International Journal of Pharmaceutics 528 (2017) 383–394

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

The flow properties and presence of crystals in drug-polymer mixtures: Rheological investigation combined with light microscopy

J. Aho[a,*], J. Van Renterghem[b], L. Arnfast[a], T. De Beer[b], J. Rantanen[a,*]

[a] University of Copenhagen, Department of Pharmacy, Universitetsparken 2, DK-2100 Copenhagen, Denmark
[b] Ghent University, Laboratory of Pharmaceutical Process Analytical Technology, Ottergemsesteenweg 460, B-9000 Ghent, Belgium

ARTICLE INFO

Article history:
Received 13 March 2017
Received in revised form 9 May 2017
Accepted 3 June 2017
Available online 11 June 2017

Keywords:
Rheology
Optical microscopy
Hot melt extrusion
Plasticization
Supersaturation
Polymer melt
Drug crystallinity

ABSTRACT

The presence of solid matter in polymer melts affects the rheological properties of a drug-polymer mixture, and thus the processability of these mixtures in melt-based processes. The particle morphological changes related to dissolution and crystal growth in the mixtures of paracetamol and ibuprofen with polyethylene oxide and methacrylate copolymer (Eudragit® E PO) were observed by polarized microscopy simultaneously while measuring their rheological properties within temperature ranges relevant for melt processes, such as hot melt extrusion and fused deposition modeling 3D printing. The dissolution of solid crystalline matter into the molten polymer and its effects on the rheological parameters showed that the plasticization effect of the drug was highly dependent on the temperature range, and at a temperature high enough, plasticization induced by the small-molecule drugs could enhance the flowability even at very high drug loads. Therefore, even supersaturated mixtures can be plasticized efficiently, enabling their melt processing, such as hot melt extrusion or 3D printing. The combination of rheometry and polarized light microscopy proved to be very useful for studying the link between morphological changes in the drug-polymer and the flow behavior of the drug-polymer mixtures at different temperature ranges and deformation modes.

1. Introduction

Continuous manufacturing using hot melt extrusion (HME), and the potential downstream manufacturing steps, such as pelletization, calendaring into films, or fused deposition modeling (FDM) 3D printing, enables manufacturing of personalized medicine in innovative ways (Bialleck and Rein, 2011; Breitenbach, 2002; Norman et al., 2017; Water et al., 2015; Wening and Breitkreutz, 2011). HME involves several critical steps: first, mixing of drug in polymeric excipient at elevated temperature and shear stress by screw rotation; second, the mixture is extruded through the die; third, the molten mixture is solidified, and finally, further processed in subsequent steps (Breitenbach, 2002). For FDM, the drug-containing feed material (i.e., the filament) can be prepared by HME (Melocchi et al., 2016; Water et al., 2015). During melt processing, the drug-polymer mixture is subjected to heat and shear stresses, which can result in varying solid form composition ranging from molecularly dispersed solid solution to a solid drug-polymer suspension (Forster et al., 2001). Molecularly dispersed solid solutions produced employing HME process can enhance the dissolution characteristics of poorly soluble drugs, as shown recently, for example, by Kalivoda et al. (2012) and Sathigari et al. (2012). However, also extruded solid suspensions, where both the drug and the carrier are in crystalline form (Thommes et al., 2011), as well as co-crystallized, extruded mixtures of two compounds (Boksa et al., 2014) have been shown to have a superior dissolution characteristics when compared to the pure drug or physical mixture of co-crystal components. Above the thermodynamic drug-polymer solubility limit the drug can be present as molecularly dispersed continuous phase, as well as in phase separated amorphous or crystalline domains. HME process may be able to produce a homogeneously mixed supersaturated solid solution, where the drug is kinetically stabilized, since this is greatly enhanced by the high temperature and shear involved in the process (Qian et al., 2010). However, recrystallization of the drug in such mixtures may occur during the storage (Qi et al., 2010, 2008). Working Diagrams – albeit not straightforward to construct – based on the experimentally and theoretically obtained miscibility and solubility studies, may assist in evaluating the

* Corresponding authors.
E-mail addresses: johanna.aho@sund.ku.dk (J. Aho), jukka.rantanen@sund.ku.dk (J. Rantanen).

http://dx.doi.org/10.1016/j.ijpharm.2017.06.012
0378-5173/

long-term stability of the extruded drug-polymer mixtures, as a function of the drug load, temperature, and the T_g of the polymer (Knopp et al., 2015; Marsac et al., 2008; Qian et al., 2010).

For orally administered high-dose drugs the relative amount of excipients must be kept as low as possible, in order to keep the dosage form size at an acceptable level. Melt processing of such highly concentrated, high-viscous dispersions poses various challenges: The interactions between closely packed solid particles in concentrated suspensions can cause formation of a reversible structural network, which needs energy to be broken down before any deformation can occur upon applied stress (Tadros, 1990). Fully insoluble or supersaturated drug-polymer mixtures may exhibit apparent yield stress, whereby their viscosity at low shear rates is very high, approaching solid-like behavior (Aho et al., 2016). On the other hand, small molecule drugs soluble in the molten polymer act like plasticizers, decreasing the viscosity and the glass transition temperature (De Brabander et al., 2002). When the temperature of the melt mixture is sufficiently close to the melting temperature of the drug, plasticization effect can also be seen in a supersaturated drug-polymer mixture, showing flow behavior similar to two-phase liquid-liquid systems (Aho et al., 2016). In the case of partially miscible, supersaturated drug-polymer mixtures, the rheological behavior is dictated by the viscosity of the plasticized phase consisting of the polymer and the drug dissolved in it, and by the immiscible drug, which could be present either as suspended, undissolved particles or amorphous phase-separated domains – or potentially, as a combination of these.

