A COMPARATIVE STUDY BETWEEN MELT GRANULATION/COMPRESSION AND HOT MELT EXTRUSION/INJECTION MOLDING FOR THE MANUFACTURING OF ORAL SUSTAINED RELEASE THERMOPLASTIC POLYURETHANE MATRICES

G. Verstraete[1], P. Mertens[1], W. Grymonpré[1], P. J. Van Bockstal[2], T. De Beer[2], M. N. Boone[3], L. Van Hoorebeke[3], J. P. Remon[1], C. Vervaet[1]

[1] Laboratory of Pharmaceutical Technology, Ghent University, Ghent, Belgium

[2] Laboratory of Pharmaceutical Process Analytical Technology, Ghent University, Ghent, Belgium

[3] Radiation Physics – Centre for X-ray Tomography, Dept. Physics and Astronomy, Ghent University, Ghent, Belgium

Corresponding author:

C. Vervaet

Ghent University

Laboratory of Pharmaceutical Technology

Ottergemsesteenweg 460

9000 Ghent (Belgium)

Tel.: +32 9 264 80 54

Fax: +32 9 222 82 36

E-mail: Chris.Vervaet@Ugent.be

Abstract

During this project 3 techniques (twin screw melt granulation/compression (TSMG), hot melt extrusion (HME) and injection molding (IM)) were evaluated for the manufacturing of thermoplastic polyurethane (TPU)-based oral sustained release matrices, containing a high dose of the highly soluble metformin hydrochloride.

Whereas formulations with a drug load between 0-70% (w/w) could be processed via HME/(IM), the drug content of granules prepared via melt granulation could only be varied between 85-90% (w/w) as these formulations contained the proper concentration of binder (i.e. TPU) to obtain a good size distribution of the granules. While release from HME matrices and IM tablets could be sustained over 24h, release from the TPU-based TSMG tablets was too fast (complete release within about 6h) linked to their higher drug load and porosity. By mixing hydrophilic and hydrophobic TPUs the in vitro release kinetics of both formulations could be adjusted: a higher content of hydrophobic TPU was correlated with a slower release rate. Although mini-matrices showed faster release kinetics than IM tablets, this observation was successfully countered by changing the hydrophobic/hydrophilic TPU ratio. In vivo experiments via oral administration to dogs confirmed the versatile potential of the TPU platform as intermediate-strong and low-intermediate sustained characteristics were obtained for the IM tablets and HME mini-matrices, respectively.

Keywords: hot melt extrusion, twin screw melt granulation, matrices, high drug load, sustained release, thermoplastic polyurethanes, metformin hydrochloride

1 INTRODUCTION

Conventional polymers used for hot melt extrusion (HME) of sustained release matrix formulations often deal with processing (i.e. high torque values) and burst-release issues when using high drug loads. [1][2] *Claeys et al.* already showed the suitability of hydrophobic thermoplastic polyurethanes (TPUs) for the production of sustained release tablets using HME in combination with injection molding (IM). [3] Those TPU-based dosage forms allowed to sustain drug release even at high drug loads (up to 70%, w/w) and release kinetics could be modified by adding release modifiers. [4][5] Recently, hydrophilic TPUs were investigated by *Verstraete et al.* to ensure a complete drug release of drugs with different physicochemical properties, without using release modifiers. The *in vitro* drug release from the TPU matrices depended on the chemical composition of the hydrophilic polyurethane grades, providing a versatile system to adjust the drug release of different types of drugs. [6]

Metformin.HCl is recommended by the International Diabetes Federation in the first-line treatment of diabetes mellitus (type II) as it decreases the basal hepatic glucose production and enhances the sensitivity for insulin in the body, resulting in lower blood glucose levels without risk for hypoglycaemia. [7][8][9] The aim of this study was to compare different techniques for the manufacturing of high drug loaded TPU-based oral sustained release matrices. The oral antihyperglycemic drug is known for its high and frequently dosage, high water solubility and narrow absorption range (i.e. mainly upper part of gastro-intestinal tract). Therefore, this API should put the versatility of the TPU polymer platform to the test for both processing techniques. [10][11] The development of a sustained release formulation that maintains drug plasma levels for 10-16h will limit plasma concentration fluctuations and thus reduce side-effects. Furthermore, once-daily intake should improve patient compliance. [12][13][14]

IM tablets, TSMG tablets and HME mini-matrices having different polymer compositions were manufactured and characterized. The influence of formulation strategy/geometry and polymer composition on the *in vitro* release kinetics was evaluated. As co-ingestion of alcoholic beverages with sustained release matrices can result in dose dumping, the influence of ethanol was evaluated on the in vitro drug release. Finally, *in vivo* performance of the most promising oral sustained release dosage forms was investigated and compared to a commercially available reference formulation.

2 EXPERIMENTAL SECTION

2.1 Materials

The hydrophobic TPU grade Tecoflex™ EG72D and the hydrophilic TPU grades Tecophilic™ SP60D60, SP93A100 and TG2000 were obtained from Merquinsa (a Lubrizol Company, Ohio, USA). As shown in **Fig. 1**, the hard segment (HS) of the hydrophobic and hydrophilic TPUs is a combination of hexamethylene diisocyanate (HMDI) and 1,4-butanediol (i.e. chain extender). Although the hydrophobic and hydrophilic TPUs have a similar hard segment, the chemical composition of the soft segment (SS) is different. The soft segment of Tecophilic™ is PEO (polyethylene oxide), while the soft segment of Tecoflex™ is polytetrahydrofuran (pTHF). [4][6][15] Metformin.HCl was purchased from Fagron (Waregem, Belgium).

2.2 Preparation of formulations

2.2.1 Hot-melt extruded mini-matrices

Hot melt extrusion (HME) was performed on a mixture of TPUs and metformin hydrochloride (60% drug load, w/w, in all cases). Physical mixtures were extruded using a co-rotating twin-screw extruder (Haake MiniLab II Micro Compounder, Thermo Electron, Karlsruhe, Germany), operating at a screw speed of 100rpm. Extrusion temperature was set at 100°C for formulations containing TG2000. For formulations based on (a mixture of) Tecoflex™ EG72D, Tecophilic™ SP60D60 and Tecophilic™ SP93A100, the extrusion temperature was set at 160°C. After HME, the extrudates were immediately processed into mini-matrices (±3.5mm height; ±3mm diameter) via manual cutting (using a surgical blade).

2.2.2 Injection molded tablets

After hot melt extrusion (using the same settings as described above), the extrudates were also processed via injection molding into tablets with a diameter and height of approximately 9 and 4mm, respectively. IM experiments were performed using a Haake MiniJet System (Thermo Electron, Karlsruhe, Germany) at a temperature equal to the extrusion temperature. During the IM process an injection pressure of 800bar (10s) forced the material into the mould. A post-pressure of 400bar (5s) avoided expansion by relaxation of the polymer.

2.2.3 Twin screw melt granulation tablets

Twin screw melt granulation (TSMG) experiments were performed using a co-rotating intermeshing twin-screw granulator (Prism Eurolab 16) (Thermo Fisher Scientific, Karlsruhe, Germany) with a barrel length of 25 *L*/*D*, where *L* is the axial screw length of the machine and *D* is the inner bore diameter corresponding to one of the screws. The screw design was identical for all experiments with two kneading zones in the third and fifth segment which consisted of 6 kneading discs at a 60° stagger angle in forward direction. To evaluate the effect of drug load, physical mixtures of metformin hydrochloride and Tecoflex™ EG72D (API concentration was varied from 60 to 85% (w/w)) were fed into the screws of the granulator using a DD Flex wall 18 gravimetric feeder (Brabender Technologie, Germany), which was set in the gravimetric feeding mode. Throughput and screw speed were kept constant at 0.7kg/h and 200rpm, respectively. The barrel was divided into 6 zones. Segment 6, which is located at the end of the barrel, had a lower temperature of 40°C during all runs in order to cool down the granules and avoid sticking of the granules when leaving the granulator. In all other zones the temperature was constant at 140°C. Granule samples were collected after melt granulation of each metformin hydrochloride/TPU mixture. Each sample collection was started after 15min of equilibration time, which is the time needed to reach a steady state process (i.e. stable torque and barrel wall temperature which were initially unstable due to layering of the screws and the screw chamber walls with material). Sample collection was executed until 500g of sample was collected.

After TSMG, granules were sieved for 10min at an amplitude of 2mm using a vibrating sieve tower (Retsch VE 1000, Haan, Germany). Granules with a particle size between 250 and 1000μm were used for tableting. Before every compression experiment, granules with a mass corresponding to 250mg metformin.HCl were weighed and manually poured into the die. All samples were tableted using a manual single punch eccentric tablet machine (Korsch EK0, Erweka, Heusenstamm, Germany) with 10mm diameter circular punches (flat faced). For all tableting experiments, a constant compaction pressure of 130MPa was used.

To investigate the influence of TPU binder concentration on the tablet properties (i.e. porosity and disintegration time) and compaction behavior (i.e. elastic recovery), all TSMG batches (sieve fraction 800-850μm) were tableted using a rotary tablet press (MODUL P, GEA Pharma Systems, Courtoy, Halle, Belgium) equipped with a round concave (radius: 24mm) Euro B punch of 10mm diameter at a tableting speed of 5rpm. All tablets (250 ± 5mg) were prepared

using a compaction pressure ranging from 65 to 260MPa, without pre-compression. All tablets were characterized for tablet mass and dimensions (immediately, 24h and 7days post-ejection). After 7days, all tablets were subjected to USP disintegration testing.

