Solubilities of Crystalline Drugs in Polymers: An Improved Analytical Method and Comparison of Solubilities of Indomethacin and Nifedipine in PVP, PVP/VA, and PVAc

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ABSTRACT: A previous method for measuring solubilities of crystalline drugs in polymers has been improved to enable longer equilibration and used to survey the solubilities of indomethacin (IMC) and nifedipine (NIF) in two homo-polymers [polyvinyl pyrrolidone (PVP) and polyvinyl acetate (PVAc)] and their co-polymer (PVP/VA). These data are important for understanding the stability of amorphous drug–polymer dispersions, a strategy actively explored for delivering poorly soluble drugs. Measuring solubilities in polymers is difficult because their high viscosities impede the attainment of solubility equilibrium. In this method, a drug–polymer mixture prepared by cryo-milling is annealed at different temperatures and analyzed by differential scanning calorimetry to determine whether undissolved crystals remain and thus the upper and lower bounds of the equilibrium solution temperature. The new annealing method yielded results consistent with those obtained with the previous scanning method at relatively high temperatures, but revised slightly the previous results at lower temperatures. It also lowered the temperature of measurement closer to the glass transition temperature. For D-mannitol and IMC dissolving in PVP, the polymer's molecular weight has little effect on the weight-based solubility. For IMC and NIF, the dissolving powers of the polymers follow the order PVP > PVP/VA > PVAc. In each polymer studied, NIF is less soluble than IMC. The activities of IMC and NIF dissolved in various polymers are reasonably well fitted to the Flory–Huggins model, yielding the relevant drug–polymer interaction parameters. The new annealing method yields more accurate data than the previous scanning method when solubility equilibrium is slow to achieve. In practice, these two methods can be combined for efficiency. The measured solubilities are not readily anticipated, which underscores the importance of accurate experimental data for developing predictive models. © 2010 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 99:4023–4031, 2010

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INTRODUCTION

One approach to delivering drugs that are poorly water soluble is to use amorphous drugs in place of their crystalline counterparts because amorphous solids are generally more soluble and faster dissolving than crystals. A key requirement for any amorphous formulation is that it be stable against crystallization during its shelf life. A common strategy for stabilizing an amorphous drug against crystallization is to disperse it in a polymer. To implement this strategy, it is desirable to know the solubilities of drugs in polymers, which define the maximal drug loading without the tendency of crystallization.

At present, there are little data on the solubilities of drugs in polymers and no standard methods for measurement. This situation exists largely because of the high viscosity of polymer solutions, which slows the attainment of solubility equilibrium (equilibrium between a crystalline solute and its solution). The difficulty is expected to be greater at lower temperatures.

In the thermodynamic sense, measuring solubility means determining the temperature and the solution concentration at which a system achieves solubility equilibrium. In reference to the binary phase diagram shown in Figure 1, the goal is to determine the coordinate (T, w) of a solubility equilibrium e, where T

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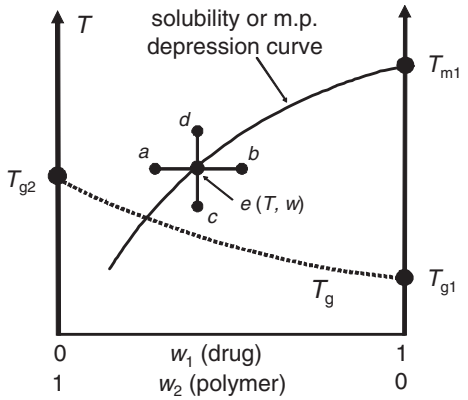


Figure 1. Phase diagram for a drug–polymer system. Point *e* is a general point on the solubility or melting point depression curve. Lines leading to *e* show different ways to reach solubility equilibrium and measure solubilities. For a drug–polymer system, the glass transition temperature T_g can be relatively high so that solubilities need to be measured near T_g.

is temperature and *w* is concentration. Depending on how solubility equilibrium is approached, solubility can be (and has been) measured in at least four different ways: (1) follow the increase of solution concentration at constant *T* as the solute dissolves into an under-saturated solution (path *ae*); (2) follow the decrease of solution concentration at constant *T* as the solute crystallizes from a super-saturated solution (path *be*); (3) measure the dissolution temperature or depressed melting point for a solute–solvent physical mixture of concentration *w* (path *ce*); and (4) measure the crystallization temperature or depressed freezing point for a saturated solution of concentration *w* (path *de*). Among these methods, path *ae* is perhaps the most familiar; it is the usual procedure for measuring the solubility of a drug in a low-viscosity solvent. We note, however, that the other methods are thermodynamically equivalent. Thus, experiments seemingly conducted for other purposes in fact yield solubilities. For example, the freezing point of benzene is measured for benzene–rubber solutions to study the thermodynamics of polymer solutions[1] and the same data provide the solubility of benzene crystals in rubber (at *T*, the solubility of crystalline benzene is its concentration in a solution that "freezes" at *T*).

