European Journal of Pharmaceutics and Biopharmaceutics 78 (2011) 506–512

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

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

Research paper

Rheological study of the mixture of acetaminophen and polyethylene oxide for hot-melt extrusion application

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ARTICLE INFO

Article history:
Received 9 November 2010
Accepted in revised form 16 March 2011
Available online 23 March 2011

Keywords:
Hot-melt extrusion
Rheology
Viscosity
Viscoelasticity
Solubility
Rheometer

ABSTRACT

There is a growing interest of extrusion drug and polymer together to manufacture various solid dosages. In those cases, the drug's release profiles are greatly affected by the miscibility of two materials. The goal of this study is to test the drug's solubility in molten polymer and obtain the mixture's rheological properties for the purpose of optimizing the extrusion process. The dynamic and steady viscosities of APAP–PEO mixture were determined using oscillatory and capillary rheometers. The curves of viscosity vs. drug loading generally have a "V" shape, and the minimal point gives the APAP's solubility in PEO. The test results suggest that different dynamic methods lead to essentially the same solubility data. At high shear rates, the mixtures show shear thinning behavior and the viscosity becomes less sensitive to the drug loading. In other words, it is desirable to use a low shear rate in order to deduce the drug's solubility in polymer from the viscosity data. On the other hand, viscosity data at high shear rates are more representative of the materials' rheological properties during extrusion.

1. Introduction

Hot-melt extrusion (HME) has been widely used in the plastic and rubber industry to manufacture a broad variety of products. The process involves mixing different materials using a screw extruder at an elevated temperature and pumping the mixture through a die to form a product of desired shape. Recently, the process has caught a great deal of interest from the pharmaceutical industry [1–5,13,14]. It has been applied to extrude combinations of drugs, polymers and plasticizers into various solid dosage forms such as tablets, transdermal patches, granules, capsules and so on.

Much of the previous research interest has been focused on utilizing HME to improve the drug's bioavailability through increasing the active pharmaceutical ingredient's (API's) dissolution rate in an aqueous solution [2–5]. A large percentage of newly developed chemical entities are poorly soluble, and HME is believed to be one of the most promising methods to improve the bioavailability of those APIs. In addition, HME offers a number of other advantages compared to the solvent methods such as spray drying: no solvents are required and fewer processing steps are needed compared to the traditional processes such as wet granulation. HME eliminates the drying step and can produce large volume of units in a relatively short time period. It is more energy efficient than high-shear granulation. Furthermore, the intensive mixing, a result of the characteristics of the equipment and elevated processing temperature, leads to a uniform dispersion.

In this study, the rheological properties of a mixture of model drug and a polymer excipient are systematically studied using oscillatory and capillary rheometers. Thus, obtained rheological data not only can be used to optimize the extrusion process but also indirectly provide the drug's solubility in polymer excipient, as elaborated in the following part of this paper. Generally speaking, if a polymer and a drug form one phase at the processing temperature, not only a more uniform product can be obtained, it may also lead to other desirable product properties such as faster drug dissolution rate. Having the solubility data can minimize the time for trial-and-error experiments and help to understand evolution of the drug's physical state during the HME process and the storage period. Despite the obvious benefit and great interest of knowing the drug's solubility in polymeric excipient, very few previous papers have discussed how to experimentally determine these basic data. Differential scanning calorimetry (DSC) method [1] requires heating a mixture sample from room temperature to the temperature of interest at an extremely slow rate so that the kinetics does not affect the solubility data obtained. As a result, a long testing period is required, which may cause the thermal degradation of

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doi:10.1016/j.ejpb.2011.03.013

the sample. In this study, we will deduce the solubility data from the mixture's viscosity at different drug loadings, which only requires relatively convenient and fast test on viscosity.

To understand why the drug's solubility in polymer can be derived from the mixture's viscosity, let us consider a series of API–polymer mixtures with different drug loadings equilibrated at a temperature lower than the drug's melting point, but higher than the polymer's melting/softening point. If the drug and the polymer form a solution, the viscosity of the mixture decreases with the drug loading because the dissolved small drug molecules increase the mobility of the polymer chain and the free volume among polymer molecules. Above the solubility limit, the mixture consists of solid drug particles and a drug–polymer solution. In the two-phase region, the dependence of the mixture's viscosity on the drug loading can be explained by the Einstein's theory [6]. Assuming the dispersed solid particles are single-sized spheres, the reduced viscosity η/η_o of the mixture increases with volume fraction χ of the dispersed phase, as described by the following equation.

$$\eta/\eta_o = 1 + 2.5\chi \quad (1)$$

Herein, η is the viscosity of the mixture and η_o is the viscosity of the pure solvent or molten polymer in our study. Eq. (1) suggests that the viscosity of the mixture will increase with the amount of the drug particles when the solubility limit is passed. The slope of the curve of η/η_o vs. χ is dependent on factors such as the shape of particles and the potential particle–particle and particle–solvent physical interactions. In other words, the slope may vary from 2.5 given here.

