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A novel approach for measuring room temperature enthalpy of mixing and associated solubility estimation of a drug in a polymer matrix

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ABSTRACT

The utility of amorphization of drug molecules, such as enhanced solubility, dissolution rate and oral bioavailability, has been well exemplified in the literature. Yet, the application of this technique is often hindered by the crystallization liability of the drug. Amorphous solid dispersions (ASD), in which polymers are mixed with the amorphous drug, are often utilized to maintain the amorphous form. Several approaches have been illustrated in the literature to quantify the degree of mixing of drug and polymer. Although successful quantification has been demonstrated, all of these approaches probe the mixing energies at temperatures close to the melting temperature and, thus, require an extrapolation to room/storage temperature. Hence, an approach to directly estimate the drug-polymer extent of mixing at room temperature would enable a more accurate prediction of the physical stabilities. Herein, solution calorimetry was used to determine enthalpies of mixing of drug and polymer dispersions. These are necessary for the estimation of the Flory-Huggins interaction parameter, and associated free energy of mixing function. The estimated free energy of mixing, in turn, enabled the calculation of the drug solubility in the polymer system, which is a critical thermodynamic parameter in predicting the physical stability of an ASD.

1. Introduction

The utility of metastable polymorphs, salts, co-crystals, and amorphous solid dispersions is motivated by the requirement to increase the rate of dissolution and kinetic solubility of new chemical entities (NCEs) with the intention to increase oral bioavailability [1–3]. The current development paradigm includes several opportunities to characterize the kinetic solubility enhancement and physical stability of NCEs. However, many of these approaches rely on exposure to stressed conditions and extrapolation of indirect measurements to assess first principle properties of the system [4–8].

Stability assessment of solid dispersion formulations are significantly less well developed and are often restricted to extensions of approaches developed in polymer chemistry some fifty years ago [9]. Some of the earliest examples of applying these principles to pharmaceutical solid dispersions include the application of solubility parameters for the determination of drug-polymer miscibility performed by Greenhalgh and co-workers [10], or the recent application of the Bagley plot [11]. However, many pharmaceutical systems still exhibit recrystallization even when the solubility parameter difference ($\Delta\delta$) < 7 $MPa^{1/2}$ required for miscibility [11] is met. This requirement in the solubility parameter approach would suggest that Flory-Huggins interaction parameter (χ) values up to 5 would be associated with miscibility, which is not supported by current theory and suggests a gap in the

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fundamental understanding of pharmaceutical dispersions. Beyond this, such approaches provide no quantitative measurement across a compositional range. Moreover, the solubility parameter approach only allows for endothermic mixing, which is not the case for the systems studied here.

High temperature measurements using melting point depression or direct measurement of drug dissolved in a material above the glass transition temperature have also been utilized to determine enthalpic interactions [12,13]. While an accurate description near the conditions of observations, the temperature dependence of intermolecular interactions may not be representative of those at room temperature. Application of differential scanning calorimetry (DSC) and Hess' law for determination of interactions at room temperature requires the use of additional measurements of both the dispersion and pure components as well as extrapolations of these measurements from high to low temperature, which may introduce significant errors [14]. Another approach is to measure the solubility of an API in low molecular weight analogs of the polymer, which mixtures reach equilibrium in a reasonable time frame, and adjust for the difference in entropy by extrapolating solubility to higher molecular weights [15]. This approach may be useful in some cases but not all polymers have liquid low molecular weight analogs and end-group effects and steric effects may also impact the result. Based on the applicability of current methods, it would be useful to develop an approach which would effectively eliminate the issues associated with each of the methods outlined above. An ideal method would allow for measurement of the heat of mixing any glassy polymer and API system at room temperature. Further, the ideal method would allow for the activity to be measured across temperatures and compositions.

