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DVS Application Note 101

Moisture Sorption Properties of Pharmaceutical Materials Studied by DVS

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Dynamic Vapour Sorption (DVS) has long been used for investigating the interaction of water vapour with active pharmaceutical ingredients (API's), excipients and pharmaceutical formulations. This overview application note summarises several examples of using DVS for pharmaceutical-related applications including: hygroscopicity, moisture content, moisture-induced phase transitions, hydrate formation/loss, and amorphous content.

Introduction

The water vapour or moisture sorption properties of pharmaceutical materials such as excipients, drug formulations and packaging films are recognised as critical factors in determining their storage, stability, processing and application performance [1,2]. According to the US Pharmacopeia, moisture is not treated as an impurity, but water in a drug substance should be monitored and controlled as strictly as possible. (USP general chapter 1241). Further, the moisture content affects crystallinity and influences storage modulus, permeability, density and melting point of pharmaceutical products. In particular to amorphous materials, moisture can significantly alter the glass transition temperature, and even initiate spontaneous transformation to the crystalline form. Additionally, water facilitates hydrolysis and induces drug degradation. Finally, water content is routinely used in determining the dry and solvent-free assay value of a drug substance [3].

For the above reasons, a rapid, highly-sensitive and automated method to study moisture sorption properties is desired. Hence, the invention of the Dynamic Vapour Sorption (DVS) instrument by Surface Measurement Systems in the early 1990's. Today, the DVS is widely used across numerous industries for investigating the vapour sorption properties of solids, fibres, gels, particulates, and composite materials. This application note summarises several DVS applications related to drugs, excipients, and pharmaceutical ingredients.

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 ±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. In addition to controlling water vapour pressure (i.e. relative humidity), the DVS-Advantage instrument has the unique capability to actively measure and control the concentration of a wide range of organic vapours. This is accomplished by utilising a proprietary optical sensor which is specifically tuned for water and a wide range of solvents. This technology allows





the instrument to measure and control water and organic vapour concentrations in real time.

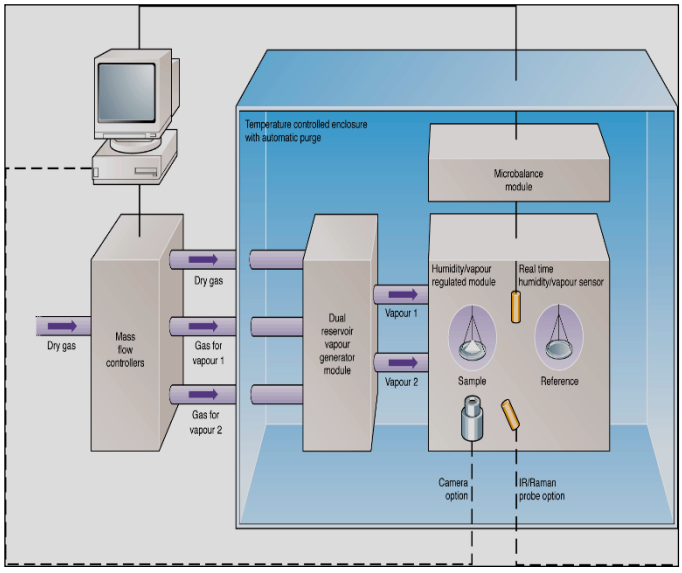
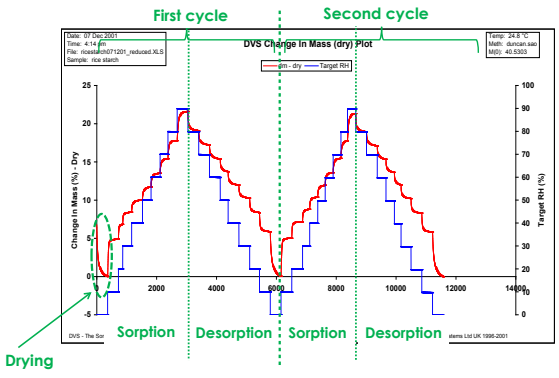


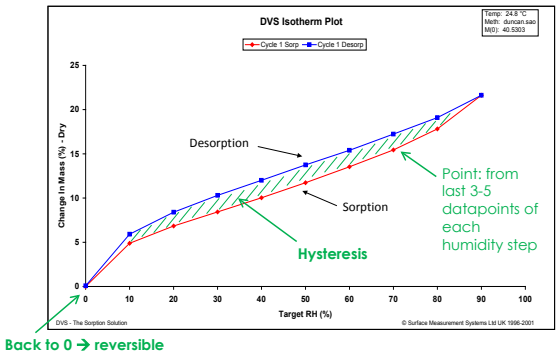
Figure 1. Schematic overview of the SMS DVS-Advantage instrument.

