International Journal of Pharmaceutics 519 (2017) 44–57

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

A rational approach towards development of amorphous solid dispersions: Experimental and computational techniques

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ARTICLE INFO

Article history:
Received 3 October 2016
Received in revised form 6 December 2016
Accepted 2 January 2017
Available online 4 January 2017

Keywords:
Miscibility
Solid-state NMR
Molecular modeling
Solubility parameter
Amorphous solid dispersion
Polymer

ABSTRACT

The purpose of this study was to determine the drug-polymer miscibility of GENE-A, a Genentech molecule, and hydroxypropyl methylcellulose-acetate succinate (HPMC-AS), a polymer, using computational and experimental approaches. The Flory-Huggins interaction parameter,χ, was obtained by calculating the solubility parameters for GENE-A and HPMC-AS over the temperature range of 25–100 °C to obtain the free energy of mixing at different drug loadings (0–100%) using the Materials Studio modeling and simulation platform (thermodynamic approach). Solid-state nuclear magnetic spectroscopy (ssNMR) was used to measure the proton relaxation times for both drug and polymer at different drug loadings (up to 60%) at RT (kinetic approach). Thermodynamically, the drug and polymer were predicted to show favorable mixing as indicated by a negative Gibbs free energy of mixing from 25 to 100 °C. ssNMR showed near identical relaxation times for both drug and polymer in the solid dispersion at RT and 40 °C for a period up to 6 months showing phase mixing between the API and polymer on <10 nm scale. Orthogonal computational and experimental approaches indicate phase mixing of the system components.

1. Introduction

Amorphous solid dispersions (ASD) are becoming increasingly popular as a viable means of drug delivery for crystalline solids with poor solubility and pKa that do not favor formation of a stable salt. The rationale for utilizing such a formulation, is to exploit the higher "apparent" solubility provided by the API in the amorphous state, which may translate to greater in-vivo bioavailability (Newman et al., 2012). The risk involved in such an undertaking is the physical and chemical instability associated with the amorphous form, i.e. its propensity to convert to the crystalline form and/or undergo chemical degradation owing to higher molecular mobility possessed by the glassy state. As a result, one or more polymers are included to obtain the ASD, in an effort to stabilize the amorphous form and maintain supersaturation in the in-vivo milieu (Newman et al., 2015; Zografi and Newman, 2016). The choice of the polymer is dictated by several factors, such as a) its degree of miscibility with the active pharmaceutical ingredient (API), b) its ability to inhibit crystallization upon storage in the solid-state, c) its ability to maintain supersaturation by inhibiting solution mediated crystallization during dissolution, d) wetting and pH-solubility properties, e) degree of hygroscopicity, and f) processability. Of all these properties, the degree of miscibility is of paramount importance in the solid-state since it has a bearing on the crystallization inhibition ability of the polymer (Newman et al., 2015). In a "well-mixed" system, the drug is molecularly dispersed in a polymer matrix, which is more effective in inhibiting molecular diffusion and therefore nucleation and crystallization, than a partially mixed or phase-separated system.

Apriori evaluation of degree of polymer-drug miscibility is obtained thermodynamically by determining ΔG_{mix}, the Gibbs free energy of mixing, between these two components at different drug loadings over the temperature range of interest. A negative ΔG_{mix} indicates favorable mixing and therefore a stable system, whereas a positive value indicates phase separation and potential destabilization. In order to obtain ΔG_{mix} for a multi-component system (i.e. ASD), the Flory-Huggins model, derived from polymer-solvent mixing principles, is commonly employed (Flory, 1942, 1953).

$$\Delta G_{mix} = \Delta H_{mix} - T\Delta S_{mix} \quad (1)$$

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http://dx.doi.org/10.1016/j.ijpharm.2017.01.003
0378-5173/

Here, ΔG_{mix} is the Gibbs free energy of mixing, ΔH_{mix} is the enthalpy of mixing, T is the absolute temperature and ΔS_{mix} is the entropy of mixing. Using Flory-Huggins interaction theory ΔG_{mix} can be represented as:

$$\Delta G_{mix} = RT\left(\phi_d ln\phi_d + \frac{\phi_p}{m} ln\phi_p + \chi_{d-p}\phi_d\phi_p\right) \quad (2)$$

Here R is the universal gas constant, m is the ratio of the molar volumes of the drug and the polymer and $\boldsymbol{\phi}_{\mathrm{d}}$ and $\boldsymbol{\phi}_{\mathrm{p}}$ are the volume fractions of drug and polymer and $\chi_{d\text{-}p}$ represents the Flory-Huggins interaction parameter between drug and polymer. The interaction parameter χ, represents the difference between the drug–polymer contact interaction and the average self-contact interactions of drug–drug and polymer–polymer. The term $''\phi_d ln\phi_d + \frac{\phi_p}{m} ln\phi_p''$ represents the entropic contribution while the term $''\chi_{d-p}\phi_d\phi_p''$ represents the enthalpic contribution to ΔG_{mix}. The Flory-Huggins phase map can be constructed by plotting the $\Delta G_{mix}/RT$ vs API volume fraction (ϕ) at different temperatures.

