HYDROPHILIC THERMOPLASTIC POLYURETHANES FOR THE MANUFACTURING OF HIGHLY DOSED ORAL SUSTAINED RELEASE MATRICES VIA HOT MELT EXTRUSION AND INJECTION MOLDING

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Abstract

Hydrophilic aliphatic thermoplastic polyurethane (Tecophilic^{TM} grades) matrices for high drug loaded oral sustained release dosage forms were formulated via hot melt extrusion/ injection molding (HME/IM). Drugs with different aqueous solubility (diprophylline, theophylline and acetaminophen) were processed and their influence on the release kinetics was investigated. Moreover, the effect of Tecophilic^{TM} grade, HME/IM process temperature, extrusion speed, drug load, injection pressure and post-injection pressure on in vitro release kinetics was evaluated for all model drugs.

^{1}H-NMR spectroscopy indicated that all grades have different soft segment/hard segment ratios, allowing different water uptake capacities and thus different release kinetics. Processing temperature of the different Tecophilic^{TM} grades was successfully predicted by using SEC and rheology. Tecophilic^{TM} grades SP60D60, SP93A100 and TG2000 had a lower processing temperature than other grades and were further evaluated for the production of IM tablets. During HME/IM drug loads up to 70% (w/w) were achieved. In addition, Raman mapping and (M)DSC results confirmed the homogenous distribution of mainly crystalline API in all polymer matrices. Besides, hydrophilic TPU based formulations allowed complete and sustained release kinetics without using release modifiers. As release kinetics were mainly affected by drug load and the length of the PEO soft segment, this polymer platform offers a versatile formulation strategy to adjust the release rate of drugs with different aqueous solubility.

Keywords: hot melt extrusion, injection molding, rheology, thermoplastic polyurethanes, high drug load, sustained release

1. INTRODUCTION

Hot melt extrusion (HME) is a continuous process of converting raw materials into a product of uniform shape and density by forcing it through a die under controlled conditions. In general, HME can be defined as a technique where an active pharmaceutical ingredient (API) is processed within a polymer carrier. This technique is one of the most widely applied processing technologies in plastic, rubber and food industries. In pharmaceutical industry HME is used to enhance dissolution rate of poorly water-soluble compounds, to develop sustained release formulations and to mask the taste of APIs. [1][2][3][4][5] HME produces strand-like extrudates that are subsequently processed into the desired end formulation (e.g. tablets, mini-matrices). [6][7][8] Injection molding (IM) is known as an efficient post-process technique for the manufacturing of tablets. [6][9]

Sustained release dosage forms have successfully been developed via HME using different polymers, but the majority of the polymers used require the need of a plasticizer to improve the elasticity/flexibility. [10] In addition, the drug load in these formulations is often limited as burst release or processing issues (i.e. high torque values) are observed for hot-melt extruded dosage forms with a high drug content. [10][11][12][13] Therefore, the design of novel sustained release dosage forms using non-conventional polymeric materials with improved characteristics for controlled drug release is of great interest. [13][14] Recently thermoplastic polyurethanes (TPUs) were found to be promising matrix formers for the production of high drug loaded oral sustained release formulations via hot melt extrusion and injection molding (HME/IM), thereby diminishing the amount of excipient needed and creating a major advantage for patient's compliance. [15] TPUs are widely used in advanced wound care, cardiology, drug delivery, medical supplies, orthopaedics, urology and vascular applications. [16][17][18][19][20] Although hydrophobic TPU matrices were successfully produced via HME/IM, drug release modifiers were needed to ensure a complete release of drugs with lower aqueous solubility. [21] Therefore, the evaluation of other (i.e. hydrophilic) TPUs is essential to obtain a flexible polymer platform that allows sustained release of a wide range of highly dosed APIs for oral intake.

We evaluated the processability of commercially available hydrophilic aliphatic thermoplastic polyurethanes as matrices for oral sustained release dosage forms. Considering the outcome of the rheological experiments, HME/IM of different model drugs was performed in

97 combination with Tecophilic™ SP60D60, SP93A100 and TG2000 that had a lower predicted
98 processing temperature than other grades, favouring the thermal stability of the drugs.
99 Diprophylline, acetaminophen and theophylline were selected as model drugs as they are all
100 highly dosed and have a different aqueous solubility.
101 All formulations were characterised and *in vitro* dissolution experiments were performed. The
102 effect of HME/IM process temperature, extrusion speed, drug load and injection pressure on
103 *in vitro* drug release was determined to evaluate the formulation robustness.

2. Experimental section

2.1. Materials

Various grades of hydrophilic Tecophilic™ TPUs were obtained from Merquinsa (a Lubrizol Company, Ohio, USA). As shown in **Fig. 1**, the hard segment of these hydrophilic and aliphatic TPUs is hexamethylene diisocyanate (HMDI) in combination with 1,4-butanediol (1,4-BD) as chain extender, while its soft segment is poly (ethylene oxide) (PEO). Different Tecophilic™ grades were evaluated: aliphatic extrusion-grade TPUs (HP60D20, HP60D35, HP60D60 and HP93A100), solution-processable TPUs (SP60D60, SP93A100 and SP80A150) and hydrogel TPUs (TG500 and TG2000). As shown in **Table 1.**, each grade has a specific equilibrium water uptake, depending on the length of the PEO soft segment. [22]

Theophylline (Theo), diprophylline (Dyph, 7-(2,3-dihydroxypropyl)-theophylline) and acetaminophen (Aceta) (Sigma Aldrich, Bornem, Belgium) were used as model drugs to investigate whether Tecophilic™ grades allowed to sustain release of highly dosed drugs with different aqueous solubility without using release modifiers.

