

A Method to Predict the Equilibrium Solubility of Drugs in Solid Polymers near Room Temperature Using Thermal Analysis

ROBERT A. BELLANTONE,¹ PIYUSH PATEL,¹ HARPREET SANDHU,² DUK SOON CHOI,² DHARMENDRA SINGHAL,² H. CHOKSHI,² A. WASEEM MALICK,² NAVNIT SHAH²

¹Division of Pharmaceutical Sciences, Arnold & Marie Schwartz College of Pharmacy and Health Sciences, Long Island University, Brooklyn, New York 11201

²Pharmaceutical and Analytical Research & Development, Hoffmann La-Roche, Inc., Nutley, New Jersey 07110

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ABSTRACT: A method is presented for determining the equilibrium solubility of a drug in a solid polymer at or near room temperature, which represents a typical storage temperature. The method is based on a thermodynamic model to calculate the Gibbs energy change ΔG_{SS} associated with forming a binary drug–polymer solid solution from the unmixed polymer and solid drug. The model includes contributions from heat capacity differences between the solid solution and the corresponding unmixed components, breaking up of the solid drug structure, and drug–polymer mixing. Calculation of ΔG_{SS} from thermal analysis data is demonstrated, and it is shown that minima of plots of ΔG_{SS} versus the dissolved drug concentration represent the equilibrium drug solubility in the polymer. Solid solutions were produced for drug–polymer systems (griseofulvin, indomethacin, itraconazole; PVP K30, Eudragit L100, Eudragit E100) in drug weight fractions up to ~25%. At 25°C, it was seen that heat capacity effects were important in determining the drug solubility. It was concluded that drug solubilities in solid polymers can be determined using thermal analysis, and must include heat capacity effects when evaluated near room temperature. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association *J Pharm Sci* 101:4549–4558, 2012

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INTRODUCTION

Formulating poorly water-soluble drugs as solid solutions in a polymer can facilitate faster dissolution and increased bioavailability compared with the drug in its stable crystalline form.^{1–3} However, at dissolved drug concentrations above the equilibrium solubility in the polymer, these systems are thermodynamically unstable and dispersed drug molecules tend to precipitate within the matrix, resulting in a loss of the solubility/dissolution benefits.⁴ If a supersaturated solid solution is stored for “infinite” time, the final dissolved drug concentration will equal its equilibrium solubility (referred to here as the solubility) in the polymer. Therefore, it is of practical interest to know the solubility at or near room temperature (taken here as 25°C), which represents a typical storage temperature.

Experimentally determining the solubility of a drug in a solid solution at typical storage temperatures is challenging. For instance, if a supersaturated solid solution is stored at room temperature, the time required for precipitation/equilibration would typically be prohibitively long. A similar comment applies to producing a physical mixture and allowing the drug and polymer to mix by diffusion at room temperature. Accelerated studies at higher temperatures introduce problems because, unlike solutions in liquid solvents, no general methods exist to calculate the drug solubility in a drug–polymer solid solution at room temperature from data obtained at elevated temperatures. As a result, much recent work has focused on other ways to determine the solubility of a drug in a polymer.

Most literature discussions have considered the drug and polymer chemical properties, and are analogous to the Hildebrand–Scott theory of real solutions for liquid solvents.^{5–7} Solubility parameters have been calculated and related to small molecule–polymer interaction parameters,^{8,9} which have been

Correspondence to: Robert Bellantone (Telephone: 1-718-780-4154; Fax: 1-718-780-4586; E-mail: rbellant@liu.edu)

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used with the Flory–Huggins model¹⁰ to calculate the enthalpy of mixing of drugs in polymers.¹¹ The heat of melting of a drug also affects the solubility, based on arguments similar to those used in liquid solution theory.^{6,7}

Methods proposed to determine the drug solubility in a polymer include: determining the solubility in monomer/dimer liquid forms of the polymer,^{12,13} drug–polymer complexation studies,¹⁴ correlating drug and polymer solubilities in common solvents,¹⁵ solubility parameter determination,^{16,17} eutectic characterization,^{18,19} determining drug melting point depression in physical mixtures,¹² determining temperatures at which phase separation vanishes as a function of drug loading in physical mixtures,^{20–22} and determining the undissolved drug amounts from observed heats of drug melting for dispersions stored above the glass transition temperature T_g .²³ However, each approach has drawbacks and shown limited success in predicting the equilibrium drug solubility in a polymer, especially near room temperature.

Methods that determine the solubility in liquid media, such as monomer/dimer solubility and complexation, neglect the limitations on molecular motion and orientation due to the solid matrix structure. Also, drug–polymer complexations in liquid solvents involve interactions in a three-component system, which can be very different from the drug–polymer interactions in the absence of a liquid solvent. Methods based on solubility parameters have met with little success—different molecules with similar solubility parameters may not show similar behavior when introduced into a polymer.⁹ Eutectics have been investigated by thermal methods and have theoretical links to interactions between the polymer and small molecules,¹⁹ but the eutectic temperature is usually not similar to the storage temperature. A similar comment applies to methods that provide data at temperatures well above room temperature, such as drug particle melting point depression, determination of temperatures at which phase separation vanishes, and using observed heats of melting of undissolved drug particles. Because temperature effects in drug–polymer solid solutions are complex, it is difficult to estimate solubilities at room temperature from data obtained with those methods. The presence of undissolved particles also introduces problems. The Flory–Huggins model has been applied to drug melting point depression data in physical mixtures to calculate drug–polymer interaction parameter. However, a uniform mixing of the drug and polymer at the molecular level is assumed when calculating the drug and polymer volume fractions, which does not hold when drug particles are present.¹¹

