period (Claeys et al.).

This paper evaluates the effect of dicarboxylic acids on the release characteristics of diprophylline from polyurethane matrices processed via hot-melt extrusion and injection molding. Malonic, succinic, maleic and glutaric acid were selected as dicarboxylic acids as their differences in aqueous solubility, melting point, pKa, polarity and chemical structure allows to identify the critical parameters towards the release enhancing effect from the polyurethane matrix.

**Experimental Section**

**Materials**

Diprophylline (Dyph, 7-(2,3-dihydroxypropyl)-theophylline) was embedded as drug in the thermoplastic polyurethane (TPUR) matrix. Tecoflex 72D (T72D, a medical-grade polyurethane) was obtained from Merquinsa (a Lubrizol company, Ohio, USA). Malonic, succinic, maleic and glutaric acid were purchased from Sigma (St-Louis, USA). The chemical structures of all materials are detailed in Figure 1, while the chemical properties of the dicarboxylic acids are listed in Table 1. Distances between various atoms were determined via Chem 3D Pro (PerkinElmer, Massachusetts, USA).

**Thermal analysis**

The glass transition temperature (Tg) and melting point (Tm) of pure components, physical mixtures and injection molded tablets were analyzed in Tzero pans (TA instruments, Zellik, Belgium) by modulated differential scanning calorimetry (MDSC Q2000, TA Instruments, Leatherhead, UK) using a heating rate of 2°C/min. The modulation period and amplitude were set at 1min and 0.318°C, respectively (heat-iso method). Dry nitrogen at a flow rate of 50mL/min was used to purge the MDSC cell. Analysis of the thermal characteristics (Tm and Tg) was done via a heating/cool/heat run between -70 and 140°C. The melting enthalpy (in the total heat flow signal), Tmelt-max (i.e. inflection point of melting endotherm) and Tmelt-onset (i.e. start of melting endotherm) were analyzed in the first heating cycle. Analysis of the glass transition temperature was done in the first and second heating cycle for the injection molded tablets and the physical mixtures, respectively. All results were analyzed using the TA Instruments Universal Analysis 2000 software.

**X-ray diffraction (XRD)**

The crystallinity of the samples was determined via X-ray diffraction using a D5000 Cu Kα diffractor (*λ* = 0.154 nm) (Siemens, Karlsruhe, Germany) with a voltage of 40 kV and current of 40 mA in the angular range of 10° < 2*θ* < 60° using a step scan mode (step width = 0.02°, counting time = 1 s/step).

**Karl Fischer**

The water content of all dicarboxylic acids was determined by volumetric Karl Fischer titration using a V30 volumetric KF titrator (Mettler Toledo, USA). Methanol (Hydranal, Sigma Aldrich, Germany) was used as solvent. Before titration, 1g was dissolved in methanol during 1000 s. All measurements were performed in triplicate.

**Fourier Transform Infrared Spectroscopy**

Attenuated total reflection Fourier-transform infrared (ATR FT-IR) spectroscopy was performed on pure substances, physical mixtures and heated physical mixtures in order to identify molecular changes upon heating. Physical mixtures of Dyph and dicarboxylic acid (PM acid) at a molar ratio of 1/1 were compared with their respective PM after heating (2°C/min up to 140°C) and recooling to room temperature (heat-treated PM).

Spectra (i.e. 10 samples per physical mixture, 1 spectrum per sample, 40 spectra for PM acid and 40 spectra for PM acid heated) were recorded using a Nicolet iS5 ATR FT-IR spectrometer (Thermo Fisher Scientific). A diamond ATR crystal was pressed against the samples. Each spectrum was collected in the 4000 - 550 cm-1 range with a resolution of 2 cm-1 and averaged over 32 scans. FTIR spectral data analysis was done using SIMCA P+ v.12.0.1 (Umetrics, Umeå, Sweden). The spectral ranges of 1000-1120cm-1 and 880-780cm-1 were evaluated via principal component analysis. All collected FTIR spectra were preprocessed using standard normal variation (SNV, see supporting information).

**Production of injection molded tablets**

Physical mixtures of drug and polymer were extruded at 140°C using a co-rotating twin-screw extruder at 100rpm (Haake MiniLab II Micro Compounder, Thermo Electron, Karslruhe, Germany). The API/TPUR ratios (wt.%) used in this study were 75/25, 65/35 and 50/50 with a processing temperature of 140°C. Biconvex tablets (diameter: 10mm/height: 5mm) were produced via injection molding (Haake MiniJet System, Thermo Electron). The injection pressure was 800bar during 10s, in combination with a post-pressure of 400bar for 5s.

***In vitro* drug release**

Drug release from the injection molded tablets was determined using the paddle method on a VK 7010 dissolution system (VanKel Industies, New Jersey, USA) with a paddle speed of 100rpm. Distilled water was used as dissolution medium (900mL) at 37 ± 0.5°C. Samples were withdrawn at 0.5, 1, 2, 4, 6, 8, 12, 16, 20 and 24 h (without replacement of medium) and spectrophotometrically analyzed for Dyph concentration at 274nm.

