Hence, if a drug is soluble in an analogue of the polymer, it is most likely also soluble in the polymer. In conclusion, the solubility of a drug in the liquid analogue N-vinylpyrrolidone (NVP). The experimental solubility of IMC in the low-molecular-weight PVP K12 was not significantly different from that in the higher molecular weight PVPs (K25, K30, and K90). The calculated solubilities derived from the solubility in NVP (0.31–0.32 g/g) were found to be lower than those experimentally determined in PVP (0.38–0.40 g/g). Nevertheless, the similarity between the values indicates that the analogue solubility can provide valuable indications on the solubility in the polymer. Hence, if a drug is soluble in an analogue of the polymer, it is most likely also soluble in the polymer. In conclusion, the solubility of a given drug–polymer system is determined by the strength of the drug–polymer interactions rather than the molecular weight of the polymer. Therefore, during the first screenings for drug solubility in polymers, only one representative molecular weight per polymer is needed.

**Keywords:** solid dispersion; PVP; molecular weight; indomethacin; polymer; amorphous; DSC; spray drying; Flory–Huggins; Gordon–Taylor

**ABSTRACT:** In this study, the influence of polymer molecular weight on drug–polymer solubility was investigated using binary systems containing indomethacin (IMC) and polyvinylpyrrolidone (PVP) of different molecular weights. The experimental solubility in PVP, measured using a differential scanning calorimetry annealing method, was compared with the solubility calculated from the solubility of the drug in the liquid analogue N-vinylpyrrolidone (NVP). The experimental solubility of IMC in the low-molecular-weight PVP K12 was not significantly different from that in the higher molecular weight PVPs (K25, K30, and K90). The calculated solubilities derived from the solubility in NVP (0.31–0.32 g/g) were found to be lower than those experimentally determined in PVP (0.38–0.40 g/g). Nevertheless, the similarity between the values indicates that the analogue solubility can provide valuable indications on the solubility in the polymer.

**INTRODUCTION**

The development of amorphous drug delivery systems is getting increased attention in the pharmaceutical industry because of the potential of these systems to enhance the oral bioavailability of poorly water soluble drugs. The free energy of the amorphous form is higher than that of the corresponding crystalline state, which will increase the apparent drug solubility and dissolution rate, compared with the crystalline form of the drug. However, as the amorphous form is thermodynamically unstable, the drug will nucleate and recrystallize over time. Therefore, stabilization of the amorphous form is critical for this formulation approach to succeed. Currently, the preferred method to stabilize amorphous drugs against crystallization is solid molecular dispersion in a polymer (glass solution). The mechanisms responsible for the stabilization are still not fully understood however, it is generally accepted that the high glass transition temperature ($T_g$) of polymers and drug–polymer intermolecular interactions play an important role. Incorporation of the drug in a polymer with a high $T_g$ elevates the $T_g$ of the drug–polymer system, compared with the $T_g$ of the pure amorphous drug, and reduces the molecular mobility and hence crystallization rate of the drug during storage. Molecular non-covalent interactions, such as hydrogen- and ionic bonds, van der Waals forces and hydrophobic interactions are also considered to be responsible for improving and maintaining a supersaturated drug concentration during dissolution in aqueous media. In order to fully stabilize the molecularly dispersed drug in the polymer against recrystallization, it is essential that the drug is present below its saturation solubility in the polymer matrix at typical storage temperature and therefore, determination of drug–polymer solubility is of great interest.

For a polymer to be useful in a commercial pharmaceutical drug application, it must have a $T_g$ well above room temperature. It is well known that the $T_g$ and other properties such as viscosity, free volume and tensile strength are dependent on the average molecular weight of the polymer. Water-soluble polymers such as polyvinylpyrrolidone (PVP) and high-molecular-weight polyethylene glycol are amongst the most commonly used carriers for solid dispersions. This is because of their high molecular weight and universal solubility in both hydrophobic and hydrophilic solvents, making them particularly suitable for solvent evaporation techniques such as spray drying.

Polyvinylpyrrolidone is a synthetic linear chain homopolymer with no branching obtained by polymerization of the monomer N-vinylpyrrolidone (NVP). It is available in several viscosity grades, ranging from low to high mean molecular weight (2500–3,000,000 g/mol), characterized by the $K$ value in the pharmacopeias. As the molecular weight of PVP
increases, so does the viscosity, whereas the aqueous solubility of the polymer decreases. The influence of molecular weight of PVP on drug dissolution from solid dispersions has been studied widely. Further, the drug dissolution rate and higher apparent drug solubility in aqueous solution compared to the solid parent compound. Furthermore, the drug dissolution rate decreases with increasing PVP molecular weight, which is probably due to increased viscosity of the stagnant diffusion layer. However, even though the aqueous drug solubility increases with polymer concentration, it does not seem to be significantly affected by the molecular weight of PVP.

