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DVS Application Note 41

Investigation of Solvate Formation and Loss Using the DVS

Dan Burnett and Frank Thielmann, Surface Measurement Systems Ltd.

Th Pharmaceutical solids can often form solvated species which can affect the material's physical and chemical stability. Dynamic Vapour Sorption (DVS) allows the fast and accurate determination of solvate stoichiometry for a range of solid-vapour systems. This paper describes acetone solvate formation of anhydrous carbamazepine and ethanol solvation of erythromycin. A 1:1 carbamazepine-acetone solvate and a 1:3 erythromycin-ethanol solvate were observed in this study.

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 behaviour 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 requests analytical data for the detection of polymorphic, solvated, or amorphous forms of drug substances. For the above reasons, it is paramount to study the solvation and desolvation behaviour over a wide range of storage and processing conditions.

This paper investigates the solvation and desolvation behaviour of carbamazepine (CBZ) with acetone vapour and erythromycin (ERM) with ethanol vapour using a Dynamic gravimetric Vapour Sorption (DVS) apparatus. Although formation of hydrates from water vapour has been widely observed (see **Application Note 36)**, to the authors' knowledge, this is the first report of solvate formation from an organic vapour. The conversion from the unsolvated state to the solvated state is a first order phase transformation [5]. Whether formed from the liquid or vapour 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 vapour phases. Therefore, solvate formation measured by vapour sorption techniques could indicate where similar transitions would occur in the liquid-phase. This may be useful for crystallizing drugs in different solvents.





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 [6,7,8,9,10]. Carbamazepine is known to form at least four anhydrous polymorphs, where two are monoclinic, one is trigonal and the fourth is triclinic [6,8]. The dihydrate of CBZ has also been identified and studied previously [10, 11,12]. Additionally, dioxane [13] and acetone [14] solvates have been identified. The structure of the acetone solvate has been determined and it contains one acetone molecule in the asymmetric unit [14]. ERM ($C_{37}H_{67}NO_{13}$), an antibiotic that has been used for over 50 years, has several reported forms (anhydrate, monohydrate, dihydrate, and various solvates). In particular, ERM has been found to form a 1:3 solvate with ethanol in solution [15].

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 [16,17]. Acetone (HPLC Grade; Sigma, St. Louis, MO) was used as the solvent. Crystalline (-) ERM·xH_2O (Sigma, St. Louis, MO) was used as received.

The samples (2-6 mg) were placed into a DVS-Advantage instrument at the desired temperature where they were 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 samples were exposed to step changes in vapour concentration (relative percentage of saturated vapour pressure; % P/P_o). For CBZ, 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_o in a similar fashion. For ERM, the ethanol concentration profile was: 0 to 95% P/P_o in 5% steps and back down to 0% P/P_o in a similar fashion. Mass equilibrium was achieved at each % P/P_o step before the experiment proceeded to the next programmed step.

Results

CBZ-Acetone Solvate Formation

Acetone vapour sorption and desorption isotherms on amorphous CBZ are displayed in Figure 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_o in the chamber. During the sorption phase (red line) there is minimal mass change below 85% P/P_o. Above this point, the sample mass increases by nearly 24%. During desorption (blue line), the sample mass does not decrease significantly until the acetone relative partial pressure drops below 10% P/P_o. The sharp transition points of mass gain and mass loss are often indicative of solvate formation and loss.