Moisture Content/Sorption Isotherm

The DVS family of instruments has been routinely used to determine moisture content isotherms. This is accomplished by exposing the sample to a certain relative humidity until equilibrium has been established. Then, this is repeated at numerous RH steps until a complete sorption and/or desorption isotherm has been established. Figure 2 displays typical moisture sorption/desorption kinetics (a.) and isotherms (b.) for a generic starch sample.



(a.)



(b.)

Figure 2. Moisture sorption kinetic (a.) and isotherm (b.) plots for starch at 25 °C.

Unlike the desiccator jar method, the DVS allows continuous measurement of the sorption kinetics, which can be used to determine moisture diffusion coefficients. This will be discussed in detail later. Also, the DVS allows the determination of sorption and desorption isotherms on the same sample; thus moisture sorption hysteresis can be measured. Finally, due to the constant flux of (partially) humidified carrier gas, the DVS allows complete sorption/desorption isotherms to be determined in hours/days instead of days/weeks/months for the desiccator jar method.

Hygroscopicity of API's

Measuring the ability of solids to take up water vapour from the atmosphere at constant temperature with changes in RH is often referred to as a measure of hygroscopicity. This measurement is now a routine preformulation activity intended to provide an early assessment of the potential effects of moisture on the physical and chemical properties of drug candidates [4]. Further, hygroscopicity is one of the most important criteria in selecting a drug crystal form for development. Thus, water sorption data are frequently used during the initial salt screening process to identify crystalline salt/neutral forms with 'acceptable' moisture stability [4].

Although the usefulness of classifying hygroscopicity in terms of definitive sorption capacities is debatable, several attempts have

been made. Also, it is important to note that defining hygroscopicity is only the first step in assessing the potential deleterious effects of moisture on API and formulation solid-state properties. With the above in mind, the European Pharmacopeia has classified the hygroscopic nature of materials as the a function of the percent water uptake at 25 °C and 80% RH [5]. These values are displayed in Table 1.

Table 1: *Hygroscopicity classification as defined by the European Pharmacopeia.*

Classification	% Water Uptake at 25°C/80% RH [w/w]
Non-hygroscopic	0 - 0.12
Slightly Hygroscopic	0.2 – 2
Moderately Hygroscopic	2.0 – 15.0
Very Hygroscopic	> 15.0

Hydrate/Solvate

The ultimate hydration state of a pharmaceutical material may influence several physico-chemical properties including physical and chemical stability [6]. For instance, some hydrated materials become amorphous upon dehydration. Also, different hydrate forms can affect the material solubility, dissolution rate, flowability, and compressibility. These factors affect the entire chain of the drug development process from preformulation to solid form development to packaging and storage. By one estimate, approximately one-third of all API's are capable of forming crystalline hydrates [7]. For these reasons above, there has been increased regulatory pressure to fully characterise and control the physical form of excipients and active drugs [8].

The DVS can be used to detect and characterize hydrate formation as a function of environment relative humidity. Detailed information about DVS and hydrate stoichiometry can be found in **SMS Application Note 36**. To illustrate, Figure 3 shows the water sorption isotherm for naloxone HCl at 25 °C. The observed hysteresis is typical for a stoichiometric hydrate. There sample ultimately sorbs approximately 9.6% of its dry weight in water vapour. Using the known molecular weight of naloxone HCl, this correlates to 1.9 water molecules per naloxone HCl molecule (i.e. dihydrate).