Besides the solubility curve, Figure 1 also shows the glass transition temperature versus concentration curve. This is a reminder that for typical drug–polymer dispersions, solubilities often need to be measured near the glass transition temperature, at which the approach to solubility equilibrium would be especially slow.

To obtain solubilities of drug crystals in polymers, Vasanthavada et al.[2,3] estimated the solution concentration after inducing the solute to crystallize in the presence of moisture. The moisture presumably accelerated the establishment of solubility equilibrium. A concern with this method is the unknown effect of moisture on solubilities. It is even possible that the absorption of moisture could lower the solubility of a hydrophobic solute in a hydrophilic polymer (anti-solvent effect), causing phase separation of a drug–polymer solution that is otherwise thermodynamically stable.

There have been attempts to determine the solubilities of crystalline drugs in polymers by measuring the dissolution temperatures (depressed melting points) of mixtures of known compositions.[4–6] In these attempts, differential scanning calorimetry (DSC) is used to detect the equilibrium solution temperature for a solute–solvent mixture of known composition.[7,8] To help attain solubility equilibrium, Tao et al.[6] used cryo-milling to prepare uniform drug–polymer mixtures of small particle sizes and performed DSC at slow and various heating rates so that dissolution temperature could be estimated at "zero" heating rate by extrapolation. This method was validated against other solubility-indicating tests and applied to the systems of D-mannitol in PVP, nifedipine (NIF) in PVP/VA, and indomethacin (IMC) in PVP/VA at temperatures approaching the glass transition temperatures.

This study was performed to improve the previous scanning method[6] for measuring drug–polymer solubilities to increase the likelihood of achieving solubility equilibrium. Even with the measures already implemented, the scanning method could still have difficulty to achieve solubility equilibrium during the slowest DSC scan practical (approximately 0.1°C/min). In the new method, the sample is annealed near the equilibrium solution temperature and then scanned at a standard heating rate (e.g., 10°C/min) to determine whether un-dissolved crystals still remain. By scanning at a relatively fast rate, the sensitivity of detecting residual crystals improves. For a drug–polymer mixture annealed at different temperatures, the method would yield the upper and lower bounds for its equilibrium solution temperature.

The new annealing method yielded results consistent with those obtained with the previous scanning method at relatively high temperatures, but revised slightly the previous results at lower temperatures. It also lowered the temperature of measurement closer to the system's glass transition temperature. In practice, the two methods can be combined for efficiency. The data collected with these methods show that: (1) for D-mannitol and IMC dissolving in PVP, the polymer's molecular weight has relatively little effect on the weight-based solubility; (2) for IMC and NIF, the dissolving powers of the polymers tested follow the order PVP > PVP/

VA > PVAc; (3) in each polymer studied, NIF is less soluble than IMC. The activities of IMC and NIF dissolved in various polymers are reasonably well fitted to the Flory–Huggins (FH) model, yielding the relevant drug–polymer interaction parameters. The data reported here are not readily anticipated, which underscores the importance of accurate experimental data to aid the development of predictive models. The method developed here has the potential of providing relevant data for understanding the stability of amorphous drug–polymer dispersions.