2.2. Polymer characterisation

Thermogravimetric analysis (TGA 2950, TA instruments, Leatherhead, UK) was performed on all types of Tecophilic™ under a dry nitrogen flow (100mL/min). Samples (±7mg) were first equilibrated at 30°C and were then heated to 500°C using a heating rate of 10°C/min.

The glass transition temperature and the melting temperature of all polymers were determined by modulated differential scanning calorimetry (MDSC) (Q2000, TA Instruments, Leatherhead, UK) using a heating rate of 2°C/min. Tzero pans (TA instruments, Zellik, Belgium) with sample masses varying between 10-15mg were used. 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. The determination of T_m and T_g was done via a heat/cool/heat run between -90°C and 180°C. The first heating cycle was used to determine the melting enthalpy (in the total heat flow signal) and T_m (i.e. inflection point of melting endotherm). The glass transition temperature was determined in the second heating cycle.

Size Exclusion Chromatography (SEC) was carried out on an Agilent 1260 system, equipped with a 1260 ISO-pump and a 1260 refractive index detector (RID). Measurements were performed in dimethylacetamide (DMA) containing 50mM LiCl at 50°C, using a flow rate of

0.593mL/min. A guard column and two PL gel 5µm Mixed-D columns were used in series, calibrated with poly (methyl methacrylate) standards having a molecular weight varying between 2.18-380kDa.

^{1}H-Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 300 MHz FT-NMR-spectrometer using deuterated chloroform (CDCl3) and deuterated dimethyl sulfoxide (DMSO-d6) as solvents. Chemical shifts (δ) were given in ppm relative to tetramethylsilane (TMS).

A Thermo Scientific HAAKE MARS III (Modular Advanced Rheometer System, Thermo Fisher Scientific, Karlsruhe, Germany) was used to determine the rheological properties of each Tecophilic™ grade: G' (storage modulus), G'' (loss modulus), tanδ and η^* (complex viscosity). A parallel plate (d = 20mm) geometrical set-up was used. The upper plate is connected with a mobile upper mount and the fixed bottom plate is connected with a temperature-controlling unit. All polymer samples were prepared using a hot plate press (set at 180°C; 3bar) and were 20mm in diameter and ± 1mm thick (Carver, USA). To determine the linear viscoelastic region (LVER), an amplitude sweep over a strain range (0.01-10%) was performed on all Tecophilic™ grades. Temperature sweeps were performed on all hydrophilic TPUs to determine the temperature range for which η^* is between 1000 and 10 000Pa.s. [23] The samples were loaded at 180°C and equilibrated for 10 minutes to erase all thermal history. Next, samples were cooled to 40°C and equilibrated for 5 minutes. After equilibration, samples were gradually heated at 2°C/min to 200°C. During heating, an angular frequency of 1Hz and a strain of 1% was applied on the sample. Furthermore, frequency sweeps were performed on the TPU grades having the lowest extrusion temperature range (based on the temperature sweeps). The material viscoelastic properties at different time scales were gathered during a frequency sweep for investigation of shear thinning and elastic behaviour.

Hot melt extrusion on the pure polymers was done on a lab-scale co-rotating twin-screw extruder at 100rpm (Haake MiniLab II Micro Compounder, Thermo Electron, Karlsruhe, Germany). Minimum processing temperature (i.e. temperature at which torque values did not exceed 20% of maximum torque) was determined and linked with polymer screening data. [23]

2.3. Production of HME/IM tablets in combination with different model drugs

HME/IM was performed on selected TPUs in combination with diprophylline, acetaminophen and theophylline (aqueous solubility in 1ml at 25°C: 0.33, 0.014 and 0.007g, respectively). Physical mixtures (50% drug load, w/w, in all cases) were extruded using a co-rotating twin-screw extruder (Haake MiniLab II Micro Compounder, Thermo Electron, Karlsruhe, Germany), operating at different screw speeds (50, 75 and 100rpm) and processing temperatures (110, 120, 130 and 140°C for SP60D60 formulations; 110°C for SP93A100 formulations and 80°C for TG2000 formulations). To evaluate the effect of drug load, physical mixtures of drug (concentration was varied from 40-80% (w/w)) and Tecophilic™ SP60D60 were processed via HME at 100rpm using a barrel temperature of 110°C.

After HME, the extrudates were immediately processed into tablets via injection molding (Haake MiniJet System, Thermo Electron, Karlsruhe, Germany) at a temperature equal to the extrusion temperature. During the IM process an injection pressure of 800bar (during 10s) forces the material into the mold. A post-pressure of 400bar (during 5s) avoids expansion by relaxation of the polymer. As not only HME processing parameters might affect drug release, injection molding pressure and post-injection pressure were varied from 600-1000bar and 200-600bar, respectively. For all experiments, one parameter was varied at a time while keeping the other parameters constant.

2.4. Characterization of HME/IM tablets

Crystallinity of the APIs was evaluated using two techniques: MDSC and XRD. A MDSC Q2000 (TA Instruments, Leatherhead, UK) with a refrigerated cooling system (RCS) was used to determine glass transition temperature, melting point, and melting enthalpy (ΔH) of pure components, physical mixtures and extruded tablets. As melting temperature of theophylline is higher than the degradation temperature of the polymers, (M)DSC data of the physical mixtures and IM tablets containing theophylline were not recorded. The MDSC data of all other physical mixtures and IM tablets (sample mass 7-15mg) were analysed using Tzero pans (TA instruments, Zellik, Belgium) at a heating rate of 2°C/min. The modulation period and amplitude were set at 1min and 0.318°C, respectively (heat-iso method). The MDSC cell was purged using dry nitrogen at a flow rate of 50mL/min. A heat/cool/heat run was performed between -90 and 180°C to analyse the thermal characteristics (T_m, T_g, melting enthalpy) of pure components, physical mixtures and IM tablets. T_m was analysed in the first heating cycle.