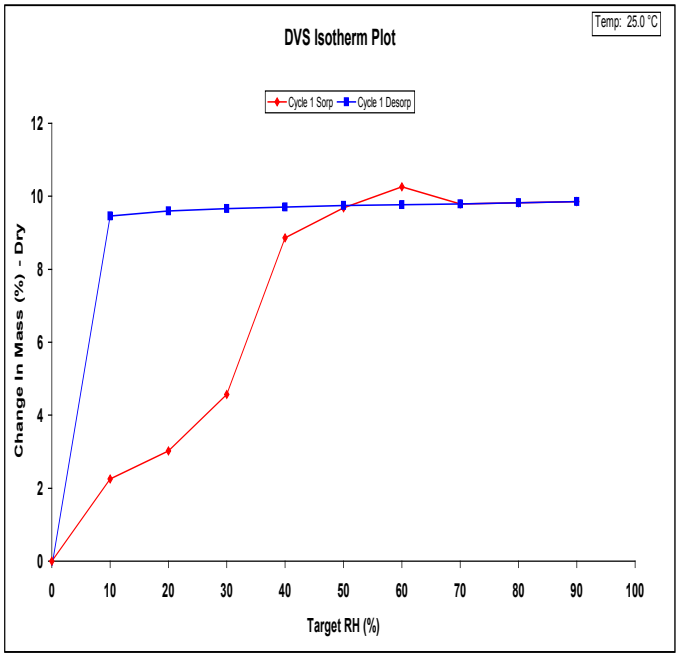


Figure 3. Water sorption (red) and desorption (blue) isotherms on naloxone HCl dihydrate at 25 °C.

Channel hydrates are a subset of pharmaceutical hydrates. For channel hydrates, the hydrated and dehydrated crystal structures are isomorphic (i.e. no distinguishable phase changes during hydration/dehydration). In a channel hydrate, water molecules fill one-dimensional channels or two dimensional planes running through the crystal structure. Detailed information on using DVS to identify and characterize channel hydrates can be found in **SMS Application Note 59**. Figure 4 shows typical water sorption results on a channel hydrate. The isotherms show sharp increases in water vapour below 15% RH, followed by minimal water uptake between 20 and 95%. The water uptake at low % RH conditions is due to the lattice channels filling with water. Similar behaviour has

been observed for other channel hydrates, and the confirmation of channel hydrate formation was supported by complimentary thermal analysis, variable-RH PXRD, vibrational spectroscopy, and NMR analysis [9,10,11].

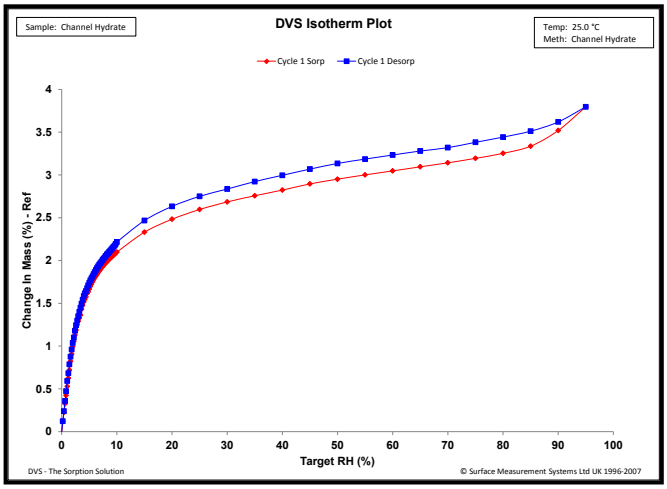


Figure 4. Water sorption kinetics Compound X at 25.0 °C.

DVS can also be extended to measuring the sorption properties of organic solvents. Therefore, the same methodology can be used to study stoichiometric solvates. **SMS Application Note 41** details this approach. Figure 5 displays the acetone vapour isotherms on a carbamazepine sample. The resulting isotherm shape and hysteresis is indicative of a 1:1 solvate formation above 80% P/Po. This solvate is relatively stable, as it does not desolvate until all of the acetone vapour is removed during the desorption drying step.

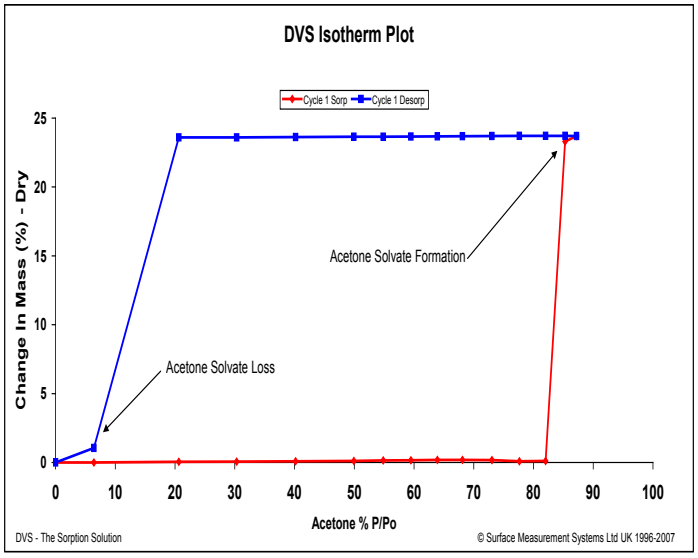


Figure 5. Acetone vapour sorption (red) and desorption (blue) isotherms for carbamazepine at 25 °C.

