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Lessons Learned

Statistical Analysis of a Method to Predict Drug–Polymer Miscibility

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ABSTRACT

In this study, a method proposed to predict drug–polymer miscibility from differential scanning calorimetry measurements was subjected to statistical analysis. The method is relatively fast and inexpensive and has gained popularity as a result of the increasing interest in the formulation of drugs as amorphous solid dispersions. However, it does not include a standard statistical assessment of the experimental uncertainty by means of a confidence interval. In addition, it applies a routine mathematical operation known as "transformation to linearity," which previously has been shown to be subject to a substantial bias. The statistical analysis performed in this present study revealed that the mathematical procedure associated with the method is not only biased, but also too uncertain to predict drug–polymer miscibility at room temperature. Consequently, the statistical inference based on the mathematical procedure is problematic and may foster uncritical and misguiding interpretations. From a statistical perspective, the drug–polymer miscibility prediction should instead be examined by deriving an objective function, which results in the unbiased, minimum variance properties of the least-square estimator as provided in this study.

Introduction

Amorphous drug formulations have gained increasing interest in both academic and industrial research because of their potential to overcome the limited and variable bioavailability often associated with poorly water-soluble drugs.[1] On its own, the amorphous drug is thermodynamically unstable and will eventually crystallize, which will neutralize the benefits. In the amorphous solid dispersion approach, this is counteracted by molecularly incorporating the amorphous drug in a polymeric matrix.[2,3] The thermodynamic stability of such a formulation can be ensured if the drug is soluble in the polymer (glass solution). However, at normal storage conditions, the solubility of most drugs in pharmaceutically relevant polymers is low unless favorable cohesive drug–polymer interactions are formed.[4,5] If this is not fulfilled, the drug will likely be supersaturated in the polymer with the risk of crystallizing during storage.[6]

The realization of the full potential of amorphous solid dispersions therefore often relies on the kinetic/physical stability provided by the polymer to prevent crystallization. Polymers are thought to improve the physical stability by increasing the glass transition temperature (T_g), thereby reducing the molecular mobility and thermodynamic driving force for crystallization.[7-9] Thus, for a polymer to be an effective crystallization inhibitor, it needs to have a high T_g and be molecularly miscible with the drug, which requires intermolecular interactions between the two components. Generally, stronger interactions will lead to increased drug–polymer miscibility and thus, physical stability of the amorphous solid dispersion.[1,10]

For an amorphous polymer–polymer mixture, miscibility is defined as a stable single-phase system with only one T_g.[11] However, as low-molecular-weight drugs are unstable in the amorphous form, the measurable miscibility in the case of amorphous drug–polymer mixtures is associated with a metastable state from which the drug does not crystallize within an experimental time frame. Hence, miscibility is usually only apparent and involves the kinetics of phase separation and structural relaxation, and may practically only be predicted from extrapolation and modeling or by performing long-term stability studies.[3]

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Nonetheless, from an industrial perspective, it is desirable to have an accurate prediction of the drug-polymer miscibility (maximum drug loading) to formulate an amorphous solid dispersion with sufficient kinetic stability to prevent crystallization during shelf-life. In order to circumvent the practical and temporal issues associated with long term stability studies, Lin and Huang[12] proposed a method to predict a complete drug–polymer phase diagram, including the miscibility curve, from experimental differential scanning calorimetry (DSC) data. The method is based on melting point depression data obtained at elevated temperatures and extrapolated to room temperature using the Flory–Huggins expression for the free energy of mixing. In order to perform this extrapolation, it is assumed that the Flory–Huggins interaction parameter χ is temperature dependent.[10,12] In the original work, Lin and Huang emphasized that the mathematical procedure associated with the method relies heavily on the validity of the underlying assumptions and the precision of the melting point depression data and therefore, should only be considered as a rough draft. This statement is underlined by the fact that the miscibility (or more specifically the interaction parameter χ) prediction is very sensitive to experimental uncertainty.[13,14] Consequently, even small variations in the measured melting temperatures will have great impact on the predicted miscibility and therefore, a statistical analysis is required to ensure reliability of the method.

