



## Rapid Communication

## A Promising New Method to Estimate Drug-Polymer Solubility at Room Temperature



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## ABSTRACT

The established methods to predict drug-polymer solubility at room temperature either rely on extrapolation over a long temperature range or are limited by the availability of a liquid analogue of the polymer. To overcome these issues, this work investigated a new methodology where the drug-polymer solubility is estimated from the solubility of the drug in a solution of the polymer at room temperature using the shake-flask method. Thus, the new polymer in solution method does not rely on temperature extrapolations and only requires the polymer and a solvent, in which the polymer is soluble, that does not affect the molecular structure of the drug and polymer relative to that in the solid state. Consequently, as this method has the potential to provide fast and precise estimates of drug-polymer solubility at room temperature, we encourage the scientific community to further investigate this principle both fundamentally and practically.

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## Introduction

On account of increasing focus on the physical stability of amorphous solid dispersions, several experimental methods to predict the solubility of drugs in polymers at room temperature have been proposed.<sup>1–6</sup> As most pharmaceutically relevant drugs and polymers are solid or highly viscous at room temperature, measuring the drug solubility under these conditions is not feasible,<sup>7</sup> and therefore, the methods are based on equilibrium thermodynamics at elevated temperature and subsequent extrapolation to room temperature. Most of the methods are based on differential scanning calorimetry (DSC) measurements and are time consuming due to slow dissolution or crystallization kinetics of the drug into or from the polymer. As a consequence, predictions from these methods are associated with a degree of uncertainty, the extent of which depends on several factors including the precision

of the measurements, the validity of the assumptions underlying the proposed model (e.g., the Flory-Huggins theory), and the magnitude of the temperature extrapolation.<sup>8</sup>

To overcome these issues, a method to estimate the solubility of drugs in polymers, based on the solubility of the drug in a liquid analogue and/or monomer of the polymer at room temperature, was proposed by Marsac et al.<sup>9</sup> A key assumption underlying this method is that the interactions between the drug and analogue and/or monomer in the liquid state are similar to the interactions between the drug and polymer in the solid state.<sup>9,10</sup> However, as the method requires a liquid analogue and/or monomer of the polymer, it is not applicable to all polymers, and furthermore, it does not account for the fundamental chemical and physical differences between monomers and polymers. In contrast to the covalently bound monomers in a polymer chain, liquid monomers have relatively unrestricted intermolecular movement, which allows for interactions with the drug molecules without steric hindrance, and therefore, the method tends to overestimate the solubility of drugs in polymers.<sup>11</sup>

Under the premise of similar interactions in the solid and liquid state, this study investigated the possibility of estimating the drug-polymer solubility from the solubility of the drug in a polymer

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solution at room temperature rather than in a liquid analogue and/or monomer. This approach appears feasible if the solvent does not influence the molecular structure of the drug and polymer relative to that in the solid state (e.g., through protonation or deprotonation) or the interactions between the drug and polymer. Consequently, we hypothesize that the solubility of a drug in a polymer can be derived from the increase of drug solubility as a function of polymer concentration in a solvent by considering the solvent as an inert component. Compared to the existing methods, this new polymer in solution method does not require extrapolations over long temperature ranges and may therefore provide faster and more precise solubility estimates. The potential of this method was investigated using chloramphenicol (CAP), celecoxib (CCX), and paracetamol (PCM) as model drugs, polyvinylpyrrolidone (PVP), polyvinyl acetate (PVA), and polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (Soluplus<sup>®</sup>, SOL) as polymers, and methanol and ethanol as solvents. To verify the solubility estimates from the new polymer in solution method, the results were compared with predictions from an established method based on melting point depression determinations.<sup>1</sup>

## Materials and Methods

### Materials

CCX ( $M_w = 381.37$  g/mol) was purchased from AK Scientific, Inc. (Union City, CA). PCM ( $M_w = 151.17$  g/mol), CAP ( $M_w = 323.13$  g/mol), methanol (>99.9%), and ethanol (~96%) were purchased from Sigma-Aldrich Co. (St. Louis, MO). Kollidon<sup>®</sup> 17 PF (PVP,  $M_w = 10,000$  g/mol) and Soluplus<sup>®</sup> (SOL,  $M_w = 118,000$  g/mol) were kindly supplied by BASF (Ludwigshafen, Germany), and PVA ( $M_w = 40,000$  g/mol) was purchased from VWR Chemicals (Leuven, Belgium).