Importantly, none of the above methods account for heat capacity changes that result when forming a solid solution. For given drug and polymer amounts,

the heat capacity of a solid solution does not equal the sum of the heat capacities of the components before mixing, which contributes to the change in Gibbs energy ΔG_{SS} due to the formation of a solid solution. These effects are not included in mixing and/or melting terms. For instance, models of drug–polymer interaction parameters, such as those based on the solubility parameters, only account for potential energy changes due to the intermolecular attraction differences,^{6,10} whereas heat capacity differences reflect changes in the available modes of molecular motion and kinetic energy.^{24,25}

Some models of the solubility of a solid drug in a liquid solvent account for heat capacity differences between the solid drug and its supercooled melt,⁶ and neglect heat capacity changes in the liquid solvent due to the dissolution. However, the heat capacity differences in a solid medium due to dissolving drug molecules are not negligible in general, so heat capacity differences between the unmixed drug and polymer versus the solid solution should be considered. Numerous studies have focused on the T_g , which is related to changes in heat capacity, and led to rules of thumb such as “ $T_g - 50$ ” for the storage temperature.²⁶ However, those were concerned with indicators of kinetic stability, not the solubility of the drug in the polymer. In addition, the glass transition is not a thermodynamic transition and T_g is not a thermodynamic parameter, so there is no fundamental link between them and the drug solubility in the polymer.

This paper presents a method to determine the equilibrium solubility of a drug in a solid polymer near room temperature. The basis for the method is a thermodynamic model that gives the Gibbs energy change ΔG_{SS} , resulting from forming a binary drug–polymer solid solution from the unmixed polymer and solid drug components, which includes contributions from heat capacity differences, breaking up of the solid drug structure, and drug–polymer mixing. The calculation of ΔG_{SS} from thermal analysis data and known thermodynamic equations is demonstrated, along with how those results are used to determine the drug solubility in the polymer. Binary drug–polymer solid solutions in various dissolved drug weight fractions were made and evaluated at 25°C. The drugs were griseofulvin (GRIS), indomethacin (INDO), and itraconazole (ITRA). The polymers were polyvinylpyrrolidone (PVP)-K30, Eudragit L100 (L100), and Eudragit E100 (E100).

THERMODYNAMIC MODEL

Binary solid solutions of a drug in a polymer will be considered for the case in which the pure drug in its stable form is a solid at room temperature. When a solid solution is formed, the ΔG_{SS} and the drug

chemical potential are given by

$$\Delta G_{SS} = G(\text{solid solution}) - G(\text{unmixed components}) \quad (1)$$

$$\begin{aligned} \Delta\mu_{1,SS} = & [\text{chemical potential of dissolved drug}] \\ & - [\text{chemical potential of pure drug in most stable form}] \end{aligned} \quad (2)$$

where the subscripts “1” and “SS” denote the drug solid solution, respectively.

At a given temperature and pressure (T, P), the chemical potential of the pure drug is constant, but the chemical potential of the dissolved drug in the solid solution changes with the drug–polymer ratio. The equilibrium solubility of the drug is the dissolved concentration for which the chemical potential of the dissolved and undissolved drug forms are equal, so $\Delta\mu_{1,SS} = 0$.

Below, the relationship between ΔG_{SS} and $\Delta\mu_{1,SS}$ will be summarized in the context of this work. Following that, a sequence of processes to determine ΔG_{SS} will be presented, along with how its numerical value is obtained as a function of the drug loading.

The Changes in Gibbs Energy and Drug Chemical Potential

The chemical potential of the drug at a given (T, P) is given by $\mu_1 = (\partial G / \partial n_1)_{T,P,n_2}$, where n_1 and n_2 denote the moles of drug and polymer.⁹ With Eqs. 1 and 2, this leads to

$$\Delta\mu_{1,SS} = \left(\frac{\partial \Delta G_{SS}}{\partial n_1} \right)_{T,P,n_2} \quad (3)$$

Materials tend to convert from higher to lower chemical potential forms.²⁷ For a supersaturated solution, $\Delta\mu_{1,SS} > 0$, precipitation is favored and the solution is unstable. For dissolved concentrations at or below the solubility, $\Delta\mu_{1,SS} \leq 0$, the solution is stable, and the dissolved concentration at which $\Delta\mu_{1,SS} = 0$ is the equilibrium solubility.

From Eq. 3, $\Delta\mu_{1,SS}$ is obtained as the slope of ΔG_{SS} versus n_1 at constant T, P and n_2 . In practice, this can be plotted as

$$\frac{\Delta G_{SS}}{n_2} \text{ versus } \frac{n_1}{n_2} \quad \text{or} \quad \frac{\Delta G_{SS}}{w_2} \text{ versus } \frac{n_1}{w_2} \quad (4)$$

where w_2 denotes the weight of polymer used. Normalizing ΔG_{SS} and n_1 with respect to w_2 is equivalent to holding the polymer content constant, so the slope of a plot of Eq. 4 is equivalent to the partial derivative in Eq. 3. This provides a graphical means of obtaining $\Delta\mu_{1,SS}$ as a function of n_1 . The drug solubility is taken as the value of n_1/w_2 for which the plot of Eq. 4 displays a minimum, corresponding to $\Delta\mu_{1,SS} = 0$.