In summary, if the viscosity of a drug–polymer mixture is plotted against the drug concentration, the slope is expected to be negative below the solubility limit and changes to positive beyond the limit. The critical point on the curve gives the drug's solubility in the polymeric excipient. The similar phenomenon has been observed in blowing agent-polymer systems [7].

Acetaminophen (APAP) and polyethylene oxide (PEO) were chosen as the model drug and polymer, respectively. The viscosities at different APAP concentrations and various temperatures were determined by a series of dynamic and steady rheological tests. The reduced viscosity was plotted as a function of APAP concentration and temperature. For each temperature, the critical point on the curve of viscosity vs. drug loading gives the solubility of APAP at that temperature.

2. Materials

Acetaminophen, with a commercial name of paracetamol, was supplied by Spectrum Quality Products, Inc. (Gardena, CA 90428). It has a formula of $C_8H_9O_2$ with the molecular weight of 156.17. Its density at 25 °C is 1.293 g/cc, and it has a melting point of 168 °C. The molecular structure of Acetaminophen is shown in Fig. 1.

Poly(ethylene oxide) was supplied by Dow Chemical Company. The glass transition is −67 °C, and the melting point is 65 °C. The average molecular weight is about 100,000 g/gmol. Its density is 1.113 g/cc at 25 °C, and the viscosity of 5% solution in water is in the range of 12–50 cP at 25 °C. The molecular structure is given in Fig. 1.

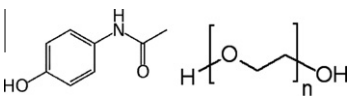

Fig. 1. The molecular structure of acetaminophen (left) and polyethylene oxide (right).

Two materials are stable at the testing temperature range. Thermal stability data can be found in one of our recently published papers [15].

3. Experimental

3.1. Oscillatory rheometer

Rheometric Mechanical Spectrometer RMS-800 from Rheometric Scientific (now TA Instruments) was used to determine the dynamic properties such as G' (elastic modulus), G'' (viscous modulus) and η^* (dynamic viscosity) of PEO and its mixture with Acetaminophen. RMS-800 is a strain-controlled and SMT (Separate Motor Transducer) rheometer. Samples were compounded in Brabender mixer and then molded at 120 °C into disks. A sample disk of 25 mm in diameter and 1 mm in thickness was loaded between two parallel plates for each test.

Dynamic frequency sweeps were conducted at constant temperatures (80, 100, 120 and 140 °C). A strain of 10%, within the linear viscoelastic region of the materials, was applied to all samples, except 5% strain for 50% APAP. The sample was subjected to a strain with frequency varying from 100 to 0.1 rad/s.

Dynamic time sweep was conducted at a constant frequency of 1 Hz (6.28 rad/s). A strain of 10%, within the linear viscoelastic region of the material, is applied to all samples except 5% strain for 50% APAP. Each sample was subjected to 1800 s time sweep.

Dynamic temperature ramp was conducted at a constant frequency of 1 Hz (6.28 rad/s). A strain of 10%, within the linear viscoelastic region of the materials, was applied to all samples. The sample was cooled down from 140 °C to the lowest possible temperature with 2 °C/min cooling rate. Herein, the lowest temperature is decided by the torque limit of the rheometer.

For all the aforementioned tests, the sample was loaded at a constant temperature of 140 °C and then quickly cooled down to the testing temperatures. Pure PEO and various concentrations of Acetaminophen in PEO were tested during the experiments (10, 20, 25, 30, 35, 40 and 50 wt.%).

Steady rate sweep was conducted from 0.01 to 10 1/s with 5 s delay and 5 s measurement times. PEO with 10, 20, 30, 40 and 50 wt.% was selected for the tests.