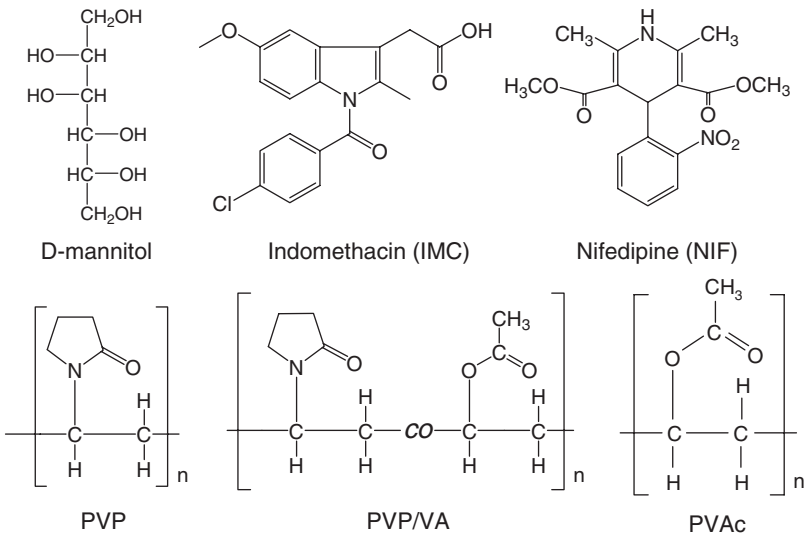
EXPERIMENTAL

D-mannitol (99+%, β-polymorph), IMC (γ-polymorph), a nonsteroidal anti-inflammatory agent, and NIF (α-polymorph), a calcium channel blocker, were obtained from Sigma–Aldrich. PVP K15 ($M_w \approx 8000$, 12% w/w moisture) was obtained from GAF Chemicals. PVP K12 ($M_w = 2000$–3000, 5% w/w moisture) and K25 ($M_w = 28{,}000$–$34{,}000$, 8% w/w moisture) were obtained from BASF. The "VP dimer" [1,3-bis(2-pyrrolidone-1-yl) butane, $M_w = 222.3$] was obtained from ISP (Wayne, New Jersey). PVP/VA (Kollidone VA64, $M_w = 45{,}000$–$70{,}000$, 5% w/w moisture) was obtained from BASF. It was a 60:40 vinyl pyrrolidone-vinyl acetate copolymer ($T_g = 101^\circ$C). PVAc ($M_w \approx 83{,}000$, 2% w/w moisture) was obtained from Sigma–Aldrich in the form of beads (Scheme 1).

Solute–polymer mixtures of desired concentrations were prepared by weighing the components. Each concentration was corrected for the amount of water present in the polymer; as a result, what is referred to later as 50% w/w NIF in PVP/VA, for example, actually contained 51.3% w/w NIF in PVP/VA on the dry basis. A cryogenic impact mill (SPEX CertiPrep model 6750) was used to prepare solute–polymer mixtures of different compositions. Liquid nitrogen was the coolant. In a typical procedure, 0.5–1 g of solute–polymer powder was milled at 10 Hz. Each cycle of milling was 2 min, followed by a 2 min cool down. The cycle was repeated for a total milling time up to 60 min. For D-mannitol–polymer mixtures, the milling time was 16 min for concentrations above 20% w/w; for lower concentrations, the milling time was longer (up to 60 min). For IMC–polymer and NIF–polymer mixtures, the milling time was 12–16 min.

The milled materials were analyzed by X-ray powder diffraction (Bruker D8 Advance diffractometer with Cu Kα radiation) to assess the potential change of polymorphic form and loss of crystallinity. For all materials used for solubility measurement, the crystals that remained after milling were of the original polymorphs (β for D-mannitol, α for NIF, and γ for IMC). For this analysis, the sample was ground with mortar and pestle, placed on a zero-background Si(510) sample holder, and scanned from 2 to 50° (2θ) at a speed of 1°/min and a step size of 0.02°.

Differential scanning calorimetry was conducted in hermetic aluminum pans using a TA Instruments DSC Q2000. Three pin holes were made in the lid to allow the escape of moisture. For annealing, 5–15 mg of sample was packed into a pan and annealed at a desired temperature from 4 to 10 h. The sample was then cooled and scanned at 10°C/min to determine whether residual crystals remained after annealing. Unless otherwise noted, the reported T_g is the onset temperature of the glass transition.



Scheme 1. Structures of chemical substances used in this study.

RESULTS AND DISCUSSION

New Annealing Method Versus Previous Scanning Method

In the previous scanning method, we start with a crystalline drug dispersed in a polymer and heat the mixture to measure the drug's solution temperature T_{end}. This process corresponds to the path *cd* in Figure 1. To improve the ease of achieving solubility equilibrium, cryo-milling is used to prepare uniform drug–polymer mixtures of small particle sizes, thereby minimizing the diffusive mixing necessary for dissolution. We also use slow and various scan rates so that T_{end} can be estimated at "zero" scan rate by extrapolation.

If solubility equilibrium can be achieved at point *e* during the DSC scan, the measured T_{end} is the equilibrium solution temperature T. If not, T_{end} is higher than T, which leads to underestimation of solubility. In the new method, isothermal annealing is used to increase the time for equilibration. If the annealing temperature is below T (e.g., point *c* in Fig. 1), crystals will remain even after long annealing and the subsequent scan of the sample will show a dissolution endotherm. If the annealing temperature is above T (e.g., point *d*), no crystals will remain after sufficiently long annealing and the subsequent scan will show no dissolution endotherm. By varying the annealing temperature, one can use this method to establish the lower and upper bounds of the equilibrium solution temperature (in the case described, $T_c < T < T_d$).

In this method, the presence or absence of residual crystals after annealing is determined by DSC at a standard heating rate (e.g., 10°C/min). The use of a relatively high heating rate improves the sensitivity of detecting residual crystals.

Besides the annealing protocol just described, another scheme can be envisioned: rather than annealing the same mixture at different temperatures, mixtures of different compositions can be annealed at the same temperature T. If the mixture composition is below the solubility at T (e.g., point *a* in Fig. 1), no crystals will remain after sufficiently long annealing and the subsequent scan will show no dissolution endotherm. If the mixture composition is above the solubility at T (e.g., point *b*), crystals will remain even after long annealing and the subsequent scan will show a dissolution endotherm. By varying the mixture composition, one can obtain the lower and upper bounds for the solubility at T (in the case described, $w_a < w < w_b$).

