Pharmaceutical Research, Vol. 26, No. 1, January 2009 (© 2008)
DOI: 10.1007/s11095-008-9721-1

Research Paper

Estimation of Drug–Polymer Miscibility and Solubility in Amorphous Solid Dispersions Using Experimentally Determined Interaction Parameters

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Received May 29, 2008; accepted August 27, 2008; published online September 9, 2008

Purpose. The amorphous form of a drug may provide enhanced solubility, dissolution rate, and bioavailability but will also potentially crystallize over time. Miscible polymeric additives provide a means to increase physical stability. Understanding the miscibility of drug–polymer systems is of interest to optimize the formulation of such systems. The purpose of this work was to develop experimental models which allow for more quantitative estimates of the thermodynamics of mixing amorphous drugs with glassy polymers.

Materials and Methods. The thermodynamics of mixing several amorphous drugs with amorphous polymers was estimated by coupling solution theory with experimental data. The entropy of mixing was estimated using Flory–Huggins lattice theory. The enthalpy of mixing and any deviations from the entropy as predicted by Flory–Huggins lattice theory were estimated using two separate experimental techniques; (1) melting point depression of the crystalline drug in the presence of the amorphous polymer was measured using differential scanning calorimetry and (2) determination of the solubility of the drug in 1-ethyl-2-pyrrolidone. The estimated activity coefficient was used to calculate the free energy of mixing of the drugs in the polymers and the corresponding solubility.

Results. Mixtures previously reported as miscible showed various degrees of melting point depression while systems reported as immiscible or partially miscible showed little or no melting point depression. The solubility of several compounds in 1-ethyl-2-pyrrolidone predicts that most drugs have a rather low solubility in poly(vinylpyrrolidone).

Conclusions. Miscibility of various drugs with polymers can be explored by coupling solution theories with experimental data. These approximations provide insight into the physical stability of drug–polymer mixtures and the thermodynamic driving force for crystallization.

KEY WORDS: amorphous; crystallization; miscibility; polymer.

INTRODUCTION

Dispersions of organic molecules in polymeric matrices are important for a number of applications, in particular for medical devices and drug delivery systems. Examples include medicated contact lenses (1–7), drug eluting stents (8–10), biodegradable implants (11–18), transdermal patches (19,20), and oral formulations (21–23). Intimately blended dispersions require miscibility between the drug and polymer and lead to an amorphous system where the apparent solubility and bioavailability of poorly water soluble drugs can be enhanced (22–26). In an era of drug discovery where approximately 50% of new molecules are estimated to have solubility problems (27), this type of formulation approach is becoming of greater importance. Miscible drug–polymer blends are also more resistant to drug crystallization than the amorphous drug alone (28,29), an important consideration when attempting to produce a drug delivery system that will perform consistently over time. Binary drug–polymer systems are usually deemed to be miscible if, after a given processing operation such as melt-extrusion, spray drying, or freeze drying, there exists a single glass transition temperature (30–38). However, the presence of a single glass transition temperature is not an infallible indicator of miscibility and provides no information about the thermodynamics of mixing. Methods which provide quantitative information about the free energy of mixing two pharmaceutically relevant components such that drug–polymer compatibility can be predicted for a variety of temperatures and compositions are therefore of interest (39). While numerous theoretical and experimental approaches have been applied to understand polymer-polymer blending (30–32,35,36,40–44), the thermodynamics of drug–polymer mixing is relatively unexplored.

It would also be useful to be able to better link the chemistry of the drug and polymer to the miscibility of the system in order to facilitate scientifically based selection of

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polymeric partners for given drug substances, again following the lead provided by polymer scientists (32,41,45). The degree of interaction and the type of interaction contribute to the overall free energy of mixing. More specifically, systems which form strong adhesive interactions at the expense of relatively weak cohesive interactions are expected to have an exothermic enthalpy of mixing. On the other hand, although strong adhesive interactions may be formed between two components in a binary mixture, if these interactions come at the cost of breaking strong cohesive interactions in the individual components, the enthalpy of mixing may not be as favorable. Clearly, it would be useful to develop a link between the relative strength of adhesive and cohesive interactions, the chemistry of the components in the mixture, and the free energy of mixing. Several authors have suggested that specific interactions play an important role in forming single phase amorphous molecular level solid dispersions (46–51).

Although the miscibility of an amorphous drug with an amorphous polymer is of great relevance, there is also interest in being able to estimate the solubility of the crystalline drug in the polymer matrix. As shown in the simplified solubility equation, Eq. 1, the mole fraction solubility, x_{drug}, is dependent on two factors; the crystal lattice energy (right hand side of the equation) and any contributions to non-ideality such as non-ideal entropy of mixing and/or a non-zero heat of mixing which are incorporated into the activity coefficient (γ_{drug}) (52,53).

$$\ln \gamma_{drug} x_{drug} = \frac{-\Delta G_{fus}}{RT} = -\frac{\Delta H_{fus}(T_m)}{RT}\left[1 - \frac{T}{T_m}\right] - \frac{1}{RT} \int_{T_m}^{T} \Delta C_P \mathrm{d}T + \frac{1}{R}\int_{T_m}^{T} \frac{\Delta C_P}{T}\mathrm{d}T \quad (1)$$

Here, ΔG_{fus} is the free energy difference between the supercooled liquid and the crystal, T is the absolute temperature, R is the universal gas constant, and γ_{drug} is the activity coefficient of the drug in the mixture at the solubility limit. Since the heat of fusion (ΔH_{fus}), melting temperature (T_m), and heat capacity values of the crystalline and supercooled liquid (ΔC_p is the heat capacity difference between the liquid and the crystal) are typically experimentally accessible and can be used to estimate ΔG_{fus} as shown by Eq. 1 (52), the problem of estimating the solubility of a crystalline component in a liquid is essentially a problem of determining the activity coefficient. With knowledge of the activity coefficient, the solubility of a crystalline drug in the polymer matrix, or the thermodynamic driving force for crystallization as a function of composition can be estimated. The activity coefficient is a function of temperature and composition (among other variables), and for simple systems, it can be estimated from experimental data, computational models, or some combination thereof (52). However, it is exceedingly difficult to access the activity coefficient of drugs in polymers due to the high viscosity and low vapor pressure of the components. In addition, these systems are typically "non-equilibrium" under ambient conditions.

The objective of the current study is to expand on previous work (39) and compare two methods of estimating the activity coefficient of a drug in the presence of a polymer. The first method utilizes melting point depression of the drug in the presence of the polymer. The second method relies on measuring the solubility of the drug in a low molecular weight liquid analog of the polymer. The utility and limitations of each of these methods will be discussed in this work. The goal of this work is to extract information about the interaction of drug with the polymer in order to provide insight into the thermodynamics of mixing the two components. Estimating the free energy of mixing will then be useful to predict the compatibility and phase stability of drug–polymer mixtures and approximate the thermodynamic driving force for crystallization of drugs in amorphous molecular level solid dispersions.