3.2. Capillary rheometer

The steady viscosities of PEO and mixtures of three different APAP concentrations, 10, 20 and 30 wt.%, were determined at 100, 120 and 140 °C using an Instron capillary rheometer. The other two concentrations, 40 and 50%, were determined at 120 and 140 °C. The barrel diameter is 9.5 mm. The stainless steel die has a length of 30 mm and a diameter of 1 mm. The crosshead speed from 0.5 to 500 mm/min was applied to cover moderate to high shear rates. The drug was mixed with the polymer in the Brabender Torque Rheometer at 120 °C and 45 rpm for 10 min. The mixture was then compressed for approximately 8 min to form a thin sheet via compression molding at 120 °C. The sheet was cut into small pieces to be fed into the barrel.

3.3. Differential scanning calorimetry

Thermal analysis of PEO–APAP system was conducted with DSC Q-100 from TA Instrument. Three to five milligrams sample of PEO–APAP mixture was from the same mixtures prepared for rheological characterization. The sample underwent heat–cool cycle from 0 to 100 °C with 10 °C/min heating and cooling rate.

4. Results and discussion

4.1. Viscoelastic properties

Dynamic frequency sweep is commonly used to determine the viscoelastic properties of the materials. Fig. 2 shows the data from dynamic frequency sweep of PEO at 140 °C. The Fig. clearly displays that G'' (viscous modulus) is always higher than G' (elastic modulus) at all frequencies investigated, indicating that PEO behaves and flows like a viscous material at this particular temperature.

Fig. 3 depicts the viscoelastic behavior of PEO at 80 °C. G' and G'' cross over at frequency of 25.6 rad/s, above which the material behaves more like a solid.

Table 1 lists the G'/G'' crossover points for pure PEO and the mixtures at different temperatures and concentrations. The crossover frequency of pure PEO decreases as the temperature decreases. Unlike the pure PEO, the mixture samples do not show crossover points at 140 °C and 120 °C within the tested frequency. The phenomena suggest that the addition of APAP transforms the mixture into a more liquid-like material, as also indicated by the lower values of the dynamic viscosity. The table also indicates that the best processing temperatures for any PEO–APAP mixtures are between 120 and 140 °C because G'' is always higher than G' in the temperature range, suggesting the viscous behavior of the mixture.

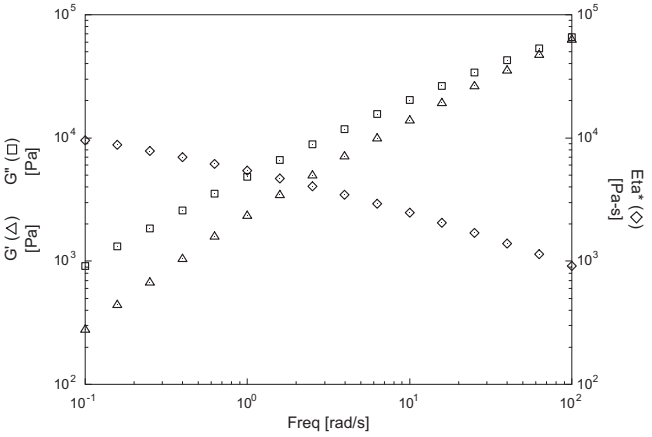

Fig. 2. Viscoelastic properties of PEO at 140 °C.

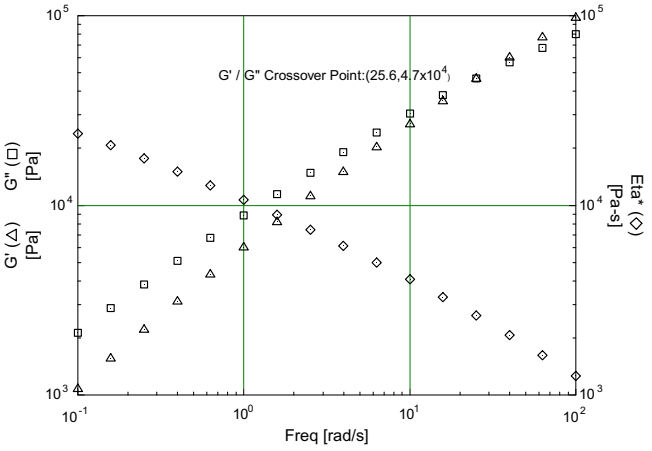

Fig. 3. Viscoelastic properties of PEO at 80 °C. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
G'/G'' crossover of PEO–APAP mixtures.

wt.% of APAP	Crossover frequency (rad/s) at various temperatures (°C)			
	140	120	100	80
0	N.A.	82.2	47.4	25.6
10	N.A.	N.A.	86.0	44.8
20	N.A.	N.A.	91.8	47.5
30	N.A.	N.A.	93.0	45.1
40	N.A.	N.A.	N.A.	44.2
50	N.A.	N.A.	88.6	49.0

For the mixtures at temperatures of 100 °C and 80 °C, the addition of APAP increases the G'/G'' crossover frequency up to certain critical value, after which the crossover frequency decreases with the increasing drug loading. The critical drug loading is the drug's solubility in polymer. As explained in the introduction part, the physical state of the drug changes beyond the solubility limit, which leads to different impact of the drug loading on the viscosity. More detailed illustration can be found in the sections under the title of solubility calculation.

