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Determination of acetaminophen's solubility in poly(ethylene oxide) by rheological, thermal and microscopic methods

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ABSTRACT

A drug's solubility in a polymeric excipient is an important parameter that dictates the process window of hot-melt extrusion (HME) and product stability during storage. However, it is rather challenging to experimentally determine the solubility and there is very few published work in this field. In this study, the solubility of a model drug acetaminophen (APAP) in a pharmaceutical grade polymer poly(ethylene oxide) (PEO) at HME processing temperature was measured utilizing rheological analysis, hot-stage microscopy and differential scanning calorimetry (DSC). The results from three methods were consistent and the solubility was found to increase from 14% at 80 °C to 41% at 140 °C. The apparent drug solubility at room temperature was estimated to be less than 10% through glass transition temperature (T_g) measurement using DSC and dynamic mechanical thermal analysis (DMTA). A "phase diagram" was constructed based on the experimental data and could be explored to design the HME process and formulation. Very few assumptions were made in the experimental study and result analysis, and the methods described here can be applied to investigate other drug–polymer systems to obtain the important thermodynamic data.

1. Introduction

Hot-melt extrusion (HME), a process involving mixing active pharmaceutical ingredients (APIs) with molten polymeric matrices, has attracted a great deal of attention from the pharmaceutical industry because it can be applied to achieve a broad spectrum of releasing profiles by selecting appropriate polymers and tailoring the process (Fukuda et al., 2008; Campbell et al., 2008). Especially, the dissolution rate of a poorly soluble drug may be increased if the crystalline drug is converted to the amorphous state through HME (Andrews et al., 2010; Liu et al., 2010; Shibata et al., 2009; Albers et al., 2009; Chokshi et al., 2007; Miller et al., 2007). However, broader applications of HME are often limited by two common technical challenges. One is that the APIs may degrade at the elevated temperature during the extrusion process. To avoid this problem and yet obtain a well mixed dispersion of API and polymer, extrusion needs to be operated in an optimal processing window, where the temperature is kept safely below API's degradation temperature (but may be higher than its dissolution temperature in polymer depending on the specific application). Another challenge is the possible physical instability of extrudate during its shelf life, assuming that the API has been transformed into the amorphous form through HME. The API's solubility can decrease significantly once the temperature is dropped from the HME processing temperature to the storage temperature, e.g., room temperature. As a result, API may phase separate from the polymeric matrix and recrystallize (Qian et al., 2010b; Hancock and Zografi, 1997). Different strategies can be applied to address this issue depending on the specific application and the material system. For example, polymer blends (Janssens et al., 2008; Prodduturi et al., 2007) and additives (Bruce et al., 2007) were utilized to inhibit API's recrystallization.

To address the aforementioned two challenges, it is critical to experimentally determine the API's solubility in polymeric excipient at both processing and storage temperature. There are very limited publications devoted to the solubility study. Marsac et al. (2006, 2009) predicted different drugs' solubility in PVP at room temperature based on solid–liquid phase equilibrium and Flory–Huggins theory of liquids. Flory–Huggins interaction parameter, a temperature dependent variable, was calculated from melting point depression method. The authors also compared the

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simulated results with experimentally obtained drug solubility in 1-ethyl-2-pyrrolidone, a low molecular weight analog of PVP. Tao et al. (2009) measured drugs' solubility in PVP and PVP/VA. They observed the endpoint T_{end} of the drug dissolution peak using modulated DSC. To ensure thermodynamic equilibrium in the DSC scanning process, very slow heating rates ranging from 0.1 to 5 °C/min were used. The method requires appreciable thermal effect associated with the dissolution process in order to determine T_{end}. Both studies did not provide direct experimental data regarding the solubility in highly viscous PVP and its copolymer at room temperature. The difficulty lies in the fact that the kinetics of reaching the drug–polymer equilibrium is extremely slow.

The goal of this study is to investigate the feasibility of utilizing several analytical methods, including rheological, thermal and microscopic methods, to measure an API's solubility in a polymeric excipient at both HME processing temperature and storage temperature. A model drug acetaminophen (APAP) and a pharmaceutical grade polymer polyethylene oxide (PEO) were selected. PEO has a low glass transition temperature T_g of ~−55 °C and melting temperature T_m of ~60 °C. The glass transition temperature is a function of chain flexibility. For a polymer, the glass transition occurs when there is enough thermal energy in the system to permit sequences of 6–10 main-chain carbons to move together as a unit. On the one hand, the low T_m and T_g facilitate the extrusion process and make the solubility measurement relatively easy since the kinetics of dissolution, phase separation and recrystallization are fast compared to excipients with higher T_g. On the other hand, fast kinetics may not be desirable if the researchers hope to kinetically inhibit API's recrystallization. Another material characteristic worthy of special attention is that PEO is a semi-crystalline material, which makes the thermodynamics of the drug–polymer mixture even more complicated compared to the amorphous polymer case since there are more physical states possible.