Nevertheless, since the method was introduced, several studies have used the method without a reflection on the requirements to provide viable predictions of the drug–polymer miscibility.[12,15-21] Because of the increasing popularity of the method, we felt obligated to stimulate critical thinking on interpretation of DSC measurements. Therefore, the aim of the current study is to assess the statistical assumptions of the mathematical procedure associated with the method proposed by Lin and Huang to predict the drug–polymer miscibility. The intention is not to cover all assumptions necessary for regression analysis but rather to address the assumptions, which we believe results in uncertain or even misleading predictions.

Theoretical Considerations

The physical basis underlying the prediction of drug–polymer miscibility was proposed by Lin and Huang and is based on the Flory–Huggins solution theory for polymers[22] and a frequently applied empirical relation for the interaction parameter, χ. According to the Flory–Huggins model, the Gibbs free energy of mixing for a drug–polymer mixture is given by[12,15]:

$$\Delta G_{\mathrm{mix}} = RT\left[\phi_{\mathrm{drug}}\ln\phi_{\mathrm{drug}} + \frac{1-\phi_{\mathrm{drug}}}{m}\ln\left(1-\phi_{\mathrm{drug}}\right) + \chi\cdot\phi_{\mathrm{drug}}\cdot\left(1-\phi_{\mathrm{drug}}\right)\right] \quad (1)$$

where ϕ_{drug} is the volume fraction of the drug, m is the molar volume ratio of the polymer to the drug, χ is the interaction parameter, R is the gas constant, and T is the absolute temperature. In order to apply this expression to measureable thermodynamic values, the Gibbs free energy of mixing can be related to the melting point depression of a drug–polymer mixture using DSC.[15,23] Crystalline materials melt at a temperature when the chemical potential of the solid and liquid state are equal. Addition of an impurity such as an amorphous polymer to the crystal may reduce the chemical potential of the material in the liquid state, leading to melting point depression.[22,24] Consequently, it is possible to extend Flory–Huggins solution theory to predict the interaction parameter, χ, from melting point depression data by assuming that the melting enthalpy is temperature independent[23]:

$$\frac{1}{T_{\mathrm{m}}^{0}} - \frac{1}{T_{\mathrm{m}}^{\mathrm{mix}}} = \frac{R}{\Delta H_{\mathrm{m}}}\left[\ln\phi_{\mathrm{drug}} + \left(1-\frac{1}{m}\right)\left(1-\phi_{\mathrm{drug}}\right) + \chi\cdot\left(1-\phi_{\mathrm{drug}}\right)^{2}\right] \quad (2)$$

where T_{m}^{0} is the melting temperature of the pure drug in absence of polymer, $T_{\mathrm{m}}^{\mathrm{mix}}$ is the melting temperature of the drug in presence of a polymer and ΔH_{m} is the melting enthalpy of the pure drug. In order to enable extrapolation to other temperatures, Lin and Huang assumed that the temperature dependence of χ can be described by:

$$\chi = A + \frac{B}{T_{\mathrm{m}}^{\mathrm{mix}}} \quad (3)$$

where A and B are constants and A is referred to as the non-combinatorial contribution to χ and $B/T_{\mathrm{m}}^{\mathrm{mix}}$ is the enthalpic contribution.[10] From the physicochemical assumptions in Eqs. 2 and 3, Lin and Huang constructed a complete drug–polymer phase diagram, including the solubility and miscibility curves. The drug–polymer miscibility can be derived from the lever rule; when the composition dependence of the free energy of mixing is convex, any mixed state has lower free energy than any state the mixtures could phase separate into.[25] The criterion for the boundary between unstable and metastable regions (the spinodal curve) is thus given by $\frac{\partial^2\Delta G_{\mathrm{mix}}}{\partial\phi_{\mathrm{drug}}^2} = 0$ and applying this criterion to Eq. 1 yields:

$$\phi_{\mathrm{drug}} = \frac{1}{4}\frac{2\chi\cdot m + m - 1 \pm \sqrt{1+4\left(\chi-\frac{1}{2}\right)^{2}m^{2} - (4\chi+2)\cdot m}}{\chi\cdot m}, \quad \chi \geq \frac{1}{2} + \frac{1}{2m} + \frac{1}{\sqrt{m}} \quad (4)$$

