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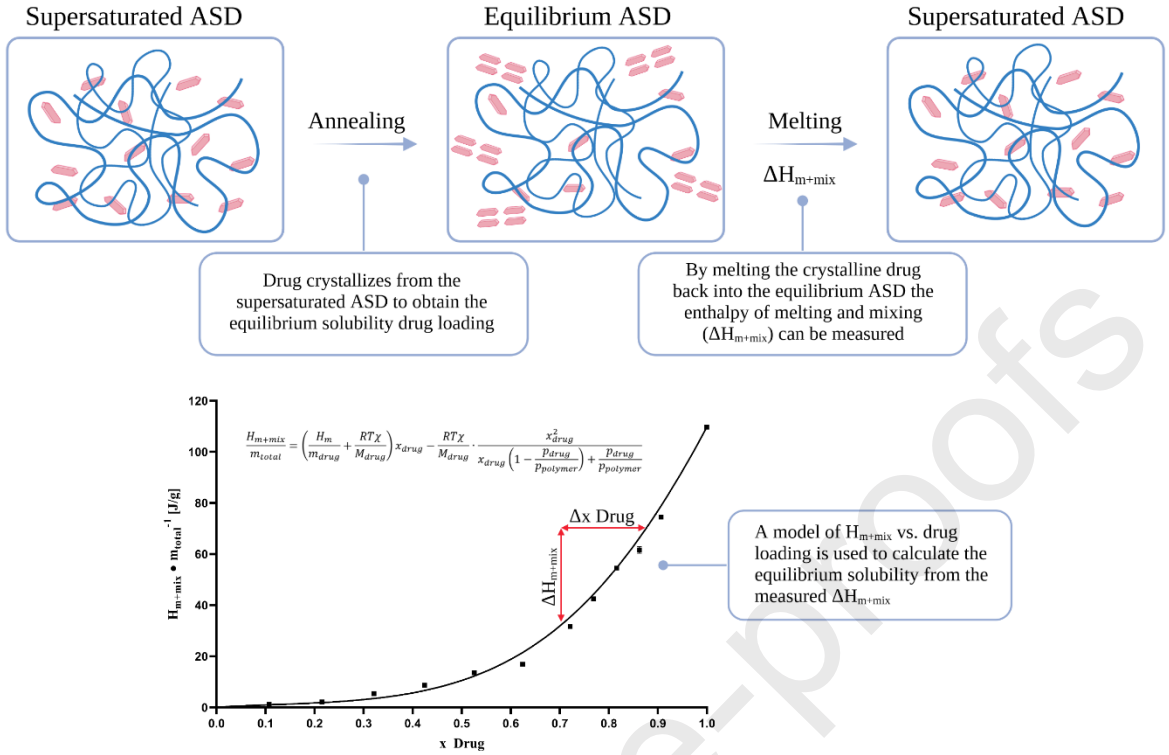
Graphical abstract



Through modelling the enthalpy of melting and mixing of a drug with a polymer, it is possible to determine the solubility of the drug in the polymeric matrix.

Original article

A New Method to Determine Drug-Polymer Solubility Through Enthalpy of Melting and Mixing

Peter Meiland [a,1], Bjarke Strøm Larsen [b,1], Matthias Manne Knopp[c], Ingunn Tho [b] and Thomas Rades [a,*]

[a]*Department of Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen, Universitetsparken 2, 2100 Copenhagen, Denmark*

[b]*Department of Pharmacy, Faculty of Mathematics and Natural Sciences, University of Oslo, Sem Sælands vei 3, 0371 Oslo, Norway*

[c]*Bioneer:FARMA, Department of Pharmacy, Universitetsparken 2, 2100 Copenhagen, Denmark*

[1]*Co-first author (equal contribution to this work)*

**Corresponding author. Tel.: +45 35336032.*

E-mail addresses: thomas.rades@sund.ku.dk (peter.meiland@sund.ku.dk), ingunn.tho@farmasi.uio.no (b.s.larsen@farmasi.uio.no), mmk@bioneer.dk.

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Author contributions

Peter Meiland: methodology, validation, investigation, writing-original draft. **Bjarke Strøm Larsen:** methodology, conceptualization, validation, investigation, writing- original draft. **Matthias Manne Knopp:** methodology, supervision, conceptualization, investigation, writing-review & editing. **Ingunn Tho:** methodology, supervision, conceptualization, investigation, writing-review & editing. **Thomas Rades:** methodology, supervision, conceptualization, investigation, writing-review & editing, administration, funding acquisition.

Conflicts of interest

The authors declare no conflicts of interest.

A New Method to Determine Drug-Polymer Solubility Through Enthalpy of Melting and Mixing

Abstract In this study, a new method to determine the solubility of crystalline drugs in (amorphous) polymers is proposed. The method utilizes annealing of supersaturated amorphous solid dispersions to achieve equilibrium between dissolved and recrystallized drug. By measuring the enthalpy of melting and mixing (H_{m+mix}) of the recrystallized drug, the equilibrium solubility of the drug in the polymer at the annealing temperature is determined. The equilibrium solubilities at these elevated temperatures were used to extrapolate to room temperature using the Flory-Huggins model. The new H_{m+mix} method showed solubility predictions in line with the melting point depression (MPD) and recrystallization (RC) methods for indomethacin (IMC) -polyvinylpyrrolidone (PVP). For IMC-hydroxypropyl methylcellulose (HPMC), the MPD method plateaued rapidly, leaving only one usable data point. The RC method showed large variations in the solubility predictions possibly due to a narrow glass transition temperature (T_g) window or inaccurate T_g determination. In contrast, the new H_{m+mix} method showed robust solubility prediction over the entire annealing temperature range with low variation and narrow error margins after extrapolation for both drug-polymer systems. The new H_{m+mix} method was able to accurately determine the drug-polymer solubility of IMC-HPMC, showing promise as a new tool to determine the solubility of problematic drug-polymer systems.

KEY WORDS Solubility; amorphous solid dispersion (ASD); differential scanning calorimetry (DSC); hydroxypropyl methylcellulose (HPMC); polyvinylpyrrolidone (PVP); indomethacin (IMC); melting point depression (MPD) method; recrystallization (RC) method

Running title: Drug-polymer solubility method: Enthalpy of melting and mixing

1. Introduction

The development of novel drug candidates for oral administration has in recent years become increasingly difficult owing to the tendency of poor aqueous solubility of new lead compounds. Therefore, conventional oral dosage forms are struggling to provide the needed dissolution characteristics to provide acceptable bioavailability for these poorly water-soluble drugs [1], [2].

The improved solubility of amorphous drug formulations, attributed to the high energy state of the amorphous drug, has shown potential to improve the solubility of poorly water-soluble drug candidates. However, this elevated energy state of amorphous drugs leads to shelf-life issues due to the propensity of the drug to recrystallize [3].

To improve stability, the amorphous drug can be dispersed in a polymer matrix, yielding an amorphous solid dispersion (ASD). The polymer can act as a barrier between drug molecules and reduce drug mobility which leads to a decreased rate of recrystallization of the amorphous drug. However, the drug can also be dissolved in the polymer to obtain a thermodynamically stable ASD referred to as a glass solution. Often the drug solubility in a polymer is low, however, if there are favourable interactions between the drug and the

polymer, it is possible to achieve higher solubility. If the drug concentration in the system is kept below the equilibrium solubility at the storage temperature of the ASD, a thermodynamically stable system is achieved. This would make it possible to completely prevent crystallization of the drug during storage. To achieve a thermodynamically stable product, it is therefore important to be able to accurately determine the solubility of the drug in a polymer to decide on an appropriate polymer for the formulation [4]–[6].

The methods used to determine drug in polymer solubility are typically based on differential scanning calorimetry (DSC) analyses at elevated temperatures. The two most widely described methods in literature are the melting point depression (MPD) method [7] and the recrystallization (RC) method [8]–[10].

The MPD method relies on DSC analysis of crystalline drug in polymer physical mixtures with known drug to polymer ratios to correlate the melting temperature to the drug load. There is still ongoing debate on how to decide on a specific melting point from the wide peaks observed when melting a physical mixture of drug and polymer. The onset, offset and even peak maximum of the melting event have all been suggested in literature [9], [11]–[15]. From a thermodynamic point of view, it would be expected that the point where the heat flow from the dissolution endotherm becomes 0 Watt indicates the temperature where all drug has dissolved in the polymer. However, using this approach often does not yield results comparable to other methods [16]. This might be due to thermal lag in the observed dissolution event in the DSC. It has been shown that the effect of thermal lag can sometimes be mitigated by using very low heating rates [17]. Rask et al. showed good correlation between another established method (RC method) and the MPD method when using the onset of melting and a heating rate of 1 °C/min [10]. This approach and heating rate were used in the current study since it is widely used and compares well with other methods, although it is not entirely justified from a theoretical perspective. It is a common feature of the MDP method that the onset of melting can only be accurately determined on high drug loads, e.g., 70% and above. At low drug loads the melting endotherm of the system will widen and become shallow making it difficult to determine the precise onset of melting. For some systems the higher viscosity of the sample at low temperatures may lead to thermal lag in the measurements, preventing accurate determination of samples with low melting points. [16], [18], [19].

