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INVESTIGATING CARBAMAZEPINE-ACETONE SOLVATE FORMATION VIA DYNAMIC GRAVIMETRIC VAPOR SORPTION

D. J. Burnett[1*], *F. Thielmann*[2] *and T. D. Sokoloski*[3]

[1]Surface Measurement Systems, Ltd., 2222 South 12th Street, Suite D, Allentown, PA 18103, USA
[2]Surface Measurement Systems, Ltd., 5 Wharfside, Rosemont Road, Alperton, Middlesex HA0 4PE, UK
[3]Emeritus status, The Ohio State University, College of Pharmacy, 500 West 12th Avenue, Columbus, OH 43210, USA

Pharmaceutical solids can often form solvated species which can affect the material's physical and chemical stability. Carbamazepine (CBZ) has been proven to form a 1:1 solvate with acetone. This report investigates the solvation behavior of CBZ over a wide temperature and acetone concentration range using Dynamic gravimetric Vapor Sorption (DVS). The solvation transition point increased from 62.5% P/P_0 at 10°C to 97.8% P/P_0 at 30°C, resulting in a 15.9 kJ mol^{-1} heat of solvation. The desolvation kinetics were studied between 15 and 30°C, indicating CBZ desolvation is a first-order reaction with autocatalysis by the desolvated product and an activation energy of 81.9 kJ mol^{-1}.

Keywords: *acetone, amorphicity, carbamazepine, dynamic vapor sorption, solid-state transitions, solvate*

Introduction

Approximately one-third of organic materials show crystalline polymorphism, with a further third capable of forming hydrates or solvates [1]. Physical and chemical stability of pharmaceutical solids is highly dependent on its polymorphic state. For instance, powder flow, hygroscopicity, solubility, dissolution rates, and stability can differ between various polymorphs [2]. Further, the behavior of pharmaceutical solvates in response to changes in the environment can have a serious affect on the drug development and performance [3]. The physicochemical stability of solvates is also a concern, because during desolvation they may convert to an amorphous form or become chemically labile [4]. The ultimate solvated state can be dependent on both temperature and concentration of the solvate. Also, the United States Food and Drug Administration requires analytical procedures for the detection of polymorphic, solvated, or amorphous forms of drug substances. For the above reasons, it is paramount to study the solid-state stability of solvates and the kinetics of desolvation behavior over a wide range of storage and processing conditions.

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 [5–9]. Carbamazepine (CBZ) is known to form at least four anhydrous polymorphs, where two are monoclinic, one is trigonal and the fourth is triclinic [5, 7]. The dihydrate of CBZ has also been identified and studied previously [9–11]. Additionally, dioxane [12] and acetone [13] solvates have been identified. The structure of the acetone solvate has been determined and it contains one acetone molecule in the asymmetric unit [13].

This paper investigates the solvation and desolvation behavior of CBZ with acetone using a Dynamic gravimetric Vapor Sorption (DVS) apparatus. The acetone solvate of CBZ was formed from acetone vapor. Although formation of hydrates from water vapor has been widely observed, to the authors' knowledge, this is the first report of solvate formation from an organic vapor. The conversion from the unsolvated state to the solvated state is a first order phase transformation [14]. Whether formed from the liquid or vapor phase, both solvation-desolvation processes are thermodynamically equivalent. If both processes are performed under equilibrium conditions, then the solvation-desolvation transition should occur at the same solvent activities in both liquid and vapor phases. Therefore, solvate formation measured by vapor sorption techniques could indicate where similar transitions would occur in the liquid-phase. This may be useful for crystallizing drugs in different solvents. The solvation and desolvation behavior of the CBZ-acetone solvate has been investigated over a wide temperature range to study both thermodynamic and kinetic limitations.

* Author for correspondence: burnett@smsna.com

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Akadémiai Kiadó, Budapest, Hungary
Springer, Dordrecht, The Netherlands

Experimental

Crystalline carbamazepine (C_{15},H_{12},N_2O; Sigma, St. Louis, MO) was used as received. 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 [15, 16]. Acetone (HPLC Grade; Sigma, St. Louis, MO) was used as the solvent.