The positive effects of PVP on drug solubility and dissolution rate are generally obtained from dispersions with the drug molecularly dispersed in the polymer (glass solutions) and hence, the solubility of the drug in the polymer is of particular importance. If the drug is molecularly dispersed in the polymer below the equilibrium solubility, it will remain physically stable during storage at least as long as significant water sorption into the glass solution can be avoided. Therefore, different methods to measure the solubility of drugs in polymers have been developed based on differential scanning calorimetry (DSC) and several studies have already determined the solubility of different drugs in PVP. Furthermore, according to Marsac et al., the solubility of a drug in PVP can be predicted from the solubility in a low-molecular-weight analogue of PVP by assuming that the analogue constitutes the lattice of the polymer. However, despite the widespread use of PVP, the influence of polymer molecular weight (chain length) on drug–polymer solubility has not been sufficiently elucidated. Only a few studies have addressed this issue and none have, to the best of our knowledge, supported the theoretical considerations and predictions with relevant experimental data. Therefore, the aim of the present study was to investigate the influence of polymer molecular weight on the drug–polymer solubility of indomethacin–PVP (IMC–PVP) binary systems prepared by spray drying using a recently proposed DSC protocol and comparing this with the prediction derived from the solubility in NVP.

**EXPERIMENTAL**

**Materials**

Indomethacin ($M_w = 357.79 \text{ g/mol}$) was purchased from Hawkins, Inc. Pharmaceutical Group (Minneapolis, Minnesota). Kollidon® 12 PF (PVP K12, $M_w = 2000–3000 \text{ g/mol}$), Kollidon® 17 PF (PVP K17, $M_w = 7000–11,000 \text{ g/mol}$), Kollidon® 30 (PVP K30, $M_w = 44,000–54,000 \text{ g/mol}$), and Kollidon® 90® F (PVP K90, $M_w = 1,000,000–1,500,000 \text{ g/mol}$) were kindly supplied by BASF (Ludwigshafen, Germany). NVP ($M_w = 111.14 \text{ g/mol}$) was purchased from Sigma–Aldrich Company (St. Louis, Missouri). All materials were used as received.

**Spray Drying**

Indomethacin and PVP (85:15, w/w, 2000 mg) were dissolved in 20 mL of aceton–ethanol (80:20, v/v) and spray dried using a 4M8-TriX spray drier from ProCepT (Zelzate, Belgium). The spray dryer was pre-conditioned using pure solvent and, when in thermal equilibrium, the solutions were fed at a rate of 3 g/min (addition rate <10% of lower explosion limit = 3.7 g/min) and atomized with a 0.5 mm two-fluid nozzle with at a pressure of 1.3 bar (20 L/min). Heated air was drawn through the open loop drying system at 500 L/min with a temperature of 100°C.

**Film Casting**

In order to reduce the time- and drug consumption, film casting was used to prepare the drug–polymer mixtures for the Gordon–Taylor relationship. IMC and PVP (20, 40, 60, 80, w/w, 100 mg) were dissolved in 1 mL of aceton–ethanol (80:20, v/v) and cast onto a Teflon coated 76 × 26 mm Menzel-glass. The solvent was evaporated on a Jenway 1100 Hotplate from Bibby Scientific Ltd. (Staffordshire, UK) using a plate temperature of 150°C. The dried samples were scraped off the Teflon-coated glass plate and gently ground using a mortar and pestle.

**Differential Scanning Calorimetry**

The spray dried powders, cast films and pure compounds were analyzed using a DSC Q2000 from TA Instruments Inc. (New Castle, Delaware). Sample powders (2–3 mg) were scanned from −10°C to 200°C and purged with 50 mL/min pure nitrogen gas using Tzero Aluminum Hermetic pans with a perforated lid. The temperature and enthalpy of the DSC instrument were calibrated using indium as a standard. The thermograms were analyzed using the Universal Analysis 2000 (version 4.5A) software.

**X-ray Powder Diffraction**

X-ray powder diffraction (XRPD) analysis was performed using an XPert PRO MRD diffractometer from PANalytical (Almelo, The Netherlands) equipped with a TCU100 temperature control unit and an X’Celerator detector using nickel-filtered CuKa radiation ($\lambda = 1.5406 \text{ Å}$) at 45 kV and 40 mA. Approximately 1 mg of sample powder was placed on zero background (0-BG) Si-plates and measured over the angular range 3°–40° 2θ at a scanning rate of 1.20° 2θ/min. The diffractograms were analyzed using the XPert Data Viewer (version 1.2) software.