When plasticization in drug-polymer mixtures is evaluated solely based on the decrease in the T_g or T_m, using thermal methods such as differential scanning calorimetry (DSC), its significance to the flowability in HME cannot be fully assessed. Therefore, rheological characterization is necessary for evaluating effects of the dissolved or suspended drug on the viscosity and viscoelasticity of the melt. Chokshi et al. (2005) suggested that indomethacin – PVP VA binary mixtures were fully miscible evaluated by thermal analysis, where a decrease of T_g was observed as a function of increasing drug load. This was supported by rheological measurements, where the drug-polymer mixtures had a lower zero-shear viscosity than the polymer alone, even when the drug load was as high as 70%. However, for indomethacin- Eudragit E PO, DSC showed an antiplasticization effect, T_g of the drug-polymer mixtures being above the T_g of the individual components. Despite that, the rheological measurements at 140 °C indicated an enhanced plasticization effect with increasing drug load. In another study Liu et al. (2012) found a strong plasticization effect in indomethacin-Eudragit E PO in oscillatory shear tests performed at 145 °C even at 80% drug load, while a similar T_g trend as in (Chokshi et al., 2005) was observed by DSC for the physical mixtures beyond 30% indomethacin content. In our previous study (Aho et al., 2016), a viscosity decrease was observed for ibuprofen-polyethyleneoxide (IBU-PEO) mixtures with 70% IBU content at 70 °C, while the thermal analysis of the mixture showed two separate T_m peaks, indicating supersaturation. On the other hand, at 60 °C the mixture had flow behavior typical of concentrated suspensions with a viscosity above that of pure PEO. This, as well as the above discussed studies show that the temperature clearly plays a significant role: At a lower temperature the drug can be present as suspended crystals, while upon increasing the temperature to the vicinity of the T_m of the drug (for IBU T_m = 76 °C) it can form an amorphous phase and thus decrease the viscosity of the mixture, even without being fully miscible with the polymer, as indicated by DSC.

The preceding discussion shows that the plasticization evaluation using only thermal analysis does not give a full picture of the plasticization in terms of processability. Capillary rheometry enables studying the plasticization effect in similar thermomechanical conditions and shear rates as those occurring in HME, as recently shown by Jones et al. (2015) in their study on the miscibility and processability of quinine base and quinine hydrochloride in Eudragit E100, in hydroxypropylcellulose, and in their blends. However, in order to study the viscoelasticity and molecular level interactions, a rotational rheometer in oscillation mode is the proper choice of test equipment.

The combined use of rheometry and polarized microscopy enables simultaneous observation of the changes in the particle morphology and the flow characteristics of the mixture, allowing for the assessment of the effects of temperature, time, and shear. The usefulness of this technique has been earlier demonstrated in investigation of ibuprofen and theophylline and their extruded mixtures with Soluplus® (Plog and Soergel, 2013). In this study the mixtures of ibuprofen and paracetamol with PEO from our earlier study (Aho et al., 2016) were investigated, with the aim of gaining a deeper understanding on the relationship between particle morphology and rheological properties. Additionally, an amorphous polymer Eudragit® E PO was used in order to enable microscopy observation of the changes in the drug morphology without the effect of a partially crystalline polymer.

2. Experimental

2.1. Materials

Model drugs, ibuprofen (IBU, T_m = 76 °C,) and paracetamol (PRC, T_m = 169 °C), both purchased from Fagron Nordic A/S (Copenhagen, Denmark), were studied as physical mixtures with either polyethylene oxide (PEO, M_v = 100,000 g/mol, T_g = –67 °C, T_m = 65 °C, Sigma-Aldrich Denmark A/S, Copenhagen, Denmark), or with an amorphous methacrylate copolymer, Eudragit® E PO (EDG, M_w = 47,000 g/ mol, T_g = 45 °C, Evonik Industries, Darmstadt, Germany). The drug-polymer ratios were chosen based on the previous results (Aho et al., 2016) with PEO, so that the lower drug content was the one found to have highest plasticizing effect on the mixture at the selected temperature, and the higher one was 20% w/w higher. For IBU these were 50% and 70% and for PRC 10% and 30% (w/w) of drug in PEO. The amorphous EDG was included in this study with the same drug contents as for PEO, due to the anticipation that the crystallization of PEO may visually obscure some morphological changes related to crystallization and crystal growth, or crystal orientation occurring in the drug-polymer mixtures during the measurement. Light microscope images at room temperature (10× magnification) showed that IBU has a broader particle size distribution (Fig. 1a), with several very large crystals, while the PRC had only few very large crystals (Fig. 1b). In addition, the fine EDG (Fig. 1c) and largely aggregated PEO in powder form (Fig. 1d) are presented for comparison.

2.2. Rheometry and microscopy

A Haake MARS III rheometer (Thermo Fischer Scientific, Karlsruhe, Germany) with 20 mm parallel plate setup was used in combination with the RheoScope microscopy and imaging module having a 20× magnification lens, a polarizer and a black and white CCD camera (Foculus FO323TB/TC IEEE1394 Digital Firewire CCD Camera, 1/3" image sensor, 1024 × 768 pix). Physical mixtures of the drugs and polymers in powder form were weighed and mixed carefully using mortar and pestle. The mixtures were dosed on the lower plate of the pre-heated rheometer, the upper plate was lowered gradually, and the sample was allowed to melt for two minutes between the plates before the excess sample around the measurement geometry was removed and the test was commenced. This sample loading and trimming time was attempted to keep equally long, 2–3 min, for all the samples.