The RC method proposed by Mahieu et al. [8] utilizes the annealing of supersaturated ASDs to determine the equilibrium solubility of the drug-polymer system at elevated temperatures. Mahieu et al. proposed that supersaturated ASDs reach equilibrium faster than physical mixtures; this has however later been challenged by Mathers et al. [20] who claim the opposite to be the case. In the RC method the T_g of the annealed sample is used to determine the equilibrium solubility at the annealing temperature. In this study a revised RC method proposed by Knopp et al. was used [8], [21].

Common limitations observed in literature for the RC method are incomplete recrystallization during annealing, T_g heating rate dependency and narrow T_g standard curve ranges [10]. Since the viscosity of the system increases at lower temperatures, the crystallization rate is reduced. Because of this, there is a limit to which annealing temperatures can be used to obtain ASDs at equilibrium within experimentally acceptable time frames. When measuring the same drug-polymer system at multiple annealing temperatures, the temperatures at which equilibrium is not obtained will commonly appear as a plateau in the solubility-temperature curve [10].

All three methods used in this study determined the equilibrium solubilities of indomethacin in polyvinylpyrrolidone and hydroxypropyl methylcellulose at elevated temperatures. However, the solubility of interest when wanting to prepare stable ASDs would usually be at room temperature. To obtain the drug in polymer solubility at 25 °C, it is therefore necessary to extrapolate the solubility results to the desired temperature. The interested reader is referred to Mathers et al. [22] for more information on extrapolation model comparison. In this study Flory-Huggins extrapolation was utilized for all methods in both drug-polymer systems to determine the solubility of the system at room temperature.

The current study aims to improve the process of determining drug in polymer solubility by presenting a novel method based on the enthalpy of melting and mixing (H_{m+mix}) of annealed supersaturated ASDs. The presented method determines the equilibrium solubility of a drug in polymer by measuring the area under the curve (AUC) of the melting event of annealed ASDs, rather than a singular kinetic parameter (T_g, onset of melting). The enthalpy obtained from these experiments are then used together with models based on the Flory-Huggins lattice theory to determine the equilibrium solubility at the annealing temperature.

2. Theoretical Considerations

2.1 Flory-Huggins Modelling

To predict the solubility of a drug in a given polymer at room temperature, Flory-Huggins extrapolation was necessary as the equilibrium solubility of the samples was determined at elevated temperatures. Based on Flory-Huggins lattice theory a model derived by Hoei et al. [21] describes the volume fractions of the polymer and drug at equilibrium, dependent on the temperature. The model can be seen below as Equation 1:

$$\frac{H_m}{R} \cdot \left(\frac{1}{T_m} - \frac{1}{T}\right) = \ln\left(\varphi_{drug}\right) + \left(1 - \frac{1}{\lambda}\right) \cdot \left(1 - \varphi_{drug}\right) + \chi \cdot \left(1 - \varphi_{drug}\right)^2 \#(1)$$

where H_m is the enthalpy of melting of the pure drug, T_m is the melting temperature of the pure drug, T is the absolute temperature at which the melting event occurs, φ_{drug} is the solubilized volume fraction of drug, λ is the molar volume ratio of polymer to drug, R is the gas constant and χ is the Flory-Huggins interaction parameter which describes the energy difference between drug-drug and polymer-polymer interactions to drug-polymer interactions. This interaction is a material-specific parameter for a given drug-polymer system, and was used as the fitting parameter in this study.

2.2 Enthalpy of Melting and Mixing of Crystalline Drug into Drug-Polymer Solutions

To describe the total enthalpy of melting and mixing of pure crystalline drug into a polymer, the mean field Flory-Huggins solution theory was applied, which defines the contribution of the enthalpy of mixing to the total enthalpy:

$$H_{mix} = kT\chi N_{drug}\varphi_{polymer} \#(2) \#\#\#\#\#$$

This expression was modified and standardized to the mass of the drug,

$$\frac{H_{mix}}{m_{drug}} = \frac{RT\chi\varphi_{polymer}}{M_{drug}} \#(3)\#\#\#\#\#$$

where H_{mix} is the enthalpy of mixing, m_{drug} is the mass of drug, $\varphi_{polymer}$ is the volume fraction of the polymer in the system and M_{drug} is the molar mass of the drug.

Equation 3 was then combined with the expression for H_m to yield the final model determining the enthalpy of melting and mixing over the total mass of the system shown below as Equation 4:

$$\frac{H_{m+mix}}{m_{total}} = \left(\frac{H_m}{m_{drug}} + \frac{RT\chi}{M_{drug}}\right)x_{drug} - \frac{RT\chi}{M_{drug}} \cdot \frac{x_{drug}^2}{x_{drug}\left(1 - \frac{p_{drug}}{p_{polymer}}\right) + \frac{p_{drug}}{p_{polymer}}} \#(4)\#\#\#\#\#$$

where H_{m+mix} is the enthalpy of melting and mixing, $m_{polymer}$ is the mass of polymer, m_{total} is the sum of the mass of drug and polymer, x_{drug} is the fraction of drug in the system, p_{drug} is the molecular density of drug and $p_{polymer}$ is the molecular density of the polymer. The derivation of this model is shown in the supporting information section.

Equation 4 describes the case in which a pure crystalline drug is fused into a pure amorphous polymer. Determination of the equilibrium solubility of the saturated ASDs is more complex. The process relies on the notion that the supersaturated ASD, for which the drug load and total mass are known, is annealed until equilibrium is reached. During annealing, both, the mass of drug dissolved in the polymer and the total mass of the ASD will change. The enthalpy of melting and mixing of the recrystallized drug into the saturated ASD is then measured. This measurement can then be used to calculate the fraction of drug still dissolved in the saturated ASD, when the drug load of the supersaturated ASD is known. However, it is important to consider the difference in mass between the supersaturated and saturated ASD. This can be achieved with Equation 5, which takes into account the change in mass of the ASD and relates it to the correlation between the ΔH_{m+mix} of the recrystallized drug to the H_{m+mix} term obtained with Equation 4,

$$\frac{H_{m+mix1}}{m_{total1}} = \left(\frac{H_{m+mix2}}{m_{total2}} - \frac{\Delta H_{m+mix}}{m_{total2}}\right) \cdot \left(\frac{x_{drug1} \cdot x_{polymer2}}{1 - x_{drug1}} + x_{polymer2}\right)^{-1} \#(5)$$

where H_{m+mix1} is the enthalpy of melting and mixing of the saturated ASD before additional drug is dissolved into it, H_{m+mix2} is the enthalpy of melting and mixing of the supersaturated ASD before annealing. ΔH_{m+mix} is the difference between H_{m+mix2} and H_{m+mix1}, which is measured as the enthalpy of melting and mixing of the drug crystallized during annealing. m_{total1} is the mass of drug and polymer for the saturated ASD before additional drug is dissolved into it, m_{total2} is the mass of drug and polymer for the supersaturated ASD, x_{drug1} is the drug load of the saturated ASD and $x_{polymer2}$ is the polymer load of the supersaturated ASD.

The equilibrium solubility of the drug in polymer after annealing is approximated by computational discrete step optimization. The aim of the optimization was to keep the difference between the results from Equation 4 and 5 to a minimum by altering the drug load of the saturated ASD. The discrete step optimization was deemed acceptable if the difference between the enthalpy calculated from Equation 4 and 5 was below 10^{-4} J/g.

3. Materials and Methods

3.1 Materials

IMC (M_w 357.79 g/mol) was purchased from Hawkins Inc. Pharmaceutical Group (Minneapolis, MN, USA). PVP, Kollidon 30 (M_w 44000-54000 g/mol) was acquired from BASF SE (Ludwigshafen, Germany) and HPMC, Pharmacoat 603 (M_w 13000 g/mol) from Shin Etsu Chemical Co. (Tokyo, Japan). The densities of IMC, PVP and HPMC were 1.38, 1.12 [23] and 1.36 [10] g/cm^3 respectively.

3.2 Sample Preparation

Physical mixtures were prepared between drug and polymer by grinding the mixtures in an agate mortar with a pestle by hand. The mixtures were ground twice for 20 minutes with repeated mixing with a spatula in between grinding. Physical mixtures were prepared with drug loads ranging from 10 % to 90 % and kept in air-tight containers until analysis. Drug loads are reported as the calculated dry weight drug percentage.

Supersaturated ASDs of the two drug-polymer systems were prepared by melt quenching. The drug-polymer mixtures were spread in a thin layer on a Teflon coated oven liner (Clas Ohlson, Insjön, Sweden) and melted twice at 169 °C (T_m + 10 °C of IMC) in a UF55 electrical furnace (Memmert GmbH + Co. KG, Schwabach, Germany). After each melting step, the samples were ground and mixed using an agate mortar and pestle. All supersaturated ASDs prepared this way were shown by x-ray powder diffraction (XRPD) to be amorphous and were prepared shortly before use to prevent recrystallization during storage.

For both, IMC-PVP and IMC-HPMC a drug load of 85% was used. The drug loads for the drug-polymer systems were chosen to achieve the highest drug loads possible without detectable recrystallization during analysis of the individual drug-polymer systems. This was determined with DSC by rapidly cooling the supersaturated ASD to -10 °C and keeping it isothermal for 2 min followed by heating to 200 °C with a heating rate of 5 °C/min. This was done without including an annealing step. If no melting endotherm was seen from heating, it could be assumed that this drug load would not produce measurable crystallization after annealing in the following experiments. The benefit of using high drug loads is that it will be possible to obtain the largest amount of data points for the subsequent Flory-Huggins extrapolation. To test the effect of using an immediately unstable drug load, an IMC-HPMC ASD with 90 % drug load was also attempted for the RC and H_{m+mix} method.

