Investigation of Desolvation Kinetics Using the DVS

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The rate of solvation/desolvation for pharmaceutical solids can often affect the material's physical and chemical stability. Dynamic Vapour Sorption (DVS) allows the fast and accurate determination of solvation/desolvation kinetics for a range of solid-vapour systems. This paper describes acetone desolvation behaviour for a 1:1 carbamazepine:aceteone solvate.

Introduction

Physical and chemical stability of pharmaceutical solids is highly dependent on its polymorphic state. Further, the behaviour of pharmaceutical solvates in response to changes in the environment can have a serious affect on the drug development and performance [1]. The physicochemical stability of solvates is of particular concern, because during desolvation they may convert to an amorphous form or become chemically labile [2].

This paper investigates the desolvation kinetics of a 1:1 carbamazepine (CBZ):acetone solvate using a Dynamic gravimetric Vapour Sorption (DVS) apparatus. The acetone vapour-induced formation of this solvate from amorphous CBZ has been described in detail previously [3].

Method

Carbamazepine ($C_{15}H_{12}N_2O$), 5H-dibenz(b,f)azepine-5-carboxamide, an anti-convulsant used in the treatment of epilepsy has often been used as a model material when studying polymorphs [4,5,6,7,8]. Carbamazepine is known to form a 1:1 solvate with acetone [3,9].

Crystalline carbamazepine (Sigma, St. Louis, MO) was used as the starting material. Amorphous CBZ was prepared by soaking crystalline CBZ in water overnight, then the sample was dried at 0% relative humidity. This has been previously proven to produce 100% amorphous carbamazepine [10,11]. Acetone (HPLC Grade; Sigma, St. Louis, MO) was used as the solvent.

An amorphous CBZ sample was placed into a DVS-Advantage instrument at the desired temperature where it was initially dried in a 100-sccm (standard cubic centimetres) stream of dry air (< 0.1% relative humidity) for several hours to establish a dry mass. The sample was then exposed to a 95% P/Po acetone vapour concentration (relative percentage of saturated vapour pressure). These conditions have previously shown to fully solvate the CBZ [3]. Then, the acetone concentration was decreaed to 0% P/Po in one step. The desolvation behaviour was monitored over time by measuring the mass loss. This was performed at several temperatures between 15 and 30 °C.

Results

Figure 1 shows representative DVS data for the desolvation of CBZ at 25 °C. The desolvation kinetics can clearly be monitored by the steady mass loss upon exposure to 0% P/Po.
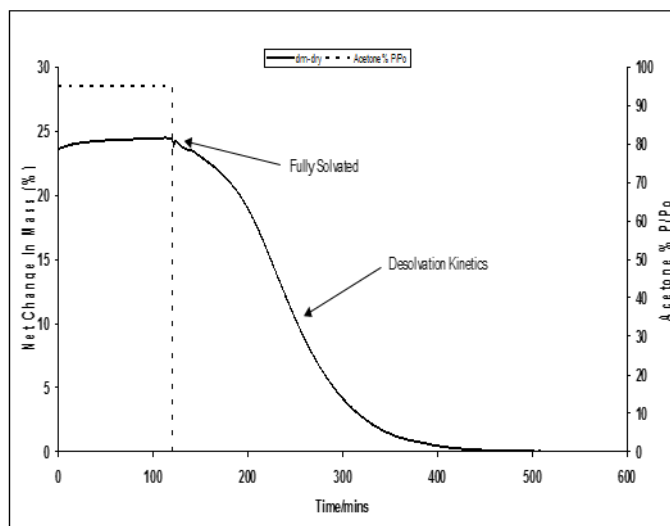

Figure 1. Acetone desolvation kinetics for CBZ at 25 °C.