MATERIALS

Felodipine was kindly donated by AstraZeneca (Södertälje, Sweden). Nifedipine, ketoconazole, and itraconazole were obtained from Hawkins, Inc. (Minneapolis, MN). Sucrose was obtained from Mallinckrodt Chemicals (Phillipsburg, NJ, USA) and 1-ethyl-2-pyrrolidone was purchased from Fluka (Switzerland). Indomethacin, ibuprofen, and acetone were purchased from Sigma-Aldrich Co. (St. Louis, MO, USA). Poly(vinylpyrrolidone) K12 (PVP K12) was purchased from BASF AG (Ludwigshafen, Germany). Dextran MD-6-X Extra Low MW (M_N=570, M_W=860) was obtained from V-Labs Inc. (Covington, LA, USA). Eudragit E 100 was obtained from Röhm GmbH (Darmstadt, Germany). Dichloromethane and ethanol were obtained from Mallinckrodt Baker, Inc. (Paris, KY, USA) and Aaper Alcohol and Chemical Co. (Shelbyville, KY, USA), respectively. The chemical structures of the compounds used in this study are given in Fig. 1.

METHODS

Melting Point Depression

Crystalline drug particles and non-crystalline polymer particles were sized using standard sieves. Particles ranging in size from 45–90 μm were dried over nitrogen for at least 1 week. The pure crystalline drug was then physically mixed with either (1) pure polymer or (2) an amorphous molecular level solid dispersion of the drug in the polymer. One to three samples were prepared at each polymer concentration. The melting temperature of each crystalline compound in the presence of (1) the pure polymer or (2) the amorphous molecular level solid dispersion was measured with a TA 2920 modulated DSC equipped with a refrigerated cooling accessory (TA instruments, New Castle, DE, USA) at a scan rate of 1°C/min. The TA 2920 was calibrated in standard mode for temperature using indium and benzophenone while the enthalpic response was calibrated using indium. Nitrogen, 45 ml/min, served as the purge gas. The offset of melting was taken as the extrapolated offset of the bulk melting endotherm.

Solubility Measurements

An excess of crystalline material was added to a capped jacketed vessel containing 1-ethyl-2-pyrrolidone

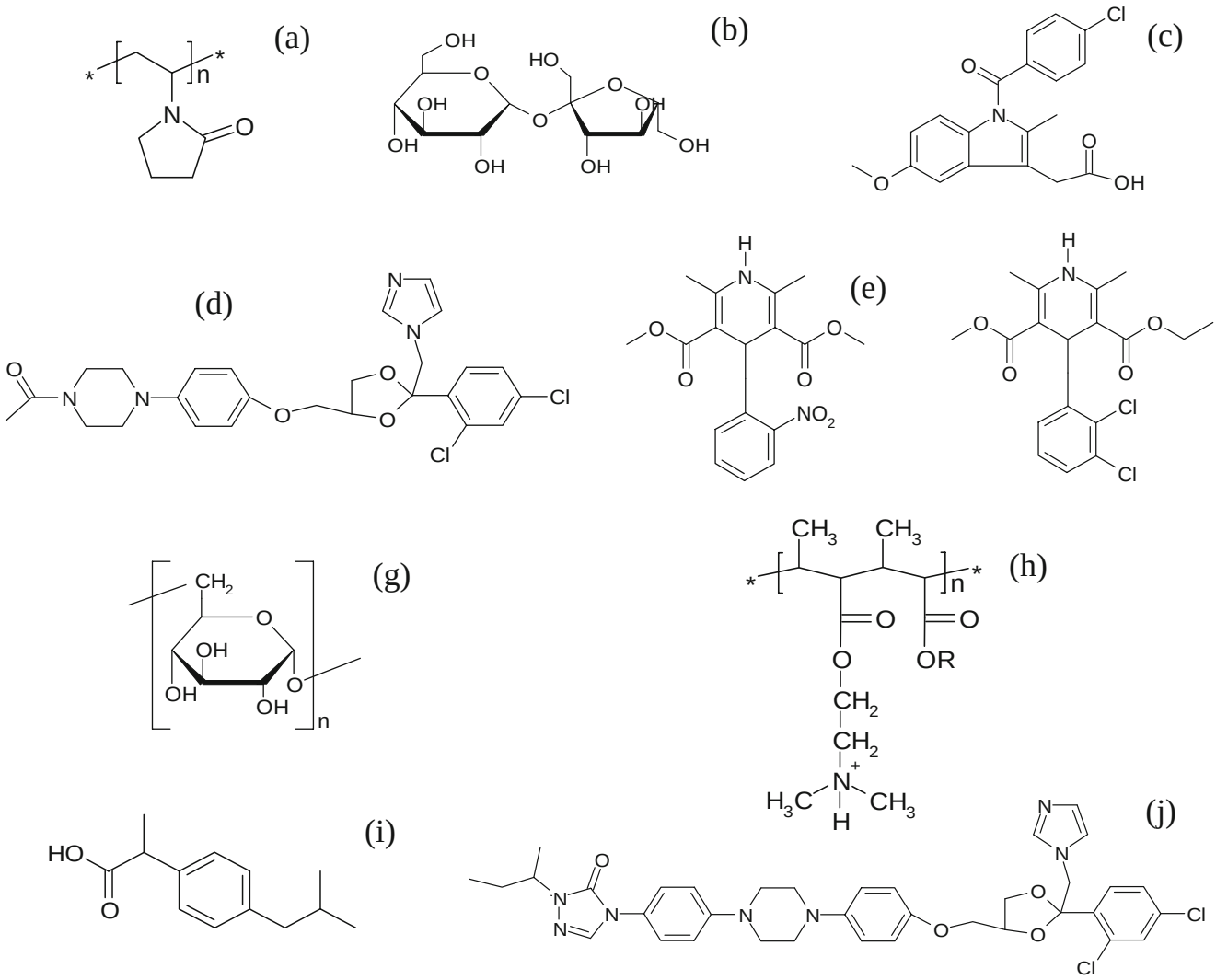

Fig. 1. Chemical structure of PVP (**a**), sucrose (**b**), indomethacin (**c**), ketoconazole (**d**), nifedipine (**e**), felodipine (**f**), dextran (**g**), Eudragit E100 (**h**), ibuprofen (**i**), and itraconazole (**j**).

maintained at 25°C for at least 24 h under stirring and in the absences of light. The mother liquor was decanted, centrifuged using an Eppendorf Centrifuge 5451C (Eppendorf AG, Germany), and filtered using an Acrodisk 13 mm 0.2 μm syringe filter with a nylon membrane; Model PN 4550T (East Hills, NY, USA). Samples were diluted with ethanol and compared to a standard concentration curve.

The solubility of nifedipine, felodipine, ketoconazole, and indomethacin in 1-ethyl-2-pyrrolidone was measured using a Cary 50 UV-Vis Spectrophotometer (Varian Inc., Palo Alto, CA, USA). The solubility of sucrose in 1-ethyl-2-pyrrolidone was measured using an 1100 Series Agilent HPLC (Palo Alto, CA, USA) equipped with a G1362A refractive index detector (RID). An injection volume of 20 μl was introduced into an Alltech 700CH carbohydrate column of length 300 mm and internal diameter of 6.5 mm (Deerfield, IL, USA). Water served as the mobile phase at 85°C at a flow rate of 0.5 ml/min for 45 min. The RID was run at a temperature of 45°C.

Preparation of Amorphous Molecular Level Solid Dispersions

Amorphous molecular level dispersions of felodipine and PVP K12 were prepared by solvent evaporation. Felodipine and PVP were dissolved in 100% ethanol and solvent removal was accomplished using a rotary evaporator apparatus (Brinkman Instruments, Westbury, NY, USA). The samples were exposed to a vacuum for at least 1 h, placed on a hot plate for several seconds until a clear matrix was obtained, ground using a mortar and pestle, sized, and geometrically mixed with crystalline drug prior to the melting point depression experiment described above.

