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DVS Application Note 44

Determining Amorphous Contents without a Standard: Hydrate/Solvate Stoichiometry

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A method to quantify low amorphous contents using DVS was developed based on the formation of a stoichiometric hydrate or solvate. If only the amorphous phase hydrates/solvates upon exposure to the appropriate vapour, then the amorphous content of a partially amorphous material can be determined. This method does not require any amorphous standards. Theophylline hydrate formation and carbamazepine-acetone solvate formation were used as examples.

Introduction

Amorphous materials are inherently metastable and therefore tend to revert to a more thermodynamically stable, crystalline form. As this instability has a potentially negative impact on storage and drug potency it is important to quantify the amorphous content of pharmaceutically relevant materials. Gravimetric vapour sorption studies have been previously used to determine amorphous contents below 5% [1,2,3,4]. These techniques are based on the fact that the amorphous material will have a greater vapour sorption capacity than the crystalline material. Therefore, the differences in uptake between crystalline and amorphous regions can be used to calculate the amorphous content of a sample. These techniques can be used with water or organic vapours. Advantages for using organic vapours are outlined in SMS Application Note 103 [5].

This study highlights a method to determine amorphous contents when the amorphous material forms a stoichiometric hydrate or solvate during vapour-induced crystallization. This is based on a method first used for hydrates [6], but the same methodology would also apply to solvates. This method has the unique advantage of not requiring any calibration standards.

Theory

The method in Ref. [6] is only suitable when the amorphous material forms a stoichiometric hydrate or solvate during vapour-induced crystallization. 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, MWA. If Sample A forms a solvated species with solvent B and molecular weight MWB, 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. This methodology has been used previously to determine the stoichiometry of hydrates [7] and solvates [8].

If the amorphous phase forms a hydrate or solvate and the crystalline phase does not, then it would be possible to determine the amorphous content in a partially amorphous sample. The uptake due to solvate or hydrate formation would be directly proportional to the amorphous fraction. Unlike other vapour sorption amorphous content procedures, this methodology does not require any amorphous standards.

Method

Theophylline ($C_7H_8N_4O_2$; 1,3-dimethylxanthine), a widely used antiasthmatic drug, can exist as an anhydrate or monohydrate and can undergo polymorphic changes during granulation [9,10]. Anhydrous theophylline (Sigma, St. Louis, MO) was used as the starting material. For crystalline theophylline (THP), it was used as received. Amorphous THP was created by first soaking in water overnight, then drying at 0% relative humidity. Partially amorphous THP samples were made by physical mixtures of crystalline and amorphous materials.

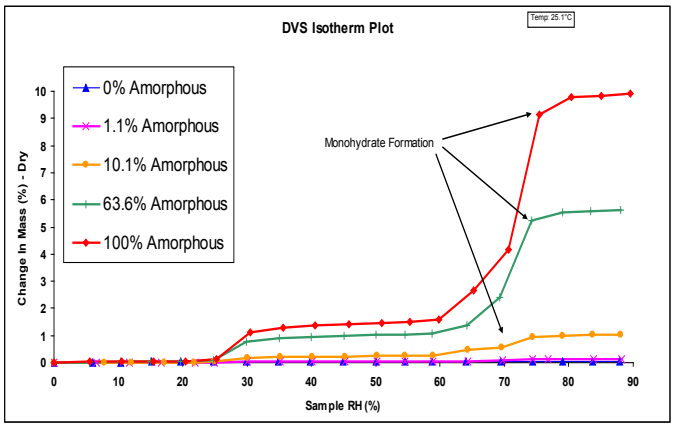
Carbamazepine ($C_{15}H_{12}N_2O$; 5H-dibenz(b,f)azepine-5-carboxamide), an anti-convulsant used in the treatment of epilepsy has often been used as a model material when studying polymorphs [11,12,13,14,15]. Carbamazepine (CBZ) is known to form a 1:1 solvate with acetone [16]. Crystalline carbamazepine (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 [17,18]. Acetone (HPLC Grade; Sigma, St. Louis, MO) was used as the solvent. Again, partially amorphous CBZ samples were prepared from physical mixtures of crystalline and amorphous materials.

The samples were placed into a DVS-Advantage instrument at the desired temperature where they were initially dried in 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/Po). For THP, the samples were exposed to the following humidity profile: 0 to 95% RH in 5% RH steps. 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/Po in a similar fashion. Mass equilibrium was achieved at each % P/Po step before the experiment proceeded to the next programmed step.