4.2. Cooling experiment

Fig. 4 shows the rheological data of PEO obtained from the cooling experiment, i.e., dynamic temperature sweep. This cooling experiment is analogous to the cooling scan in the differential scanning calorimeter as shown in Fig. 5. In Fig. 4, G'' is always higher than G' at the starting temperature, 140 °C. However, G' grows faster with the drop of the temperature and the two equals at the crossover point. Further, lowering the temperature makes G'' less than G', and the material behaves more like a solid. The experiment has to cease once the instrument reaches the maximum torque limit of 2000 g cm. The crossover point gives the minimum processing temperature and the values are found always close to the PEO crystallization temperature determined from DSC tests, as shown in Table 2. The result also suggests that the minimum processing temperature for pure PEO is close to 100 °C, as concluded in the previous work [3]. It is very common to choose the processing temperature to be 50 °C or more than the transition point, in this case the crystallization temperature of the PEO.

4.3. Solubility calculation: dynamic time sweep

Fig. 6 shows the overlay of dynamic viscosity of PEO at different temperatures. As expected, the viscosity at 140 °C is the lowest,

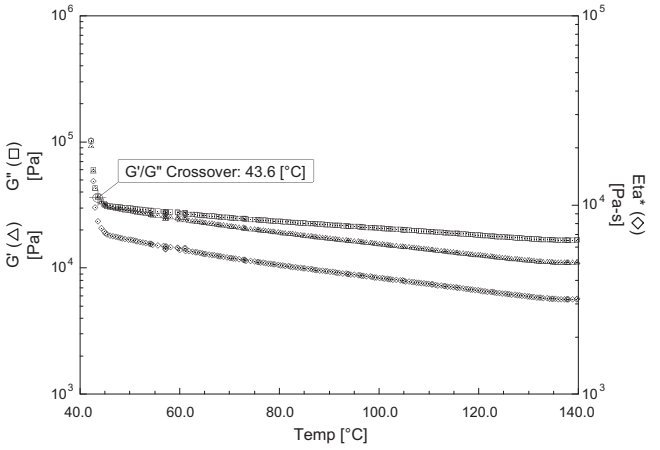

Fig. 4. G', G'' and the viscosity of pure PEO obtained from the cooling experiment.

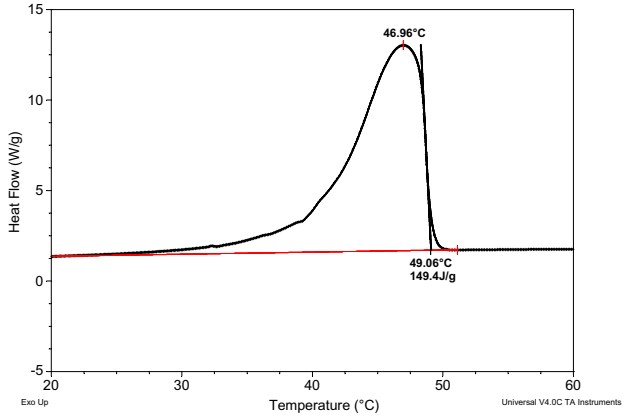

Fig. 5. Crystallization peak of PEO during the cooling scan in DSC. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Crystallization temperature determined from DSC and rheological tests.

wt.% of APAP	Crystallization temperature (°C)	
	Cooling in DSC	Cooling in rheometer
0	47.0	43.8
10	41.0	43.8
20	38.6	40.0
30	36.9	39.3
40	41.5	43.0
50	–	42.6