**Particle Density**

The particle densities of the raw materials were determined using an AccuPyc 1330 helium pycnometer from Micromeritics Instruments Corporation (Norcross, Georgia). Prior to the measurements, approximately 1 g of the samples was annealed in an oven just above the melting point and quenched cooled to remove any sorbed moisture and yield the amorphous form. The samples were weighed before analysis and purged with 19.5 psig dry helium. The reported results are averages of 10 consecutive measurements.

**Solubility Determination in Analogue**

The solubility of IMC in NVP was assayed using a HPLC system comprised of a L-7110 pump, a L-7200 auto sampler, a L-7300 pump, and a L-7481 auto sampler. Prior to the measurements, approximately 1 g of the samples was annealed in an oven just above the melting point and quenched cooled to remove any sorbed moisture and yield the amorphous form. The samples were weighed before analysis and purged with 19.5 psig dry helium. The reported results are averages of 10 consecutive measurements.
Heto Lab Equipment (Birkerod, Denmark). A sample was withdrawn, filtered using a 0.2 μm PTFE syringe filter from Merck Millipore Ltd. (Darmstadt, Germany) and properly diluted with mobile phase. The diluted sample was then injected in the HPLC and analyzed using the aforementioned method.

Solubility Determination in Polymers

The method used to determine the solubility of IMC in PVP was a DSC scanning protocol based on recrystallization of a supersaturated amorphous dispersion.\(^{27,28}\) A supersaturated amorphous dispersion of IMC–PVP (85:15, w/w), prepared by spray drying, was loaded into the DSC and annealed at different temperatures (120°C–145°C) for 3 h to crystallize the excess drug in the mixture and reach equilibrium solubility. After annealing, the sample was cooled to −10°C and ramped at a rate of 5°C/min to 100°C to determine the \(T_g\) of the demixed material. The concentration of drug remaining in the polymer matrix was then derived directly from the \(T_g\) of the demixed material using the Gordon–Taylor model.\(^{31}\) By repeating this protocol at different annealing temperatures, a part of the solubility curve was obtained and by fitting to the Flory–Huggins theory,\(^{32}\) the solubility at ambient temperature was obtained by extrapolation. For a more detailed description of the method, the interested reader is referred to Mahieu et al.\(^{29,30}\) and Knopp et al.\(^{28}\)

**THEORETICAL CONSIDERATIONS**

Statistical Analysis

The Flory–Huggins theory\(^ {32}\) was used to model the measurements of the \(T_g\) for various values of the annealing temperature (\(T_a\)) by adjusting the interaction parameter \(\chi\). In order to find the least-square estimate of \(\chi\), it is important to understand which variable is subject to experimental noise. The \(T_g\) is the variable under control and will be regarded as free of error whereas the \(u_{IMC}\) is subject to error as it is derived from the \(T_m\). The least-squares estimate \(\hat{\chi}\) is therefore found by minimizing the residuals sum-of-square given SSR(\(\chi\)) = \(\sum_{i=1}^{N} (v_{IMC}^{\text{measurement}}(i) - v_{IMC}^{\text{fitted}}(i; \hat{\chi}))^2\) by, where \(N\) is the number of measurements. The standard deviation is given by \(s_{\hat{\chi}} = \sqrt{\frac{\text{SSR}(\hat{\chi})}{J N - J}}\), where \(J\) denotes the Jacobian matrix at \(\hat{\chi}\). The 1−\(\alpha\) prediction interval for a future observation of \(\chi\) is given by:

\[
\hat{\chi} \pm t_{\alpha/2,N-1} s_{\hat{\chi}} \sqrt{1 + \frac{1}{N}}
\]

where \(t_{\alpha/2,N-1}\) is the \(\alpha/2\) quantile in the \(t\) distribution with \(N−1\) degrees of freedom.

Prediction of Drug–Polymer Solubility from Drug–Analogue Solubility

It is possible to estimate the solubility in the polymer from the solubility in a low molecular weight analogue using the Flory–Huggins theory,\(^ {32}\) by assuming that the analogue constitutes the lattice of the polymer, and that the activity coefficient and solubility limit of the drug in the polymer is equal to that of the analogue.\(^ {29,30}\) In this study, NVP (the monomeric precursor to PVP) was considered as the lattice in the model.

