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Cosolvency approach for assessing the solubility of drugs in poly (vinylpyrrolidone)

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ABSTRACT

The log-linear cosolvency model was applied for estimating the solubility of four drugs: ritonavir, griseofulvin, itraconazole and ketoconazole in poly(vinylpyrrolidone) (PVP). Cosolvent mixtures consisted of PVP mixed in different proportions with *N*-ethylpyrrolidone, which served as the monomeric analogue of the repeating unit of the polymer. Solubility in the monomer–polymer mixtures was determined by HPLC. As the configuration of the solvating unit in the solvent mixture changed from entirely monomeric to increasingly polymeric, the solubility of the drugs decreased in a fashion that follows the log-linear cosolvency model. The linear relationship was used to obtain estimates for the solubility of the drugs in the different grades of PVP. The solubility of the drugs in PVP is low (from <1% to ~15% w/w). Among the set of drug solutes, ritonavir exhibited the highest solubility in PVP (w/w). Mixing with the monomer is most favorable for griseofulvin among the four drugs. However, the detrimental effect of polymerization on its solubility is more pronounced than for ritonavir. The mixing of itraconazole with the monomer is more favorable than the mixing of ketoconazole. However, despite the molecular similarity between ketaconazole and itraconazole, the solubility of the latter is particularly affected by the polymeric configuration of the solvating unit, to the point of exhibiting differences in solubility resulting from the chain length of the grade of PVP used. The log-linear cosolvency model is a useful tool for estimating the solubility of the drugs in the polymer at room temperature, while providing quantitative information on the differences in mixing behavior of the four model compounds.

1. Introduction

A considerable number of new chemical entities (NCEs) fail to move forward in the pharmaceutical pipeline due to their low *in vivo* exposure, which is often associated with low aqueous solubility. In fact, over one third of the drugs listed in the U.S. Pharmacopeia have issues related to their low water solubility (Liu, 2008). Low aqueous solubility often leads to reduced bioavailablity of the drug and subsequent clinical failures due to inadequate pharmacokinetics (Caldwell et al., 2001). A poorly water soluble compound has been defined as one dissolving in less than 1 part per 10,000 parts of water, or 0.1 mg/mL (Martin, 1993). More recently, Hörter and Dressman proposed a performance based definition for a 'poorly soluble drug,' as one whose dissolution takes longer than the transit time required to pass through its absorptive sites (Hörter and Dressman, 1997). There are a number of formulation strategies for addressing low solubility/slow dissolution issues. These include salt formation, particle size reduction, the use of solubility enhancers such as cosolvents, surfactants, complexing agents, etc. and solid (drug-polymer) dispersion formulations. Among these approaches, solid dispersions have been shown to be a promising alternative method of solubility enhancement (Van Arnum, 2012; Janssens and Van den Mooter, 2009).

Solid dispersions are pharmaceutical formulations where the active ingredient is dispersed in a solid polymer matrix with the aim of achieving increased solubility and stability, sustained release, accelerated dissolution rate, etc. The solid dispersion approach has been employed as a solubility enhancement approach following the initial work of Sekiguchi and Obi (1961), who proposed the formation of a eutectic mixture of a poorly aqueous soluble drug, sulfathiazole, and a water soluble inert carrier, urea. Although the very first solid dispersion was produced in the form of a eutectic mixture, solid dispersion formulations in amorphous state have been a subject of great and increasing interest in recent times (Forster et al., 2001). An example of a commercially available pharmaceutical product of this

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type is the lopinavir/ritonavir mixture (AbbVie). The product has been formulated in a stable amorphous formulation (Rosenberg et al., 2013). Nevertheless, the potential of amorphous solid dispersions has not been fully realized. The number of marketed pharmaceutical products exploiting this approach remains limited, mainly due to issues pertaining to the physical instability of amorphous formulations, which can lead to crystallization during storage, thus eliminating the very formulation advantage of the amorphous dispersion.

The solubility of the drug in the polymer is an important parameter in the development of a stable amorphous dispersion (Janssens and Van den Mooter, 2009). The solubility value of the drug in the polymer fundamentally defines the type of stability of the formulation as being of kinetic or thermodynamic character (Paudel et al., 2010). When the concentration of the drug in the amorphous dispersion exceeds the solubility of the drug in the polymer, the formulation is a supersaturated mixture, thus making it thermodynamically unstable. In such cases, the shelf life stability of the product depends on the ability of the amorphous system to arrest molecular mobility, to the point of retarding the impending crystallization. Conversely, when the concentration of the drug in the dispersion is lower than its solubility in the polymer, the formulation is then a thermodynamically stable dispersion, turning it physically stable for an indefinite period.

A single-phase (molecularly mixed) amorphous solid dispersion exhibits a single glass transition event, hence a single glass transition temperature, T_g (Coleman et al., 1991; Chee, 1995). A single T_g value is regarded as an indication of complete miscibility between the drug and the polymer molecules in the dispersion. It should be pointed out that observing a single glass transition does not unequivocally represent a stable single phase amorphous mixture. On the other hand, the observation of more than one T_g is considered an indication of the presence of more than one amorphous phase (Olabisi et al., 1979).