A final area of characterization in the formation of hydrates/solvates of pharmaceutical materials is the combined use of DVS with *in-situ* vibrational spectroscopy. As moisture is absorbed by a sample, the intermolecular structure and forces within it adapt to accommodate water molecules. This leads to changes in the sample's molecular vibrational characteristics, which can be monitored by changes in the Raman spectrum [12] or Near-IR spectrum [13]. To illustrate, Figure 6 shows the Raman spectra for Nedocromil sodium at 13 and 15% RH. DVS water sorption data in this region indicates the absorption of two moles of water. The Raman spectra confirm the transition from the monohydrate to the tri-hydrate state. As the compound changes hydration state, substantial modifications in pharmaceutically important properties can occur, such as solubility and bio-availability of the drug.

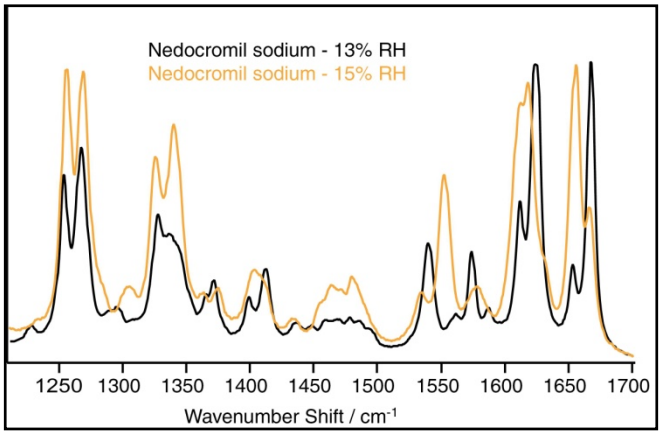


Figure 6. Raman spectra of nedocromil sodium at 13% and 15% RH.

The examples in this section illustrate how DVS studies can be a powerful tool in characterizing hydrates and solvates over a wide range of solvent concentrations and environmental temperatures.

Moisture-Induced Phase Changes

Amorphous solids often absorb relatively large amounts of water vapour compared to their corresponding crystalline phases. Sorbed water can act as a plasticising agent, thus significantly lowering the glass transition temperature causing spontaneous phase transitions and lyophile collapse. In fact, there is often a critical humidity at which the glass transition will occur at room temperature. In addition, this can lead to increased cohesiveness, powder caking and adhesion to other surfaces. To illustrate, it was determined that cohesion was related to the combined effects of temperature and moisture [14]. Only investigating one (i.e. temperature or moisture content alone) is not sufficient to understand the likelihood of a powder to cake. The mechanism for sticking and caking of amorphous sugars is through the phase change of the amorphous sugar from a glass to a rubber at conditions above the glass transition point [14]. Therefore, determining the necessary threshold temperature and humidity conditions to prevent a glass transition is critical for storage and processing of amorphous pharmaceutical ingredients.

Detailed information and theory about moisture-induced glass transitions can be found in **SMS Application Note 32** and in Reference [15]. In short, a linear RH ramping experiment is performed, whereas several moisture-induced phase transitions can be identified by the non-linear moisture sorption response of the sample. This phenomenon is illustrated in Figure 7 for a spray-dried lactose sample.

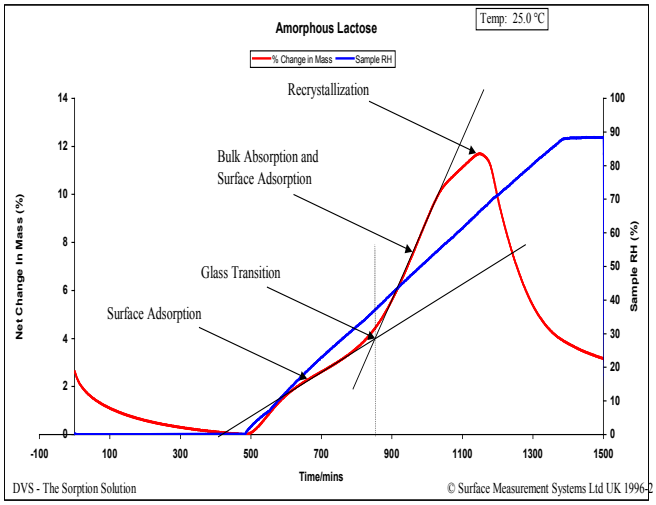


Figure 7. Relative humidity ramping experiment (6.0% RH/hour) for an amorphous lactose sample at 25.0 °C.