The activity coefficient in NVP (\(\gamma_{NVP}\)) is the ratio of ideal mole fraction solubility (\(X_{id}\)) and the experimental mole fraction solubility of IMC in NVP (\(X_{exp}\)). The \(X_{exp}\) was obtained from HPLC analysis as described previously and \(X_{id}\) was calculated using:\(^ {29}\)

\[
\ln(X_{id}) = \frac{-\Delta H_m(T_m - T)}{RT} + \frac{\Delta C_p(T_m - T)}{R} - C_P \ln \left(\frac{T_m}{T}\right)
\]

where \(\Delta H_m\) and \(T_m\) are the enthalpy of fusion and melting temperature for IMC, respectively, \(\Delta C_p\) is the heat capacity change at the glass transition of amorphous IMC, \(R\) is the gas constant, and \(T\) is the temperature where the solubility estimate is desired. The activity coefficient in NVP (\(\gamma_{NVP}\)) can now be used to calculate the activity coefficient in PVP (\(\gamma_{PVP}\)) at the solubility limit using\(^ {29}\):

\[
\ln(\gamma_{PVP}) = \ln(\gamma_{NVP}) + \frac{MV_{IMC}}{MV_{NVP}} \left[ \frac{1}{m_{IMC}} \ln \left( \frac{\nu_{IMC}}{\nu_{exp}} \right) + \frac{1}{m_{PVP}} \left( 1 - \frac{1}{m_{PVP}} \nu_{PVP} \right) \right]
\]

where \(MV_{IMC}\) and \(MV_{NVP}\) are the molar volume of IMC and NVP, \(m_{IMC}\) and \(m_{PVP}\) are the ratio of the volume of IMC and PVP to the NVP, and \(\nu_{IMC}\) and \(\nu_{PVP}\) are the volume fraction of IMC and PVP, respectively. Finally, the mole fraction solubility of crystalline IMC in PVP can be derived from the ratio of \(X_{id}\) to \(\gamma_{PVP}\) and converted to mass fraction (w/w) for comparison with the experimentally determined solubility. It must be noted that this approach provides an estimate of the solubility in a liquid rather than a glass and therefore, should be evaluated with caution.\(^ {29}\)

**RESULTS**

Solid-State Characterization

Figure 1 presents the XRPD patterns for unprocessed IMC and PVP, amorphous IMC, and spray dried IMC–PVP (85:15, w/w)
before and after annealing. The diffraction patterns for all the PVP grades (K 12, 25, 30, 90) and spray dried IMC–PVP (85:15, w/w) systems were similar, and therefore only representative diffractograms with PVP K12 are shown. The diffraction pattern of crystalline IMC (Fig. 1a) shows Bragg peaks at 11.6°, 19.6°, 21.8°, and 26.6° 2θ, characteristic for the stable γ-form of IMC. After spray drying (Fig. 1c), the characteristic peaks for γ-IMC were absent and replaced by a diffuse halo with no Bragg peaks, indicating that IMC was amorphous. The diffraction patterns of pure PVP (Fig. 1d) and spray dried IMC–PVP (85:15, w/w) (Fig. 1e) also revealed a diffuse halo, indicating that spray drying successfully produced a supersaturated amorphous dispersion. Further studies revealed that the IMC–PVP (85:15, w/w) systems remained amorphous during the course of investigation. As can be identified from the Bragg peaks, the IMC recrystallized into the initial γ-form of the drug after annealing of the IMC–PVP (85:15, w/w) systems (Fig. 1b). Increasing the annealing time from 3 to 12 h did not cause any polymorphic conversion (data not shown).

Thermal Analysis

In Figure 2, the DSC scans of crystalline and amorphous IMC, PVP K12 and processed IMC–PVP K12 (85:15, w/w) mixture are shown. The thermograms for all the PVP grades provided similar DSC patterns (apart from increasing Tg as a function of molecular weight) and therefore only representative scans with PVP K12 are included in the figure. The DSC scan for crystalline IMC (Fig. 2a) showed a melting with a peak around 160°C as the only thermal event. The temperature and enthalpy of melting were similar to those expected for the γ-form of IMC previously identified on XRPD. After amorphization of pure IMC, through film casting (see Experimental section), the DSC scan showed a clear Tg of 45°C followed by a strong recrystallization event ranging from 80°C to 110°C and a melting peak around 160°C (Fig. 2b). Prior to the DSC scan of PVP K12 the sample was annealed for 5 min at 100°C to evaporate the sorbed water from the hygroscopic polymer. The subsequent scan showed a change in the Tg with a midpoint around 107°C (Fig. 2c). The thermogram for the spray dried IMC–PVP K12 (85:15, w/w) (Fig. 2d) mixture revealed a single Tg located between that of pure amorphous IMC and PVP K12, indicating that spray drying produced a homogenous amorphous mixture where IMC and PVP were mixed at a molecular level. The scan did not display recrystallization and consequently also did not exhibit melting, however, during the annealing stage a clear exothermic recrystallization signal was present, which indicates that IMC was supersaturated in PVP. The data obtained from the DSC scans are summarized in Table 1.