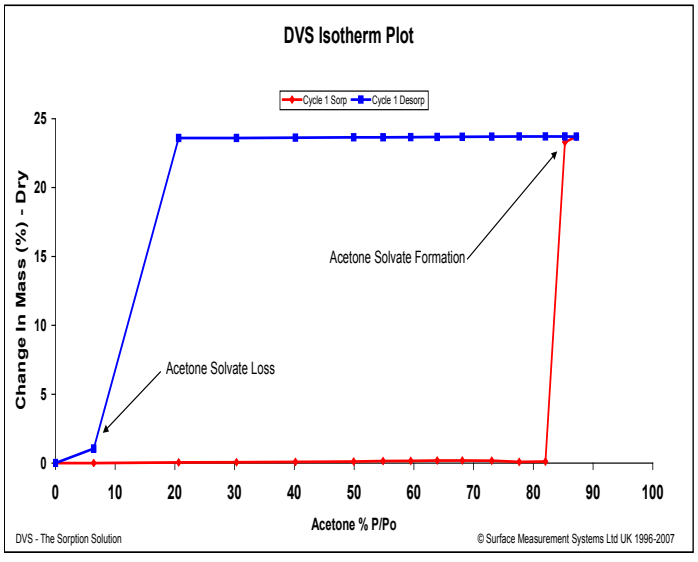

Figure 1. Acetone vapour sorption (red) and desorption (blue) isotherms for CBZ at 25 °C.

If a material forms a stoichiometric solvate in the vapour 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 weight MW_B, then the net

percentage weight gain at the solvation partial pressure, WG, can be used to calculate the stoichiometry, S, of the solvate as in Equation 1.

$$S = \frac{WG}{100\%} \times \frac{MW_A}{MW_B} = Solvate \quad Stoichiometry \qquad (1)$$

Equation 1 assumes formation of a stoichiometric solvate.

Using Equation 1 and 236.28 amu for anhydrous carbamazepine, the stoichiometry of the acetone solvate in Figure 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 found previously [14]. Therefore, the transition point above 85% P/P_o strongly indicates the acetone concentration needed to allow formation of the solvate.

To investigate the impact of temperature on the solvation transition point, similar experiments to Figure 1 were performed between 10 and 30 °C. There was no change in the desolvation point with increasing temperature. This is most likely due to kinetic limitations where desolvation must overcome a strong activation barrier to desorb. However, Figure 2 clearly shows the solvation point increases significantly with measurement temperature.

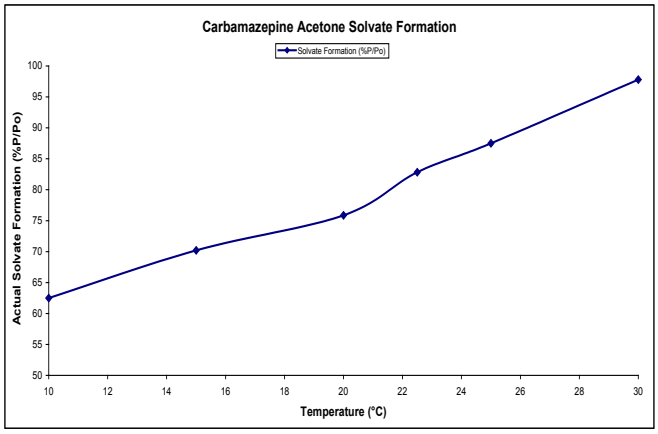

Figure 2. Acetone vapor concentration required to induce solvation as a function of temperature for amorphous CBZ.

According to Carstensen [18] the thermodynamic formation of a hydrate can be described by Equation 2:

$$Salt(solid) + xH \Leftrightarrow Salt \cdot xH(solid) \qquad (2)$$

where H signifies a water molecule and x is the stoichiometry of the hydrate. The equilibrium constant (K) and its relation to temperature according to the van't Hoff equation are shown in Equation 3 where P_H is water vapour pressure and ΔH_x is the heat of reaction.

$$K = P_H^{-x} = A\exp\left(\frac{\Delta H_x}{RT}\right) \qquad (3)$$

According to Equation 3 an increase in temperature would require a subsequent increase in water vapour pressure to drive the equilibrium constant towards hydrate formation. It can be assumed that solvate formation would be similar to Equations 2 and 3, so the trend in this study is thermodynamically supported. Using Equation 3 and linearising the data (R^2>0.99) in Figure 2 a heat of reaction of 15.9 kJ/mol was obtained from the slope.

The large hysteresis gap between solvate formation and loss was present at all temperatures studied. In fact, the solvate loss transition during the desorption isotherm remained unchanged (below 10% P/Po) even if 6-hour 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 [19]. Investigating the kinetics of desolvation is the focus of **Application Note 45**.