In summary, the mathematical procedure suggested by Lin and Huang to obtain the complete phase diagram is given by the following three steps: (i) determine the melting point depression of drug–polymer physical mixtures of different composition using DSC and calculate the χ values using Eq. 2, (ii) fit the interrelated χ, $T_{\mathrm{m}}^{\mathrm{mix}}$ values with Eq. 3 in order to estimate A and B, and (iii) extrapolate the fitted empirical χ, T relationship in Eq. 4 to predict the drug–polymer miscibility curve.

Results and Discussion

Demonstration of the Original Method Including Confidence Assessment

For good measure, the method proposed by Lin and Huang is initially demonstrated. In order to do this, the data used in the original work was adapted. The melting point depression measurements, however, were not tabulated and therefore, the data had to be adapted by graphical inspection. The data basis for the current study can be found in Tables 1 and 2. As the method did not include an uncertainty analysis, great emphasis has been put on assessing the confidence of the prediction. In the mathematical procedure by Lin and Huang the first step (i) involves finding χ by Eq. 2 from the experimental melting point depression data in Table 2. Here, Lin and Huang calculated χ from the average value of $T_{\mathrm{m}}^{\mathrm{mix}}$ at each composition. This averaging operation will discard

Table 1
Physical Properties Adapted From Lin and Huang

Component	M_w (g/mol)	ρ (g/cm^3)	ΔH_m (J/g)
Felodipine	384.26	1.28	78.5[a]
Poly (acrylic acid)	1800	1.27	–

[a] Data reported in the literature.

some of the variability in the data and in the current case the consequences there of are severe as will be elaborated later.

The next step in the procedure, step (ii), is to fit the interrelated χ, T_m^{mix} values with Eq. 3 in order to estimate A and B and enable extrapolation of χ to any temperature. Here, Lin and Huang made another routine mathematical operation to obtain a simple linear regression by inverting the 1st-axis before fitting the equation to the experimental data, given by $x = 1/T_m^{mix}$. This procedure is historically one of the most used mathematical operations in nonlinear regression analysis, referred to as "transformation to linearity,"[26] and the drawbacks of this will also be elaborated later.

For now however, we will disregard the consequences of the two mathematical operations described above and use the unverified assumptions of Lin and Huang for statistical inference. Fitting the mean values of T_m^{mix} from Table 2 with the procedure proposed by Lin and Huang, the least-square estimates obtained were given by $\chi = -18.790 + 8084\frac{1}{T_m^{mix}}$. This implies that the estimates reported in the original work $\chi = -18.843 + 8105\frac{1}{T_m^{mix}}$ were reproduced with a good approximation in this work, thus validating the values adapted from graphical inspection. In addition to the least-square estimate the confidence intervals for the coefficients should always be calculated when performing a regression analysis. Consequently, the 95% approximate Wald confidence interval for the expected response at x_0 is[27]:

$$x_0^T\hat{\theta} \pm s\sqrt{x_0^T(X^TX)^{-1}x_0}\,t(N-P;\alpha/2) \quad (5)$$

where $\hat{\theta} = (\hat{A}, \hat{B})^T$ is the estimate of the parameters, $x_0 = (1, 1/T_m^{mix})^T$ is the level at which the prediction is desired, N is the number of observations, $P = 2$ is the number of predictor variables, X is a $N \times P$ matrix of the regressor variables, $s = \sqrt{\frac{SSR}{N-P}}$ is the estimate of the sample standard deviation, SSR is the sum of squared residuals and $t(N - P; \alpha/2)$ is the $\alpha/2$ quantile in the t distribution with $N - P$ degrees of freedom. The 95% confidence intervals for the coefficients were given as $A = [-34.378, -3.202]$ and $B = [1611\ K, 14{,}557\ K]$ and the least-square estimate including the 95% confidence interval as given by Eq. 5 is shown in Figure 1.