Measurement/Estimation of Intermolecular Interactions

Hydrogen Bonding Interactions

Spin-coating was performed inside a glovebox at a relative humidity of less than 10% using a KW-4A spin-coater (Chemat

Technology Inc., Northridge, CA, USA). The drug–polymer systems were dissolved in a suitable solvent; ethanol, 1:1 dicloromethane:ethanol, or acetone for systems prepared with PVP and 1:2 acetonitrile/water for systems containing sucrose and dextran. A small drop of the solution was placed on a clean, rotating ZnSe substrate. The resulting film was heated to 110°C for several minutes to remove volatiles and immediately placed in the nitrogen purged sample holder. This procedure resulted in optically transparent films. Infrared (IR) spectra were collected using a Bio-Rad FTS-6000 (Bio-Rad, Cambridge, MA, USA). Reference spectra of the pure amorphous compound were obtained by spin coating a thin film followed by melting and cooling. Spectra of reference crystalline materials were acquired after spin coating a film and allowing the drugs to completely crystallize. 128 scans were averaged at a resolution of 4 cm^{-1} for each sample over the wavenumber region 4500–400 cm^{-1}. The optics and sample compartment were purged with dry, CO_2-free air to prevent absorption of moisture into the sample and other spectral interference from water vapor and CO_2.

Estimated Dipole Moments of Individual Molecules

Single molecules of the compounds were optimized by Gaussian 03 (Wallingford, CT 06492). The method and basis set was B3LYP/6-311G(d,p). The optimized single molecules were further calculated with B3LYP/6-311++G(2d,p).

THEORETICAL CONSIDERATIONS

Estimating the Activity Coefficient of Drugs in Polymers of High Glass Transition Temperature

Melting Point Depression

Melting point depression measurements have been widely utilized to investigate polymer-polymer mixing thermodynamics (34,54–56). The melting point of a crystalline drug in the presence of a polymer, T_M^{mix} , can be used to extract a value for the Flory Huggins interaction parameter, χ (39). This information can then be used to estimate the free energy of mixing the two components. The melting point of a pure drug occurs at the temperature when the chemical potential of the crystalline drug is equal to the chemical potential of the molten drug (54). If the drug is miscible with a polymer, then the chemical potential of the drug in the mixture must be less than the chemical potential of the pure amorphous drug. Strong exothermic mixing should produce a large melting point depression while weakly exothermic, athermal, and endothermic mixing, should give progressively less melting point depression. Alternatively, if the drug and the polymer are immiscible, no melting point depression is expected since the chemical potential of the molten drug is unaltered by the presence of the polymer. Equation 2 shows the relationship between the melting temperature of the pure drug, T_M^{pure} , the depressed melting point, T_M^{mix} , and the Flory–Huggins interaction parameter, χ.

$$\left(\frac{1}{T_M^{mix}}-\frac{1}{T_M^{pure}}\right)=\frac{-R}{\Delta H_{fus}}\left(\frac{MV_{drug}}{MV_{lattice}}\right)\left[\frac{\ln \Phi_{drug}}{m_{drug}}+\left(\frac{1}{m_{drug}}-\frac{1}{m_{polymer}}\right)\Phi_{polymer}+\chi\Phi_{polymer}^2\right] \quad (2)$$

Here ΔH_{fus} is the heat of fusion of the pure drug, m_{PVP} is the ratio of the volume of the polymer to that of the lattice site, m_{drug} is the ratio of the volume of the drug to the lattice site, R is the universal gas constant, Φ_{drug} is the volume fraction of the drug, and $\Phi_{polymer}$ is the volume fraction of the polymer. Equation 2 was linearized with respect to χ as described previously (39) and the melting point depression data were used to estimate this value. This parameter then provides an indication of the enthalpy of mixing and any deviations from the combinatorial entropy of mixing the drug and the polymer at the temperature and composition at which the experiments were conducted.

Several important points should be made with respect to the application of this method to pharmaceutical systems. First, a melting event must precede chemical decomposition. Second, the melting point of the drug should be sufficiently high such that the polymer is in a supercooled liquid-like state so that it can interact and mix with the molten drug. Therefore, this method is most appropriate for polymers which have a glass transition temperature that is significantly lower than the melting point of the drug. However, if the polymer has a significantly higher T_g but is miscible with the drug, the drug might act as a plasticizer. Third, this method provides an estimation of the interaction parameter close to the melting point of the drug. Finally, the polymer drug ratio over which Eq. 2 shows linearity is limited to relatively low polymer concentrations—likely a result of the kinetics of mixing during the experiment. It is therefore important to note that the interaction parameter determined represents a composite value over this limited concentration range.

Limitations of the Melting Point Depression Approach

Flory–Huggins lattice theory includes several assumptions that may lead to inconsistencies between theoretical predictions and experimental data (54,57,58), some of which are relevant to our study. Other drawbacks of the melting point depression approach result from problems associated with the experiments themselves. In particular, in mixing a crystalline drug with an amorphous polymer, it is assumed that the kinetics of mixing take place over the timescale of the experiment. However, initially, the crystalline drug is in contact with the amorphous polymer at particle interfaces. Local concentrations are not truly representative of bulk concentrations. Once the melting event begins, the drug and the polymer will begin to mix and the kinetics of this process are finite. As described in the methods section, these variables were controlled with the aim of providing the best opportunity to access the true thermodynamic melting point depression; however, mixing may still be kinetically limited.

Solubility in Low Molecular Weight Analog

The activity coefficient in any solvent can be calculated at the solubility limit of the drug as long as both (1) the free energy difference between the amorphous form and the crystalline form and (2) the equilibrium solubility are known (52). The equilibrium solubility in 1-ethyl-2-pyrrolidone, which is a low molecular weight analog of PVP, was measured as described above. The enthalpy of fusion, melting point, and heat capacity of the crystalline form and the heat capacity

of the amorphous form of felodipine, nifedipine, sucrose, and indomethacin, have been previously reported (51,59) and literature values were used in Eq. 1 to estimate the ideal solubility. For ketoconazole, heat capacity data were not available and the difference in heat capacity between the two forms was approximated by the difference at the glass transition temperature (integrated between the glass transition temperature and the melting temperature). This value has been used previously to calculate the heat capacity contribution to the solubility equation (60). The activity coefficient, derived from the ratio of the ideal solubility to the experimental solubility in ethyl pyrrolidone, can then be adjusted by applying a simple solution theory model to provide an estimate of the activity coefficient of the drug in PVP. To use this approach, it is assumed that the measured thermodynamic solubility of the drug provides an indication of the compatibility of the drug with a polymerized version of the solvent. Further, it should be noted that this approach provides an estimate of the solubility in an equilibrium liquid rather than a glass. The activity coefficient can be broken down into two components (52). First, the combinatorial component represents the non-idealities in the entropy of mixing. Second, the residual component is a reflection of the enthalpy of mixing whereby exothermic mixing will lower the overall activity coefficient and endothermic mixing will raise the overall activity coefficient. Of course, the two are linked since, for instance, any order imposed on the mixture as a result of exothermic interactions will decrease the entropy of mixing relative to ideal mixing. The activity coefficient of the drug in ethyl pyrrolidone, γ_{drug}^{EP}, is shown in Eq. 3 in terms of the combinatorial component, $\gamma_{drug}^{EP-combinatorial}$, and the residual component, $\gamma_{drug}^{EP-residual}$. The corresponding equation for the activity coefficient of the drug in PVP is shown in Eq. 4.

