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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.

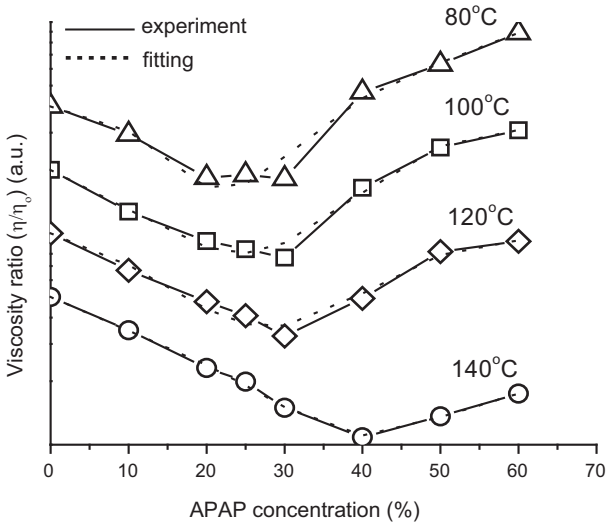

Fig. 1. Viscosity ratio (η/η_o) of 0, 10, 20, 25, 30, 40, 50 and 60% APAP in PEO at temperatures (T_f) of 80 °C (△), 100 °C (□), 120 °C (◊) and 140 °C (○).

2.6. Dynamic mechanical thermal analysis (DMTA)

Dynamic mechanical thermal analyzer DMTA-IV from Rheometric Scientific (now TA Instruments, New Castle, DE) was used to determine the glass transition temperatures of pure PEO and its mixtures with APAP that were stored at room temperature for 4 weeks after hot-melt mixing. The experiment was conducted using dual cantilever with small frame. A sample bar (14 mm × 10 mm × 2.7 mm) was first quenched to −70 °C and then ramped to 30 °C at a heating rate of 2 °C/min using liquid nitrogen as a cooling medium and 5 ml/min N_2 gas to prevent the build-up of moisture during the experiment. A strain of 0.02%, within the linear viscoelastic region of the material (that is below the strain limit of linear viscoelastic response), and a frequency of 1 Hz were applied for each sample. The elastic (in-phase) modulus (E'), viscous (out-of-phase) modulus (E'') and tan δ (E''/E') were recorded during the experiment. T_g was determined from the peak of the tan δ curve in the glass transition region.

3. Results

3.1. Determination of drug solubility at elevated temperatures by rheological analysis

The objective of the rheological study is to find drug's solubility at different temperatures within the extrusion processing window by tracking the viscosity change of the binary mixtures with different drug loadings. The selected testing temperatures are above the melting point of PEO (~60 °C) and below the melting temperature of APAP (~170 °C).

In general, steady viscosity of PEO (η_o) and those of APAP–PEO mixtures (η) decrease with increase in temperature due to the increasing Brownian motion of the constituent molecules. The viscosity ratio of APAP–PEO mixture to PEO (η/η_o), i.e., the normalized viscosity of the mixture, was calculated and plotted against drug concentration in Fig. 1. The four η/η_o curves at different T_f exhibit a similar trend that η/η_o value drops first with the drug loading, and then increases after reaching a certain concentration. Take η/η_o curve at T_f = 140 °C as an example, it decreases from 1 for pure PEO to 0.22 for 40 wt% of APAP, after which it climbs up to 0.35 for 60 wt% of APAP. The initial decrease of viscosity indicates disruption of the polymer structure due to the drug dissolution (Zhang et al., 2005; Hodge et al., 1996; Heijboer, 1978). The dissolved drug acts as a plasticizer in this case, which leads to decrease of the viscosity with the increase of drug concentration. On the other hand, the rise of the viscosity at higher drug concentration occurs when the drug solubility is exceeded and undissolved solid drug particles act as suspended fillers. Many previous studies have shown that the viscosity of a filler–polymer melt suspension system depends on the interfacial energy as well as the filler's concentration and shape (Kaully et al., 2007; Inn and Wang, 1995; Kitano et al., 1981; Guth, 1945). Generally, the viscosity increases with the filler's concentration (Mutel and Kamal, 1984), which can be explained by the increased viscous dissipation due to shearing between particles and the melt, and particle/particle interactions.

