

# Organic Solvent Sorption using a Dynamic Vapour Sorption Instrument-an Overview

DVS Application Note 103

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Dynamic Vapour Sorption (DVS) has long been used for investigating the interaction of water vapour with solid materials. However, the versatility and impact of DVS can be greatly expanded by also studying organic vapour sorption phenomena. This overview application note summarises several examples of using organic vapours with the DVS: solvate formation, amorphous contents, BET surface areas, porosity, and surface energies.

## Introduction

The interactions of water vapour (moisture) with solid materials have impact over a wide range of industries and materials. For instance, in the pharmaceutical industry, the physical and chemical performance (i.e. flow, compaction, dissolution, stability, storage, and formulation) of drugs, excipients, and packaging materials are dependent on the presence and interaction of/with water [1]. In addition, moisture-solid interactions have significant impact on foods [2,3], fuel cell membranes [4], polymers [5], and cements [6].

Although the focus of DVS measurements has traditionally been water vapour sorption, the study of organic vapours can vastly increase the application range of the DVS instruments. The current technology used in DVS instrumentation (DVS-Advantage and DVS-HT systems) allows for real-time monitoring and controlling of both water and organic vapour concentration. This unique capability of DVS instrumentation allows the complete utilization of investigating organic vapour sorption properties. This paper explains the ability of the DVS instruments to actively control organic vapours and summarises various established and novel applications.

## Method

A schematic of the DVS-Advantage instrument is shown in Figure 1. The instrument measures the uptake and loss of vapour gravimetrically using the SMS UltraBalance with a mass resolution of at least ±0.1 µg. The vapour partial pressure around the sample is generated by mixing saturated and dry carrier gas streams using electronic mass flow controllers. The DVS-Advantage instrument has the unique capability to actively measure and control the concentration of water and a wide range of organic vapours. This is accomplished by utilising a proprietary optical sensor which is specifically tuned for a wide range of solvents. This technology allows the instrument to measure and control organic vapour concentrations in real time. Figure 2 displays the target % partial pressure (red) and actual % partial pressure (blue) for octane as a function of time at 25 °C. The instrument was run in closedloop mode, resulting in excellent agreement between target and actual octane % partial pressure. Also, Figure 2 indicates the fast response to changes in vapour concentration exhibited by the system and sensor. The vapour



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generation and measurement principles of operation are similar for the DVS-HT instrument.



Figure 1. Schematic overview of the SMS DVS-Advantage instrument.



Figure 2. Target (red) and actual (blue) partial pressure profiles for octane at 25 °C.

#### **Organic Vapour Applications**

#### Solvate Formation

DVS has been used previously for the determination of stoichiometric hydrates [7]. The same methodology can be used to study stoichiometric solvates. If a material forms a stoichiometric solvate species at distinct vapour pressures, then the corresponding equilibrium uptake and resulting isotherm can be used to calculate the 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.

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

Equation 1 assumes formation of a stoichiometric or true solvated species.

Vapour-induced solvate formation may be related to solvate formation in different solvent mixtures. Both solvation-desolvation processes are thermodynamically equivalent [8]. 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, solvation formation measured by DVS could indicate where similar transitions would occur in the liquid-phase. This information may be useful for crystallizing materials in different solvents.

Carbamazepine is reported to exist in several polymorphic forms, including an acetone solvate [9]. Amorphous carbamazepine was created by first soaking it in water and then drying at 0% RH [10]. The amorphous carbamazepine was then exposed to an increasing acetone vapour pressure from 0 to 95% P/Po and then back down to 0%. Figure 3 displays the acetone vapour sorption kinetics (a.) and isotherm (b.) for the amorphous carbamazepine at 25.0 °C. The carbamazepine mass does not increase significantly until the 90% P/Po. Above this point, the sample mass increases dramatically until a 23.7% change in mass is achieved. Using Equation 1 and 236.28 amu for anhydrous carbamazepine, the stoichiometry of the acetone solvate is 0.96 or a 1:1 solvate. The acetone is not desolvated until the acetone partial pressure is decreased below 10% P/Po. This is clearly



shown in the acetone isotherm (see Figure 3b). Note, Figure 3b displays the percentage uptake in mass referenced from the dry mass as a function of the Actual acetone % partial pressure measured by the sensor. This allows the determination of the exact acetone % partial vapour pressure where solvation begins.



Figure 3a.





Figure 3. Acetone vapour sorption kinetics (a.) and isotherm (b.) for Carbamazepine at 25.0 °C.

