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Injection molding as a one-step process for the direct production of pharmaceutical dosage forms from primary powders

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ABSTRACT

The objective of the present study was to develop a one-step process for the production of tablets directly from primary powder by means of injection molding (IM), to create solid-dispersion based tablets. Fenofibrate was used as the model API, a polyvinyl caprolactame-polyvinyl acetate-polyethylene glycol graft co-polymer served as a matrix system. Formulations were injection-molded into tablets using state-of-the-art IM equipment. The resulting tablets were physico-chemically characterized and the drug release kinetics and mechanism were determined. Comparison tablets were produced, either directly from powder or from pre-processed pellets prepared via hot melt extrusion (HME). The content of the model drug in the formulations was 10% (w/w), 20% (w/w) and 30% (w/w), respectively. After 120 min, both powder-based and pellet-based injection-molded tablets exhibited a drug release of 60% independent of the processing route. Content uniformity analysis demonstrated that the model drug was homogeneously distributed. Moreover, analysis of single dose uniformity also revealed geometric drug homogeneity between tablets of one shot.

1. Introduction

Oral solid dosage forms are preferred by patients and have a market share of approximately 80%. Patient compliance (Bhakay et al., 2012; Fasano, 1998), as well as solubility, permeability and stability (Qian et al., 2010), must be considered during the development process. It is well known that many active pharmaceutical ingredients (APIs) show poor aqueous solubility, as APIs in development are more specific and active than their older counterparts. Currently, around 40% of APIs are poorly water-soluble, including BCS Class II (i.e., low solubility, high permeability) or BCS Class IV (i.e., low solubility, low permeability) molecules. An even higher percentage of molecules in the development pipeline exhibit poor solubility.

In general, solubility can be enhanced by changes in the molecular structure or by formulation strategies, such as crystal habit modification (i.e., salt formation, meta-stable polymorphism and co-crystal formation) (Thakuria et al., 2013), co-solvent/solvent evaporation (Pandya et al., 2008), increase of specific area by particle size reduction (nano-particle dispersions, micronization) (Kocbek et al., 2006), self-emulsification (SEDDS) (Singh et al., 2009) and solid-solid drug dispersion (Verhoeven et al., 2006; Stepto and Tomka, 1987; Eith et al., 1986). In addition, molecular solid dispersions have gained increased attention and have been widely investigated. They offer improved bio-availability (Leuner and Dressman, 2000; Ford, 1986) of BCS II drugs (Chokshi et al., 2005; Forster et al., 2001) as the drug's particle size is reduced to molecular dimensions. In such molecular dispersions, the (amorphous) polymer containing the molecularly dispersed drug, exhibiting increased solubility compared to the crystalline counterpart, since dissolution is limited by the lattice energy barrier.

One technique to produce solid dispersion is hot melt extrusion (HME), which is widely applied in the plastics industry. The process (involving a polymeric or lipid carrier, the API and modifiers) is performed at elevated process temperatures (typically close to the drug's melting point), causing material softening or even melting. Thereby, the formation of molecular solid dispersions is favored as the API melts as well, or dissolves in the polymer melt. Without the

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need of solvents, drug product characteristics such as solubility and bioavailability can be improved, the drug release behavior can be tailored and taste masking for bitter or salty APIs can be achieved (Jedinger et al., 2015; Maniruzzaman et al., 2013; Roblegg et al., 2011).

A wide range of dosage forms can be produced including granules, pellets, tablets, implants or transdermal systems (Breitenbach, 2002). Granules and pellets need further processing (i.e., tableting (Verreck et al., 2004) or capsule filling (Verhoeven et al., 2006)). In contrast, injection molding (IM) allows for the creation of the final products in one step. In addition to HME, IM is another well-established technique in the plastics industry. Like HME, IM is performed at elevated temperatures, i.e., above the polymer's melting point where shaping to any desired form is possible. During IM, the molten material is injected into a closed mold cavity of specific shape, where it is cooled to solidify, creating a ready-made product (Quinten et al., 2009a, 2009b). Hence, IM offers the possibility to manufacture products based on solid dispersions with improved release characteristics, via a lean and efficient route (Vaz et al., 2003). The approach of processing primary material directly into the final dosage form is an innovative and efficient route for the continuous production of oral drug delivery systems. However, it is most suited to manufacture dosage forms that exhibit special geometries, such as IUDs (intrauterine devices) and specific implants or other complex structures with high dimensional accuracy (Ndindayino et al., 2002). Short cycle times (i.e., 2 s to 2 min) are possible for small parts (Stratasys Technical Application Guide; Zema et al., 2012), by using state-of-the-art manifold tools (100–200 cavities) production capacity is enhanced significantly, enabling production of up to a few hundred thousand parts per hour.