Gravimetric vapor sorption experiments have been carried out using the DVS-Advantage instrument (Surface Measurement Systems, London, UK). This instrument measures the uptake and loss of vapor gravimetrically using a recording ultra-microbalance with a mass resolution of ±0.1 μg. The vapor partial pressure (±1.0%) around the sample is controlled by mixing saturated and dry carrier gas streams using electronic mass flow controllers. The desired temperature is maintained at ±0.1°C.

The samples (2–5 mg) were placed into the DVS-Advantage instrument at the desired temperature where they were initially dried in a 100-sccm (standard cubic centimeters) stream of dry air (<0.1% relative humidity) for several hours to establish a dry mass. For the isotherm experiments, the samples were exposed to step changes in acetone vapor concentration (relative percentage of saturated vapor pressure; % P/P_0). The acetone concentration profile was as follows: 0 to 50% in 10% steps, 55 to 95% steps in 5% steps, and back down to 0% P/P_0 in a similar fashion. Mass equilibrium was achieved at each % P/P_0 step before the experiment proceeded to the next programmed step. For the desolvation kinetic studies, the sample was also dried at 0% P/P_0, then the concentration was increased to 95% P/P_0 until the sample was completely solvated. Finally, the concentration was decreased to 0% P/P_0 in one step and the mass loss (i.e. desolvation) was measured until complete. These experiments were performed at several temperatures between 15 and 30°C.

The modeling of the desolvation data was done using the routines found in NETZSCH Thermokinetics® software. This software allows for visual/manual manipulation of fit parameters and then performs the least squares optimization itself to generate the best fit parameters. Initial model selection is experience based as well as based on observation of the consequence of effects visually seen upon manual parameter manipulation.

Results and discussion

Acetone vapor sorption and desorption isotherms on amorphous CBZ are displayed in Fig. 1. The y-axis displays the equilibrium net % change in mass, referenced from the dry mass, while the *x*-axis displays the acetone % P/P_0 in the chamber. During the sorption phase (solid line) there is minimal mass change below 85% P/P_0. Above this point, the sample mass increases by nearly 24%. During desorption (dashed line), the sample mass does not decrease significantly until the acetone relative partial pressure drops below 10% P/P_0. The sharp transition points of mass gain and mass loss are often indicative of solvate formation and loss.

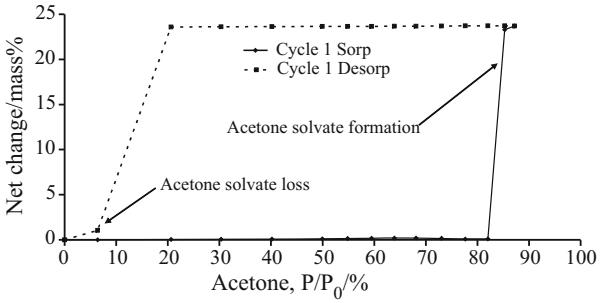

Fig. 1 Acetone vapor sorption (solid) and desorption (dashed) isotherms on amorphous CBZ at 25.0°C. Solvation occurs above 85% P/P_0 during the sorption phase, but is not desolvated until below 10% P/P_0 during the desorption phase

If a material forms a stoichiometric solvate in the vapor phase, then the corresponding isotherm can be used to determine the exact stoichiometry of the solvated species. To illustrate, consider a dry material, Sample A with molecular weight, MW_A. If Sample A forms a solvated species with solvent B and molecular mass MW_B, then the net percentage mass gain at the solvation partial pressure, WG, can be used to calculate the stoichiometry, *S*, of the solvate as in Eq. (1).

$$S = \frac{WG}{100\%}\frac{MW_A}{MW_B} = \text{solvate stoichiometry} \qquad (1)$$

Equation (1) assumes formation of a stoichiometric solvate.

Using Eq. (1) and 236.28 amu for anhydrous carbamazepine, the stoichiometry of the acetone solvate in Fig. 1 can be determined. The mass uptake due to solvate formation was 23.7% which correlates to a stoichiometry of 0.96 or a 1:1 solvate. This is in agreement with the CBZ/acetone solvate determined previously [13]. Therefore, the transition point above 85% P/P_0 strongly indicates the acetone concentration needed to allow formation of the solvate.

