# Investigation of Miscibility Estimation Methods Between Indomethacin and Poly(vinylpyrrolidone-co-vinyl acetate)

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## Abstract

The investigation of the miscibility between active pharmaceutical ingredients (API's) and polymeric excipients is of great interest for the formulation and development of amorphous solid dispersions, especially in the context of the prediction of the stability of these systems. Two different methods were applied to determine the miscibility between model compounds poly(vinylpyrrolidone-co-vinyl acetate) (PVPVA) and indomethacin (IND), viz. the measurement of the glass transition temperature ($T_g$) and the melting point depression method framed on the Flory-Huggins theory. Measurement of the glass transition temperatures of the binary blends showed the formation of an amorphous single phase system between the PVPVA and the IND regardless of the composition. Variation of $T_g$ with the composition was well described by the Gordon-Taylor equation leading to the error of concluding lack of intermolecular interactions between the materials. Application of the Brostow–Chiu–Kalogeras–Vassilikou-Dova (BCKV) model shows a negative interaction parameter ($a_0$) suggesting the presence of drug-drug intermolecular interactions. Application of the melting point depression method within the framework of the Flory-Huggins theory proved the miscibility of the system at temperatures close to the melting point of IND.



**Keywords:**
Amorphous solid dispersions
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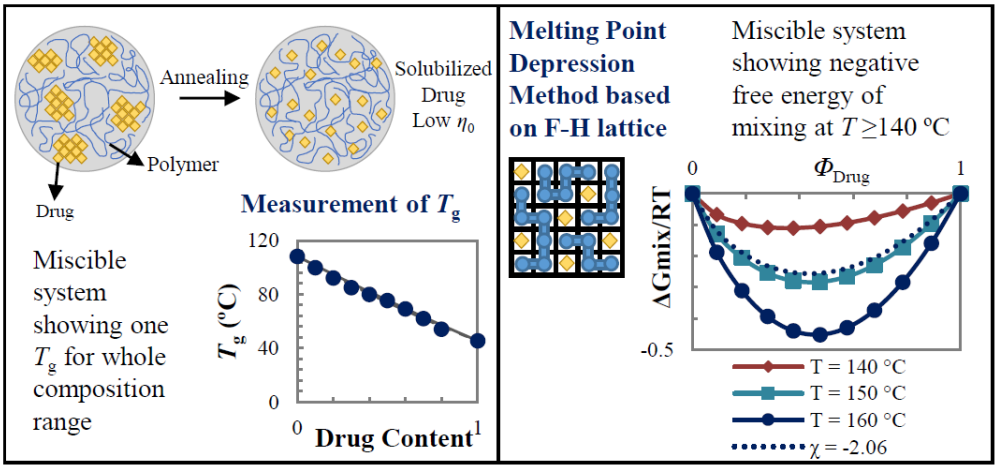
**Graphical Abstract:**



## 1. Introduction

Amorphous solid dispersions have been extensively studied as a strategy to overcome the poor water solubility of class II drugs but restrictedly applied in the industry (Leuner and Dressman, 2000; Vasconcelos et al., 2007). The lack of physical stability over time along with humidity and temperature, may translate to poor dissolution behaviours and generally represent the primary barrier for the commercialisation of these solid doses (Craig, 2002; Vasconcelos et al., 2016). In order to target physically stable amorphous solid dispersions, the miscibility between the drug and the polymer is a key factor to be considered at the time of their formulation (Marsac et al., 2006a; Meng et al., 2015).

The term miscibility, or lack of it, has been applied to describe the amorphous drug-polymer phase behaviours. A miscible drug-polymer system is described as a single phase system in which the amorphous drug is homogeneously dispersed at the molecular level and exhibits properties different to the pure materials alone (Baird and Taylor, 2012).

The term solubility is also used in the study of drug-polymer systems, and it refers to the interactions between the polymer and the drug in its crystalline form. The solubility of small molecule solutions is defined as an equilibrium thermodynamic parameter and occurs when the chemical potential of the solute and the solvent are equal. Extrapolation of this concept to polymer solvents (carriers in solid dispersions) can be made at temperatures well above the polymer glass transition temperature ($T_g$), where equilibrium conditions can be reached. At temperatures close to or below the $T_g$, the system is under non-equilibrium conditions and solubility is referred to as "apparent" (Qian et al., 2010b).

The recrystallisation of small molecules in amorphous solid dispersions represents a significant disadvantage of this strategy. The amorphous active pharmaceutical ingredient (API) is in a metastable state, tending toward reaching equilibrium and crystallisation. The reduced molecular mobility represents the kinetic barrier that lowers the probability of crystallisation by inhibiting the molecules' diffusion and orientation. In this state, the equilibrium composition of the mixture would be the solubility of the crystalline drug in the polymer (Lust et al., 2015; Qian et al., 2010b).

Different methods have been employed to estimate the miscibility between small molecules and polymers. The measurement of the glass transition temperature of amorphous binary systems and its comparison with values predicted for ideally mixed systems, is predominantly the most commonly used (Baird and Taylor, 2012; Bochmann et al., 2016; Kalogeras, 2011; Meng et al., 2015). This method, despite having proved to be effective to provide a useful and reasonable prediction of the $T_g$ changes with the composition, is not infallible in the study of miscibility as it does not give

information about the thermodynamics of mixing (Lu et al., 2015; Marsac et al., 2009; Palazi et al., 2018; Van den Mooter et al., 2001). To complement the understanding of the thermodynamics of mixing, more detailed methods have also been used such as the melting point depression method based on the reduction of the drug melting temperature in the presence of the polymer (Marsac et al., 2006b). This thermodynamic approach allows the calculation of quantitative parameters to explore the level of miscibility and its dependence on the temperature and composition. This work investigates and reviews the use of both approaches for the estimation of the miscibility of indomethacin (IND) and poly(vinylpyrrolidone-co-vinyl acetate) (PVPVA) in order to analyse the validity and correlation between the information both approaches provide.