2.3 Characterization of TSMG granules

2.3.1 Particle size distribution

Sieve analysis was performed using a Retsch VE 1000 sieve shaker (Haan, Germany). Granules were placed on the shaker during 5min at an amplitude of 2mm using a series of sieves (75, 150, 250, 500, 800, 1000 and 2000μm). The amount of granules retained on each sieve was determined. The amount of fines and oversized granules were defined as the fractions <250μm and >1000μm. The yield of the granulation process was defined as the fraction between 250 and 1000μm.

2.3.2 Friability

A friabilator (PTF E Pharma Test, Hainburg, Germany) was used to determine the TSMG granule friability (n=3) at a speed of 25rpm for 10min, by subjecting 10g (*Iwt*) of granules together with 200 glass beads (4mm mean diameter) to falling shocks. Prior to determination, the granule fractions <250μm and >1000μm were removed to assure the same starting conditions. Afterwards, the glass beads were removed and the weight retained on a 250μm sieve (*Fwt*) was determined. The friability was calculated as described by equation 1:

$$Friability\ (\%) = \left(\frac{Iwt - Fwt}{Iwt}\right)\ x\ 100 \qquad (1)$$

2.4 Characterization of HME mini-matrices, IM tablets and TSMG tablets

2.4.1 Thermal analysis

Metformin crystallinity was evaluated using differential scanning calorimetry. A DSC Q2000 (TA Instruments, Leatherhead, UK) with a refrigerated cooling system (RCS) was used to determine melting point (T_m) and melting enthalpy (ΔH) of pure components, physical mixtures, mini-matrices, IM tablets and TSMG tablets. All physical mixtures and TPU-based formulations (sample mass 7-15mg) were analysed using Tzero pans (TA instruments, Zellik, Belgium) at a heating rate of 10°C/min. The DSC cell was purged using dry nitrogen at a flow rate of 50mL/min. One single heating run from 20 to 250°C was performed to analyse the

thermal characteristics (T_m and melting enthalpy) of pure components, physical mixtures, mini-matrices and IM tablets.

2.4.2 Fourier-transform infrared spectroscopy

Attenuated total reflection Fourier-transform infrared (ATR FT-IR) measurements were performed to detect possible hydrogen bonds between API and polymer. Spectra (n=5) were collected of pure substances, physical mixtures and final formulations using a Nicolet iS5 ATR FT-IR spectrometer (Thermo Fisher Scientific). Each spectrum was collected in the 4000 to 550cm^{-1} range with a resolution of 4cm^{-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 FT-IR spectra were preprocessed using standard normal variation (SNV).

2.4.3 Raman spectroscopy

The distribution of the drugs in the different formulations was evaluated by Raman microscopic mapping using a Raman Rxn1 Microprobe (Kaiser Optical System, Ann Arbor, MI, USA) equipped with an Invictus NIR diode (wavelength 785nm; laser power 400mW). Two areas (one surface and one cross section) 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), HoloMAP™ data analysis software (version 2.3.5, Kaiser Optical Systems) and Matlab software (MATLAB 8.6, The MathWorks, Natick, USA). Each map was analysed using multivariate curve resolution (MCR) to evaluate the homogeneous drug distribution in the matrices. Therefore, for each map all 234 spectra were introduced in a data matrix. Since 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 to 800-1500 cm^{-1} since clear spectral differences between drug and polymer could be observed in this spectral range. Prior to MCR, all spectra were baseline corrected using Pearson's method and 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 2:

$$D = CS + E \qquad (2)$$

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 time non-negative spectra.

2.4.4 Axial recovery

Axial recovery of the TSMG tablets was calculated immediately, 1 day and 7 days after ejection via the Armstrong and Haines-Nutt equation (equation 3):

$$Axial\ elastic\ recovery\ (\%) = \left(\frac{Ta - Tid}{Tid}\right)\ x\ 100 \qquad (3)$$

where *Ta* denotes the tablet height after ejection (immediate, after 1 day or after 7 days in mm) and *Tid* the tablet height under maximum compression force (mm). [16] [17] The dimensions of 3 tablets, manufactured at equal conditions, were used to calculate the axial elastic recovery of each formulation at 3 compaction pressures.

2.4.5 Tablet porosity

2.4.5.1 Helium pycnometry

The porosity of the tablets (n=3) was calculated using equation 4:

$$Tablet\ porosity\ (\%) = \left(1 - \frac{\rho\ app}{\rho\ true}\right) x\ 100 \qquad (4)$$

where $\rho\ app$ and $\rho\ true$ denote the apparent and true density (g/mL), respectively. Apparent density was calculated by diving the tablet mass by the volume of the tablet, while the true density of all powders was measured using helium pycnometry (AccuPyc 1330, Micrometrics,

Norcross, USA) at an equilibration rate of 0.0050 psig/min with the number of purges set to 10. [17]

2.4.5.2 X-ray tomography

The porosity of one IM tablet and one TSMG tablet was investigated using high-resolution X-ray computed tomography (custom-designed µCT setup HECTOR of the Ghent University Centre for X-ray Tomography (UGCT)). [18] A voxel size of 5.5 x 5.5 x 5.5µm³ was used, which is well within the specification of the focal spot size. At this magnification, the tablets were completely inside the field-of-view using a 2048x2048 pixels detector.

The µCT data was reconstructed using Octopus Reconstruction [19] and analysed using Octopus Analysis (both Inside Matters, Ghent, Belgium). [20] To remove phase-contrast edge enhancement artefacts and improve the contrast-to-noise ratio, a single-image phase retrieval filter was applied. [21][22] The same workflow was used for all tablets, hence resulting porosities can be compared (but it must be noted that absolute values depend strongly on grey value threshold). Besides the contrast between sample and air, a clear contrast between the polymer matrix and active product can be observed, as theoretically predicted using the NIST XCOM database. [23]

2.5 Dissolution experiments

The in vitro release experiments were based on the USP guidelines for metformin hydrochloride sustained release tablets. Drug release from the injection molded tablets, mini-matrices and TSMG tablets was determined using the paddle method on a VK 7010 dissolution system (VanKel Industries, New Jersey, USA) with a speed of 100rpm. Simulated intestinal fluid (SIF, pH 6.8), simulated gastric fluid (SGF, pH 1.2) and SGF + ethanol (20%, V/V) were used as dissolution media (900mL) at 37±0.5°C, without the addition of enzymes. [24] 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 at a wavelength of 232nm.

After 12h dissolution experiments, all IM tablets were lyophilized in a Lyobeta 25^{TM} laboratory scale freeze-dryer (Telstar, Terrassa, Spain) to prepare them for X-ray tomography experiments. The 60% (w/w) drug loaded TSMG tablets were not subjected to freeze-drying

as they completely disintegrated during dissolution. Immediately after in vitro dissolution testing, the tablets were put in individual vials and placed on the shelves in the drying chamber (cooled to –50°C). Primary and secondary drying were performed at -30°C and 20°C, respectively, both at a pressure of 10Pa. The vials were closed under a controlled nitrogen atmosphere.

2.6 Disintegration experiments

A USP disintegration apparatus (Pharma Test, Hainburg, Germany, disk method) was used to investigate the impact of mechanical stress on the geometry of the IM tablets, HME mini-matrices and Glucophage™ SR reference formulations. All experiments were conducted over a time period of 12h in SIF at a temperature of 37°C. The disintegration times of 3 individual tablets were recorded and the average was reported. To visualize geometry changes, images were taken with a digital C3030 Olympus camera (attached to an image analysis system (analySIS®)), before and after 12h disintegration testing.

2.7 *In vivo*

The in-vivo study (application ECD 2013/127) was approved by the Ethical Committee of the Faculty of Veterinary Medicine (Ghent University) before starting the experiments.

2.7.1 Subjects and study design

In vivo experiments were performed using the most promising formulations: mini-matrices (metformin.HCl/Tecoflex™ EG72D, 60/40, w/w) and IM tablets (metformin.HCl/Tecophilic™ SP60D60/Tecoflex™ EG72D, 60/20/20, w/w/w). Both formulations were compared with Glucophage™ SR 500 mg (½ tablet) as a reference. Open label cross-over assays were performed on 6 male beagle dogs (10-13kg) with a wash-out period of at least 8 days. The IM tablets, mini-matrices and reference formulations were administered to fasted dogs with 20mL of water. During the experiment the dogs were only allowed to drink water. Plasma samples were collected 1, 2, 3, 4, 5, 6, 8 and 12 hours post administration and were stored at -25°C until analysis. All TPU-based formulations were recovered from faeces to determine the residual metformin.HCl content. Moreover, the gastro-intestinal residence time of the formulations was recorded.