The enthalpy of mixing (ΔH_{mix}) at the temperature of interest can be directly calculated using solution calorimetry by employing a Hess's Law approach (Aukett and Brown, 1988; Calahan et al., 2015). The direct experimental approach of determining ΔH_{mix} is tedious and prone to significant errors in measurement since the ΔH_{mix} values are much smaller in magnitude compared to the heat of solution of the individual components. In other words, one of the rate limiting steps of this method is the precision of the heat of solution values, which is affected by several experimental parameters (Calahan et al., 2015). Alternatively ΔH_{mix} can be computed using F-H theory by calculating $\chi_{d\text{-}p}$. $\chi_{d\text{-}\mathrm{p}}$ cab be calculated by utilizing solubility parameters of the materials (Eq. (3)) (Rubenstein and Colby, 2003).

$$\chi = \frac{V_m(\delta_d - \delta_p)^2}{RT} \quad (3)$$

Here, V_m is the molar volume of the drug while δ_d and δ_p are the solubility parameters of drug and polymer respectively.

The solubility parameter is a number representing the relative solvency behavior of a given solvent and a comprehensive discussion on this parameter can be obtained in the literature (Barton, 1991; Burke, 1984). The solubility parameter (δ) approach for determining χ is either experimental or computational. Solubility parameters can be determined experimentally using the melting point depression approach (Marsac et al., 2009; Nishi and Wang, 1975; Zhao et al., 2011) but in such a case, the value of χ so obtained is valid only near the melting point of the API (Calahan et al., 2015; Marsac et al., 2009). Moreover, this method may not work in the presence of increasing amount of polymer or in cases where substantial melting point depression is not observed for the API in the ASD or if the API is prone to degradation at its melt. The polymer T_g needs to be at a substantially lower temperature than the melting point of the API to allow for the mixing of both components (Marsac et al., 2009). Computational methods involve determining δ by calculating cohesive energy density (CED), i.e. the energy needed to completely remove a unit volume of molecules from their neighboring molecules to infinite distance (i.e. ideal gas). This is essentially the heat of vaporization of a liquid divided by its molar volume in the condensed phase, as shown in Eq. (4).

$$\delta = \sqrt{CED} = \sqrt{\frac{E_v}{V_m}} = \sqrt{\frac{\Delta H_v - RT}{V_m}} \quad (4)$$

Here, E_v is the energy of vaporization, H_v is the enthalpy of vaporization and $\mathrm{V_m}$ is the molar volume of the liquid at the temperature of vaporization.

This method of calculating the solubility parameter by utilizing CED was proposed by Hildebrand and Scott (Gupta et al., 2011; Hancock et al., 1997; Hildebrand and Scott, 1950). The CED takes into account the electrostatic, van der Waals and hydrogen bonding interactions. The second computational method of obtaining δ is by utilizing a group contribution method, such as Hoftyzer-Van Krevelen method (Eqs. (5) and (6)), to obtain a solubility parameter value and thus χ. The group contribution method involves determining δ from the summation of the molar attraction constants and hydrogen bonding energy of molecular fragments, as explained in Eqs. (5) and (6). The overall δ value for the molecule is considered to be a summation of the dispersion, polar and hydrogen bonding components (Van Krevelen and Te Nijenhuis, 2009).

$$\delta_d = \frac{\sum F_{di}}{V}\delta_p = \frac{\sqrt{\sum F_{pi}^2}}{V}\delta_h = \sqrt{\frac{\sum E_{hi}}{V}} \quad (5)$$

$$\delta^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 as \quad (6)$$

Here, δ_d is the dispersion component, δ_p is the polar component and δ_h is the hydrogen bonding component. F_{di} and F_{pi} are the corresponding molar attraction constants while E_{hi} is the hydrogen bonding energy. V is the molar volume of the molecule.

Although widely used, this method has several drawbacks. A group contribution based method works best for simple molecules, provides δ values at room temperature and does not take into account directional bonds such as hydrogen bonding or long range electrostatic interactions (Gupta et al., 2011). Since χ is both temperature and composition dependent (Janssens and Van den Mooter, 2009; Koningsveld and Macknight, 1997; Lin and Huang, 2010; Qian et al., 2010; Rubenstein and Colby, 2003), often the group contribution method and the melting point depression method are used in conjunction to determine χ at two different temperatures and then extrapolate to other temperatures using Eq. (7) (Rubenstein and Colby, 2003).

$$\chi = A + \frac{B}{T} \quad (7)$$

Eq. (7) is the simplified temperature dependence of χ where A and B are entropic and enthalpic contributions respectively. The values of A and B are obtained from two sets of values of χ at two different temperatures (melting point and room temperature using the group contribution and the melting point depression methods respectively) and then this relationship is used to obtain χ at different temperatures to construct the Flory-Huggins phase diagram (Tian et al., 2013).

A third computational approach of determining χ is by directly calculating the mixing energy (ΔE_{mix}) between the API and the polymer, which is the difference in the free energy due to interaction between the mixed and the pure states of the two components (Pajula et al., 2010). ΔE_{mix} is obtained computationally by implementing the extended Flory-Huggins theories combined with molecular modeling (Eq. (8)) and then χ is calculated from ΔE_{mix} using Eq. (9). The original Flory-Huggins model is a constant lattice size/volume model and does not take into account volume changes upon mixing. In the extended F-H model, an off-lattice theory is implemented wherein molecules are not placed in a regular lattice and a co-ordination number Z is generated on the basis of molecular packing of a pair of interacting components (A and B) based on all of their possible combinations