Similar experiments can be performed over a range of temperatures to establish a 2-dimensional phase diagram (Figure 8). This can be used to determine the ideal storage and processing conditions to limit any moisture-induced phase transformations and subsequent powder caking.

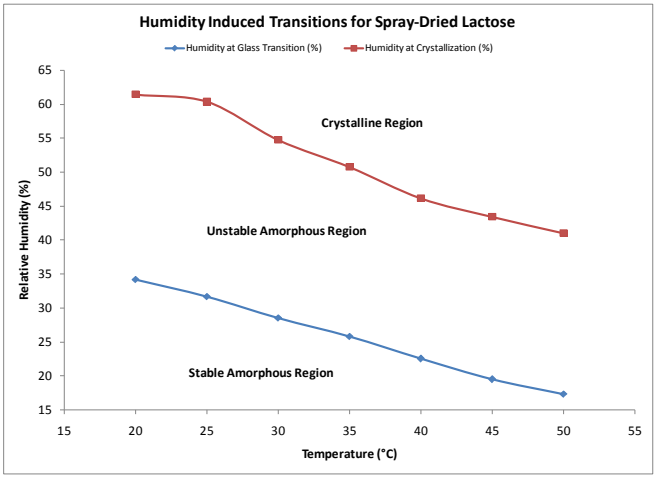
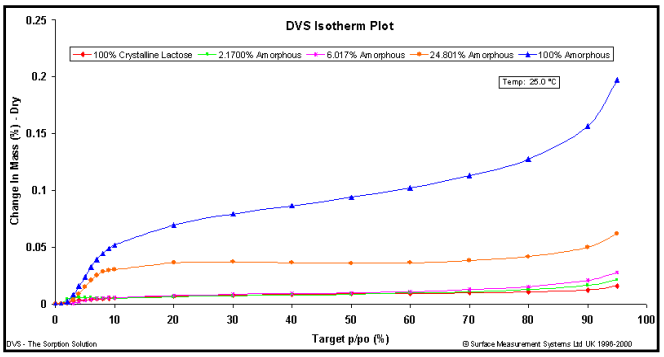


Figure 8. Humidity-induced phase transitions for spray-dried lactose measured via DVS.

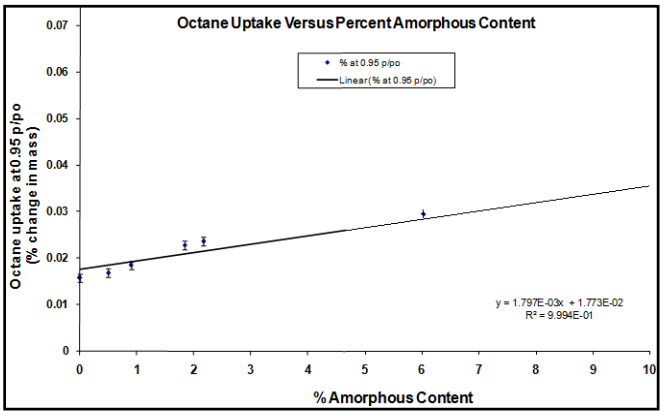
Amorphous Content

The presence of the amorphous phase can yield unique challenges in the formulation, processing, and storage of these materials. In particular, the caking behaviour of powders can depend on the amount of material present in the amorphous state [16]. There are several methods in the literature using gravimetric vapour sorption techniques to quantify amorphous contents [17,18,19,20,21]. Most of these methods are based on the amorphous phase sorbing more vapour than the crystalline phase. Amorphous materials typically have a higher surface area and vapour affinity than their crystalline counterparts. For vapour sorption methods a calibration of known amorphous contents is typically necessary. Then, the equilibrium vapour uptake at a particular vapour concentration is plotted versus the known amorphous content. The result is a calibration curve to which unknown amorphous contents can be compared. Due to the above mentioned changes in crystalline state induced by water (solvation, polymorph conversion, etc.), use of a non-polar organic vapour is recommended for hydrophobic materials. To illustrate, Figure 9 shows the octane vapour sorption isotherms (a.) and calibration curve (b.) for lactose samples with varying amorphous contents. The error margins in Figure 9b were based on the 1st standard deviation for repeat measurements (n=3).

Amorphous standards were created by making physical mixtures of 100% amorphous and 100% crystalline lactose. The resulting calibration curve and correlation coefficient (R^2=0.9994) suggests that amorphous contents below 0.5% were achievable with an accuracy of ± 0.3%.