2.7.2 Metformin hydrochloride assay

An extraction method developed by *Gabr et al.* was optimized. [25] After de-freezing, plasma samples were centrifuged using a Centric 322A (Tehtnica, Slovenia) at 2300g for 10min. 280µL of the supernatant was spiked with 20µL of 0.05mg/mL ranitidine solution. During a first extraction step, 50µL of 10M sodium hydroxide solution and 3mL organic phase (1-butanol/hexane, 50/50, V/V) were added. The tubes were mixed using a Turbula™ mixer (Willy A. Bachofen Maschinenfabrik, Switzerland) during 30min at an intensity of 79rpm. The upper organic layer was transferred to a clean test tube after centrifugation. Back extraction was performed by adding 1mL of 2M HCl. Consecutively, tubes were mixed (79rpm, 10minutes) and centrifuged. After centrifugation (10min, 2300g) the organic layer was removed, 400µL of sodium hydroxide (10M) and 2mL organic phase (1-butanol/hexane, 50/50, V/V) were added. After mixing (79rpm, 30min) and centrifugation (10min, 2300g), the organic layer was transferred into a clean glass tube and evaporated to dryness under a nitrogen stream.

The HPLC system (Merck-Hitachi, Darmstadt, Germany) consisted of an isocratic solvent pump (L-7100) set at a constant flow rate of 0.7mL/min, an auto-sampler injection system (L-7200) with a 100µL loop (Valco Instruments Corporation, Houston, Texas, USA), a reversed-phase column and pre-column (LiChroCart® 250-4 and LiChrospher® 100RP-18 5µm, respectively) and a variable wavelength UV-detector (L-7400) set at 236nm. The mobile phase consisted of potassium dihydrogen phosphate buffer (adjusted to pH 6.5 with 2M NaOH)/acetonitrile (66/34, V/V) and 3mM sodium dodecyl sulphate (SDS). Peak integration was performed using the software package D-7000 HSM Chromatography Data Station.

2.7.3 Method validation

Based on the guidelines of the International Conference on Harmonization (ICH), the following parameters were evaluated: linearity, specificity, accuracy, precision, recovery, lower limit of detection (LOD) and lower limit of quantification (LOQ). [26]

2.7.4 Data analysis

Peak integration was performed using the software package D-7000 HSM Chromatography Data Manager. The peak plasma concentration (C_{max}), time to reach C_{max} (T_{max}), half value duration ($HVD_{t50\%Cmax}$) and area under the curve ($AUC_{0\text{-}12h}$) were calculated using a commercial

software package (MATLAB 8.6, The MathWorks, Natick, USA, 2015). The sustained-release characteristics of the tested formulation were evaluated by calculating the R_D ratio between the $HVD_{t50\%Cmax}$ values of a test formulation and an immediate-release formulation. A ratio of 1.5, 2 and >3 indicates low, intermediate and strong sustained release characteristics, respectively.

2.7.5 Statistical analysis

The effect of metformin.HCl formulation on the bioavailability was assessed by repeated-measures ANOVA (univariate analysis). To further compare the effects of the different treatments, a multiple comparison among pairs of means was performed using a Bonferroni post-hoc test with $P < 0.05$ as significance level. The normality of the residuals was evaluated with a Kolmogorov-Smirnov test. To test the assumption of variance homogeneity, a Levene's test was used. The statistical analysis was performed using SPSS (IBM SPSS Statistics for Windows, version 23.0, Armonk, New York, USA, 2015).

3 RESULTS AND DISCUSSION

The TPU polymer platform offers a versatile formulation strategy to adjust the release kinetics of several high drug loaded drugs with different aqueous solubility. As metformin hydrochloride is highly soluble and characterized by a narrow absorption range, various hydrophilic/hydrophobic TPU (mixtures) were used to put the versatility of this polymer platform to the test using three different manufacturing techniques: HME, IM and TSMG/compression.

During preliminary extrusion experiments, physical mixtures of metformin.HCl and various ratios of hydrophilic/hydrophobic TPUs (Metformin.HCl/TPU ratio: 60/40, w/w) were processed. Whereas processing of TPU formulations via HME was possible at 60% (w/w) drug load using other drugs (acetaminophen, theophylline and diprophylline), high torque values and shark skinning was observed for metformin.HCl formulations using the same processing temperatures (i.e. 80°C and 110°C for Tecophilic^{TM} TG2000 and all other TPU grades, respectively). [6] This phenomenon was even more pronounced at higher drug loads (up to 70%, w/w) and is linked to the higher friction of the metformin.HCl particles in the extruder barrel. [27][28][29] By increasing barrel temperature to 100°C and 160°C for formulations based on Tecophilic^{TM} TG2000 and other TPUs, respectively, less shark skinning and lower torque values (i.e. 20% of maximum torque) were observed. This finding could be explained by the lower complex viscosity of all polymers at higher temperatures. [6] In all cases, a white extrudate strand was obtained after HME which was immediately processed into non-crushable tablets (via IM) and mini-matrices (via manual cutting). During the IM process, no sticking to the mould was seen. [4][6] Whereas formulations with a drug load between 0-70% (w/w) could be processed via HME/(IM), the drug content of granules prepared via melt granulation could only be varied between 85-90% (w/w) as these formulations contained the proper concentration of binder (i.e. TPU) to obtain a good size distribution of the granules **(Fig. 2)**. At higher drug loads (i.e. 5% (w/w) TPU binder concentration) the metformin powder particles were not sufficiently agglomerated (i.e. 36% of granules had a particle size below 250μm). In contrast, a large fraction of oversized granules was obtained (i.e. 39% of granules had a particle size above 1000μm) when the drug load was below 85% (w/w). Although several other process parameters (i.e. screw speed, screw configuration, barrel temperature, feed rate) were varied during preliminary TSMG experiments, a yield fraction (i.e. 250-1000 μm)

higher than 70% (w/w) could only be obtained using 10-15% (w/w) TPU binder. The implementation of an additional cryomilling step after TSMG was efficient to reduce the fraction of oversized granules and thus increase the TSMG process yield (supplementary data). Finally, a lower friability was found when a higher TPU binder concentration was used **(Table 1)**.

The aim of this research was to evaluate the usefulness of the TPU polymer platform for the manufacturing of different high drug loaded oral sustained release dosage forms using HME/(IM) and TSMG/compression. Therefore, all formulations (i.e. HME mini-matrices, HME/IM tablets and TSMG tablets) were evaluated for their release retarding potency in vitro. Whereas hydrophilic TPUs were unable to prolong metformin release from HME/IM formulations for more than 6h in SIF medium, hydrophobic TPU-based IM tablets only released 12% metformin after 24h. By mixing hydrophilic and hydrophobic TPUs the *in vitro* release kinetics could be adjusted: a higher content of hydrophobic TPU was correlated with a slower release rate. In addition of the hydrophilic/hydrophobic TPU ratio, drug release depended on the geometry of the formulation: mini-matrices showed faster release kinetics than IM tablets. *Verhoeven et al.* already investigated the influence of mini-matrix dimensions and diffusion coefficient on the release profile. As both the IM tablets and the mini-matrices have the same drug load and polymer composition, the faster release kinetics of the mini-matrices could be attributed to the larger surface area (1.6-fold increase) and shorter diffusion pathways. [32] This observation was successfully countered by changing the hydrophobic/hydrophilic TPU ratio: incorporating a higher fraction of hydrophobic TPU reduced release kinetics **(Fig. 3)**. Although the hydrophobic TPU (i.e. Tecoflex^{TM} EG72D) was an efficient release retarding excipient for HME/(IM) formulations, it was not able to sustain metformin release from TSMG tablets (**Fig. 4)**. The TPU concentration was too low to achieve sustained release kinetics at high drug loads (i.e. 85%, w/w), even when the hydrophobic TPU grade was incorporated in the formulation. In contrast to HME/IM experiments this phenomenon could not be countered by increasing the amount of TPU, as a higher TPU binder concentration yielded oversized granules. Besides problems related to granule particle size, more elastic recovery occurred during tableting of formulations with a higher TPU concentration, as shown in **Fig. 5**. As a result, the interparticular bonding area was lowered (i.e. higher porosity of TSMG tablets containing a high TPU fraction) and the disintegration time was reduced **(Fig. 6 and Table 2)**, correlated with the faster release kinetics of TSMG

tablets that contain more than 15% (w/w) TPU (despite the hydrophobic nature of the Tecoflex™ EG72D grade). During dissolution testing, a gel-like layer was formed around the Glucophage™ SR tablet due to the hydration of hydroxypropylmethylcellulose and sodium carboxymethylcellulose fraction which are incorporated in the matrix tablet as release retarding agents. [31] In contrast to the reference formulation and TSMG tablets, no disintegration or erosion was observed for all HME mini-matrices and IM tablets, as displayed in **Fig. 7**. Based on their promising in vitro release kinetics in SIF media, IM tablets (metformin.HCl/Tecophilic™ SP60D60/Tecoflex™ EG72D, 60/20/20, w/w/w) and HME mini-matrices (metformin.HCl/Tecoflex™ EG72D, 60/40, w/w) were selected for further investigation in SGF media. All formulations showed slower release kinetics when SGF media was used, in comparison to dissolution tests performed in SIF media as shown in **Figs. 3 and 8**. *Desai et al.* linked this observation to the higher charge (i.e. diprotonation) of metformin.HCl (pKa values 2.8 and 11.5) at pH 1.2, leading to a stronger solvation, larger hydrodynamic radius and thus lower diffusion coefficient. [30] As patients may co-ingest alcoholic beverages with their medication, this can potentially disrupt the sustained release mechanism of formulations and result in dose dumping and safety issues, a SGF medium containing 20% (V/V) ethanol was used for testing the mini-matrices, IM tablets and reference formulation. [33] Both, the hydrophilic TPU based formulations and the reference formulation showed faster metformin.HCl release kinetics in the presence of ethanol. As displayed in **Fig. 8**, this phenomenon was not observed when the hydrophobic TPU Tecoflex™ EG72D was used as a matrix former, making these formulations resistant to dose-dumping in case of co-ingestion with alcohol.