Similar experiments were performed over a range of temperatures to investigate if the solvation and desolvation % vapour pressures were affected by temperature. There was no change in the **desolvation** point with increasing temperature. However, Figure 4 clearly shows the **solvation** point increases significantly with measurement temperature. According to Carstensen [11] the thermodynamic formation of a hydrate can be described by Equation 2:

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

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

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

where  $P_H$  is water vapour pressure and  $\Delta H_x$  is the heat of reaction. 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. Solvate formation would be similar to Equations 3 and 4, so the trend in this study is thermodynamically supported.

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 6hour 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 [12].



Figure 4. Carbamazepine-acetone solvate formation point versus measurement temperature.



#### BET Surface Area

The BET surface area can also be determined using organic vapours in the DVS [13]. The classical BET equation is given below where x is the partial vapour pressure above the surface and V is the amount of vapour adsorbed.

$$\frac{1}{V}\frac{x}{1-x} = \frac{c-1}{cV_m}x + \frac{1}{cV_m}$$
 (4)

A plot of (1/V)[x/1-x] as the ordinate and x as the abscissa should give a straight line. By determining the slope and the intercept of this line, V<sub>m</sub> the amount of gas adsorbed if a monolayer was to form and c, a constant related to the adsorbate-adsorbent interaction strength, can be determined. Measuring surface areas via DVS has many advantages over traditional, volumetric techniques. First, the DVS experiments are performed at atmospheric pressure and room temperature, as opposed to vacuum and cryogenic temperatures. The latter has a possibility to alter the structure of fragile materials (i.e. magnesium stearate and microcrystalline cellulose). Second, sample masses necessary for DVS experiments (typically 100 mg or below) are often much lower than for volumetric instrumentation. This can be particularly advantageous when quantities are limited (i.e. new drug entities) or with very low surface area materials (i.e. below 1 m<sup>2</sup>/g). Finally, since DVS is a dynamic flow technique, equilibration can often occur more rapidly than in static, volumetric techniques.

Since the BET equation requires surface adsorption only and no bulk absorption, the appropriate probe molecule must be used in the DVS. For most materials, straight-chain alkanes (i.e. heptane or octane) or cyclohexane are appropriate choices. The only exception may be very hydrophobic materials, where alkanes may absorb into the bulk and other more polar probe molecules may me more appropriate.

Figure 5 displays the cyclohexane vapour sorption kinetics (a.) and isotherm (b.) for a magnesium stearate sample. The complete sorption cycle is completed in approximately 6 hours. For the BET calculations, only the isotherm data between 5 and 35% P/Po is typically required. Therefore, the BET surface area could be determined after only three hours of measurement time. The resulting BET surface area measured via DVS was 12.2 m<sup>2</sup>/g.

To compare the BET surface areas measured via DVS with those from volumetric, nitrogen sorption studies a certified BET surface area standard (CRM 170) was measured. The resulting BET surface area measured by cyclohexane sorption on the DVS was 1.03 ± 0.10  $m^{2}/g$  (n=2). These values compare quite favourably to the nitrogen values obtained for the CRM 170 sample of  $1.05 \pm 0.05 \text{ m}^2/\text{g}$ . DVS has been used to determine the surface areas for a wide range of materials, including: crystalline lactose (0.26 m<sup>2</sup>/g via DVS, 0.25-0.43 m<sup>2</sup>/g via N<sub>2</sub> volumetric techniques); zirconia (43.67 m<sup>2</sup>/g via DVS, 43 m<sup>2</sup>/g via N<sub>2</sub> volumetric measurements); and alumina (95.10 m<sup>2</sup>/g via DVS, 95 m<sup>2</sup>/g via N<sub>2</sub> volumetric measurements). Clearly, DVS is a valid technique for measuring BET surface areas for a wide range of materials.







Figure 5b.



Figure 5. Cyclohexane sorption kinetics (a.) and isotherm (b.) for magnesium stearate at 25.0 °C.

## **Mesopore Size Distribution**

Porosity is another important parameter regarding industrial applications and performance of many materials [14]. Mesopores are classically defined between 2.0 and 50 nm (20 to 500 Å). As with BET surface area determination, a common method for the determination of mesopore size distributions is volumetric nitrogen adsorption measurements at 77 K [15]. An alternative to nitrogen adsorption is DVS at ambient conditions using non-polar organic vapours [16]. This approach has several benefits, especially for organic solids such as pharmaceutical and food materials, as outlined in the BET section. As with the BET surface area determination, a probe molecule with minimal bulk absorption must be used.