3.3 Thermal Analysis

Thermal analysis was performed in triplicates using a Q2000 DSC (TA instruments Inc., New Castle, DE, USA). The DSC was calibrated with an indium standard and the calibration was verified at the start of each

day. Samples for the DSC were prepared by accurately weighing 2-3 mg of material into aluminium Tzero pans. The pans were closed with manually punctured hermetic Tzero lids. The water content of pure drugs and polymers was determined using thermal gravimetric analysis (TGA) using a Discovery TGA from TA instruments Inc. by heating approximately 10 mg of sample to 120 °C after which isothermal conditions were kept for 30 minutes. Analysis of thermograms was done using the TRIOS software of TA Instruments Inc.

Two DSC programs were designed. The first DSC program analysed the physical mixtures to determine the onset of melting, as well as the T_g and H_{m+mix} correlated to the known drug load in the physical mixture. The onset of melting and the H_{m+mix} (J/g of the total sample mass) were determined by heating samples from 75 °C with a heating rate of 1 °C/min to 10 °C above the melting point of the pure drug. Then the physical mixture samples were kept isothermal at 10 °C above the melting point of the pure drug for 2 minutes. The samples were then rapidly cooled to -10 °C and kept isothermal for 2 minutes, thereby preparing *in situ* melt-quenched ASDs with known drug loads within the DSC. These *in-situ* ASDs were then heated to 175 °C with a heating rate of 5 °C/min to determine the T_g.

The second DSC program analysed the supersaturated ASDs prepared in the electrical furnace. Annealing of the prepared ASDs was performed with the DSC by rapid heating to the appropriate annealing temperature between 110 °C and 150 °C after which the ASDs were kept isothermal for 180 minutes. After annealing, the samples were rapidly cooled to -10 °C and kept isothermal for 2 minutes. The T_g and ΔH_{m+mix} (J/g of the total sample mass) were subsequently measured by heating of the annealed samples to 200 °C at a rate of 5 °C/min.

4. Results

4.1 Data Analysis of DSC Thermograms

DSC was used to measure the onset of melting temperature, T_g and H_{m+mix}. Figure 1 shows excerpts of the raw thermograms used in the data analysis. Thermogram A in Figure 1 is an example of the *in-situ* melt-quenched physical mixture, which is used to determine the standard curve for the RC method. Here it is important to note the T_g and the absence of a melting endotherm, confirming that no recrystallization is happening during the DSC measurement. Thermogram B is an example of the melting endotherm of a physical mixture, which is used to measure the onset of melting for the MPD method and the H_{m+mix} for the calibration curve used in the H_{m+mix} method. Thermogram C is an example of the supersaturated ASD after annealing, which is used to calculate the solubility based on the T_g in the RC method and the H_{m+mix} of the recrystallized drug in the H_{m+mix} method.

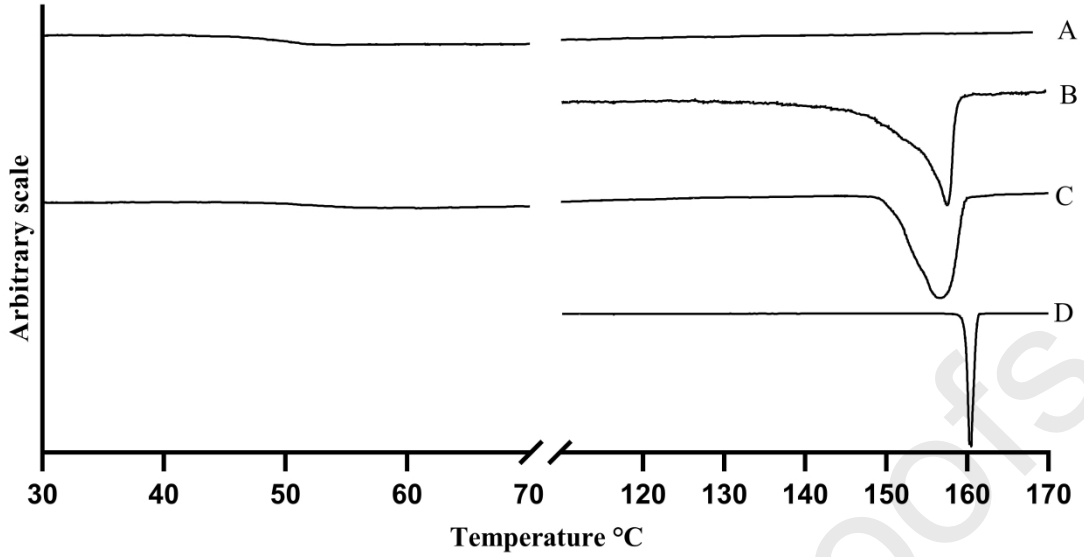

Figure 1. DSC thermogram excerpts of *in-situ* melt-quenched 85% IMC in HPMC physical mixture (A). 85% IMC in HPMC physical mixture melting endotherm (B), 85% IMC in HPMC supersaturated ASD annealed at 135 °C for 3 hours (C) and pure crystalline IMC melting endotherm (D).

4.2 Solubility Predictions Utilizing the MPD, RC and H_{m+mix} Methods

The onsets of melting of physical mixtures with varying drug loads were determined using DSC for both drug-polymer systems. For IMC-PVP the measured onset of melting was indistinguishable for samples with drug loads of 70% and below. Flory-Huggins extrapolation of the experimentally determined onset of melting events as well as the 95% confidence interval (CI) are shown in Figure 2. The solubility prediction at 25 °C for IMC-PVP using the MPD method was found to be 38.0% (95% CI: 25.3%, 46.3%).

IMC-HPMC showed clear melting endotherms above 50% drug load. However, a plateau of the melting point was observed for the onset of melting of physical mixtures at 85% drug load and below. Flory-Huggins extrapolation was carried out on the 80% to 90% drug load range, because it was considered necessary to have a minimum of three data points for the fitting. However, it was not possible to obtain a good fit with this data, since the plateau appears already from the samples with 85 % drug load. As can be seen in the figure, this resulted in a wide CI at 25 °C, for a predicted solubility of 25.6% (95% CI: 2.1%, 41.1%).

The curves of the T_g dependence on the composition of the drug-polymer systems were fitted with the Kwei function as suggested by Mathers et al. [20], and resulted in R^2-values of 0.995 and 0.973 for IMC-PVP and IMC-HPMC, respectively. However, when plotting the residuals describing the variance of the Kwei fits, some T_g measurements had a difference from the fit of more than 4 °C. This difference can change the calculated drug-polymer composition by around 5-10 percentage points depending on the drug-polymer system. This residual variance was much greater than any variance between replicate measurements of the T_g. Because of this, it was decided that the Kwei fit did not provide a good enough fit for the entire range of T_g to drug-polymer compositions. As an alternative the T_g data was fitted using point-to-point linear regressions (Supporting Information, Figures S1-S5).

The RC method requires the preparation of supersaturated ASDs of drug in polymer, which are then annealed at elevated temperatures. The T_g of the annealed sample is measured by DSC and correlated to the T_g curve fit to determine the equilibrium solubility at the elevated annealing temperature.

IMC-PVP showed a plateau at annealing temperatures below 130 °C. This phenomenon has been suggested by Rask et al. [10] to be most likely due to incomplete recrystallization during the annealing step, leading to an overestimation of the equilibrium solubility at these annealing temperatures. The annealing temperatures contained in the plateau were not used in the Flory-Huggins extrapolation for the system and are marked red in Figure 2. The predicted solubility at 25 °C for IMC-PVP using the RC method was found to be 39.8% (95% CI: 33.2%, 44.9%).

IMC-HPMC showed relatively higher standard deviations between individual data points compared to IMC-PVP. The reason for the increased standard deviation is likely to be the narrow range of the IMC-HPMC T_g dependency curve, which exacerbates small experimental measuring and data analysis errors. However, in contrast to IMC-PVP, a plateau did not seem to form even at annealing temperatures as low as 110 °C, as can be seen in Figure 2. The predicted solubility at 25 °C for IMC-HPMC using the RC method was found to be 37.7% (95% CI: 31.9%, 42.3%).