This analysis can also be expressed in terms of the drug weight fraction f_1 by plotting

$$\frac{\Delta G_{SS}}{w_2} \text{ versus } f_1 \quad (5)$$

where $f_1 = w_1/(w_1 + w_2) = n_1 M_1/(n_1 M_1 + w_2)$, w_1 is the weight of drug and M_1 is the gram molecular weight of the drug. Noting that $\partial/[\partial(n_1/w_2)] = [\partial f_1 / \partial(n_1/w_2)] \times (\partial/\partial f_1)$, Eqs. 4 and 5 give

$$\begin{aligned} \Delta\mu_{1,SS} = & \left[\text{slope of } \frac{\Delta G_{SS}}{w_2} \text{ versus } f_1 \right] \\ & \times \left(\frac{w_2 M_1}{w_1 + w_2} \right) \end{aligned} \quad (6)$$

Because $[(w_2 M_1)/(w_1 + w_2)] > 0$, the slope of a plot of Eq. 5 has the same sign as $\Delta\mu_{1,SS}$, and the drug solubility in the polymer is the f_1 at which the plot of Eq. 5 displays a minimum. The top plot in Figure 1 shows a typical example. (In practice, some systems do not display a clear minimum, but instead show a flattened region. In those cases, the solubility is taken as the maximum value of f_1 for which the slope is not positive.)

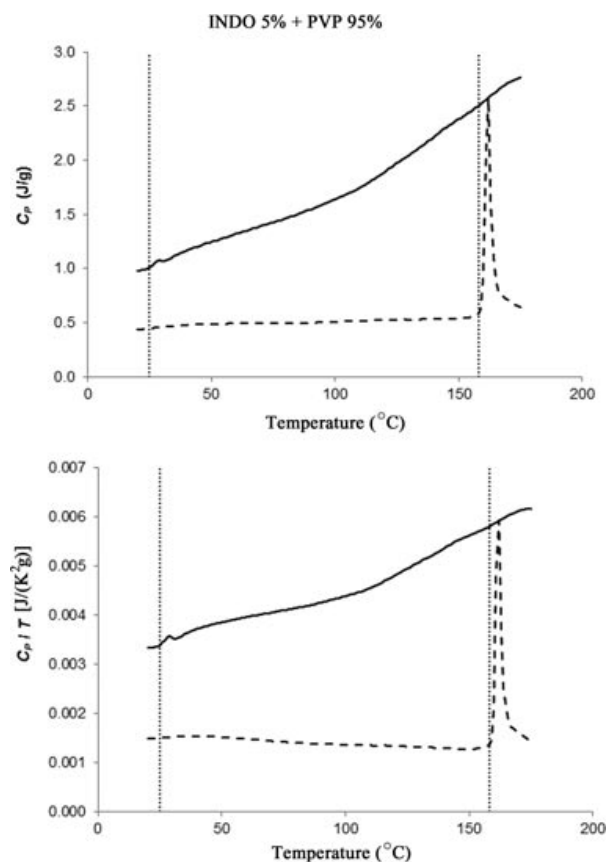


Figure 1. DSC data used to determine ΔH_1 and ΔS_1 for INDO 5% and PVP 95%.

Determining ΔG_{SS}

As discussed in the previous section, the solubility of a drug in a polymer is related to the chemical potential difference $\Delta\mu_{1,SS}$ between the dissolved and pure forms, which is related to the ΔG_{SS} due to making a solid solution by Eq. 3. The ΔG_{SS} depends on the change in enthalpy and entropy associated with producing the solid solution, as well as the temperature. Factors that can contribute to changes in the enthalpy and entropy include mixing, drug–polymer interactions, and heat capacity differences.

To calculate ΔG_{SS} , a continuous sequence of processes is postulated for which the initial state is unmixed polymer and solid drug in its most stable form, and the final state is a drug–polymer solid solution of uniform drug concentration and with no undissolved drug particles. The temperatures of the initial and final states are the same and denoted by T , which is the temperature at which the solubility is to be evaluated. The Gibbs energy, enthalpy, and entropy are state functions and extensive.²⁸ Thus, the postulated sequence of processes does not have to be the one actually used to make the solid solution—it is only required that the initial and final states of the postulated sequence be the same as those in the formulation method actually used. (In fact, the postulated sequence is different from the process used in this work.) This allows choosing a sequence for which the enthalpy and entropy changes in each step can be determined, and thus allows calculation of ΔG_{SS} .

The postulated sequence of processes is as follows.

1. Process 1: Heat the unmixed drug from the initial temperature T to the nominal drug melting temperature T_{M1} and melt the drug.
2. Process 2: Heat the unmixed polymer from the initial temperature T to T_{M1} .
3. Process 3: Mix the drug and polymer to make a solution at T_{M1} .
4. Process 4: Cool the solid solution from T_{M1} to T .

Not all of the processes postulated are isothermal, but because the starting and ending temperatures for the sequence are the same, the total change ΔG_{SS} is given by

$$\Delta G_{SS} = \Delta H_{SS} - T\Delta S_{SS} \quad (7)$$

where ΔH_{SS} and ΔS_{SS} are the total enthalpy and entropy changes resulting from making the solid solution, and are calculated as

$$\Delta H_{SS} = \sum_{n=1}^4 \Delta H(n) \text{ and } \Delta S_{SS} = \sum_{n=1}^4 \Delta S(n) \quad (8)$$

where $n = 1, 2, 3, 4$ denotes the particular process in the sequence, and $\Delta H(n)$ and $\Delta S(n)$ represent the enthalpy and entropy changes of the n th process. Equation 7 is a consequence of the fact that the enthalpy, entropy, and Gibbs energy are thermodynamic state functions. Thus, any process or sequence with the same starting and ending states (including any isothermal process at constant T) will have values of ΔH_{SS} , ΔS_{SS} , and ΔG_{SS} that are identical to the ones calculated using the sequence postulated above.²⁸ The contributions to ΔH_{SS} and ΔS_{SS} are described below for each process.