(a)



(b)

Figure 9. Octane vapor sorption isotherms (a.) and resulting calibration curve (b.) for lactose samples with various amorphous fractions.

Video Microscopy

The physical changes inferred from the gravimetric data can be further supported by *in-situ* microscopic images collected during the experiment. This is done using the DVS-Video accessory. The long-working distance digital microscope allows the automatic collection of images during a DVS experiment with magnification up to 200X.

Figure 10 shows 100x images of amorphous lactose taken at 0% (A), 50% (B),

60% (C), and 90% RH (D). This is the same material used in Figure 7. By 50% RH the sample is clearly changed to the rubbery form due to the humidity-induced glass transition. By 60% RH, the sample begins to crystallize, where at 90% RH crystallization of amorphous lactose is evident by an increase in the opacity of the image. When combined with the change in mass results in Figure 7, the images shown in Figure 10 clearly identify different humidity-induced phase changes.

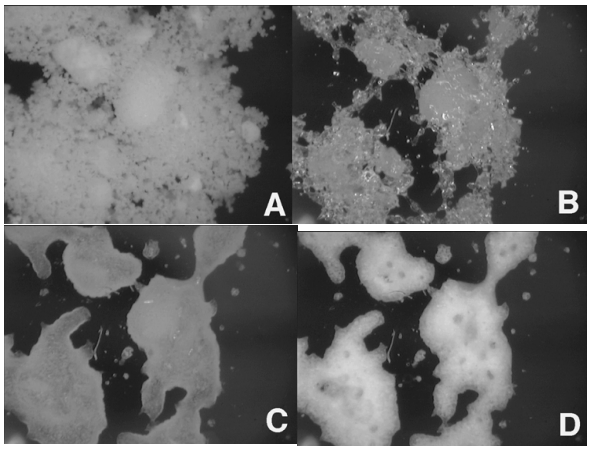
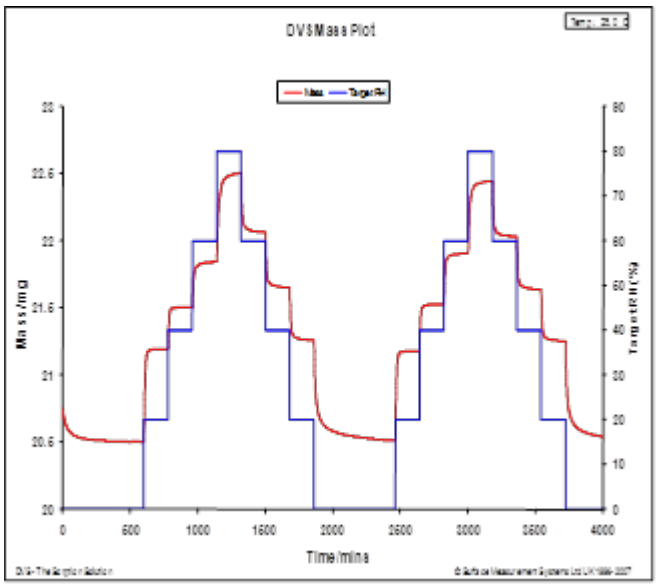


Figure 10. In-situ images collected on amorphous lactose at 0% (A), 50% (B), 60% (C), and 90% RH (D).

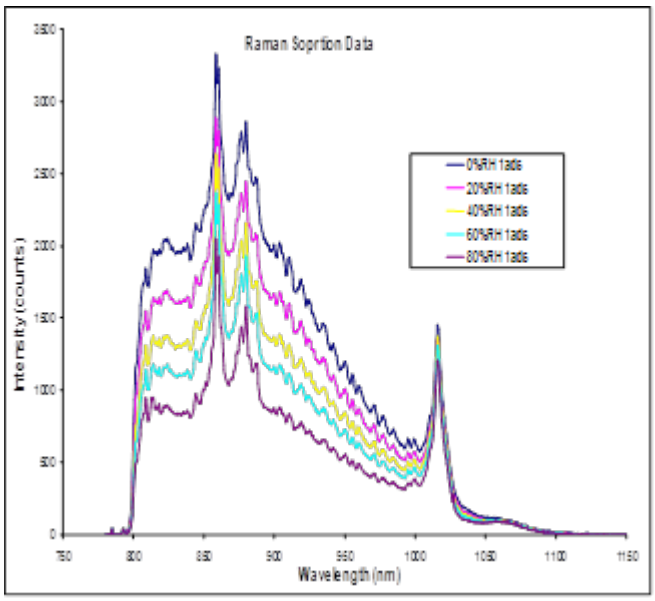
Raman/Near-IR

Vibrational spectroscopic techniques, such as Near-IR [22,23] and Raman spectroscopy [24] have also been combined with gravimetric sorption methods. As moisture is absorbed by a sample, the intermolecular structure and forces within it adapt to accommodate water molecules. This leads to changes in the sample's molecular vibrational characteristics, which can be monitored by changes in the Raman spectrum [25] or Near-IR spectrum [26].