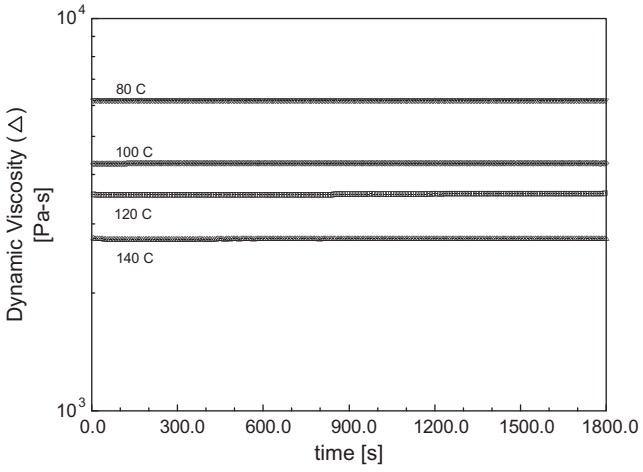

Fig. 6. Overlay of dynamic viscosity of PEO at different temperatures.

followed by 120, 100 and 80 °C. The mixture's viscosity η at the end of the time sweep is normalized with the pure PEO's viscosity η_o. The reduced viscosity of PEO–APAP η/η_o at different temperature and concentration was calculated and shown in Fig. 7. Each curve was fitted using 5th degree polynomial, and a minimum point was obtained for each curve. As explained in the introduction part, the minimal viscosity point gives the drug's solubility in polymer. Table 3 displays the solubility of APAP in molten polymer at four different temperatures.

4.4. Solubility calculation: zero shear viscosity

The above section explains how the drug's solubility can be obtained using the dynamic viscosity data from the dynamic time

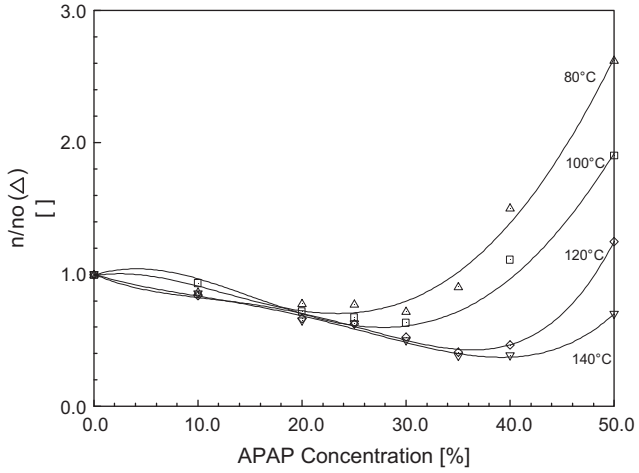

Fig. 7. Overlay of reduced viscosity data and the fitting curves.

Table 3
Solubility of APAP in molten PEO at different temperatures (data from dynamic time sweep).

Temperature (°C)	Solubility (wt.%)
80	23.0
100	30.0
120	36.3
140	39.3

sweep. It is interesting to find out whether the data from the dynamic frequency sweep can also be used to calculate the solubility. For that end, the zero shear viscosity of PEO–APAP mixture was calculated from the data obtained from dynamic frequency sweep of the mixture. The dynamic viscosity of the mixtures at different frequency was fitted with the following Cross' constitutive equation [8]:

$$\eta = \frac{\eta_o}{1 + (c_2\omega)^{(1-c_3)}} \tag{2}$$

where c_2 is associated with relaxation time and c_3 with the power law index. Fig. 8 shows the data obtained from the dynamic frequency sweep of PEO at 140 °C and the fitting parameters. As the figure indicates, the equation fits the curve perfectly.

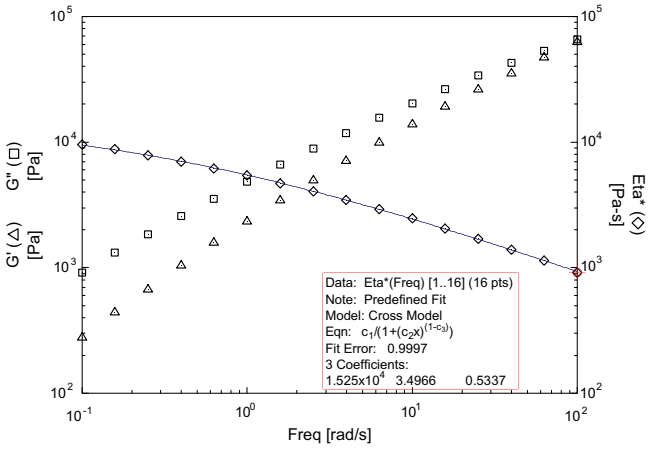

Fig. 8. Dynamic frequency sweep of PEO at 140 °C. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 4 gives the values of Cross' parameters for PEO at various temperatures. The reduced viscosity is defined as the ratio of zero shear viscosity of PEO–APAP to that of PEO at the same temperature. The reduced viscosity was plotted against wt.% of APAP at different temperature, and the curve at each temperature was fitted with 5th degree polynomial, as the case with dynamic time sweep.