Table 1
Summary of APAP solubility in PEO at elevated temperatures measured by rheometric mechanical spectrometer, hot-stage microscope and DSC.

Temperature	Solubility by rheological evaluation (%)	Solubility by hot-stage microscopy (%)	Solubility by DSC (%)
80 °C	22	10–20	14
100 °C	24	20–30	20
120 °C	31	30–40	30
140 °C	41	40–50	n.a.

The viscosity ratio (η/η_o) data are further fitted with fourth-degree polynomial using Polymath 5.1 (Polymath Software, Willimantic, CT) to determine the minimum value. Theoretically, the drug concentration with the lowest η/η_o value is the drug solubility at the specific temperature T_f. Dotted curves in Fig. 1 were obtained from polynomial fitting with $R^2 > 0.99$ and the drug solubility values determined from the fitting curves are listed in Table 1. The result shows that the drug solubility increases steadily with temperature. It should be mentioned that the predicted solubility at 80 °C (22%) may be slightly higher than the real value because η/η_o values of 20, 25 and 30 wt% of APAP are very close to each other, which makes it more difficult to identify the critical point. These solubility data obtained by relatively simple rheological experiments are of great help for determining the processing window of HME. For example, to prepare a fully miscible APAP–PEO system with drug loading of 20%, the lowest processing temperature is 100 °C. Otherwise, the drug crystals will not fully dissolve into the polymer melt no matter how intensive the mixing is.

3.2. Visual determination of drug solubility at elevated temperatures

To check the solubility data obtained from the rheological test, a hot-stage microscope was used to directly observe the physical state of the drug particles in the molten polymer mixtures. The same temperatures (T_f) as those in rheological experiments were used. To facilitate observation and assure intimate contact between two materials, PEO and APAP were first hot-melt mixed. The sample was placed on a glass slide, slightly heated on the hot stage, and pressed carefully with a cover glass. The mixture was further equilibrated at the temperature of interest. At T_f of 80 °C and APAP loading of 10% (Fig. 2a), crystalline APAP fully dissolves in the molten PEO with no visible particles left. In contrast, at drug loading of 20%, APAP crystals can be found even after 15 min of heating at 80 °C (Fig. 2b). Therefore, APAP solubility at 80 °C should fall between 10 and 20%. Experiments were also conducted at 100, 120 and 140 °C (Fig. 2c–h) and the results are summarized in Table 1. Clearly, most solubility data obtained from rheological tests fall into the range determined by HSM. The only slight mismatch was found at 80 °C. As discussed in the previous part, the critical point on the curve of viscosity versus drug loading cannot be accurately determined at 80 °C because the transition is not sharp enough. It should be mentioned that the optical microscopic method is a rough method and