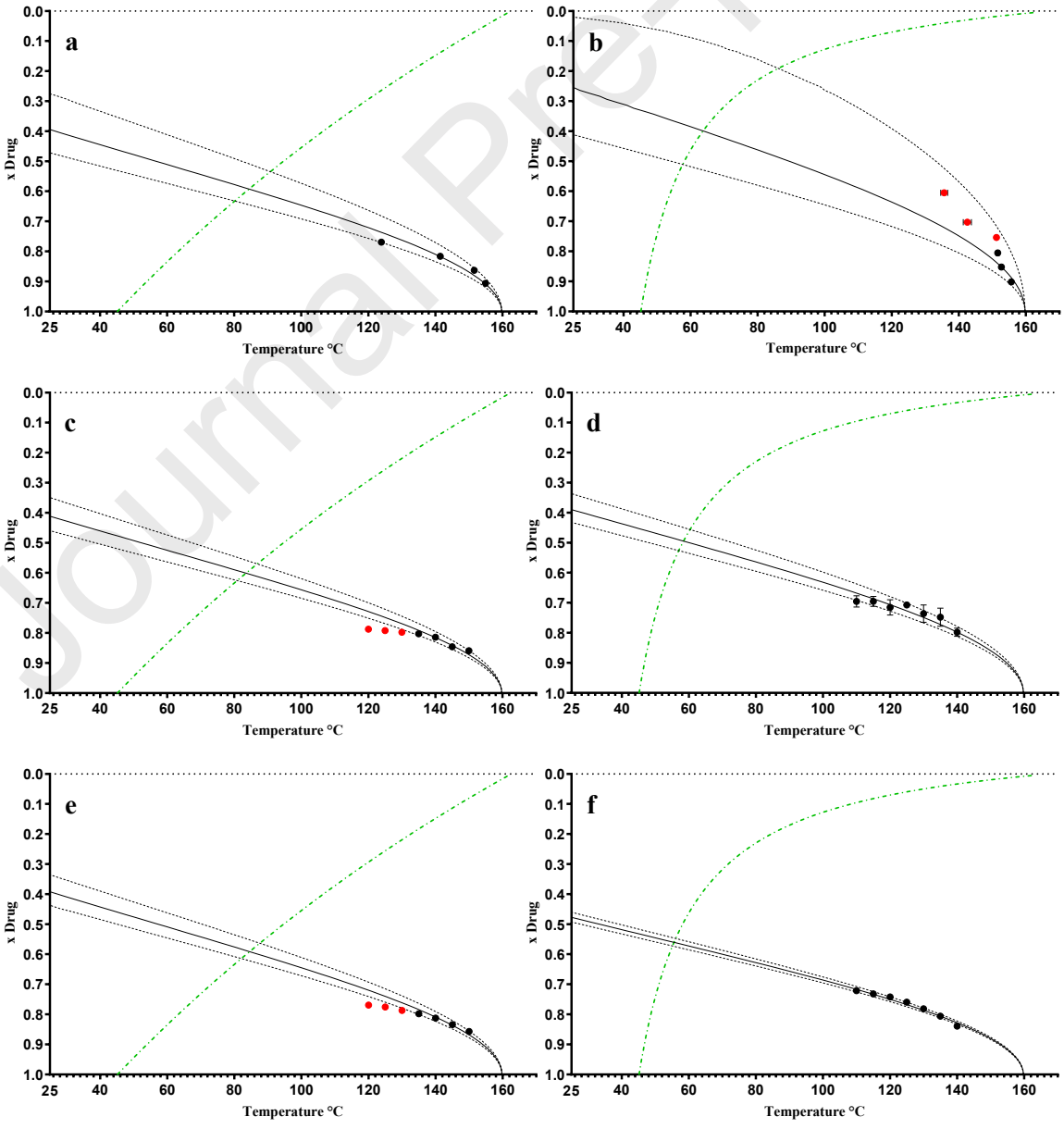

Figure 2. Flory-Huggins extrapolation of the MPD method data for IMC-PVP (a) and IMC-HPMC (b). Data points represent experimentally determined onset of melting values. Flory-Huggins extrapolation of the RC method for IMC-PVP (c) and IMC-HPMC (d). Data points represent experimentally determined equilibrium solubilities at varying annealing temperatures. Flory-Huggins extrapolation of the Hm+mix method for IMC-PVP (e) and IMC-HPMC (f) with an initial ASD drug load of 85%. Data points represent experimentally determined equilibrium solubilities at varying annealing temperatures. The Gordon-Taylor fit for IMC-PVP and IMC-HPMC is visualized as a green dash-dotted line fit for the respective systems. All data points are shown as mean ± SD, n = 3, red data points were excluded from the fit.

The H_{m+mix} standard curve describes the relationship between the experimentally determined enthalpy of melting of pure crystalline drug together with polymer in a known ratio from physical mixtures. The fit used to describe the H_{m+mix} of the drug-polymer systems is modelled using Equation 4.

As can be seen in Figure 3, H_{m+mix} from both IMC-PVP and IMC-HPMC fitted well to the equation. The high deviation from linearity for IMC-PVP indicates a substantial enthalpy of mixing relative to the enthalpy of melting. This underlines the necessity of including both, enthalpy of melting and mixing in the models.

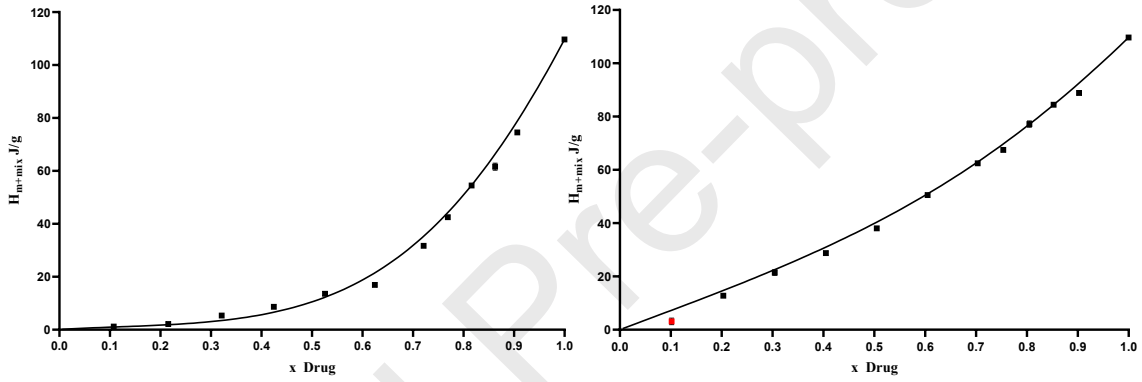

Figure 3. H_{m+mix} curves for IMC-PVP (left) and IMC-HPMC (right). Data points represent experimentally determined H_{m+mix} values (J/g of the total sample mass, mean ± SD, n = 3) at different drug loads. The fit is modelled using Equation 4. Red data point was excluded from the fit.

Similar to the RC method, the H_{m+mix} method uses annealing of supersaturated ASDs at elevated temperatures to determine the equilibrium solubility of the drug-polymer system. However, the measured variable in this method is the $\Delta H_{m+mix,}$ which is determined from drug that crystallized during the annealing step. Correlating this value with the H_{m+mix} standard curve (Figure 3) by using Equation 5 as described in Section 2.2, the equilibrium solubilities at the elevated annealing temperatures can be determined. Subsequently, Flory-Huggins extrapolation is carried out to determine the equilibrium solubility of drug in polymer at 25 °C shown in Figure 2.

IMC-PVP showed a plateau at annealing temperatures below 130 °C, *i.e.,* at the same range as for the RC method. This is to be expected as the annealing time and temperatures are identical for the two methods. Insufficient recrystallization shows lower observed ΔH_{m+mix} values leading to an overestimation of the equilibrium solubility at the elevated annealing temperatures and thus, also at 25 °C. The predicted solubility at 25 °C for IMC-PVP using the H_{m+mix} method was found to be 37.8% (95% CI: 31.7%, 42.6%).

All the annealing temperatures used in this method for IMC-HPMC fitted well to the Flory-Huggins model. This was also the case for the RC method and therefore it is expected that an annealing time of 3 hours was sufficient for this drug-polymer system. IMC-HPMC showed a predicted solubility at 25 °C of 47.7% (95% CI: 46.0%, 49.3%).

4.3 Solubility Prediction using ASDs with 90% Drug Load Utilizing the RC and H_{m+mix} Methods

The RC and H_{m+mix} methods were also applied on IMC-HPMC using a supersaturated ASD with 90% drug load. The IMC-HPMC ASD with 90% drug load was shown to have a measurable melting event when utilizing the DSC protocol for measuring the T_g and ΔH_{m+mix} without the annealing step. Typically, this would have excluded this drug load from the method since it was shown in the DSC to be immediately unstable to prevent additional crystallization from occurring after the annealing step (the lowest drug load that did not show this melting event was the 85% drug load which was used for the samples shown in Figure 2). The two methods were however, still carried out on the ASD with 90% drug load to investigate whether similar results would be obtained when more crystallized drug was present after annealing, as well as to investigate the effect on the final result when using an ASD that was immediately unstable.

As can be seen in Figure 4, for the RC method this resulted in more variance between replicates as well as a wider CI for the fit. For the H_{m+mix} method, no significant change was observed for the variance between replicates nor for the CI of the fit. However, for both methods the data points with annealing temperatures of 145 °C and 150 °C were lower than the Flory-Huggins fit predicts and thus excluded from the fit. These two annealing temperatures correspond to higher drug loads than the highest one observed not to crystallize during DSC analysis (>85%). This indicates that perhaps the saturated ASDs obtained after annealing at 145 °C and 150 °C were not sufficiently stable during the T_g and ΔH_{m+mix} measurements. The drug in polymer solubility prediction at 25 °C was 44.5% (95% CI: 34.9%, 50.9%) and 46.1% (95% CI: 44.3%, 47.8%) for the RC and H_{m+mix} method respectively.