The time to anneal a drug–polymer mixture must be long enough for the system to reach solubility equilibrium. Assuming no chemical degradation (see below), the required annealing time depends on how well the drug and polymer components have been mixed and the viscosity of the solution in which solubility equilibrium is to be established. Better mixing of components can shorten the time required to reach solubility equilibrium.[6] For the mixtures studied here, we used the longest cryo-milling time possible; for NIF and IMC, this means stopping just before all solute crystals were rendered amorphous. As to the viscosity effect, the required annealing time is expected to increase as the solution viscosity increases. For a particular drug–polymer combination, this occurs as the equilibrium solution temperature approaches the glass transition temperature of the saturated solution (Fig. 1).

The annealing time used in this work was up to 10 h. This choice was made in part because we decided to perform the entire analysis (both annealing and scanning) in the same DSC instrument. Although a separate oven could be used for annealing, the DSC chamber has the advantage of precise and stable temperature control and constant N_2 purge to minimize chemical decomposition. With this choice, it was impractical to anneal for much longer times. As we show below, our annealing time proved sufficient for many drug–polymer mixtures, for the results obtained in this work agree with those obtained with the previous scanning method, indicating the longer equilibration time provided by the annealing method was unnecessary. For limited systems tested, equilibrium appeared to be attained during our annealing time. We do not claim, however, that our annealing time is suitable for all systems under all conditions, especially as T_{end} further approaches T_g.

Figure 2 shows typical data collected to implement the constant–concentration–variable–temperature annealing scheme. A 40% w/w IMC in PVP/VA mixture was annealed at 102 or 105°C for 4 h and then scanned at 10°C/min. The first thermal event is

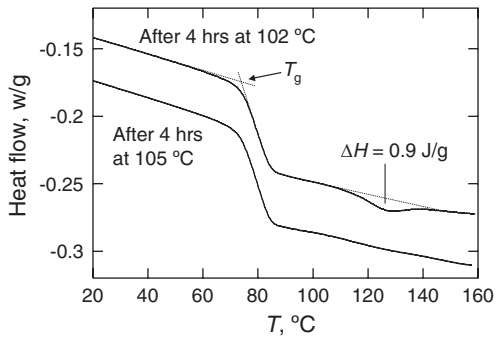


Figure 2. DSC traces of 40% w/w IMC/PVP/VA mixture annealed for 4 h at 102 and 105°C. T_g is the glass transition temperature. No significant amount of crystals were detected after annealing at 105°C, but crystals remained after annealing at 102°C. Increasing the annealing time at 102°C to 10 h did not change the amount of residual crystals within the error of DSC.

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the glass transition. The sample annealed at 105°C showed no other thermal event, whereas the sample annealed at 102°C showed an additional endotherm. This difference is interpreted as resulting from the complete dissolution of crystals at 105°C and incomplete dissolution at 102°C. Increasing the annealing time at 102°C to 10 h did not eliminate the residual crystals; the change of the dissolution endotherm appeared to be within the error of DSC (estimated to be ±0.3 J/g for a 1 J/g thermal event). In this work, we treated 105 and 102°C as the upper and lower bounds for the equilibrium solution temperature T_{end} for the mixture studied. It is relevant to note that this particular mixture (40% w/w IMC in PVP/VA) is one of the most difficult to equilibrate in this study because of the small difference between T_{end} and T_g.

Figure 3 compares the results of the scanning and annealing methods for the three systems studied. For D-mannitol dissolving in PVP K15, the annealing method yielded consistent results as the scanning method[6] (Fig. 3a). This consistency suggests that for this system, the scanning method is sufficiently accurate, for the longer equilibration provided by the annealing method did not alter the results significantly. It also follows that the annealing time chosen was adequate for the system to reach equilibrium.

For the systems NIF in PVP/VA and IMC in PVP/VA, the annealing method yielded results consistent with those obtained with the scanning method at higher temperatures, but revised slightly the results at lower temperatures (Fig. 3b and c). The agreement between the two methods at higher temperatures suggests that the longer annealing of the new method was unnecessary and that the annealing time used was sufficient for the system to reach equilibrium. For 30% and 40% w/w NIF in PVP/VA, the solution temperatures obtained with the annealing method are ca. 7°C below those obtained with the scanning method. The same observation was made for 40% and 50% w/w IMC in PVP/VA.

The greater difference between the results of the scanning and annealing methods at lower drug concentrations (Fig. 3b and c) is probably due to the closeness of the equilibrium solution temperature and the glass transition temperature of the saturated solution. If dissolution takes place in a highly viscous system, solubility equilibrium may be too slow to establish during the time scale of DSC scans. Because the new annealing method allows longer equilibration times, its results should be more accurate.