Analysis of T_g was done during the first and second heating cycle for IM tablets and physical mixtures, respectively. XRD of pure components and IM tablets is performed using a D5000 CuKα diffractor (λ = 0.154nm) (Siemens, Karlsruhe, Germany) with a voltage of 40mA in the angular range of 10° < 2θ < 60° using a step scan mode (step width = 0.02°, counting time = 1s/step).

Attenuated total reflection Fourier-transform infrared (ATR FT-IR) measurements were performed to detect possible chemical interactions between API and polymer. Spectra (n=5) were collected of pure substances, physical mixtures and IM tablets 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 4 cm^{-1} and averaged over 64 scans. FT-IR spectral data analysis was done using SIMCA P+ v.12.0.1 (Umetrics, Umeå, Sweden). Different spectral ranges were evaluated via principal component analysis. All collected FTIR spectra were preprocessed using standard normal variation (SNV).

The homogenous distribution of the drugs in the different IM tablets was evaluated by Raman microscopic mapping using a Raman Rxn1 Microprobe (Kaiser Optical System, Ann Arbor, MI, USA) equipped with an air-cooled CCD detector. The laser wavelength employed was 785nm from a Invictus NIR diode laser having a laser power of 400mW. Raman microscopic mapping was done on the surface and on a cross-section of the injection-molded tablets, these areas were scanned by a 10x long working distance objective lens (spot size 50μm) in mapping mode using an exposure time of 4s and a step size of 50μm in both the x (18points) and y (13points) direction (=234 spectra or 850 x 600μm per mapping segment). Data collection and data transfer were automated using HoloGRAMS™ data collection software (version 2.3.5, Kaiser Optical Systems), the HoloMAP™ data analysis software (version 2.3.5, Kaiser Optical Systems) and Matlab software (version 7.1, The MathWorks, Natick, MA, USA).

Each mapping was analysed using multivariate curve resolution (MCR) approach to determine the composition homogeneity of the samples. Therefore, for each mapping segment all 234 spectra were introduced in a data matrix. Because each sample consisted of two components, 2-factor MCR was applied. Additionally, both a spectrum of pure drug and TPU were added to this data matrix. The spectral range was narrowed until 800-1500cm^{-1}, containing specific peaks for both components. First, all spectra were baseline corrected using Pearson's method and subsequently they were normalized, obtaining data matrix **D** containing the pre-processed spectra. MCR aims to obtain a clear description of the individual contribution of

each pure component in the area from the overall measured variation in **D**. Hence, all collected spectra in the area are considered as the result of the additive contribution of all pure components involved in the area. Therefore, MCR decomposes **D** into the contributions linked to each of the pure components in the system, described by the equation 1:

$$\mathbf{D} = \mathbf{CS} + \mathbf{E} \quad (1)$$

where **C** and **S** represent the concentration profiles and spectra, respectively. **E** is the error matrix, which is the residual variation of the dataset that is not related to any chemical contribution. Next, the working procedure of the resolution method started with the initial estimation of **C** and **S** and continued by optimizing iteratively the concentration and response profiles using the available information about the system. The introduction of this information was carried out through the implementation of constraints. Constraints are mathematical or chemical properties systematically fulfilled by the whole system or by some of its pure contributions. The constraint used for this study was the default assumption of non-negativity; that is, the data were decomposed as non-negative concentration times non-negative spectra.

2.5. *In vitro* dissolution

Drug release from the injection-molded tablets (n=3) was determined using the paddle method on a VK 7010 dissolution system (VanKel Industries, New Jersey, USA) with a speed of 100rpm. Distilled water was used as dissolution medium (900mL) at 37±0.5°C. Samples were withdrawn at predetermined time points (0.5; 1; 2; 4; 6; 8; 12; 16; 20 and 24h) and spectrophotometrically (UV-1650PC, Shimadzu Benelux, Antwerp, Belgium) analysed using a wavelength of 244, 273 and 273nm for acetaminophen, theophylline and diprophylline, respectively. *In vitro* drug release data were fitted to zero order release kinetics and R^2 values were calculated. At the same time points, formulations (n=3) were withdrawn from the medium and weighed after removing excess surface water. Images were made with a digital camera (C3030 Olympus) attached to an image analysis system (analySIS®) to visualize swelling behaviour. A digital calliper (Bodson, Luik, Belgium) was used to measure the height and diameter of the injection-molded tablets (n=3) in order to determine the axial and radial swelling, respectively. The water uptake (% weight gain of the hydrophilic TPU) was calculated from the weight of the IM tablets (n=3), taking into account the drug released as described in equation 2. [8]

$$\% \text{ water uptake } = \frac{(Ww - Drt) - (Wi - Dr0)}{(Wi - Dr0)} \text{ x } 100 \quad (2)$$

Where W_w = weight of the IM tablet at time 't' (hours after immersion)

W_i = initial weight of the IM tablet before dissolution

Dr_0 = amount of drug in the IM tablet before dissolution

Dr_t = amount of drug in the IM tablet at time 't' (hours after immersion)

The effect of HME/IM process temperature, extrusion speed, drug load and injection pressure on *in vitro* drug release and swelling behaviour was determined to evaluate robustness.

3. Results and discussion

TGA indicated that no thermal degradation of the different TPUs occurred below 220°C. All grades had similar glass transition temperatures varying between -42.5°C and -50.5°C, explaining the flexibility of the TPUs at room temperature. Except Tecophilic™ HP60D35, SP60D60, TG500 and TG2000, each TPU grade showed multiple endothermic peaks on the MDSC thermograms (detailed values are listed in **Table 2**), probably due to the presence of different crystal lattices in the hard segments of the hydrophilic TPU. As each grade was characterized by different melts, a specific extrusion temperature could not be predicted based on DSC data. In addition, samples were not subjected to shear stresses during (M)DSC experiments, further hindering the prediction of processing temperature. [24] In order to ensure maximum drug stability, processing temperature should be predicted and kept as low as possible. [25] Although MDSC did not allow to predict processing temperature of the hydrophilic TPUs, it was a useful tool to determine the plate press temperature, needed for rheology sample preparation as all polymers were molten at 180°C.