$$\ln \gamma_{drug}^{EP} = \ln \gamma_{drug}^{EP-combinatorial} + \ln \gamma_{drug}^{EP-residual} \tag{3}$$

$$\ln \gamma_{drug}^{PVP} = \ln \gamma_{drug}^{PVP-combinatorial} + \ln \gamma_{drug}^{PVP-residual} \tag{4}$$

The difference in the activity coefficients of the drug in the two systems is given by Eq. 5. If it is assumed that the drug mixes with ethyl pyrrolidone with an ideal entropy of mixing (i.e. the activity coefficient arises purely from enthalpy of mixing effects), then Eq. 6 results.

$$\begin{aligned}\ln \gamma_{drug}^{PVP} - \ln \gamma_{drug}^{EP} &= \left(\ln \gamma_{drug}^{PVP-combinatorial} + \ln \gamma_{drug}^{PVP-residual}\right) \\ &\quad - \left(\ln \gamma_{drug}^{EP-combinatorial} + \ln \gamma_{drug}^{EP-residual}\right)\end{aligned} \tag{5}$$

$$\ln \gamma_{drug}^{PVP} - \ln \gamma_{drug}^{EP} = \ln \gamma_{drug}^{PVP-combinatorial} - \ln(1) + \ln \gamma_{drug}^{PVP-residual} - \ln \gamma_{drug}^{EP-residual} \tag{6}$$

If it is further assumed that the residual components to the activity coefficients are identical (i.e., the interactions between the ethyl pyrrolidone and the drug are identical to the interactions between the repeat unit of PVP and the drug) then Eq. 7 results. The excess (non-ideal) combinatorial entropy of mixing a drug with a polymer can be predicted from Flory–Huggins lattice theory and this term can be substituted into Eq. 7 which after rearrangement gives Eq. 8.

$$\ln \gamma_{drug}^{PVP} - \ln \gamma_{drug}^{EP} = \ln \gamma_{drug}^{PVP-combinatorial} \tag{7}$$

$$\ln \gamma_{drug}^{PVP} = \frac{MV_{drug}}{MV_{lattice}} \left[\frac{1}{m_{drug}} \ln \frac{\Phi_{drug}}{x_{drug}} + \left(\frac{1}{m_{drug}} - \frac{1}{m_{PVP}}\right)\Phi_{PVP}\right] + \ln \gamma_{drug}^{EP} \tag{8}$$

Equation 8 states that the activity coefficient of the drug in PVP is equal to the activity coefficient of the drug in ethyl pyrrolidone after scaling for the reduced entropy of mixing the drug with the polymer relative to the entropy of mixing the drug with ethyl pyrrrolidone. It should be noted that this is the estimated activity coefficient of the drug *at the solubility limit in ethyl pyrrolidone*. Assuming that the activity coefficient is the same at the solubility limit of the drug in the polymer, it can be used to calculate the solubility of the drug in PVP as shown in Eq. 1.

Conversion Between Activity Coefficients and Flory–Huggins Interaction Parameter

The activity coefficient and the Flory–Huggins interaction parameter can be related *via* Eq. 9 taking into consideration that the interaction parameter is defined by the volume of the lattice site. This equation aids in making comparisons between the activity coefficient measured by solubility and the interaction parameter as measured by melting point depression.

$$\ln \gamma_{drug}^{PVP} = \frac{MV_{drug}}{MV_{lattice}} \left[\frac{1}{m_{drug}} \ln \frac{\Phi_{drug}}{x_{drug}} + \left(\frac{1}{m_{drug}} - \frac{1}{m_{PVP}}\right)\Phi_{PVP} + \chi \Phi_{PVP}^2\right] \tag{9}$$

RESULTS

Melting Point Depression

Table I lists several systems which have been previously studied and identified as miscible, immiscible, or partially miscible and Figs. 2, 3 and 4 show melting point data for several of these systems. It can be seen from Eq. 2 that there are two factors that would be expected to contribute to melting point depression; entropy of mixing and non-idealities of mixing as reflected by the magnitude of the interaction parameter. The hashed lines of Figs. 2, 3 and 4 represent the extent of melting point depression that would be predicted if mixing were athermal, that is where the melting point depression results only from the mixing entropy. A greater extent of melting point depression would arise from negative

Table I. Examples of Miscible, Partially Miscible, and Immiscible Small Molecule–Polymer Systems

API	Polymer	Miscibility	Evidence for Miscibility
Nifedipine	PVP	Misc	T_g, FTIR (51)
Felodipine	PVP	Misc	T_g, FTIR (51)
Ketoconazole	PVP	Misc	T_g (63)
Sucrose	PVP	Misc	T_g, FTIR (66)
Indomethacin	PVP	Misc	T_g, FTIR (67)
Sucrose	Dextran	Misc	T_g (66)
Ibuprofen	Dextran	Immisc	Microscopy (64)
Indomethacin	Dextran	Immisc	T_g (this study)
Itraconazole	Eudragit E100	Partially	T_g (65)

values of the interaction parameter, as would be expected for exothermic mixing, while a lesser extent of melting point depression leads to a positive interaction parameter and is consistent with endothermic mixing. Systems which exhibit a sufficiently positive interaction parameter would not be expected to mix and hence would not be expected to show melting point depression. In this case, the enthalpy of mixing cannot be measured and there is no configurational entropy introduced by the presence of the second component.

Systems which have been identified as miscible (Table I) show melting point depression of the drug while systems identified as immiscible or partially miscible show little or no melting point depression of the drug. Thus indomethacin (Fig. 2) and ketoconazole (Fig. 3) show varying degrees of melting point depression when mixed with PVP. Furthermore, it can be seen from data presented for indomethacin, that the observed extent of melting point depression is greatest when using the onset melting point and least when using the offset value. Sucrose shows melting point depression when mixed with either PVP or dextran (data not shown). It is appropriate to note here that sucrose can degrade on melting and, therefore, the data represent a gross estimation of the true effect of the polymer. The miscibility and melting point depression of nifedipine and felodipine in the presence of PVP K12 have been reported previously (39) and similar results were obtained in this study for these systems (data not shown). In contrast, itraconazole mixed with Eudragit E100 showed essentially no melting point depression (Fig. 4). In addition, melting point depression was not observed for either ibuprofen or indomethacin mixed with dextran (data not shown).

Using the melting point depression data, and applying Eq. 2 enables values of the interaction parameter to be determined and the results are listed in Table II. The value of the interaction parameter varies considerably depending if onset, midpoint, or offset values of the melting event are used. For example, for indomethacin the interaction parameter was determined to be −6.16, −1.94 and −0.82 for the onset, midpoint, and offset melting point values, respectively. Theoretically, the offset value should be used since this shows the melting point at the final composition, assuming complete mixing has occurred (56); all values reported in Table II represent interaction parameters determined using the offset melting point. From Table II, it can be observed that negative or close to zero interaction parameters are estimated for all systems which have been reported as miscible with PVP. In contrast, those systems which have been reported as immiscible give larger positive interaction parameters. The calculated values for the interaction parameter were used to generate the solid lines in Figs. 2, 3 and 4 and serve as a useful comparison with the melting point depression that would be predicted for athermal mixing (hashed lines in Figs. 2, 3 and 4). The interaction parameters calculated by this method vary from −0.82 for the indomethacin-PVP K12 system to as high as 0.72 for the ibuprofen–dextran system. Larger negative interaction parameters reflect a greater thermodynamic driving force for mixing the drug with the polymer near the melting temperature of the drug. It should be noted that, in the limit of complete immiscibility, the melting temperature will remain unaffected by the presence of the polymer and the estimated interaction parameter represents the lower limit of the value. Finally, it is important to note that because dextran has a T_g of around 140°C, the extent of melting point depression may be underestimated for these compounds.