One of the most used analytical methods to predict the change of the $T_g$ with the composition of binary miscible mixtures is the Gordon-Taylor (GT) equation (Gordon and Taylor, 1952). This model was initially conceived to describe the behaviour of copolymers but have proved to provide a good prediction for polymer blends and other systems of pharmaceutical interest (Gupta et al., 2004; Li et al., 2014; Seong et al., 2016; Zhang et al., 2003). This model assumes ideal-volume mixing between the components implying no contraction or expansion of the molecular volume occurs with mixing. The expression for the calculation of $T_g$ is given by

$$T_g = \frac{(w_1 T_{g1}) + (k w_2 T_{g2})}{w_1 + k w_2} \qquad \text{Equation 1}$$

where $w_1$ and $w_2$ are the weight fractions of each component, $T_{g1}$ and $T_{g2}$ are the glass transition temperatures of each component and $k$ is a relationship between the density of the amorphous compounds ($\rho_1$ and $\rho_2$) and their expansion coefficient at the glass transition temperature.

Couchman & Karasz (1978) developed an equation describing the effect of the composition of the glass transition temperature of a binary system using a thermodynamic approach. The Couchman-Karasz (CK) equation is essentially identical to the GT expression apart from the constant $k_{ck,}$ which is expressed in terms of the changes of heat capacity. The change of heat capacity at the glass transition temperature can be easily measured using DSC, which makes this approach useful for the description of drug–polymer amorphous solid dispersions (Bochmann et al., 2016; Marsac et al., 2006a; Rumondor et al., 2009).

Similarly, the Fox equation (Fox, 1956), derived from the GT equation, was developed to estimate the behaviour of blends of components with equal densities. The Fox equation (Fox, 1956) predicts the relation between the composition and the glass transition temperature of a plasticised polymer assuming that the components are compatible and that they are not strongly polar (Equation 2).

$$\frac{1}{T_g} = \frac{w_1}{T_{g1}} + \frac{w_2}{T_{g2}}$$ Equation 2

All three previous models assume the existence of an ideal additivity of volumes of the two components at the glass transition temperature and no occurrence of any specific interaction between them. Deviations between the models and the experimental data obtained indicate non-ideal mixing, and this has been attributed to the existence of specific cohesive and/or adhesive interactions between the components. However, due to the lack of more detailed information on the thermodynamics of mixing, this interpretation may lead to a simplification of the complexity of the systems (Baird and Taylor, 2012; Kalaiselvan et al., 2006; Kwei, 1984; Lu and Weiss, 1992).

Among other expressions developed, Brostow *et al.* (2008) proposed a model to describe the deviation from linearity of the glass transition temperature variation with the mixture composition. The Brostow–Chiu–Kalogeras–Vassilikou-Dova (BCKV) equation proposed a definition of the deviation from linearity for non-ideal systems as expressed in Equation 3 (Brostow et al., 2008).

$$\Delta T_g = T_g - T_g^{lin} = T_g - \left[w_1 T_{g1} + (1 - w_1) T_{g2}\right]$$ Equation 3

If $\Delta T_g$ is expressed as a parabola: $\Delta T_g = w_1(1\text{-}w_1)a_0$ where $a_0$ is a parameter for a given system, $\Delta T_g$ will have the highest value at $w_1=w_2=0.5$. At that point $w_1\text{-}w_2=2w_1\text{-}1=0$. In consequence, for systems of any complexity, the authors defined a quadratic polynomial centred around $2w_1\text{-}1=0$ as shown in Equation 4.

$$\Delta T_g = w_1(1 - w_1)[a_0 + a_1(2w_1 - 1) + a_2(2w_1 - 1)^2 + a_3(2w_1 - 1)^3]$$ Equation 4

Combining Equation 3 and Equation 4, the BCKV expression results in Equation 5 which corresponds to the simple rule of mixing if $a_0=a_1=a_2=0$.

$$T_g = w_1 T_{g1} + (1 - w_1) T_{g2} + w_1(1 - w_1)[a_0 + a_1(2w_1 - 1) + a_2(2w_1 - 1)^2]$$ Equation 5

This equation provides a fit for miscible systems of different complexities that cannot be described with Fox and Gordon-Taylor equations, for example, when partial crystallisation of one of the blend components occurs or when asymmetrical changes of entropy and enthalpy take place (Kalogeras, 2011). The number of $a_i$ parameters required to represent the experimental data indicates the complexity of the system (Brostow et al., 2008).

The parameter $a_0$ is the main descriptor of the type and level of the deviation from linearity, the parameters $a_1$ and $a_2$ give a measurement of the strength of the asymmetric contributions. It has been observed, by the comparison of the fit among polymeric biphasic systems, that the empirical parameter $a_0$ and its normalised form $a_0/\Delta T_g$ with $\Delta T_g = T_{g2} - T_{g1}$ reflect differences between the

energies of the inter-component and intra-component interactions. The magnitude and sign of $a_0$ provides a quantitative measure of the system complexity and can be related with the energetic contributions of hetero-contacts, entropic effects and structural nanoheterogeneities that may be observed in blended composites (Kalogeras, 2011).

The melting point depression approach for the prediction of miscibility is based on the measurement of the melting point reduction of a crystalline drug in the presence of a polymeric carrier. A pure drug melts when the chemical potential of the crystalline drug equals the chemical potential of the molten drug. When analysing a physical mixture between a crystalline drug and a polymer, if miscibility occurs, the chemical potential of the drug in the presence of the polymer should be less in comparison to that in its pure crystalline state. Consequently, this depression of the chemical potential of the drug results in the depression of its melting point when blended with a miscible polymer (Nishi and Wang, 1975).

The Flory-Huggins (F-H) lattice-based theory is a well-known theory that describes the polymer-solvent or polymer-polymer miscibility in terms of the change of the Gibbs free energy. Polymer-solvent miscibility is described in terms of the interactions between a small molecule and a macromolecule. If substituting the solvent for another small molecule, e.g. a drug molecule, this theory can be applied to predict the thermodynamics of systems of pharmaceutical interest at temperatures close to the melting point of the drug. (Zhao et al., 2011).

