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In vitro and *in vivo* behavior of ground tadalafil hot-melt extrudates: How the carrier material can effectively assure rapid or controlled drug release

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ABSTRACT

Different types of ground hot-melt extrudates loaded with 10, 20 or 30 % of the poorly water-soluble drug tadalafil were prepared and characterized *in vitro* and *in vivo* (in rats). Soluplus was used as an amorphous carrier material, whereas mannitol and lactitol were studied as crystalline matrix formers. The systems were characterized using X-ray powder diffraction, thermogravimetric analysis coupled with quadruple mass spectrometry, differential scanning calorimetry, X-ray computed microtomography, *in vitro* drug release measurements and monitoring of drug plasma levels upon oral administration to rats. The pure drug substance and physical mixtures of tadalafil with the carrier materials were used as references. Importantly, the bioavailability of this poorly water-soluble drug could be substantially increased with the proposed formulations, and the *in vitro* and *in vivo* release rates could be effectively adjusted by choosing the appropriate type of carrier material: Whereas mannitol-based ground hot-melt extrudates rapidly released the drug and led to an early rise in drug plasma concentrations, Soluplus-based systems released tadalafil more slowly, resulting in delayed plasma peaks. These behaviors could be explained by the rapid disintegration/dissolution of the porous mannitol-based formulations, whereas Soluplus significantly swelled and the dissolved drug had to diffuse through the polymeric network prior to release. Blending these formulations can be expected to allow providing elevated drug concentrations *in vivo* during prolonged periods of time upon one single administration with a rapid onset of drug action.

1. Introduction

At least five new hot-melt extruded products, containing either a single poorly soluble drug (itraconazole, Onmel®), or a combination of drugs (vildagliptin/metformin, Eucreas®) have been approved by the FDA/EMA during the last decade (Vasconcelos et al., 2016). The possibility to mix a poorly soluble drug with appropriate excipients at the molecular level during hot-melt extrusion (HME) is considered as one of the main advantages of this co-processing method, allowing to increase the drug's bioavailability. HME can be used as a continuous, solvent-free technique, suitable to prepare amorphous solid solutions (or solid dispersions) of either low- or high-dose drugs. This is the reason why the number of patents related to HME applications in pharmaceutics has steadily increased over the past years (Vasconcelos et al., 2016). Apart from the opportunity to potentially form drug-polymer blends at the molecular level, other potential advantages of HME include: high throughput, suitability for poorly compressible or oxygen-sensitive drugs, the possibility of taste masking (Patil et al., 2016; Repka et al., 2008) and the development of abuse-deterrent formulations (Cantin et al., 2016; Maddineni et al., 2014; Maincent and Zhang, 2016). On the other hand, HME is preferably used for heat stable compounds with melting points below 150 °C and good flowability, which

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limits the number of drugs and carriers that can be successfully co-processed (Repka et al., 2008; Vasconcelos et al., 2016).

Often, the dissolution rate of a poorly water-soluble drug is increased from a hot-melt extrudate, because the drug is either dissolved (dispersed at the molecular level) or dispersed in the form of amorphous particles in a water-soluble polymeric carrier. This is because the solubility of a drug is generally higher in the amorphous state compared to a crystalline state (Baghel et al., 2016; Brough and Williams, 2013), and in the case of a solid solution, the drug is already molecularly dispersed. However, the drug might also be dispersed in the form of tiny crystals in a crystalline carrier (Reitz et al., 2013; Thommes et al., 2011). For example, Thommes et al. (2011) reported the preparation of hot-melt extrudates with poorly soluble drugs exhibiting high melting points (T_m = 135–220 °C), combined with mannitol, resulting in the formation of *crystalline solid suspensions* (CSSs). From a thermodynamic point of view, a great advantage of such CSSs (in comparison to amorphous solid solutions/dispersions) can be their higher stability. Reitz et al. (2013) showed promising results *in vitro* and *in vivo* with the poorly soluble drug griseofulvin (T_m = 220 °C) using this approach. Similarly to griseofulvin, tadalafil (TD) is also an example for a drug exhibiting a high melting point (T_m = 299 °C) and poor solubility: not only in water (<5 μg mL^{-1}), but also in ICH approved organic solvents (<1%) (Krupa et al., 2017; Krupa et al., 2016a,b).

Several attempts to either transform pure tadalafil into an amorphous state or to form amorphous solid solutions using a variety of carriers have been described (e.g., Mehanna et al., 2010; Park et al., 2014; Włodarski et al., 2014). Despite the fact that some of them were successful at the laboratorial scale, in general the transformation of tadalafil into an amorphous form is considered to be troublesome. Furthermore, the yield of such transformations can be low and the scale-up of the respective techniques can be complicated, especially in case of melt-quenching, solvent casting, or freeze-drying. For these reasons, HME was used in the present study to improve the dissolution rate and bioavailability of tadalafil.