For Process 1, the change in enthalpy and entropy are

$$\Delta H(1) = \int_T^{T_{M1}} C_{P1} dT + n_1 \Delta h_{M1} \quad (9)$$

$$\Delta S(1) = \int_T^{T_{M1}} \frac{C_{P1}}{T} dT + \frac{n_1 \Delta h_{M1}}{T_{M1}} \quad (10)$$

where C_{P1} denotes the constant pressure heat capacity of the unmixed drug and Δh_{M1} denotes the molar enthalpy of melting of the drug at T_{M1} .

Denoting the constant pressure heat capacity of the polymer by C_{P2} , the enthalpy and entropy changes for Process 2 are

$$\Delta H(2) = \int_T^{T_{M1}} C_{P2} dT \quad (11)$$

$$\Delta S(2) = \int_T^{T_{M1}} \frac{C_{P2}}{T} dT \quad (12)$$

For Process 3, the enthalpy and entropy changes are calculated using the Flory–Huggins model,¹⁰ giving

$$\Delta H(3) = RT_{M1} n_1 \phi_2 \chi(T_{M1}) \quad (13)$$

$$\Delta S(3) = -R[n_1 \ln \phi_1 + n_2 \ln \phi_2] \quad (14)$$

Here, ϕ_1 and ϕ_2 denote the drug and polymer volume fractions in the solid solution, $\chi(T_{M1})$ denotes the drug–polymer interaction parameter at temperature T_{M1} , and R is the universal gas constant.

In Process 4, there are enthalpy and entropy changes due to the heat capacity that are analogous to those in Processes 1 and 2. There is also a change in the enthalpy of mixing due to the temperature change. From Eq. 13, the temperature term changes directly, plus $\chi(T)$ can change with the temperature.^{9,29} Denoting the constant pressure heat

capacity of the solid solution by C_{P12} , the enthalpy and entropy changes are given by

$$\Delta H(4) = \int_{T_{M1}}^T C_{P12} dT + [RTh_1\phi_2\chi(T) - RT_{M1}n_1\phi_2\chi(T_{M1})] \quad (15)$$

$$\Delta S(4) = \int_{T_{M1}}^T \frac{C_{P12}}{T} dT \quad (16)$$

Adding the contributions from Processes 1 to 4 gives the total enthalpy and entropy changes due to the formation a solid solution. Doing this, canceling appropriate terms, and noting that $\int_{T_{M1}}^T f(T)dT = -\int_T^{T_{M1}} f(T)dT$ for Eqs. 15 and 16 lead to

$$\Delta H_{SS} = \int_T^{T_{M1}} [C_{P1} + C_{P2} - C_{P12}] dT + n_1 \Delta h_{M1} + RTh_1\phi_2\chi(T) \quad (17)$$

$$\Delta S_{SS} = \int_T^{T_{M1}} \left[\frac{C_{P1} + C_{P2} - C_{P12}}{T} \right] dT + \frac{n_1 \Delta h_{M1}}{T_{M1}} - R(n_1 \ln \phi_1 + n_2 \ln \phi_2) \quad (18)$$

The total ΔG_{SS} is then found from Eq. 7. It is convenient to group terms and write

$$\Delta G_{SS} = \Delta G_1 + \Delta G_2 + \Delta G_3 \quad (19)$$

where

$$\Delta G_1 = \int_T^{T_{M1}} [C_{P1} + C_{P2} - C_{P12}] dT - T \int_T^{T_{M1}} \left[\frac{C_{P1} + C_{P2} - C_{P12}}{T} \right] dT \quad (20)$$

$$\Delta G_2 = n_1 \Delta h_{M1} \left(1 - \frac{T}{T_{M1}} \right) \quad (21)$$

$$\Delta G_3 = RTh_1\phi_2\chi(T) + RT(n_1 \ln \phi_1 + n_2 \ln \phi_2) \quad (22)$$

In evaluating Eq. 19, ΔG_1 and ΔG_2 can be determined from thermal analysis, and ΔG_3 can be calculated from the equations provided above. The heat capacities were calculated from the sample weights and specific heats.

The use of calculated values of χ has been established previously^{12,29} and calculated values were also

Table 1. Material Property Values used to Calculate the Interaction Parameter χ

	MW (g/mol)	δ at 25°C (J/cm ³) ^{1/2}	\bar{V}_1 at 25°C (cm ³ /mol)
GRIS	353	24.5	255
INDO	357	27.9	270
ITRA	706	26.5	510
PVP	—	26.0	—
L100	—	23.5	—
E100	—	20.4	—

Solubility parameters δ were calculated using the method of van Krevelen.⁸ Molecular weights (MW) and molar volumes \bar{V}_1 were taken from the literature for GRIS,³⁰ INDO,³¹ and ITRA.³²

Table 2. Calculated Values of χ at 25°C for Drug–Polymer Pairs

	GRIS	INDO	ITRA
PVP	0.561	0.747	0.399
L100	0.454	2.498	2.259
E100	2.100	6.518	8.087

Values were calculated using Eq. 23 and data in Table 1.

used in this study. For each drug–polymer pair, χ at 25°C was calculated using the equation⁹

$$\chi = \frac{\bar{V}_1(\delta_1 - \delta_2)^2}{RT} + 0.34 \quad (23)$$

where δ_1 and δ_2 denote the drug and polymer van Krevelen solubility parameters,⁸ and \bar{V}_1 denotes the drug molar volume. The factor of 0.34, although not universally used, was included because it improves correlations between the calculated and experimental results when the predicted value of χ is small.⁹ Table 1 lists the drug and polymer solubility parameters at 25°C, and drug molar volumes. Table 2 lists the calculated interaction parameters.