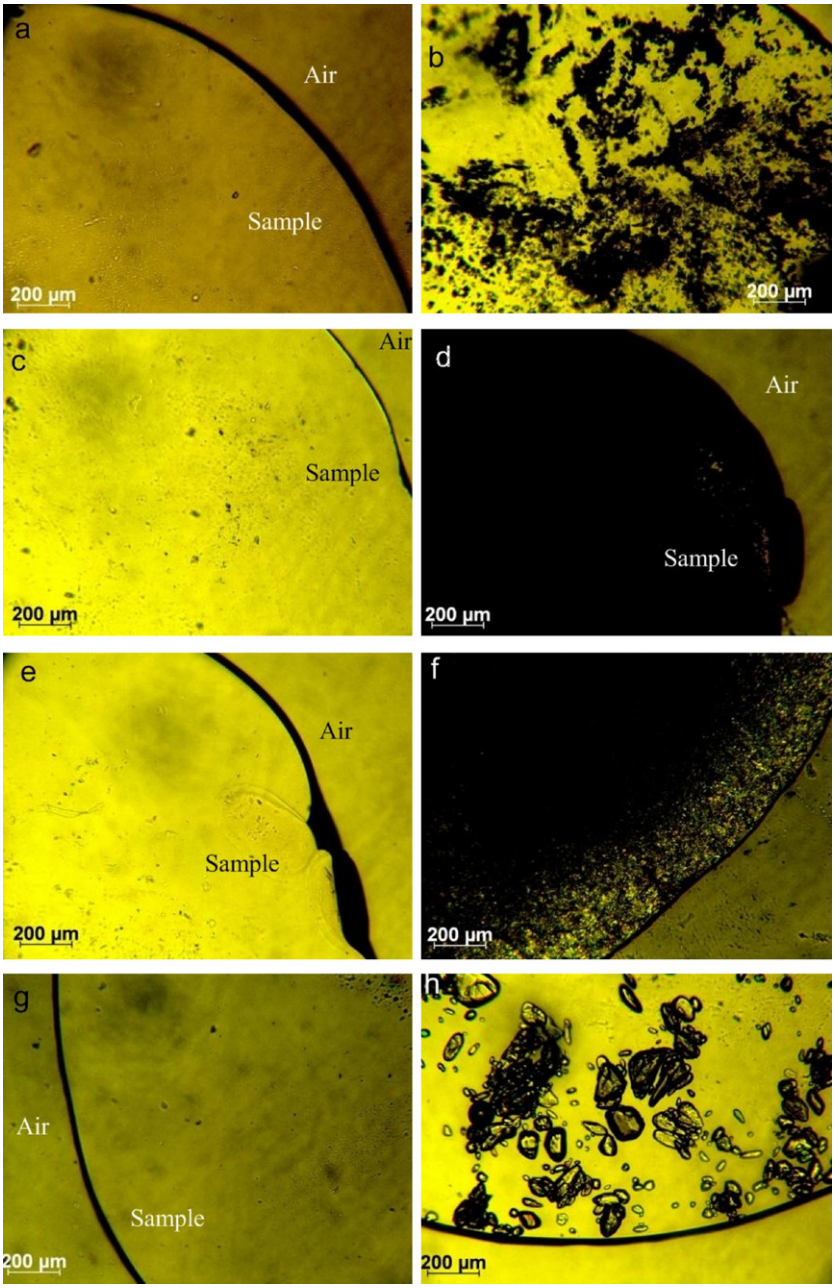

Fig. 2. Hot-stage microscopic images of samples after being kept isothermally at different temperatures for 15 min. a) 10% APAP–PEO at 80 °C; b) 20% APAP–PEO at 80 °C; c) 20% APAP–PEO at 100 °C; d) 30% APAP–PEO at 100 °C; e) 30% APAP–PEO at 120 °C; f) 40% APAP–PEO at 120 °C; g) 40% APAP–PEO at 140 °C; h) 50% APAP–PEO at 140 °C.

cannot be applied to accurately identify the solubility. Nevertheless it is quite straightforward, readily accessible, and can be applied to obtain a rough estimate of the solubility. Another advantage is that the microscopy method can be applied to more mixture systems compared to other analytical methods due to less assumptions involved.

3.3. Determination of drug solubility at elevated temperatures using DSC

A third approach using DSC were explored to determine the drug solubility at high temperatures. The method is based on the assumption that the glass transition temperature should vary with APAP's concentration in the APAP–PEO solution. Similar to rheological and microscopic analysis, temperatures within the HME processing window were selected, namely 80, 100, 120 and 140 °C. In the 1st heating cycle, the sample was heated to a final temperature T_f and then held at the temperature for 15 min. Depending on the drug loading and the temperature, the crystalline drug may be partially or fully dissolved in the molten polymer at T_f. The sample was then quenched to −80 °C, a temperature below the glass transition temperatures of both PEO and APAP. In the 2nd heating scan, T_g of the APAP–PEO mixture was determined.

