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Elucidation and visualization of solid-state transformation and mixing in a pharmaceutical mini hot melt extrusion process using in-line Raman spectroscopy

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ABSTRACT

Mixing of raw materials (drug + polymer) in the investigated mini pharma melt extruder is achieved by using co-rotating conical twin screws and an internal recirculation channel. In-line Raman spectroscopy was implemented in the barrels, allowing monitoring of the melt during processing. The aim of this study was twofold: to investigate (I) the influence of key process parameters (screw speed – barrel temperature) upon the product solid-state transformation during processing of a sustained release formulation in recirculation mode; (II) the influence of process parameters (screw speed – barrel temperature – recirculation time) upon mixing of a crystalline drug (tracer) in an amorphous polymer carrier by means of residence time distribution (RTD) measurements. The results indicated a faster mixing endpoint with increasing screw speed. Processing a high drug load formulation above the drug melting temperature resulted in the production of amorphous drug whereas processing below the drug melting point produced solid dispersions with partially amorphous/crystalline drug. Furthermore, increasing the screw speed resulted in lower drug crystallinity of the solid dispersion. RTD measurements elucidated the improved mixing capacity when using the recirculation channel. In-line Raman spectroscopy has shown to be an adequate PAT-tool for product solid-state monitoring and elucidation of the mixing behavior during processing in a mini extruder.

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1. Introduction

New active pharmaceutical ingredients (API) are often very expensive and available in limited quantity (only a few grams) at the early stage of formulation development. Moreover, laboratory-scale extruders require large amounts of drug substance and matrix products as their throughputs are in the range of kg/h (e.g. 16 mm Eurolab, Thermo Fisher Scientific). Nowadays, mini pharmaceutical hot-melt extruders (grams per batch) are available for the pharmaceutical industry to allow cost effective screening in formulation development. This throughput can be reduced somewhat by using supercritical CO2 as a diluent (Verreck et al., 2006; Vigh et al., 2014b). A mini extruder consists of co-rotating conical twin-screws and an internal recirculation channel to achieve (complete) mixing of the raw materials (drug substance + matrix). The design of a mini extruder is mostly fixed (i.e., screw design), therefore a recirculation channel is provided to improve distributive mixing. This is completely different compared to lab-scale extruders, since their segmental screw design allows to adjust the screw configuration to improve distributive mixing. The intended purpose of a hot-melt extruder is to homogenously mix the raw materials until the desired solid dispersion is obtained. The degree of mixing required between the drug and the polymer matrix may depend on the type of solid dispersion (i.e., product solid-state: e.g. molecularly dispersed or crystalline dispersed drug in an amorphous polymer matrix), the properties (e.g. drug melting temperature, miscibility) of the components, the formulation composition and the Quality Target Product Profile (QTPP) (Sakai and Thommes, 2014). The final solid-state of the drug product is determined by the processing history. Hence, the

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product solid-state is altered by the main process parameters in a mini extrusion process: screw speed, barrel temperature and recirculation time.

The QbD/PAT initiative (Administration, 2004) supports bottom-up formulation and process development, for instance by using process analyzers, also at a small scale. Since real-time data collection of the melt properties (e.g., solid-state) during processing is possible via spectroscopic techniques, the influence of process factors upon the critical quality attributes (CQA) (such as, solid-state, melt homogeneity) can be visualized during processing. Furthermore, information of material and processing behavior gathered on the small scale extruder could be used for later scale-up towards laboratory and industrial scale hot-melt extruders. Immersion probes connected via fiber optical cables to spectrometers can be implemented in the hot-melt extrusion process stream for real-time monitoring of the melt. In-line Raman and NIR analyzers are complementary techniques (De Beer et al., 2011) already used in laboratory-scale hot-melt extruders to improve understanding of the material and processing behavior. Saerens et al. visualized the material behavior in the extrusion barrel (along the entire length) using Raman spectroscopy to gain process understanding of a laboratory-scale extrusion process (Eurolab 16 mm, Thermo Fisher Scientific) (Saerens et al., 2013). The influence of key process parameters (screw speed and barrel temperature) could be linked with the product solid-state and drug-polymer interactions. Since the product solid-state was monitored along the entire extruder barrel length, it was possible to determine the barrel segment where the final product solid-state was formed. Comparison between Raman spectra of the physical mixtures and the in-line collected spectra showed Raman peak shifts, which were attributed to the chemical interactions between drug and polymer. Raman spectrometry allows to predict the properties of melt extruded solid dispersion (Vigh et al., 2014a). Also NIR diffuse reflectance spectroscopy showed these spectral shifts and proved to be an adequate PAT-tool to visualize the drug-polymer interactions during processing (Saerens et al., 2012). However, NIR diffuse reflectance spectroscopy showed larger noise levels when monitoring transparent samples compared to opaque samples. Therefore, transmission NIR spectroscopy was used by Islam et al. to monitor the drug (Indometacine) transformation (i.e., solid-state change) when mixing with Kollidon VA64 and Soluplus (Islam et al., 2015). To our knowledge, no attempt was made so far to implement spectroscopic techniques in a mini-extruder of this type. Raman backscattering spectroscopy was chosen as a monitoring technique because of the ease of implementation in the splittable and removable barrel-liners and because it provided a good signal for both transparent and opaque samples.