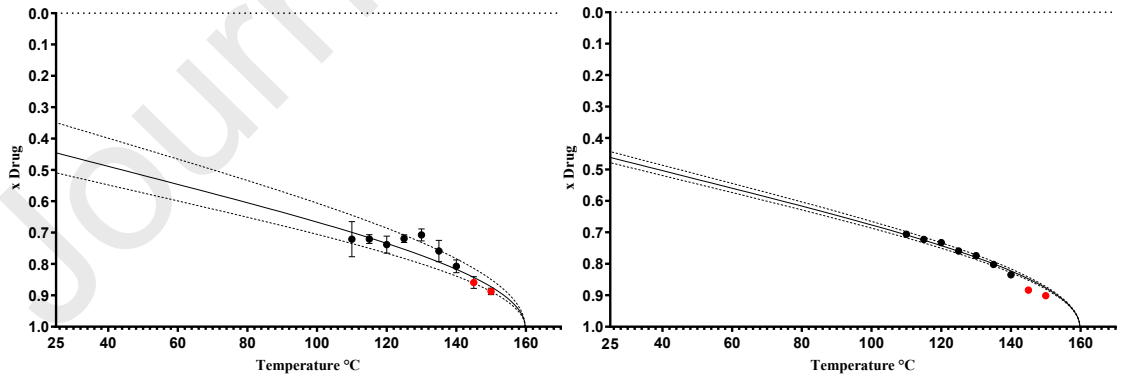

Figure 4. Flory-Huggins extrapolation of the RC (left) and H_{m+mix} method (right) for IMC-HPMC with an initial ASD drug load of 90%. Data points represent experimentally determined equilibrium solubilities at varying annealing temperatures (mean ± SD, n = 3). Red data points were excluded from the fit.

5. Discussion

The purpose of this study was to test the performance of the newly developed H_{m+mix} method compared to the established RC and MPD methods in terms of determining the solubility of crystalline drug in polymers. The drug-polymer systems were IMC-PVP and IMC-HPMC. IMC were chosen, as they are well-known and widely reported in literature [23][24]. Reviewing the literature, it is clear that HPMC is a difficult polymer for which to predict drug solubility [10]. This is likely due to the complex nature of HPMC containing high variation between chain links and various side chains. HPMC variations often have high T_gs, which will improve storage stability of supersaturated ASDs, however, this also makes it difficult to predict drug solubility using the MPD method due to increased thermal lag and slower mixing with the drug. From Figure 2, it is clear that the solubility curve for IMC-HPMC contains few data points that fit the Flory-Huggins model when using the MPD method. It can be argued that a starting plateau can be observed with decreasing drug loads already from 85 %. This may be because at drug loads at or below 85 %, the mixing of the drug and polymer happens so slowly that the melting event observed in the thermogram does not correspond to the equilibrium melting temperature of the drug (thermal lag). The variability increases with decreasing drug load, further confirming the poor validity of the measurements. The same issue was not observed for the MPD method with IMC-PVP. The T_g of PVP and HPMC was found to be 159.3 °C and 167.4 °C, respectively. It might be possible to obtain more accurate measurements for lower drug loads with lower heating rates, however this will increase experimental timeframes and lower sensitivity of the measurement. For the RC method, the data points fit the Flory-Huggins model at annealing temperatures below the T_g of the polymers. The method seems to be less sensitive to the slower kinetics of viscous samples compared to the MPD method. This is due to the long annealing times at high temperatures, increasing molecular mobility and allowing more time to obtain equilibrium. Additionally, the system is plasticized by the drug being molecularly dispersed in the polymer, increasing the mobility compared to the pure polymer. It is thus recommendable to explore the necessary annealing time when working with ASDs that are slow to crystallize. Figure 2 suggests that IMC-PVP does not follow the Flory-Huggins model at annealing temperatures below 135 °C. The same trend was observed for the H_{m+mix} method shown in Figure 2. Since both methods utilize identical annealing times, it is likely that at temperatures below 135 °C equilibrium is not obtained within the 3 hours. This causes an overprediction of the solubility when using supersaturated ASDs. It should be possible to utilize lower annealing temperatures if the corresponding annealing time was to be increased. It is therefore important to optimize the annealing time within the boundaries of the experimental timeframe to ensure sufficient data collection when using the two methods.

It can be seen in Figure 2, that the results obtained for IMC-PVP were comparable when using the RC and new H_{m+mix} methods. The methods predict the solubility of IMC in PVP to be 39.8% (95% CI: 33.2%, 44.9%) and 37.8% (95% CI: 31.7%, 42.6%) at 25 °C for the RC and H_{m+mix} method respectively (Table 1). The annealing temperatures that follow the Flory-Huggins fit are the same for both methods. The solubility prediction for the H_{m+mix} method shows a narrower CI compared to the RC method, however the difference between the predicted solubilities obtained with the two methods was not found to be statistically significant.

Table 1: Overview of solubility predictions at 25 °C using Flory-Huggins extrapolation for the three included methods.

	IMC-PVP	IMC-HPMC	IMC-HPMC 90%
MPD	38.0% (CI: 25.3%, 46.3%)	25.6% (CI: 02.1%, 41.1%)	N/A
RC	39.8% (CI: 33.2%, 44.9%)	37.7% (CI: 31.9%, 42.3%)	44.5% (CI: 34.9%, 50.9%)
H_{m+mix}	37.8% (CI: 31.7%, 42.6%)	47.7% (CI: 46.0%, 49.3%)	46.1% (CI: 44.3%, 47.8%)

For IMC-HPMC, the two methods yield very different results. The predicted solubilities at 25 °C were 37.7% (95% CI: 31.9%, 42.3%) and 47.7% (95% CI: 46.0%, 49.3%) for the RC and H_{m+mix} method respectively. The data clearly show less uncertainty with regards to both variance of replicates and goodness of fit to the Flory-Huggins model for the H_{m+mix} method. It is expected that this is due to the accuracy of measuring the enthalpy compared to the T_g, as well as relating those measurements to a specific drug load. While enthalpy is a specific thermodynamic parameter with clear signals in a DSC analysis, the T_g is a kinetic parameter sensitive to both thermal history and DSC parameters. The solubility of IMC in HPMC at 25 °C was reported to be 8 % by Rask et al. [10] with the RC method. This was neither in line with the results obtained for the RC method nor the H_{m+mix} method in this study, indicating a high variance between laboratories when measuring the T_g of these complicated two phase drug-polymer systems.

Interestingly, when using a supersaturated ASD of IMC-HPMC with a higher drug load, seen in Figure 4, a very different result was obtained for the RC method. Here, both the variance between replicates and the fit increased. This was not seen for the H_{m+mix} method, which gave very similar results for every annealing temperature used for both the ASD with 85 % and 90 % drug load. This indicates that different starting drug loads reach the same equilibrium drug load after annealing at a specific temperature, and that relating the ΔH_{m+mix} of crystallized drug to the equilibrium drug load can be done reproducibly even when more drug has crystallized. The T_g may however be affected by the larger portion of crystallized drug in the sample, giving rise to inaccurate measurements. When using a higher starting drug load, it is also possible to use higher annealing temperatures, since the higher drug loads will allow for equilibrium to be reached at higher temperatures. However, for both methods it was seen that the two higher annealing temperatures, 145 °C and 150 °C, did not fit with the rest of the data to the Flory-Huggins model. This shows the importance of assuring that the obtained drug loads are stable during the measurements. It would theoretically be possible to adjust for additional crystallization during the enthalpy measurement by subtracting the enthalpy of additional crystallization from the measured enthalpy of melting and mixing, though this can be difficult if the events are very wide or coincide with other thermal events in the DSC thermogram.

When comparing the RC method and the H_{m+mix} method to the results from the MPD method in Figure 2, it can be seen that the MPD method gives similar predictions for IMC-PVP at 25 °C (38.0% (95% CI: 25.3%, 46.3%)), though there is more uncertainty in the prediction. This is, however, not the case for IMC-HPMC, where it is dubious if any of the data points from the MPD method even fits the Flory-Huggins model. The solubility predicted for this method was 25.6% (95% CI: 2.1%, 41.1%). It is possible that the slow mixing of the IMC and HPMC upon melting does not allow for any accurate measurement under these experimental conditions. Of the three methods used in this project, the new H_{m+mix} method gave the highest predicted solubility of IMC in HPMC, as well as the highest reproducibility and closest fit to the theoretical model.

These findings show promise for higher precision of solubility prediction with the use of the new H_{m+mix} method in certain drug-polymer systems. It should be brought to the attention of the reader that the H_{m+mix} method utilizes two distinct χ-values for the same drug-polymer system. One that is determined for the enthalpy model shown in Equation 4 and used to determine the equilibrium solubility at elevated temperatures. Another χ-value is determined for the Flory-Huggins model shown in Equation 1 and used for the temperature extrapolation. In both cases, the χ-value was used as the fitting parameter to generate the models. It is not currently known why the two determined values are. There has been discussion on whether the χ-value is truly a material constant, and it is typically considered that the χ-value varies with multiple factors, e.g. temperature and composition [19], [25], [26]. Furthermore, there is an ongoing discussion on whether the Flory-Huggins solution theory even applies to glass solutions and whether it should be used for temperature extrapolations [27], [28]. Multiple alternative approaches have been suggested, e.g. by Prudic et al. [29], Bellantone et al. [30] and Kyerematenge et al [31]. In this study, it was not evaluated whether the Flory-Huggins model was the best approach for temperature extrapolations or whether the χ-value should have been modelled with temperature or composition. In any case, the Flory-Huggins models made did fit well with the experimental data obtained, except for the case of IMC-HPMC with the MPD method. More research on the χ-value might be needed when used in modelling the H_{m+mix} as well as generally in temperature extrapolations of drug solubility in ASDs.