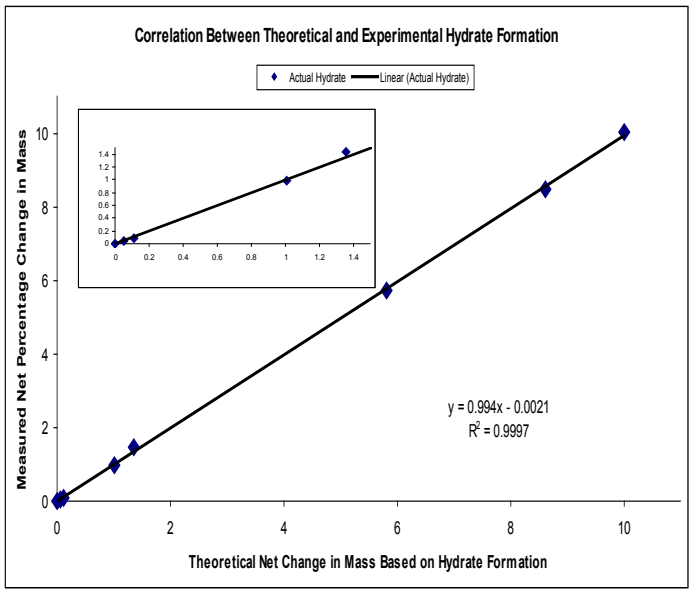
Results

Theophylline Hydrate

Water sorption isotherms of theophylline are shown in Figure 1. Amorphous THP is anhydrous, while exposure to humidities above 70% RH converts this to a monohydrate species (red trace in Figure 1a), while the crystalline species does not (blue trace in Figure 1a). The molecular weight of anhydrous theophylline is 180.16 amu. Therefore, if the sample is 100% amorphous, the formation of a monohydrate will result in a 10.0% change in mass according to Equation 1. If the sample is partially amorphous (green, pink, and orange lines in Figure 1a), the percentage change in mass during hydrate formation will be directly related to the amorphous fraction. Figure 1b plots the theoretical net change in mass at 85% RH versus the actual net change in mass for several amorphous/crystalline theophylline mixtures. The insert in Figure 1b highlights the results below 10% amorphous content (1% change in mass due to hydrate formation correlates to a 10% amorphous sample). Clearly, a direct correlation (R2=0.9997) is evident. For theophylline, the amorphous content of an 'unknown' sample (below 1%) can be determined without a calibration curve of known standards.



(a.)

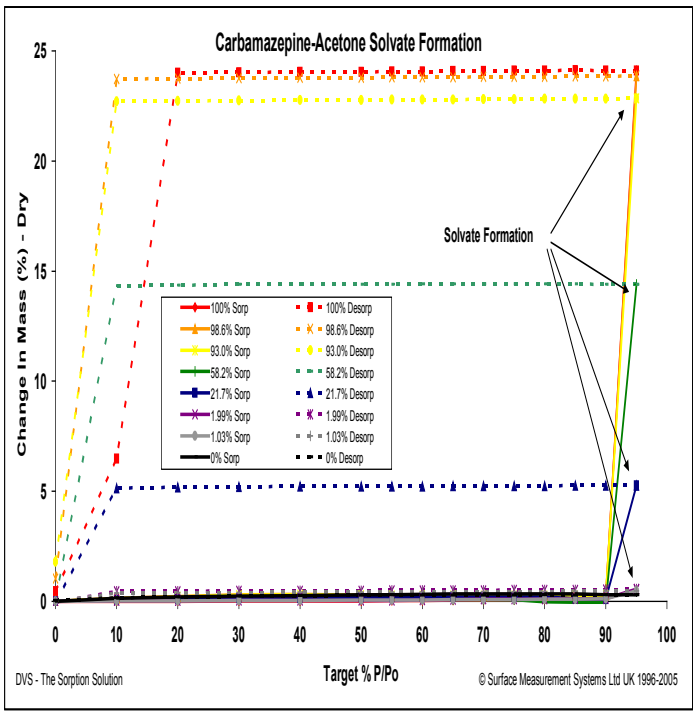


(b.)