The better agreement between the annealing and scanning methods in the case of D-mannitol dissolving in PVP (Fig. 3a) than NIF and IMC dissolving in PVP/VA (Fig. 3b and c) may have to do with the limited milling times (12–16 min) that could be used for the IMC and NIF systems, because longer milling rendered these solutes fully amorphous. The crystals

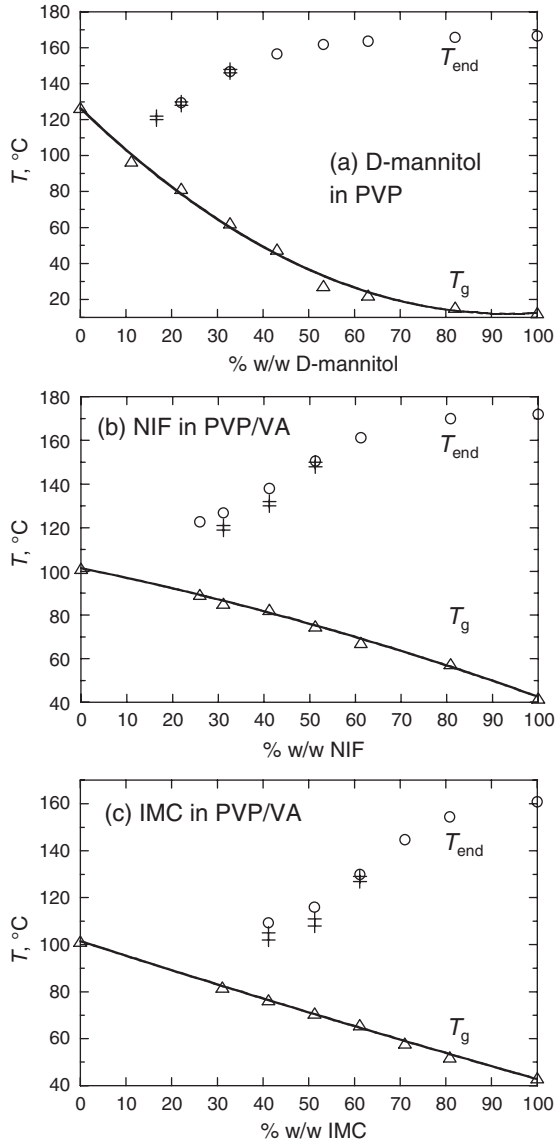

Figure 3. Comparison of T_{end} obtained with the scanning (circles, Ref. 6) and annealing (crosses, this work) methods for three systems. The two crosses at each concentration are the upper and lower bounds of T_{end}. The lower curves are glass transition temperatures. For the D-mannitol–PVP mixtures, T_g is the inflection point because the onset temperature is difficult to define at high polymer concentrations; for the other mixtures, T_g is the onset temperature.

of D-mannitol, on the other hand, are present after longer milling (up to 60 min), which could lead to more intimate mixing of components and easier attainment of solubility equilibrium.

In an alternative annealing scheme, mixtures of different concentrations were held at the same temperature to determine the lower and upper bounds for the solubility at the annealing temperature. The lower- and upper-concentration mixtures were chosen to bracket a guessed solubility value. In this way, we determined that the solubility of

D-mannitol in PVP K15 is between 20% and 30% w/w at 130°C, the solubility of NIF in PVP/VA is between 30% and 40% w/w at 123°C, and the solubility of IMC in PVP/VA is between 50% and 60% w/w at 110°C. These results are consistent with those of the constant–concentration–variable–temperature method (Fig. 3b and c).

Between the two versions of the annealing method, the constant-concentration-variable-temperature scheme seems the preferred. It is more convenient to vary temperature precisely in small increments than to vary the composition of drug–polymer mixtures precisely in small increments. In practice, a small number of mixtures at different compositions can be prepared and each mixture tested at precisely and finely controlled temperatures. This seems preferred over making many mixtures at small and precise composition increments and testing them at a few fixed temperatures.

The annealing method is expected to be more accurate than the scanning method for measuring drug–polymer solubilities at low temperatures. In practice, the two can be combined for efficiency: the scanning method is used for a quick assessment of the solubility–temperature curve and the annealing method is used for more accurate measurements at low temperatures.

Possibility of Chemical Degradation During Annealing

The new annealing method involves longer heating of drug–polymer mixtures at various temperatures below the drug's melting point. A relevant question is whether chemical degradation occurs during this treatment. Forster et al.[9] reported that IMC does not decompose significantly upon melt–extrusion with PVP or PVP/VA at zone temperatures up to 170°C. Zhu et al.[10] reported that IMC does not decompose significantly upon melt–extrusion with Eudragit at zone temperatures up to 140°C. Aso et al.[11] reported that NIF–PVP mixtures are chemically stable upon heating to 190°C. For the polymers used in this study, our annealing temperatures do not seem excessive.[12] We have also observed that even after the longest annealing, there was no significant change of the sample's glass transition temperature, which is consistent with the lack of significant decomposition. These observations provide some assurance of chemical stability of our materials against heating; however, they are not direct proof of chemical stability under the conditions of this study.

