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Estimating the Aqueous Solubility of Pharmaceutical Hydrates

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ABSTRACT

Estimation of crystalline solute solubility is well documented throughout the literature. However, the anhydrous crystal form is typically considered with these models, which is not always the most stable crystal form in water. In this study, an equation which predicts the aqueous solubility of a hydrate is presented. This research attempts to extend the utility of the ideal solubility equation by incorporating desolvation energetics of the hydrated crystal. Similar to the ideal solubility equation, which accounts for the energetics of melting, this model approximates the energy of dehydration to the entropy of vaporization for water. Aqueous solubilities, dehydration and melting temperatures, and log *P* values were collected experimentally and from the literature. The data set includes different hydrate types and a range of log *P* values. Three models are evaluated, the most accurate model approximates the entropy of dehydration (ΔS_d) by the entropy of vaporization (ΔS_{vap}) for water, and utilizes onset dehydration and melting temperatures in combination with log *P*. With this model, the average absolute error for the prediction of solubility of 14 compounds was 0.32 log units.

Introduction

The estimation of solubility for a drug or drug candidate is an important aspect to the drug development process for both academic and industrial research. Predictive models for the estimation of solubility provide the researcher with vital information of the compound to aid in experimental design and minimize expenses. As such, the development of models to predict solute solubility in both aqueous and organic solvents, as well as the effects cosolvents, surfactants, and pH have on solubility have been investigated for decades.[1-11] Computational models for solubility based on lipophilicity, solvation interactions, and substructure components can be found throughout the literature.[12-18] The advantages and disadvantages of different prediction models have been discussed in review articles.[19-22] Importantly, the impact of different crystal forms on solubility should be taken into consideration when evaluating solubility and the preparation of stable dosage forms.[23-25] Moreover, a specific crystal may affect the adsorption of the active drug from its dosage form.[26]

Crystalline hydrates are a pharmaceutically important type of crystal form. An estimated one-third of active pharmaceutical substances are capable of forming a hydrate.[27] The addition of the water molecule(s) in the crystal lattice alters the physical structure and properties of the drug substance including changes to the dimensions, shape, symmetry, and the unit cell.[28] These changes lead to differences in pharmaceutical properties such as solubility and chemical stability.[28] The alteration of the physical structure and the properties that occur when a hydrate is formed should be considered for a solubility predictive model; however, the majority of solubility estimation methods either assume the most stable anhydrous crystal form or do not address the impact of different crystal forms, including hydrates. This can be problematic considering that the meta-stable anhydrous form has been shown to be 2×, 3×, and even 22× more soluble than its hydrate.[29,30] As a result, it would be theoretically expected that aqueous solubility estimations, based on the anhydrous crystal form alone, would tend to over-predict the solubility of a drug that forms a more stable hydrate in water.

A theoretical model has been developed to predict the solubility ratio of polymorphs.[31] However, there are no models that take into consideration additional energies present with hydrates, nor how those energies would affect the overall solubility. Therefore, the aim of this study is to describe a mathematical model based on an extension of the ideal solubility equation, which reasonably estimates the solubility of a hydrate. This model investigates the concept of accounting for the dehydration energetics of the hydrated solute in addition to the anhydrous melting energy. This model will lend itself to the appreciation of the solubility differences that can exist between hydrate and anhydrous drug forms.

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Theoretical Background

The solubility of a solid solute is related to the energy necessary to break up the crystal and the mixing with a solvent. The contribution of the crystal term can be derived as a function of the melting point (MP), whereas the mixing term is considered for non-ideal conditions and is dependent on the chemical structure of the solute and how it interacts with the solvent (activity coefficient). For aqueous conditions, the mixing term is often accounted for by the solute's octanol-water partition coefficient (K_{ow} or P).

Ideal Solubility of Crystalline Anhydrous Solutes

The influence of the crystal on solubility can be related to how much energy it takes to convert the crystal into a hypothetical supercooled liquid at a given temperature. Kirchhoff's law states that the energy of an irreversible process is equal to the energy of a series of reversible processes between the same end points.[32] As such, the energy of melting at temperature T (converting the solid to a hypothetical supercooled liquid) can be described by the sum of the enthalpies of the following processes: heating the solid to its MP, melting the solid at its MP, and cooling the liquid back down to temperature T. Based on these processes, the crystalline contribution to the ideal solubility of a solid solute can be determined from its solid state properties via the following equation:

$$RlnX_u^{ideal} = -\Delta H_m\left(\frac{T_m - T}{T_m T}\right) + \Delta C_p\left[\left(\frac{T_m - T}{T}\right) - ln\left(\frac{T_m}{T}\right)\right] \quad (1)$$

where X_u, ΔH_m, T_m, T, ΔC_p, and R correspond to the mole fraction solubility, heat of melting, MP of the solid (K), reference temperature (K), heat capacity change on melting, and the gas constant, respectively.[33] It has been demonstrated that when calculating the ideal solubility, the ΔC_p term results in a small impact on the ideal solubility (especially for lower MP compounds) and can be assumed to be equal to zero.[34] However, it is important to note that for compounds with a higher MP the term can become significant[34] and it has been reported that in instances of increased molecular flexibility, ΔC_p is better approximated by using the value for the entropy of melting (ΔS_m).[35]