Currently, there are only a few pharmaceutical applications of IM described in literature. With respect to oral drug delivery, IM was used for the production of oral capsules based on starch (Eith et al., 1986; Idrissi, 1991), as an alternative to gelatin dip-molded capsules. In addition, IM was applied to the manufacturing of immediate release tablets (Vilivalam et al., 2000), oral non-disintegrating matrices (Quinten et al., 2011a; Quinten et al., 2011b) and oral multi-layer devices (Pedersen and Hemmingsen, 2006; Washington and Wilson, 2006). Each of the cited studies first used HME to process the primary powders, prior to IM. To the authors' knowledge, direct powder feeding into IM for manufacturing oral solid dosage forms has not been reported in literature.

In the present study a simple, two-component system comprising fenofibrate, being a poorly soluble model drug (BCS class II), and the graft co-polymer polyvinyl caprolactame-polyvinyl acetate-polyethylene glycol (PVCL-PVAc-PEG), as matrix material, were processed via IM without any pre-processing based on HME. Since fenofibrate is practically insoluble in water (Ming-Thau et al., 1994), yet highly lipophilic (Munoz et al., 1994), the dissolution rates are expected to limit absorption. Bioavailability enhancement of fenofibrate has been reported in literature, i.e., by particle size reduction via milling (Mochalin et al., 2009; Vogt et al., 2008), melting to form a eutectic (Law et al., 2003), preparation of nano-suspensions (Hanafy et al., 2007; Zhang et al., 2010) and transformation into an amorphous state via spray drying (Ming-Thau et al., 1994) or HME (He et al., 2010; Kalivoda et al., 2012; Kanaujia et al., 2011). The graft co-polymer PVCL-PVAc-PEG was also reported to be suitable for processing via HME (Hardung et al., 2010; Kalivoda et al., 2012), for the formation of amorphous solid dispersions with poorly soluble drugs and for integrating nano-systems (Baumgartner et al., 2014; Khinast et al., 2013).

The goal of the present study was to evaluate IM as a one-step process for the production of tablets from primary powder (i.e., no pre-processing via HME) to create solid-dispersion based tablets containing fenofibrate as model API. HME was used for comparison purposes, to create pellets that were then further processed via IM. Thus, two different processing approaches were evaluated and compared. For characterization of the obtained injection-molded tablets, the solid state of fenofibrate was studied, as well as the *in vitro* dissolution behavior and the homogeneity of the tablets (i.e., content uniformity and homogeneity). Additionally, characteristics of the directly processed IM tablets were compared to those made via pre-processing by HME.

2. Materials and methods

2.1. Materials

Fenofibrate (FF) of European Pharmacopoeia (Pharm. Eur.) grade was purchased from Haihang (Shanghai, China). Polyvinyl caprolactame-polyvinyl acetate-polyethylene glycol graft co-polymer (PVCL-PVAc-PEG, Soluplus®) was donated by BASF (Ludwigshafen, Germany).

Hydrochloric acid (Carl Roth, Karlsruhe, Germany) was used for dissolution medium preparation. The mobile phase, used for HPLC measurements, consisted of acetonitrile (Merck, Darmstadt, Germany) and *ortho*-phosphoric acid (AppliChem, Darmstadt, Germany).

2.2. Methods

2.2.1. Solid state characterization

The solid state of the pure substances (FF, graft co-polymer), physical mixtures, pellets and IM tablets was characterized using differential scanning calorimetry (DSC) and small and wide angle X-ray scattering (SWAXS). Pellet samples were ground in a ball mill (60 rpm for 10 min) prior to the measuring, and the fraction below 400 μm was used for characterization. Due to their exceptional mechanical stability (i.e., high hardness), IM tablets could not be milled and had to be manually crushed.

2.2.2. Differential scanning calorimetry (DSC)

DSC measurements were carried out with a DSC 204 F1 Phoenix (Netzsch, Selb, Germany), equipped with an automated sampling unit. Samples (sample weight 5–10 mg) were accurately weighed and transferred into aluminium pans that were closed with a pierced lid via cold welding. Samples were heated from 20 to 220 °C with a heating rate of 10 and 60 K/min, respectively. Subsequently, the samples were cooled to 20 °C with a cooling rate of −10 K/min. All experiments were performed under nitrogen atmosphere (20 ml/min) and in triplicate.

2.2.3. Small and wide angle X-Ray scattering (SWAXS)

Pellets and IM tablets were characterized with respect to the solid state of fenofibrate. SWAXS spectra were generated using an S3-MICRO high-flux laboratory small- and wide-angle X-ray scattering camera (Hecus X-Ray Systems, Graz, Austria) equipped with a high-brilliance micro-beam delivery system. CuKα radiation ($\lambda = 1.542$ nm) operating at 30 kV/0.4 mA was used, and the beam size was 200 μm. Prior to the measurements, pellet samples and tablets were prepared as described above. Samples were placed into a glass capillary, with an inner diameter of 2 mm, which was later sealed with wax and placed into the SpinCap. The SAXS spectra were recorded with a position-sensitive 1D-detector (PSD-50, Hecus X-ray Systems, Graz, Austria) in the angular range of $0.06° < 2\Theta < 8°$. The measurements were carried out in triplicate at ambient temperature, with an exposure time range of 800 s.

2.2.4. Rheological measurements

To determine optimal process parameters (i.e., lowest and highest possible process temperature) for both HME and IM, melt