T_g of PEO and APAP are −54.7 °C and 24.7 °C, respectively. Glass transition temperatures of amorphous APAP–PEO from the 2nd heating cycle are plotted in Fig. 3. One finding is that the T_g profiles for T_f = 80, 100 and 120 °C show quite similar trend. T_g increases with APAP concentration but the glass transition temperature stops rising after certain drug loadings. When the APAP concentration is less than the critical value, APAP particles fully dissolve in the molten polymer at T_f during the first heating scan. Beyond the limit, no more crystalline APAP is able to dissolve in PEO and thus the

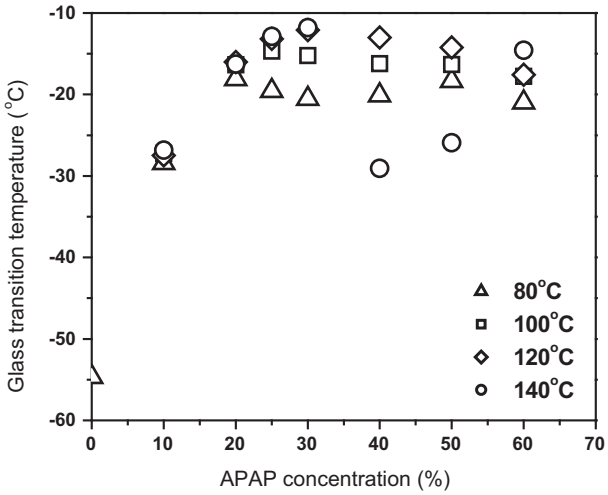

Fig. 3. Glass transition temperatures of mixtures at different drug loadings determined from the 2nd heating cycle in DSC with the ending temperatures (T_f) in the 1st heating cycle of 80 °C (△), 100 °C (□), 120 °C (◊) and 140 °C (○), respectively.

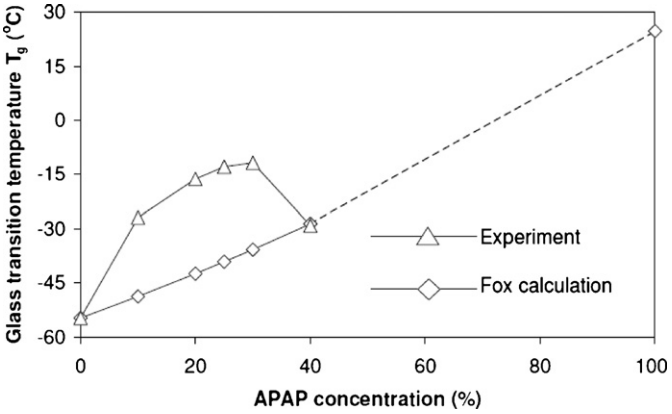

Fig. 4. Calculated (◊) and experimentally determined (△) glass transition temperatures of APAP–PEO. Experimental data were obtained from the 2nd heating cycle in DSC with the ending temperature (T_f) in the 1st heating cycle of 140 °C.

curve reaches a plateau (in the case of 140 °C, T_g dips at the region of high drug loading, which will be discussed later). Hence, the critical concentration is taken as the drug's solubility at T_f. The solubility data were summarized in Table 1. It should be mentioned that one assumption for the DSC method is that the drug does not recrystallize during the quench and the second heating scan. The fact that the solubility values predicted by all three methods are very close to each other seems to support this assumption. Overall, the data show that the solubility increases from 14% at 80 °C to 41% at 140 °C.