When studying solid-state reactions, it is customary to represent that data in terms of fractional conversion or extent of reaction ($0 \leq \alpha \leq 1$) [12,13]. If extent of reaction experiments are completed over several temperatures, it is possible to obtain a model free activation energy. This is based on an isoconversion method. Since several kinetic curves are necessary (either multiple temperatures for isothermal experiments or multiple heating rates for non-isothermal experiments) this type of analysis is also called 'multicurve' analysis [12]. A commonly used isoconversional method used is the Friedman method. This method is based on the isothermal rate law shown in Equation 1.

$$\frac{d\alpha}{dt} = Ae^{\frac{-E_a}{RT}} f(\alpha) \qquad (1)$$

In Equation 1, $d\alpha/dt$ is the reaction rate, $f(\alpha)$ is the differential reaction model, A is the pre-exponential factor, E_a is the activation energy, T is the temperature, and R is the universal gas constant. In the Friedman method, the logarithm of the isothermal rate law yields Equation 2.

$$\ln\left(\frac{d\alpha}{dt}\right) = \ln Af(\alpha) - \frac{E_a}{RT} \qquad (2)$$

A plot of $\ln(d\alpha/dt)$ versus $1/T$ at each α (or fractional reaction) gives the activation energy, E_a, regardless of the model.

Figure 2 displays the fraction of CBZ-Acetone desolvated as a function of time at several temperatures between 15 and 30 °C.
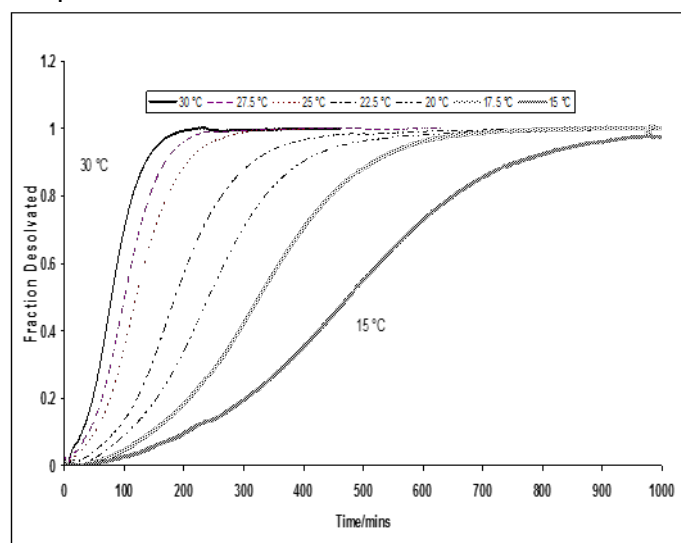

Figure 2. Fraction of CBZ-acetone desolvated as a function of time between the temperature range of 15 and 30 °C.

The time axis has been shifted such that t=0 is the point at which the acetone concentration was set to 0% P/Po. As Figure 2 indicates, the material desolvates faster at higher temperatures. A Friedman plot (activation energy as a function of fraction desolvated) was calculated over a range of reaction fractions (see Figure 3). The activation energy is relatively constant between fractions 0.1 and 0.9, with an average value of 81.9 kJ/mol. This value is in good agreement with the CBZ dihydrate dehydration activation energy of 87.7 kJ/mol [10]. The slightly lower value obtained for acetone desolvation might be due to decreased hydrogen bonding with the matrix for acetone compared to water molecules. At very low fractions, the activation energy decreases significantly, which is most likely due to increased experimental errors. Overall, the Friedman

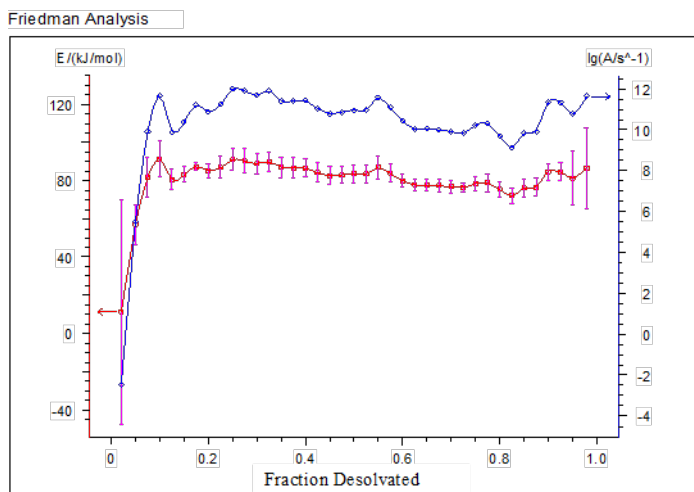analysis suggests desolvation occurs in a single step.