PEO and APAP should be partially miscible based on their difference in solubility parameter, 7.46 $MPa^{1/2}$ to be exactly (Mididoddi and Repka, 2007; Breitkreutz, 1998), and the criteria suggested by Greenhalgh et al. (1999). Our previous results (Yang et al., 2010) also show that APAP dissolves in molten PEO at high processing temperature, but recrystallizes after being cooled to room temperature when the drug loading is between 10 and 30 wt%. Therefore, it is expected that there will be a strong dependence of APAP's solubility on temperature, which also makes the system an interesting candidate for the current study.

2. Experimental

2.1. Materials

Crystalline APAP, with melting temperature of ~170 °C, was purchased from Spectrum Chemicals (Gardena, CA). PEO N10 ($M_w = 1 \times 10^5$ g/mol), a semi-crystalline polymer with the glass transition temperature of ~−55 °C and melting temperature of ~60 °C, was kindly donated by the Dow Chemical Co. (Midland, MI).

2.2. Sample preparation

The APAP–PEO mixture samples with APAP weight percentage of 0, 1, 2, 3, 4, 5, 10, 20, 25, 30, 40, 50 and 60% were prepared by hot-melt mixing using a Brabender FE-2000 batch intensive mixer with two counter rotating screws. 50 g of pre-mixed powder was processed each batch at the temperature of 120 °C and rotor speed of 50 rpm. After 10 min of mixing, the melt was removed from the mixer and compression molded at 120 °C into 25 mm diameter × 1 mm thickness discs as well as 14 mm × 10 mm × 2.7 mm bars separately. All samples were cooled down to 25 °C with cooling water circulated in the compression mold. They were stored at room temperature in a vacuum desiccator with silica gel before further testing.

2.3. Rheological experiments

Rheometric mechanical spectrometer RMS-800 from Rheometric Scientific (now TA Instruments, New Castle, DE), a strain-controlled rheometer, was used to determine the steady viscosity of PEO and its mixtures with APAP. A step rate test was conducted at a constant shear rate of 0.5/s using 25 mm parallel plate. A sample disc (25 mm diameter × 1 mm thickness) was loaded between the plates at 140 °C but was quenched to the testing temperatures (T_f) in less than 2 min. It was held isothermally at T_f for 15 min to reach the equilibrium before testing. Each sample was tested individually at T_f of 80, 100, 120 and 140 °C for 10 min.

2.4. Hot-stage microscopy (HSM)

Mixtures of 10, 20, 30, 40 and 50 wt% of APAP in PEO were evaluated by hot-stage microscopy using an optical microscope (Carl Zeiss Universal Research Microscope) equipped with a Zeiss AxioCam MRc5 (5 MB-pixel resolution) digital camera and coupled with a Mettler FP82HT hot stage and Mettler FP90 temperature controller (Mettler-Toledo Inc., Columbus, OH, USA). Samples were heated between two glass slides from room temperature to a final temperature (T_f) of 80, 100, 120, and 140 °C at a heating rate of 10 °C/min and kept isothermally at T_f for 15 min. Images were taken at the end of the experiment.

2.5. Differential scanning calorimetry (DSC)

DSC measurements were carried out using a TA Instruments Q100 (New Castle, DE) equipped with a refrigerated cooling system. The chamber was flushed with N_2 at a flow rate of 40 ml/min during the testing. A sample of about 4 mg was weighed and placed in an aluminum pan with lid and crimp sealed. The glass transition temperatures of PEO and APAP were measured in the 2nd heating cycle of a heat–cool–heat loop. Pure PEO was heated from 30 °C to 80 °C at 10 °C/min, quenched to −80 °C and reheated to 80 °C at 10 °C/min. Pure APAP powder was heated from 30 °C to 180 °C at 10 °C/min, quenched to −25 °C and reheated to 180 °C at 10 °C/min.

Binary mixture samples, with 10, 20, 25, 30, 40, 50 and 60 wt% of APAP, were tested using the following heat–cool–heat cycle for determination of the glass transition temperature T_g of the mixture, which were further utilized to estimate APAP's solubility at high temperatures, i.e., above the PEO's melting point, and the melting temperature T_m of the mixture.

1. A sample was heated from 30 °C at 10 °C/min to a final temperature (T_f) of 80, 100, 120 or 140 °C, which were subsequently held isothermally at T_f for 15 min.
2. The sample was quenched from T_f to −80 °C at 20 °C/min.
3. The sample was reheated from −80 °C to 80 °C at 10 °C/min to measure T_g and T_m.

APAP's apparent solubility at room temperature was estimated by T_g measurement in a single heating ramp. Samples were stored at room temperature for 4 weeks. APAP–PEO mixtures with APAP concentration varying from 1 to 50% were quenched to −80 °C and then heated to 80 °C at 10 °C/min. Melting temperature T_m (onset) was also recorded in the same cycle.