Solution calorimetry has previously been used in pharmaceutical applications for understanding the relative stability between polymorphs [16–18]. The difference in the heat of solution of polymorph A and polymorph B gives precisely the energetic difference between the two forms, as shown in Fig. 1. This approach can be extended to directly measure the difference in energy between an amorphous API and the crystalline counterpart [19]. The sample can be measured at the temperature of choice and requires no continuous heating as would be done in a DSC experiment. Although recrystallization or form change can occur upon contact with the solvent, as long as the solvent readily dissolves the drug in any form, the sum of the total heat signature will have the same difference between the original solid state and the final state in solution. Solubility measurements are also often used to determine the relative stability between polymorphs. However, the energetic differences cannot always be determined since recrystallization may occur during the solubility measurement. Further, DSC can sometimes be used to measure the energetic differences but adequate resolution is not always achieved and changes in relative stability with temperature may make these measurements difficult in certain cases. Solution calorimetry is therefore a useful tool to determine the relative stability of materials and potentially characterize fundamental material properties without the limitations of other commonly used methods. As an example, applying solution calorimetry to cyclopenthiazide polymorphs, Form I and II gave similar heats of solution (~6 kJ/mol) while form III yielded a heat of solution of 15 kJ/mol which indicated that Form III was the most stable polymorph [20].

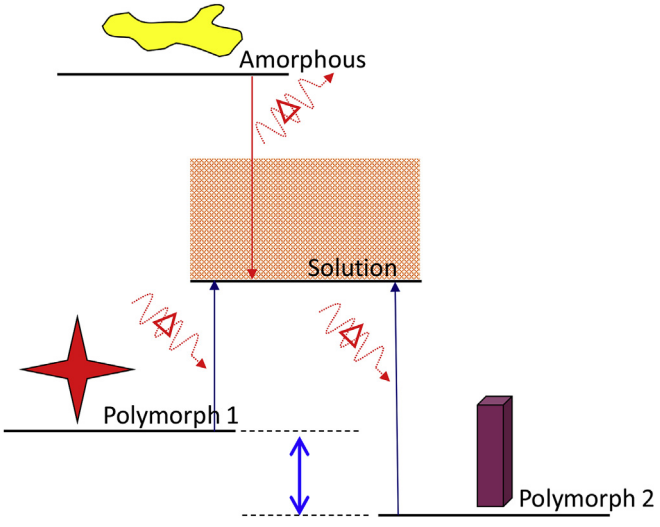

Fig. 1. Schematic illustrating the enthalpy differences between crystalline and amorphous forms. The difference in the heat of solution of the drug in the amorphous form and the crystalline form gives the total enthalpy difference between the two forms.

Extensions of solution calorimetry have been used to determine the heat of mixing (ΔH_{mix}) for polymer systems. Utilizing this approach, the heat of solution can be measured along with measurements of specific heat changes to account for relaxation, allowing for accurate determination of the heat of mixing. Applying this technique to polymer blends has led to the successful determination of ΔH_{mix} for a number of systems. For example, Weeks and co-workers demonstrated a negative ΔH_{mix} for all compositions of poly(2,6-dimethyl phenylene oxide) and polystyrene which was supported by the observed compatibility of the blend [21]. Other examples of characterizing polymer blends with solution calorimetry have included poly(vinyl chloride):poly(ethylene-co-vinyl acetate) [22] and polystyrene and poly(α-methylstyrene) [23]. It is important to acknowledge that, similar to the melting-point depression method, this method is not suitable for highly endothermic heats of mixing since stable and fully mixed dispersions will be required for the measurements.

The objective of the present study was first to demonstrate the utility of solution calorimetry for the determination of ΔH_{mix} for a series of drug-polymer solid dispersions (Fig. 2). Within the scope of this study, heat of solution measurements for solid dispersions were performed in conjunction with configurational heat capacity (ΔC_p) assessments using DSC. Measured values were used to directly determine the ΔH_{mix} of the systems at room temperature. This data was then extended using theories of Flory-Huggins and Hoffman to estimate free energies of mixing and crystallization, respectively, which in turn enabled the estimation of solubility of the drug substance in the polymer. The Flory-Huggins model provides an estimate of the translational entropy change associated with mixing small molecules with polymers. An assumption also made in the study was that the measured ΔH_{mix} values can be used as the sole measured quantities in determining the Flory-Huggins interaction parameter (χ), in accordance with the original model's assumptions which treats this parameter as a purely enthalpic contribution.

2. Experimental

2.1. Materials

Sucrose, with a melting temperature (T_m) of 188 °C [24], felodipine (T_m: 143 °C) [25], indomethacin (T_m: 160 °C) [26] and itraconazole were purchased from Sigma-Aldrich Co. (St. Louis, MO). Polyvinylpyrrolidone (PVP) K29-32, with a glass transition temperature (T_g) of 164 °C [27] was obtained from ISP Corporation (Newtown, PA). Eudragit E PO was obtained from Evonik (Piscataway, NJ). The chemical structures of the compounds used in this study are given in Fig. 3.