Comparison of Solubilities

Figures 4 and 5 summarize the solubility data measured in this study and from Ref. 6. Both the scanning and the annealing methods have been used; the annealing method was applied to check the results from the scanning method and be the more definitive method at lower temperatures. For the solution temperature from the scanning method, the average value of at least two measurements is

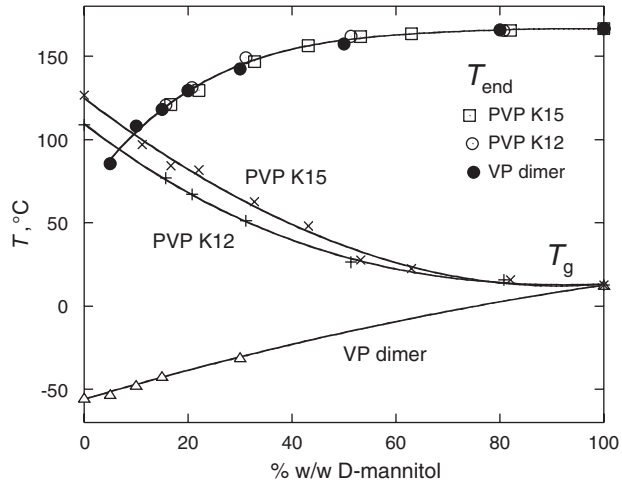

Figure 4. T_{end} and T_g versus D-mannitol concentration in PVP K15 and PVP K12, and the VP dimer. T_g is the inflection point because the onset temperature is difficult to define at high polymer concentrations.

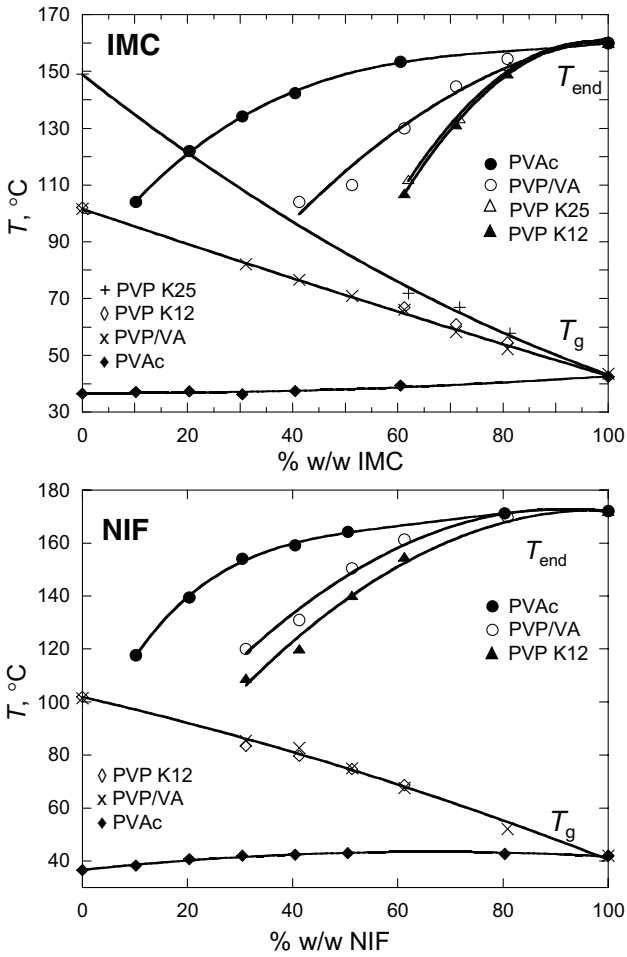

Figure 5. T_{end} and T_g versus concentration for mixtures of IMC or NIF with various polymers.

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reported; for the solution temperature from the annealing method, the lower bound value from at least two measurements is reported; the difference between replicate measurements is less than 2°C. The new data include the solubilities of D-mannitol in PVP K12 and the VP dimer and of IMC and NIF in PVP and PVAc. With these data, two comparisons are made below.

(1) *Solubilities of D-mannitol in PVP of different molecular weights*: It is of interest to learn how the solubility of the same solute varies in polymers of different molecular weights. Figure 4 compares the solubilities of crystalline D-mannitol in PVP K15 ($M_w \approx 8000$), PVP K12 ($M_w \approx 2500$), and the VP dimer ($M_w = 222.3$). The VP dimer was included here because it has been used as a small-molecule solvent for estimating drug solubilities in PVP. The low viscosity of the VP dimer (it is a viscous liquid at room temperature) allowed its solubility to be measured down to 5% w/w with our method.