The volume fractions were calculated as⁹

$$\phi_1 = \frac{n_1}{n_1 + rm_2} \quad \phi_2 = \frac{rm_2}{n_1 + rm_2} = 1 - \phi_1 \quad (24)$$

where r is the polymer-to-drug molar volume ratio, which is commonly approximated as the degree of polymerization¹⁰, which can be calculated in terms of the molecular weight (MW) of the drug and polymer as

$$r = \frac{\text{MW polymer}}{\text{MW monomer}} \quad (25)$$

METHODS

Materials

- GRIS and INDO were obtained Sigma–Aldrich (St. Louis, Missouri).
- ITRA and methylene chloride were obtained from Spectrum Chemical (New Brunswick, New Jersey).

- PVP K30 was obtained from ISP Technologies (Wayne, New Jersey).
- L100 and E100 were obtained from Degussa (Parshippany, New Jersey).
- Ethanol was obtained from Pharmaco Products (Brookfield, Connecticut).
- Methanol was obtained from J.T. Baker (Phillipsburg, New Jersey).

Preparation of Solid Solution Formulations

Formulations were prepared by solvent evaporation. The drug and polymer were both dissolved in a suitable solvent, and then the solvent was removed using a rotary evaporator (ethanol and methylene chloride at 70°C, methanol at 62°C) to form the solid formulation. Formulations were further dried under a vacuum for at least 12 h.

Thermal Analysis—Differential Scanning Calorimetry

Thermal analysis was carried out using a Q200 differential scanning calorimeter (TA Instruments, Wilmington, Delaware). Samples were accurately weighed and placed in aluminum pans with punctured lids. A three step procedure was performed on all samples. (1) Samples were heated from room temperature to approximately 10°C–20°C above the boiling point of the solvent used to make the solid solution, then held at that temperature for 1 min. (2) Samples were cooled to –10°C, and held at that temperature for 1 min. (3) Samples were heated to approximately 20°C above the drug melting temperature. All heating/cooling rates were 5°C/min.

To satisfy the assumptions of the model equations, it was required solid solution samples show no effects from residual solvent or undissolved drug particles in the third step, which was used in the calculation of ΔG_1 . Samples not satisfying these requirements were not used in the model analysis. The parameters of the first step were chosen, with some trial and error, to remove residual solvent without melting any drug particles that might be present. The data from the third step were examined to ensure there was no evidence of solvent evaporation or peaks associated with melting of undissolved particles.

Plots to Evaluate ΔG_{SS} as a Function of Drug Loading

For each drug load, $\Delta G_{SS}/w_2$ was determined using Eq. 19. Drug loads were expressed as weight fractions f_1 , and plots of $\Delta G_{SS}/w_2$ versus f_1 were constructed. A similar approach was employed for plots of $\Delta G_1/w_2$, $\Delta G_2/w_2$, and $\Delta G_3/w_2$ versus f_1 , according to Eqs. 20–22.

To determine $\Delta G_{SS}/w_2$ for any formulation with drug and polymer weight fractions f_1 and f_2 , each term in Eq. 19 was evaluated per gram of formulation (denoted as ΔG_1^* , ΔG_2^* , ΔG_3^* , and ΔG_{SS}^*). Subsequently,

$\Delta G_{SS}/w_2$ was calculated as

$$\frac{\Delta G_{SS}}{w_2} = \frac{\Delta G_{SS}^*}{f_2} \quad (26)$$

Heat capacity data were obtained from the third step of differential scanning calorimetry (DSC), as described in the section *Thermal analysis—Differential Scanning Calorimetry*, as specific heats, so Eq. 20 was evaluated using the modified form

$$\Delta C_P^* = f_1 C_{P1}^* + f_2 C_{P2}^* - C_{P12}^* \quad (27)$$

where C_{P1}^* , C_{P2}^* , and C_{P12}^* represent the experimentally obtained specific heats of the drug, polymer, and solid solution, respectively. The corresponding enthalpy and entropy changes per gram due to heating were calculated as

$$\Delta H_1^* = \int_{T_{M1}}^{T_{M11}} \Delta C_P^* dT \quad (28)$$

$$\Delta S_1^* = \int_{T_{M1}}^{T_{M11}} \frac{\Delta C_P^*}{T} dT \quad (29)$$

Equations 28 and 29 were numerically integrated using the trapezoid rule. An example of the calculations carried out to evaluate Eqs. 27–29 is given in Table 3, which shows the start of the calculation for the case of INDO 5% (w/w) and PVP 95% (w/w). Figure 1 shows the result of the entire calculation. The top part of Figure 1 shows two curves, $f_1 C_{P1}^* + f_2 C_{P2}^*$ versus T and C_{P12}^* versus T . The bottom part shows two other curves, $(f_1 C_{P1}^* + f_2 C_{P2}^*)/T$ versus T and C_{P12}^*/T versus T . The two vertical lines denote 25°C and 158°C (corresponding to the onset of melting for the pure INDO). The top part of Figure 1 shows that ΔH_1^* corresponds to –1 times the area between the two curves and the two vertical lines. Similarly, the bottom part of Figure 1 shows that ΔS_1^* corresponds to –1 times the area between the curves and the vertical lines.