Table 5 shows the values of solubility at different temperature obtained by zero shear viscosity method. Fig. 9 compares the solubility data obtained by two different methods (reduced viscosity from the dynamic time sweep and reduced zero shear viscosity from dynamic frequency sweep). The results suggest that solubility data obtained from two methods only have very minor differences, with the dynamic time method giving slightly and yet consistently lower solubility. This slight difference may be a result of the frequency difference: the dynamic time sweep is conducted at a frequency of 1 Hz, while the zero shear viscosity essentially is the viscosity at extremely small frequency.

4.5. Steady viscosity measurement

Steady experiments were conducted using both oscillatory and capillary rheometer. Oscillatory rheometer gives the steady viscosity at low shear rates, usually between 0.01 and 10 1/s or less. In contrast, capillary rheometer gives the steady viscosity at higher shear rates, in the range of 1–10,000 1/s, which covers the ranges usually seen in extrusion and injection molding operations.

Table 4
Cross' parameters for PEO at various temperatures.

Temperature (°C)	η_0 (Pa s)	c_2	c_3
140	15,250	3.5	0.5337
120	22,420	5.3	0.5232
100	32,500	7.7	0.5079
80	47,980	11.1	0.4905

Table 5
Solubility of APAP in molten PEO at different temperatures, zero shear viscosity method.

Temperature (°C)	Solubility (wt.%)
80	24.5
100	33.0
120	37.6
140	42.2

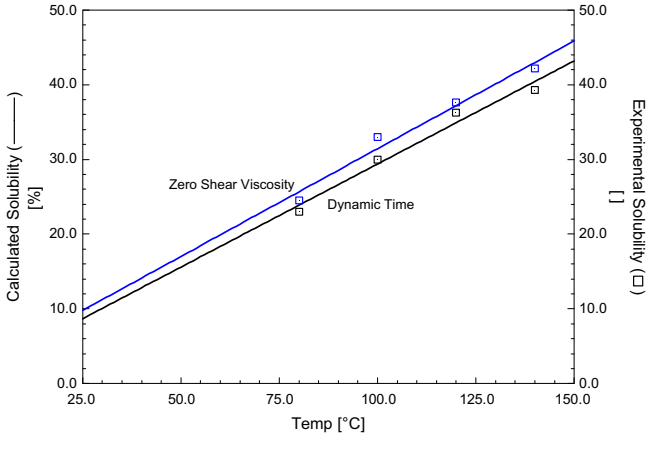

Fig. 9. Solubility of APAP in PEO determined from two different methods. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

The shear rate for the oscillatory rheometer is limited by the torque and edge effect. The edge effect becomes more severe as the shear rate increases [9]. The maximum torque for the oscillatory rheometer used in this study is 1500 g cm, while the edge effect is often manifested by the sudden drop of the torque.

The viscosity in a capillary flow is calculated using following Eq. [10]:

$$\tau_w = \eta\dot{\gamma}_w \tag{3}$$

and

$$\tau_w = \frac{D_c\Delta P}{4L} = \frac{R\Delta P}{2L} = \frac{F/A_{barrel}}{4L/D_c} \tag{4}$$

Eq. (4) does not take into consideration of Bagley's correction [11]. L/D, the ratio of the die length to the diameter, used in all experiments was 30. The values of τ_w, shear stress at the wall, calculated without Bagley's correction typically have less than 2% error. Two or three dies with similar diameter and different length are usually employed for Bagley's correction. F is the force required at each shear rate, and A is the area of the barrel.

The corrected shear rate at the wall, $\dot{\gamma}_w$, can be calculated after Rabinowitsch's [12] correction using the following equation:

$$\dot{\gamma}_w = \frac{1}{4}\Gamma\left[3 + \frac{d\log(\Gamma)}{d\log(\tau_w)}\right] \tag{5}$$

and

$$\Gamma = \frac{4Q}{\pi R^3} = \frac{4(CHS)(A)_{barrel}}{\pi(D_c/2)^3} \tag{6}$$

where Γ is apparent shear rate, and CHS is the crosshead speed of the plunger in the rheometer. Finally, the corrected shear viscosity can be calculated from following equation:

$$\eta = \tau_w/\dot{\gamma}_w \tag{7}$$

The shear viscosity data from the oscillatory rheometer were combined with the data obtained from the capillary rheometer. The combined data of shear viscosity of PEO at 140 °C are shown on Fig. 10. The steady shear viscosity was fitted using Cross' constitutive equation. The zero shear viscosity of PEO–APAP mixtures at different temperature is given in Table 6.