Mesopores size distribution calculations are commonly based on the analysis of the desorption branch of a type IV isotherm, using the BJH theory [17]. It assumes a mono-/multilayer formation in the mesopores and subsequent capillary condensation. The capillary condensation process can be described by the Kelvin equation. This equation relates the shape of the pore structure and the partial pressure where condensation/evaporation of vapour occurs.

$$\ln(p/po) = \frac{-2\gamma V \cos\Theta}{RTr_k}$$
(5)

In Equation 5,  $\gamma$  is the surface tension of the vapour, *V* the molecular volume of the condensed phase,  $\Theta$  the contact angle between adsorbed and solid phase, *R* the gas constant, *T* the absolute temperature and  $r_k$  the mean radius of the liquid meniscus. Assuming a cylindrical pore shape the pore volume  $V_P$  can be calculated if the thickness *t* of an adsorbed layer is known, as shown below:

$$V_P = V_K \left(\frac{r_k + t}{r_k}\right)^2 \tag{6}$$

where  $V_{\kappa}$  the volume of the condensed probe. The thickness of the adsorbed layer is related to the partial pressure by the t-Plot [15]. The t-plot compares the probe molecule uptake on the surface under investigation with a standard, nonporous surface. If the measured material is nonporous a straight line is obtained in the t-plot, while for a mesoporous solid a positive deviation (upward from linear) is expected.

To illustrate how a mesopores size distribution can be measured via DVS, octane vapour isotherms were measured on non-porous (Figure 6a) and agglomerated (Figure 6b) alumina samples of the same origin. As expected the isotherm shape is type II for the non-porous and the isotherms show a characteristic hysteresis for the porous, agglomerated alumina. For a detailed discussion of isotherm shapes and mechanisms see the following references [18, 19].









Figure 6. Octane vapour isotherms on non-porous (a.) and agglomerated (b.) alumina samples at 25.0 °C.



The resulting t-plot (not shown) shows clear positive deviation from linearity, thus confirming the mesoporous structure of the agglomerated alumina sample. Based on the calculations described above the mesopores size distribution for the agglomerate has been calculated using the non-porous alumina as a reference. The resulting mesorpores size distribution (by radius) is displayed in Figure 7. The maximum is located at 21 nm (210 Å). This is in good agreement with the value of 18 nm obtained from nitrogen adsorption at 77 K, given the dissimilar measurement conditions and slightly different calculation procedures. In all, DVS is a valid technique for the determination of mesopores size distributions using non-polar organic vapours.





#### **Amorphous Content**

DVS with organic vapours has been previously used to determine amorphous contents below 5% [20,21,22]. 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. This technique is similar to that developed by Zografi et al. [23] using water vapour. Using organic vapours have several distinct advantages. First, for a hydrophilic sample, a hydrophobic probe molecule could be used and vice versa. This will limit the chances of the probe forcing any sample recrystallisation. Therefore, vapour-induced crystallisation is prevented allowing multiple cycles to be run. Finally, the sorption of organic vapours is typically much faster than for water.

The example in Figure 8 shows octane vapour isotherms (a.) and the resulting calibration curve (b.) for several amorphous/crystalline lactose mixtures with known amorphous contents. The calibration curve is obtained by taking the octane vapour uptake at 0.95 P/Po. Based on the error bars in the calibration curve and linearity of the fit in Figure 8b, amorphous contents down to 0.5 ± 0.3% can be obtained. This methodology was used to determine the amorphous content for lactose samples exposed to different milling times [22]. These results are displayed in Figure 9. After approximately 50 minutes of milling, the amorphous content plateaus around 12%, suggesting the amorphous material is predominantly on the surface.









#### Figure8b

Figure 8. Octane vapour sorption isotherms (a.) and resulting calibration curve (b.) for several physical mixtures of amorphous and crystalline lactose.



Figure 9. Amorphous contents for lactose samples exposed to different milling times.

A second method to determine amorphous contents with organic vapours is suitable when the amorphous material forms a stoichiometric solvate during vapour-induced crystallization. This is based on a method first designed for hydrates [24], but the same methodology would also apply to solvates. This method has the unique advantage of not requiring any calibration standards. Experiments using carbamazepineacetone solvate formation as an example are shown in Figure 10. As discussed above, amorphous carbamazepine will convert to an acetone mono-solvate above 85% P/Po at 25 °C (red trace in Figure 10a). However, the crystalline species will not (black trace in Fig. 10a). 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. 10a), the percentage change in mass during solvate formation will be directly related to the amorphous fraction. Fig. 10b 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 (R<sup>2</sup>=0.999) 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.



#### Figure 10a



#### Figure 10b

Figure 10: (a.) Acetone sorption (solid) and desorption (dashed) isotherms of carbamazepine with different amorphous contents at 25  $^{\circ}$ C. (b.)

Theoretical versus measured net mass change due to solvate formation showing direct correlation.