Negative free energy of mixing predicts miscibility between the components. The change of free energy of mixing of a drug-polymer binary system can be described by an enthalpic and entropic contribution as expressed in Equation 6. Enthalpic contributions are linked with the adhesive interactions (intermolecular interactions between the two components of the blend) and cohesive interactions (interactions within each pure component). These interactions can be interpreted as familiar interactions like van der Waals forces, ionic interactions, charge transfer complexation and hydrogen bonding. On the other hand, the entropy of mixing is related to the molecular size. Through the comparison of nifedipine-PVP systems with different polymer molecular weights, down to its small molecule analogue methyl pyrrolidone, it was found that the entropy of mixing of the drug-polymer system is much less favourable than the entropy of mixing of the drug-methyl pyrrolidone system. This is because of the reduced conformational entropy of the polymer when compared with a low molecular weight molecule due to chain connectivity. Nevertheless, it was also demonstrated that among drug-polymer systems the entropic contributions remained almost constant with the change of molecular weight (Marsac et al., 2006b). This finding leads to the conclusion that for drug-

polymer systems, the magnitude of the enthalpic contribution will necessarily determine if the system is miscible.

$$\Delta G_{mix} = \Delta H_{mix} - T\Delta S_{mix} \quad \text{Equation 6}$$

The Gibbs free energy of mixing $\Delta G_{\text{mix}}$ can be expressed as a function of the F-H interaction parameter $\chi$, a term that reflects the enthalpic interactions of the system and also has an entropic component that varies with temperature and composition. The expression is presented in Equation 7 where $\phi$ is the volume fraction, $N$ is the molecular volume of the drug or polymer, $R$ is the gas constant and $T$ the temperature.

$$\Delta G_{mix} = RT\left(\frac{\phi_{API}}{N_1}\ln\phi_{Drug} + \frac{\phi_{poly}}{N_2}\ln\phi_{poly} + \chi\phi_{Drug}\phi_{poly}\right) \quad \text{Equation 7}$$

In the framework of the lattice theory, the lattice site can be defined as the drug volume. If $N_1$ is the molecular volume of the drug, the molecular volume of the polymer $N_2$ can be expressed as $N_2 = m\ N_1$ where $m$ is the ratio of the volume of the polymer to the lattice site which is defined as the drug volume and can be expressed in the following way:

$$m = \frac{\frac{M_{w\,poly}}{\rho_{poly}}}{\frac{M_{w\,Drug}}{\rho_{Drug}}} \quad \text{Equation 8}$$

where $M_w$ and $\rho$ are the molecular weight and density of the polymer and drug as indicated. Including this term, $\Delta G_{mix}$ can be then calculated for a particular system at a specific temperature and its corresponding interaction parameter as expressed in Equation 9.

$$\Delta G_{mix} = RT\left(\phi_{Drug}\ln\phi_{Drug} + \frac{\phi_{poly}}{m}\ln\phi_{poly} + \chi\phi_{Drug}\phi_{poly}\right) \quad \text{Equation 9}$$

The change of the Gibbs free energy can also be expressed by the change of the chemical potential of the solid and the molten liquid as expressed in Equation 10 where $\mu_{\text{liq}}$ is the chemical potential of the molten drug, $\mu_{\text{solid}}$ the chemical potential of the solid drug and $a$ the activity coefficient of the species. Additionally, Equation 11 defines the coefficient of activity, where $T_m^{mix}$ is the melting temperature of the drug in the presence of the polymer, $T_m^{pure}$ is the melting temperature of the pure drug and $\Delta H_{fus}$ is the heat of fusion of the pure drug (Marsac et al., 2006a; Ott and Boerio-Goates, 2000).

$$\Delta G_{fus} = \mu_{liq} - \mu_{solid} = RTln(a) \quad \text{Equation 10}$$

$$\ln(a) = -\frac{\Delta H_{fus}}{R}\left(\frac{1}{T_m^{mix}} - \frac{1}{T_m^{pure}}\right) \quad \text{Equation 11}$$

For a crystalline drug–amorphous polymer binary blend, the melting point depression data obtained using DSC can be used to predict the F-H interaction parameter $\chi$ at temperatures close to the $T_m$ of the drug using Equation 12. This expression is obtained differentiating Equation 9 and combining it with equations 10 and 11 (Flory, 1953; Marsac et al., 2006b).

$$\frac{1}{T_m^{mix}} - \frac{1}{T_m^{pure}} = \frac{-R}{\Delta H_{fus}}\left[ln\phi_{API} + \left(1 - \frac{1}{m}\right)\phi_{poly} + \chi\phi_{poly}^2\right] \quad \text{Equation 12}$$

The interaction parameter depends on both the composition and temperature. The temperature dependence of $\chi$ can be empirically described by Equation 13, where *A* corresponds to the entropic contributions and *B* the enthalpic contributions. Using the melting point depression data, a series of values of $\chi$ at different melting temperatures can be obtained. Plotting those values according to Equation 13 allows the calculation of parameters *A* and *B* which are necessary for the construction of phase diagrams (Lin and Huang, 2010; Tian et al., 2013).

$$\chi = A + \frac{B}{T} \quad \text{Equation 13}$$

This investigation proposes a comprehensive analysis of the most common methods used for the estimation of drug-polymer compatibility through the use of simple calorimetric techniques. In the literature, miscibility analysis has been presented in an isolated manner and often leading to erroneous or simplified interpretations. This work offers a novel compilation and comparison of the miscibility estimation methods, which offer useful and valuable practical considerations for the miscibility analysis, and therefore, for the formulation of amorphous solid dispersions. The model polymeric carrier, PVPVA, and the model class II drug, IND, were used in this study in order to gain an understanding of the compatibility between the two materials and to validate the results through the application of the different techniques outlined above.

## 2. Experimental Details

### 2.1. Materials

Copolymer poly(vinylpyrrolidone-co-vinyl acetate) in a ratio of 6:4 by mass, was purchased from BTC Chemical Distribution. Model drug IND, 1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-3-indoleacetic acid, was purchased from Tokyo Chemical Industry UK Ltd. All materials were dried in an oven for 24 hours at 40 °C prior to processing and testing. Physical mixtures of PVPVA with a

content of IND from 10 to 90 wt% were accurately weighted and mixed using a Nanomill from Nanosystems with an integrated Barnant mixer controller to homogenise the mixtures and reduce the particle size.

### 2.2. Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) was carried out using a Perkin Elmer Pyris 6 DSC. Samples between 4 and 6 mg were weighed and placed into non-perforated aluminium pans that were immediately crimped. Calorimetry scans were performed under a nitrogen atmosphere with a steady flow of 20 ml/min into the chamber to prevent oxidation. Samples were tested in triplicates. Details of the applied methods are presented below.

Prior to measuring the glass transition temperatures, an annealing step was applied to the mixtures to ensure the sufficient dissolution of the drug into the polymer. After the annealing step, samples were cooled down to 20 ºC at a rate of 40 ºC/min, held isothermal for 10 min and reheated to 180 ºC. A second heating run was applied and the glass transition temperatures ($T_{g2}$) of the completely amorphous systems were recorded. The glass transition temperature $T_{g2}$ obtained from the second heating run was used for the analysis of the system miscibility by the different models explored in this work as outlined in Section 1.

