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Mini-Review

Qualitative and quantitative methods to determine miscibility in amorphous drug–polymer systems

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ABSTRACT

Amorphous drug–polymer systems or amorphous solid dispersions are commonly used in pharmaceutical industry to enhance the solubility of compounds with poor aqueous solubility. The degree of miscibility between drug and polymer is important both for solubility enhancement as well as for the formation of a physically stable amorphous system. Calculation of solubility parameters, Computational data mining, T_g measurements by DSC and Raman mapping are established traditional methods used to qualitatively detect the drug–polymer miscibility. Calculation of Flory–Huggins interaction parameter, computational analysis of X-Ray Diffraction (XRD) data, solid state Nuclear Magnetic Resonance (NMR) spectroscopy and Atomic Forced Microscopy (AFM) have been recently developed to quantitatively determine the miscibility in amorphous drug–polymer systems. This brief review introduces and compiles these qualitative and quantitative methods employed in the evaluation of drug–polymer miscibility. Combination of these techniques can provide deeper insights into the true miscibility of the drug–polymer systems.

Contents

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1. Introduction

In a pharmaceutical development process, hydrophilic polymers are commonly used to enhance the aqueous solubility and subsequently to improve the bioavailability of Active Pharmaceutical Ingredients (API) belonging to BCS class II (low solubility, high permeability) (Le-Ngoc Vo et al., 2013). Drug–polymer systems are widely used in solid dispersions for the enhancement of drug aqueous solubility (Chauhan et al., 2013, 2014; Prasad et al., 2014). The phase behavior of a drug–polymer system can be extremely complicated, since the drug can be present in a crystalline form (one or more polymorphic forms), a partially amorphous form, or a completely amorphous form (Vasconcelos et al., 2007). For the amorphous drug–polymer system in which both the drug and the polymer are present in an amorphous form, the phase behavior depends on the miscibility between the drug and polymer (Baird and Taylor, 2012). The term "miscibility" is commonly used in polymer science to describe the polymer–polymer, or the polymer–solvent systems (Patterson, 1982). Applying this term to the drug–polymer systems, a 'miscible' drug–polymer system have been described as a "single homogeneous phase in which the drug and the polymers are intimately mixed at a molecular level, and the mixed system has different physical properties compared to the pure components" (Baird and Taylor, 2012). Miscibility of the components in a blended system is extremely important for the stabilization of the amorphous drug–polymer system, since it is generally believed that miscibility at molecular level is necessary to achieve maximum physical stabilization (Marsac et al., 2006; Rumondor et al., 2009; Djuris et al., 2013). Immiscibility between the drug and the polymer is known to negatively influence the ability of a polymer to inhibit the crystallization of an amorphous drug (Ivanisevic, 2010; Meng et al., 2015).

2. Qualitative methods

2.1. Solubility parameter

The calculation of the solubility parameter differences have been used as predictors to evaluate the miscibility in drug–polymer systems by determining the cohesive energy density (CED) of individual components (Hancock et al., 1997; Vattanagijyingyong et al., 2013; Maniruzzaman et al., 2013). The solubility parameters of the drugs and the pharmaceutical excipients can be calculated in a variety of ways. Among the most commonly used methods is the 'group-contribution method' modified by Hansen, using the relationship shown below (Eq. (1)) (Van Krevelen, 1990).

$$\delta^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \quad (1)$$

where δ is the total solubility parameter, δ_d refers to the contribution from dispersion forces, δ_h represent the contribution of hydrogen bonding and δ_{pi} stands for the contribution from polar force. The individual components are calculated using the group contributions, as shown in Eqs. (2)–(4) below, where,

$$\delta_d = \frac{\sum F_{di}}{V} \quad (2)$$

$$\delta_p = \frac{\sqrt{\sum F_{pi}^2}}{V} \quad (3)$$

$$\delta_h = \frac{\sqrt{\sum E_{hi}}}{V} \quad (4)$$

F_{di} is the functional group contribution due to dispersion component, F_{pi} is the functional group contribution due to polar component, E_{hi} is the hydrogen bonding energy and V is the molar volume. $\Delta\delta$ describes the difference in solubility parameter (δ) between the two components.

