Rapid Communication

A Promising New Method to Estimate Drug-Polymer Solubility at Room Temperature

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ABSTRACT

The established methods to predict drug-polymer solubility at room temperature either rely on extrapolation over a long temperature range or are limited by the availability of a liquid analogue of the polymer. To overcome these issues, this work investigated a new methodology where the drug-polymer solubility is estimated from the solubility of the drug in a solution of the polymer at room temperature using the shake-flask method. Thus, the new polymer in solution method does not rely on temperature extrapolations and only requires the polymer and a solvent, in which the polymer is soluble, that does not affect the molecular structure of the drug and polymer relative to that in the solid state. Consequently, as this method has the potential to provide fast and precise estimates of drug-polymer solubility at room temperature, we encourage the scientific community to further investigate this principle both fundamentally and practically.

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Introduction

On account of increasing focus on the physical stability of amorphous solid dispersions, several experimental methods to predict the solubility of drugs in polymers at room temperature have been proposed.[1-6] As most pharmaceutically relevant drugs and polymers are solid or highly viscous at room temperature, measuring the drug solubility under these conditions is not feasible,[7] and therefore, the methods are based on equilibrium thermodynamics at elevated temperature and subsequent extrapolation to room temperature. Most of the methods are based on differential scanning calorimetry (DSC) measurements and is time consuming due to slow dissolution or crystallization kinetics of the drug into or from the polymer. As a consequence, predictions from these methods are associated with a degree of uncertainty, the extent of which depends on several factors including the precision of the measurements, the validity of the assumptions underlying the proposed model (e.g., the Flory-Huggins theory), and the magnitude of the temperature extrapolation.[8]

To overcome these issues, a method to estimate the solubility of drugs in polymers, based on the solubility of the drug in a liquid analogue and/or monomer of the polymer at room temperature, was proposed by Marsac et al.[9] A key assumption underlying this method is that the interactions between the drug and analogue and/or monomer in the liquid state are similar to the interactions between the drug and polymer in the solid state.[9,10] However, as the method requires a liquid analogue and/or monomer of the polymer, it is not applicable to all polymers, and furthermore, it does not account for the fundamental chemical and physical differences between monomers and polymers. In contrast to the covalently bound monomers in a polymer chain, liquid monomers have relatively unrestricted intermolecular movement, which allows for interactions with the drug molecules without steric hindrance, and therefore, the method tends to overestimate the solubility of drugs in polymers.[11]

Under the premise of similar interactions in the solid and liquid state, this study investigated the possibility of estimating the drug-polymer solubility from the solubility of the drug in a polymer

solution at room temperature rather than in a liquid analogue and/ or monomer. This approach appears feasible if the solvent does not influence the molecular structure of the drug and polymer relative to that in the solid state (e.g., through protonation/deprotonation) or the interactions between the drug and polymer. Consequently, we hypothesize that the solubility of a drug in a polymer can be derived from the increase of drug solubility as a function polymer concentration in a solvent by considering the solvent as an inert component. Compared to the existing methods, this new polymer in solution method does not require extrapolations over long temperature ranges and may therefore provide faster and more precise solubility estimates. The potential of this method was investigated using chloramphenicol (CAP), celecoxib (CCX), and paracetamol (PCM) as model drugs, polyvinylpyrrolidone (PVP), polyvinyl acetate (PVA), and polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (Soluplus®, SOL) as polymers, and methanol and ethanol as solvents. To verify the solubility estimates from the new polymer in solution method, the results were compared with predictions from an established method based on melting point depression determinations.[1]

Materials and Methods

Materials

CCX (M_w = 381.37 g/mol) was purchased from AK Scientific, Inc. (Union City, CA). PCM (M_w = 151.17 g/mol), CAP (M_w = 323.13 g/mol), methanol (>99.9%), and ethanol (~96%) were purchased from Sigma-Aldrich Co. (St. Louis, MO). Kollidon® 17 PF (PVP, M_w = 10,000 g/mol) and Soluplus® (SOL, M_w = 118,000 g/mol) were kindly supplied by BASF (Ludwigshafen, Germany), and PVA (M_w = 40,000 g/mol) was purchased from VWR Chemicals (Leuven, Belgium).