Prediction of Drug–Polymer Solubility

The experimental solubility of IMC in PVP was determined using the analytical protocol described in the Experimental section. The equilibrium solubility of IMC in PVP at a given temperature can be derived directly from the Tg of the demixed material after annealing using the Gordon–Taylor model:

\[
X_{\text{IMC}} = \frac{\frac{T_g(\text{PVP})}{T_g(\text{IMC})} - \frac{T_g(\text{IMC})}{T_g(\text{PVP})}}{\frac{T_g(\text{PVP})}{T_g(\text{IMC})} - \frac{T_g(\text{IMC})}{T_g(\text{PVP})} + T_g(\text{PVP})}
\]

where \(X_{\text{IMC}}\) is the mass fraction of amorphous IMC in the mixture, \(T_g(\text{IMC})\) is the glass transition temperature of the mixture as a function of \(X_{\text{IMC}}\), \(T_g(\text{PVP})\) and \(T_g(\text{IMC})\) are the glass transition temperatures of IMC and PVP respectively, and K is ratio of the heat capacity change over the glass transition (\(\Delta C_p\)) of the polymer to the drug.

Table 1 gives all parameters necessary to determine the Gordon–Taylor relationship using Eq. (4). The Gordon–Taylor relationship and experimentally determined data points are illustrated along with the solubility curves in Figure 3.

Having established the Gordon–Taylor relationship, it was possible to obtain data points on the solubility curve. Experimental points were obtained in 5°C intervals and the equilibrium solubility of IMC in PVP at each temperature was derived from the \(T_g\) of the demixed material after annealing using Eq. (4). The \(T_g\) of the demixed materials, after annealing, and the corresponding equilibrium solubility of IMC in PVP are listed in Table 2. As can be seen, the solubility increases with increasing annealing temperature.

The solubility at ambient temperature was predicted by extrapolation from the solubility data from Table 2 using the Flory–Huggins theory:

\[
\frac{\Delta H_m}{R} \left(\frac{1}{T_m} - \frac{1}{T_a}\right) = \ln(v_{\text{IMC}})
\]

\[
+ \left(1 - \frac{1}{\lambda}\right)(1 - v_{\text{IMC}}) + \chi(1 - v_{\text{IMC}}^2)
\]

where \(\Delta H_m\) and \(T_m\) are the enthalpy of fusion and melting temperature for IMC, respectively, \(R\) is the gas constant, \(T_a\) is the annealing temperature, \(\lambda\) is the molar volume ratio of the polymer to the drug, \(\chi\) is the Flory–Huggins interaction parameter, and \(v_{\text{IMC}}\) is the volume fraction of IMC.

Tables 1 and 2 provide the data needed to obtain the solubility curves of IMC in PVP using Eqs. (4) and (5) and the resulting solubility curves can be found in Figure 3. The solubility at 20°C is predicted by extrapolation and can be found in Table 3. This extrapolation of course requires that the model assumptions are valid in the entire extrapolated temperature range. The greatest difference in the experimental solubility...
**Table 1.** Experimental Physical and Thermodynamic Values Measured by DSC and Density Measured by Helium Pycnometry (Values are Mean ± SD, n = 3)

<table>
<thead>
<tr>
<th>Material</th>
<th>$M_w$ (g mol$^{-1}$)$^a$</th>
<th>Density (g cm$^{-3}$)</th>
<th>$T_g$ (°C)</th>
<th>$\Delta C_p$ (J g$^{-1}$ K$^{-1}$)</th>
<th>$\Delta H_m$ (J g$^{-1}$)</th>
<th>$T_m$ (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMC</td>
<td>357.79</td>
<td>1.38 ± 0.00</td>
<td>45.5 ± 0.2</td>
<td>0.38 ± 0.02</td>
<td>113.4 ± 2.6</td>
<td>161.0 ± 0.1</td>
</tr>
<tr>
<td>N-vinylpyrrolidone</td>
<td>111.14</td>
<td>1.04 ± 0.00</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PVP K12</td>
<td>2500</td>
<td>1.19 ± 0.00</td>
<td>107.1 ± 0.5</td>
<td>0.37 ± 0.02</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PVP K25</td>
<td>25,000</td>
<td>1.18 ± 0.00</td>
<td>152.4 ± 0.3</td>
<td>0.30 ± 0.01</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PVP K30</td>
<td>40,000</td>
<td>1.12 ± 0.00</td>
<td>159.3 ± 0.1</td>
<td>0.28 ± 0.02</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PVP K90</td>
<td>1,100,000</td>
<td>1.21 ± 0.00</td>
<td>173.3 ± 0.3</td>
<td>0.29 ± 0.05</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

$a$ Average $M_w$ according to the supplier.