One peculiar phenomenon is found on the curve corresponding to T_f of 140 °C, where T_g drops as much as 17 °C when the drug loading increases from 30% to 40%. It is known from rheological and microscopic analysis that drug solubility is around 41% at 140 °C. Thus, the sharp T_g decrease is not caused by drug recrystallization or phase separation. To further investigate this issue, Fox equation (Fox, 1956) is used to calculate the theoretical glass transition temperatures for APAP–PEO with different drug concentrations and is expressed as:

$$\frac{1}{T_g} = \frac{w_1}{T_{g_1}} + \frac{w_2}{T_{g_2}}$$

where w_1 and w_2 refer to the weight fraction and T_{g_1} and T_{g_2} refer to the glass transition temperatures of the drug and polymer, respectively.

Fox equation is often applied to predict the glass temperature of random copolymers (Tang et al., 2010; Liu and Urban, 2009; Wei et al., 2009) and plasticized polymers (Gutierrez-Villarreal and Rodríguez-Velazquez, 2007; Blasi et al., 2007; Pillin et al., 2006) based on compositions of two components. This semi-empirical equation, as well as Gordon Taylor equation (Gordon and Taylor, 1952), has been applied to drug–polymer systems to study the miscibility of the binary components (Qian et al., 2010a; Haddadin et al., 2009; Tong and Zografi, 2001; Matsumoto and Zografi, 1999). Since APAP solubility is about 41% at 140 °C, T_g is only calculated for samples having less than 40% APAP loading. As shown in Fig. 4, most experimental T_g values are significantly higher than theoretical values, suggesting possible specific physical interactions between APAP and PEO. When APAP concentration is 40%, however, theoretical T_g is able to match the experimental value. The hydroxyl group of acetaminophen is a good proton donor and can form strong hydrogen bonds with the oxygen acceptor on the PEO chain (Shekunov et al., 1999, 2007), which is capable of leading to a nonlinear relationship between T_g and the composition. Strong intermolecular interaction is usually beneficial for miscibility and solid solution stabilization (Chokshi et al., 2008; Miyazaki et al., 2006; Taylor and Zografi, 1997), but the H-bonding in the current case does not seem to prevent APAP from recrystallizing at room temperature (Yang et al., 2010). According to Wen et al. (2005, 2008) the high flexibility of PEG and the high mobility of the function groups involved in the H-bonds is the reason why the crystallization of APAP cannot be inhibited. The unusual drop of T_g at drug concentration between 30 and 40% may due to the saturation of hydrogen bond at high drug concentration.

In conclusion, drug solubilities at HME processing temperatures determined from the DSC method basically match those from rheological and microscopic methods.

3.4. Estimation of apparent drug solubility at room temperature via DSC and DMTA measurements

Apparent APAP solubility in PEO at room temperature was estimated with similar T_g evaluation method described in the previous DSC section. The difference is that samples were stored at room temperature for four weeks before testing, and the T_g was determined during the first heating scan. In other words, the T_g value reflects the mixtures' physical state at room temperature instead of the state at elevated temperatures. Glass transition temperatures were determined using both DSC and DMTA methods. It should be mentioned that the system probably has not reached thermodynamic equilibrium after four weeks at room temperature, although the recrystallization does drop to an almost undetectable slow rate (Yang et al., 2010) by that time. Hence, the solubility obtained is apparent solubility, which may be higher than the thermodynamic solubility. In real application though, it might not be necessary to get the room temperature thermodynamic solubility. One may be more concerned of the apparent solubility of a drug product during its designed shelf life. In that case, a long-term stability test will be sufficient to provide the information.

Dynamic mechanical thermal analysis (DMTA) is a thermoanalytical technique. While DSC detects the change in heat capacity when a polymer shifts from glassy to rubbery state, DMTA detects the change of modulus. T_g is determined from the peak of the mechanical loss tangent tan δ, which is responsible for dissipation of energy during deformation and is defined as:

$$\tan\delta = \frac{E''}{E'}$$

where E' is the elastic modulus and represents how much energy the polymer stores, and E'' is the viscous modulus and indicates the polymer's ability to dissipate energy as heat. The modulus relate