As displayed in **Table 2**, large differences were observed in rheological properties among the different TPUs. *Gupta et al*. linked the observed torque values during HME of Soluplus™ to the complex viscosity of rheology experiments. The viscosity of a melt should be within a specific range in order to avoid the torque limit of the extrusion equipment to be exceeded, whereas a certain melt viscosity is needed to ensure sufficient mixing. [23] It was stated that HME processing of polymers was possible if the complex viscosity was between 1000 and 10000Pa.s. [23] Although Soluplus™ and TPUs have different physicochemical properties, similar temperature sweep experiments (**Fig. 2**) were performed on all hydrophilic TPUs to verify the influence of increasing temperature on the polymer processability and to predict the temperature range in which acceptable complex viscosity values (i.e. 1000 - 10 000Pa.s) were obtained. As expected, the complex viscosity of all polymers was lower at higher temperatures, predicting lower torque values during processing at higher temperatures. As all TPUs had a storage modulus larger than the loss modulus at lower temperatures, they can all be considered as elastic solids. At higher temperature, the viscous properties of all TPUs increased and a cross-over point (i.e. temperature at which material starts to flow) was reached when tanδ (i.e. storage modulus/loss modulus) equals 1. Among the hydrophilic TPU grades, differences were observed for: the cross-over point (i.e. $T_{\tan\delta = 1}$) and the temperature range in which processing was considered to be acceptable (i.e. $T_{\eta^* = 1000 - 10\,000 Pa.s}$). To link

rheological properties to molecular weight, SEC analysis was performed on all grades. It is known that differences in average molecular weight can significantly affect rheological properties of polymers with similar chemical structures. [25] SEC analysis provided an explanation for the observed differences in rheological parameters: with increasing molecular weight of the hydrophilic TPU higher $T_{tan\delta = 1}$ and $T_{\eta^* = 1000Pa.s- 10\ 000Pa.s}$ values were observed during rheology measurements. To validate these predictions, all grades were extruded at a temperature ranging between $T_{\eta^* = 10\ 000Pa.s}$ and $T_{\eta^* = 1000Pa.s}$ ±10°C. For all TPUs the extrusion temperature (T_{extr}) was considered as the temperature at which torque values did not exceed 20% of the maximum torque. After HME of pure TPUs, it was found that SEC and rheology data predicted the lower extrusion temperatures of the Tecophilic™ grades SP60D60, SP93A100 and TG2000. Moreover, ^{1}H-NMR spectroscopy indicated that all grades TPUs have different soft segment to hard segment ratios (**Table 3**), resulting in a different water uptake capacity and thus potential differences in release kinetics. Due to their low predicted processing temperatures (i.e. ensuring the thermal stability of the API), and large differences in water uptake capacity, Tecophilic™ grades SP60D60, SP93A100 and TG2000 were further evaluated for the production of HME/IM oral sustained release dosage forms.

During a first series of HME/IM experiments, three selected hydrophilic TPUs were processed with different model drugs. Although 50% (w/w) drug loading was used, the torque values only slightly increased in comparison to the extrusion of pure polymers. Therefore, processing of the mixtures remained possible and was done at the same temperature of the pure polymers, i.e. 80°C for Tecophilic™ TG2000, 110°C for Tecophilic™ SP60D60 and Tecophilic™ SP93A100. Similar to the observations reported by *Claeys et al.* no adhesion to the mold was observed for hydrophilic TPU-based tablets. [15] In addition, all different compositions resulted in a non-crushable tablet making them less susceptible to abuse. A phenomenon that was linked to the low T_g of the TPUs (i.e. flexibility at room temperature).

In a next series of experiments, drug loading and process parameters were varied. For all model drugs, except theophylline, 70% (w/w) drug loading could be achieved without the need to increase the process temperature. As complex viscosity values were inversely correlated to the extrusion temperature, torque values were succesfully lowered by increasing the barrel temperature and even higher drug loads (up to 80%, w/w) could be used. Notably, injection pressure and post-injection pressure did not affect the dimensions of the IM tablets.

MDSC data indicated that the API remained mainly crystalline (varying between 71% and 99%) after processing as shown in **Fig. 3** and **Table 4**. Diffractograms of hydrophilic TPU, model drug and HME/IM tablets are shown in **Fig. 4**. Peaks corresponding to crystalline drug were present in all injection-molded tablets for all drugs used, confirming the unchanged crystalline state of the drug after processing.

The MCR contribution plots in **Fig. 5** showed that contributions of API and hydrophilic polyurethane were similar in all spectra, indicating that the drug was homogeneously distributed throughout the tablet, for both cross sections and surfaces.