In-line process analyzers (Raman and NIR spectroscopy) are fast measuring techniques that are ideal for real-time data collection as no sample pretreatment is necessary (De Beer et al., 2011). This advantage over slow offline techniques (e.g. HPLC) is helpful to study the melt flow behavior and mixing during processing. Often the residence time distribution (RTD) of a tracer molecule is measured to elucidate the mixing capacity of the mixing device under investigation. In-line Raman spectroscopy was used by Common et al. for residence time measurements in a single screw extrusion process (Common et al., 2014). Their research elucidated the improved mixing capacity of adding a static mixer between the screw and die. In contrast to their research, the in this study investigated mini-extruder has a recirculation channel to improve distributive mixing. Not only the recirculation channel, but also the screw speed and barrel temperature could influence the melt flow behavior and thus the mixing degree (i.e., mixing endpoint) of the tracer molecule with the polymer matrix. To our best knowledge, the use of RTD measurements has not yet been described in literature to examine the influence of the recirculation channel upon the mixing capacity and the melt flow behavior in a mini extruder of this type.

The aim of this study was twofold: (i) to investigate the influence of key process parameters (screw speed and barrel temperature) upon the product solid-state during processing of a sustained release formulation in a pharmaceutical mini hot-melt extruder using in-line Raman spectroscopy, (ii) to elucidate the influence of process parameters (screw speed, barrel temperature and recirculation time) upon the mixing capacity by means of RTD measurements (measured via in-line Raman spectroscopy) when processing a crystalline drug (tracer molecule) in an amorphous polymer matrix.

2. Materials and methods

2.1. Influence of process parameters on product solid-state

2.1.1. Hot-melt extrusion: pharmaceutical formulation and experimental setup

Physical mixtures containing 10 and 40% w/w Metoprolol tartrate (MPT) (Esteve Quimica, Barcelona, Spain) in Eudragit® RS PO (Evonik, Germany) were prepared with a mortar and pestle. The melting temperature (T_m) of MPT is 120 °C. Eudragit® RS PO is a copolymer of ethyl acrylate, methyl methacrylate and a low content of methacrylic acid ester with quaternary ammonium groups. It is an amorphous polymer with a glass transition temperature (T_g) of 65 °C that shows good miscibility with MPT (Saerens et al., 2013). The physical mixtures (6 g) were manually fed and extruded with an Xplore Pharma Micro Extruder (PME5, Xplore Instruments, Geleen, Netherlands) with a 5 ml splittable barrel (Fig. 1). The extrusion process was carried out in recirculation mode. Screw speed (25–50 rpm) and barrel temperature (105–140 °C) were varied, resulting in a total of 8 experiments. The relatively narrow range of screw speeds was selected based on practical considerations. Higher screw speeds could potentially damage the probe's sapphire window since the screws are very close to the immersion probe (position 2, Fig. 1). The

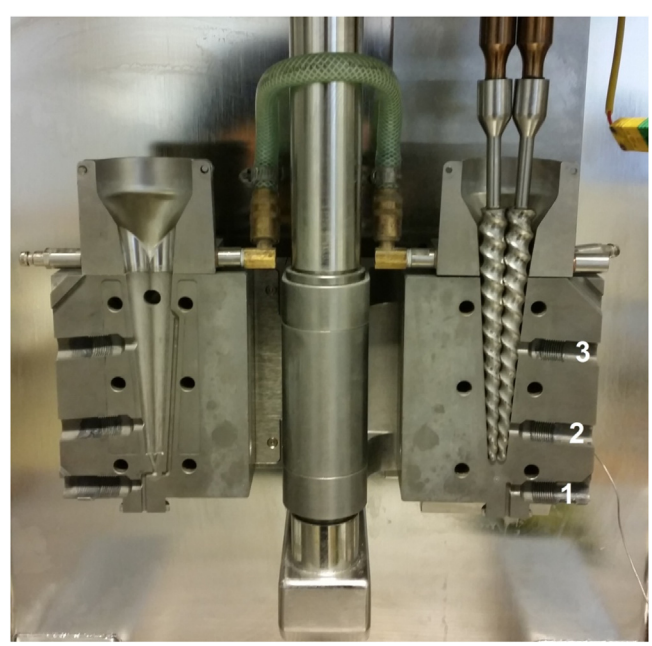

Fig. 1. PME 5 with splittable, removable barrel liners. Three implementation zones for the Raman Dynisco probe: (1) In the extruder die (2) lowest position against the screws (3) highest position against the screws.

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