As discussed above, it is recognized that the timescale of the experiment needs to allow for adequate mixing of the drug with the polymer such that the observed melting temperature is not significantly hindered by the mixing event. In order to evaluate if mixing between the drug and polymer are kinetically limited under the experimental conditions employed, the melting point depression of one model system, felodipine and PVP, was examined in more detail. Specifically, the melting point depression of crystalline felodipine was

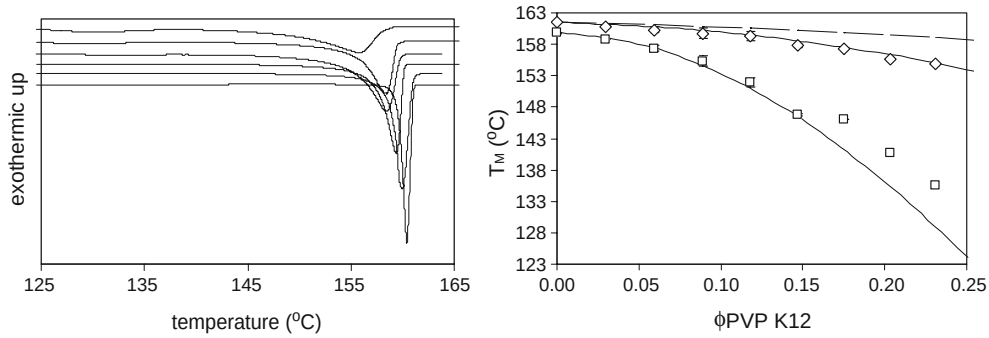

Fig. 2. DSC thermograms of physical mixtures of indomethacin with increasing volume fraction of PVP K12 measured at a heating rate of 1°C/min. Onset of melting (*square*) and offset of melting (*diamond*) as a function of volume fraction of PVP K12, experimental data fit to melting point depression equation (*solid line*), and predicted melting point depression for an athermal mixture (*hashed line*).

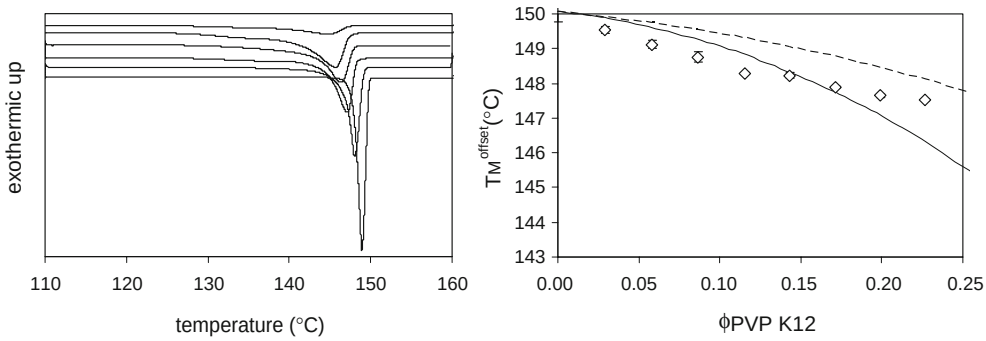

Fig. 3. DSC thermograms of physical mixtures of ketoconazole with increasing volume fraction of PVP K12 measured at a heating rate of 1°C/min (**a**). Offset of melting as a function of volume fraction of PVP K12 (*diamond*), experimental data fit to melting point depression equation (*solid line*), and predicted melting point depression for an athermal mixture (*hashed line*).

examined both in the presence of pure PVP K12 and in the presence of amorphous molecular level solid dispersions of PVP K12 and felodipine. It was found that the observed melting point depression of crystalline felodipine in contact with an amorphous molecular level solid dispersion of felodipine in PVP K12 was slightly lower than when in contact with pure PVP K12 containing the same overall concentration of each component (data not shown). This suggests that mixing of the drug and the polymer over the timescale of the experiment does contribute to an underestimation of the true interaction between the components. This underestimation will be most noticeable for systems with small differences between the melting temperature of the drug and the glass transition temperature of the polymer. The data presented in Table II for felodipine represent the interaction parameter measured for felodipine in contact with an amorphous dispersion containing 50wt.% felodipine.

Solubility in Low Molecular Weight Analog

The solubility of several model compounds in 1-ethyl-2-pyrrolidone is given in Table III along with the corresponding activity coefficient as calculated by Eq. 1. All compounds have a solubility which is greater than the ideal solubility as predicted by Eq. 1. Therefore, the resulting activity coefficient is less than 1. The weight fraction solubility ranges from 0.074 for sucrose to 0.396 for indomethacin in 1-ethyl-2-pyrrolidone. Next, the solubility of each model compound in the polymer was estimated as described in the methods section and the results are listed in Table III. It is noted that the predicted solubility initially decreases quite drastically with increasing molecular weight of PVP followed by a less dramatic decrease as the molecular weight of PVP reaches a critical value. For example, consider that the measured solubility of indomethacin in 1-ethyl-2-pyrrolidone is 0.396 weight fraction indomethacin. The estimated solubility in PVP K12 is reduced by a factor of more than two to 0.144 weight fraction indomethacin due to the reduced entropy of mixing. In contrast, increasing the molecular weight from 2,500 g/mol (PVP K12) to 40,000 g/mol (PVP K29/32) results in only a slight further reduction in estimated solubility to 0.134 weight fraction indomethacin and when mixing with PVP K90, the solubility remains approximately equal to that estimated for PVP K29/32. This trend is easily rationalized when considering the derivation of the Flory–Huggins equation since the term $(1/m_{\mathrm{drug}} - 1/m_{\mathrm{polymer}})$ quickly approaches $1/m_{\mathrm{drug}}$ as m_{polymer} increases.

DISCUSSION

Thermodynamics of Mixing Drugs and Polymers

Amorphous molecular level solid dispersions are ideally homogeneous single phase systems. In order to form a one phase system, the two components have to be thermodynamically miscible during processing. Ideally, miscibility will also

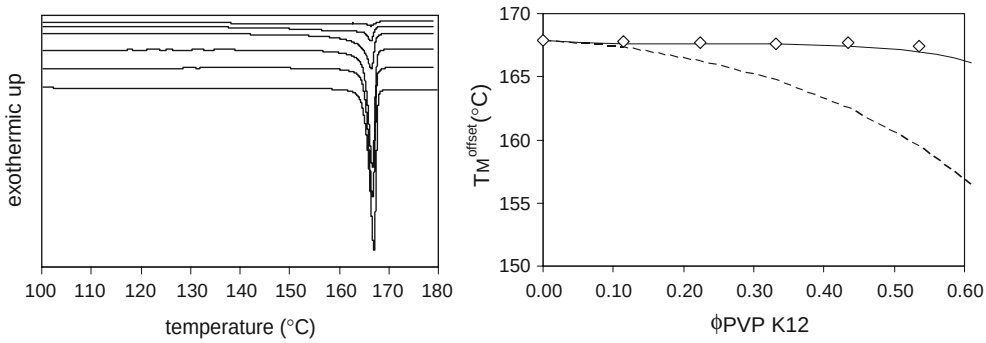

Fig. 4. DSC thermograms of physical mixtures of crystalline itraconazole with increasing weight fraction of Eudragit E100 measured at a heating rate of 1°C/min. Offset of melting as a function of volume fraction of PVP K12 (*diamond*), experimental data fit to melting point depression equation (solid line), and predicted melting point depression for an athermal mixture (*hashed line*).