### Thermal Analysis

The melting temperature ( $T_m$ , onset) of the pure materials and physical mixtures was determined using DSC. The analyses were performed using a Q2000 DSC from TA Instruments Inc. (New Castle, DE). Sample powders (2–3 mg) were packed into Tzero aluminum hermetic pans with a perforated lid and scanned at 1°C/min from 60°C–180°C under 50 mL/min dry nitrogen gas purge. The instrument was calibrated for enthalpy and temperature using indium as a standard and the heat capacity was calibrated using a sapphire standard. The melting temperature ( $T_m$ , onset), melting enthalpy ( $\Delta H_m$ ), and glass transition temperature ( $T_g$ , inflection) were determined using the Universal Analysis 2000 (version 4.5A) software.

### Quantitative Analysis

A reversed phase HPLC method was developed for quantification of CAP, CCX, and PCM. The HPLC system consisted of an L-7100 pump, an L-7200 auto sampler, a T-6000 column oven, an L-7400 UV-detector, and a D-7000 Interface all from Merck-Hitachi LaChrom (Tokyo, Japan). A total of 25  $\mu$ L was injected into a reverse phase X-Bridge C-18 column (4.6  $\times$  150 mm, 3.5  $\mu$ m) from Waters (Milford, MA) for the separation. The mobile phase consisted of methanol and 20-mM ammonium phosphate buffer (65:35 v/v) adjusted to pH 2.35  $\pm$  0.05 with phosphoric acid and was eluted at a flow rate of 1.0 mL/min. The effluent was monitored at 280 nm, 235 nm, and 250 nm and retention times of 2.0 min, 6.2 min, and 1.6 min for CAP, CCX, and PCM, respectively.

### Established Method (Melting Point Depression)

If the dissolution of a crystalline drug into an amorphous polymer is favored by the thermodynamics of mixing, the melting point of the drug will be depressed. According to the Flory-Huggins model, it is possible to relate the magnitude of this melting point depression to the solubility of the crystalline drug in the polymer<sup>1,12</sup>:

$$\frac{\Delta H_m}{R} \times \left( \frac{1}{T_m} - \frac{1}{T} \right) = \ln(v_{\text{drug}}) + \left( 1 - \frac{1}{\lambda} \right) \times (1 - v_{\text{drug}}) + \chi \times (1 - v_{\text{drug}})^2 \quad (1)$$

where  $\Delta H_m$  and  $T_m$  are the enthalpy of fusion and melting temperature for the pure drug, respectively,  $R$  is the gas constant,  $\lambda$  is the molar volume ratio of the polymer and drug,  $\chi$  is the Flory-Huggins interaction parameter, and  $T$  is the melting temperature (onset) at a given volume fraction of drug ( $v_{\text{drug}}$ ). To obtain the solubility of the drug in the polymer at room temperature, the melting points at different drug fractions were determined at elevated temperatures, fitted to Equation 1 and extrapolated to 25°C. Therefore, physical mixtures of crystalline drug and polymer of known composition were prepared by gentle milling using a mortar and pestle. The exact drug fraction after the milling procedure was determined using HPLC, and the samples were stored in air-tight vessels at room temperature until use. The melting points of the different physical mixtures were determined at a heating rate of 1°C/min using the DSC. For a more detailed description of the theoretical background and experimental protocol of the method, the interested reader is referred to Marsac et al.<sup>1</sup>

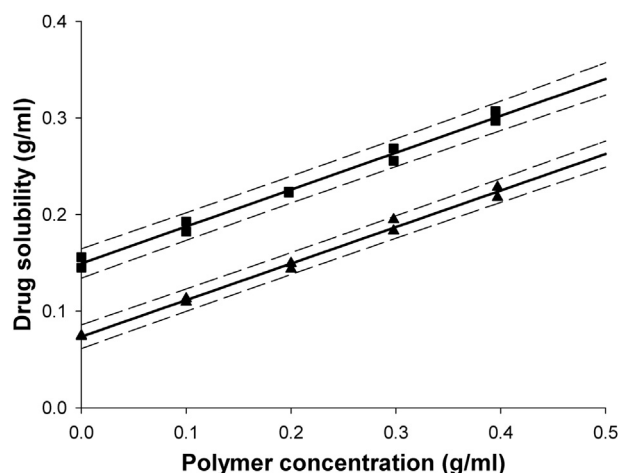
### New Method (Polymer in Solution)