## Surface Energy

The surface energy is a powerful parameter to describe the energetic situation on the surface of a solid material. Surface energies can be related to material performance, processing issues and stability [25]. For instance, surface energies have been able to discriminate between two batches, where they were equivalent according to FT-Raman spectroscopy and X-ray powder diffraction [26]. Feeley et al. studied a DPI formulation and correlated surface energetics to powder flowability, measured by a powder avalanching analyzer [27]. Additionally, changes



in surface energy have been attributed to changes in exposed crystal faces due to different milling conditions [28].

Further, the surface energy can be used to calculate the thermodynamic work of adhesion of multiple component systems, which can be used as a measure of strength for drug-binder interactions, drug release rates, and drugexcipient interactions. To illustrate, Galligan et al. reported how surface energy values could be used to predict powder mix uniformity of theophylline with different excipients [29]. Additionally, Zhang et al. showed that surface energies and subsequent work of adhesion/cohesion balances could be used to predict the performance of granulating solvents and ultimate granule performance [30]. Tüske, et al. also reported on the correlation of works of adhesion, obtained from surface energy measurements, to pellet properties (i.e. friability, bulk and tapped density, and porosity) [31].

The surface energy of a wide range of materials can be obtained by measuring the spreading pressures of different vapours with the DVS. The complete details and equations for this methodology can be found in Ref. [32]. In short, this is done by combining Young's equation with Fowkes theory [33]:

WA = 
$$2\gamma L + \pi e = 2 (\gamma L \cdot \gamma S) 1/2$$
 (7)

In Equation 7,  $\gamma L$  and  $\gamma S$  are the surface tensions of the liquid and the solid, respectively and WA is the solid-liquid work of adhesion. The spreading pressure  $\pi e$  can be calculated from the total amount adsorbed ( $\Theta$ ) as a function of partial pressure (p) and the specific surface area ( $\sigma$ ), as shown in Equation 8.

$$\pi_{e} = \frac{RT}{\sigma} \int \Theta d \ln p \tag{8}$$

To solve this equation the adsorption isotherm needs to be measured over a wide range of partial pressures and integrated. As a result, the work of adhesion, WA, and the dispersive and specific surface energies,  $\gamma$ DS and  $\gamma$ SPS, can be obtained.

Measuring surface energies via DVS has advantages over other contact angle or liquid penetration techniques. Liquid penetration methods are limited due to difficulties in estimating the effective pore radius as well as a number of other complicating effects, such as non-liquid penetration, non uniform flow, and powder bed packing problems [34]. Further, wetting force techniques are subject to a range of factors, including surface roughness, swelling, liquid penetration, powder contamination by the adhesive, and mechanical induced changes during compact formation. Since DVS is a vapour adsorption technique the above limitations are minimized or eliminated completely. The only consideration when measuring surface energies via DVS is the selection of probe molecules. The spreading pressure calculations assume a surface adsorption dominated mechanism. Therefore, probe molecules should be used that minimise bulk absorption.

Table 1 displays the dispersive ( $\gamma$ dS) and specific (yspS) surface energy values measured via DVS on  $\alpha$ -lactose monohydrate and caffeine. These values were calculated using octane and isopropyl alcohol as probe molecules. The  $\gamma$ dS values of 30.4 mJ/m2 determined in the current work for  $\alpha$ -lactose monohydrate and 39.9 mJ/m2 for caffeine were about 25% lower than IGC measurements on similar materials [34,35]. This observation is consistent with the notion that IGC experiments at infinite dilution involve probing the higher energy surface sites at very low surface coverages, while the DVS method obtains average information based on complete surface coverage. Thus, the DVS values are similar to traditional wetting experiments in which the solid surface is covered completely by either vapour or liquid species. To illustrate, the total surface energy for caffeine is in good agreement with two different Wilhelmy wetting balance approaches [36].

Table 1. Surface energetics measured via DVS for lactose and caffeine.

Solute	γ <sup>d</sup> s/ <b>mJ⁻²</b>	γ <sup>sp</sup> s/mJm⁻²	γ <sup>⊤</sup> s/mJ m⁻²
Lactose	30.4	5.6	36.0
Caffeine	31.1	14.2	45.4



## Conclusion

Expanding the functionality of DVS

instrumentation to include organic vapour sorption analysis greatly increases the ability to study the physico-chemical properties of solid materials. Organic vapour sorption studies allow the determination of solvate formation, amorphous content, BET surface areas, porosity, and surface energetics. The vapour sensor employed by current DVS instrumentation allows the user to monitor and actively control vapour concentrations for a wide range of organic solvents in real-time. By combining water and organic vapour sorption analysis, the true power and versatility of the DVS can be achieved.

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