In order to predict the miscibility and confidence interval at other temperatures (e.g. room temperature), Equation 3 needs to be extrapolated. In this context, it is obvious that the further the extrapolation is made from the empirical data, the more vulnerable the prediction will be. This is evident from Figure 2, where the influence of extrapolation on the least-square estimate for χ including the approximate 95% confidence interval is illustrated. Particularly at temperatures of practical relevance (e.g., 20°C), the extrapolation resulted in relatively large confidence intervals which will affect the confidence of the miscibility curve.

Table 2
Melting Point Depression Data (T_m^{mix}) for Different Drug–Polymer Compositions (ϕ_{drug}) and the Interrelated Average χ Values Adapted from Lin and Huang (T_m^{mix} Values are Mean ± SD, $n = 2$)

ϕ_{drug}	T_m^{mix}(°C)	Average χ
1.00	144.66 ± 0.32	–
0.85	143.20 ± 0.40	0.6241
0.80	142.79 ± 0.62	0.6678
0.75	142.25 ± 0.10	0.6493
0.70	141.73 ± 0.64	0.6589
0.65	141.43 ± 0.50	0.7160
0.60	141.00 ± 0.60	0.7459

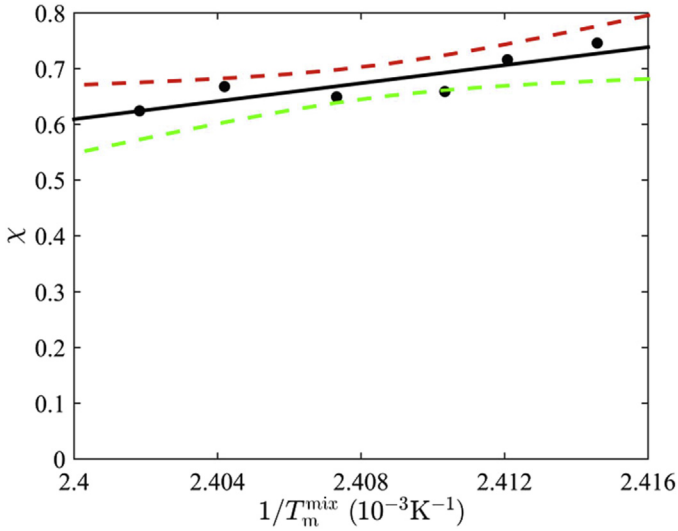

Figure 1. Linear fit of χ as a function of $1/T_m^{mix}$ based on Eq. (2) to estimate A and B (from mean T_m^{mix} values) as illustrated by Lin et al. including the 95% confidence interval.

To demonstrate this, the fitted empirical χ, T relationship was extrapolated using Eq. 4 to predict the drug–polymer miscibility curve as shown in Figure 3. It is seen that the large confidence intervals for the χ prediction (shown in Fig. 2) was not directly translated into a wide confidence interval of the predicted miscibility at 20°C. However, the measurements were subject to some additional error which was disregarded in the original work as mentioned previously. Consequently, in order to better reflect how the standard deviations of T_m^{mix} influenced the prediction of a future observation of the miscibility, a Monte Carlo simulation was conducted as shown Figure 4. The procedure proposed by Lin and Huang was simulated 1000 times using the mean and standard deviations of T_m^{mix} shown in Table 2. Even though the Monte Carlo simulation of the miscibility curves were seen to cover all possible values of ϕ_{drug}, only 453 of the 1000 simulations fell into the defined space (0 K to T_m^0). This means that the inclusion of the inherent uncertainty of the T_m^{mix} measurements resulted in an indefinite prediction interval where only the lower limit of the 95% prediction interval of the miscibility curve could be identified. Consequently, the central estimate becomes extremely vague and does not tell much about the miscibility curve, which could not have been predicted in advance. This could indicate that the DSC is not currently at a stage where the melting point can be determined with sufficient precision to predict the drug–polymer miscibility curve with any statistical significance. However, it is important to emphasize that the legitimacy of this provisional assessment relies on the assumptions made by Lin and Huang to be valid.