**Results and Discussion**

**The standard formulation: processability, release behavior and solid state characterization**

Processing of TPUR/Dyph mixtures via HME and IM at 140°C required a minimum of 25% of thermoplastic polymer to provide sufficient plasticity to the formulations, as Dyph remained mainly crystalline during thermal processing. Mixtures with higher drug loads (>75wt.%) could not be processed as the powder fraction was too high to ensure an adequate flow in the extruder (i.e. too high screw torque). Dyph release (Figure 2A) from the standard formulation was incomplete: 9, 41 and 55% Dyph was released after 24h from TPUR matrices with drug loads of 50, 65 and 75%, respectively. This indicated that - despite the high drug load - a continuous interconnecting network was not achieved in the TPUR matrix and that a release modifier is required to enhance Dyph release. Although 2 polymorphs of Dyph with distinct melting temperatures, melting enthalpies and crystallographic spectra (Figure 2B and 2C) have been described, after thermal processing only Form I (Tm 162°C, 175J/g, a thermodynamically stable form) was detected in the DSC signal of TPUR/Dyph matrices. This observation was confirmed via XRD (Figure 2C). The formation of the kinetically stable Form II (Tm 150°C, 135J/g) has been described after recrystallization from solvents/melts (Griesser et al., 1999).

**Addition of dicarboxylic acids as drug release modifiers**

Figure 3 evidences that the release of Dyph was improved via the addition of dicarboxylic acids. This improvement was concentration driven, as higher concentrations of dicarboxylic acids induced faster drug release. However, figure 3E shows that the solubility of the dicarboxylic acids is not the main contributing factor for the enhanced release rate. Malonic acid (Fig 3B), having the highest water solubility (1400g/L), was the least successful drug release modifier. No correlation was found between the drug release modifying capacity and logP, pKa or Tm of the dicarboxylic acids. Succinic and maleic acid yielded the highest release modifying effect, which might indicate that the specific chemical structure of these two acids (i.e. two methylene groups between the carboxylgroups) is important for their superior drug release altering capacity.

The effect of dicarboxylic acids on drug release was not linked to changes in polymorphic structure of Dyph. XRD profiles of thermally processed Dyph/TPUR matrices in combination with maleic acid (Figure 4) only showed signals of the innate crystallographic form of Dyph (i.e. Form I) as the specific peaks of Dyph Form II (10.0, 24.1, 25.2 and 28.2°) were absent in the formulation. Moreover, there was no correlation found between the water content of the dicarboxylic acids and their drug release modifying capacity. Karl Fisher experiments indicated that the water content of all dicarboxylic acids was similar and lower than 1% ($\pm $ 0.05, n=3, data not shown).

**Interaction between diprophylline and dicarboxylic acids**

The probability of interactions between the different dicarboxylic acids and Dyph were evaluated via thermal analysis (MDSC) and spectroscopic analysis (ATR-FTIR combined with PCA-analysis).

**MDSC**

The thermal results presented in this section are, for the sake of clarity, limited to a comparison between malonic and maleic acid, as both dicarboxylic acids have the same Tm (134°C), but their impact on the release characteristics is markedly different (the lowest and highest drug release modifying capacity was attributed to malonic and maleic acid, respectively).

The themograms of the physical mixtures revealed an interaction between Dyph and both dicarboxylic acids based on the reduction of the thermal parameters (Tmelt-max, Tmelt-onset and degree of crystallinity) of Dyph during the first heating cycle. The interaction between a crystalline API and an excipient can induce, depending on their respective molar ratio, (partial) dissolution of the API, and as the resulting smaller API crystals are intrinsically less stable, peak broadening of the melting endotherm is observed. These phenomena were more pronounced when Dyph was combined with maleic acid compared to malonic acid (Figure 5, left). The second heating cycle of Dyph/dicarboxylic acid mixtures revealed a glass transition signal which was constant in combinations with malonic acid, whereas Tg varied when maleic acid was used, indicating a change in molecular mobility due to interactions at a molecular level (Figure 5, middle). These thermal results of the physical mixtures provide a clear indication of stronger interactions between Dyph and maleic acid, compared to Dyph/malonic acid mixtures. Thermal investigation of the injection molded tablets (IM) illustrated similar effects (Figure 5, right): the addition of 5% malonic and maleic acid reduced Tmelt-max of Dyph from 162 to 159 and 154°C, respectively. Moreover, without the addition of dicarboxylic acids, 80% of the Dyph fraction remained crystalline in a TPUR matrix. The degree of crystallinity of Dyph in formulations processed with malonic acid was not affected, whereas Dyph crystallinity was reduced to 73 and 68%, respectively, when 2.5 and 5% maleic acid was used as release modifier. These results confirmed the higher affinity between Dyph and maleic acid, compared to malonic acid.

**ATR-FTIR**

As thermal analysis indicated the importance of molecular interactions for the release-enhancing effect of dicarboxylic acid in a TPUR matrix, the affinity between the different dicarboxylic acids and Dyph was further explored via FTIR analysis.