For the application of the melting point depression method, milled physical mixtures with 10, 20, 30, 40 and 50 wt % of IND were analysed using DSC. Samples were heated from 40 to 170 ºC at 1 ºC per minute and the peak temperature of the melting endotherm and heat of fusion were recorded.

### 2.3. Rheology Studies

An oscillatory rheometer TA Discovery Hybrid Rheometer 2 with a plate geometry of 25 mm of diameter and a gap height of 0.75 mm was used. An amplitude of 5.5 % was applied and verified by an amplitude sweep. Frequency sweeps were conducted from 10 Hz to 0.1 Hz. Annealing temperatures were set up around the glass transition temperature of the material and varied in 10 ºC steps with a holding time of one hour prior to each testing. Complex viscosity profile was transformed to normal viscosity using Cox Merz model. The obtained data was fitted to the Carreau-Yasuda equation (Equation 14).

$$\eta = \eta_\infty + (\eta_0 - \eta_\infty)[1 + (\lambda\gamma)^a]^{(n-1)/a} \qquad \text{Equation 14}$$

Where $\eta_0$ and $\eta_\infty$ are the zero shear and infinite shear viscosity, $\lambda$ is the characteristic time, $n$ is the power law index and $a$ is the Yasuda constant.

The approach developed by Bochmann *et al.* (2016) was followed to determine the annealing temperature for each composition, employing the CK equation to predict the glass transition temperature for each physical mixture. The CK equations are expressed in Equation 15 and Equation 16 where $w$ is the weight fraction, $k_{ck}$ is the Couchman-Karasz constant and $C_p$ is the heat capacity at the glass transition. Sub-indices 1 and 2 corresponds to the drug and polymer respectively.

$$T_g^{ck} = \frac{w_1 T_{g1} + k_{ck}(1-w_1) T_{g2}}{w_1 + k_{ck}(1-w_1)} \quad \text{Equation 15}$$

$$k_{ck} = \frac{\Delta C_{p2}}{\Delta C_{p1}} \quad \text{Equation 16}$$

The estimated glass transition temperatures for the whole range of compositions were taken into account to set the annealing temperature for each mixture.

## 3. Results and Discussion

Two different methods were applied for the evaluation of the miscibility between amorphous IND and PVPVA, and the estimation of the solubility between crystalline IND and PVPVA. The aim of this study is to gain understanding about the compatibility between the two materials and to compare the results through the application of different techniques.

### 3.1. Glass Transition Temperature Measurement

The experimental data analysed in this section corresponds to the glass transition temperature of milled physical mixtures after one hour of annealing. In order to set an appropriate annealing temperature, the viscosity of the physical mixture containing 20 w/w % of IND was measured varying the temperature in 10 ºC steps. Equation 14 was applied to determine the zero shear viscosity values after one-hour annealing in-situ. The results obtained are presented in Figure 1, and show the expected reduction of the viscosity profile with the increase of temperature.

In polymer-drug systems, due to the high viscosity of the carrier, the viscosity of the system could kinetically inhibit or allow the diffusion of the drug, and in consequence, affect the time necessary to achieve the solubility equilibrium. To minimise the effect of the high viscosity of PVPVA, the annealing temperature must be set at a point above the polymer glass transition temperature where

the system has sufficient mobility to facilitate the diffusion of the drug within the matrix. From Table 1, it can be noted that there is a drop in η0 of around a fifth of the value when the annealing temperature changed from 140 ºC to 150 ºC. In view of this reduction, the annealing temperature of the physical mixture with 20 % of IND was set around 150 ºC. Considering the prediction of the glass transition made for this same composition following the CK equation, the annealing temperature for all the samples was set as $T_{g,ck}$ + 60 ºC following with the approach taken by Bochmann et al., (2016) (see Table 2) (Sun et al., 2010).

**Table 1:** Zero shear viscosity values obtained from the Carreau-Yasuda fit of physical mixtures of PVPVA with 20 w/w % IND.

| **T (ºC)** | **$\eta_0$ (Pa.s)** | |
|---|---|---|
| | **0 % IND** | **20% IND** |
| 140 | 324,359 | 79,603 |
| 150 | 195,579 | 14,854 |
| 160 | 43,338 | 4,090 |
| 170 | 10,824 | 1,551 |

**Table 2:** Estimated Couchman-Karasz glass transition temperature for PVPVA and IND physical mixtures and their corresponding annealing temperatures.

| IND (w/w %) | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 |
|---|---|---|---|---|---|---|---|---|---|
| $T_{g,ck}$ (°C) | 97 | 88 | 80 | 73 | 67 | 61 | 57 | 53 | 49 |
| $T_{Annealing}$ (°C) | 157 | 148 | 140 | 133 | 127 | 121 | 117 | 113 | 109 |

Results of the DSC trials of PVPVA-IND annealed physical mixtures is presented in Figure 2 where $T_{g1}$ and $X_c$ correspond to the glass transition temperature and the percentage of crystallinity recorded on the post-annealing heating cycle. $T_{g2}$ corresponds to the glass transition temperature of the second heating cycle after heating the material above the melting temperature of IND. It can be noted that for the lower drug contents, the values of both of the $T_g$'s are equal, and the crystalline fraction is zero suggesting that the annealing treatment was appropriate in temperature and time, in order to solubilise the drug within the polymer. However, with the increment of the drug content, a deviation between the glass transition temperatures occurred and the fraction of non-solubilised crystalline drug increased making it apparent that setting a linear extrapolation of the annealing temperature for all the compositions is not appropriate. As a consequence, all miscibility analyses were performed using $T_{g2}$ as the descriptor of the amorphous system morphology.

Miscible systems are expected to show one glass transition temperature in between the $T_g$ of each of the two materials. This single $T_g$ is expected to change progressively with the composition. Starting with the properties of the individual components, the glass transition temperature of mixtures of PVPVA and IND were calculated using three different empirical approaches. The results obtained using the Fox equation and Gordon-Taylor equation are compared with the experimental data in Figure 3. For all the compositions, PVPVA and IND presented one $T_g$, indicating miscibility, and that the system exists in an apparent single phase. However, it is important to point out that the evaluation of the miscibility of multicomponent systems is limited to the evaluation of the homogeneity of the phase. Hence, this method does not have the sensitivity to reflect phase separation that may occur in domains smaller than the size of the segment responsible for the cooperative movement associated with the $\alpha$ relaxation (Olabisi et al., 1979). Phase separations at the scale of tens of microns may not be detected by DSC (Qian et al., 2010a).

