Determination of the Solubility of Crystalline Low Molar Mass Compounds in Polymers by Differential Scanning Calorimetry

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ABSTRACT: A mathematical equation has been derived to calculate the liquidus for a binary system consisting of an amorphous polymer and a crystalline low molar mass compound. The experimental input to this equation is an interaction enthalpy, which is derived from the variation of the melting enthalpy with composition in differential scanning calorimetry (DSC) experiments. The predictive power of the equation has been tested with mixtures of acetylsalicylic acid, carbamazepine, or intraconazole with poly(ethylene glycol) as well as mixtures of carbamazepine with poly(acrylic acid), poly(hydroxystyrene), or poly(vinylpyrrolidone). It has been confirmed that the evaluation of the melting enthalpy in DSC is a suitable method to identify the preferred solute–polymer combinations for thermodynamically stable molecular dispersions. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

Keywords: amorphous; calorimetry (DSC); liquidus; mathematical model; polymeric drug carrier; solid dispersion; solid solution; solubility; stability; thermodynamics

INTRODUCTION

Many technical applications require that polymers are mixed on a molecular level with low molar mass substances. Additives such as antioxidants or plasticizers have to be homogeneously distributed in the polymer matrix to have an optimal effect on the material properties. Alternatively, polymers modify the properties of molecularly dispersed low molar mass substances. An application, which has found increasing attention over several decades, consists of amorphous solid solutions of pharmaceutical or agricultural active ingredients.[1–7] A primary purpose for preparing these amorphous formulations is to improve the bioavailability of the active ingredient. This is based on the consideration that amorphous solids represent a state of high energy as compared with their crystalline counterparts. This translates into a higher solubility in a given liquid, although the improvement is noticeably lower than predicted from a simple evaluation of thermal properties.[8,9] Dispersing the active ingredient in a (typically hydrophilic) polymer is intended to prevent the spontaneous recrystallization of the amorphous material.

No matter which application is considered, it is important that the amorphous mixtures have long-term stability. In principle, *kinetic* stability over the intended period of usage suffices, and in many instances, demixing and crystallization may be suppressed successfully by the glassy state of the system over a long time. However, higher reliability is given when the mixture is *thermodynamically* stable. Thermodynamic stability is synonymous with the requirement that the solubility limit for the most stable crystalline form of the solid in the polymer matrix is not exceeded. The determination of the solubility of low molar mass substances in polymers has consistently been of long-standing concern in the context of polymer additives[10] and has found renewed attention with regard to molecular solid dispersions.

In general, solubility can be driven by entropy and by enthalpy. With regard to the entropy term, the Flory-Huggins theory states that it decreases rapidly with increasing molar mass of at least one of the components.[11,12] In addition, the possibilities to influence the mixing entropy by chemical means are very limited. Thus, the relevant contribution to miscibility comes from the mixing enthalpy, and the pivotal parameter to change the solubility is the strength of the interactions between the polymer and the solute.

Determination of solubility in polymers is a nontrivial task. Molecular mixing and demixing processes in polymers can be extremely slow because of the highly viscous or even glassy state of the system. Nonetheless, numerous methods have been proposed to determine the degree of compatibility of low-molar mass compounds with polymers. These include optical methods, correlation of octanol–water and polymer–water partition coefficients,[13] extrapolation from solubilities in low molar mass analogues,[12] equilibration and diffusion experiments with stacks of polymer sheets and additives,[14,15] and comparison of Hildebrand solubility parameters (δ).[16] A prominent position is taken by thermoanalytical methods.[17] A classical approach is based on the evaluation of the number of glass transitions.[18–24] The presence of only one T_g at an intermediate temperature indicates that the components are mixed on a molecular level in the amorphous state. With this approach, essentially no information is gained on the homogeneity of the mixture.[25] Also, no statement can be made on the thermodynamic equilibrium involving the crystalline form of the solute,[12b] unless the method is combined with long-term storage tests. Furthermore, glass transitions are sometimes difficult to detect—in particular in the case of mixtures—which may lead to incorrect conclusions.

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In an extension of the T_g approach, the concentration dependence of the glass transition temperature has been used to quantify the solute content.[26,27] The Gordon-Taylor, Couchman-Karasz, and Fox equations have been applied with variable success for a theoretical prediction of the interdependence between T_g and composition.

As an alternative class of evaluations, the melting point of the crystalline solute has been investigated. Several authors have analyzed the decrease of the *melting temperature*, which results from the addition of increasing amounts of polymer.[12,28–32] In some cases, this melting point depression has been used to determine the Flory–Huggins interaction parameter (χ) between polymer and solute.[12,30,32] The interaction parameter gives an indication of the compatibility of the two amorphous components and permits a calculation of the solubility curve for the crystalline solute.[32] However, correct results from melting point depression can only be expected when the system is close to equilibrium during the differential scanning calorimetry (DSC) measurement. This condition might not be fulfilled in the presence of a highly viscous polymer melt, and the observed melting point may be shifted to a higher temperature relative to the equilibrium value for kinetic reasons. On the other hand, degradation problems may arise when the mixtures are equilibrated for an extended time at an elevated temperature. Furthermore, peak broadening with increasing polymer content will lower the accuracy for determination of the transition endpoint.