Based on the *in vitro* dissolution experiments in SIF media, the most promising IM tablets (metformin.HCl /SP60D60/EG72D, 60/20/20, w/w/w) and mini-matrices (metformin.HCl/ EG72D, 60/40, w/w) were characterized using DSC, FT-IR and Raman mapping and were subsequently evaluated *in vivo*. As shown in **Table 3,** DSC data confirmed the crystalline state of metformin.HCl after processing. In addition, FT-IR results ensured the absence of hydrogen bonds between the API and the polymers. Moreover, MCR contribution plots of the IM tablets and mini-matrices ensured the homogenous distribution of metformin.HCl.

As displayed in **Fig. 9**, plasma concentrations of metformin hydrochloride were plotted as a function of time. Maximum plasma level and time to reach this concentration (T_{max}) were 1857ng/mL (4.8h) and 1923ng/mL (3.0h) for the IM tablets and mini-matrices, respectively. In

case of Glucophage™ SR, a significant higher C_{max} value of 2425 ng/mL was observed 2.8 hours (T_{max}) after oral intake. The $HVD_{T50\%Cmax}$ values were 9.2, 5.5 and 5.6h for IM tablets, mini-matrices and Glucophage™ SR, respectively. The $HVD_{T50\%Cmax}$ value of 3.2h for immediate release reference tablets administrated to beagle dogs was derived from literature and used for R_D calculation. [36] The R_D values of 2.9, 1.7 and 1.7 indicated intermediate-strong, low-intermediate and low-intermediate sustained release properties of IM tablets, mini-matrices and Glucophage™ SR, respectively. Although the reference formulation and IM tablet showed comparable dissolution rates *in vitro*, a faster *in vivo* drug release from the Glucophage™ SR was observed. This is correlated with the higher sensitivity of the hydrated gel layer at the surface of the Glucophage tablets which is more sensitive gastrointestinal shear forces. [37][38][39] This effect of gastro-intestinal peristalsis on the reference formulation was also evidenced from the tablet residues recovered in the faeces: whereas no residue of the reference tablet was detected, intact TPU-based formulations were recovered without changes of the geometric shape of the TPU matrices. Although hydrophobic TPU mini-matrices had a similar *in vitro* performance as the IM tablets, the sustained release properties were not reflected to the same extent during the *in vivo* study. This is linked to their shorter GI residence time (i.e. faster gastric emptying) (12.8 and 17.5h for HME mini-matrices and IM tablets, respectively), resulting less metformin absorption in the upper part of the GI tract and significantly lower bioavailability (i.e. lower $AUC_{0\text{-}12h}$ value), as listed in **Table 4**. [40] Despite their shorter gastrointestinal residence time, mini-matrices still obtained a similar R_D value and significant lower C_{max} value than the reference formulation, indicating an equal sustained release potential without possible dose-dumping issues.

4 CONCLUSION

As a result of the limited TPU binder concentration range and the higher porosity of TSMG tablets, HME/(IM) was found to be more effective for the production of TPU-based oral sustained release metformin matrices. Although metformin hydrochloride was released too fast from a pure hydrophilic TPU-based IM tablet, mixing of hydrophilic TPUs with hydrophobic TPUs overcame this problem. As mini-matrices had a faster *in vitro* drug release, this phenomenon was successfully countered by increasing the concentration of hydrophobic TPU. The versatile potential of this TPU-based polymer platform was also confirmed in vivo as sustained release properties for the IM tablets and mini-matrices, respectively, were maintained after oral administration to dogs.

Acknowledgements

This work was financially supported by the Research Foundation – Flanders (FWO). The Special Research Fund of the Ghent University (BOF) is acknowledged for the post-doctoral grant to Dr. M. N. Boone. The authors would like to thank Mrs. J. Buysens and Mr. D. Tensy for their experimental help.

References

1 Claeys, B., 2015. Non-conventional polymers as matrix excipients for hot melt extruded oral-release formulations. PhD Thesis. Ghent University. Faculty of Pharmaceutical Sciences, Ghent, Belgium, 171-172.

2 Vynckier, A. K., Voorspoels, J., Remon, J.P., Vervaet, C., 2016. Co-extrusion as a processing technique to manufacture a dual sustained release fixed-dose combination product. J Pharm Pharmacol., 1-7.

3 Huang, X., Brazel, C.S., 2001. On the importance and mechanisms of burst release in matrix-controlled drug delivery systems. J Control Release. 73, 121-136.

4 Claeys, B., Vervaeck, A., Hillewaere, X.K.D., Possemiers, S., Hansen, L., De Beer, T., Remon, J.P., Vervaet, C., 2014. Thermoplastic polyurethanes for the manufacturing of highly dosed oral sustained release matrices via hot melt extrusion and injection moulding. Eur. J. Pharm. Biopharm. 90, 44-52.

5 Claeys, B., De Bruyn, S., Hansen, L., De Beer, T., Remon, J.P., Vervaet, C., 2014. Release characteristics of polyurethanes tablets containing dicarboxylic acids as release modifiers – a case study with diprophylline. Int. J. Pharm. 477, 244-250.

6 Verstraete, G., Van Renterghem, J., Van Bockstal, P.J., Kasmi, S., De Geest, B.G., De Beer, T., Remon, J.P., Vervaet, C., 2016. Hydrophilic thermoplastic polyurethanes for the manufacturing of highly dosed oral sustained release matrices via hot melt extrusion and injection molding. Int. J. Pharm. 506, 214-221.

7 Graham, G.G., Punt, J., Arora, M., Day, R.O., Doogue, M.P., Duong, J., Furlong, T.J, Greenfield, J.R., Greenup, L.C., Kirkpatrick, C.M., Ray, J.E., Timmins, P., Williams, K.M., 2011. Review article: Clinical pharmacokinetics of metformin. Clin Pharmacokinet. 50 (2), 81-98.

8 Campbell, R.K., White, J.R, Saulie, B.A., 1996. Metformin: a new oral biguanide. Clin Ther. 18 (3), 360-371.

9 Tucker, G.T., Casey, C., Phillips, P.J, Connor, H., Ward, J.D., Woods, H.F., 1981. Metformin kinetics in healthy subjects and in patients with diabetes mellitus, Br J Clin Pharmacol. 12 (2), 235–46.

10 Jabbour, S., Ziring, B., 2011. Advantages of extended-release metformin in patients with type 2 diabetes mellitus. Postgrad Med. 123, 15-23.

538 11 Timmins, P., Donahue, S., Meeker, J., Marathe, P., 2005. Steady-state pharmacokinetics of
539 a novel extended-release metformin formulation. Clin Pharmacokinet. 44 (7), 721-729.
540 12 Gusler, G., Gorsline, J., Levy, G., Zhang, S.Z., Weston, I.E., Naret, D., Berner, B., 2001.
541 Pharmacokinetics of metformin gastric-retentive tablets in healthy volunteers. J Clin
542 Pharmacol. 41, 655-661.
543 13 He, W., Huang, S., Zhou, C., Cao, L., Yao, J., Zhou, J., Wang, G., Yin, L., 2014. Bilayer matrix
544 tablets for prolonged actions of metformin hydrochloride and repaglinide, AAPS Pharm
545 SciTech. 16 (2), 343-353.
546 14 Blonde, L., Dailey, G.E., Jabbour, S.A., Reasner, C.A., Mills, D.J., 2004. Gastrointestinal
547 tolerability of extended-release metformin tablets compared to immediate-release
548 metformin tablets: results of a retrospective cohort study. Curr Med Res Opin. 20 (4), 565-
549 572.
550 15 Jansen, B., Goodman, L.P., Ruiten, D., 1993. Bacterial adherence to hydrophilic polymer-
551 coated polyurethanes stents. Gastrointest Endosc. 39, 670-673.
552 16 Armstrong, N.A., Haines-Nutt, R.F., 1972. Elastic recovery and surface area changes in
553 compacted powders systems. J. Pharm. Pharmacol. 24, 135-136.
554 17 Grymonpré, W., De Jaeghere, W., Peeters, E., Adriaensens, P., Remon, J.P., Vervaet, C.,
555 2015. The impact of hot-melt extrusion on the tableting behaviour of polyvinyl alcohol.
556 Int. J. Pharm. 498, 254-262.
557 18 Masschaele, B., Dierick, M., Van Loo, D., Boone, M., Brabant, L., Pauwels, E., Cnudde, V.,
558 2013. HECTOR: a 240kV micro-CT setup optimized for research. Journal of Physics
559 Conference Series 463, Presented at the 11th International conference on X-ray
560 Microscopy, Bristol, UK: IOP.
561 19 Vlassenbroeck, J., Dierick, M., Masschaele, B., Cnudde, V., Van Hoorebeke, L., Jacobs, P.,
562 2007. Software Tools for Quantification of X-ray Microtomography. Nuclear Instruments
563 & Methods in Physics Research Section A-accelerators Spectrometers Detectors and
564 Associated Equipment. 580 (1), 442-445.
565 20 Brabant, L., Vlassenbroeck, J., De Witte, Y., Cnudde, V., Boone, M., Dewanckele, J., Van
566 Hoorebeke, L., 2011. Three-dimensional Analysis of High-resolution X-ray Computed
567 Tomography Data with Morpho+. Microscopy and Microanalysis. 17 (2), 252–263.