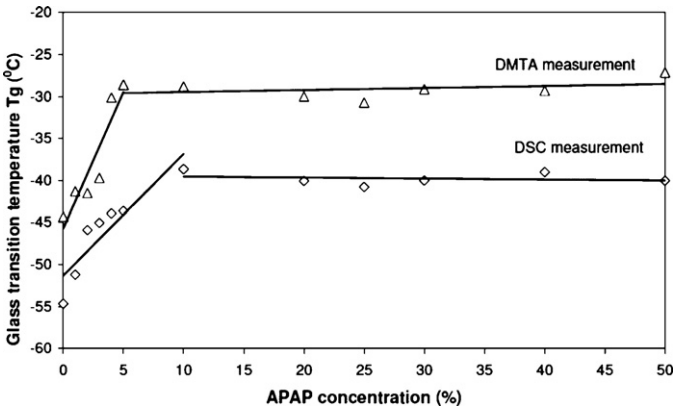

Fig. 5. Glass transition temperatures of 4-week old melt-mixed samples measured using DSC (◊) and DMTA (△).

to the stiffness of the material and to its damping capacity (energy dissipation).

The peak of the tan δ is the center of the T_g relaxation while in DSC the onset temperature of the T_g relaxation is usually reported. In such a case the DSC T_g will be lower than that for DMTA. In addition, a frequency effect puts the mechanical (ca. 1 Hz) T_g higher than that for a DSC measurement (0.0001 Hz) (Cheremisinoff, 1996). DMTA determined T_g of pure PEO is −44.3 °C, while T_g from DSC measurement is −54.7 °C. Despite the difference in absolute numbers, both methods show similar T_g evolution trend with drug concentration. Only one T_g in each APAP–PEO sample is observed. For DSC, T_g increases from −51.2 °C for 1 wt% of APAP to −38.7 °C for 10 wt% of APAP and basically keeps constant afterwards. DMTA data show similar trend: T_g first increases with APAP loading, but then reaches a plateau at the concentration around 5%. As presented in Fig. 5, the critical turning point is around 10% for DSC and 5% for DMTA. The result is consistent with the findings by our group (Yang et al., 2010) that above 10% drug loading, APAP will recrystallize from PEO after the sample is cooled from the HME processing temperature to room temperature.

4. Discussion

Fig. 6 shows the relationships of dissolution temperature $T_{dissolution}$, melting temperature T_m and glass transition temperature T_g with the drug concentration. APAP's solubility between 25 and 120 °C was determined by DSC analysis, while the solubility at 140 °C was estimated to be 41% based on rheological evaluation. T_g curve with APAP concentration ≥10% was a partial replot of Fig. 3 and the data were obtained from the DSC 2nd heating cycle. T_m values were acquired from the same DSC heating cycle as T_g. For APAP concentration from 1 to 5%, both T_g and T_m were read from the first DSC heating cycle.

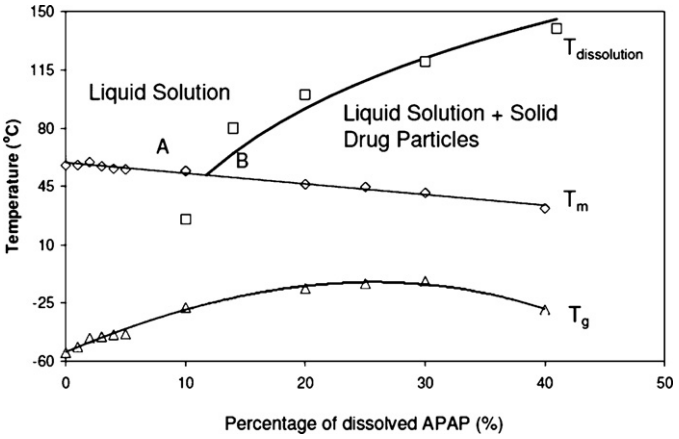

Fig. 6. Dissolution temperature $T_{dissolution}$ (□), melting temperature T_m (◊) and glass transition temperature T_g (△) of APAP–PEO with different percentages of APAP dissolved.