It is also observed that the two applied models are in good agreement with the experimental data, which according to the literature, points to ideal mixing between the components due to the lack of strong inter/intramolecular interaction within the system (Barmpalexis et al., 2013; Dengale et al., 2014). This finding seems to contradict the existence of intermolecular interactions formed between the polymer carbonyl groups and the drug hydrogen donor groups and the formation of IND dimers reported by other authors (Saerens et al., 2012; Song et al., 2013; Taylor and Zografi, 1997). It is then hypothesised that the non-ideal mixing had no effect on the free volume of the system or that their contributions cancel out. This contradicting finding provides evidence of the limitation of attempting to describe the strength of the intermolecular interactions in the system based only on the information provided by the model, leading to potentially erroneous results (Baird and Taylor, 2012).

Other authors have applied the same analysis to similar PVPVA-IND systems (see Table 3). Molecular dispersions of PVPVA and IND prepared by solvent evaporation reported an excellent fit between model results and the experimental data obtained using DSC (Matsumoto and Zografi, 1999). In contrast, results from the GT analysis of untreated physical mixtures of PVPVA-IND exhibited a negative deviation from the experimental values (Chokshi et al., 2005). It could be suggested that for miscibility screening purposes, the level of mixing obtained by in-situ annealing processes at the micro-scale can be satisfactory compared to a molecular dispersion obtained by solvent evaporation.

**Table 3:** Gordon-Taylor parameters results for mixtures of PVPVA and IND.

| *k* | $R^2$ | Max. Deviation (°C) | Reference |
|---|---|---|---|
| 0.92 | 0.9911 | ±3 | Current work |
| 0.93 | 0.9961 | N.R.* | (Kalogeras, 2011) |
| 0.95 | N.R.* | ±9 | (Chokshi et al., 2005) |

*Not reported

The same experimental data was also analysed using the BCKV equation and the resultant fit is presented in Figure 4. It is observed that the BCKV model was also able to describe the course of the variation of the glass transition temperature with the composition, showing an excellent fit to the experimental data ($r^2 \approx 0.999$) which corroborates the miscibility between the materials.

Rearranging the BCKV equation (Equation 5) to an ordered polynomial equation of degree 3, Equation 17 was obtained. Comparing this equation with the one obtained from the fit of the experimental data, values of the fitting parameters $a_i$ were calculated. Results are presented in Table 4 and compared with the literature.

$$T_g = -4a_2w_1^4 + (8a_2 - 2a_1)w_1^3 + (3a_1 - 5a_2 - a_0)w_1^2 + \left(T_{g1} - T_{g2} + a_0 - a_1 + a_2\right)w_1 + T_{g2}$$

Equation 17

**Table 4:** BCKV curve fitting results for mixtures of PVPVA and IND.

| $a_0$ | $a_1$ | $a_2$ | $a_0/\Delta T_g$ | $R^2$ | **Reference** |
|---|---|---|---|---|---|
| -6.24 | 8.55 | -36.76 | -0.097 | 0.999 | Current work |
| -6.4 | 0 | 0 | -0.107 | 0.996 | (Kalogeras, 2010) |
| N.R.* | | | | 0.990 | (Bochmann et al., 2016) |

*Not reported

It has been reported that an increase of the interaction parameter $a_0$ translates into an increase in the energetic contribution of hetero-contacts (interaction between the two different components of the blend). Considering the existence of hydrogen bonding between PVPVA and IND reported in the literature, a positive and high value of this interaction parameter might be expected. However, a negative value was obtained which may be due to stronger interactions occurring between the drug

molecules than between the drug-polymer molecules. The results obtained agree with those reported in the literature (Kalogeras, 2011, 2010; Matsumoto and Zografi, 1999).

### 3.2. Melting Point Depression Method

The estimation of the Flory-Huggins interaction parameter was performed through the application of the melting point depression method in the context of the Flory Huggins lattice theory (Marsac et al., 2006b; Tian et al., 2013; Zhao et al., 2011). The value of $\chi$ is an indicator of the drug-polymer miscibility as it reflects the enthalpic and entropic contributions of a system. The enthalpic component is the determinant factor for miscibility of these systems. Results are presented in Figure 5. A substantial depression of IND melting point in the presence of PVPVA was observed. This depression of IND melting point in the mixture when compared to its pure state, results in a negative difference of their chemical potentials and therefore, in a negative value of the Gibbs free energy (Equation 10), quantitative indication of the miscibility between the materials.

Results relevant to point out that the samples were previously nanomilled to reduce the particle size and scanned with a heating rate of 1 ºC/min. It has been reported in a study by Marsac *et al*. (2006) that if this procedure was not carried out, no melting point depression would be observed due to the high viscosity of the polymer at the temperature and timescale of the test.

By rearranging Equation 12, this expression can be plotted to make the interaction parameter to be equal to the slope of a linear function and the fit is presented in Figure 5 b). The data displayed corresponds to physical mixtures with a polymer content from 10 to 30 wt% and for higher polymer contents, deviation from linearity was observed. This behaviour has been reported for nifedipine and felodipine assays with PVP K12 and is attributed to the composition dependence of $\chi$ and the decrease of favourable drug-polymer interactions, as the melting temperatures are closer to the glass transition temperature of the polymer (Marsac *et al.* 2006). An interaction parameter of -2.06 ($r^2$=0.9994) was obtained. This value represents an estimation of the miscibility of the system at temperatures close to the melting point of the drug. The negative value of the interaction parameter corresponds to a system where the miscibility is favoured due to the presence of strong and abundant adhesive interactions (Marsac et al., 2006b).

Using Equation 12, the melting temperature–interaction parameter pairs were calculated and plotted according to the empirical expression that describes the temperature dependence of $\chi$ (Equation 13) (Figure 6). Values of -102.33 for *A* and 42254 for *B* were obtained with a linear fit and $r^2$ = 0.9024.

The interaction parameter for the composition with the higher content of IND deviated from linearity and was excluded from the fit. This observation has been previously reported by other authors (Tian et al., 2013; Zhao et al., 2011).