In this study, we hypothesize that the drug-polymer solubility may also be derived from the increase of drug solubility as a function of polymer concentration in an inert solvent (slope of the linear regression). The solubilities of the drugs in the pure solvents and polymer solutions were determined using the shake-flask method. Polymer solutions of known concentration (10%–40% w/v) were prepared by dissolving the polymer in the solvent (methanol or ethanol). An excess of crystalline drug was added to a capped glass tube containing 1 mL of the pure solvent or the polymer solution and rotated at 5 rpm using a mechanical rotor from Heto Lab Equipment (Birkerød, Denmark). The suspensions were rotated at 25°C  $\pm$  1°C for 1 week to ensure that equilibrium was reached. Thereafter, the samples were filtered using 0.2- $\mu$ m polytetrafluoroethylene hydrophobic syringe filters from Merck Millipore Ltd. (Darmstadt, Germany) and diluted with methanol to appropriate concentrations. The diluted samples were quantified using the HPLC method described previously.

### Statistical Analysis

The Flory-Huggins model (Eq. 1) was used to describe the measurements obtained by the melting point depression method. The optimal fit with  $\chi$  as an adjustable parameter was found by regression analysis, and the 95% prediction interval was obtained by extrapolation to 25°C as previously described by Knopp et al.<sup>8</sup>

The data from the polymer in solution method, proposed in this work, were analyzed by linear regression, that is,  $X_{\text{drug}} = a \cdot X_{\text{polymer}} + b$ , where  $X_{\text{drug}}$  is the solubility of the drug in the polymer solution,  $X_{\text{polymer}}$  is the concentration of the polymer in



**Figure 1.** Illustration of the basic principle behind the new polymer in solution method. The increase in CCX solubility is plotted as a function of PVP concentration in methanol (■) and ethanol (▲) at 25°C. The solid line is the best linear fit, and the dotted lines are the (nonlinear) prediction intervals. Data points represent raw data ( $n = 2$ ).

the solvent, and  $b$  is the solubility of the drug in the pure solvent.

The mean drug-polymer solubility estimate in the solid state  $\hat{X}_{\text{drug}}^{\text{solid}}$  was found by the slope of the regression ( $a$ ). As the solubility of the drug in the pure solvent ( $b$ ) is also subject to uncertainty, both  $a$  and  $b$  should be used as fitting parameters, and thus, the prediction interval for this estimate was found by  $\hat{X}_{\text{drug}}^{\text{solid}} \pm t_{0.025, N-2} \times (\sigma_a + 2\sigma_b) \times \sqrt{1 + 1/N}$ , where  $\sigma_a$  and  $\sigma_b$  are the standard deviations of the 2 fitting parameters (assumed to be independent),  $t_{0.025, N-2}$  is the 2.5% quantile in the  $t$ -distribution and  $N$  is the number of measurements.

## Results and Discussion

To illustrate the basic principle behind the polymer in solution method, the increase of CCX solubility as a function of PVP concentration in methanol and ethanol is shown in Figure 1. As can be seen, the solubility of CCX in ethanol and methanol increased linearly with increasing PVP concentration. Furthermore, the slopes of the 2 regressions were almost identical, which means that the increase in solubility of CCX in a solution of PVP was probably independent on the solvent and thus indicates that the assumptions underlying the method were met in this case.

To confirm that this trend observed for CCX in PVP solutions was not an isolated incident, the validity of the new polymer in solution method was investigated using a range of different drugs, polymers, and solvents and compared with solubility predictions from the established method based on melting point depression. The

predicted drug-polymer solubility obtained from the melting point depression method and the estimated drug-polymer solubility obtained from the new polymer in solution method using methanol and ethanol as solvents for all drug-polymer systems at 25°C, including the prediction intervals, are presented in Table 1 and illustrated in Figure 2. The raw data from both methods, along with the experimental physical and thermodynamic values used to predict the drug-polymer solubility from the melting point depression method (including an illustration of the Flory-Huggins fit), can be found in the Supporting Information.