In Eqs. 21 and 22, n_1 and n_2 were taken as the number of moles of drug and polymer in 1 g of the formulation. In evaluating ΔG_3 from Eq. 22, the interaction parameters were calculated from Eq. 23 using values listed in Table 1.

RESULTS

To be consistent with the model, only solid solutions with no undissolved drug particles were considered in the data analysis. Drug particles were considered absent when there were no observed melting peaks in DSC thermograms. X-ray diffraction was performed when needed as a secondary check. Nine systems with

Table 3. DSC Data and Start of Calculation of ΔH_1 and ΔS_1 for INDO 5% plus PVP

Temperature (K)	C_{P1}^*	C_{P2}^*	C_{P12}^*	ΔC_P^*	$\frac{\Delta C_P^*}{T}$	Cumulative ΔH_1 (J/g)	Cumulative ΔS_1 [J/(K g)]
298	0.307	0.453	1.005	-0.559	-0.00188	0	0
299	0.335	0.454	1.027	-0.579	-0.00194	-0.569	-0.00191
300	0.360	0.455	1.049	-0.599	-0.00199	-1.158	-0.00387
301	0.381	0.456	1.071	-0.619	-0.00205	-1.767	-0.00590
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮

C_{P1}^* , C_{P2}^* , and C_{P12}^* represent the experimentally obtained specific heats of the drug, polymer, and solid solution, respectively. ΔC_P^* is given by Eq. 28, where $f_1 = 0.05$ and $f_2 = 0.95$. The specific heats are in units of J/(K g).

various drug fractions were evaluated for solubility at 25°C. They were: GRIS in PVP, L100, and E100; INDO in PVP, L100, and E100; and ITRA in PVP, L100, and E100.

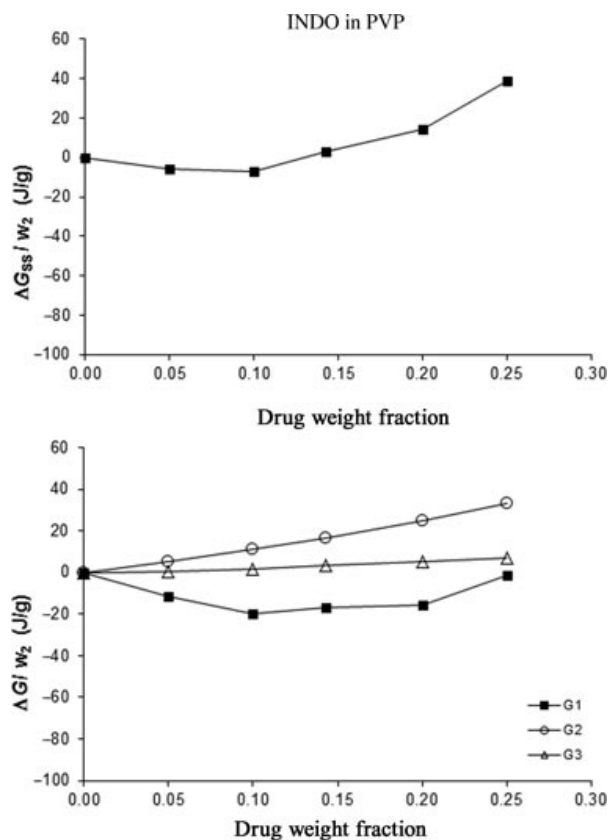
The experimental results were sensitive to changes in the dissolved drug loading, and allowed straightforward construction of plots of $\Delta G_{SS}/w_2$ versus the drug fraction f_1 . All plots of $\Delta G_{SS}/w_2$ versus f_1 showed a negative slope at low drug fractions that transitioned to a positive slope when f_1 was increased sufficiently. For some, there was an identifiable minimum value, which was taken as the solubility. Currently, there is no physical model equation that can be used to fit for the values of f_1 corresponding to minima of $\Delta G_{SS}/w_2$ versus f_1 plots. However, in most cases, quadratic fits were readily performed using points near the minima to identify the minima locations. In a few cases, the plot was somewhat flat at the bottom, with no clear location for the minimum, and the maximum stable drug load was identified by visually estimating the drug load at which the plot started to display a positive slope.

Figure 2 shows the results for INDO/PVP formulations. As seen in the top part, the $\Delta G_{SS}/w_2$ versus f_1 plot displays a minimum indicating up to ~8% (w/w) drug loading was stable, so the solubility was taken as $f_1 \sim 8\%$. Figure 3 shows the results for INDO/E100, which indicated a solubility of $f_1 \sim 9\%$. Data for the INDO/L100 formulations (not shown) indicated a solubility of $f_1 \sim 10\%$.

Data for the GRIS and ITRA formulations are not shown, but were qualitatively similar. For GRIS, the solubility is $f_1 \sim 9\%$ in PVP, $f_1 \sim 12\%$ in L100, and $f_1 \sim 9\%$ in E100. For ITRA, the solubility is $f_1 \sim 9\%$ in PVP, $f_1 \sim 13\%$ in L100, and $f_1 \sim 8\%$ in E100.