As shown in **Fig. 6**, drug release depended on the hydrophilic TPU grade: 58, 67 and 94% acetaminophen was released after 24h from matrices containing Tecophilic™ SP60D60, SP93A100 and TG2000, respectively. Whereas complete drug release of theophylline and diprophylline was not obtained without the use of release modifiers in hydrophobic TPU matrices, a complete and sustained release was observed when using hydrophilic TPU matrices. [21] Since the rate and extent of swelling might influence the drug release mechanism and kinetics, swelling of the IM tablets was plotted as a function of dissolution time. As the soft segment/hard segment ratio increased, more PEO was present in the polymer structure (SP60D60<SP93A100<TG2000). This resulted in a higher water uptake, which could be linked to the faster release kinetics. Although the water uptake of formulations containing TG2000 was about 6- and 10- fold higher than the water uptake of formulations based on SP93A100 and SP60D60, respectively, the *in vitro* release kinetics did not reflect this observation in the same magnitude. In addition, a fast water uptake was observed for all formulations during the first 8 hours, without burst release issues. Both phenomena, as earlier reported by *Verhoeven et al.* and *Siepmann et al.,* might be attributed to the instantly formed gel outer layer upon contact with the dissolution medium which delays drug release as displayed in **Fig. 7 and Fig. 8**. [8][26]

Besides the length of the soft segment (i.e. Tecophilic™ grade), drug release was affected by drug loading as TPU matrices with a high drug load (up to 70%, w/w) yielded faster release kinetics **(Fig. 9)**. Similar to the results described by *Claeys et al.* for hydrophobic TPU matrices, no burst-effect issues were observed for hydrophilic TPU formulations containing up to 70% (w/w) drug. [15] In addition, release kinetics of all model drugs were not affected by modifying HME screw speed, barrel temperature nor by changing downstream processing parameters (i.e. injection pressure and post-injection pressure).

4. Conclusion

Based on their lower processing temperatures (predicted via rheology), Tecophilic™ SP60D60, SP93A100 and TG2000 were successfully used for the manufacturing of high drug loaded (up to 70%, w/w) oral sustained release dosage forms via HME/IM. In addition, Raman mapping and (M)DSC results indicated a homogeneous distribution of mainly crystalline API in all matrices. As the in vitro drug release from the hydrophilic TPU matrices depended on the length of the PEO soft segment, this concept provides a versatile system to adjust the drug release of different types of drugs without using release modifiers.

Acknowledgements

The authors would like to thank Mrs. Elien Van Stappen for experimental help. This work was supported by the FWO-Flanders.

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Figures

Fig. 1. Chemical structure of the aliphatic hydrophilic TPU Tecophilic™.

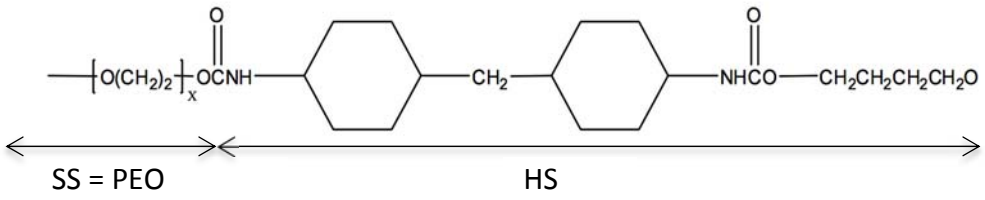


Fig. 2. Output of temperature sweep experiment on Tecophilic™ TG2000. Cross-over point ($T_{tan\delta} = 1$ = 56°C) and predicted processing temperature range (i.e. $T_{\eta^* = 1000\text{-}10\,000 Pa.s}$ = [73-150°C]) are shown.

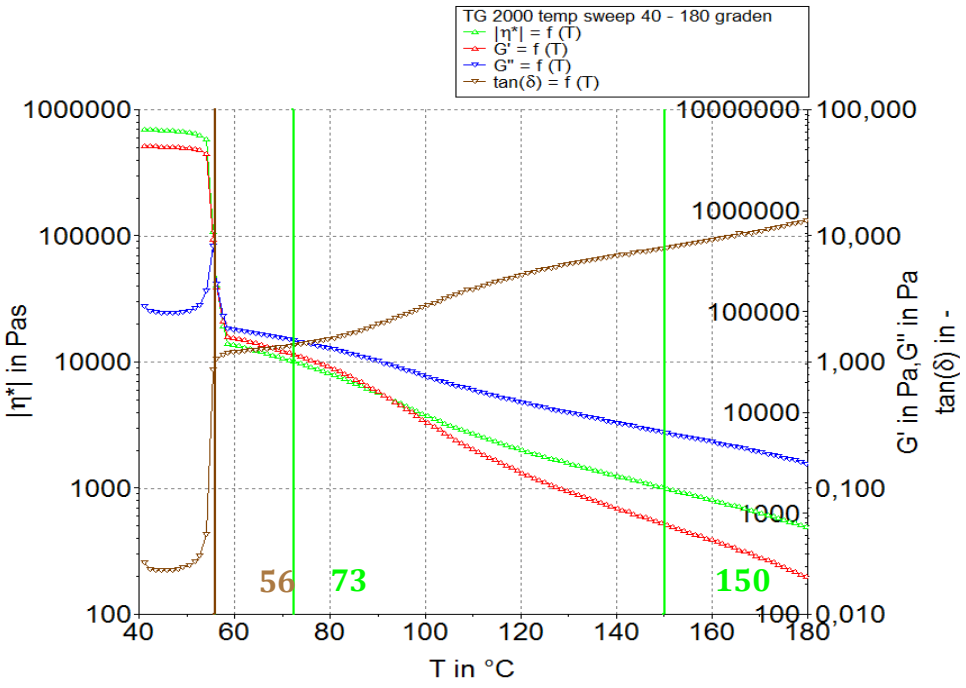


Fig. 3. MDSC thermograms of pure diprophylline **(A)**, pure polymer Tecophilic™ TG2000 **(B)**, physical mixture diprophylline/TG2000 (50/50, w/w) **(C)** and IM tablet diprophylline/TG2000 (50/50, w/w) **(D)**.