Assessment of the Underlying Statistical Assumptions

As the underlying statistical assumptions of the procedure have not yet been assessed, the prediction has limited credibility. In order to make such an assessment, the raw data from Lin and Huang

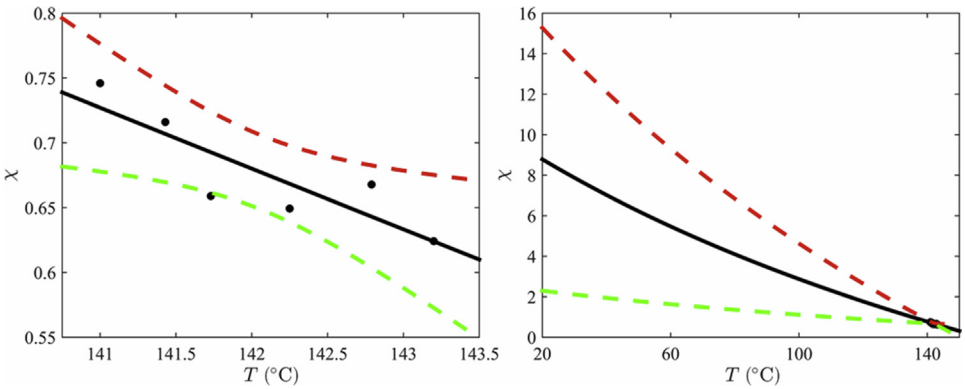

Figure 2. The least-square estimate of $\chi = A + \frac{B}{T_m^{mix}}$ including the 95% confidence intervals as a function of temperature in (left the measurement range and (right) extrapolated to 20°C. Note that the 1st-axis is now displayed on the normal temperature scale as opposed to Figure 1.

was required. In the original work, the average values from two replicate experiments were used to fit Eq. 3. Therefore, it was possible to deduce the values of the raw data from the standard deviations of the average data. Remarkably, when repeating the mathematical procedure proposed by Lin and Huang with the raw data (i.e., without the averaging treatment), the B value becomes negative and the least-square estimate is given by $\chi = 30.830 - 12520^{\frac{1}{T_m^{mix}}}$.

In Figure 5, the difference between fitting to the raw data and mean values is illustrated. Note that the χ prediction is increasingly sensitive toward experimental uncertainty as T_m^{mix} approaches T_m^0 as stated previously. At a first glance, the discrepancy between the fit to the raw data and mean values was surprising. There was, however, nothing erroneous in the fits as can be inspected from Figure 5 (right), where both the raw data and the mean values are shown together with the two best fitted lines. This discrepancy is in fact known to be a result of the routine mathematical operation "transformation to linearity" as outlined below.

As previously described, the least-square estimator is optimal in a statistical sense, as it is unbiased and has the lowest variance (among the group of unbiased estimators). However, the optimality is based on several assumptions; here, we will only address the main assumptions that are violated resulting in the bias shown in Figure 5. The least-square estimate can be found by minimizing a proper objective function and the implicit objective function used in the mathematical procedure by Lin and Huang is defined by the sum-of-square of the residuals of χ:

$$SSR\left(T_m^{mix}(i); A, B\right) = \sum_{all\ i} \left(\chi(i)^{measurement} - \chi(i)^{model}\right)^2 \quad (6)$$

where $\chi(i)^{measurement}$ is the measurement of the interaction parameter, $\chi(i)^{model}$ is the model of the interaction parameter, and $SSR\,(T_m^{mix}(i); A, B)$ are the sum-of-square of the residuals, which is a function of the parameters A and B, and i is an index variable for the level of $T_m^{mix}(i)$ where the measurements were conducted. The model of the measurement was given by $\chi(i)^{model} = A + \frac{B}{T_m^{mix}(i)}$, which has two parameters, A and B, and one predictor variable, $T_m^{mix}(i)$. By this definition of the objective function, Lin and Huang implicitly assumed that the predictor variable $T_m^{mix}(i)$ is free of noise. However, the experimentally measured quantity is the melting temperature and not χ. Therefore, it is the melting temperature, which in the first place is subject to experimental noise. As the value of $\chi(i)^{measurement}$ associated with each value of $T_m^{mix}(i)$ is calculated from the Flory–Huggins equation, it is clear that $\chi(i)^{measurement}$ also will be subject to noise. Thus, the variance of the predictor variable $\frac{1}{T_m^{mix}}$ cannot be neglected and the residuals are highly correlated and therefore, the regression function $\chi = A + \frac{B}{T_m^{mix}}$ is no longer deterministic, but stochastic. This means that the