In the experimental setups used in this study, the MPD method was the least time consuming and is recommended for initial screenings, however this method was also the one with the lowest precision. It is not recommended to use this method to predict the solubility in polymers with high T_gs. From a theoretical point of view, the end of the dissolution endotherm gives the temperature where the drug load in the physical mixture is completely dissolved. This however, requires that the heating rate is low enough that the mixture is in a quasi-equilibrium situation at the given temperature and that the exact endpoint can be accurately determined. This might not always be possible to experimentally determine due to sensitivity limits of the equipment and a low rate of dissolution from the viscous drug-polymer mixtures. In this study, if anything but the onset had been used, none of the results would have been comparable to the other two methods. Both the RC and the H_{m+mix} method requires a comparable amount of experimental time, while the H_{m+mix} method provided the most precise solubility predictions. Grinding the supersaturated ASDs before annealing in the DSC can increase the rate of recrystallization by offering additional sites of nucleation. To reduce experimental times, it might be possible to increase the rate of crystallization even further by adding nucleation sites or a nucleation catalysts to the sample, e.g. small amounts of crystal drug or silica.

It should be noted that it is possible to do all three methods simultaneously as was shown in this study. The enthalpy/drug load model in the H_{m+mix} method can be measured together with all the experimental data required for the MPD method, while it is possible to measure both the T_g and ΔH_{m+mix} from the same annealed samples. However, crystallization might occur from annealed ASDs with high drug loads when cooling the samples in order to measure the T_g. This can cause inaccuracy for the H_{m+mix} method if the T_g is measured for the same samples. Rask et al. [10] showed that a significant limitation of the RC method is the need for the measured T_gs to correspond to a single drug load, which is not the case for some drug-polymer

system. This is not a requirement for using the H_{m+mix} method. In a similar fashion, many drug-polymer systems show only minor changes in the T_g when varying the drug load [10]. These systems are especially sensitive to small inaccuracies in the T_g determination. It is therefore recommended to use the new H_{m+mix} method in cases where the two established methods cannot be accurately used.

5. Conclusions

In this study, the performance of the proposed H_{m+mix} method compared to the established RC and MPD methods in terms of determining the solubility of crystalline drug in polymers was investigated. IMC-PVP showed consistent results across all three methods, RC, MPD and H_{m+mix}. This suggests that the novel H_{m+mix} method is reliable and accurate compared to established methods. The plateau observed at lower annealing temperatures with the H_{m+mix} method for IMC-PVP was likely due to insufficient recrystallization during annealing as similar results were observed for the RC method. For IMC-HPMC, the highest reproducibility in replicates and the best fit to the Flory-Huggins model were obtained with the H_{m+mix} method. This indicates that this new method can measure the solubility of drugs in HPMC with precision, which has not previously been possible. In general, it is expected that the new H_{m+mix} method will prove useful for more drug-polymer systems compared to the RC method, and that it could lead to more precise results for many drug-polymer systems.

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Supporting Information:

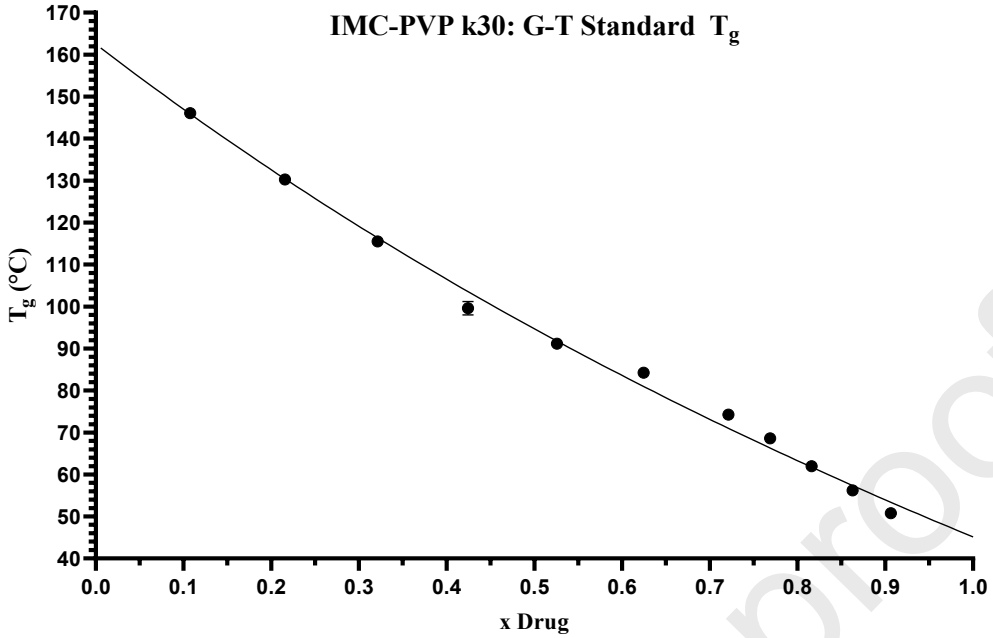

Figure S1: *T_g standard curve of IMC-PVP modelled using the G-T equation (mean ± SD, n = 3).*

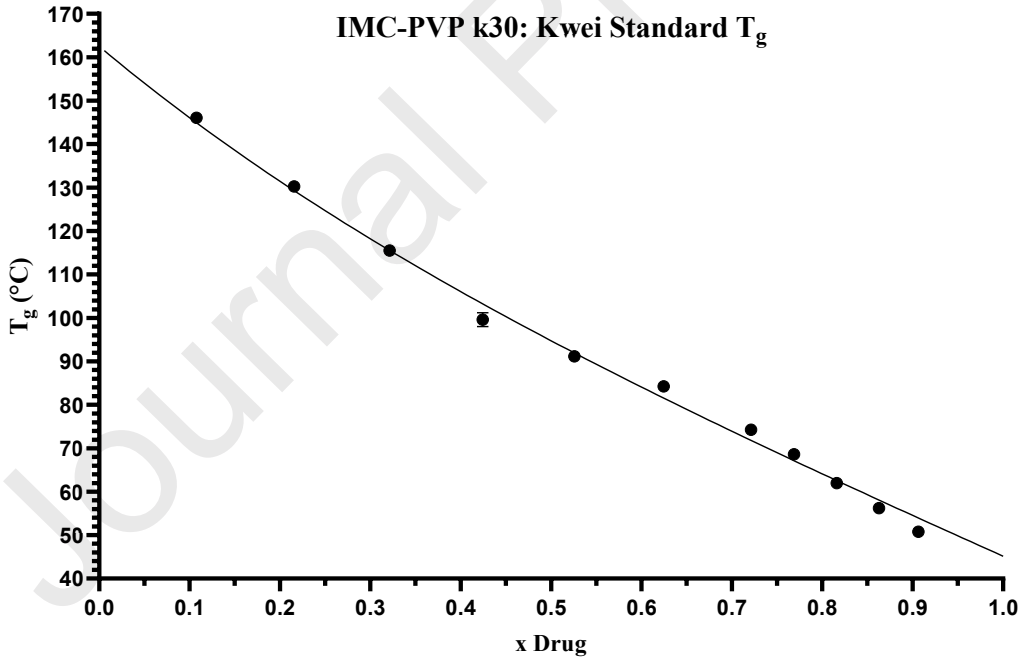

Figure S2: *T_g standard curve of IMC-PVP modelled using the Kwei equation (mean ± SD, n = 3).*

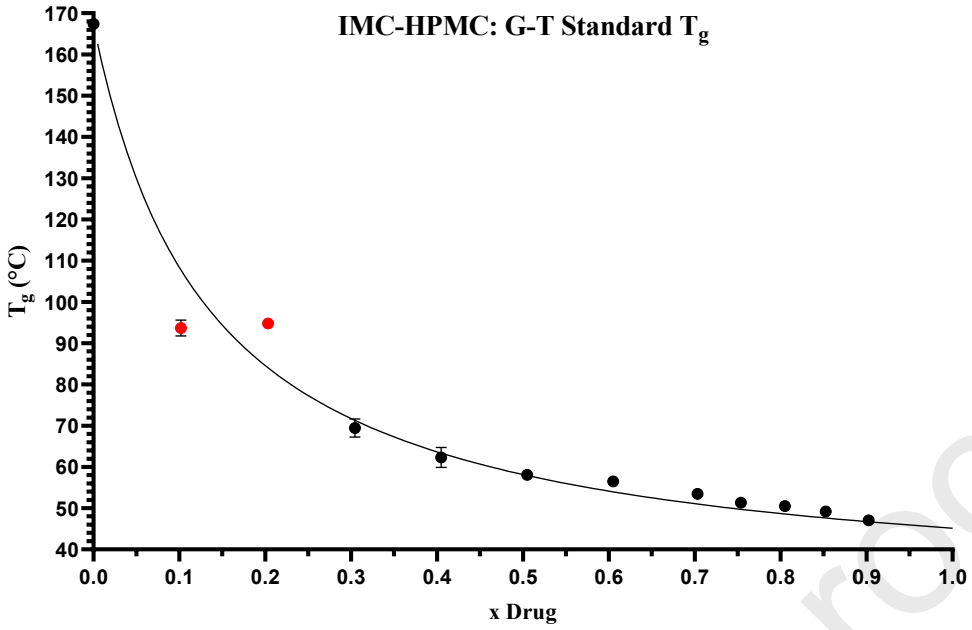

Figure S3: *T_g standard curve of IMC-HPMC modelled using the Gordon-Taylor equation (mean ± SD, n = 3). Red data points were not included in the modelling of the fit.*