If the sample in Fig. 1 was completely amorphous and the crystalline form of anhydrous CBZ will not form a solvate when exposed to acetone vapor, then the solvate formation measured via DVS can be used to determine the amorphous content of partially

amorphous CBZ samples. DVS with organic vapors has been previously used to determine amorphous contents below 5% [17, 18]. The current experiments are based on a method first designed for hydrates [19], but the same methodology would also apply to solvates. This method has the unique advantage of not requiring any calibration standards.

Experiments using CBZ-acetone solvate formation with different amorphous contents are shown in Fig. 2. As discussed above, amorphous carbamazepine will convert to a 1:1 acetone solvate above 85% P/P_0 at 25°C (□ trace in Fig. 2). Figure 2 clearly shows the crystalline species does not form a solvated species (– trace). If the sample is 100% amorphous, the formation of a mono-solvate will result in a 24.58% change in mass, using Eq. (1) and a stoichiometry of 1:1. If the sample is partially amorphous (Δ, o, ◊, × traces in Fig. 2), the percentage change in mass during solvate formation will be directly related to the amorphous fraction. Figure 3 plots the theoretical net change in mass due to solvate formation *vs.* the actual net change in mass for several amorphous/crystalline carbamazepine mixtures. Clearly, a direct correlation (R^2=0.999) is evident. For CBZ, the amorphous content of an 'unknown' sample

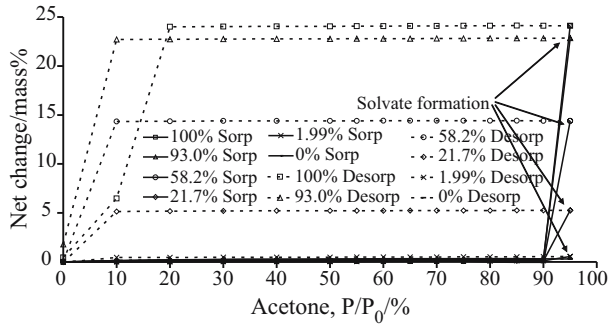

Fig. 2 Acetone vapor sorption (solid) and desorption (dashed) isotherms for CBZ with different amorphous contents: □ – 100% amorphous; Δ – 93.0% amorphous; o – 58.2% amorphous; ◊ – 21.7% amorphous; × – 1.99% amorphous and – – 100% crystalline

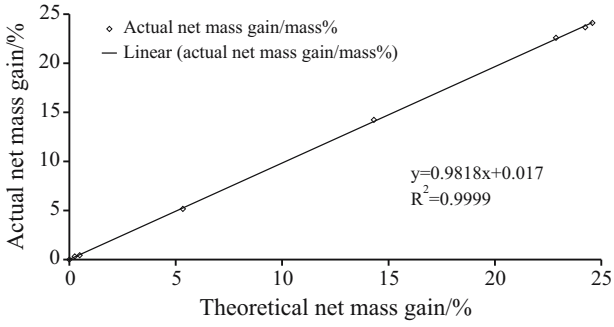

Fig. 3 Actual net mass gain *vs.* theoretical net mass gain due to solvate formation for different amorphous fractions of CBZ

(down to ±1%) can be determined without a calibration curve of known standards. To illustrate, a sample of crystalline, anhydrous CBZ was milled for 30 s in a high speed grinder. Then, the acetone vapor isotherm was measured at 25°C (data not shown). A 2.94% change in mass was measured due to solvate formation. Therefore, the milled sample was determined to be 12.0% amorphous based on a 24.58% mass change for a completely 100% amorphous sample. This methodology would apply to any species that forms a stoichiometric solvate assuming 100% conversion.