These results show that the linear increase in drug solubility with increasing polymer concentration observed for the CCX in PVP solutions was observed for all systems under investigation. Furthermore, a  $t$ -test revealed that the mean drug-polymer solubility estimates from the methanol and ethanol solutions were not significantly different ( $p > 0.05$ ). As the solvents do not influence the molecular structure of the drugs or polymers compared to that in the solid state, it is rational to assume that the solvents were inert in this context. The increase in drug solubility with increasing polymer concentration was therefore more likely a reflection of other factors, such as interactions between the drug and polymer. By assuming that the interactions between the drug and polymer in the liquid (dissolved) state were similar to the interactions between the drug and polymer in the solid state, the solubility of the drug in the polymer in the solid state could be estimated from the solubility of the drug in a polymer solution. Consequently, if the solvent is inert, it is expected that the increase in drug solubility with increasing polymer concentration will be linear for any given drug-polymer combination.

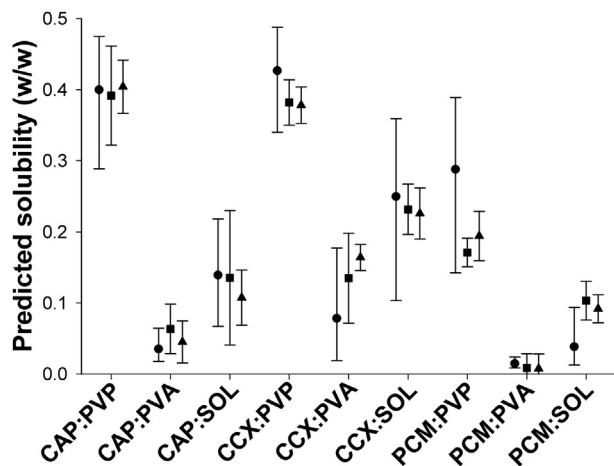
As demonstrated in Table 1 and Figure 2, only 2 of the 18 mean estimates (PCM:PVA in ethanol and PCM:SOL in methanol) from the new polymer in solution method were not within the prediction interval from the melting point depression method. In addition, half of the prediction intervals (9 of 18) from the new polymer in solution method were equivalent to the prediction intervals from the melting point depression method (i.e., the prediction interval from the new polymer in solution method was within the prediction interval from the melting point depression method), and most of the prediction intervals (13 of 18) were narrower than the prediction intervals from the melting point depression method. This indicates that the new polymer in solution method provides more precise solubility estimates, which is probably because it is based on measurements made at room temperature and thus, does not rely on extrapolation from data obtained at elevated temperature. Based on these findings, we feel that it is reasonable to propose that the 2 different methods to predict drug-polymer solubility provide equivalent results, at least for the systems investigated in this study.

In theory, the new polymer in solution method can be applied to all drugs that are stable in solutions and polymers that can be dissolved (preferably  $>100$  mg/mL) by any given solvent that does not influence the molecular structure of the drug and polymer or the interactions between the drug and polymer compared to that in

**Table 1**  
Predicted Solubilities From the Melting Point Depression Method and the Estimated Solubilities From the New Polymer in Solution Method in Methanol and Ethanol

Method	CAP:PVP	CAP:PVA	CAP:SOL	CCX:PVP	CCX:PVA	CCX:SOL	PCM:PVP	PCM:PVA	PCM:SOL
Melting point depression	0.40 (0.29-0.48)	0.04 (0.02-0.06)	0.14 (0.07-0.22)	0.43 (0.34-0.49)	0.08 (0.02-0.18)	0.25 (0.10-0.36)	0.29 (0.14-0.39)	0.01 (0.01-0.02)	0.04 (0.01-0.09)
Polymer in methanol solution	0.39 (0.32-0.46)	0.06 (0.03-0.10)	0.14 (0.04-0.23)	0.38 (0.35-0.41)	0.13 (0.07-0.20)	0.23 (0.20-0.27)	0.17 (0.15-0.18)	0.01 (0.00-0.03)	0.10 (0.08-0.13)
Polymer in ethanol solution	0.40 (0.37-0.44)	0.05 (0.02-0.07)	0.11 (0.07-0.15)	0.38 (0.35-0.40)	0.16 (0.15-0.18)	0.23 (0.19-0.26)	0.19 (0.16-0.23)	0.01 (0.00-0.03)	0.09 (0.07-0.11)

Values represent mean drug-polymer solubility (w/w) at 25°C with the prediction intervals in parentheses.