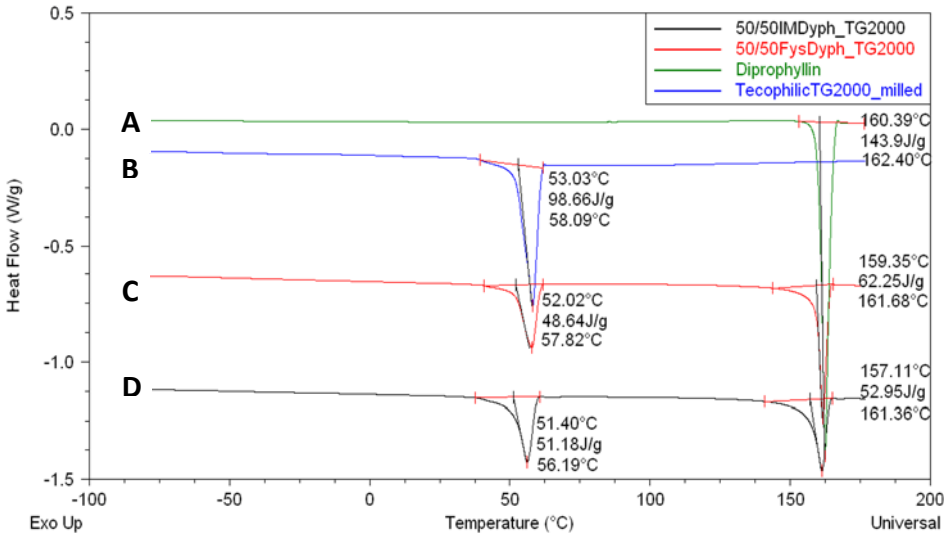


Fig. 4. XRD patterns of **(A)** IM tablet theophylline/SP60D60 (50/50, w/w) **(B)** theophylline and **(C)** Tecophilic™ SP60D60.

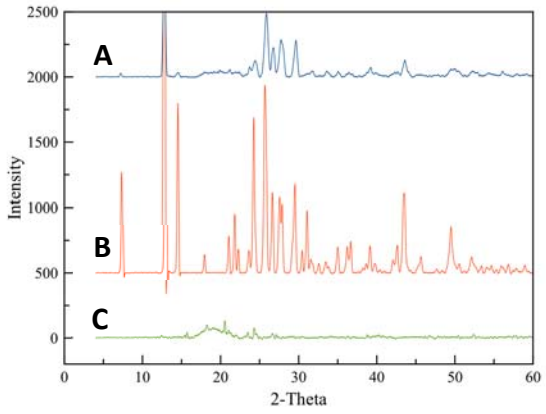


Fig. 5. Raman spectra of **(A)** IM tablet cross section diprophylline/SP60D60 (50/50, w/w), **(B)** diprophylline and **(C)** Tecophilic™ SP60D60. MCR contribution plot showing the equal contribution of diprophylline **(D)** and Tecophilic™ SP60D60 **(E)** to the Raman spectrum of the IM tablet.

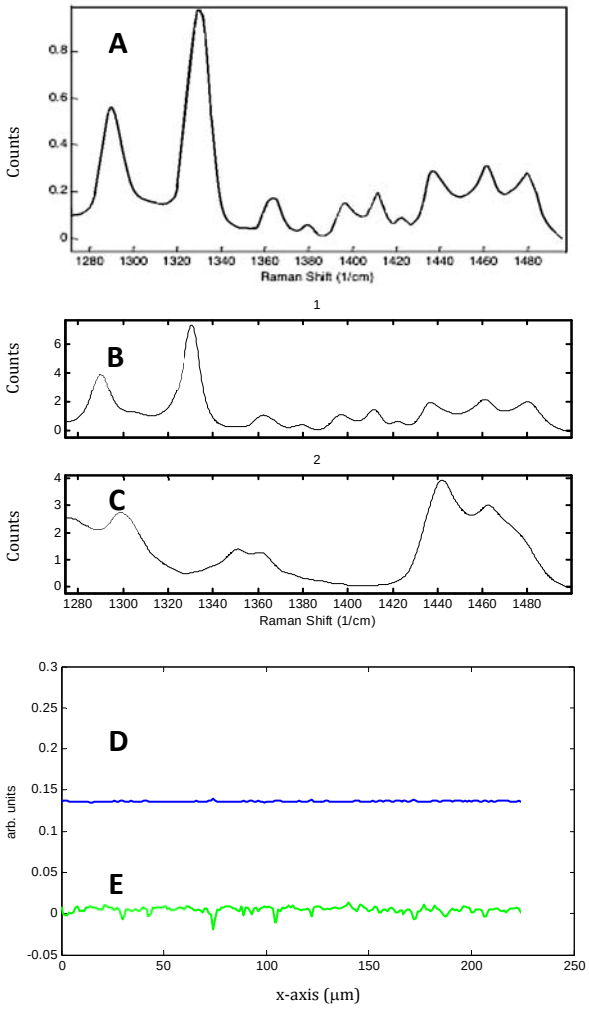


Fig. 6. Influence of length of the soft segment (poly ethylene oxide) on the *in vitro* release kinetics (mean ±SD, n=3) of drugs with different aqueous solubility from TPU-based matrices formulated with different TPU grades (SP60D60, SP93A100 and TG2000).