The composite figure of $T_{dissolution}/T_g/T_m$ vs. drug loading (Fig. 6) is in essence a "phase diagram" and, as such, provides valuable information for formulation and HME process development. It should be mentioned that APAP and PEO were chosen only as model materials; the focus is not on any specific commercial application. Nevertheless, a discussion of Fig. 6 can help us appreciate the significance of such a "phase diagram" in HME process practice. HME is often processed at temperatures above the T_m curve where PEO is in molten state. APAP and PEO are fully miscible and form liquid solution in region A. In region B, however, APAP does not totally dissolve in PEO and thus the system contains solid drug particles. In order to obtain a true solution, it is more favorable to process the mixture in region A as compared to region B. Of course, other factors such as potential thermal degradation need to be taken into consideration. Between the curve of T_m and T_g is the solid dispersion region, where APAP can either disperse molecularly in PEO and form solid solution, or it can partially recrystallize. Based on the apparent solubility obtained from DSC and DMTA, 10 wt% is the boundary separating solid solution and solid dispersion with crystalline drug at room temperature. When drug loading is very small (<10 wt%), solid solution is stable and drug recrystallization is not a concern. On the contrary, at high drug loading (≥10 wt%), APAP tends to recrystallize from the polymeric matrix even if two components have formed a liquid solution previously under the processing condition in region A. Since room temperature is above the glass transition temperature, the recrystallization rate is not going to be slow enough to keep the drug at amorphous state during shelf time, as demonstrated by our experimental finding. Different strategies may be applied to address the issue depending on the specific application: a third component can be introduced to either inhibit or accelerate the drug recrystallization. Either way it is critical to prepare a mixture that is stable during the HME product shelf life.

Insightful information regarding the mixture's physical state can be obtained using three methods, i.e., rheological, microscopic and thermal analysis, described in this study. Understandably, each method has its own limitation. The rheological method can only be applied to study the upper range of the processing temperature due to the instrument's toque limitations. More specifically, rheometers generally can only be applied to study the system at a temperature significantly higher than the melting point of the polymer excipient. For the solubility testing described in this article, the temperature also needs to be lower than the melting point of the drug particles. Otherwise, the drug will exist as a liquid and increase of drug loading will lead to decrease of the viscosity of the mixture even if the drug liquid is not fully miscible with the molten polymer. On the other hand, the advantage of rheological method lies in the relative simple relationship between the viscosity and the mixture composition, which makes it easy to identify the critical point in the viscosity vs. composition curve, i.e., the solubility point, compared to the DSC method. The rheological data themselves are of great interest for process optimization as well. The microscopic method allows for a straightforward observation of the physical state of the materials. However, it is almost impossible to determine the exact solubility due to the limitation of resolution. The solubility data can also be determined from the shift of the glass transition temperature measured via DSC. DSC method also provides other valuable information such as the melting point of the mixture. However, one has to be careful when using the trend of the glass transition temperature to determine the drug's solubility because it is not

uncommon to a drug–polymer mixture to have a complicated and non-monotonic relationship between the T_g and the composition, such as the 140 °C case described in this article.

5. Conclusion

Rheological, microscopic and thermal methods have been used to measure APAP's solubility in PEO at both HME processing temperatures and storage temperature. The strain-controlled rheometer measured the viscosity of APAP–PEO and the solubility data were obtained from the critical point on the curve of viscosity vs. drug loading. The solubility of APAP in PEO was also obtained from measuring the glass transition temperature at different drug loadings. Results from the two methods match each other and are further confirmed by hot-stage optical microscopic inspection. Apparent drug solubility at room temperature was estimated through T_g measurement using DSC and DMTA. The $T_{dissolution}/T_g/T_m$ diagram developed in this work (essentially a "phase diagram") can be referred to determine the optimal HME processing conditions and mixture composition. 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.

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