21 Paganin, D., Mayo, S. C., Gureyev, T. E., Miller, P. R. and Wilkins, S. W., 2002. Simultaneous phase and amplitude extraction from a single defocused image of a homogeneous object. Journal of Microscopy. 206, 33-40.

22 Boone, M., De Witte, Y., Dierick, M., Almeida, A., Van Hoorebeke, L., 2012. Improved Signal-to-noise Ratio in Laboratory-based Phase Contrast Tomography. Microscopy and Microanalysis. 18 (2), 399–405.

23 Berger, M.J., Hubbell, J.H., Seltzer, S.M., Chang, J., Coursey, J.S., Sukumar, R., Zucker, D.S., and Olsen, K., 2010. XCOM: Photon Cross Section Database (version 1.5). Available: http://physics.nist.gov/xcom (02-Aug-2016).

24 United States Pharmacopeia and National Formulary, 26th Edition, 2003. United States Pharmacopeial Convention Inc., Rockville, MD, USA.

25 Gabr, R.Q., Padwal, R.S., Brocks, D.R., 2010. Determination of metformin in human plasma and urine by high-performance liquid chromatography using small sample volume and conventional octadecyl silane column. J Pharm Sci. 13, 486-494.

26 http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q2_R1/Step4/Q2_R1__Guideline.pdf (12-Apr-2016)

27 Özgüney, I., Shuwisitkul, D., Bodmeier, R., 2009. Development and characterization of extended release Kollidon® SR mini-matrices prepared by hot-melt extrusion. Eur J Pharm Biopharm. 73 (1), 140-145.

28 Liu, J., Zhang, F., McGinity, J.W., 2001. Properties of lipophilic matrix tablets containing phenylpropanolamine hydrochloride prepared by hot melt extrusion. Eur J Pharm Biopharm. 52 (2), 181-190.

29 Minagawa, N., White, J.L., 1976. The influence of titanium dioxide on the rheological and extrusion properties of polymer melts. J Appl Polym Sci. 20, 501-523.

30 Desai, D., Wong, B., Huang, Y., Ye, Q., Tang, D., Guo, H., Huang, M., Timmins, P., 2014. Surfactant-mediated dissolution of metformin hydrochloride tablets: wetting effects versus ion pairs diffusivity. J Pharm Sci. 103, 920-926.

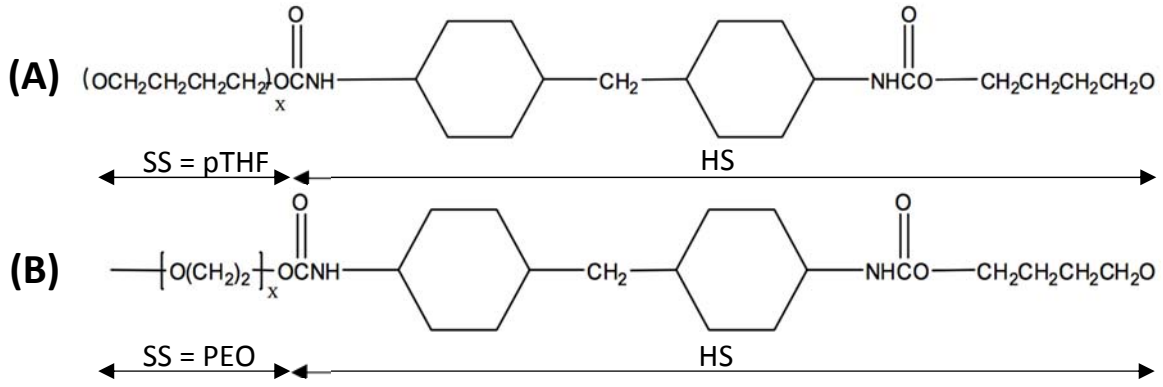
31 https://www.medicines.org.uk/emc/PIL.26350.latest.pdf (12/04/2016)

32 Verhoeven, E., Siepmann, F., De Beer, T., Van Loo, D., Van den Mooter, G., Remon, J.P., Siepmann, J., Vervaet, C., 2009. Modeling drug release from hot-melt extruded mini-matrices with constant and non-constant diffusivities. Eur J Pharm Biopharm. 73, 292-301.

599 33 Rubbens, J., Brouwers, J., Wolfs, K., Adams, E., Tack, J., Augustijns, P., 2015. Intraluminal
600 ethanol concentrations in humans after intake of alcoholic beverages. Eur J Pharm Sci. 86,
601 91-95.
602 34 Gabrielsson, J., Weiner, D., 2000. Pharmacokinetic and Pharmacodynamic Data Analysis:
603 concepts and applications. 3rd edition. Swedish Pharmaceutical Press. Stockholm,
604 Sweden, ISBN 91 8627 492 9.
605 35 Meier, J., Nüesch, E., Schmidt, R., 1974. Pharmacokinetic criteria for the evaluation of
606 retard formulations. Europ J Clin Pharmacol. 7 (6), 429-432.
607 36 Lalloo, A.K., McConnell, E.L., Jin, L., Elkes, R., Seiler, C., Wu, Y., 2012. Decoupling the role
608 of image size and calorie intake on gastric retention of swelling-based gastric retentive
609 formulations: Pre-screening in the dog model. Int J Pharm. 431, 90-100.
610 37 Davis, J., Burton, J., Connor, A.L., MacRae, R. and Wilding, I.R., 2009. Scintigraphic study to
611 investigate the effect of food on a HPMC modified release formulation of UK-294,315. J.
612 Pharm. Sci. 98, 1568–1576.
613 38 Klančar, U., Baumgartner, S., Legen, I., Smrdel, P., Kampuš, N.J., Krajcar, D., Markun, B.,
614 Kočevar, K., 2015. Determining the polymer threshold amount for achieving robust drug
615 release from HPMC and HPC matrix tablets containing a high dose BCS class I model drug:
616 *in vitro* and *in vivo* studies. AAPS Pharm SciTech. 16 (2), 398-406.
617 39 Jain, A.K., Söderlind, E., Viridén, A., Schug, B., Abrahamsson, B., Knopke, C., Tajarobi, F.,
618 Blume, H., Anschütz, M., Welinder, A., Richardson, S., Nagel, S., Abrahmsén-Alami, S.,
619 Weitschies, W., 2014. The influence of hydroxypropyl methylcellulose (HPMC) molecular
620 weight, concentration and effect of food on in vivo erosion behavior of HPMC matrix
621 tablets. J. Control Release. 187, 50-58.
622 40 Davis, S.S., Hardy, J.G., Fara, J.W., 1986. Transit of pharmaceutical dosage forms through
623 the small intestine. Gut. 27 (8), 886-892.
624

Figures

Fig. 1. Chemical structure of the aliphatic **(A)** hydrophobic TPU Tecoflex™ and **(B)** hydrophilic TPU Tecophilic™.



630 **Fig. 2.** Impact of Metformin.HCl/TPU ratio (●95/5; ♦90/10; +85/15; x80/20; *70/30; ▲60/40)
631 (w/w) on the cumulative particle size distribution of TSMG granules.
632