Utilizing the assumption that the ΔC_p term is equal to zero, and recalling that at the MP the Gibbs free energy (ΔG) is equal to zero (so that $\Delta H = T\Delta S$), Equation 1 can be rearranged to the following:

$$lnX_u^{ideal} = -\Delta S_m\frac{(T_m - T)}{RT} \quad (2)$$

or

$$logX_u^{ideal} = -\Delta S_m\frac{(T_m - T)}{2.303RT} \quad (3)$$

To further simplify, it is convenient to apply Walden's rule,[36] which states the ΔS_m of polycyclic aromatic derivatives can be approximated at 13.5 cal/K·mol, and evaluate the solubility at room temperature (298 K). This rendering provides a convenient model (Eq. 4) to describe the anhydrous crystal contribution to the ideal solubility of non-electrolytes[33]:

$$logX_u^{ideal} \approx -0.01(T_m - 298) \quad (4)$$

Aqueous Solubility of Crystalline Hydrates

The focus of this research is to develop a method for estimating the solubility of crystalline hydrates by extending the theoretical constructs of the anhydrous ideal solubility theory to include the additional energetics of a hydrated solute. Specifically, it is postulated that the ideal mole fraction solubility for a hydrate can be estimated by considering both the energy necessary to break up the crystal (melting) and the energy of transition from hydrate to anhydrous (dehydration). Experimentally, these energies can be observed from differential scanning calorimetry (DSC), which is commonly used to characterize pharmaceuticals.[37] By way of example, Figure 1 shows the DSC profiles of the anhydrous (top) and monohydrate (bottom) forms of beclomethasone dipropionate. Both profiles show the melting of the solid (209°C); however, the hydrate has an additional energy event for dehydration (onset of 82°C).

Taking into consideration this additional energy, the energy of melting at temperature T can be described by the sum of the enthalpies of the following processes: heating the solid to its dehydration temperature, dehydrating the solid at its dehydration temperature, heating the solid to its MP, melting the solid at its MP, and cooling the liquid back down to temperature T. As discussed above, the last 3 steps in this sequence can be estimated by Equation 4. Thus, an additional term must be considered to account for the transition from hydrate to dehydrate (anhydrous). By analogy to the derivation of Equation 4, this energy can be described by Equation 5 where ΔS_d and T_d correspond to the entropy of dehydration and the onset dehydration temperature (K), respectively.

$$logX_u^{dehydration} = -\Delta S_d\frac{(T_d - T)}{2.303RT} \quad (5)$$

Adding the hydrate term (Eq. 5) to Equation 4 yields the following:

$$logX_u^{ideal} \approx -\Delta S_d\frac{(T_d - T)}{2.303RT} - 0.01(T_m - 298) \quad (6)$$

which can be considered the ideal mole fraction solubility of a hydrated crystal.

In order to estimate the aqueous solubility, it is necessary to account for the aqueous activity coefficient (deviation from ideality) of the solute in water. A convenient approach which utilizes the octanol-water partition coefficient (log P) to estimate the aqueous activity coefficient of a solute has previously been reported.[38] As a means of practicality, it is beneficial to convert the units of Equation 6 from mole fraction to molarity. To do so, the mole fraction solubility is multiplied by 55.5 (the molarity of water).[38] This mathematically corresponds to the addition of 1.74 (log 55.5) to the log mole fraction solubility. Thus, by adding a constant to convert to molarity, and incorporating the log P term

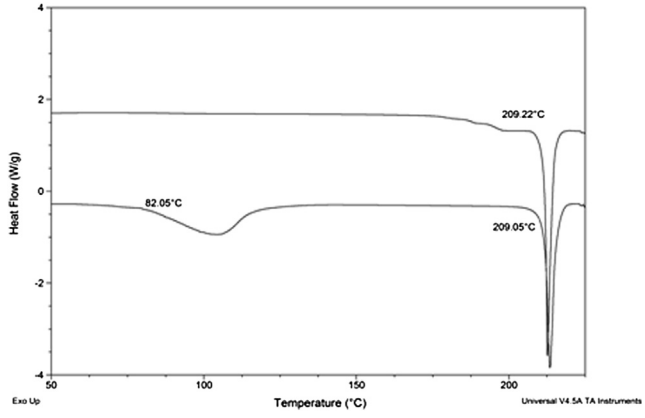

Figure 1. DSC profiles of anhydrous (top) and monohydrate (bottom) forms of beclomethasone dipropionate.