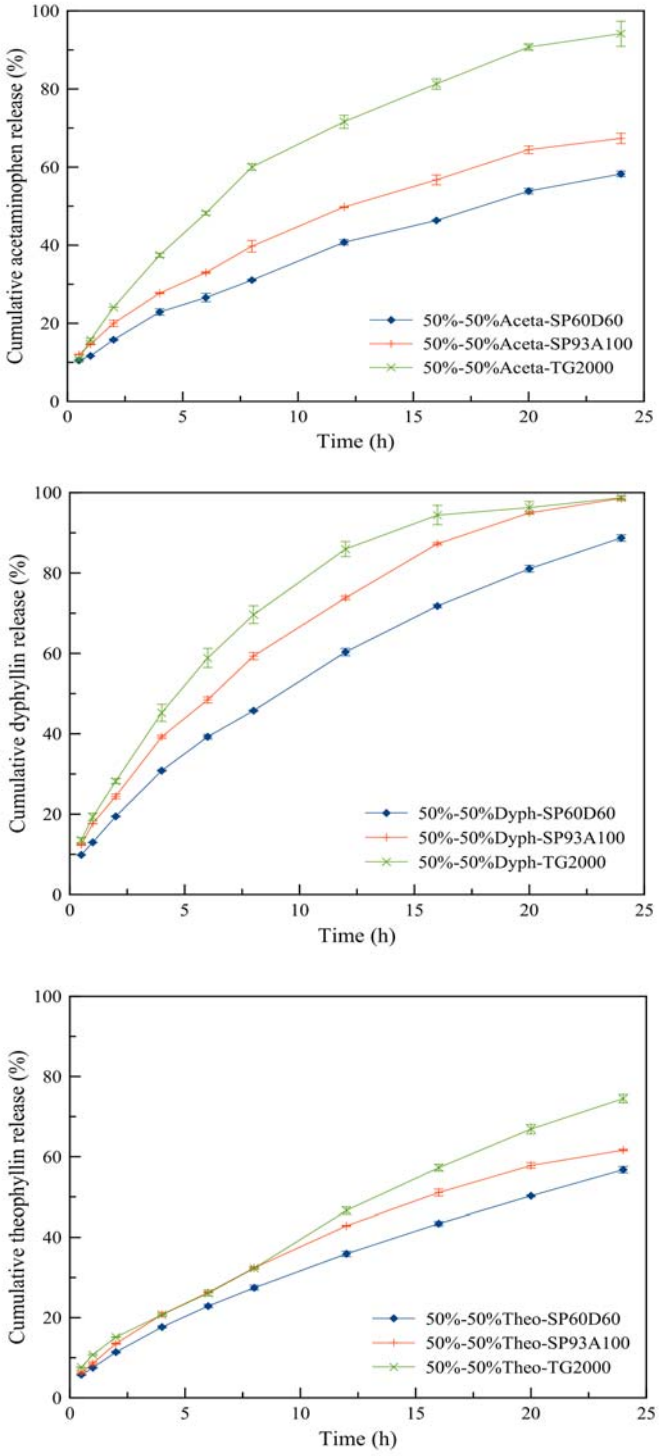


Fig. 7. Influence of length of the soft segment (poly ethylene oxide) on the swelling behavior (mean ±SD, n=3) of TPU matrices containing 50% (w/w) diprophylline and different TPU grades (SP60D60, SP93A100 and TG2000).

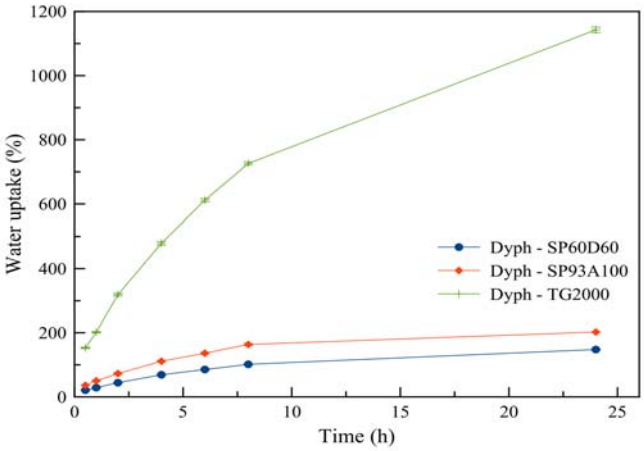
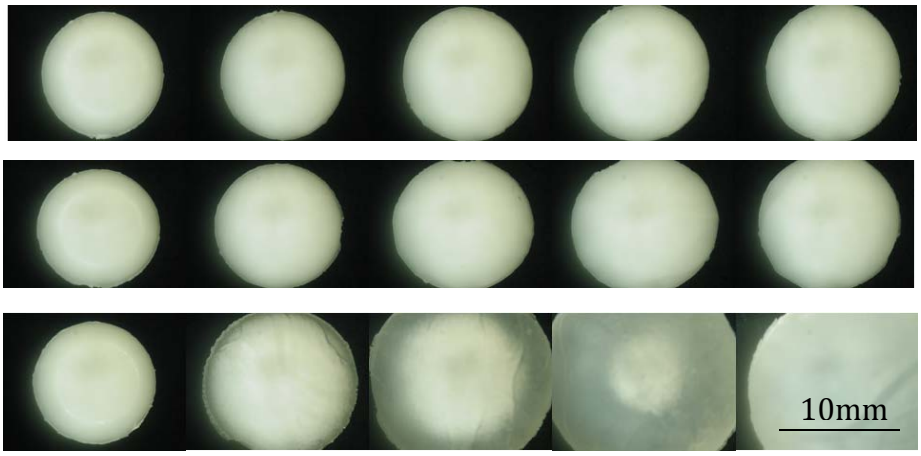
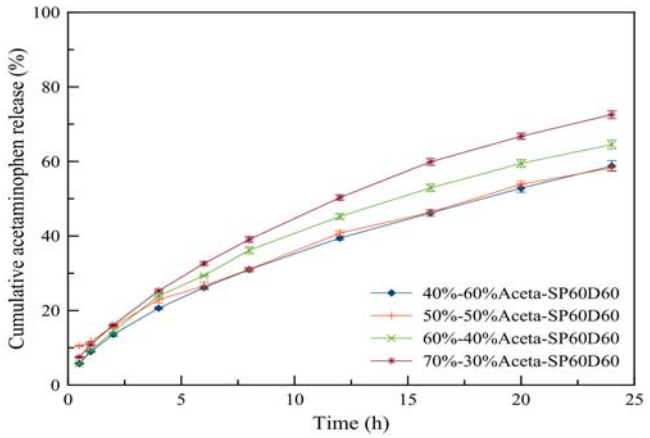
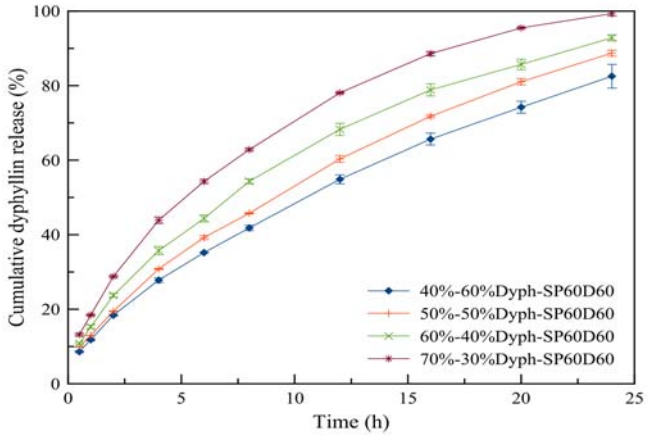