Figure 3. Friedman analysis for the desolvation curves displayed in Figure 6. The activation energy is plotted on the left y-axis (pink line) and the pre-exponential factor is plotted on the right y-axis (blue line). A constant activation energy is observed between 0.2 and 0.8 fractions. Very high and very low fractions show a decrease in activation energy.

Elementary solid-state reactions can depend on many factors, including, rate of nuclei formation, interface advance, diffusion, and/or shape of particles [12]. These different factors can lead to several reaction models which are summarized in References 12 and 13. The shape of the conversion plot (α versus time) can indicate the classification of model and reveal information about the reaction mechanism [12,13]. The sigmoidal shapes of the curves in Figure 2 suggest a nucleation type reaction mechanism. One of the most widely accepted nucleation mechanisms used to describe the desolvation of solvates is the 'reaction interface theory' [14,15]. This theory indicates that desolvation is initiated at surface defect sites, leading to nucleation and growth of the anhydrate phase. At defect sites, the lattice is strained and the neighboring molecules are more energetic. Desolvation and anhydrate recrystallization occur within a reaction interface that propagates inwards. The advance of this transition front may be anisotropic and even favor certain crystallographic directions [16]. The data in Figures 2 and 3 are consistent with

nucleation and propagation desolvation mechanism.

Kinetic modeling software was applied to elucidate the reaction mechanism using the data in Figure 2. The resulting mechanism and fit is displayed in Figure 4, showing a correlation coefficient for this mechanism is 0.99824. The mechanism (A → B) in Figure 4 indicates a first order (n=1.06) reaction, autocatalyzed by the product (B). This mechanism is consistent with the 'reaction interface theory' described above. As the initial sites desolvate, further desolvation would propagate, thus creating more desolvated CBZ.
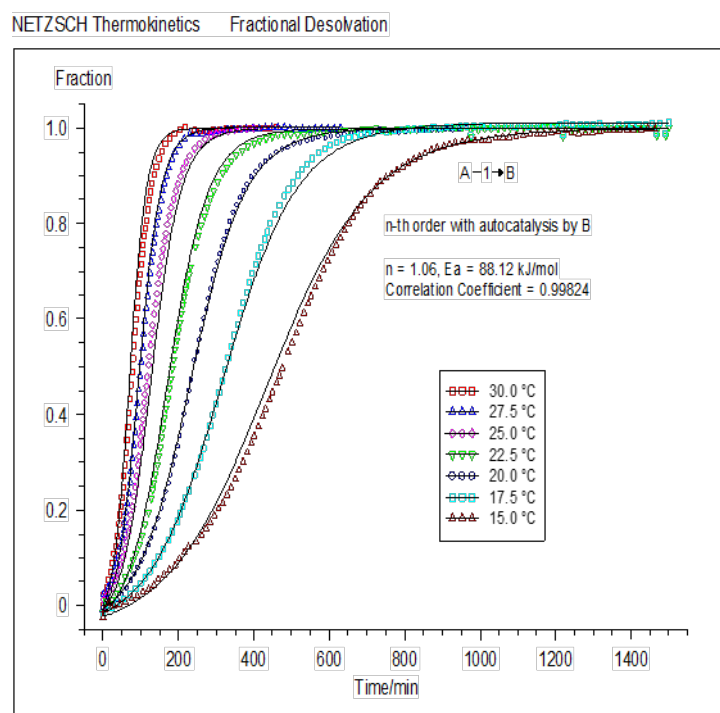

Figure 4. Best-fit reaction model showing a first order reaction, autocatalyzed by the product.

Conclusion

The desolvation behaviour of a 1:1 CBA:acetone stoichiometric solvate was studied over a range of temperatures. Isothermal desolvation studies indicated a complex desolvation mechanism, most likely involving nucleation at defect sites followed by propagation. Between desolvation fractions of 0.1 and 0.9 an average activation energy of desolvation was 81.9 kJ/mol.

Multicurve modeling indicates a first order reaction autocatalyzed by the product (desolvated CBZ). Gravimetric vapor sorption studies can be a powerful tool in characterizing vapor-induced solid state transitions.

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