Table II. Physical Properties Used with Melting Point Depression Data to Calculate the Flory–Huggins Interaction Parameter of Each Model Compound in PVP K12, Dextran, and Eudragit E100

Compound	M_W (g/mol)	Density (g/cm^3)[a]	Molecular Volume (cm^3/mol)	ΔH_{fus} (kJ/mol)	T_M (K)	χ^{offset}[b]
PVP K12	2,500	1.11	2,252.25	–	–	–
Felodipine	384.26	1.28	300.20	30.83	414.75	−0.08
Nifedipine	346.34	1.20	288.62	39.89	445.25	0.00
Ketoconazole	531.43	1.30 (63)	408.79	54.10	421.25	−0.08
Sucrose	343.30	1.43 (68)	240.07	44.70	448.84	0.02
Indomethacin	357.79	1.34 (69)	268.01	39.68	432.93	−0.82
Dextran	860	1.02 (66)	843.14	–	–	–
Sucrose	343.30	1.43 (68)	240.07	44.70	448.84	0.20
Ibuprofen	206.28	1.05 (70)[c]	158.68	24.11	347.88	0.38[e]
Indomethacin	357.79	1.34 (69)	268.01	39.68	432.93	0.72[e]
Eudragit E100	4,840[d]	1.1	4,400	–	–	–
Itraconazole	705.63	1.30 (71)	542.79	56.70	438.35	0.11[e]

[a] As measured by helium pycnometry or from indicated reference
[b] Based on a lattice volume equal to the volume of 1-ethyl-2-pyrrolidone
[c] Assuming amorphous density is 5% less than crystalline density
[d] Assuming 20 repeat units in the polymer
[e] In the limit of complete immiscibility, the melting temperature will remain unaffected by the presence of the polymer

be maintained at the storage conditions of the solid dispersions. Miscibility is governed by the balance between the entropy and enthalpy of mixing. As previously discussed, Flory–Huggins lattice theory provides a useful tool for describing drug–polymer systems since this theory takes into account the large size discrepancy between the two components (Eq. 10) (39). The first two terms on the right hand side of the equation represent the entropy of mixing and the last term represents the enthalpy of mixing (54,57).

$$\frac{\Delta G}{RT} = \frac{\Phi_{drug}}{m_{drug}} \ln \Phi_{drug} + \frac{\Phi_{polymer}}{m_{polymer}} \ln \Phi_{polymer} + \chi \Phi_{drug} \Phi_{polymer} \quad (10)$$

When mixing APIs with polymers, the entropy contribution to miscibility is relatively fixed (and favorable to mixing) given that the MW of APIs typically range from between 200 and 600 and those of pharmaceutical polymers range between 10,000 and 1,000,000 (39). Since entropy will always favor mixing, any API–polymer system can tolerate a certain maximum (unfavorable) enthalpy of mixing and still achieve a negative free energy of mixing. Therefore, in order to predict miscibility between a drug and polymer, it is necessary to estimate the magnitude if the interaction parameter. The methods described here, melting point depression and solubility in the low molecular analog of the polymer provide experimental data that can be used to approximate the interaction parameter and thus enable comparisons to be made about the mixing thermodynamics for different systems. The melting point depression experiments provide information about the thermodynamics of mixing over a given composition range near the melting point. Solubility measurements in low molecular weight analogs of the polymer, if available, can be used to extract information about thermodynamics of mixing at room temperature at a fixed composition (i.e. the solubility limit of the drug). Although the interaction parameters derived from the two methods were obtained under different temperatures and compositions, referral to Table II and Table III indicate a reasonable consistency between the two sets of values. In general, the values estimated from solubility measurements indicate more favorable interactions and this is most probably due to the aforementioned compositional/temperature differences in addition to the potential for kinetically hindered mixing in the melting point depression experiments.

It is apparent from Table II and Table III, that the majority of the miscible systems have interactions parameters close to or less than zero, indicating athermal or slightly exothermic mixing. These results indicate that miscibility in

Table III. Measured Solubility in 1-Ethyl-2-Pyrrolidone Expressed as a Weight Fraction, w_{drug}, and as a Mole Fraction, x_{drug}, and the Corresponding Activity Coefficient Calculated from the Simplified Solubility Equation (Eq. 1), γ_{drug}

	1-Ethyl-2-pyrrolidone				PVP K12		PVP K29/32		PVP K90	
Compound	w_{drug}	x_{drug}	γ_{drug}	χ	w_{drug}	γ_{drug}	w_{drug}	γ_{drug}	w_{drug}	γ_{drug}
Felodipine	0.268	0.099	0.89	−0.08	0.072	3.94	0.065	4.34	0.065	4.37
Nifedipine	0.215	0.083	0.26	−0.81	0.054	1.18	0.049	1.30	0.049	1.31
Ketoconazole	0.079	0.018	0.68	−0.12	0.011	5.04	0.010	5.92	0.010	5.97
Sucrose	0.074	0.026	0.37	−0.53	0.016	1.76	0.015	1.93	0.015	1.94
indomethacin	0.396	0.173	0.15	−1.83	0.144	0.50	0.134	0.54	0.134	0.54

Also Shown is the Predicted Solubility and Activity Coefficient in Various Grades of PVP