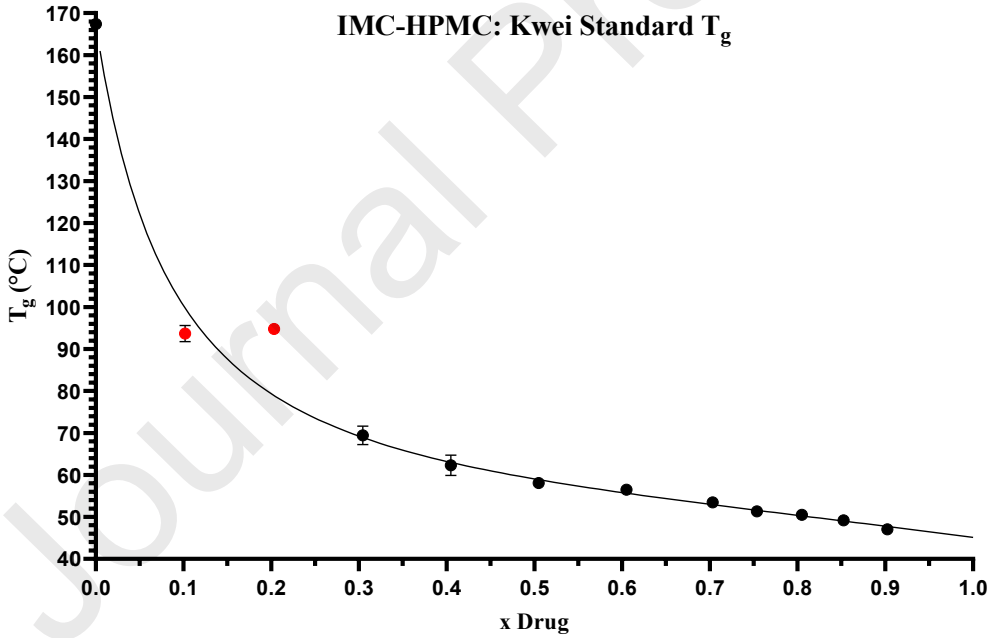

Figure S4: *T_g standard curve of IMC-HPMC modelled using the Kwei equation (mean ± SD, n = 3). Red data points were not included in the modelling of the fit.*

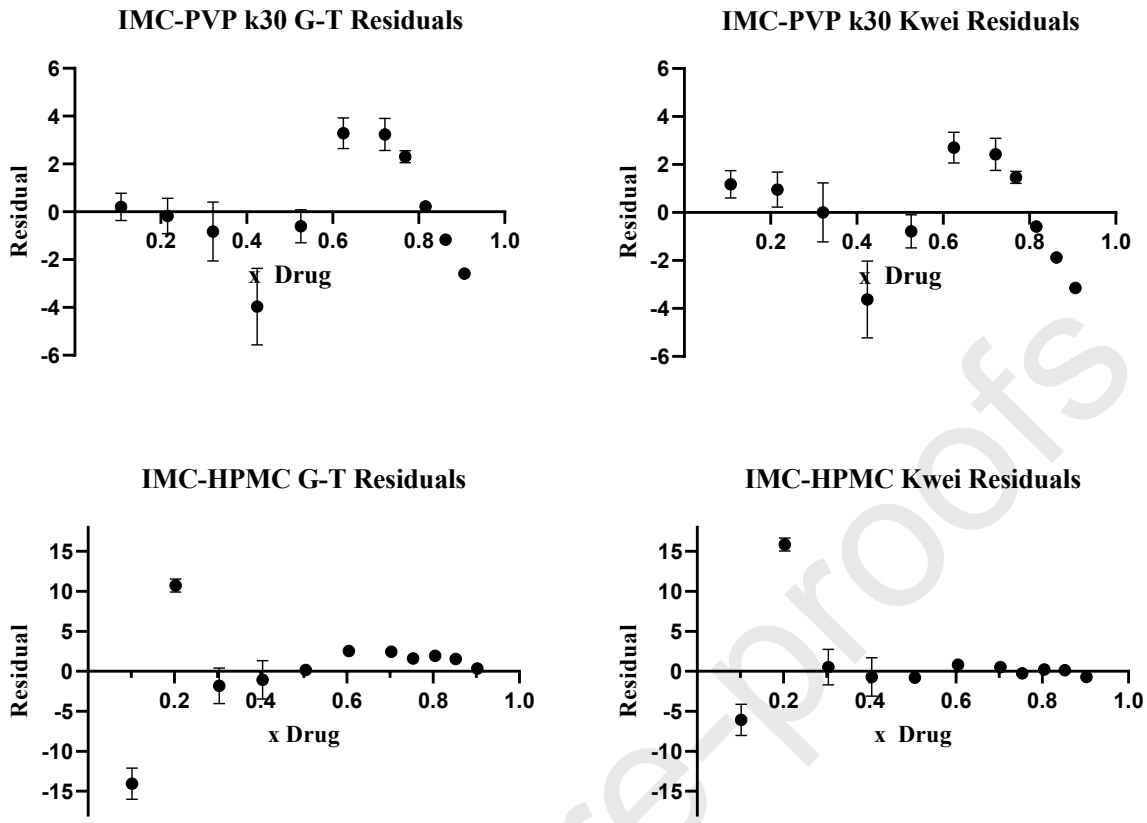

Figure S5: *Collection of residual plots for IMC-PVP and IMC-HPMC using both the Gordon-Taylor and Kwei equation (mean ± SD, n = 3).*

Derivation of thermodynamic model for enthalpy of melting and mixing of drug into polymeric glass solutions containing drug

When a crystalline drug is heated in the presence of a polymer in which the drug is miscible, the drug will mix with the polymer upon melting. This means that there is a contribution from mixing to the total change in enthalpy. This contribution in enthalpy will be different between the scenario where pure drug is mixed into pure polymer and the more complicated scenario where additional drug is mixed into a polymer that already has drug dissolved within it. In order to use the change in enthalpy to determine the drug load of an ASD at equilibrium in this method, it is important to be able to model both these scenarios accurately.

In experimental setups of intimately mixed drug and polymer particles, mixing or dissolution is typically assumed to occur simultaneous with melting when mixing is favorable. Therefore, there is an equilibrium between crystalline drug and drug-polymer solution. For this equilibrium, the endothermic event observed during heating is considered to be the sum of the enthalpy of melting and enthalpy of mixing. Since mixing is favored ($H_{mix}<0$), a depression of the melting point would also be observed.

$$\Delta H_{mm} = \Delta H_{melt} + \Delta H_{mix}$$

$$\frac{\Delta H_{mm}}{m_{total}} \cdot m_{total} = \frac{\Delta H_{melt}}{m_{drug}} \cdot m_{drug} + \frac{\Delta H_{mix}}{m_{drug}} \cdot m_{drug}$$

$$\frac{\Delta H_{mm}}{m_{total}} = \frac{\Delta H_{melt}}{m_{drug}} \cdot \frac{m_{drug}}{m_{total}} + \frac{\Delta H_{mix}}{m_{drug}} \cdot \frac{m_{drug}}{m_{total}} \#S1$$

Where ΔH_{melt} is the enthalpy of melting, ΔH_{mix} is the enthalpy of mixing, ΔH_{mm} is the enthalpy of melting and mixing, m_{drug} is the mass of the drug and m_{total} is the mass of drug and polymer.

H_{melt} is the contribution to the total enthalpy that comes from melting the pure drug, since this is an extensive thermodynamic property and not influenced by the presence of the polymer it can be calculated from the mass of drug and the relative change in enthalpy from melting pure drug. In a DSC experiment, this will be total energy required to melt pure drug. H_{mix} is also an extensive thermodynamic property, although this case is more complicated since this enthalpy term depends on the ratio of polymer present, and can become even more complicated if some drug is already dissolved within the polymer. First a model describing the case where pure drug is mixed into pure polymer will be derived. The specific case where drug is melted and mixed into polymer that already contains some drug is described in detail later.

The mean field Flory-Huggins solution theory provides the following expression for the enthalpy of mixing, where the change in enthalpy is proportional to the amount of new possibly drug-polymer interactions [32], [33].

$$\Delta H_{mix} = kT\chi N_{drug}\varphi_{polymer} \#S2$$

Where ΔH_{mix} is the enthalpy of mixing, k is the Boltzmann's constant, T is the absolute temperature, χ is the Flory-Huggins interaction parameter, N_{drug} is the number of drug molecules, $\phi_{polymer}$ is the volume fraction of polymer.