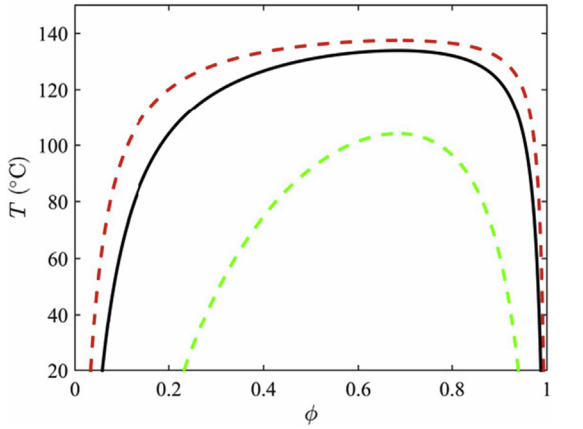

Figure 3. Drug–polymer miscibility curve for the felodipine–PAA system based on Eq. 4 including the 95% confidence interval.

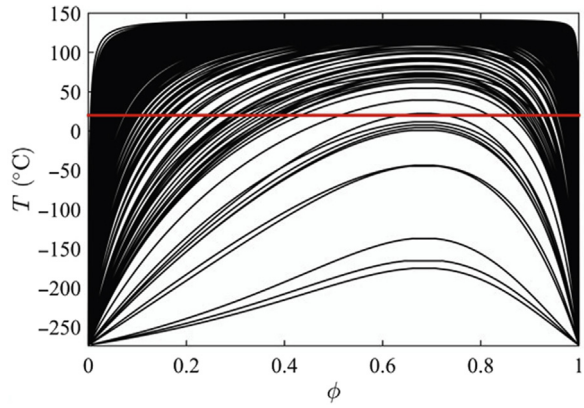

Figure 4. Monte Carlo simulations (453 runs of 1000) of the miscibility curve based on the data from Table 2 including the standard deviations. The red line indicates 20°C.

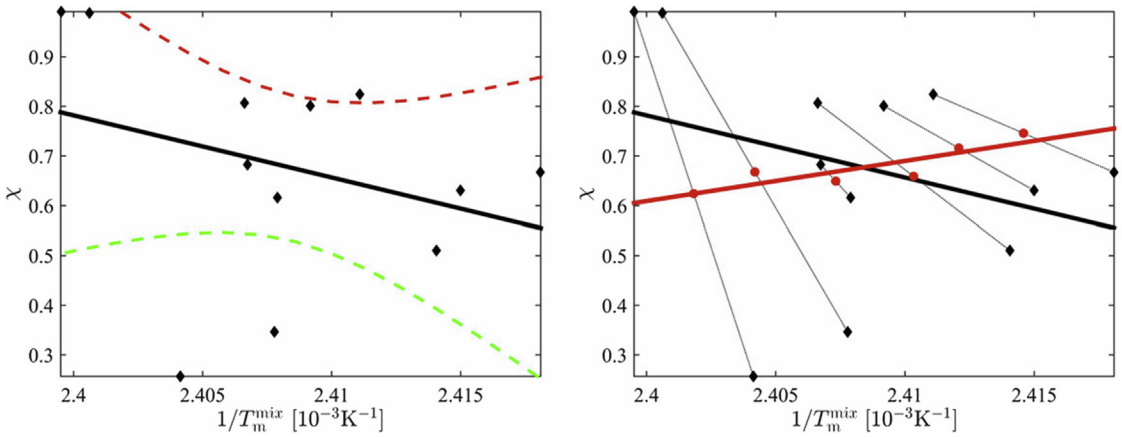

Figure 5. (Illustration of left) The least-square estimate of $\chi = A + \frac{B}{T_m^{mix}}$ including the 95% confidence intervals fitted to the raw data and (right) comparison of the fit to the raw data (black line) and the mean values (red line). The interrelated values (ϕ_{drug}) are connected by dotted lines.

assumptions of the regression analysis are violated,[27] resulting in biased predictions.