Erythromycin-Ethanol Solvation Formation

Ethanol vapour sorption and desorption isotherms for ERM are shown in Figure 3. The y-axis displays the equilibrium net % change in mass, referenced from the dry mass, while the x-axis displays the ethanol % P/P_o in the chamber. During ethanol sorption (red line) the sample mass increases gradually below 65% P/P_o.

Between 65 and 90% P/P_o there is a dramatic increase in sample weight, until the sample mass increases by over 22% (based on dry mass). During ethanol desorption (blue line), the sample mass does not decrease significantly until the ethanol relative partial pressure drops below 10% P/P_o. As with the CBZ-acetone results in Figure 1, the sharp transition points of mass gain and mass loss observed in Figure 3 are often indicative of solvate formation and loss. Using Equation 1 and measuring the difference in uptake between sorption and desorption isotherms (i.e. hysteresis) it is possible to estimate the stoichiometry of the solvate. Between 15 and 40% P/P_o the average hysteresis was 18.34%. Using this value and 733.93 amu for the molecular weight of anhydrous ERM, Figure 3 indicates the uptake of 2.92 ethanol molecules. Therefore, the DVS results in this study support the formation of a 1:3 ERM-ethanol solvate above 90% P/P_o ethanol vapour.

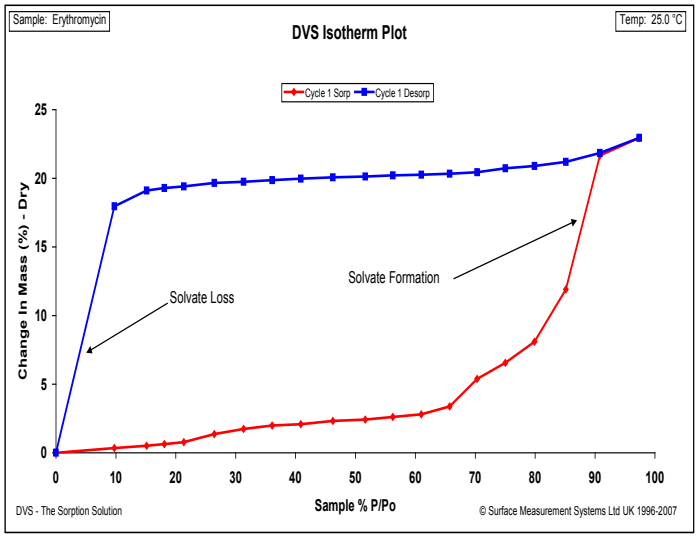

Figure 3. Ethanol vapour sorption (red) and desorption (blue) isotherms for ERM at 25 °C.

Close inspection of the sorption isotherm in Figure 3 suggests there may be an intermediate solvate formed between 70 and 80% P/Po. The percentage weight change in this range is around 6.5%. Using Equation 1, this would correlate to 1.0 ethanol molecules. Previous researchers have also observed a 1:1 ethanolate with ERM during TGA studies [15]. Additional experiments using smaller partial pressure steps or multiple cycles in this partial pressure range may confirm this intermediate species.

Conclusion

Amorphous carbamazepine was found to form a 1:1 stoichiometric solvate with acetone when exposed to sufficiently high concentrations of acetone vapour. Solvation was found to occur at increasing acetone concentrations with increasing temperatures, resulting in a 15.9 kJ/mol heat of solvation. The desolvation concentration did not change with temperature, most likely due to the slow desolvation kinetics. Erythromycin formed a 1:3 solvate with ethanol above 90% P/P_o and possibly a 1:1 intermediate around 70% P/Po and 25 °C. Gravimetric vapour sorption studies can be a powerful tool in characterizing solvates over a wide range of solvent concentrations and environmental temperatures.

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Head Office:
Surface Measurement Systems, Ltd
5 Wharfside, Rosemont Road
LondonHA0 4PE, UK
Tel: +44 (0)20 8795 9400
Fax: +44 (0)20 8795 9401
Email: science@surfacemeasurementsystems.com

United States Office:
Surface Measurement Systems, Ltd, NA
2125 28th Street SW, Suite I
Allentown PA, 18103, USA
Tel: +1 610 798 8299
Fax: +1 610 798 0334