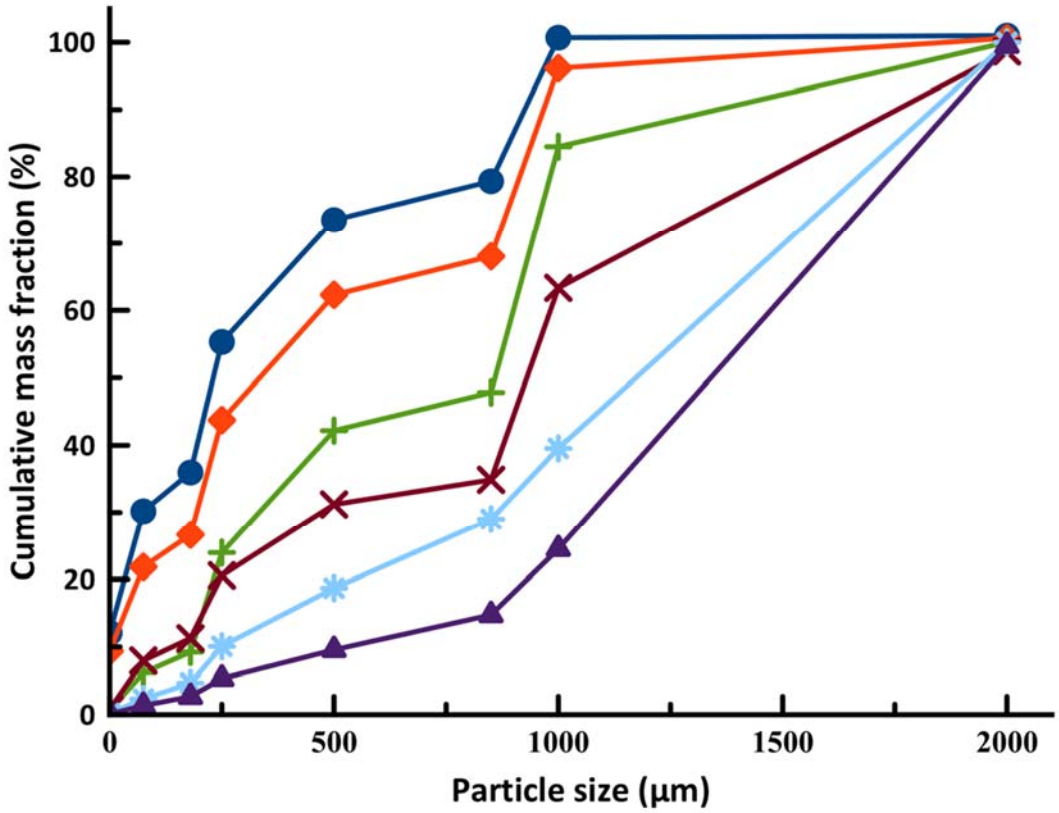
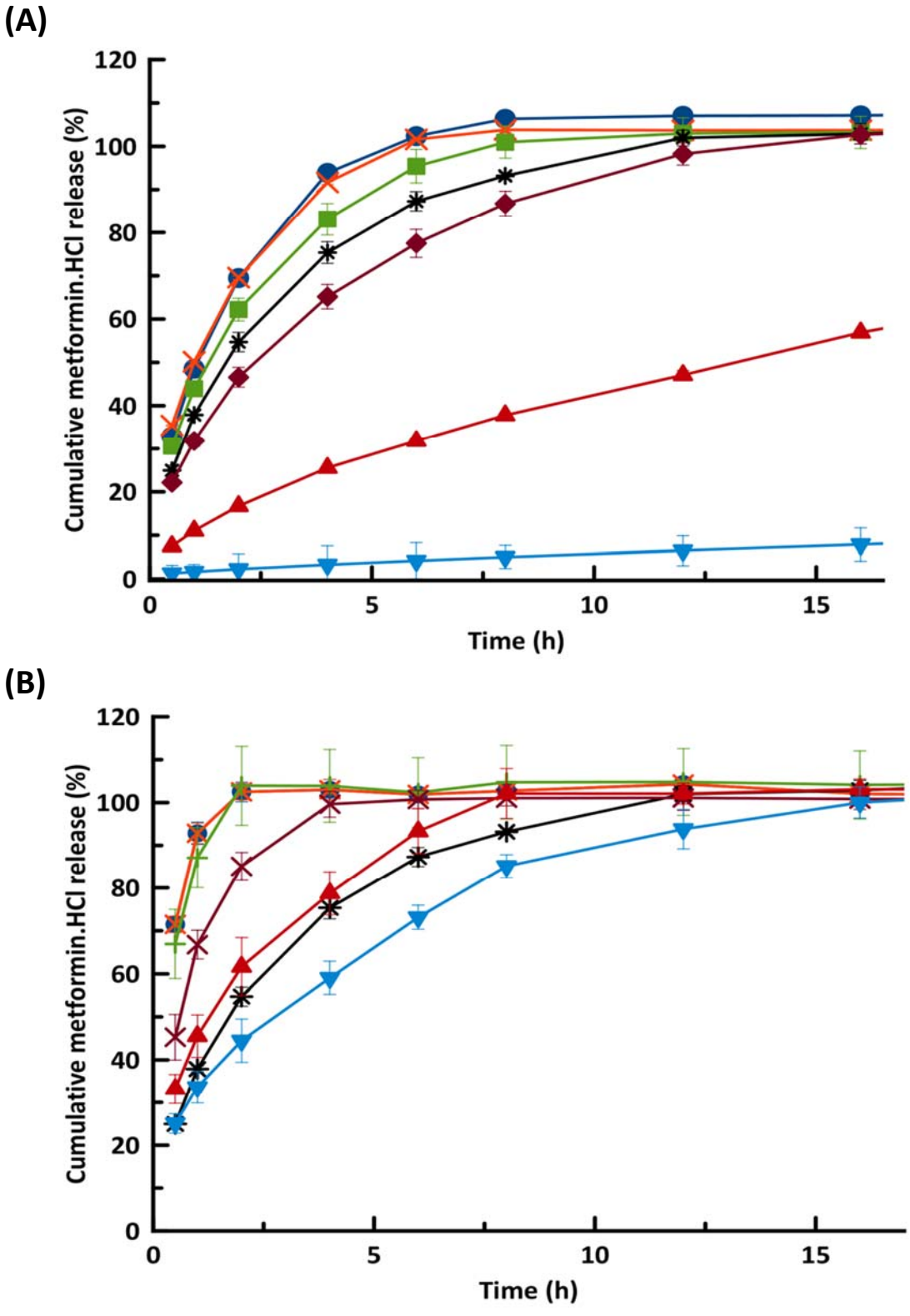
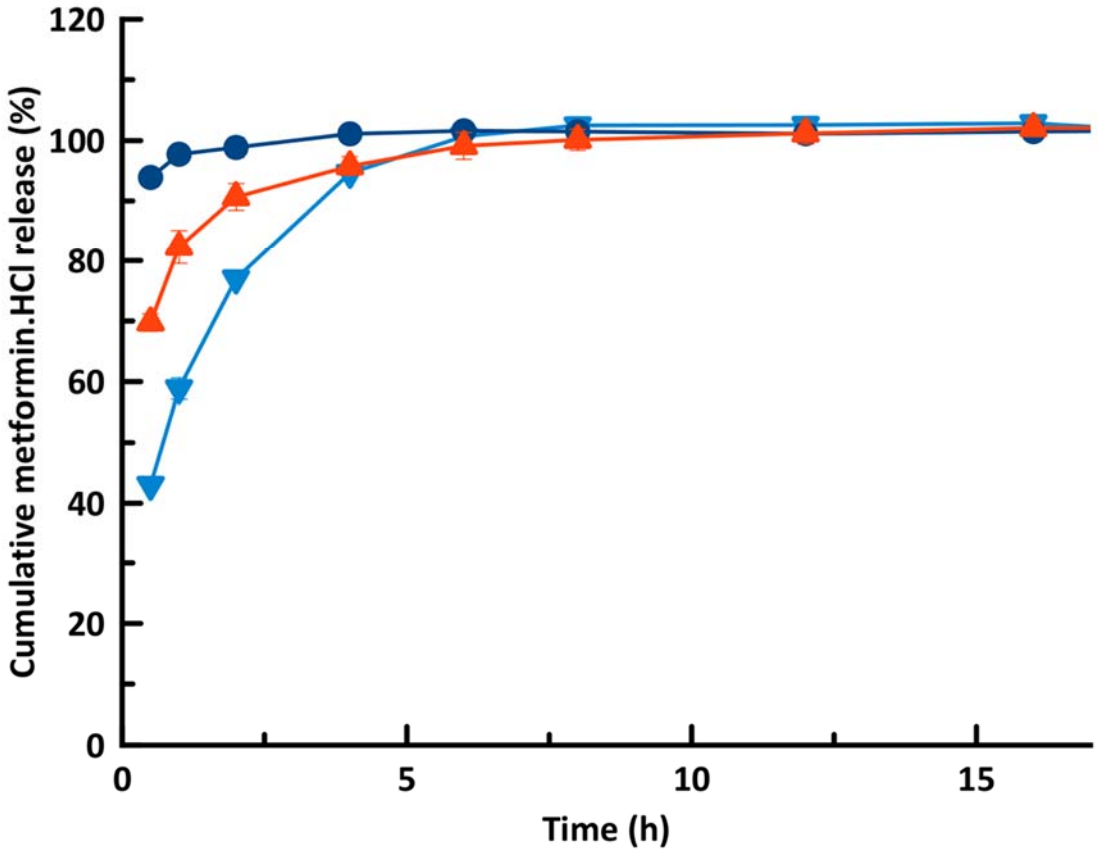