Pharmaceutical scientists widely use differential scanning calorimetry (DSC) to screen for the attainment (or not) of miscibility in amorphous solid dispersions with different drug loads, based on the single T_g principle. We should point out that the detection of one single T_g presents some limitations. While miscibility between the amorphous drug and polymer is sought at room (storage) temperature, amorphous solid dispersions are often prepared at temperatures well above room temperature. Specifically, at temperatures above the T_g of the polymer and close to or above the melting point of the drug. This is precisely the case when hot melt extrusion (HME) is used. In the case of spray-drying (SD), the temperature utilized is higher than the boiling point of the solvent used. This means that even if complete miscibility between drug and polymer is achievable under the elevated processing temperatures, it is possible (likely) that thermodynamic equilibrium conditions at room temperature result in a supersaturated (immiscible) mixture. It follows that a miscible (single phase) mixture obtained by processing at some elevated temperature, can lead to a supersaturated (thermodynamically unstable), hence kinetically stabilized, single phase dispersion at room temperature. Such conditions imply a tendency toward phase separation and subsequent crystallization over time. This situation is presumably an important factor regarding the limited number of successful commercial products involving single-phase amorphous dispersions. Moreover, formation of domains smaller than ~15–30 nm in binary amorphous mixtures containing multiple phases could fail to show more than a single T_g value (Olabisi et al., 1979; Newman et al., 2008). Another confounding factor is that the increase or decrease of the temperature during DSC measurements can lead to a shifting miscibility (Rumondor et al., 2009).

There has been considerable effort on methods for estimating the miscibility and solubility of small molecules in polymers. One approach uses melting point depression measurements in combination with the Flory-Huggins (FH) model to obtain the interaction parameter between drug and polymer (Marsac et al., 2009; Marsac et al., 2006). Paudel et al. found that FH interaction parameters obtained by different methods (melting point depression, experimental solubility and solubility parameters) vary significantly because the interaction parameter of interest is in fact dependent on both temperature and composition (Paudel et al., 2010). Another approach is based on estimating the solubility of drugs in polymers near the T_g by DSC (Tao et al., 2009). In this approach, the solubility of drugs is estimated by merging T_{end} and T_g curves, obtained by determining the end point temperature where a known composition of premixed cryomilled drug dissolves in the polymer. The mixture is subsequently cooled to yield a solid dispersion from which T_g is measured. The most significant advantage of this thermal analysis method is that it can be readily applied to different polymeric matrices. However, the cryogenic milling process can induce crystal defects or phase transformations of the drug, leading to potential variation in the solubility determination. There are also reported investigations on the solubility of drugs in aqueous and organic solvents using DSC (Mohan et al., 2002; Park et al., 2003; Haddadin et al., 2009; Tamagawa et al., 2006).

The solubility of the drug in the polymer is a parameter of great significance in the development of drug-polymer amorphous formulations since it demarcates the separation between the kinetic and thermodynamic physical stability of the formulation. However, the solubility of a drug in a polymer cannot be ascertained by direct measurement, hence the different estimation approaches proposed in the literature. In this report, we introduce the use of a cosolvency based approach for estimating the solubility of different drugs in poly (vinylpyrrolidone) (PVP), one of the most widely used polymers for the study of amorphous solid dispersions. The study includes griseofulvin, ketoconazole, itraconazole, and ritonavir used as model compounds. These drugs exhibit a variety of chemical structures and molecular flexibility and have been studied in amorphous solid dispersion formulations.

2. Rationale

The log-linear cosolvency model describes the solubility of organic compounds in a solvent mixture made from solvents **1** and **2**, according to the following expression (Yalkowsky and Roseman, 1981a):

$$\log S_{mix} = f_1 \log S_1 + f_2 \log S_2 \quad (1)$$

where S_{mix},$S_{\mathbf{1}}$ and $S_{\mathbf{2}}$ are the solubilities in the solvent mixture, in the pure solvent **1** and in the pure solvent**2**, respectively, and $f_{\mathbf{1}}$ and $f_{\mathbf{2}}$ denote the volume fraction concentration of solvent **1** and **2** in the mixture, respectively. Alternatively, the log-linear model can be represented as follows:

$$\log \frac{S_{mix}}{S_1} = f_2 \sigma \quad (2)$$

where $\sigma = \log(S_2/S_1)$ is a parameter that reflects the ability of solvent **2** (termed the cosolvent) to solubilize the solute, relative to the solubilizing ability of solvent **1**.

The log-linear cosolvency model is based on the additivity of the free energy of solution thus encompassing both enthalpic and entropic contributions:

$$\Delta G_{mix} = f_1 \Delta G_1 + f_2 \Delta G_2 \quad (3)$$

where ΔG_{mix}, ΔG_1 and ΔG_2 represent the free energy of solution in the solvent mixture, in the pure solvent **1** and in the pure solvent **2**, respectively. The weighted average of the free energy of solution (Eq. (3)), results in a predicted solubilization profile in the form of a