Principal component analysis of the FTIR spectra of the heat-treated PM was performed using the 1000-1120cm-1 spectral range. All preprocessed FTIR spectra were decomposed into four principal components (PCs) explaining 98.6% of the total spectral variance where PC1 accounted for 65.1%, PC2 24%, PC3 6.1%, and PC4 3.4% of the spectral variance, respectively. Figure 6A illustrates the scores clustering according to PC1 and PC2. Interestingly, PC1 distinguishes two groups: mixtures with succinic and maleic acid (i.e. dicarboxylic acids inducing the highest drug release modifying capacity, Fig. 3) and mixtures with malonic and glutaric acid (having the lowest drug release modifying capacity, Fig. 3). Examination of the PC1 loadings plot (Figure 6B) to identify the spectral variability responsible for this clustering in group 1 and 2 revealed four important peaks, all attributed to the chemical structure of Dyph: 1105 and 1096
cm-1 of the C-O stretching of the secondary alcohol, 1058cm-1 of the C-O stretching of the primary alcohol, and 1032cm-1 of the C-N stretching of the tertiary aliphatic amine (Socrates and Socrates, 2001).

Figure 7A and 7B illustrate the FTIR spectra of the physical mixtures (full line) and the heat-treated samples (dotted lines) over the 1000-1120cm-1 spectral range. Before heating, the peaks of interest were identical for all PM, independent of the type of dicarboxylic acid. Although the intensity of C-O stretching of the primary and secondary alcohol decreased upon heating and cooling of all samples, these peaks (1 and 2 on Figure 7) completely disappeared in the heat-treated mixtures containing maleic and succinic acid. The peak indicative of C-N stretching of tertiary aliphatic amines shifted towards lower wavenumbers (peak 3 on Figure 7). This shift was larger in combination with maleic and succinic acid. A new peak was formed at 820cm-1 and 812cm-1 for the heat-treated samples of Dyph/maleic acid and Dyph/succinic acid, respectively (peak 4 and 5 on Figure 7). This was attributed to a C-H vibration shift due to the interaction between both components (Socrates and Socrates, 2001). These spectral changes clearly confirmed the more extensive interactions between Dyph and maleic/succinic acid (compared to malonic/glutaric acid). A structural fit between the primary and secondary alcohol of Dyph and both carboxylic groups of the acids is, most likely, at the origin of this enhanced interaction (Figure 7E): the distance (i.e. two methyl groups) between the two oxygens groups of the carbonyl of maleic (2.7Ǻ) and succinic acid (2.5Ǻ) is similar to the distance between the two hydroxyl groups of Dyph (2.8Ǻ). Hence, 2 H-bonds can easily be formed, yielding more interactions and the complete disappearing of their respective C-O stretch peaks. Malonic acid (i.e. one methyl group) and glutaric acid (i.e. three methyl groups, Figure 7E) did not structurally match with Dyph, resulting in a lower degree of molecular interactions (distance between oxygens of the carbonyl group being 3.9 and 4.7Ǻ for malonic and glutaric acid, respectively). Hence, the peak of the C-O stretch was still observed in these peaks, although its intensity had dropped.

To confirm that stronger interactions between Dyph and maleic/succinic acid are due to a structural fit between these components, the interaction between fumaric acid (enantiomeric form of maleic acid) and Dyph was monitored. The carboxylic acid groups of fumaric acid are in trans-form (both COOH at the opposite side of the backbone), while in maleic acid they are in cis-form (similar side of the backbone). FTIR spectra and in vitro release data illustrated that fumaric acid did not interact with Dyph to the same extent as maleic acid (data not shown): the C-O stretch of both hydroxyl groups and the shift of C-N stretch in Dyph were less affected in this combination. Moreover, in vitro Dyph release was lower for fumaric acid in comparison to maleic acid formulations: 39 and 50% after 4 h for fumaric and maleic acid, respectively. These observations confirmed that the superior release modifying capacity of maleic/succinic acid is attributed to a structural fit between Dyph and dicarboxylic acids.

Ester bond formation between the OH-groups of Dyph and maleic/succinic acid was excluded as the addition of a drop of 0.5g/ml LiBr solution to a heat-treated Dyph/maleic acid sample neutralized the spectral changes, confirming the reversible nature of the molecular interactions between Dyph and maleic acid and the absence of an irreversible ester-bond. The addition of a LiBr solution results in a breakdown of the reversible inter- and intra-molecular H-bonds, since the bromide anion acts as a strong nucleophilic component, whereas Li+ interacts with the carbonyl group (Marcus, 2009).

**Conclusion**

A high dosed sustained release formulation was developed via hot melt extrusion and injection molding. Despite the high drug load (75wt.% Dyph), a drug release modifying agent was essential to release the entire Dyph fraction in a sustained manner from the TPUR matrix. Succinic and maleic acid had a superior release modifying capacity which was attributed to more intense molecular interaction with Dyph (H-bonds). A structural fit between the primary and secondary alcohol of Dyph and both carboxylic groups of the acids was at the origin of this enhanced interaction.

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