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Rheological analysis of itraconazole-polymer mixtures to determine optimal melt extrusion temperature for development of amorphous solid dispersion

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ABSTRACT

The objective of this investigation was to develop a systematic method for the determination of optimal processing temperatures of drug-polymer mixtures for the development of amorphous solid dispersion (ASD) by melt extrusion. Since melt extrusion is performed at high temperature, it is essential that the processing temperature should be as low as possible to minimize degradation of drug and polymer, and yet the temperature should be high enough that the drug-polymer mixture attains certain viscosity that is extrudable and the drug dissolves in the molten polymer. By using itraconazole (ITZ) and polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft co-polymer (Soluplus®, BASF) as, respectively, the model drug and the polymeric carrier, melt viscosities of drug-polymer mixtures with 5, 10, 20 and 30% ITZ were studied as functions of temperature and angular frequency. All these concentrations were below the miscibility limit as it was shown separately by film casting that ITZ was miscible with the polymer up to 40%. Since the angular frequency of a rheometer may not be high enough to simulate the shear rate within an extruder, torque analysis as a function of temperature during melt extrusion of selected drug-polymer mixtures was also conducted. The presence of dissolved ITZ had a plasticizing effect on the polymer used, and an intersection point around 150–155 °C was observed, above which viscosities of drug-polymer mixtures were lower than that of polymer itself. Drug-polymer mixtures with 5 to 30% ITZ were extrudable at 150 °C, and torque analysis showed that the mixture with 20% ITZ can be extruded even at 145 °C. These temperatures were 17 to 22 °C below the melting point of ITZ (167 °C). ITZ dissolved due to the drug-polymer miscibility, the viscosity attained, and the shear rate generated. It was confirmed by PXRD and DSC that the extrudates were amorphous. Viscosity and miscibility of drug-polymer mixtures during melt extrusion were identified as critical factors in determining optimal processing temperature.

1. Introduction

Amorphous solid dispersion (ASD) has been investigated extensively to increase dissolution rate and bioavailability of poorly water-soluble drugs (Leuner and Dressman 2000; Tong et al. 2008). Depending on the nature of drugs and carriers used and their relative concentrations, drugs may be molecularly dispersed in ASD as follows: (a) solid solution, where the solute (drug) replaces solvent (carrier) molecule, (b) interstitial solid solution by the distribution of solute in the interstices, and (c) random distribution of solute in the amorphous carrier, which is sometimes referred to as amorphous solid solution (Baghel et al. 2016). How the drug is dispersed in the carrier may influence the miscibility between them. However, for the successful development of ASD as the pharmaceutical product, it is essential that both drug and carrier are miscible in such a way that there is no crystallization of drug during shelf life of the formulation. As defined by Baghel et al. (2016), the drug-polymer miscibility is the ability of the drug to remain dissolved in the polymeric carrier by molecular distribution, interstitial distribution or random distribution. Water-soluble amorphous polymers are commonly used in the ASD of poorly water-soluble drugs. Once the polymeric carrier is dissolved in aqueous media in the gastrointestinal tract after oral administration of such a formulation, the drug is released in the form of an aqueous solution or in the finely divided state having high surface area that redissolves rapidly (Tong et al. 2008).

Despite many potential advantages of ASD, its use in drug products was hampered for a long time because of various issues related to its preparation and processing into dosage forms (Serajuddin 1999). For example, the solvent evaporation was for a long time the most common method of preparing an ASD, where large amount of organic solvent was necessary to dissolve a water-insoluble drug and the water-soluble

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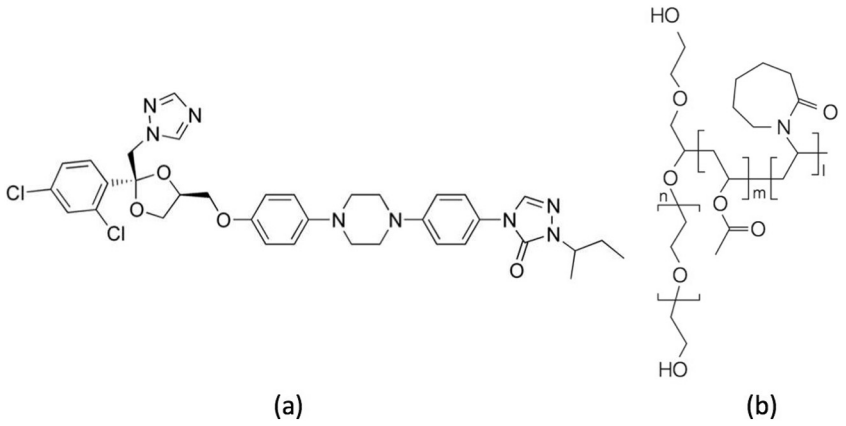

Fig. 1. Chemical structures of (a) itraconazole and (b) Soluplus®.