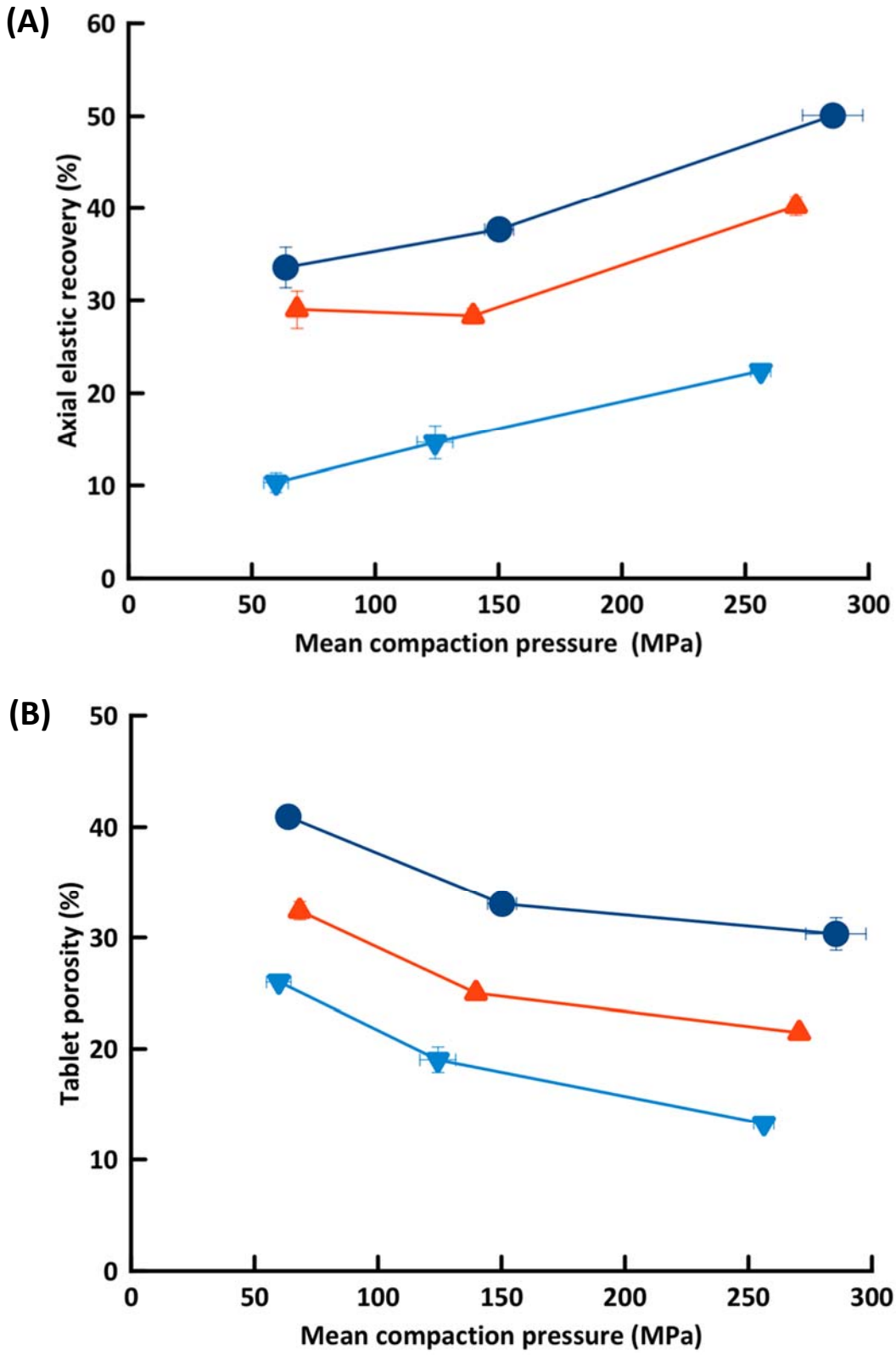
Fig. 3. Influence of TPU grade (●TG2000; xSP93A100; ■SP60D60; ▼EG72D) and ratio (w/w) of hydrophilic/hydrophobic TPU (SP60D60/EG72D ratio: ♦50/50; ▲25/75; ▼0/100) on *in vitro* release kinetics (mean ±SD, n=3) in SIF medium of **(A)** IM tablets and **(B)** mini-matrices containing 60% (w/w) Metformin.HCl. The black curve (*) represents the mean release kinetics (±SD, n=3) of Glucophage™ SR 500 (1/2 tablet).



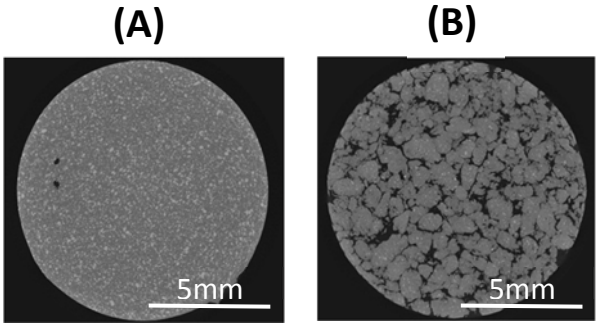
639 **Fig. 4.** Influence of metformin.HCl/Tecoflex^{TM} EG72D ratio (w/w) (•60/40; ▲70/30; ▼85/15)
640 on the *in vitro* release kinetics (mean ±SD, n=3) of TSMG tablets in SIF medium.



641 **Fig. 5.** Influence of metformin.HCl/Tecoflex™ EG72D ratio (w/w) (•60/40; ▲70/30; ▼85/15)
642 on **(A)** out of die axial elastic recovery and **(B)** tablet porosity. All experiments were performed
643 in triplicate and mean values (±SD) were plotted as a function of mean compaction pressure
644 (±SD).



646 **Fig. 6.** X-ray tomography images of **(A)** IM tablet (60/20/20, w/w/w,
647 metformin.HCl/Tecoflex™ EG72D/Tecophilic™ SP60D60) and **(B)** TSMG tablet (60/40, w/w,
648 metformin.HCl/ Tecoflex™ EG72D) before dissolution experiments.
649



650 **Fig. 7.** Optical images of **(A)** IM tablet (60/20/20, w/w/w, metformin.HCl/Tecoflex™
651 EG72D/Tecophilic™ SP60D60), **(B)** mini-matrices (60/40, w/w, metformin.HCl/Tecoflex™
652 EG72D), **(C)** TSMG tablet (85/15, w/w, metformin.HCl/Tecoflex™ EG72D), **(D)** TSMG tablet
653 (60/40, w/w, metformin.HCl/Tecoflex™ EG72D) and **(E)** Glucophage™ SR 500 (1/2 tablet)
654 reference formulation before (left) and after (right) 12h disintegration testing in SIF.
655

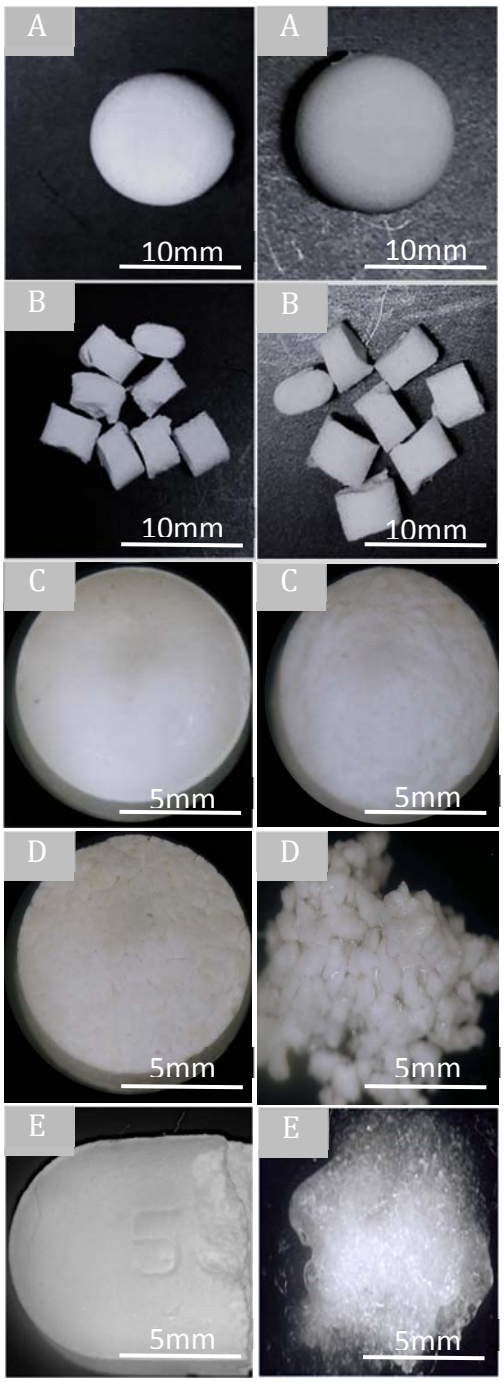


Fig. 8. In vitro release kinetics (mean ±SD, n=3) of (◊) IM tablets (60/20/20, w/w/w, metformin.HCl/Tecoflex™ EG72D/Tecophilic™ SP60D60), (∇) mini-matrices (60/40, w/w, metformin.HCl/Tecoflex™ EG72D) and (*) Glucophage™ SR 500 (1/2 tablet) formulations in SGF (open symbols) and SGF containing 20% (V/V) ethanol (closed symbols).