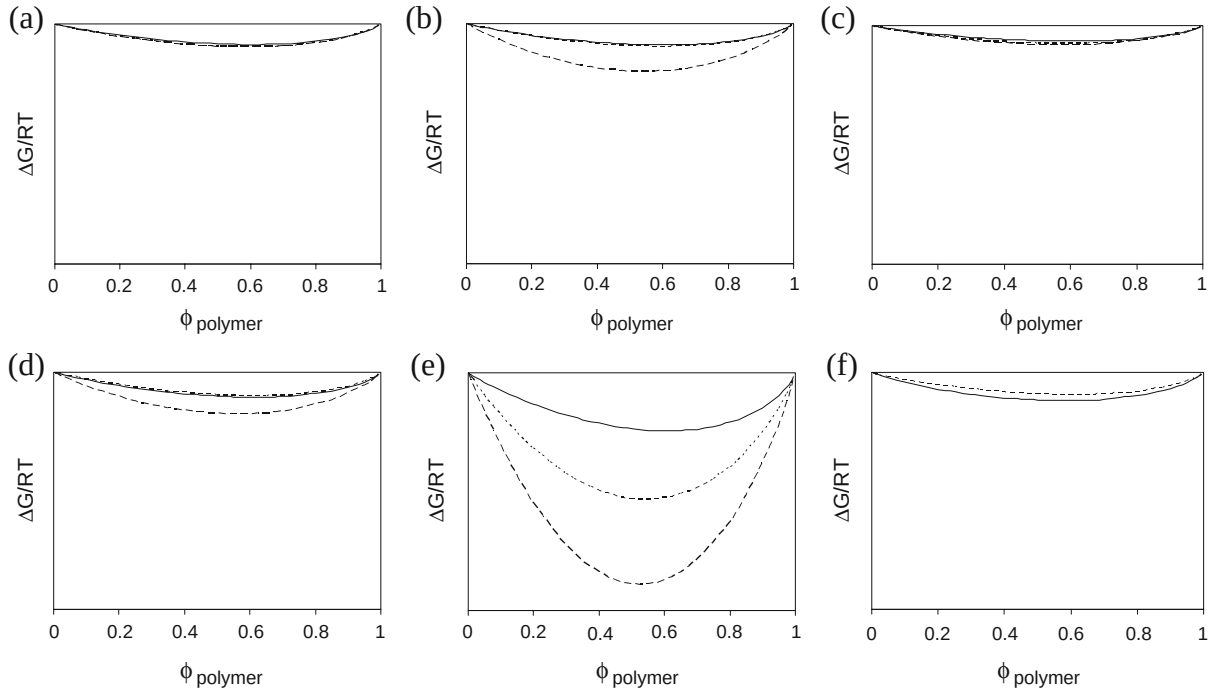

Fig. 5. Free energy of mixing model compounds with PVP using solubility measurements (*long hashed lines*), using melting point depression measurements (*short hashed lines*) and the free energy of mixing an athermal system (*solid lines*) for felodipine (**a**), nifedipine (**b**), ketoconazole (**c**), sucrose (**d**), and indomethacin (**e**). Also shown for comparison is the free energy of mixing sucrose with dextran (**f**).

these systems is largely driven by entropy. Indomethacin has the lowest value of interaction parameter suggesting mixing is more exothermic for this system. In contrast, the immiscible systems yield large, positive values of the interaction parameter. The interaction parameters estimated for the miscible systems can be used to estimate the free energy of mixing using Eq. 10 as discussed above.

The free energy of mixing as predicted by each method for each compound is shown in Fig. 5 (to generate these plots**,** the simplifying assumption has been made that the interaction parameters are independent of composition). Data from melting point depression predicts a free energy of mixing which is most negative for indomethacin-PVP, and approximately the same for nifedipine, felodipine, ketoconazole, and sucrose mixed with PVP. For values derived from solubility measurements, the free energy of mixing is predicted to be more negative with the largest free energy of mixing again observed for indomethacin-PVP, followed by the nifedipine and sucrose, with felodipine and ketoconazole PVP systems again very similar to one another. In addition, curves showing the free energy of mixing that would result from athermal mixing (i.e. entropy driven mixing) are also shown. Free energy profiles for the immiscible/partially miscible systems, ibuprofen–dextran, indomethacin–dextran, and itraconazole–Eudragit E100 are not shown. As described above, the enthalpy of mixing for immiscible systems cannot be accessed and the entropy goes to zero. These simulations of the free energy of mixing illustrate how the magnitude of the interaction parameter rather than the entropy term leads to differences between the various compounds. This is because the contribution of the mixing entropy (assuming that mixing is purely combinatorial) is virtually constant across all of the systems.

Estimating the Solubility of Drugs in Polymers of High Glass Transition Temperature and the Thermodynamic Driving Force for Crystallization

The solubility will depend both on the crystal lattice properties and the thermodynamics of mixing (activity coefficient) as described in Eq. 1. From Eq. 1 it can be seen that compounds with high enthalpy of fusion and high fusion temperature are expected to have a low solubility. The solubility will be further modified by the value of the activity coefficient. Estimates of solubility of each drug in the polymer can be made using the values provided in Table II and Table III. Given that the activity coefficient varies with composition and temperature, it would seem most appropriate to estimate the solubility of the drug in the polymer based on the activity coefficient of the drug as estimated from the solubility in the low molecular analog, 1-ethyl-2-pyrrolidone. Consider the solubility of each compound as shown in Table III. It is expected that the interactions between the compound and 1-ethyl-2-pyrrolidone will be similar to the interactions between each compound and PVP. However, for each compound, the entropy of mixing with PVP will be greatly reduced as compared to the entropy of mixing with 1-ethyl-2-pyrrolidone as described in the methods section. Therefore, the solubility is predicted to be reduced in the polymer. From the estimated solubility, it is possible to approximate the fraction of drug which is available for crystallization as a function of the weight percent polymer in the amorphous molecular level solid dispersion. For example, consider the solubility of indomethacin in 1-ethyl-2-pyrrolidone. The weight fraction solubility was measured to be 0.396. After adjusting for the decrease in the entropy of mixing, the predicted solubility in K29/32 is 0.144. Therefore, any weight

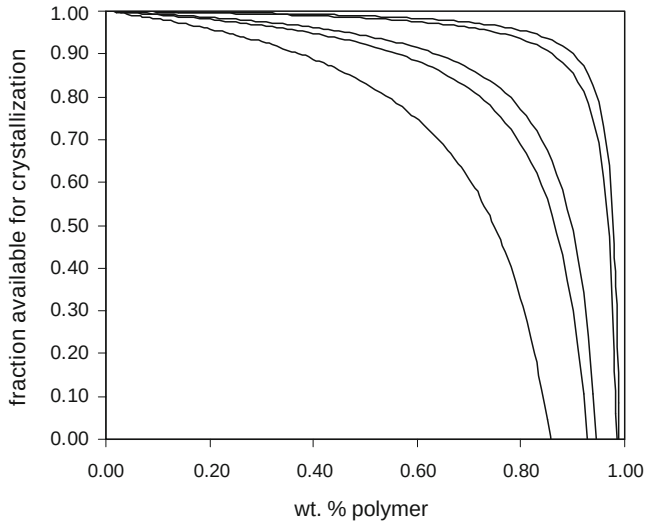

Fig. 6. Estimated fraction of drug available for crystallization as a function of wt.% polymer. The root of each line represents the solubility in PVP K29/32 as estimated from the solubility in 1-ethyl-2-pyrrolidone after accounting for the reduced entropy of mixing with PVP K29/32. *From left to right* The *lines* represent indomethacin, felodipine, nifedipine, sucrose, and ketoconazole.

fraction of compound in excess of 0.144 in PVPK29/32 leads to an amorphous molecular level solid dispersion which is "supersaturated" and the difference between the drug loading and the "solubilized" drug represents the amount of drug which is available for crystallization. The results of such calculations for various systems are shown in Fig. 6. It is clear that these predictions suggest that there is a thermodynamic driving force for crystallization of the drug at most practical polymer concentrations. Therefore, "thermodynamically stable solid dispersions" are difficult to achieve and any apparent stability is most likely achieved through modification of the kinetics of the system. Furthermore, these results may help explain why 100% crystallization of the drug is not always observed from solid dispersion—in essence because a small fraction of the drug is thermodynamically stable and will not undergo this phase transformation.