In another approach, the *melting enthalpy* of the undissolved fraction of a crystalline drug was used for concentration determination in a silicone rubber.[33,34] The concentration at which the melting enthalpy dropped to zero was interpreted as the drug solubility either at the melting point of the drug[33] or at ambient temperature.[34] Similar investigations were performed with physical mixtures of felodipine and a glassy methacrylate copolymer,[31] where it was recognized that a positive transition enthalpy should be observed at all concentrations under such circumstances and that the determination of the solubility limit is no longer straight forward.

Forster et al.[19] contented themselves with using the decrease of the melting enthalpy as a qualitative indication of the miscibility between drug and polymer. Bellantone et al.[35] recently combined experimental melting and heat capacity data from DSC with calculated mixing enthalpies and entropies based on the Flory–Huggins theory. This provided the free energy of solid solution formation. The solubility limit was derived from the minimum of the free energy per mass of dissolved drug when plotted as a function of the drug content.

None of these methods is fully satisfying with regard to the quality of the results, the experimental effort or the applicability to pharmaceutically relevant systems with glassy polymers. A tempting alternative to experimental work are theoretical calculations. Such calculations are typically based on solubility parameters.[10,12,15,16,19] The underlying model assumes isotropic interaction forces,[36] whereas directed interactions (typically hydrogen bonds) will dominate for the most promising polar systems. As a result, the predictions cannot be expected to be particularly accurate.[12a] We therefore propose a new experimental approach for solubility determination, which is based on an in-depth analysis of the melting enthalpies from DSC measurements.

THEORY

In general, the solubility curve (liquidus) of any crystalline solute is defined by the van't Hoff equation[37,38]

$$\left(\frac{\partial \ln a}{\partial T}\right)_p = \frac{\Delta_s H}{RT^2} \tag{1}$$

with a being the activity of the solute in solution, T the absolute temperature, and $\Delta_s H$ the enthalpy for the solid–liquid phase transition at the given temperature and activity. Under the assumption that an ideal solution is formed (i.e., that the activity equals the mole fraction x of the solute in the mixture and that $\Delta_s H$ does not depend on temperature or composition), integration of Eq. (1) leads to the Schröder–van Laar equation

$$\ln x = -\frac{\Delta_{\text{fus}} H}{R}\left(\frac{1}{T_x} - \frac{1}{T_{\text{fus}}}\right) \tag{2}$$

where $\Delta_{\text{fus}} H$ is the melting enthalpy of the pure solute (which is identical to $\Delta_s H$ under the given assumptions), T_{fus} the melting temperature of the pure solute, and T_x the melting temperature at the composition x.

In a real system, the interactions between molecules of the same type and molecules of different types usually will be different. As a consequence, the melting enthalpy of the mixture ΔH_{mix} will vary with composition. The simplest approach to account for this is to assume a concentration-independent interaction enthalpy Δh according to:

$$\Delta H_{\text{mix}} = w_{\text{A}} \cdot \Delta_{\text{fus}} H - w_{\text{A}} \cdot (1 - w_{\text{A}}) \cdot \Delta h \tag{3}$$

with w_{A} being the mass fraction of the solute and ΔH_{mix} the experimentally observed melting enthalpy (which may equally well be termed heat of solution) for a given amount of the mixture. Scaling the observed melting enthalpy by the amount of solute leads to

$$\Delta_s H = \frac{\Delta H_{\text{mix}}}{w_{\text{A}}} = \Delta_{\text{fus}} H - (1 - w_{\text{A}}) \cdot \Delta h \tag{4}$$

The mass fraction w_{A} can be written in terms of the mole fraction x of the solute and the molar masses M_{A} and M_{P} of the solute and the polymer, respectively. Eq. (4) then becomes

$$\begin{aligned}\Delta_{\text{s}} H &= \Delta_{\text{fus}} H - \left(1 - \frac{x \cdot M_{\text{A}}}{x \cdot M_{\text{A}} + (1-x) M_{\text{P}}}\right) \cdot \Delta h \\ &= \Delta_{\text{fus}} H - \left(1 - \frac{x \cdot M_{\text{A}}}{x(M_{\text{A}} - M_{\text{P}}) + M_{\text{P}}}\right) \cdot \Delta h\end{aligned} \tag{5}$$

Under the assumption that the activity is again equal to the mole fraction, this expression can be inserted into Eq. (1). Separation of the variables gives

$$\int_x^1 \frac{1}{\Delta_{\text{fus}} H - \left(1 - \frac{x \cdot M_{\text{A}}}{x(M_{\text{A}} - M_{\text{P}}) + M_{\text{P}}}\right) \cdot \Delta h} d \ln x = \int_{Tx}^{Tfus} \frac{1}{RT^2} dT \tag{6}$$

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