From Eq. 21, ΔG_2 and the slope of $\Delta G_2/w_2$ versus f_1 are positive over the range of drug loads evaluated. However, ΔG_3 and the slopes are negative for most of the formulations. Exceptions to this are the INDO/E100 and ITRA/E100 formulations, where the slopes of $\Delta G_2/w_2$ versus f_1 are positive due to the relatively large positive value of χ .

In all formulations for drug loads up to the solubility, the magnitude of the slope of $\Delta G_2/w_2$ versus f_1 is greater than the magnitude of the slope of $\Delta G_3/w_2$ versus f_1 , so the slope of $(\Delta G_2 + \Delta G_3)/w_2$ versus f_1

**Figure 2.** INDO in PVP results at 25°C for ΔG_{SS} and contributions of ΔG_1 , ΔG_2 , and ΔG_3 .

is positive in all cases. However, over the same loading range, the slope of $\Delta G_1/w_2$ versus f_1 is negative and its magnitude is greater than that of $(\Delta G_2 + \Delta G_3)/w_2$ versus f_1 , which results in a negative slope for $\Delta G_{SS}/w_2$ versus f_1 at loads up to the solubility in all cases.

DISCUSSION

This paper presents a method to calculate the solubility of a drug in a solid polymer using thermal analysis data, and is novel in part because it includes effects because of the heat capacity differences between the solid solution and the unmixed components. These heat capacity changes represent a major difference

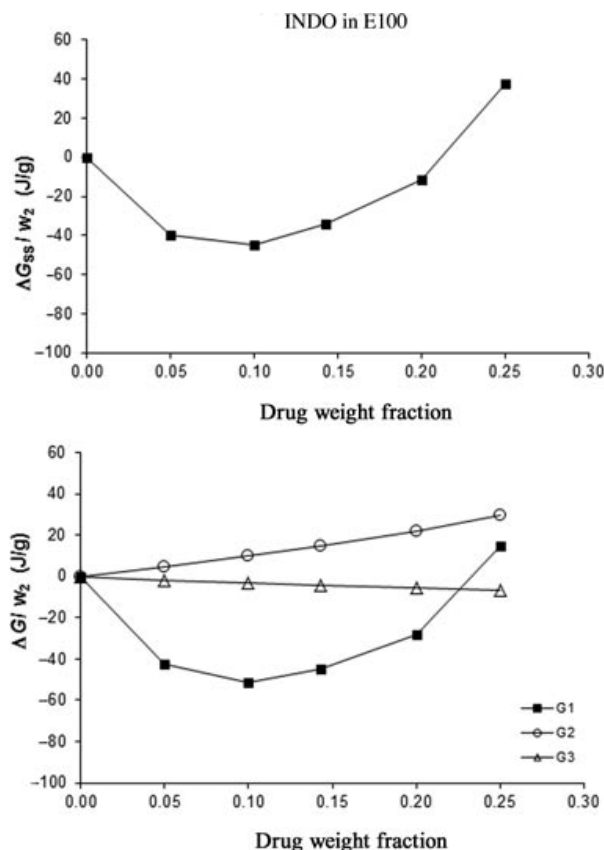


Figure 3. INDO in E100 results at 25°C for ΔG_{ss} and contributions of ΔG_1 , ΔG_2 , and ΔG_3 .

between liquid versus solid solvent media. Most liquid solvents have negligible structure and dissolving a drug with poor aqueous solubility typically has a small relative effect on the heat capacity. On the contrary, dispersing drug molecules in a solid polymer alters the molecular level motion of both the drug and polymer compared with their unmixed states, which will result in altered heat capacities.

One of the goals of this work was to calculate the effect of the heat capacity differences on the solubility of the drug in the polymer. The approach taken was to calculate the contribution of the heat capacity differences to ΔG_{ss} , which would then allow thermodynamic arguments to be applied to determine $\Delta\mu_{1,ss}$ and the drug solubility. The thermodynamic sequence of processes described in this paper was chosen to facilitate this calculation, and led to ΔG_1 as given by Eq. 20.

The results indicate that the heat capacity differences are an important factor in determining the drug solubility in the polymers at 25°C. As noted in the *Results* section, the slope of $(\Delta G_2 + \Delta G_3)/w_2$ versus f_1 is positive in all cases at 25°C. It was the inclusion of $\Delta G_1/w_2$ versus f_1 that numerically resulted in the

negative slopes at drug loads below the solubility, and minima in plots of $\Delta G_{ss}/w_2$ versus f_1 .

Although the basis of the approach is thermodynamic, some parameters are obtained by calculation. For instance, the interaction parameter χ was calculated using an established method. Errors arising from calculating χ are not likely to significantly affect the determined solubilities for the systems and temperatures studied in this work, as evidenced by the large contribution of ΔG_1 compared with ΔG_3 . However, at higher temperatures, errors in the evaluation of χ could be more significant, and alternative methods to χ might need to be evaluated.

