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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.

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

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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

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

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 (ρ_1 and ρ_2) and their expansion coefficient at the glass transition temperature.

Couchman and 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 (Eq. (2)).

$$\frac{1}{T_g} = \frac{w_1}{T_{g1}} + \frac{w_2}{T_{g2}} \quad (2)$$

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 Eq. (3) (Brostow et al., 2008).

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

If ΔT_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, ΔT_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 Eq. (4).

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

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

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

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 Eq. (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,