Typically, blends with a lower number of $\Delta\delta$ are predicted to have higher miscibility. Further, the drug–excipient mixtures with $\Delta\delta < 7.0\ MPa^{1/2}$ are likely to be miscible whereas with $\Delta\delta > 10.0\ MPa^{1/2}$ are likely to be immiscible (Greenhalgh et al., 1999; Ghebremeskel et al., 2007). This method however, has limitations because the theoretical models used in this approach are only applicable to simple molecular structures wherein Van der Waals force plays a predominant role. For the drug–polymer systems which are known to form highly directional interactions (e.g. hydrogen bonding), or long range interactions (e.g. electrostatic interaction), this approach can be erroneous (Marsac et al., 2006; Gupta et al., 2011). Li and Chiappetta have studied the miscibility between VeTPGS and different polymers. The study found that polymer pairs with similar solubility parameters did not form a miscible system, and hence it was concluded that a similar solubility parameter cannot ensure a complete miscible system (Li and Chiappetta, 2007). The study also demonstrated that the solubility parameter is limited in predicting miscibility of molten system, since the properties such as the viscosity of the polymers might change significantly during thermal events (Liu et al., 2013).

2.2. Computational data mining

In the pharmaceutical drug development process, data mining have been employed for various purposes including, the understanding of the structure–activity relationships, the prediction of absorption, distribution, metabolism and elimination of drugs, and the prediction of the changes in the solid-state properties of pharmaceutical compounds (Butina et al., 2002; Colbourn et al., 2011; Mahlin et al., 2011; Mendyk et al., 2008). Recently computational data mining have been developed as a theoretical approach to evaluate the drug–excipient miscibility. Alhalaweh et al have used "K-means" algorithm to predict the miscibility of indomethacin with a set of more than 30 compounds based on their solubility parameter. They compared the miscibility calculated by computational data mining with that determined by the DSC method. They found that the results of K-means algorithm showed a high correlation to the experimental results. The authors thus reported "K-means" algorithm as an efficient, and a time-saving approach in predicting the miscibility in amorphous drug–excipient systems (Alhalaweh et al., 2014). The computational data mining has great potential because it can effectively evaluate the miscibility of drug–polymer systems (i.e. miscible or immiscible), it is easy to use, time and cost effective and material sparing (Alhalaweh et al., 2014).

2.3. Glass transition temperature measurement (DSC)

Measuring the glass transition temperature (T_g) of a binary, or a tertiary drug–polymer system using differential scanning calorimetry (DSC) is a commonly employed technique for qualitative evaluation of the drug–polymer miscibility (Nanaki et al., 2010, 2012). If a drug–polymer system is completely miscible, typically only a single T_g event is observed; whereas if the system is fully or partially separated into individual amorphous phases, two or more T_g values may be detected (Rumondor et al., 2009). The drug–polymer systems often exhibit a concentration dependent miscibility (Newman and Munson, 2012; Al-Obaidi et al., 2013). For example, felodipine-Polyacrylic acid systems containing 70% or 90% polymer showed only one T_g, indicating miscible systems, while systems containing 30% or 50% polymer showed two distinct T_g events, indicating the immiscibility in the blends (Rumondor et al., 2009). Although considered as a "gold standard" to evaluate the miscibility in amorphous systems, this technique

has several limitations. For example, traditional DSC is not able to successfully differentiate between the T_g if they are not at least 10 °C apart from each other. Moreover, the formation of small domains (less than 30 nm) in the systems containing more than one amorphous phase may result in a failure of the technique in detecting separate T_g values. In addition, the constant heating rate in a traditional DSC may change the miscibility of the system with an increase in the temperature. The detection of a single T_g above the T_g of the lowest individual component may not give sufficient information about the number of amorphous phases present at ambient conditions (Lodge et al., 2005; Newman et al., 2008; Ivanisevic et al., 2009).

It should be noted that the T_g value of the drug–polymer system can also provide valuable information regarding the drug–polymer miscibility, since the deviation between experimental T_g and theoretically calculated T_g might suggest the evolved molecular interaction (Baird and Taylor, 2012; Papageorgiou et al., 2009a,b). Papageorgiou et al. investigated the miscibility of nimodipine-PVP systems by using DSC, modulated temperature scanning calorimetry (MDSC) and other techniques. They applied the measured T_g values into the Gordon-Taylor equation, and found that the k values are much higher than 1, which indicated the presence of molecular interaction between nimodipine and PVP (Papageorgiou et al., 2009a).