To investigate the impact of temperature on the solvation transition point, similar experiments to Fig. 1 were performed between 10 and 30°C. There was no change in the desolvation point with increasing temperature. However, Fig. 4 clearly shows the solvation point increases significantly with measurement temperature. According to Carstensen [20] the thermodynamic formation of a hydrate can be described by Eq. (2):

$$\text{salt(solid)} + xH \Leftrightarrow \text{salt}\cdot xH\text{(solid)} \qquad (2)$$

where H is a water molecule and x is the stoichiometric ratio of the hydrate. The equilibrium constant and its relation to temperature according to the van't Hoff equation are shown below:

$$K = P_{\text{H}}^{-x} = A\exp\left(\frac{\Delta H_{\text{x}}}{RT}\right) \qquad (3)$$

where P_{H} is water vapor pressure and ΔH_{x} is the heat of reaction. According to Eq. (3) an increase in temperature would require a subsequent increase in water vapor pressure to drive the equilibrium constant towards hydrate formation. It can be assumed that solvate formation would be similar to Eqs (2) and (3), so the trend in this study is thermodynamically supported. Using Eq. (3) and linearizing the data (R^2>0.99) in Fig. 4 a heat of reaction of 15.9 kJ mol^{-1} was obtained from the slope.

The large hysteresis gap between solvate formation and loss was present at all temperatures studied.

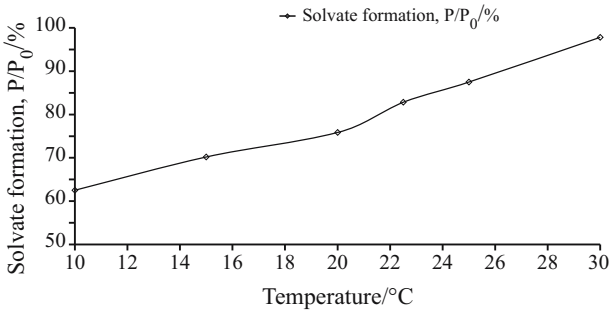

Fig. 4 Concentration of acetone vapor required to induce solvation as a function of temperature for amorphous CBZ

In fact, the solvate loss transition during the desorption isotherm remained unchanged (below 10% P/P_0) even if 6 h desorption steps were used. Since the formation of a solvate is a first-order, thermodynamic transition, it is expected that solvation and desolvation would occur at the same conditions. Therefore, the hysteresis gaps may be due to kinetic limitations. Induction periods for desolvation can be rather long, thus may be beyond the time scales of these experiments [21].

To investigate the kinetic limitations in desolvation behavior, the desolvation step during desorption was studied over a range of temperatures. In these experiments, the amorphous CBZ was fully solvated at 95% P/P_0, then the acetone concentration was decreased to 0% P/P_0 in one step. Figure 5 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/P_0.

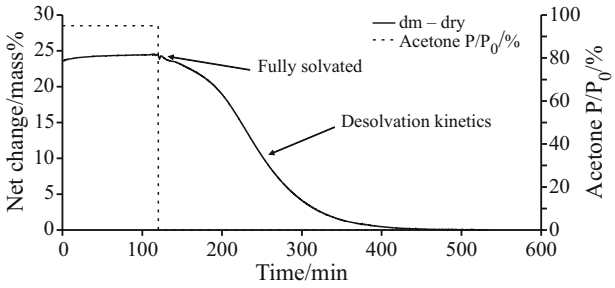

Fig. 5 Acetone desolvation kinetics for CBZ at 25°C

When studying solid-state reactions, it is customary to represent that data in terms of fractional conversion or extent of reaction ($0 \leq \alpha \leq 1$) [4, 22]. 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 [4]. A commonly used isoconversional method used is the Friedman method. This method is based on the isothermal rate law shown in Eq. (4).

$$\frac{d\alpha}{dt} = A e^{\frac{-E_a}{RT}} f(\alpha) \qquad (4)$$

In Eq. (4), $d\alpha/dt$ 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 Eq. (5).

$$\ln\frac{d\alpha}{dt} = \ln A f(\alpha) - \frac{E_a}{RT} \qquad (5)$$

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

Figure 6 displays the fraction of CBZ-Acetone desolvated as a function of time at several temperatures between 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/P_0. As Fig. 6 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 (Fig. 7). The activation energy is relatively constant between fractions 0.1 and 0.9, with an average value of 81.9 kJ mol^{-1}. This value is in good agreement with the CBZ dihydrate dehydration activation energy of 87.7 kJ mol^{-1} [15]. 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.