**Figure 3.** Equilibrium solubility of IMC ($X_{IMC}$) in PVP of different molecular weight as a function of annealing temperature ($T_a$). Red circles (○) represent the data from PVP K12, green squares (■) represent the data from PVP K25, blue diamonds (♦) represent the data from PVP K30, and purple triangles (▲) represent the data for PVP K90. The evolution of solubility of the four data sets has been fitted with the Flory–Huggins model (black curves) including the 95% prediction interval (dotted curves). The gray circles (●) represent the experimental relationship between $T_g$ and $X_{IMC}$ and the gray curve is the theoretical Gordon–Taylor relationship.

**Table 2.** Glass Transition Temperatures ($T_g$) of the Demixed Material and the Corresponding Equilibrium Solubilities of IMC in PVP ($X_{IMC}$) Obtained at Different Annealing Temperatures ($T_a$) (Values are Mean ± SD, n = 3)

<table>
<thead>
<tr>
<th></th>
<th>IMC–PVP K12</th>
<th>IMC–PVP K25</th>
<th>IMC–PVP K30</th>
<th>IMC–PVP K90</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_a$ (°C)</td>
<td>$T_g$ (°C)</td>
<td>$X_{IMC}$ (w/w)</td>
<td>$T_g$ (°C)</td>
<td>$X_{IMC}$ (w/w)</td>
</tr>
<tr>
<td>145</td>
<td>55.2 ± 0.3</td>
<td>0.836</td>
<td>59.7 ± 0.2</td>
<td>0.834</td>
</tr>
<tr>
<td>140</td>
<td>56.4 ± 0.8</td>
<td>0.815</td>
<td>62.2 ± 0.2</td>
<td>0.805</td>
</tr>
<tr>
<td>135</td>
<td>57.9 ± 1.3</td>
<td>0.790</td>
<td>63.9 ± 1.4</td>
<td>0.786</td>
</tr>
<tr>
<td>130</td>
<td>59.4 ± 0.9</td>
<td>0.765</td>
<td>65.5 ± 1.3</td>
<td>0.768</td>
</tr>
<tr>
<td>125</td>
<td>60.6 ± 0.9</td>
<td>0.745</td>
<td>67.9 ± 0.3</td>
<td>0.741</td>
</tr>
<tr>
<td>120</td>
<td>61.8 ± 0.6</td>
<td>0.725</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

$a$ Data not obtained as system did not reach equilibrium solubility within the annealing period.
Table 3. Predicted Solubilities of IMC in PVP of Different Molecular Weight Obtained from Calculations and Experimental Solubility along with the Corresponding Flory–Huggins Interaction Parameter γ, Activity Coefficient γ, and the 95% Prediction Interval

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity coefficient γ</td>
<td>0.076</td>
<td>0.120</td>
<td>0.126</td>
<td>0.128</td>
<td>0.126</td>
</tr>
<tr>
<td>Solubility at 20°C (g/g)</td>
<td>0.52</td>
<td>0.33</td>
<td>0.31</td>
<td>0.31</td>
<td>0.31</td>
</tr>
<tr>
<td>Interaction parameter χ</td>
<td>–</td>
<td>–8.9</td>
<td>–9.3</td>
<td>–9.5</td>
<td>–9.1</td>
</tr>
<tr>
<td>Values obtained from experimental solubility in PVP</td>
<td>–</td>
<td>0.27–0.46</td>
<td>0.32–0.45</td>
<td>0.28–0.44</td>
<td>0.33–0.43</td>
</tr>
</tbody>
</table>

was seen between NVP and PVP K12. In contrast, the difference between the solubility in the low-molecular-weight PVP K12 and that of the high-molecular-weight PVP K90 was negligible.

The importance of including statistical analysis in the assessment of solubility measurements of this kind has previously been emphasized. This is because the solubility curve fit is very sensitive even to small variations in the inter-replicate variance (reproducibility) and intra-replicate variance (fit to the Flory–Huggins theory). Consequently, in order to evaluate the goodness-of-fit, a statistical analysis was performed and expressed as a prediction interval using Eq. (1) as described in the Experimental section. The prediction intervals from the four different IMC–PVP systems are given in Table 3 and illustrated in Figure 3. All the intervals were relatively narrow, indicating a combination of good fit to the Flory–Huggins theory and good reproducibility of the measurements.