2.4. Micro-Raman mapping

Raman spectroscopy has received a lot of attention in recent years in the drug development process in general; and specifically in the preformulation stages. Raman spectroscopy allows chemical mapping of a material or a system through depth analysis. Raman mapping has been extensively used in the polymer science for studying the phase behavior of polymer–polymer systems (Keen et al., 2002). Recently, a more advanced technique, "micro-Raman" has been utilized in evaluating the phase homogeneity of amorphous drug–polymer systems (Qian et al., 2010; Padilla et al., 2011; Papageorgiou et al., 2006; Docoslis et al., 2007). The micro-Raman has much higher detection limit as compared to traditional Raman technique. It uses a micro-cavity coated with reflective Au or Ag, which enhances the entire Raman signal through multiple ways (Misra et al., 2009). Padilla and coworkers evaluated the phase behavior of polyvinyl pyrrolidone (PVP)-dextran system by micro-Raman mapping, and compared the sensitivity of this technique in detecting phase separation with traditional thermal methods such as DSC (Padilla et al., 2011). The study results showed that micro-Raman mapping is able to detect phase separation in systems in which multiple glass transition events are not resolved by DSC (Padilla et al., 2011). Qian and coworkers compared the micro-Raman images of the compositional distribution of two drug–polymer systems. From the images, they found differences in the homogeneity of the two systems, which could be attributed to the different miscibility in the systems. The study claimed that this technique could be an important supplemental technique to evaluate the miscibility in drug–polymer systems since it provides localized compositional information that is distinctive from the bulk characterization (Qian et al., 2010). This method however, is limited by its low spatial resolution since the step size is on the micrometer scale (Yuan et al., 2014).

3. Quantitative method

3.1. Flory–Huggins interaction parameter

The Flory–Huggins interaction parameter is a well-established parameter in the pharmaceutical industry to measure the interactions of the polymer chains with the solvent molecules, as well as the polymer–polymer interaction (Frezzotti and Ravanetti, 1994). Recently, the Flory–Huggins interaction parameter χ was developed to describe the thermodynamic of mixing in drug–excipient systems by using Flory–Huggins lattice theory (Marsac et al., 2009).

3.1.1. Solubility parameter method

The Flory–Huggins interaction parameter (χ) can be calculated from the difference in the solubility parameters (δ) between drug and polymer (Eq. (5)), where V_{Site} is the volume of the hypothetical lattice and can provide a quantitative estimate of the miscibility in drug–polymer systems (Marsac et al., 2006).

$$\chi = \frac{V_{\text{Site}}}{RT}\left(\delta_{\text{drug}} - \delta_{\text{polymer}}\right)^2 \tag{5}$$

As shown in Eq. (3), it assumes that the enthalpic interactions between unlike species are equal to the geometric mean of enthalpic interactions between like species (Teja et al., 2013). Thakral et al. have investigated the Flory–Huggins interaction parameter by using the solubility parameter for a number of drugs with PEG 600 as a model matrix former. The study reported that it is possible to predict the free energy phase diagram of drug–polymer systems by using this approach. The authors used Bagley's plot to provide a reasonable approximation of the miscibility in the drug–polymer systems. However, it was observed that the dependence of miscibility on the composition in the systems cannot be clearly determined (Thakral and Thakral, 2013). Similar to using the solubility parameter to qualitatively predict miscibility, this method has several limitations. This method is applicable for simple systems containing mainly interactions like Van der Waals forces, but not for systems with interactions such as hydrogen-bonding or ionic interactions. With complex systems involving these interactions, this approach may not be reliable or accurate (Marsac et al., 2006).

3.1.2. Melting point depression method

The melting point depression of the drug in the presence of polymers have also been explored to evaluate the miscibility in drug–polymer systems (Lu et al., 2015; Donnelly et al., 2015). In this method, a DSC study is performed on drug–polymer physical mixtures, and the melting behavior of drug–polymer systems is compared to that of the pure drug. Generally, if the drug and the polymer are miscible, a significant melting point depression is observed due to the exothermic mixing. On the contrary, in an immiscible system, the melting point depression is negligible or absent, since the mixing is endothermic (Marsac et al., 2006).