Since the Avogadro constant, N_A, is defined by the gas constant, R, and Boltzmann's constant, R, and since the amount of drug in moles, n_{drug}, can be converted to mass, m_{drug}, with the molar mass, M_{drug}, this equation can be rewritten as follows:

$$\Delta H_{mix} = RT\chi\frac{N_{drug}}{N_A}\varphi_{polymer} = RT\chi n_{drug}\varphi_{polymer} = RT\chi\frac{m_{drug}}{M_{drug}}\varphi_{polymer}$$

$$\frac{\Delta H_{mix}}{m_{drug}} = \frac{RT\chi\varphi_{polymer}}{M_{drug}} \#S3$$

By combining Equation S1 and S3, the following relationship for the enthalpy change per total mass and the drug loading, x_{drug}, can be deduced.

$$\frac{\Delta H_{mm}}{m_{total}} = \frac{\Delta H_{melt}}{m_{drug}} \cdot x_{drug} + \frac{RT\chi\varphi_{polymer}}{M_{drug}} \cdot x_{drug} \#S4$$

Where ΔH_{melt} is the enthalpy of melting, ΔH_{mm} is the enthalpy of melting and mixing, m_{drug} is the mass of the drug, m_{total} is the mass of drug and polymer, M_{drug} molar mass, x_{drug} is the drug loading, R is the gas constant, T is the absolute temperature, χ is the Flory-Huggins interaction parameter and $\phi_{polymer}$ is the volume fraction of polymer.

The volume fraction of the polymer can also be expressed in terms of the mass and molecular density of the drug and polymer, p_{drug} and $p_{polymer}$. The volume fraction of the polymer is defined as the volume

of polymer over the sum of the volumes of both the drug and polymer, ϕ_{drug} and $\phi_{polymer}$. Therefore, the sum of the two volume fractions are equal to 1.

$$1 = \varphi_{polymer} + \varphi_{drug}$$

$$\varphi_{polymer} = 1 - \frac{\frac{m_{drug}}{m_{total}}}{\frac{m_{drug}}{m_{total}} + \frac{m_{polymer} \cdot p_{drug}}{m_{total} \cdot p_{polymer}}} = 1 - \frac{x_{drug}}{x_{drug}\left(1 - \frac{p_{drug}}{p_{polymer}}\right) + \frac{p_{drug}}{p_{polymer}}} \#S5$$

Where m_{drug} is the mass of drug, $m_{polymer}$ is the mass of polymer, m_{total} is the mass of drug and polymer, ρ_{drug} is the molecular density of drug, $\rho_{polymer}$ is the molecular density of polymer, ϕ_{drug} is the volume fraction of drug, $\phi_{polymer}$ is the volume fraction of polymer and x_{drug} is the drug loading.

By substituting this term for the volume fraction of polymer in Equation S4, the total change in enthalpy of both melting and mixing can be expressed without the volume fraction.

$$\frac{\Delta H_{mm}}{m_{total}} = \left(\frac{\Delta H_{melt}}{m_{drug}} + \frac{RT\chi}{M_{drug}}\right)x_{drug} - \frac{RT\chi}{M_{drug}} \cdot \frac{x_{drug}^2}{x_{drug}\left(1 - \frac{p_{drug}}{p_{polymer}}\right) + \frac{p_{drug}}{p_{polymer}}} \#S6$$

Where ΔH_{mm} is the enthalpy of melting and mixing, m_{drug} is the mass of drug, $m_{polymer}$ is the mass of polymer, m_{total} is the sum of the mass of drug and polymer, M_{drug} is the molar mass of drug, x_{drug} is the drug loading, ρ_{drug} is the molecular density of drug, $\rho_{polymer}$ is the molecular density of polymer, χ is the Flory-Huggins interaction parameter, R is the gas constant and T is the absolute temperature.

The above enthalpy expression describes the case where the pure drug is melted into the pure polymer. As can be seen, the cases where the drug loading is either 0 or 1 has no change in enthalpy from the mixing component and either have no change in enthalpy or only the change in enthalpy from the melting of pure drug. This relates to the intuitive understanding of a situation where no drug or only drug is present.

This enthalpy term becomes more complex when a crystalline drug is heated along with polymer in which drug is already dissolved. Since enthalpy is a thermodynamic property for a specific conversion, it does not depend on the path through which this conversion was achieved. This means, that the

difference in total enthalpy from mixing and melting drug into polymer for a solution with one drug loading to a solution with a higher drug loading, can be used to determine the total enthalpy from mixing and melting for the first solution, when the other is known. The below equation was used to calculate the drug loading before more drug is melted and mixed into the glass solution from the total change in enthalpy.

$$\Delta\Delta H_{mm} = \Delta H_{mm2} - \Delta H_{mm1}$$

$$\frac{\Delta H_{mm1}}{m_{total}} = \frac{\Delta H_{mm2}}{m_{total}} - \frac{\Delta\Delta H_{mm}}{m_{total}} \#S7$$

Where ΔH_{mm1} is the enthalpy of melting and mixing for the ASD before more drug is dissolved into it, ΔH_{mm2} is the enthalpy of melting and mixing for the ASD after more drug is dissolved into it, $\Delta\Delta H_{mm}$ is the difference between ΔH_{mm2} and Δ_{Hmm1} and m_{total} is the mass of the drug and polymer.

It is important to realize that the total mass expressed in the above equation has to be equal for the two drug-polymer solutions even though they contain different drug loadings. For the case described here, where more drug is melted into a drug-polymer solution the total mass also increases. Therefore, a conversion between the two mass dependent enthalpy changes should be used in this case. The total mass is the sum of the mass of drug and polymer, and in this case the mass of the polymer remains the same.

$$\frac{m_{total1}}{m_{total2}} = \frac{m_{drug1} + m_{polymer}}{m_{drug2} + m_{polymer}} = \frac{\frac{m_{drug1}}{m_{total2}} + \frac{m_{polymer}}{m_{total2}}}{\frac{m_{drug2}}{m_{total2}} + \frac{m_{polymer}}{m_{total2}}} = \frac{m_{drug1}}{m_{total2}} + x_{polymer2} \#S8$$

Where $m_{drug\ 1}$ is the mass of drug in the ASD before more drug is dissolved into it, m_{drug2} is the mass of drug in the ASD after more drug is dissolved into it, $m_{polymer}$ is the mass of polymer, m_{total1} is the mass of drug and polymer in the ASD before more drug is dissolved into it, m_{total2} is the mass of drug and polymer in the ASD after more drug is dissolved into it and $x_{polymer2}$ is the polymer loading in the ASD after more drug is dissolved into it.

The drug loading at one state, is the mass of drug over the total mass at that state.

$$x_{drug1} = \frac{m_{drug1}}{m_{drug1} + m_{polymer}} = \frac{\frac{m_{drug1}}{m_{total2}}}{\frac{m_{drug1}}{m_{total2}} + \frac{m_{polymer}}{m_{total2}}}$$

$$x_{drug1} \cdot x_{polymer2} = \frac{m_{drug1}}{m_{total2}}(1 - x_{drug1}) \#S9$$

Where $m_{drug\ 1}$ is the mass of drug in the ASD before more drug is dissolved into it, m_{drug2} is the mass of drug in the ASD after more drug is dissolved into it, $m_{polymer}$ is the mass of polymer, m_{total1} is the mass of drug and polymer in the ASD before more drug is dissolved into it, m_{total2} is the mass of drug and polymer in the ASD after more drug is dissolved into it, x_{drug1} is the drug loading in the ASD before more drug is dissolved into it and $x_{polymer2}$ is the polymer loading in the ASD after more drug is dissolved into it.

By combining Equation S8 and S9, the following relationship for the total masses for the two glass solutions with different drug loadings can be obtained. This can be used to describe the total enthalpy of melting and mixing for the first drug-polymer solution (shown in Equation S6) in mass terms according to the drug-polymer solution where more drug is dissolved into the solution.

$$\frac{m_{total1}}{m_{total2}} = \frac{x_{drug1} \cdot x_{polymer2}}{1 - x_{drug1}} + x_{polymer2}$$

$$\frac{\Delta H_{mm1}}{m_{total1}} = \frac{\Delta H_{mm1}}{m_{total2}} \cdot \frac{m_{total2}}{m_{total1}} = \left(\frac{\Delta H_{mm2}}{m_{total2}} - \frac{\Delta\Delta H_{mm}}{m_{total2}}\right) \cdot \left(\frac{x_{drug1} \cdot x_{polymer2}}{1 - x_{drug1}} + x_{polymer2}\right)^{-1} \#S10$$

Where ΔH_{mm1} is the enthalpy of melting and mixing for the ASD before more drug is dissolved into it, ΔH_{mm2} is the enthalpy of melting and mixing for the ASD after more drug is dissolved into it, $\Delta\Delta H_{mm}$ is the difference between ΔH_{mm2} and Δ_{Hmm1}, m_{total1} is the mass of drug and polymer for the ASD before more drug is dissolved into it, m_{total2} is the mass of drug and polymer for the ASD after more drug is dissolved into it, x_{drug1} is the drug loading of the ASD before more drug is dissolved into it and $X_{polymer2}$ is the polymer loading of the ASD after more drug is dissolved into it.

Conflicts of interest

The authors declare no conflicts of interest.

Author contributions

Peter Meiland: methodology, validation, investigation, writing-original draft. **Bjarke Strøm Larsen:** methodology, conceptualization, validation, investigation, writing- original draft. **Matthias Manne Knopp:** methodology, supervision, conceptualization, investigation, writing-review & editing. **Ingunn Tho:** methodology, supervision, conceptualization, investigation, writing-review & editing. **Thomas Rades:** methodology, supervision, conceptualization, investigation, writing-review & editing, administration, funding acquisition.