A more productive opportunity is to derive an objective function which results in the unbiased, minimum variance properties of the least-square estimator. Consequently, using melting point depression

$$SSR(\phi_d(i); A, B) = \sum_{all\ i} \left(T_m^{mix}(i)^{measurement} - T_m^{mix}(i)^{model} \right)^2 \qquad (7)$$

where the regression function $T_m^{mix}(i)^{model}$ can be found by inserting the empirical relation for $\chi = A + \frac{B}{T_m^{mix}}$ into Eq. 2, and solving for T_m^{mix}:

$$T_m^{mix}(i)^{model} = \frac{B \cdot \left(1 - \phi_{drug}(i)\right)^2 + \frac{\Delta H_m}{R}}{-A \cdot \left(1 - \phi_{drug}(i)\right)^2 - \ln\left(\phi_{drug}(i)\right) - \left(1 - \frac{1}{m}\right)\left(1 - \phi_{drug}(i)\right) + \frac{1}{T_m^0}\frac{\Delta H_m}{R}} \qquad (8)$$

Application of Eq. 8 would result in more sound miscibility prediction from a statistical point of view. In addition to the statistical assumption discussed above, the physical assumptions for the model to allow an extrapolation are crucial and in order to truly believe in the predictions, the underlying physical assumptions (e.g., the temperature dependence of χ) need to be assessed. However, this is far beyond the scope of this work and will have to be elaborated in detail in future work.

Conclusions

In this study, a statistical analysis of a method proposed by Lin and Huang to predict drug–polymer miscibility from melting point depression measurements was performed. The concerns raised by Lin and Huang in the original work turned out to be justified. Using the mathematical procedure and raw data from Lin and Huang, the predicted miscibility curve could not be trusted with statistical confidence. This could indicate that the DSC is not currently at a stage where the melting point can be determined with sufficient precision to predict the drug–polymer miscibility. Furthermore, a comparison of the fit to the mean values and the fit to the raw data resulted in two qualitative contradictive conclusions, which indicates that the mathematical procedure is biased because of the operation "transformation to linearity." Consequently, the statistical inference based on the mathematical procedure is problematic and may foster uncritical and misguiding interpretations. From a statistical perspective, the potential of DSC measurements to make miscibility predictions should instead be examined by deriving an objective function, which results in the unbiased, minimum variance properties of the least-square estimator. However, even though this objective function will provide more sound miscibility predictions from a statistical point of view, arguments in favor of the underlying physical assumptions (e.g., the temperature dependence of χ) needs to be put forward in order to truly believe in the predictions.

References

1. Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. *Drug Discov Today*. 2007;12:1068-1075.
2. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. *Eur J Pharm Biopharm*. 2000;50:47-60.
3. Qian F, Huang J, Hussain MA. Drug-polymer solubility and miscibility: stability consideration and practical challenges in amorphous solid dispersion development. *J Pharm Sci*. 2010;99:2941-2947.
4. 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.
5. Huang Y, Wei-Guo D. Fundamental aspects of solid dispersion technology for poorly soluble drugs. *Acta Pharm Sin B*. 2014;4:18-25.
6. Newman A, Knipp G, Zografi G. Assessing the performance of amorphous solid dispersions. *J Pharm Sci*. 2012;101:1355-1377.
7. Hancock BC, Shamblin SL, Zografi G. Molecular mobility of amorphous pharmaceutical solids below their glass transition temperatures. *Pharm Res*. 1995;12:799-806.
8. Bhugra C, Pikal MJ. Role of thermodynamic, molecular, and kinetic factors in crystallization from the amorphous state. *J Pharm Sci*. 2008;97:1329-1349.
9. Rumondor AC, Ivanisevic I, Bates S, Alonzo DE, Taylor LS. Evaluation of drug-polymer miscibility in amorphous solid dispersion systems. *Pharm Res*. 2009;26:2523-2534.
10. Janssens S, Van den Mooter G. Review: physical chemistry of solid dispersions. *J Pharm Pharmacol*. 2009;61:1571-1586.
11. Olabisi O. Interpretations of polymer–polymer miscibility. *J Chem Educ*. 1981;58:944-950.