Fig. 11 shows a representative overlay of steady shear viscosity of PEO–APAP mixture at 100, 120 and 140 °C, respectively. The graphs contain the steady shear viscosity obtained from both oscillatory and capillary rheometer. It is worthwhile to point out that

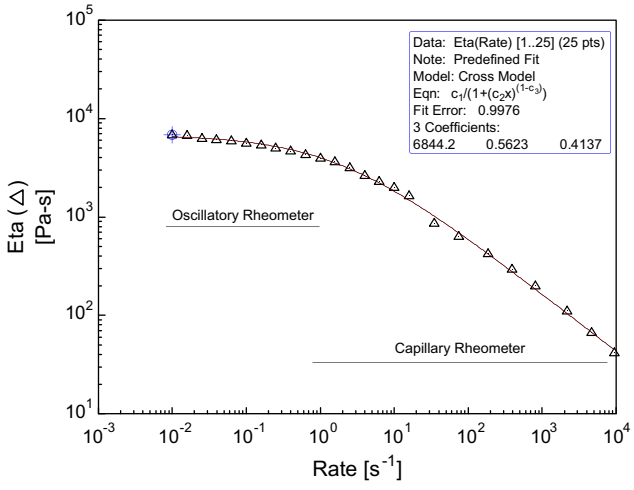

Fig. 10. Steady viscosity of PEO at 140 °C. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 6
Zero shear viscosity of PEO–APAP mixture at different temperature.

Material	wt.% of APAP	Zero shear viscosity (Pa s)		
		100 °C	120 °C	140 °C
PEO	0	–	11,550	6844
PEO-10	10	12,160	9929	6218
PEO-20	20	10,590	7011	5092
PEO-30	30	7091	3704	3722
PEO-40	40	–	3562	1657
PEO-50	50	–	6571	2411

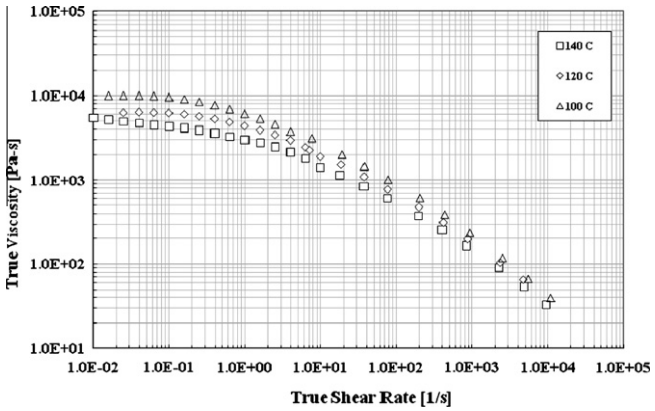

Fig. 11. Overlay of steady viscosity of PEO-20 at 100, 120 and 140 °C.

the shear rates of common processes such as extrusion and injection molding typically fall in the test range of the capillary rheometer. The figure clearly indicates that the viscosity decreases as the temperature increases. PEO–APAP mixtures exhibit Newtonian behavior at low shear rates and shear thinning behavior at high shear rates for all temperatures. Also, the temperature-induced viscosity difference becomes smaller at high shear rates.

Fig. 12 shows the effect of the APAP concentration on the steady viscosity. At 120 °C, the viscosity decreases with the APAP concentration up to 40%, indicating the plasticizer effect of the APAP. The viscosity for 50% APAP is higher than that of 40% APAP, indicating that the system had reached the solubility of APAP at that temperature. The decrease in viscosity is very pronounced at lower shear rates up to 10 1/s and becomes insignificant at high shear rates. The phenomenon suggests that it is better to use lower shear rate to obtain the drug's solubility data as shown later in Figs. 13 and 14.

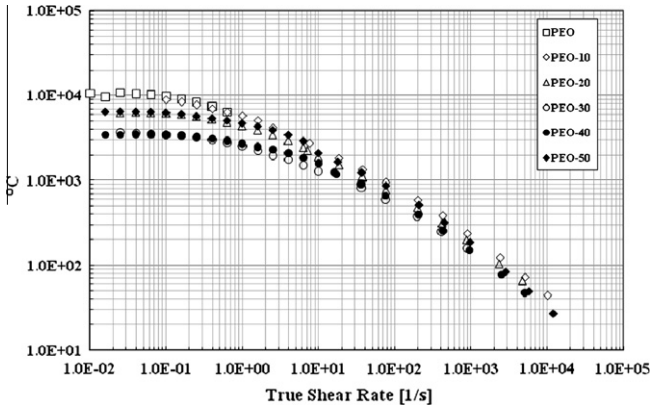

Fig. 12. Overlay of the steady viscosity of PEO–APAP at 120 °C.