For a given value of $\chi(T)$, even if heat capacity effects are neglected, there is still a calculated solubility of the drug in the polymer, but it is much smaller than what is calculated when heat capacity effects are included. This can be seen by not including ΔG_1 in Eq. 19, applying Eq. 3, then setting $\Delta\mu_{1,ss} = 0$. This gives

$$0 = \frac{\Delta h_{M1}}{R} \left(\frac{1}{T} - \frac{1}{T_{M1}} \right) + \phi_2^2 \chi(T) + \ln(1 - \phi_2) + \left(1 - \frac{1}{r} \right) \phi_2 \quad (30)$$

Equation 30 can be solved numerically for ϕ_2 , from which the corresponding f_1 can be calculated. Numerically, this is sensitive to the value of the interaction parameter in that making χ less positive will increase the drug solubility calculated from Eq. 30. Using the interaction parameter values from Table 2 and nominal drug melting enthalpies, and noting that $1/r < 1$ for the polymers in this study, the calculated solubilities at 25°C without including heat capacity effects were $f_1 \sim 0.5\%$ for INDO/PVP, and $f_1 < 0.1\%$ for all other drug-polymer combinations in this study.

On the contrary, if the solubility of GRIS in PVP at 25°C is taken as $f_1 \sim 10\%$, for example, this can be accounted for without including the contribution from heat capacity differences by setting $\chi = -4.60$ in Eq. 30. However, this value of χ differs greatly from the value of 0.561 calculated using solubility parameter methods. Although calculated values of χ should not be taken as absolutely accurate, the discrepancy is large and corroborates the inclusion of ΔG_1 , which helps to resolve this apparent conflict. Although the value of f_1 calculated in this study was used for the comparison here, this notion holds regardless of how the solubility is determined. Such numerical discrepancies would arise for the materials used in this study for any case in which the determined value of f_1 exceeds approximately 1% at room temperature.

Although the data indicated that the heat capacity effects are important at 25°C, at higher temperatures the energy contributions from ΔG_3 , which can

be associated with mixing, would be expected to become greater relative to those of ΔG_1 and ΔG_2 . This is because the temperature term multiplicatively increases the contributions of the mixing entropy and enthalpy terms in Eq. 22. In addition, as the temperature increases, $\chi(T)$ will become less positive T is increased, typically according to^{9,29}

$$\chi(T) = A + \frac{B}{T} \quad (31)$$

As mentioned above, less positive values of $\chi(T)$ predict higher solubility. In addition, the contribution of ΔG_2 in Eq. 21 will become smaller as T is increased because T/T_{M1} is closer to 1. Also, there is significantly more molecular motion above the T_g than below it, so heat capacity effects due to the increased molecular motion might be of less relative importance at higher temperatures. Thus, this work does not contradict earlier reports of work performed at higher temperatures, but instead provides an enhanced understanding of determining drug solubilities at typical storage temperatures.

Aside from the inclusion of heat capacity effects in the thermodynamic model, this method of this paper differs experimentally from previous solid state thermal methods in two important respects. First, it does not rely solely on data obtained at elevated temperatures. Second, it avoids the presence of undissolved drug particles.

Methods that obtain data at elevated temperatures, such as those employing melting or melting point depression, are not directly applicable to the estimation of behavior near room temperature because there are no general models to relate them. In the approach presented here, however, ΔG_1 reflects physical behavior over all temperatures from the storage to the drug melting temperature. Thus, the need to project behavior from elevated to lower temperatures is replaced by the fundamental thermodynamic information contained in ΔG_1 and ΔG_{ss} .

Avoiding undissolved drug particles presents a potential advantage over methods that implicitly require their presence, such as those based on the observed heats of melting and melting point depression. As noted in the *Introduction* section, the amount of undissolved drug present at lower temperatures can be underestimated because of the partial drug dissolution during heating in the thermal analysis.^{11,23} Also, calculating $\chi(T)$ from a depressed drug melting temperature requires knowing the local volume fractions of the dissolved drug and polymer ϕ_1 and ϕ_2 in the vicinity of the undissolved particle surfaces. In practice, they are not known but instead approximated by the overall volume fractions in the formulation, which can be very different.¹¹ Such errors in

the local volume fractions can introduce inaccuracies in the calculation of χ at elevated temperature.

Because the method of this paper is based on a thermodynamic model, some points are worth mentioning. First, the results are theoretically independent of the process actually used to produce the solid solutions, as long as the final formulations made by different methods are identical on a molecular scale. Because the method of preparation can affect the formulation properties somewhat, some variation in results would be expected when comparing solid solutions made by solvent evaporation, hot melt extrusion, and so on. Second, although thermodynamic models provide no method for assessing kinetics or shelf lives, the analysis may benefit further modeling beyond determining the equilibrium solubility. For instance, in supersaturated solid solutions, $\Delta\mu_{1,ss}$ might be related to net energy barriers for diffusion and/or precipitation in the solid state, and thus, might provide a potential link to future kinetic models to predict shelf lives. Finally, knowledge of $\Delta\mu_{1,ss}$ may be useful in future models for the prediction of dissolution enhancement of a drug formulated in a supersaturated solid solution.

CONCLUSIONS

A method is presented to determine the solubility of a drug in a solid polymer near room temperature. The basis of the method is a thermodynamic model that includes thermodynamic contributions from heat capacity differences between the drug-polymer solid solution and the unmixed components. We believe that this is the first report in which the consequences of heat capacity differences between the unmixed drug and polymer versus the solid have been considered as part of a thermodynamic model. Equations and methods are given to quantitatively predict the solubility of a drug in a polymer from thermal analysis data and known thermodynamic equations. It was found that the heat capacity effects were very important in determining the drug solubility in polymers at 25°C, and must be considered at typical storage temperatures.

The information obtained from this work is potentially beneficial because it would establish the maximum stable drug concentration in a drug-polymer solid solution at a particular storage temperature. In addition, determination of the dissolved drug concentration at which the solution becomes unstable can be performed relatively quickly and easily.

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