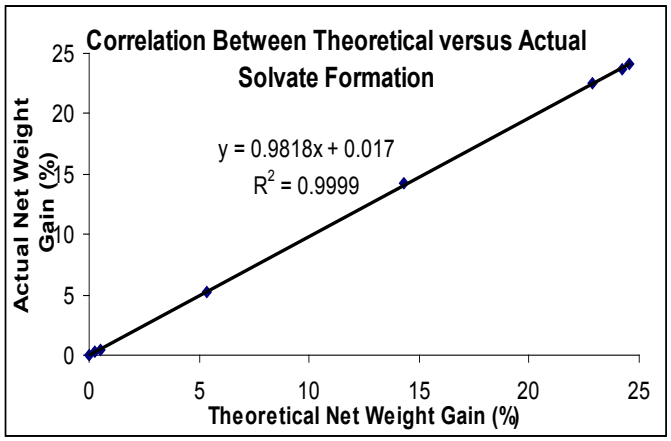
Figure 1. (a.) Water sorption isotherms for theophylline with different percentages of amorphous material. (b.) Correlation between actual change in mass and theoretical mass change due to hydrate formation of amorphous phase.

CBZ-Acetone Solvate

Experiments using carbamazepine-acetone solvate formation are shown in Figure 2. Amorphous carbamazepine will convert to an acetone monosolvate above 85% P/Po at 25 °C (red trace in Figure 2a). However, the crystalline species does not (black trace in Fig. 2a). If the sample is 100% amorphous, the formation of a mono-solvate will result in a 24.58% change in mass, using Equation 1. If the sample is partially amorphous (orange, yellow, green, blue, purple, and grey lines in Fig. 2a), the percentage change in mass during solvate formation will be directly related to the amorphous fraction. Figure 2b plots the theoretical net change in mass due to solvate formation versus the actual net change in mass for several amorphous/crystalline theophylline mixtures. Clearly, a direct correlation (R2=0.9999) is evident. For carbamazepine, the amorphous content of an 'unknown' sample (below 1%) can be determined without a calibration curve of known standards. Again, this methodology would apply to any species that forms a stoichiometric solvate.



(a.)



(b.)

Figure 2: (a.) Acetone sorption (solid) and desorption (dashed) isotherms of carbamazepine with different amorphous contents at 25 °C. (b.) Theoretical versus measured net mass change due to solvate formation showing direct correlation.

To mimic an industrial application, a sample of crystalline CBZ was milled in a high-energy grinder for 30 seconds. Then, the acetone vapour sorption and desorption isotherms were collected as done previously. As Figure 3 indicates, the percentage weight gain due to solvate formation was 2.940%. This weight gain correlates to an amorphous content of 12.0%.

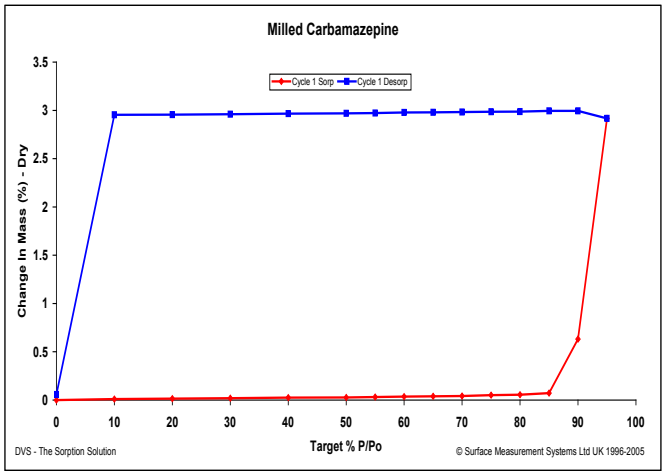


Figure 3. Acetone vapour sorption (red) and desorption (blue) isotherms for milled CBZ at 25.0 °C.

Conclusion

A methodology was described for the determination of amorphous contents for materials that can form a solvate or hydrate when exposed to the appropriate vapour. The method is based on the preferential hydration/solvation of the amorphous phase compared to the crystalline phase. Amorphous theophylline formed a monohydrate when exposed to humidities above 70% RH at 25 °C, but the crystalline phase did not. Similarly, amorphous carbamazepine formed a monosolvate when exposed to acetone vapour above 90% P/Po at 25 °C, but the crystalline material did not. This phenomenon was used to determine the amorphous content of a milled CBZ sample (12.0 %). The described methodology could be used for any material that forms a stoichiometric hydrate or solvate.

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