The Flory Huggins interaction parameter (χ) can also be calculated using the melting point depression method (Eq. (6)) (Marsac et al., 2006).

$$\frac{1}{T_{\text{mix}}} - \frac{1}{T_{\text{pure}}} = -\frac{R}{\Delta H_{\text{fus}}}\left[\ln \phi_{\text{API}} + \left(1 - \frac{1}{m}\right)\phi_{\text{polymer}} + \chi \phi_{\text{polymer}}\right] \tag{6}$$

where T_{mix} and T_{pure} are the melting points of the physical mixture and the pure drug respectively, ΔH_{fus} is the heat of fusion of the drug, ϕ_{drug} and ϕ_{polymer} are the volume fraction of drug and polymer respectively and m is the ratio of the volume of the polymer to that of the drug (Marsac et al., 2006, 2009).

The Flory Huggins parameter obtained from the melting point depression values is commonly used to quantitatively describe the miscibility. Positive χ value indicates immiscibility while negative χ value usually suggests miscibility of the system. Quantitatively, the greater negative χ value indicates higher miscibility. Using this method, it is generally observed that systems with low T_g, e.g. polymers such as Eudragit E PO (T_g = 49 °C)

are more kinetically favorable, since these polymers are already in a molten/rubbery state for a relatively long time before the melting of the drug. Thus, the polymers have sufficient time and mobility to interact with the drug. In contrast, High T_g polymers such as PVP K90 (T_g = 174 °C) may not be very "liquid like" at the melting temperature of drugs. This may lead to insufficient molecular mobility, and may require a longer time for the polymers to interact with the drug, resulting in unfavorable kinetics of mixing (Marsac et al., 2006). There are other drawbacks of the melting point depression method, which limit its applications. When using this technique to determine the drug–polymer miscibility, it is important to note that the melting point of API should be higher than the T_g of polymer, so that the super-cooled liquid polymer can sufficiently interact with the molten API. Also care should be taken to avoid the degradation of components during heating (Marsac et al., 2009). In addition, when this technique is applied to systems in which a semi-crystalline polymer with a low melting point is used as carrier (e.g. PEG), the results could be misleading. This is due to the possibility that the drug might get dissolved inside the melted polymer matrix during the heating process, resulting in more significant melting point depression, or even the absence of melting event, and hence led to erroneous conclusions about the drug–polymer miscibility (Bikiaris et al., 2005).

3.2. Computational analysis of X-ray diffraction (XRD) data

XRD is a commonly used technique in the determination of the crystallinity in multi-component mixtures (Le-Ngoc Vo et al., 2013). The XRD pattern of a crystalline material or a mixture typically exhibits sharp crystalline peak, while an amorphous material, or a mixture shows a broad background describe as a halo pattern. Although XRD pattern is able to verify the amorphous state of a multi-component mixture, it is not possible to further differentiate individual compositions. In order to assess the miscibility of a mixture, the XRD pattern is usually combined with computational methods such as Pair Distribution Function Calculations (PDFs), Pure Curve Resolution Method (PCRM) and Alternate Least Squares (ALS) (Newman et al., 2008; Ivanisevic et al., 2009; Moore and Wildfong, 2011).

The first approach calculates Pair Distribution Function (PDF) data, which is derived from the XRD pattern of both the amorphous API, and the polymers. The PDF data is highly sensitive to the subtle changes between the reference patterns, and can be used to characterize the nearest-neighbor interactions and the change of local state, from which the drug–polymer miscibility can be qualitatively inferred (Ivanisevic et al., 2009; Newman et al., 2008; Bates et al., 2006; Nollenberger et al., 2009). This method requires especially high quality of the XRD data and longer experimental times as compared to most routine XRD experiments. Recently, Ivanisevic et al. modified the application of XRD in determining miscibility (Ivanisevic et al., 2009). They proposed that the PCRM can be used to reconstruct the reference XRD patterns for individual components (i.e. API and polymer) from the measured data of the mixture. The variance between the patterns collected on a set of mixtures (with different API loadings) can be used to identify the number of variable components that characterize the mixed patterns. For immiscible systems, there should be no significant component contributing to the variance. Whereas, for miscible systems, due to the presence of molecular interaction, additional significant contribution to the variance is expected. When the system is identified as miscible, ALS can be applied to quantitatively estimate the drug–polymer miscibility by determining the nearest neighbor (NN) coordination number for the API and the polymer (Ivanisevic et al., 2009).