Once the dependence of $\chi$ with temperature is defined, interaction parameters can be calculated at different temperatures, which can subsequently be used to calculate the change of the Gibb's free energy of mixing with the composition using Equation 12. The plot of $\Delta G_{mix}/RT$ as a function of the drug volume fraction is presented in Figure 7 including the curves obtained from the interaction parameters obtained from Figure 5, and the calculated values at 140 ºC and 160 ºC. It can be observed that the Gibb's free energy of mixing is negative for all compositions predicting miscibility for the system at temperatures close to the melting temperature of IND. This finding suggests that the optimal temperature for hot melt extrusion processing would be temperatures close to 140 ºC and higher (Tian et al., 2013).

Drug-polymer interaction parameters reported by two authors for PVPVA-IND systems are presented in Table 5. They correspond to the value obtained at temperatures close to the melting point of IND. A negative value is reported for all cases, corroborating the miscibility between the materials. However, a large variation is observed, and the value obtained in this investigation is between the two other reported values. At this stage, with the information provided, it is not possible to determine the cause of the differences observed. However, this may be related to morphology differences that may be due to the initial particle size distribution of the samples.

**Table 5:** Drug-Polymer interaction parameters of PVPVA-IND system obtained by melting temperature depression method.

| Drug-Polymer Interaction Parameter ($\chi$) | Reference |
|---|---|
| -2.06 | Current work |
| -4.5 | (Sun et al., 2010) |
| -0.64 | (Zhao et al., 2011) |

## 4. Conclusions

The miscibility estimation between PVPVA and IND was performed by the measurement of the glass transition temperature, and the melting point depression method. The first method demonstrated the formation of a single phase amorphous system for all the compositions analysed. The occurrence of strong intermolecular interactions is suspected due to the negative value of the BCKV model

interaction parameter, $a_0$. However, the application of the GT model to the data revealed no deviation from the experimental data, which could lead to the incorrect assumption of a lack of interactions between the components. Through the application of the melting point depression method, a negative interaction parameter $\chi$ was found, confirming the miscibility of the system and the occurrence of intermolecular interactions between the materials. Overall, miscibility between PVPVA and IND was demonstrated for the entire composition range down to temperatures close to the glass transition temperature of IND. Comparison between the two methodologies cannot be directly established as they predict miscibility at different temperatures. However, the information provided by each approach can be thought of as complementary and offer a wider understanding of the phase behaviour of the system.

## 5. Acknowledgments

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Figure 1: Viscosity profile of physical mixtures of PVPVA with 20 w/w % IND after one-hour of annealing at different temperatures.

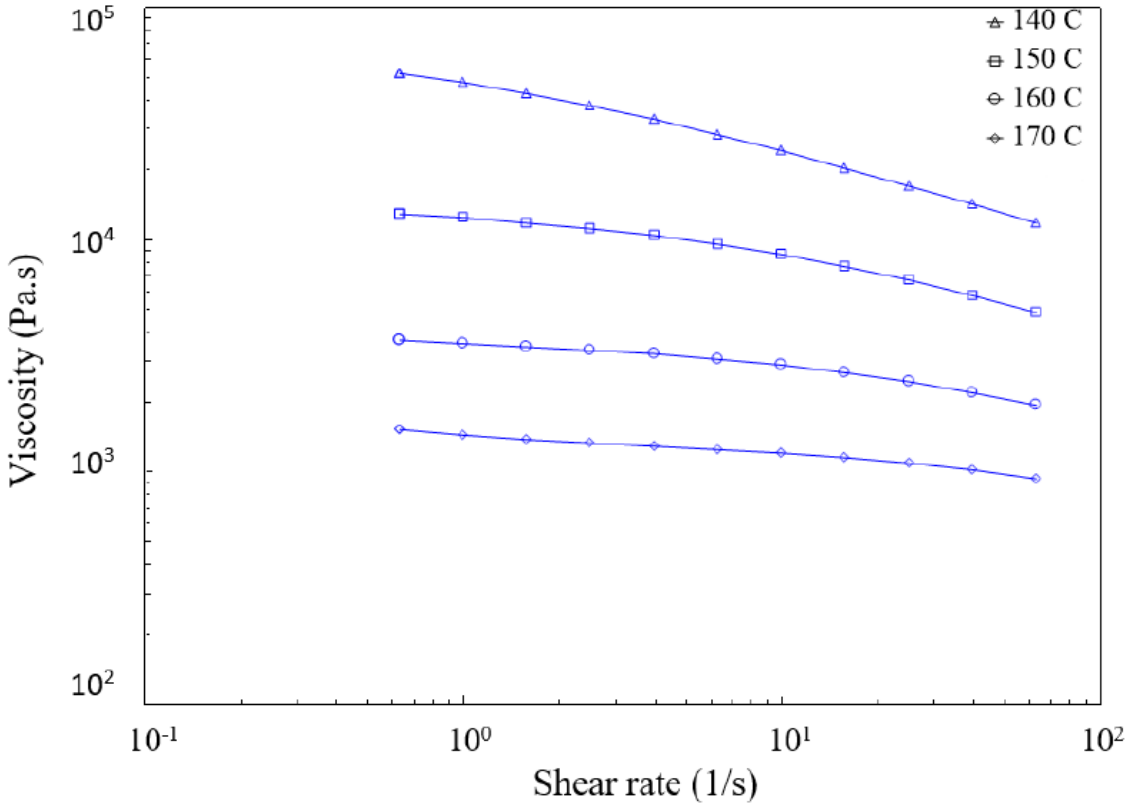

Figure 2: Glass transition temperature and crystalline fraction of annealed physical mixtures $T_{g1}$ and $X_c$, and amorphous system $T_{g2}$.