One of the crucial steps during the development of hot-melt extrudates is the choice of the matrix forming excipient. The type of carrier generally determines critical key features of the final drug product, including for instance its wettability, the physical state of the drug, its release rate and the product's stability during long term storage (Mitra et al., 2016; Patil et al., 2016; Vasconcelos et al., 2016). Given the fact that tadalafil particles are highly hydrophobic and tend to float at the surface of aqueous fluids, different types of matrix forming excipients able to improve the wettability of this drug were selected in this study. As an amorphous carrier, a polyvinyl caprolactam – polyvinyl acetate – polyethylene glycol graft co-polymer, available under the trade name Soluplus® (SL), was used. Its glass transition temperature (T_g) is about 70 °C. So far, Soluplus has been found effective to improve the dissolution of tadalafil after co-milling and super critical CO_2 impregnation, although not all these methods were found suitable to form amorphous solid dispersions (Krupa et al., 2016a,b). Also, crystalline excipients, e.g. polyols such as mannitol, can significantly increase the dissolution rate of poorly soluble drugs with high melting points [for example furosemide (T_m = 206 °C) and spironolactone (T_m = 135 °C)] using HME (Thommes et al., 2011). In this study, mannitol was chosen as a crystalline carrier for the preparation of tadalafil hot-melt extrudates. Mannitol (MAN, T_m = 165–169 °C) is a well-known pharmaceutical excipient and can offer interesting advantages, such as high solubility in water, the possibility to mask bitter tastes, high stability at elevated temperatures, non-hygroscopicity, no cariogenic effects and a low glycemic index (Grembecka, 2015; Ohrem et al., 2014). In contrast to mannitol, relatively little is yet known about lactitol (LAC) as a potential carrier for poorly water-soluble drugs. Therefore, also lactitol was studied as an alternative crystalline carrier material for tadalafil. It is a disaccharide, composed of sorbitol and galactose, with a melting point of about 150 °C (Yajima et al., 2002). Similar to mannitol, lactitol is freely soluble in water, non-hygroscopic, non-cariogenic and displays high thermal stability. It does not take part in Maillard's reaction, and is stable regardless of the pH (Grembecka, 2015; Yajima et al., 2002).

The major aims of this study were to: (i) prepare hot-melt extrudates of tadalafil using either an amorphous polymer or a crystalline polyol as matrix forming excipient; (ii) determine the physical states of the drug and carriers in the hot-melt extrudates; (iii) monitor the impact of the type of carrier material on the 3D structure of the hot-melt extrudates; and (iv) evaluate the *in vitro* and *in vivo* (in rats) performance of the systems.

2. Materials and methods

2.1. Materials

Tadalafil (TD; M_w = 380.40 g/mol) was obtained from Polpharma S.A. (Starogard Gdański, Poland) and used as received. Optionally, the tadalafil powder was milled for 12 h in a planetary high-energy ball mill (Pulverisette 7, Fritsch, Idar-Oberstein, Germany) to obtain an amorphous form of this drug (Krupa et al., 2016b). Polyvinylcaprolactam-polyvinyl acetate-polyethylene glycol graft co-polymer (SL, Soluplus®, M_w = 90,000–140,000 g/mol) was kindly donated by BASF (Warsaw, Poland). Mannitol (MAN, C*PharmMannidex 16700, M_w = 182.17 g/mol) was obtained from Cargill, Castelmassa, Italy. Lactitol (LAC, directly compressible grade, Mw = 344.31 g/mol) was purchased from Danisco (Thomson, IL, USA). Acetonitrile and methanol of HPLC grade as well as hydrochloric acid (37%) were obtained from Merck

Table 1
Temperatures of the barrel zones used during hot-melt extrusion of the different formulations (SL: Soluplus; MAN: mannitol; LAC: lactitol).

Formulation	TD loading, wt.%	State of the carrier	Carrier, °C		Temperature, °C				
			T_g $	T_m #	Zone 1	Zone 2	Zone 3	Zone 4	Die
SL1	10	Amorphous	70		RT*	140	150	155	160
SL2	20	Amorphous	70		RT	140	150	155	160
SL3	30	Amorphous	70		RT	140	150	155	160
MAN1	10	Crystalline		166–8	RT	140	145	150	160
MAN2	20	Crystalline		166–8	RT	140	145	150	160
MAN3	30	Crystalline		166–8	RT	140	145	150	160
LAC1	10	Crystalline		146	RT	110	120	125	130

*RT– room temperature, $$T_g – glass transition temperature, #$T_m – melting point.