12. Lin D, Huang Y. A thermal analysis method to predict the complete phase diagram of drug-polymer solid dispersions. *Int J Pharm*. 2010;399:109-115.
13. Knopp MM, Olesen NE, Holm P, et al. Evaluation of drug–polymer solubility curves through formal statistical analysis: comparison of preparation techniques. *J Pharm Sci*. 2015;104:44-51.
14. Knopp MM, Olesen NE, Holm P, Langguth P, Holm R, Rades T. Influence of polymer molecular weight on drug–polymer solubility: a comparison between experimentally determined solubility in pvp and prediction derived from solubility in monomer. *J Pharm Sci*. 2015;104:2905-2912.
15. Zhao Y, Inbar P, Chokshi HP, Malick AW, Choi DS. Prediction of the thermal phase diagram of amorphous solid dispersions by Flory–Huggins theory. *J Pharm Sci*. 2011;100:3196-3207.
16. Donnely C, Tian Y, Potter C, Jones DS, Andrews GP. Probing the effects of experimental conditions on the character of drug–polymer phase diagrams constructed using Flory–Huggins theory. *Pharm Res*. 2015;32:167-179.
17. Tian Y, Booth J, Meehan E, Jones DS, Li S, Andrews GP. Construction of drug–polymer thermodynamic phase diagrams using Flory–Huggins interaction theory: identifying the relevance of temperature and drug weight fraction to phase separation within solid dispersions. *Mol Pharm*. 2013;10:236-248.
18. Tian Y, Caron V, Jones DS, Healy AM, Andrews GP. Using Flory–Huggins phase diagrams as a pre-formulation tool for the production of amorphous solid dispersions: a comparison between hot-melt extrusion and spray drying. *J Pharm Pharmacol*. 2014;66:256-274.
19. Thakral S, Thakral NK. Prediction of drug-polymer miscibility through the use of solubility parameter based Flory-Huggins interaction parameter and the experimental validation: PEG as model polymer. *J Pharm Sci*. 2013;102:2254-2263.
20. Keen JM, Martin C, Machado A, Sandhu H, McGinity JW, DiNunzio JC. Investigation of process temperature and screw speed on properties of a pharmaceutical solid dispersion using corotating and counter-rotating twin-screw extruders. *J Pharm Pharmacol*. 2014;66:204-217.
21. Lu J, Shah S, Jo S, et al. Investigation of phase diagrams and physical stability of drug–polymer solid dispersions. *Pharm Dev Technol*. 2015;20:105-117.
22. Flory PJ. Principles of Polymer Chemistry. Ithica, New York: Cornell University Press; 1953.
23. Marsac PJ, Shamblin SL, Taylor LS. Theoretical and practical approaches for prediction of drug–polymer miscibility and solubility. *Pharm Res*. 2006;23:2417-2426.
24. Hoei Y, Yamaura K, Matsuzawa S. A lattice treatment of crystalline solvent-amorphous polymer mixtures on melting point depression. *J Phys Chem*. 1992;96:10584-10586.
25. Rubinstein M, Colby R. *Polymer Physics*. New York City, New York: Oxford University Press; 2003.
26. Motulsky H, Christopoulos A. *Fitting Models to Biological Data Using Linear and Nonlinear Regression: A Practical Guide to Curve Fitting*. New York City, New York: Oxford University Press; 2004.
27. Bates DM, Watts DG. *Nonlinear Regression Analysis and its Applications*. Hoboken, New York: John Wiley & Sons; 1988.