3.3. Solid-state NMR (ssNMR)

Recently, the use of solid-state NMR (ssNMR) to investigate the miscibility of a drug–polymer systems has been explored (Pham et al., 2010; Aso et al., 2007; Yuan et al., 2014). Basically, a single relaxation time for both components indicates that they are completely miscible. A single ^{1}H T_1 relaxation time for both components indicate that they are miscible at a domain size around 100 nm, and a single ^{1}H $T_{1\rho}$ relaxation time for both components indicate that they are miscible at a domain size around 5 nm (Newman and Munson, 2012). Also Aso and coworkers used ^{1}H NMR relaxation measurements to study the miscibility between nifedipine and PVP (Aso et al., 2007). The NMR analysis showed that nifedipine and PVP are miscible at all the drug polymer ratios tested, e.g. 30:70, 50:50, and 70:30 (w/w) (Aso et al., 2007). More recently, Yuan and coworkers quantitatively determined the miscibility in nifedipine-PVP system by comparing the ^{1}H T_1 relaxation times, ^{1}H $T_{1\rho}$ relaxation times, and the differences in the relaxation times between the drug and the polymer. The study showed that the nifedipine-PVP systems were miscible on the 2–5 nm length scale at 75:35, 60:40 and 50:50 drug polymer ratios (w/w); whereas at 95:5 and 90:10 drug:polymer ratios, these systems were immiscible on the 2–5 nm length scale, and were borderline miscible on the 20–50 nm length scale (Yuan et al., 2014). In this method, the size of the miscible domain was estimated by the following rules: (1) If the ^{1}H $T_{1\rho}$ and T_1 values obtained from the drug and the polymer are similar, the domain size is smaller than 2–5 nm. (2) If the $T_{1\rho}$ value is different for the drug and the polymer but the T_1 value is the same, the domain size is between the 5 and 20 nm range. (3) If both, $T_{1\rho}$ and T_1 values are different for the drug and the polymer, the domain size is larger than 20–50 nm.

3.4. Techniques used in combination

Atomic Force Microscopy (AFM) have been used to study the growth rates of a drug crystal within different polymer combinations in amorphous pharmaceutical formulations for several decades (Mahlin et al., 2004, 2006; Ward et al., 2005). Recently, the ability of AFM in determining the miscibility of amorphous drug–polymer systems has been reported (Lauer et al., 2011; Fule and Amin, 2014a,b). AFM is capable of identifying nanometer-sized grains, which enables it to measure/compare the homogeneity of amorphous drug–polymer systems at a nanoscale. Lauer et al. have utilized AFM in combination with Raman microscopy to discriminate between homogenously and heterogeneously mixed drug/polymer combinations. In their studies, AFM have been demonstrated to be able to identify molecularly dispersed mixture successfully, and quantitatively determine phase separation through imaging at a molecular level (Lauer et al., 2011).

Apart from AFM, the use of electron microscopies such as Transmission Electron Microscopy (TEM) and Scanning Electron Microscopy (SEM), in combination with micro-Raman to study the drug–polymer miscibility has been developed. Electron microscopy uses an electron beam with small wavelength instead of light, and has a higher resolution as compared to light microscopy, and thus can reveal the structure of smaller objects (Karavas et al., 2007a). In combination with micro-Raman, TEM and SEM can be used in identifying the morphology and particle size distribution of drug in the solid dispersion (Karavas et al., 2006, 2007b; Papadimitriou et al., 2012; Kanaze et al., 2006). It might also provide valuable information about the drug–polymer miscibility.