Role of Chemistry in Miscibility

Since entropy will always favor mixing, any API-polymer system can tolerate a certain maximum (unfavorable) enthalpy of mixing and still achieve a negative free energy of mixing. Thus, the factors that contribute to the enthalpy of mixing for API-polymer systems are critical to understanding miscibility. The sign and magnitude of the mixing enthalpy will be determined by the relative strength and number of the interactions in the mixture relative to those of the pure materials (53). Exothermic mixing can only occur if interactions are formed between the two components that are stronger and/or more numerous than those found in the pure components. Conversely, if one (or both) components self-associate, forming stronger and/or more numerous interactions with itself than with the other component, mixing will be endothermic. Athermal mixing implies that interactions are formed between the two components; however, these are similar in magnitude and/or extent to the cohesive interactions.

In general, intermolecular interactions among organic molecules stem from (partial) electron transfer and sharing, electrostatic force, and polarization contributions. Hydrogen bonding is a special case of electron transfer and sharing between a hydrogen atom and specific atoms that can share a pair of electrons (the strength is typically 10–20 kJ/mol). A molecule with a large value of dipole moment is indicative of the molecule being polar and some regions of the molecule are positive while others are negative. These molecules may then interact considerably with other molecules containing a large dipole moment *via* electrostatic force. Conversely, the polarization contribution, or van der Waals interaction, is universal among organic molecules. For a molecule with no dipole moment or close contacts (such as hydrogen bonding) with other molecules, the van der Waals interaction is dominant but is weak.

It is well known from the solubility literature that systems interacting only *via* van der Waals interactions would be expected to have an endothermic heat of mixing (53). The magnitude of the heat of mixing in such systems can be estimated from the difference in the solubility parameters of each component. However, examination of the molecular structures of the drugs and polymers used in this study (Fig. 1) indicate that all the compounds are polar and hence are capable of forming additional types of interaction. It is thus pertinent to consider the potential cohesive and adhesive interactions of the various systems and how these might influence the experimentally observed activity coefficients/interaction parameters.

Felodipine, nifedipine, sucrose and ketoconazole mixed with PVP or 1-ethyl-2-pyrrolidone all yield slightly negative or close to zero interaction parameters. Further, these compounds are more soluble in 1-ethyl-2-pyrrolidone than predicted by calculating their ideal solubility. This indicates that all of these compounds are able to form favorable interactions with the solvent/polymer. Felodipine, nifedipine and sucrose can all form intermolecular hydrogen bonds in the amorphous state (61,49) however disruption of this self-association is compensated for by formation of hydrogen bonds with PVP (51). These are examples where the API-polymer hydrogen bond is stronger than the API–API hydrogen bond (49,51). This situation arises because the polymer contains a better acceptor group than is found in the API. As shown in Table IV, the PVP carbonyl peak is shifted to a lower wavenumber providing evidence for the drug–polymer hydrogen bonding interaction (62). Interestingly, ketoconzole appears to have a close to zero/slightly negative heat of mixing, even though this molecule cannot form

Table IV. Dipole Moments as Estimated from Gaussian 03 Calculations and Carbonyl Peak Shift in an Amorphous Dispersion Containing one Hydrogen Bond Donor Group for Each Carbonyl Acceptor Group

	Dipole moment (Debye)	ΔPVP C=O (cm^{-1})
Nifedipine	9.58	–
Felodipine	5.30	25
Indomethacin	2.68	45
Sucrose	5.40	25
Ibuprofen	1.76	–
Alpha-D-glucose	4.22	–
Vinyl pyrrolidone	3.91	–
Ketoconazole	6.03	0

hydrogen bonding interactions with PVP since it lacks hydrogen bond donors (63). This is confirmed by the lack of shift of the PVP carbonyl peak position to a lower wavenumber as illustrated in Table IV. Given the absence of hydrogen bonding, it seems reasonable to speculate that these two compounds can interact *via* dipole-dipole interactions, consistent with their structures. Molecular calculations confirm that ketoconazole has a dipole moment which is quite large in magnitude (Table IV) and may therefore interact strongly with other polar molecules such as PVP. The large molecular size of the drug is also believed to contribute considerably to the van der Waals interactions. These observations highlight the importance of considering intermolecular interactions other than hydrogen bonding interactions.

For indomethacin mixed with PVP, the interaction parameter as predicted from melting point depression, $\chi = -0.82$, is much larger in magnitude, and the activity coefficient in 1-ethyl-2-pyrrolidone, $\gamma = 0.146$, lower than for the other compounds studied. This result can most likely be rationalized by considering the relative acidity of the hydrogen bond donor in indomethacin as compared to the other compounds. Hence, the carboxyl group of indomethacin is expected to form stronger hydrogen bonds with PVP than the NH groups of felodipine and nifedipine or the hydroxyl groups of sucrose. Evidence for the formation of a stronger hydrogen bond between PVP and indomethacin is provided by the greater shift of the PVP carbonyl for this system as shown in Table IV. Therefore, from the standpoint of the thermodynamics of mixing, indomethacin appears to form the most energetically favorable mixture with PVP.

As stated above, there is always a favorable contribution from the mixing entropy to the free energy of mixing. However, the magnitude of the entropy term is not however sufficient to drive miscibility in all polymer–small molecule systems, as can be seen from Table I. Dextran has been reported to be immiscible with ibuprofen (64) and was also observed to be immiscible with indomethacin. Consistent with this observation, no melting point depression was observed for either system resulting in larger positive interaction parameters. Based on the chemical structures, it can be seen that neither of these two systems would be expected to form any intermolecular interactions that are energetically more favorable than those found in each of the pure components and hence it can be speculated that mixing is not achieved because the mixing entropy is not sufficient to offset the unfavorable adhesive interactions.

Another example of a system reported to exhibit phase separation is itraconazole and Eudragit E100 (a cationic methacrylate polymer) (65). This system can be categorized as consisting of a polymer with strong self-interactions of ionic origin arising from the charged groups and an API with mainly dispersive interactions. Likewise, it can be predicted that adhesive interactions are not energetically favorable relative to cohesive interactions resulting in the reported miscibility gap. Again, the lack of melting point depression is consistent with the substantial immiscibility of the two components.

CONCLUSIONS

Interaction parameters provide important information about the thermodynamics of mixing between small molecules and polymers, in other words their miscibility. However, interaction parameters can be challenging to determine experimentally. Some success in estimating these parameters was achieved using melting point depression or (for PVP systems) measuring solubility in a low molecular weight analog of the polymer. For miscible systems, the melting point of the crystalline drug is depressed in the presence of the polymer; in contrast systems with limited miscibility showed little, if any, melting point depression. Limitations were found with both experimental approaches. The experimentally derived interaction parameters were used to generate free energy of mixing profiles for the various systems and to estimate the solubility of active pharmaceutical ingredients in PVP. It can be concluded that the solubility of most drugs in polymeric matrices is likely to be low at room temperature unless extremely favorable cohesive interactions are formed.

ACKNOWLEDGEMENTS

This work was supported in part by a fellowship from Merck Research Laboratories. AstraZeneca is acknowledged for financial support. Jared Baird is thanked for his help in measuring the solubility of the model compounds in 1-ethyl-2-pyrrolidone. Håkan Wikström is thanked for his help in measuring the solubility of sucrose using HPLC and Sheri Shamblin is thanked for providing heat capacity values for indomethacin and sucrose. Professors George Zografi, Rodolfo Pinal, Ken Morris, and Steve Byrn are acknowledged for their input. The PhRMA Foundation is acknowledged for a pre-doctoral fellowship to PJM. LST thanks AFPE/AACP for a New Investigator Award.

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