Figure 4 shows that if expressed in % w/w, the solubilities of crystalline D-mannitol are comparable in PVP of various molecular weights. The more limited data for IMC (see later) are consistent with this conclusion. These results suggest a possibility of using a small-molecule solvent to estimate the solubilities in polymers. Given the difficulty of measuring the solubility of crystalline solutes in polymers, especially at low temperatures, the use of small-molecule solvents for estimating solubilities in polymers is of considerable interest.

(2) *Solubilities of IMC and NIF in different polymers*: We next compare the solubilities of IMC and NIF in two homo-polymers (PVP and PVAc) and their co-polymer (PVP/VA). For both solutes, the solubilities follow the order PVP (most soluble) > PVP/VA > PVAc (least soluble). The solubilities of IMC in PVP K12 and PVP K25 (expressed in % w/w) are comparable, which is consistent with a similar observation made for the D-mannitol/PVP system (Fig. 4).

The different dissolving powers of PVP (highest), PVP/VA, and PVAc (lowest) for IMC and NIF apparently contradict the notion "like dissolves like." If IMC and NIF are considered hydrophobic substances, they should be less soluble in more hydrophilic solvents. Meanwhile, PVP is considered more hydrophilic than PVP/VA and PVP/VA is considered more hydrophilic than PVAc. (PVP is more hygroscopic than PVP/VA.) Thus, one would expect the solubility trend to be PVP (lowest) < PVP/VA < PVAc (highest), precisely the opposite of our observation. This inconsistency shows the importance of accurate experimental data for developing predictive models.

Solute Activity and Flory–Huggins Interaction Parameter χ

The solubility of a crystalline drug in a polymer allows the calculation of the drug's activity a_1 in the saturated solution:

$$\ln a_1 = (\Delta H_m/R)\,(1/T_m - 1/T) \qquad (1)$$

where T_m is the melting point of the pure drug, ΔH_m is its molar heat of melting, and T is the temperature at which the drug's solubility is measured (or its depressed melting point). Figure 6 shows the result of this calculation for IMC and NIF dissolving in different polymers. In each case, the solute activity decreases with the increase of polymer weight fraction w_2. The rate of this decrease, however, depends strongly on the polymer used. For the polymers studied, PVP reduces the activity of the solute the most, in keeping with its highest dissolving power, followed by PVP/VA and then by PVAc. We note that this comparison is not made across polymers of the same molecular weight, although the change of the PVP molecular weight by ca. 10-fold (from K12 to K25) has little effect on the solubility of IMC.

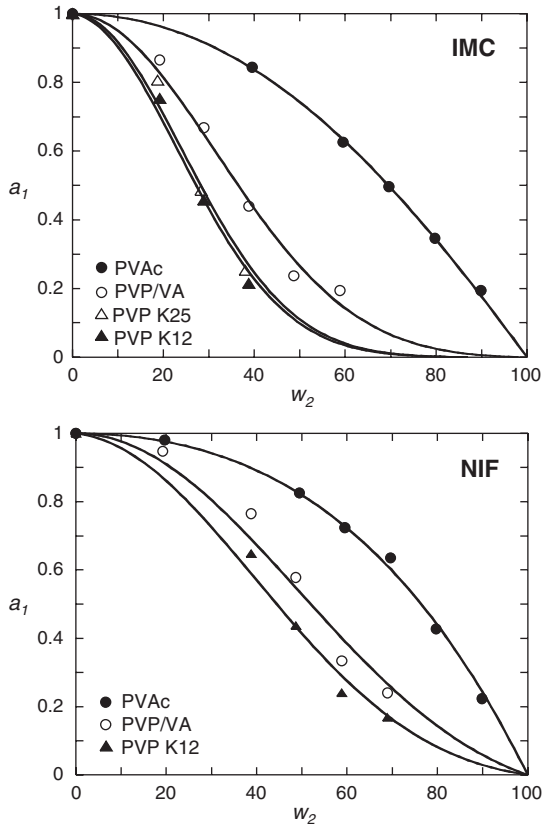

Figure 6. Activity of IMC or NIF a_1 versus polymer weight fraction w_2. The solid curves are FH fits.

If the Flory-Huggins (FH) model[1] is applied to the drug–polymer solutions studied here, the activity of IMC or NIF in the solution is given by

$$\ln a_1 = \ln v_1 + \left(1 - \frac{1}{x}\right) v_2 + \chi v_2^2 \qquad (2)$$

where v_1 is the volume fraction of IMC or NIF, v_2 is the volume fraction of the polymer, x is the molar volume ratio of the polymer and the drug, and χ is the drug–polymer interaction parameter. The solid curves in Figure 6 are the results of fitting the activities to the FH model. In this analysis, we have assumed that the volume fraction is the same as the weight fraction and the parameter x is the ratio of the molecular weights of the polymer and the drug.

