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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