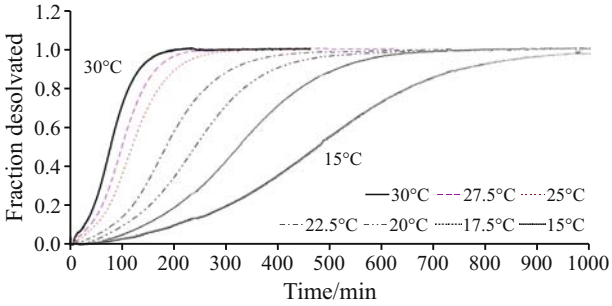

Fig. 6 Fraction of CBZ-acetone desolvated as a function of time between the temperature range of 15 and 30°C

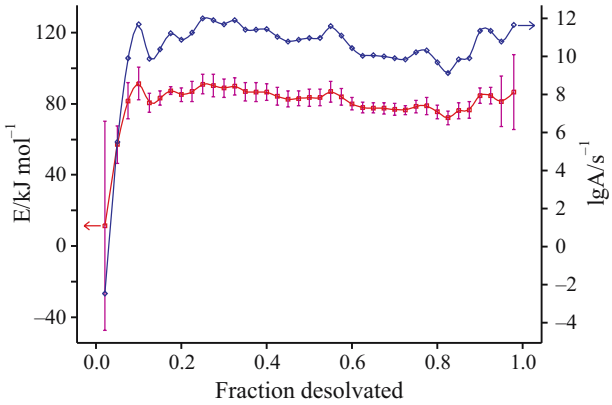

Fig. 7 Friedman analysis for the desolvation curves displayed in Fig. 6. A constant activation energy is observed between 0.2 and 0.8 fractions

Elementary solid-state reactions can depend on many factors, including, rate of nuclei formation, interface advance, diffusion, and/or shape of particles [4]. These different factors can lead to several reaction models which are summarized in Refs [4] and [22]. The shape of the conversion plot (α *vs.* time) can indicate the classification of model and reveal information about the reaction mechanism. The sigmoidal shapes of the curves in Fig. 6 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' [23, 24]. 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 [25]. The data in Figs 6 and 7 are consistent with nucleation and propagation desolvation mechanism.

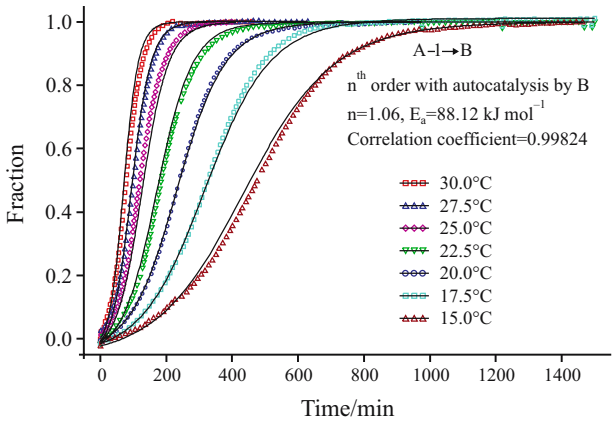

Fig. 8 Best-fit reaction model showing a first order reaction, autocatalyzed by the product

The Netzsch Thermokinetics® software was applied to elucidate the reaction mechanism using the data in Fig. 6. The resulting mechanism and fit is displayed in Fig. 8, showing a correlation coefficient for this mechanism is 0.99824. The mechanism (A→B) in Fig. 8 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.

Conclusions

Amorphous carbamazepine was found to form a 1:1 stoichiometric solvate with acetone when exposed to sufficiently high concentrations of acetone vapor. The formation of the solvate was only observed for amorphous CBZ and not crystalline CBZ, which allowed for the amorphous content determination of unknown partially amorphous CBZ materials. This amorphous content method requires no amorphous 'standards'. Solvation was found to occur at increasing acetone concentrations with increasing temperatures, resulting in a 15.9 kJ mol^{-1} heat of solvation. The desolvation concentration did not change with temperature. 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^{-1}. Multicurve modeling indicates a first order reaction autocatalyzed by the product (desolvated CBZ). Gravimetric vapor sorption studies can be a powerful tool in characterizing solvates over a wide range of solvent concentrations and environmental temperatures.

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