To illustrate, Raman spectroscopy can be sensitive to changes in hydrogen bonding and other subtle reorientation of the solid material. For instance, Raman spectroscopy has been previously used to determine the changes in the strength of hydrogen bonding between water and different pharmaceutical polymers [27]. In the same study, changes in Raman spectra due to water plasticizing the polymers have been observed. Figure 11 displays the water sorption/desorption (a.) and Raman spectra (b.) for microcrystalline cellulose (MCC) at 25 °C. MCC is not expected to form a stoichiometric hydrated species or undergo any first-order phase change when exposed to increasing humidity. However, there are clear differences in the Raman spectra as the humidity is increased. MCC does experience a significant amount of bulk water absorption as humidity is increased. Therefore, the changes observed in Figure 11b could be due to increased hydrogen bonding, decrease in void spaces, or other structural rearrangements.



(a.)



(b.)

Figure 11. DVS water sorption/desorption results (a.) and in-situ Raman spectra (b.) for MCC at 25 °C.

Diffusion/Flux Experiments

Real-time mass change data can be collected as frequently as once every second, which allows the determination of diffusion coefficients for various geometries. DVS has been successfully used to measure diffusion coefficients for films, powders, and fibres. Diffusion into films can be particularly useful for packaging applications. **SMS Application Note 16** outlines the theory and method for thin film diffusion coefficient determination. In short, diffusion constants for the thin films utilises diffusion equations first employed by Crank and Park [28]. For a single step in humidity, and a thin film of known thickness, the initial kinetics of sorption into the bulk may be used to determine the diffusion coefficient. This can be performed over a range of temperatures to investigate a range of storage conditions. Figure 12 displays the water diffusion coefficients into a fluoropolymer-copolymer film over a range of temperatures.

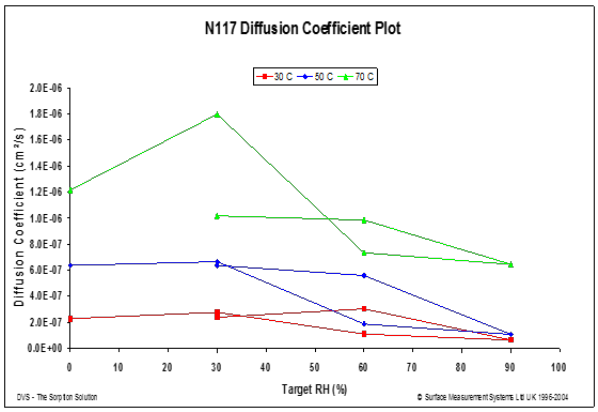


Figure 12. Diffusion coefficients at 30 ° C (red), 50 °C (blue), and 70 °C (green) for a fluoropolymer-copolymer film (183 microns).

Water Vapour Transmission Rates (WVTR)

A novel Payne style diffusion cell was designed and developed to measure the permeability/rate of diffusion of a thin film. The design of this cell is shown in Figure 13. Full description of the cell, including dry-cup and wet-cup methods, can be found in **SMS Application Note 52**. This cell can be readily used to determine WVTR values. Combined with the diffusion coefficients mentioned previously, WVTR determination can be used for packaging/barrier applications.

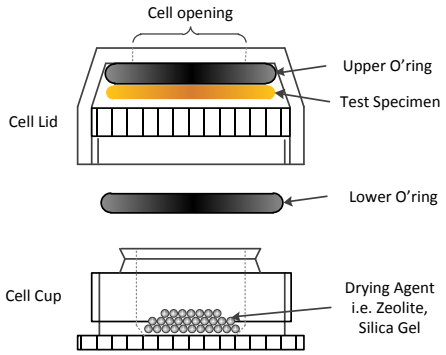


Figure 13. Experimental set-up for moisture vapour transmission rate measurement.

To illustrate the utility of this Payne cell, Table 2 displays the steady-state water vapour flux values on an electro spun PCL membrane over a range of humidity boundary conditions. As expected, when the surrounding relative humidity increases, the flux across the membrane also increases.