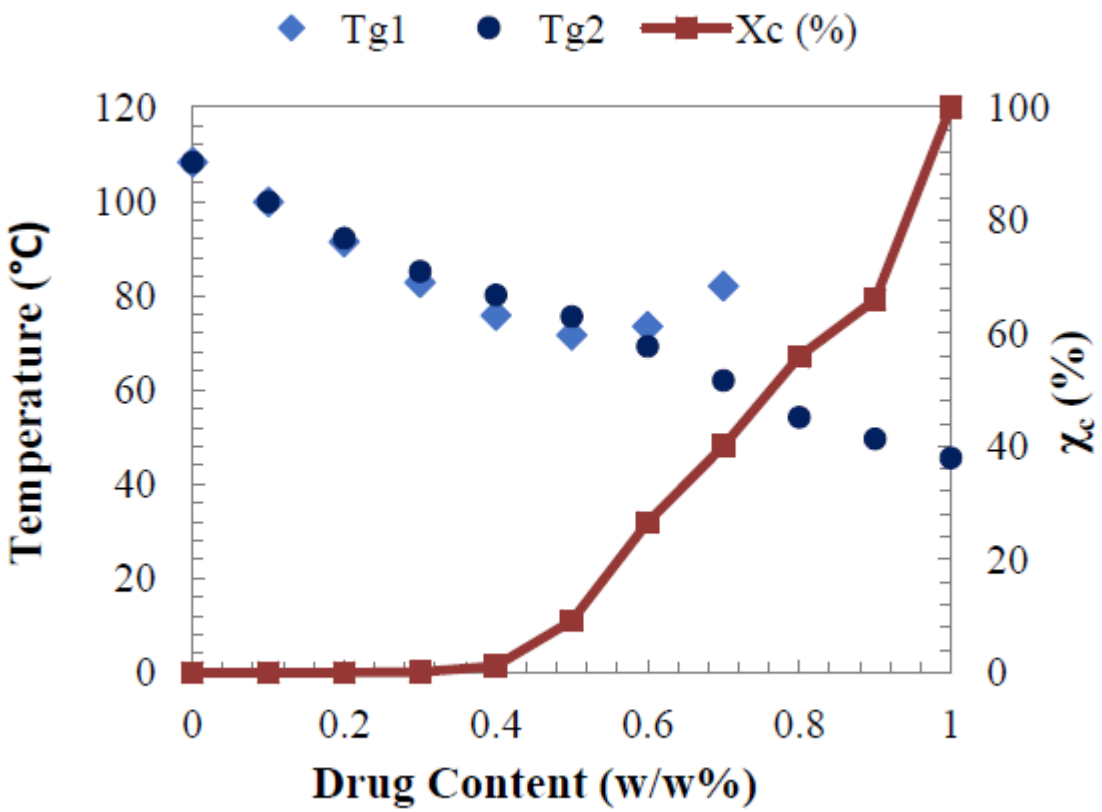

Figure 3: Gordon Taylor and Fox equations fit to the variation of the glass transition temperature of annealed physical mixtures of PVPVA and IND with the concentration.

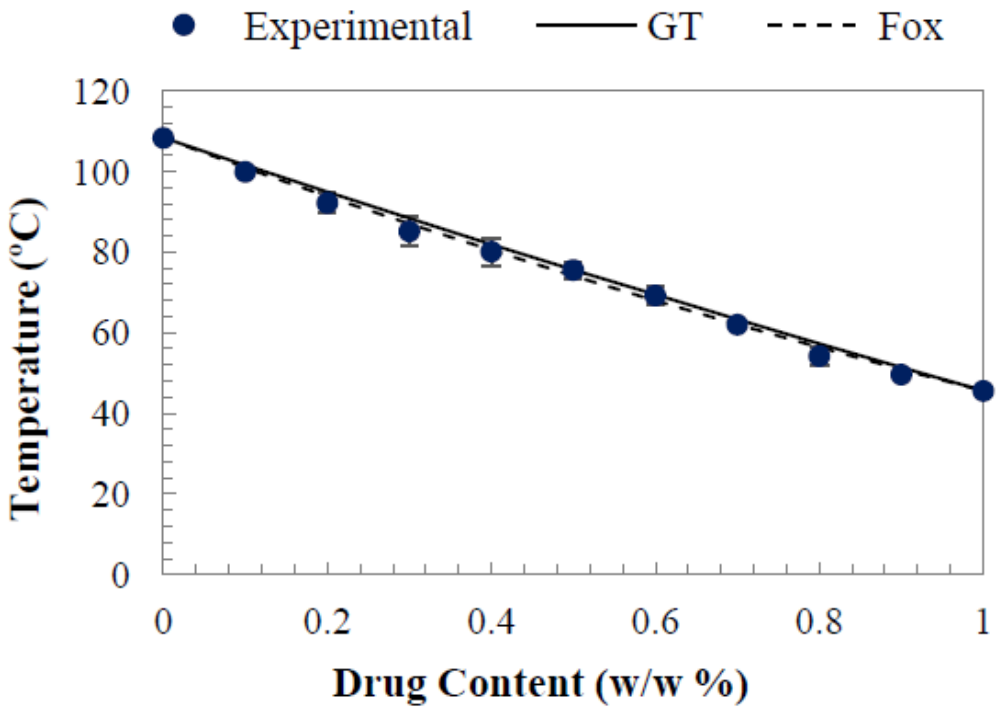

Figure 4: Glass transition temperature of annealed physical mixtures of PVPVA and IND as a function of the concentration. The points represent the experimental values; the line represents the BCKV fit.