carrier in a common medium, and the solvent handling during subsequent drying created formulation and manufacturing difficulties (Serajuddin 1999; Tong et al. 2008). The situation has improved greatly during the past 10 to 15 years because of the introduction of hot melt extrusion (HME) for the preparation of ASD, and, indeed, HME has now emerged as the most promising technique for this purpose. Using HME, the drug is dissolved in the amorphous polymer at an elevated temperature (Breitenbach 2002; Crowley et al. 2007; Patil et al. 2016) to produce ASD. However, there are only very limited reports in the literature on the identification of optimal temperature for melt extrusion of drug-polymer mixtures. The chemical stability of drug could be a major issue with HME, especially at or near the melting point of drug (Lakshman et al. 2008; Verreck et al. 2006). There is also the potential for the degradation of polymer at a high temperature (Sarode et al. 2014). It is, therefore, essential that the drug-polymer mixture should be processed in a melt extruder at as low temperature as possible. Even when there is no thermal degradation, the temperature should not be so high that the extrudates are very soft and do not form filaments that can be further processed into dosage forms. At the same time, the temperature should also not be so low that the drug does not dissolve in the polymer or the material is not extrudable. It is essential to select an operating temperature such that the drug dissolves in the polymer during extrusion, the drug-polymer mixture is extrudable and there is no chemical degradation.

For melt extrusion, the drug-polymer mixture has to be heated to a temperature where the melt viscosity of drug-polymer mixture inside the barrel is within the extrudable range (Aho et al. 2016; Gupta et al. 2014). Such a processing temperature has to be above the glass transition temperature (T_g) of polymer used. However, if the drug has a melting point higher than the T_g of polymer, it is not necessary that the drug-polymer mixture has to be heated above the melting point of drug. The mixture may be extruded to form ASD at a temperature much lower than the melting point of the drug, provided (a) the drug dissolves in the molten polymer and (b) the viscosity of the polymer is within the extrudable range.

Although it may be possible to decrease melt viscosity and thus lower processing temperature for hot melt extrusion by incorporating a plasticizer, the added plasticizer may not be miscible with the polymer and its presence may cause crystallization of drug from the system (Gumaste et al. 2016). Gupta et al. (2015) demonstrated that it may not be necessary to add a separate plasticizer during melt extrusion as the dissolved drug may itself serve as the plasticizer. They were successfully able to prepare ASD by extruding mixtures of carbamazepine (CBZ) and Soluplus® (T_g = 72 °C) at a temperature almost 60 °C below the CBZ melting point of 191 °C as the drug had major impact in lowering viscosity of the polymer. For the drug to be able to act as a plasticizer, it has to be miscible with the polymer, where the degree of plasticizing effect depends on drug concentration and processing temperature. There are also several other reports on the effect of drug on the rheology of drug-polymer mixtures, such as acetaminophen-polyethylene oxide (Suwardie et al. 2011; Yang et al. 2011), ibuprofen-ethyl cellulose (De Brabander et al. 2002), indomethacin-HPMCAS MF (Sarode et al. 2013), indomethacin-polyethylene oxide (Aho et al. 2016) and indomethacin-Eudragit EPO (Liu et al. 2012). Aho et al. (2016) asserted that the rheological measurement should be a standard part of material characterization for hot melt extrusion. However, no systematic study to take advantage of the plasticizing effect of drug in identifying processing conditions has been reported in the literature.

As mentioned above, the Soluplus®-CBZ mixture was considered to be a miscible system where the drug dissolved in molten polymer at temperatures almost 60 °C below its melting point of 191 °C (Gupta et al. 2015). This may not be a model system for all drugs as there may be drug-polymer combinations that may not be as freely miscible and, even when they are miscible, they may not adequately reduce the viscosity of the system for melt extrusion. In order to investigate such a possible scenario, we chose itraconazole (ITZ) as a model drug in the present study. ITZ (Fig. 1) with molecular weight of 706 g/mol is a much bulkier molecule than CBZ (236 g/mol). Parikh et al. (2015) reported that ITZ is miscible with Soluplus® up to 40% w/w. Given that ITZ is miscible with Soluplus® and it has a lower melting point (166 °C) than that of CBZ (191 °C), one could hypothesize that melt extrusion of Soluplus®-ITZ mixture could be performed at lower temperatures than Soluplus®-CBZ systems. Because of the much lower melting point of ITZ than CBZ, one could also consider the viscosity of Soluplus®-ITZ system at different drug concentrations and various processing temperatures could be lower than that of the Soluplus®-CBZ system. In the present investigation, we put this hypothesis to test.

Earlier, Six et al. (2004) performed melt extrusion of ITZ with Kollidon® VA 64 (vinylpyrrolidone-vinyl acetate copolymer) at a barrel temperature above the melting point of the drug without considering the possibility of performing the experiment below the drug melting point. Zhang et al. (2013) reported the preparation Soluplus®-ITZ melt extrudates at a lower temperature of 160 °C; however, there was no justification given for the selection of this specific extrusion temperature. Yang et al. (2016) demonstrated that nifedipine-copovidone amorphous solid dispersion can be prepared by extrusion at 13 °C below the melting point of nifedipine (173 °C), which they referred to as the critical temperature. The processing temperature had to be at or above the critical temperature for optimal melt extrusion and molecular level mixing of drug and polymer. However, the authors used only 50:50-mixture of nifedipine and copovidone in their study and there was no mention of whether the critical temperature would vary depending on drug to polymer ratios. In the present study, we conducted rheological analysis of Soluplus®-ITZ mixtures at different ratios to identify processing conditions for the preparation of ASD by melt extrusion. The results obtained from rheological analysis were confirmed by preparing extrudates, which were then analyzed by modulated differential scanning calorimetric (mDSC) analysis and powder X-ray diffraction (PXRD)