The solubility of IMC in the monomer NVP at 20°C was determined using the analytical protocol described in the Experimental section and was measured to be 0.539 g/cm³. From this value, the predicted solubility in the polymers was calculated using Eqs. (2) and (3). The predicted solubilities of IMC in the different PVPs can also be found in Table 3.

**DISCUSSION**

The relatively high solubility predicted in this study is to some extent contradicted by the correlation between the experimental and theoretical Gordon-Taylor relationship, as this indicates that the interactions between the two compounds are weak. However, as identified by Taylor and Zografi, there is strong hydrogen bonding between the carbonyl group of PVP and the hydroxyl group of IMC. The pure amorphous IMC is mainly composed of carboxylic acid dimers involving two hydrogen bonds and thus, the formation of the IMC–PVP hydrogen bond requires the disruption of a hydrogen bond in the IMC dimer. As these two kinds of hydrogen bonds are similar in terms of energy, this explains the seemingly “weak” interactions between the compounds suggested by the correlation between the experimental and theoretical Gordon-Taylor relationship.

Although the solubility data at elevated temperature is in accordance with values reported in literature based on DSC, there seems to be some discrepancy between the predicted solubility at 20°C and predictions based on molecular dynamics. However, as this is out of scope of this study, it needs to be addressed in detail in future work.

In order to support the experimentally determined solubility with the calculated solubility, the solubility of IMC in the liquid NVP was determined. The solubility of IMC in NVP at room temperature was higher than the values extrapolated from the solubility in the PVP polymers at elevated temperatures (see Table 3). This difference was most likely due to the reduced entropic contribution to the mixing free energy in the PVP system compared with the NVP solution. As described previously by Marsac et al., the entropy of mixing for a solid drug–polymer system is less favorable than for a liquid drug–analogue system because of the reduced configurational entropy of the polymer compared to the analogue — a consequence of the connectivity of the repeat units in the polymer chain. However, the effect of polymer molecular weight on mixing thermodynamics is less pronounced and in fact, the entropy contribution has been found to be relatively constant regardless of molecular weight.

Consequently, it is presumed that the mixing thermodynamics of a drug–polymer system is governed by the relative strength of the enthalpic interactions between the drug and polymer rather than the entropy of mixing. In other words, the solubility of a given drug–polymer system is essentially determined by the drug–polymer interactions and not the anti-plasticizing effect, and thus molecular weight, of the polymer. This means that if a drug is immiscible in a polymer, a change to a different polymer is more likely to induce solubility than to switch to a different molecular weight of the same polymer. Furthermore, any observed difference of solubility in relation to molecular weight of the polymer is only expected with polymers consisting of a few monomers.

This is in accordance with the observations made in this study where the greatest difference in the experimental solubility was seen between NVP and PVP K12. In contrast, the experimental solubility in the low-molecular-weight PVP K12 was not significantly different from that of the high-molecular-weight PVP K90 (see Table 3). Furthermore, after correcting for the reduced entropic contribution to the mixing free energy in the PVP systems using Eqs. (2) and (3), the calculated solubilities (0.31–0.33 g/g) were lower than the experimentally determined values (0.38–0.40 g/g). This could imply that either Eq. (3) underestimates solubility or that the annealing method overestimates the solubility of IMC in PVP. Nonetheless, the close similarity between the values indicates that the analogue solubility approach can provide valuable indications on the solubility of a drug in a polymer where a liquid analogue is available. Thus, if a drug is soluble in an analogue of the polymer it is most likely also soluble in the polymer, particularly if the
molecular structure of the analogue is not altered significantly during polymerization.

Polyvinylpyrrolidone is obtained by radical polymerization, which involves the breaking of the carbon-carbon double bond in NVP. The product is mainly polymerized in aqueous solution using hydrogen peroxide as initiator and therefore, the polymers have hydroxyl and carbonyl end groups. Consequently, these end groups have more and different functional groups than the repeat units in the polymer chain, which can interact non-covalently with the drug and potentially influence solubility due to additional intermolecular interactions. However, even for the lowest molecular weight polymer in this study, PVP K12, the end groups constitute less than 10% of the total molecular weight and therefore, the relative influence of the end groups on drug solubility in the larger polymers is presumed to be minor.

These theoretical considerations all support the hypothesis that molecular weight of a polymer does not influence the solubility of a drug significantly. This is in accordance with the findings reported by Marsac et al. and Paudel et al., who investigated the solubility of a number of poorly water soluble drugs in a low-molecular-weight analogue to PVP and used this to calculate the solubility in different molecular weight grades of PVP. Although these calculations were not verified with experimental data, and thus no definite conclusion about the influence of molecular weight of the polymer could be drawn, they support the hypothesis of the present study. Consequently, when a new solid glass solution is to be formulated, only one representative molecular weight per polymer seems needed during the initial screening of drug–polymer solubility. However, it is important to emphasize that this does not mean that the influence of polymer molecular weight on other important factors such as dissolution rate, physical stability, degree of supersaturation, apparent drug solubility and crystallization inhibition should not be considered in the polymer selection process.