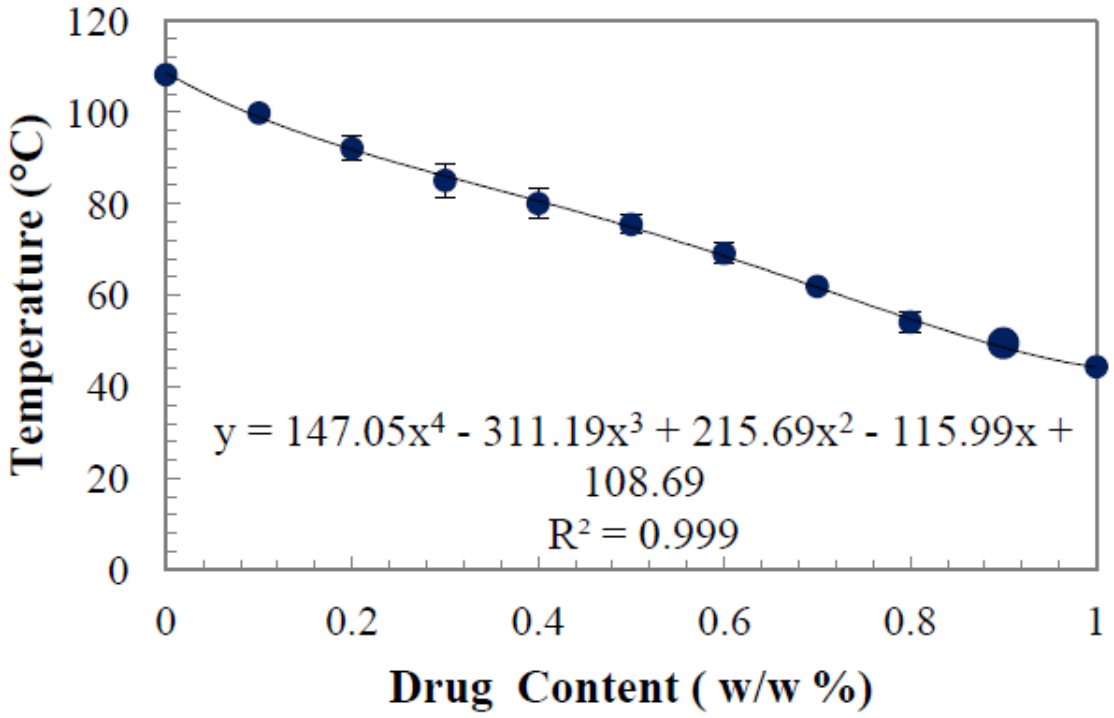

Figure 5: a) Melting temperature of IND as a function of its volume fraction. b) Plot used to determine the F-H interaction parameter of PVPVA-IND system close to the melting temperature of the drug.

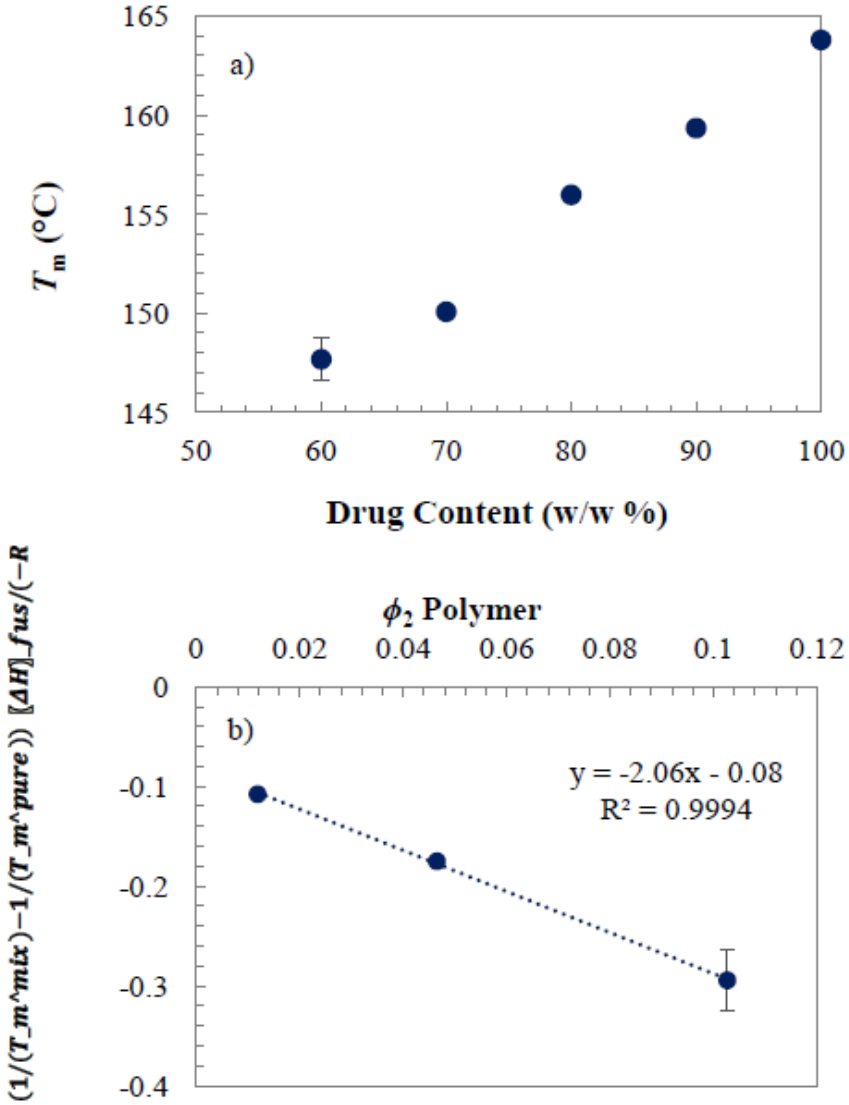

Figure 6: Polymer-drug interaction parameter as a function of temperature. The line represents the best fit of Equation 13 to experimental data.

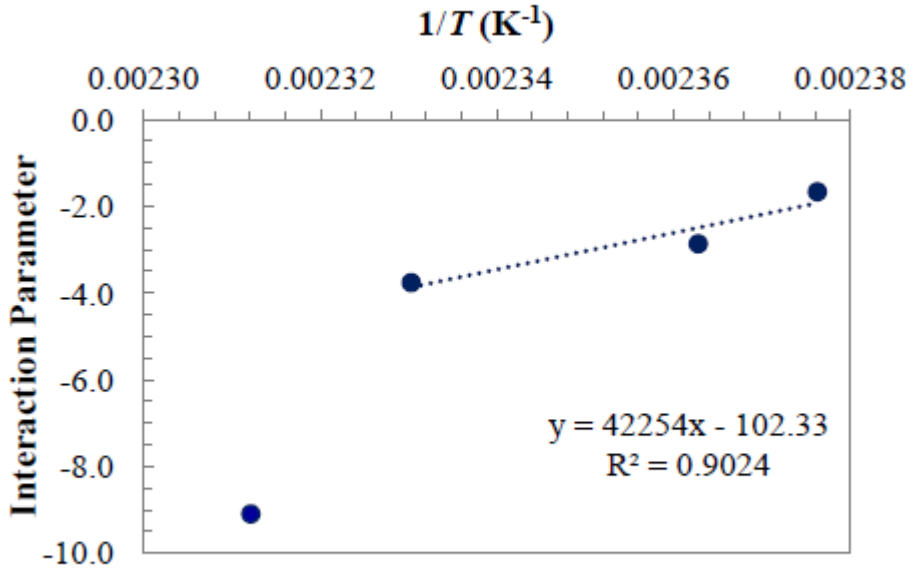


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Figure 7: Plot of $\Delta G_{mix}/RT$ as a function of the drug volume fraction for IND and PVPVA.

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