Thermal Analysis

The melting temperature (T_m, onset) of the pure materials and physical mixtures was determined using DSC. The analyses were performed using a Q2000 DSC from TA Instruments Inc. (New Castle, DE). Sample powders (2-3 mg) were packed into Tzero aluminum hermetic pans with a perforated lid and scanned at 1°C/min from 60°C-180°C under 50 mL/min dry nitrogen gas purge. The instrument was calibrated for enthalpy and temperature using indium as a standard and the heat capacity was calibrated using a sapphire standard. The melting temperature (T_m, onset), melting enthalpy (ΔH_m), and glass transition temperature (T_g, inflection) were determined using the Universal Analysis 2000 (version 4.5A) software.

Quantitative Analysis

A reversed phase HPLC method was developed for quantification of CAP, CCX, and PCM. The HPLC system consisted of an L-7100 pump, an L-7200 auto sampler, a T-6000 column oven, an L-7400 UV-detector, and a D-7000 Interface all from Merck-Hitachi LaChrom (Tokyo, Japan). A total of 25 μL was injected into a reverse phase X-Bridge C-18 column (4.6 × 150 mm, 3.5 μm) from Waters (Milford, MA) for the separation. The mobile phase consisted of methanol and 20-mM ammonium phosphate buffer (65:35 v/v) adjusted to pH 2.35 ± 0.05 with phosphoric acid and was eluted at a flow rate of 1.0 mL/min. The effluent was monitored at 280 nm, 235 nm, and 250 nm and retention times of 2.0 min, 6.2 min, and 1.6 min for CAP, CCX, and PCM, respectively.

Established Method (Melting Point Depression)

If the dissolution of a crystalline drug into an amorphous polymer is favored by the thermodynamics of mixing, the melting point of the drug will be depressed. According to the Flory-Huggins model, it is possible to relate the magnitude of this melting point depression to the solubility of the crystalline drug in the polymer[1,12]:

$$\frac{\Delta H_m}{R} \times \left(\frac{1}{T_m} - \frac{1}{T}\right) = \ln\left(v_{\text{drug}}\right) + \left(1 - \frac{1}{\lambda}\right) \times \left(1 - v_{\text{drug}}\right) + \chi \times \left(1 - v_{\text{drug}}\right)^2,$$

(1)

where ΔH_m and T_m are the enthalpy of fusion and melting temperature for the pure drug, respectively, R is the gas constant, λ is the molar volume ratio of the polymer and drug, χ is the Flory-Huggins interaction parameter, and T is the melting temperature (onset) at a given volume fraction of drug (v_{drug}). To obtain the solubility of the drug in the polymer at room temperature, the melting points at different drug fractions were determined at elevated temperatures, fitted to Equation 1 and extrapolated to 25°C. Therefore, physical mixtures of crystalline drug and polymer of known composition were prepared by gentle milling using a mortar and pestle. The exact drug fraction after the milling procedure was determined using HPLC, and the samples were stored in air-tight vessels at room temperature until use. The melting points of the different physical mixtures were determined at a heating rate of 1°C/min using the DSC. For a more detailed description of the theoretical background and experimental protocol of the method, the interested reader is referred to Marsac et al.[1]

New Method (Polymer in Solution)

In this study, we hypothesize that the drug-polymer solubility may also be derived from the increase of drug solubility as a function of polymer concentration in an inert solvent (slope of the linear regression). The solubilities of the drugs in the pure solvents and polymer solutions were determined using the shake-flask method. Polymer solutions of known concentration (10%-40% w/v) were prepared by dissolving the polymer in the solvent (methanol or ethanol). An excess of crystalline drug was added to a capped glass tube containing 1 mL of the pure solvent or the polymer solution and rotated at 5 rpm using a mechanical rotor from Heto Lab Equipment (Birkerod, Denmark). The suspensions were rotated at 25°C ± 1°C for 1 week to ensure that equilibrium was reached. Thereafter, the samples were filtered using 0.2-μm polytetrafluroethylene hydrophobic syringe filters from Merck Millipore Ltd. (Darmstadt, Germany) and diluted with methanol to appropriate concentrations. The diluted samples were quantified using the HPLC method described previously.

Statistical Analysis

The Flory-Huggins model (Eq. 1) was used to describe the measurements obtained by the melting point depression method. The optimal fit with χ as an adjustable parameter was found by regression analysis, and the 95% prediction interval was obtained by extrapolation to 25°C as previously described by Knopp et al.[8] The data from the polymer in solution method, proposed in this work, were analyzed by linear regression, that is, $X_{\text{drug}} = a \cdot X_{\text{polymer}} + b$, where X_{drug} is the solubility of the drug in the polymer solution, X_{polymer} is the concentration of the polymer in