Table 2: *Water vapour flux through electrospun PCL membrane at varying relative humidity values*

% Relative Humidity	Diffusion rate [mg/min]	Water vapour flux [g/(hr.m^2)]
100	0.1152	444.82
80	0.1109	428.28
50	0.0751	289.94
30	0.0432	166.90

In addition, the Payne cell can be used to determine water activity values (Aw) for a wide range of materials. For more information on this application, please refer to **SMS Application Note 62**.

BET Surface Area

The BET surface area can also be determined using organic vapours in the DVS. This approach is outlined in detail in **SMS Application Note 18**. 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^2/g). Finally, since DVS is a dynamic flow technique, equilibration can often occur more rapidly than in static, volumetric techniques.

To illustrate, Figure 14 shows the BET plot for octane sorption on a hydrophobic drug (Metformin Hydrochloride). Repeat experiments show the average surface area was 0.116 +/- 0.005 m^2/g. These experiments were performed with approximately 450mg of sample. It was not possible to obtain the BET surface area with this relatively small sample size using traditional nitrogen, volumetric sorption systems.

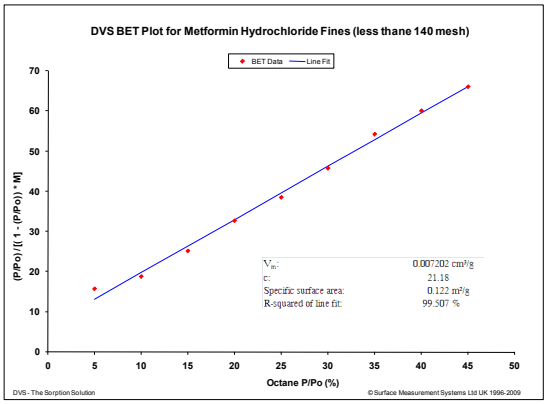


Figure 14. BET surface area plot for a hydrophobic drug using octane vapour at 25 °C.

Sorption Mechanisms

Often it is important to know the vapour sorption mechanism on pharmaceutical related materials to further understand the interaction between vapours and solid materials. This can be aided by understanding the heat of sorption (see **SMS Application Note 19**) or the isotherm shape (see **SMS Application Note 26**). The heat of sorption measurements on α-lactose monohydrate as a model pharmaceutical excipient using water and 1-butanol is an example to demonstrate significant information about the sorption mechanism in a solid-vapour system.

For instance, the n-butanol sorption isotherm on α-lactose monohydrate (see Figure 15) indicates a Type II sorption mechanism - monolayer, followed by multilayer sorption. This isotherm shape is in contrast to water on α-lactose monohydrate, where a Type III isotherm results – no monolayer formation. The change in isotherm shape shows a clear shift in the sorption mechanism from water to n-butanol. Water is highly polar, so the water-water interactions dominate, forming island or clusters at low coverages. In contrast, n-butanol is significantly less polar, so the interaction with the lactose surface dominates at low coverages, leading to monolayer formation. This information could be useful in selecting solvents as dispersion liquids.

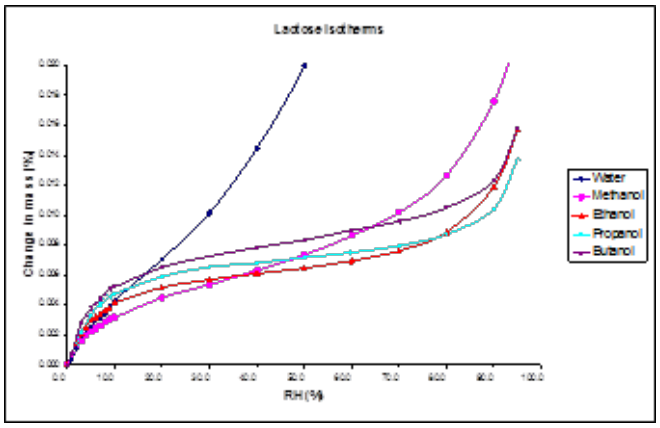


Figure 15. Adsorption isotherms for methanol, ethanol, 1-propanol and 1-butanol on the lactose sample at 25.0 °C (with water isotherm for comparison).

Conclusion

Utilizing the functionality of Dynamic Vapour Sorption instrumentation allows the vapour sorption characteristics to be studied on API's, excipients, final formulations, tablets, capsules, and packaging materials. Water sorption on these materials can be vital in understanding material stability and performance. This overview application note only summarises a handful of these applications, but hopefully illustrates how DVS technology could be applied to a wide range of pharmaceutical-related materials and challenges.

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