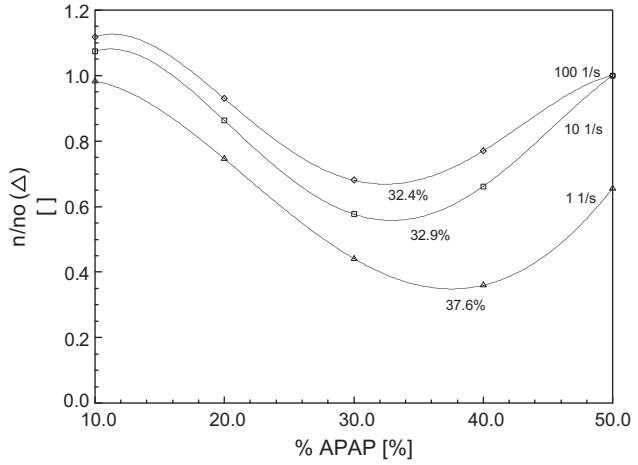

Fig. 13. Overlay steady viscosity of PEO–APAP at 120 °C at various shear rates.

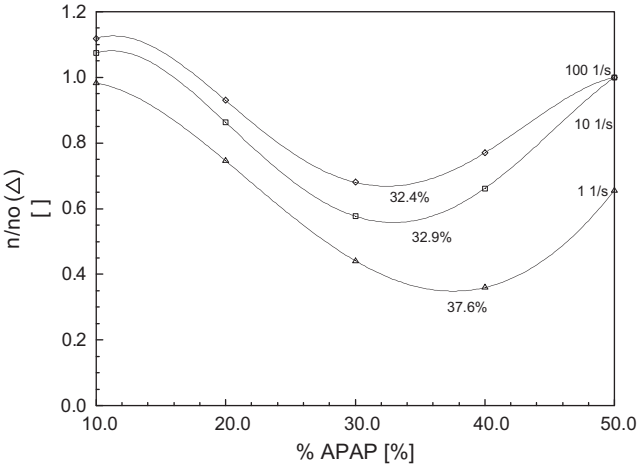

Fig. 14. Overlay steady viscosity of PEO–APAP at 140 °C at various shear rates.

Figs. 13 and 14 show how the reduced viscosity of the mixture changes with the drug loading at 120 °C and 140 °C, respectively, at three different shear rates: 1, 10 and 100 1/s. The critical drug loadings are 37.6%, 32.9% and 32.4% for the shear rates of 1, 10 and 100 1/s, respectively. The critical drug loadings change to 44.1%, 44.4% and 45.4% for the same shear rates at 140 °C. The critical point for each shear rate was obtained based on 5th degree polynomial fitting, same as the dynamic method in previous paragraph. The critical drug loading decreases with increasing shear rates at 120 °C, while it is almost independent of the shear rates at 140 °C. This apparent discrepancy is probably due to that 5th degree polynomial equation is not accurate enough to describe the relationship between the viscosity and the drug loading.

5. Conclusions

The dynamic and steady viscosities of APAP–PEO mixture were determined using oscillatory and capillary rheometers. The comprehensive rheological study on the drug–polymer binary system not only helps to determine the extrusion processing parameters such as the temperature but also provides the drug's solubility data in polymer. The curves of viscosity vs. drug loading generally have a "V" shape, and the minimal point gives the APAP's solubility in PEO.

The results suggest that different dynamic methods lead to essentially the same solubility data. The solubility can also be calculated from the steady viscosity data. However, the data seem to be more sensitive to the shear rate used.

The mixtures show shear thinning behavior at high shear rates. Furthermore, the viscosity becomes less sensitive to the drug loading at high shear rates. On the other hand, it is better to use lower shear rate in order to use the viscosity data to deduce the drug's solubility in polymer. Furthermore, viscosity data at high shear rates are more representative of the materials' rheological properties during extrusion.

This comprehensive study for the first time determines the solubility of the drug in the polymer system using solely rheological method in both dynamic and steady measurements from low to moderate shear rates.

Acknowledgment

This research work was partially financially supported by National Science Foundation under Grant CMMI-0927142.

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