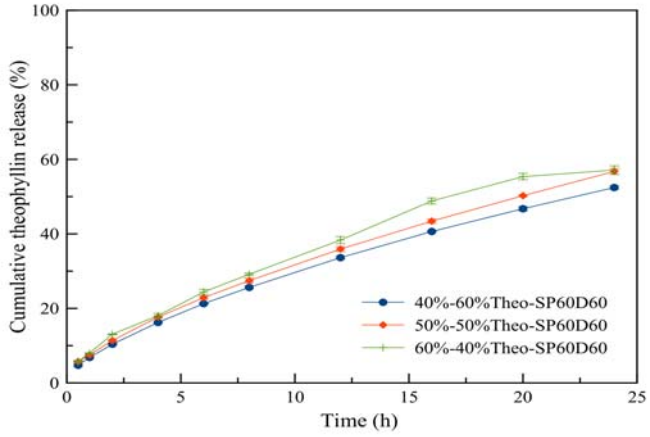
Fig. 8. Pictures of IM tablets containing 50% (w/w) diprophylline in combination with Tecophilic™ SP60D60, SP93A100 and TG2000 (top to bottom), at different sampling time points (0h, 1h, 4h, 8h and 12h) (left to right).



562 **Fig. 9.** Influence of drug load on the *in vitro* release kinetics (mean ±SD, n=3) of formulations
563 containing drugs with different aqueous solubility and different TPU grades (SP60D60,
564 SP93A100 and TG2000).
565
566







Tables

Table 1. Overview of different Tecophilic™ grades and their equilibrium water uptake. [11]

Tecophilic™ grade	Equilibrium water uptake (w/w, %)
HP60D20	20
HP60D35	35
HP60D60	60
HP93A100	100
SP60D60	60
SP93A100	100
SP80A150	150
TG500	500
TG2000	900

Table 2. Overview of screening data and extrusion temperature of all hydrophilic TPU grades. Minimum processing temperature T_{extr} was defined as the temperature at which torque values did not exceed 20% of maximum torque.

Tecophilic™ grade	T_g (°C)	T_m (°C)	M_n (g/mol)	M_w (g/mol)	$T_{tan\delta = 1}$ (°C)	$T_{range10000 - 1000Pas}$ (°C)	$T_{extr.}$ (°C)
HP60D20	-46.8	55.1; 86.4	52 461	119 151	132	172-... [a]	170
HP60D35	-42.5	72.9	111 348	189 881	158	194-... [a]	180
HP60D60	-44.9	55.6; 107.3	112 136	209 649	136	176-... [a]	180
HP93A100	-47.0	44.4; 129.2	77 277	159 031	122	163-... [a]	170
SP60D60	-49.3	71.2	33 399	63 870	131	124-161	110
SP93A100	-47.7	8.8; 40.8; 73.8; 126.2	45 719	88 843	105	117-167	110
SP80A150	-48.7	16.7; 55.8; 104.1	110 979	184 937	112	156-199	170
TG500	-50.5	55.7	141 772	219 466	117	122-187	170
TG2000	-49.6	58.1	82 643	130 331	56	73-150	80

[a] $T_{1000Pas}$ (°C) was not determined as it exceeded the temperature limit of the rheometer module (i.e. 200°C)

575 **Table 3.** Overview of different Tecophilic™ grades and their soft segment (SS)/hard segment
576 (HS) ratio, based on ^{1}H-NMR results. With increasing SS (i.e. PEO) length higher equilibrium
577 water uptake values were observed.

Tecophilic™ grade	SS[b]/HS[c]
HP60D20	3.3
HP60D35	5.7
HP60D60	7.8
HP93A100	11.8
SP60D60	6.9
SP93A100	11.8
SP80A150	21.0
TG500	39.8
TG2000	82.3

578 [b] soft segment polyethylene oxide (PEO)
579 [c] hard segment hexamethylene diisocyanate (HMDI) in combination with 1,4-butanediol (1,4-BD) as chain extender
580

581 **Table 4.** Melting enthalpy of acetaminophen and diprophylline in physical mixtures and IM
582 tablets.

Drug	Polymer	$\Delta H_{Physical\ mixture}$ (J/g)	$\Delta H_{IM\ Tablet}$ (J/g)	%Crystallinity
Acetaminophen	SP60D60	42.6	32.0	75.0
	SP93A100	41.1	29.0	70.6
	TG2000	17.7	17.6	99.5
Diprophylline	SP60D60	51.2	45.2	88.3
	SP93A100	48.0	46.2	96.2
	TG2000	62.3	53.0	85.1

583