The FH model fits the data in Figure 6 reasonably well. In contrast, the model does not give a good fit of the activity of D-mannitol in PVP (result not shown). To the extent the reasonable fitting in Figure 6 justifies the use of the FH model, the interaction parameters χ could be obtained for various drug–polymer pairs and compared. The χ values thus obtained (Table 1) suggest that for each solute (IMC or NIF), the interaction with PVP is the strongest, followed by PVP/VA, and then by PVAc, and that for each polymer studied, the interaction with IMC is stronger than that with NIF.

Where comparable, our χ values are substantially more negative (indicating stronger attractive interactions) from those of Marsac et al.[5] (Table 1, last column). This difference probably results from the different experimental conditions of the two studies. Marsac et al. used a scanning method to measure polymer-depressed melting points of crystalline drugs; their sample was a physical mixture of a drug and a polymer (or a drug and a drug–polymer dispersion); their DSC scan rate was 1°C/min. In our method, cryo-milling is used to improve the uniformity and reduce the particle size of drug–polymer mixtures so that solubility equilibrium is more easily achieved. In the scanning version of our method, slow and various heating rates are used so that melting point depression can be estimated at "zero" heating rate by extrapolation. The annealing version of our method provides even longer equilibration time to improve the likelihood of achieving solubility equilibrium. Together, these measures likely have provided more accurate results, especially at low temperatures.

Table 1. Drug–Polymer Interaction Parameters χ

Drug	Polymer	χ (This Work)[a]	χ (Ref. 5)
NIF (α form) $T_m = 172$°C, $\Delta H_m = 39.9$ kJ/mol[5]	PVPK12	-2.5 ± 0.2	0.0
	PVPVA64	-1.8 ± 0.2	—
	PVAc	-0.02 ± 0.03	—
IMC (γ form) $T_m = 160$°C, $\Delta H_m = 39.7$ kJ/mol[5]	PVPK12	-8.2 ± 0.6	-0.82
	PVPK25	-8.0 ± 0.7	—
	PVPVA64	-4.5 ± 0.3	—
	PVAc	-0.41 ± 0.02	—

[a]Values after the ± sign are standard deviations of fitting.

Concerning the stronger interaction between IMC and PVP, PVP/VA, or PVAc than between NIF and the same polymers, one possible explanation is that IMC can form hydrogen bonds with the polymers. IMC has a good hydrogen bond donor, whereas NIF has none. PVP, PVP/VA, and PVAc have no good hydrogen bond donors, but have hydrogen bond acceptors. Taylor and Zografi[13] found using infrared spectroscopy that IMC and PVP can hydrogen bond. It would be of interest to establish how useful this hydrogen-bonding analysis is for understanding drug–polymer solubilities.

One utility of the FH analysis is that if the model is applicable, it could be used to predict[4,5] the drug–polymer solubility at lower temperatures, at which direct measurements would be more difficult. It is important, however, to first verify the validity of this model and ensure the accuracy of the drug–polymer interaction parameters. This study found that the FH model can fit reasonably well the activities of IMC and NIF dissolved in PVP, PVP/VA, and PVAc, whereas it fits poorly the activity of D-mannitol dissolved in PVP.

Future Studies

Given the difficulty to achieve solubility equilibrium in polymer matrices, it is worthwhile to consider additional ways to improve the technique of measurement. Larger DSC pans could be used to increase the amount of sample and the sensitivity of detecting the crystals that remain after annealing. Annealing times could be systematically varied to define optimal values for different annealing temperatures. Chemical analysis could be performed to determine whether chemical degradation occurs during long annealing. More systems could be tested and compared to develop models for prediction.

CONCLUSIONS

We have developed a new annealing method to complement the scanning method previously reported for measuring the solubility of crystalline drugs in polymers. In this method, cryo-milling is used to prepare uniform drug–polymer mixtures of small particle sizes to facilitate the attainment of solubility equilibrium. Samples are annealed at various temperature to achieve phase equilibrium and then scanned at a standard heating rate (10°C/min) to determine whether un-dissolved crystals remain. For a drug–polymer mixture annealed at different

temperatures, the method yields the upper and lower bounds for its equilibrium solution temperature.

The new annealing method yielded results consistent with those obtained with the previous scanning method at relatively high temperatures, but revised slightly the previous results at lower temperatures. It also lowered the temperature of measurement closer to the glass transition temperatures. In practice, the two methods can be combined for efficiency. The data collected with these methods show that (1) for D-mannitol and IMC dissolving in PVP, the molecular weight of the polymer has relatively little effect on the percent-by-weight solubility; (2) for IMC and NIF, the dissolving powers of the polymers tested follow the order PVP > PVP/VA > PVAc; and (3) in each polymer studied, NIF is less soluble than IMC. The activities of IMC and NIF dissolved in various polymers are reasonably well fitted to the Flory-Huggins model, yielding the relevant drug–polymer interaction parameters. The data reported here are not readily anticipated, which underscores the importance of accurate experimental measurements to aid the development of predictive models. The method developed here has the potential of providing relevant data for understanding the stability of amorphous drug–polymer dispersions.

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