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A comparative study between melt granulation/compression and hot melt extrusion/injection molding for the manufacturing of oral sustained release thermoplastic polyurethane matrices

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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 and 70% (w/w) could be processed via HME/(IM), the drug content of granules prepared via melt granulation could only be varied between 85 and 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 24 h, release from the TPU-based TSMG tablets was too fast (complete release within about 6 h) 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.

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 (Claeys, 2015; Vynckier et al., 2016). *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) (Huang and Brazel, 2001). 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 (Claeys et al., 2014a, 2014b). 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 (Verstraete et al., 2016).

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 (Graham et al., 2011; Campbell et al., 1996; Tucker et al., 1981). 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.

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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 (Jabbour and Ziring, 2011; Timmins et al., 2005). The development of a sustained release formulation that maintains drug plasma levels for 10–16 h will limit plasma concentration fluctuations and thus reduce side-effects. Furthermore, once-daily intake should improve patient compliance (Gusler et al., 2001; He et al., 2014; Blonde et al., 2004).

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) (Claeys et al., 2014a; Verstraete et al., 2016; Jansen et al., 1993). 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 100 rpm. 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 (±3.5 mm height; ±3 mm 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 4 mm, 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 800 bar (10s) forced the material into the mould. A post-pressure of 400 bar (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 0.7 kg/h and 200 rpm, 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 15 min 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 500 g of sample was collected.

After TSMG, granules were sieved for 10 min at an amplitude of 2 mm using a vibrating sieve tower (Retsch VE 1000, Haan, Germany). Granules with a particle size between 250 and 1000 μm were used for tableting. Before every compression experiment, granules with a mass corresponding to 250 mg 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 10 mm

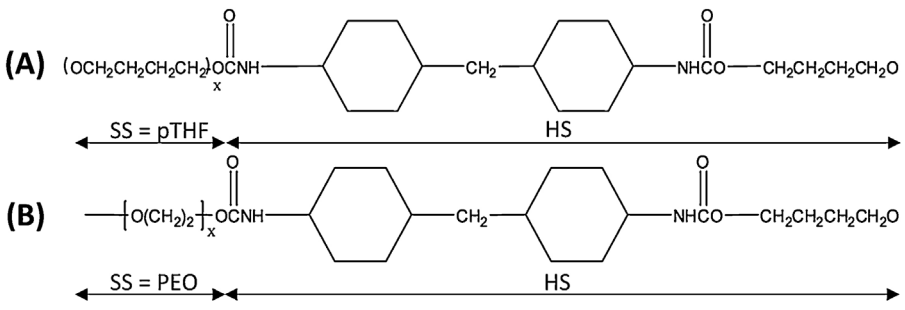

Fig. 1. Chemical structure of the aliphatic (A) hydrophobic TPU Tecoflex™ and (B) hydrophilic TPU Tecophilic™.