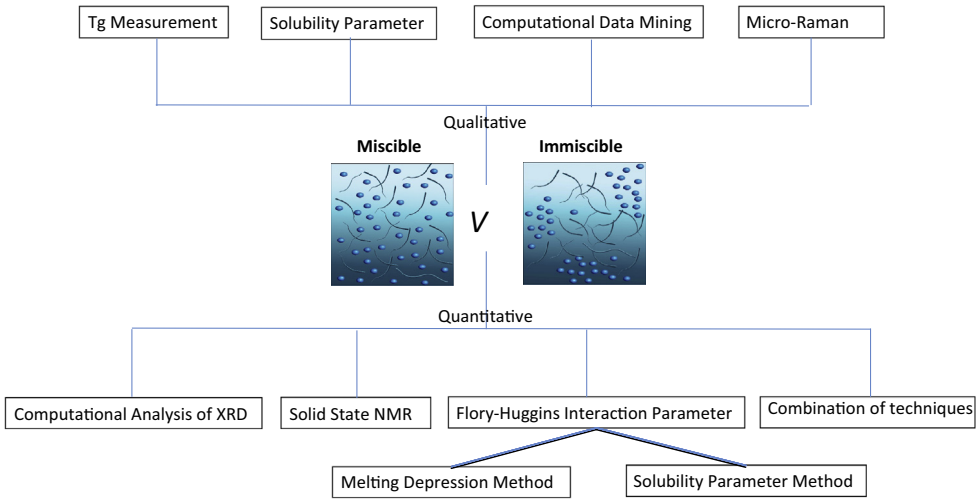

Fig. 1. Qualitative and quantitative characterization techniques used in evaluating miscibility of amorphous drug–polymer systems.

4. Solubility determination

Drug–polymer miscibility describe the tendency of a molten/amorphous form of drug to disperse in the polymer matrix, whereas the solubility refers to the ability of a polymer, which act as a solvent, to dissolve the crystalline drug (Marsac et al., 2006). The presence of crystallization during storage does not necessarily indicate the immiscibility between molten/amorphous drug and the polymer, it could also be explained that the solubility limit has been exceeded. Hence, to understand the solubility of drug in the polymer provides complimentary information about the drug–polymer miscibility (Marsac et al., 2006). If it is assumed that the polymer can assume the role of a solvent, then the solubility of a crystalline drug in a polymeric matrix could be described by the following equation (Eq. (7)):

$$\ln \gamma_{drug}\chi_{drug} = -\frac{\Delta H_{fus}}{RT}\left[1-\frac{T}{T_m}\right] - \frac{1}{RT}\int_{T_m}^{T}\Delta C_p^{config}dT + \frac{1}{R}\int_{T_m}^{T}\times\frac{\Delta C_p^{config}}{T}dT \quad (7)$$

where $\ln \gamma_{drug}$ is the activity coefficient and χ_{drug} is the mole fraction. Non-idealities in mixing are reflected by γ_{drug}. Applying Flory–Huggins lattice theory, for an API-polymer system, the activity coefficient of the API can be described by the following equation (Eq. (8)):

$$\ln \gamma_{drug} = \ln\frac{\phi_{drug}}{\chi_{drug}} + \left(1-\frac{1}{m}\right)\phi_{polymer} + \chi\phi_{polymer}^2 \quad (8)$$

This method uses thermodynamic model to estimate solubility of drug in polymer matrix (Marsac et al., 2006). It could be determined experimentally, Paudel et al. investigated the solubility of naproxen in n-Methylpyrrolidone (NMP) (a low molecular weight analogue of PVP) using HPLC, and extrapolate to that in PVP with different molecular weights (Paudel et al., 2010). They found thermodynamic solid solubility estimated of naproxen in PVP was considerably lower than the kinetic miscibility calculated by Flory–Huggins theory. Hence they concluded that naproxen was highly supersaturated in the PVP solid dispersions and only stabilized kinetically (Paudel et al., 2010).

5. Summary

Fig. 1 summarizes the techniques used in evaluating the miscibility of amorphous drug–polymer systems. Calculation of solubility parameters, computational data mining, T_g measurements by DSC and Raman mapping are established traditional methods used to qualitatively detect the drug–polymer miscibility. Calculation of Flory–Huggins interaction parameter, computational analysis of XRD data, solid state NMR spectroscopy, and AFM have been recently developed to quantitatively determine the miscibility in amorphous drug–polymer systems. A combination of these techniques can provide deeper insights into the true miscibility of the drug–polymer systems.

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