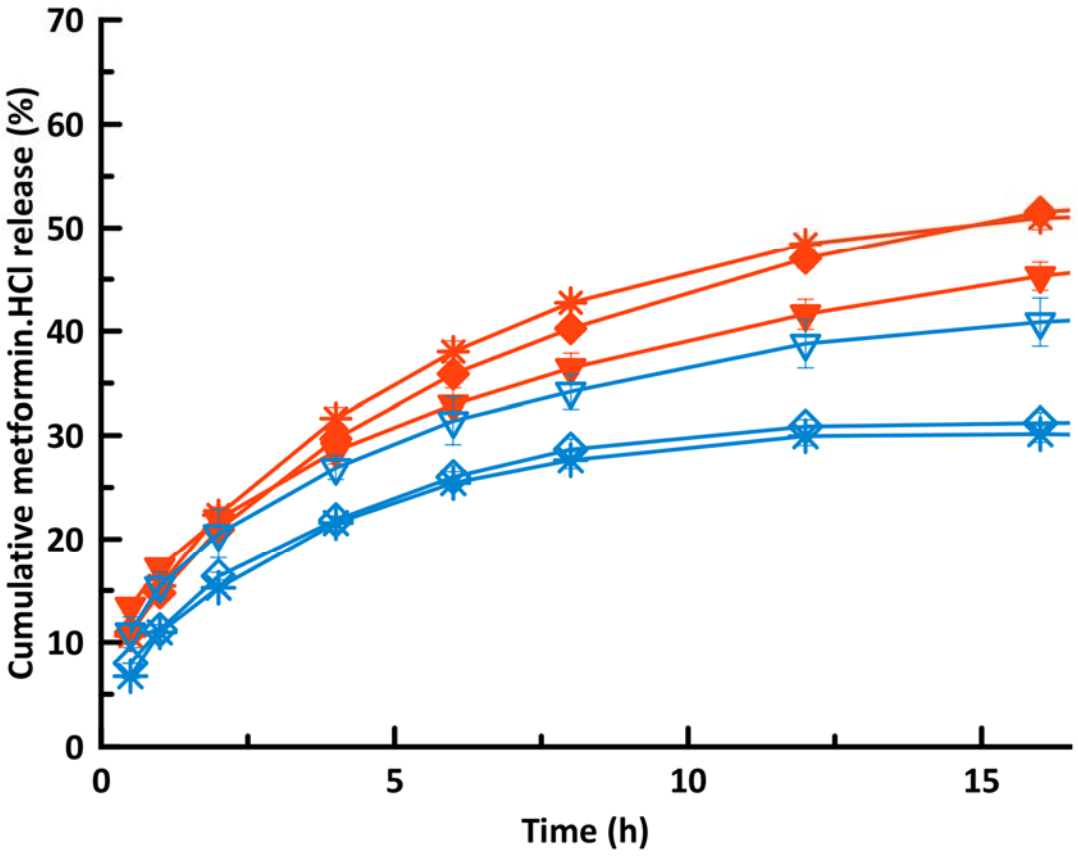
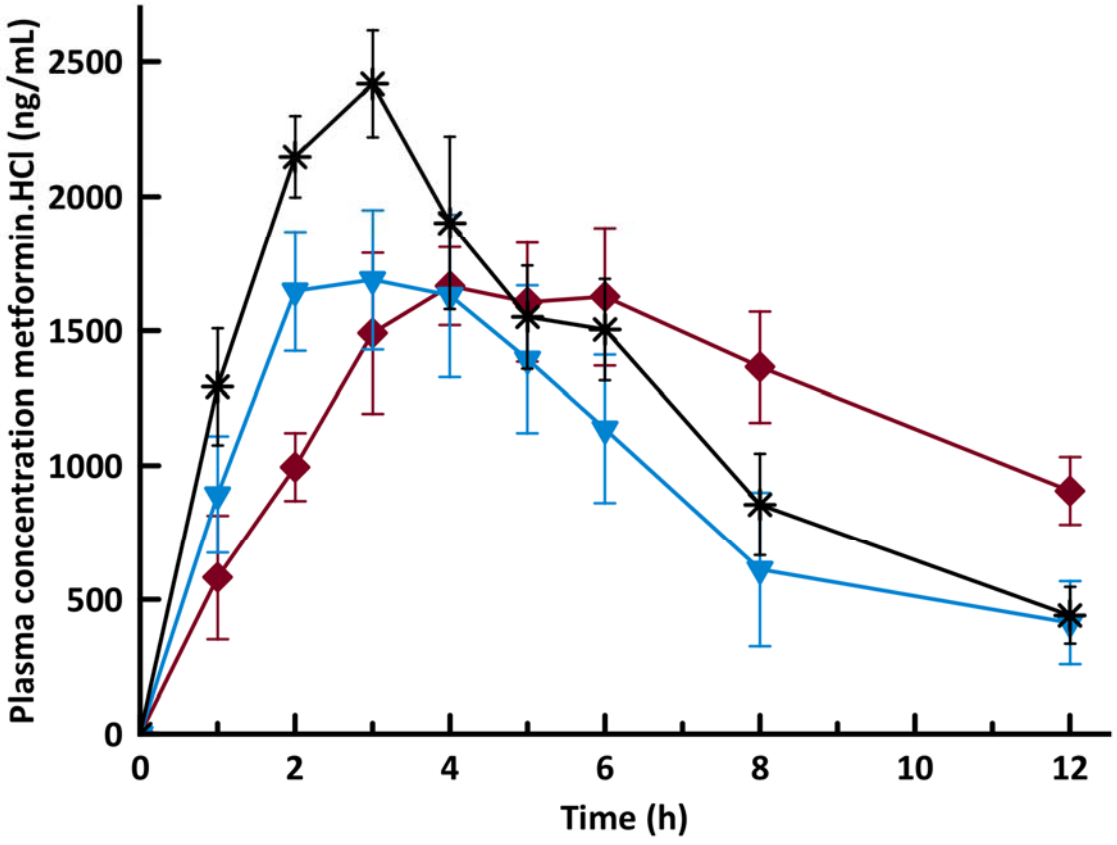


Fig. 9. Mean plasma concentration-time profiles (±SD, n=6) after oral administration of 250mg Metformin.HCl to dogs: (♦) IM tablets (60/20/20, w/w/w, metformin.HCl/Tecoflex™ EG72D/Tecophilic™ SP60D60), (▼) mini-matrices (60/40, w/w, metformin.HCl/Tecoflex™ EG72D) and (*) Glucophage™ SR 500 (1/2 tablet) reference formulations.



Tables

Table 1. Impact of TPU binder concentration on mean friability of TSMG granules (±SD, n=3).

TSMG granule composition (w/w)	%Friability (±SD, minutes)
90/10 Metformin.HCl/EG72D	23.9 ± 2.1
85/15 Metformin.HCl/EG72D	16.5 ± 1.2
70/30 Metformin.HCl/EG72D	11.4 ± 1.7
60/40 Metformin.HCl/EG72D	9.2 ± 0.9

Table 2. Mean disintegration time (±SD, n=3) of different TSMG tablets.

TSMG tablet composition (w/w)	MCP(MPa)	Disintegration time (±SD, minutes)
85/15 Metformin.HCl/EG72D	± 65	-[a]
	± 130	-[a]
	± 260	-[a]
70/30 Metformin.HCl/EG72D	± 65	13.0 ± 0.5
	± 130	26.3 ± 1.5
	± 260	33.8 ± 1.6
60/40 Metformin.HCl/EG72D	± 65	1.3 ± 0.1
	± 130	2.6 ± 0.1
	± 260	6.0 ± 0.4

[a] Tablets did not disintegrate after 12h testing

Table 3. Melting enthalpy of metformin.HCl in physical mixtures (PM), IM tablets (60/20/20, w/w/w, metformin.HCl/Tecoflex™ EG72D/Tecophilic™ SP60D60), HME mini- matrices (60/40, w/w, metformin.HCl/Tecoflex™ EG72D), and TSMG tablets (85/15, w/w, metformin.HCl/Tecoflex™ EG72D.

Sample	ΔH (J/g)	%Crystallinity
Metformin.HCl	288.3	100.0
PM used for IM tablets	170.9	98.8
PM used for HME mini-matrices	155.1	89.7
PM used for TSMG tablets	240.4	98.1
IM tablets	158.5	91.6
HME mini-matrices	156.0	90.2
TSMG tablets	226.9	92.6

685 **Table 4.** Mean pharmacokinetic parameters (±SD, n=6) after oral administration of 250mg
686 metformin.HCl to dogs as IM tablets (60/20/20, w/w/w, metformin.HCl/Tecoflex™
687 EG72D/Tecophilic™ SP60D60), mini- matrices (60/40, w/w, metformin.HCl/Tecoflex™
688 EG72D) and Glucophage™ SR 500 (1/2 tablet) reference formulations.
689

Formulation	C_{max} (ng/mL)	T_{max} (h)	$AUC_{0\text{-}12h}$ (ng.h/mL)	$HVD_{t50\%Cmax}$ (h)	R_D
IM tablets	1857.1 ± 111.7^a	4.8 ± 1.2^a	14689.5 ± 1019.5^a	9.2 ± 1.8^a	2.9 ± 0.6^a
mini-matrices	1923.3 ± 182.3^a	3.0 ± 0.9^b	11630.0 ± 1785.1^b	5.5 ± 0.6^b	1.7 ± 0.2^b
Glucophage™ SR	2425.1 ± 191.6^b	2.8 ± 0.4^b	15011.7 ± 912.2^a	5.6 ± 0.6^b	1.7 ± 0.2^b

690 [a, b] Means in the same column with different superscript are different at the 0.05 level of significance
691
692

Supplementary data

S. 1. Cumulative particle size distribution of TSMG granules containing different metformin.HCl/Tecoflex™ EG72D ratios (w/w) (■70/30 and •60/40) before (closed symbols) and after (open symbols) 15 seconds cryomilling.