**Figure 2.** Comparison of the solubility predictions for all investigated drug-polymer systems obtained from the melting point depression method (●) with the solubility estimates obtained from the new polymer in solution method using methanol (■) and ethanol (▲) as solvents. Data points represent mean drug-polymer solubility (w/w) at 25 °C including the prediction intervals.

the solid state. Compared to the melting point depression method, it seems that the new polymer in solution method provides faster and more precise estimates, and because of its simplicity the method, if refined, has the potential to enable high-throughput screening of polymers suitable for amorphous solid dispersions or glass solutions (e.g., using a 96 well-plate setup). Therefore, we encourage the scientific community to investigate and challenge this principle, both fundamentally and practically, to identify the advantages of the method and define its limitations.

## Conclusion

With the introduction of the new polymer in solution method in this study, the issues associated with the established methods to predict the drug-polymer solubility at room temperature may be overcome. The method is based on the solubility of a drug in a polymer solution and thus does not rely on temperature extrapolations and only requires the polymer and a solvent in which the polymer is soluble. Unlike the melting point depression method,

the new polymer in solution method does not require advanced equipment or complex nonlinear data treatment, and as it is based on the simple shake-flask method and HPLC quantification, it can be implemented in most laboratory setups. If refined, the method could enable high-throughput screening of polymers suitable for amorphous solid dispersions or glass solutions, which would significantly reduce the time to obtain drug-polymer solubility estimates compared to the existing thermal methods. Consequently, we believe that this method has potential to provide fast and precise estimates of drug-polymer solubility at room temperature.

## References

- Marsac PJ, Shamblin SL, Taylor LS. Theoretical and practical approaches for prediction of drug-polymer miscibility and solubility. *Pharm Res.* 2006;23:2417–2426.
- Sun Y, Tao J, Zhang GG, Yu L. Solubilities of crystalline drugs in polymers: an improved analytical method and comparison of solubilities of indomethacin and nifedipine in PVP, PVP/VA, and PVAc. *J Pharm Sci.* 2010;99:4023–4031.
- Bellantone RA, Patel P, Sandhu H, et al. A method to predict the equilibrium solubility of drugs in solid polymers near room temperature using thermal analysis. *J Pharm Sci.* 2012;101:4549–4558.
- Mahieu A, Willart JF, Dudognon E, Danede F, Descamps M. A new protocol to determine the solubility of drugs into polymer matrixes. *Mol Pharm.* 2013;10:560–566.
- Amharar Y, Curtin V, Gallagher KH, Healy AM. Solubility of crystalline organic compounds in high and low molecular weight amorphous matrices above and below the glass transition by zero enthalpy extrapolation. *Int J Pharm.* 2014;472:241–247.
- Kyeremateng SO, Pudlas M, Woehrle GH. A fast and reliable empirical approach for estimating solubility of crystalline drugs in polymers for hot melt extrusion formulations. *J Pharm Sci.* 2014;103:2847–2858.
- Tao J, Sun Y, Zhang GG, Yu L. Solubility of small-molecule crystals in polymers: D-mannitol in PVP, indomethacin in PVP/VA, and nifedipine in PVP/VA. *Pharm Res.* 2009;26:855–864.
- Knopp MM, Tajber L, Tian Y, et al. Comparative study of different methods for the prediction of drug-polymer solubility. *Mol Pharm.* 2015;12:3408–3419.
- Marsac PJ, Li T, Taylor LS. Estimation of drug-polymer miscibility and solubility in amorphous solid dispersions using experimentally determined interaction parameters. *Pharm Res.* 2009;26:139–151.
- Paudel A, Van HJ, Van den Mooter G. Theoretical and experimental investigation on the solid solubility and miscibility of naproxen in poly(vinylpyrrolidone). *Mol Pharm.* 2010;7:1133–1148.
- Rask MB, Knopp MM, Olesen NE, Holm R, Rades T. Influence of PVP/VA copolymer composition on drug-polymer solubility. *Eur J Pharm Sci.* 2016;85:10–17.
- Flory PJ. *Principles of polymer chemistry.* Ithaca, NY: Cornell University Press; 1953.