Although the solubility of a drug in a polymer is mainly governed by drug–polymer interactions, previous studies have shown that the physical stabilization of the drug is associated with the anti-plasticizing effect of the polymer, that is, increased viscosity and decreased molecular mobility of the binary system will decrease the nucleation rate of the drug molecule. Therefore, even though the solubility of IMC in PVP may not be influenced by the molecular weight of the polymer, the kinetic stability of a supersaturated system might.

The molecular mobility and \( T_g \) are correlated to the molecular weight of the polymer and increasing the chain length will generally increase viscosity and \( T_g \) and hence, decrease the molecular mobility. If the molecular mobility is decreased, the crystallization kinetics may become slower than the time scale of the annealing period in this study. Because of the slow crystallization kinetics, the \( T_g \) of the demixed material remains the same after a given annealing temperature, which may be seen as a plateau effect.

The effect of polymer molecular weight on the kinetic stability of the supersaturated drug-polymer systems is directly reflected in the results of this study, more particularly the onset temperature of this plateau effect. For example, after annealing of the IMC–PVP K90 mixture for 3 h at 120°C–130°C, the \( T_g \) was not different from that measured after annealing at 135°C (data not shown). In practice, this means that the system did not reach equilibrium solubility within the 3 h of annealing at these lower temperatures. Hence, depending on the molecular weight of the polymer and the associated annealing time, this plateau effect will set in at different temperatures. Increasing the annealing time will generally allow for more data points to be obtained, but as the crystallization kinetics are slow, even doubling the annealing time might not provide additional data points. In fact, the crystallization kinetics can be so slow that it is not observable as an exotherm in the DSC and therefore, the system can falsely be considered in equilibrium. However, a single-point determination at 140°C revealed that increasing the annealing time from 3 to 12 h did not influence the \( T_g \) (and thus solubility) significantly (data not shown), indicating that the system was in equilibrium after 3 h. Accordingly, from a cost-benefit point of view, the annealing time was fixed at 3 h and consequently, the onset temperature of the plateau effect increased with increasing molecular weight of the polymer (see Table 2), indicating that kinetic stabilization is directly proportional to molecular weight of the polymer.

These considerations and observations are in accordance with Paudel et al., who showed a correlation between recrystallization temperature and polymer molecular weight in the order PVP K90 > PVP K25 > PVP K12. However, other parameters including glass stability, miscibility, and degree of supersaturation also affect the nucleation and crystallization rate of drugs in amorphous dispersions. It is therefore important to establish the annealing time needed to reach crystallization equilibrium every time a new drug–polymer mixture is studied. The exothermic crystallization event can be monitored from the heat flow during the isothermal annealing of the mixtures and the process is considered to be in equilibrium after the signal reaches a baseline. However, as the crystallization rate decreases rapidly when the concentration approaches equilibrium solubility, the “true equilibrium” may not be reached. Consequently, it is rational to assume that the annealing method might overestimate the true saturation solubility of the drug in the polymer, but this assumption has not been verified in this study.

It is likely that the findings reported in the present study are applicable for most amorphous homopolymers, alternating copolymers, and even block copolymers if the subunit ratio can be controlled. If any, the biggest difference in solubility was expected for low-molecular-weight polymers as the end groups potentially have different functional groups than the repeat units in the polymer chain and because the relative difference in the entropic contribution becomes larger with decreasing molecular weight. Further studies are needed in order to confirm these findings, which could include a validation with different drug–polymer systems and long term stability to confirm the solubility at room temperature.

**CONCLUSIONS**

In the present study, the influence of molecular weight of a polymer on drug–polymer solubility was investigated. It was found that the experimentally determined solubility of IMC in PVP was independent of the molecular weight of the polymer. Even though the calculated solubilities in the PVPs, based on the solubility in NVP, were found to be slightly lower than the experimental solubilities, their proximity indicates that the analogue solubility can provide valuable indications on the solubility in the polymer in an early development process. Hence, if a drug is poorly soluble in an analogue of the polymer, it
is presumably also poorly soluble in the polymer and thus, a change to a chemically different polymer is more likely to induce solubility than to switch to a different molecular weight of the same polymer. Therefore, during the first screenings for drug solubility in polymers, only one representative molecular weight per polymer is needed.

REFERENCES