The Characterisation of Pharmaceutical Materials by Dynamic Vapour Sorption

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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]. Moisture sorption properties are routinely determined for many pharmaceutical materials and have traditionally been evaluated by storing samples over saturated salt solutions of established relative humidities and then regularly weighing until equilibrium is reached [3-5]. However, there are a number of disadvantages with these methods, including:

(i) the prolonged period of time taken for the samples to reach equilibrium using a static method, often many days commonly many weeks.

(ii) inherent inaccuracies as the samples have to be removed from the storage container to be weighed which can cause weight loss or gain.

(iii) static methods necessitate the use of large samples sizes (typically >1gm).

(iv) the highly labour intensive nature of static methods.

A new, highly sensitive, accurate and rapid means for determining the moisture sorption properties of solid pharmaceutical materials is described below.

Experimental

The data described below were obtained using the Dynamic Vapour Sorption (DVS) methodology developed by Surface Measurement Systems (SMS) Ltd. for the rapid quantitative analysis of the water sorption properties of solids including pharmaceutical materials.

A schematic of a DVS automated gravimetric sorption system is shown in Figure 1. The Surface Measurement Systems DVS instrument, now in use by many pharmaceutical companies world-wide, rapidly measures uptake and loss of moisture by flowing a carrier gas at a specified relative humidity (RH) over a sample (1mg - 1.5g) suspended from the weighing mechanism of a Cahn D-200 ultra-sensitive recording microbalance. This particular microbalance is used as it is capable of measuring changes in sample mass lower than 1 part in 10 million and provides the unrivalled long-term stability required for the accurate measurement of vapour sorption phenomena, which may take from minutes to days to complete depending upon the sample size and material. Indeed, a major factor in determining the water sorption behaviour of materials is the need to establish rapid water sorption equilibrium, therefore the DVS instrument allows sorption behaviour to be accurately determined on very small sample sizes (typically 10 mg), thus minimising the equilibration time required.

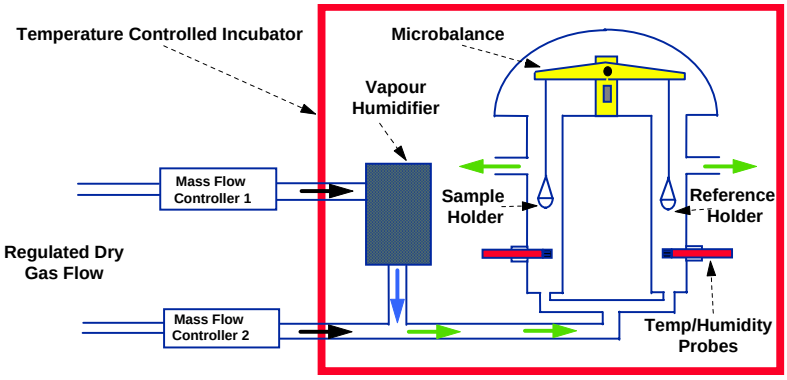

Figure 1. Schematic of a DVS-1 instrument.

One of the most critical factors for any instrumentation used

for investigating moisture sorption behaviour is the temperature stability of the measurement system. The main DVS instrument systems are therefore housed in a precisely controlled constant temperature incubator with a temperature stability of ±0.1°C. This ensures very good instrument baseline stability as well as accurate control of the relative humidity generation. The required relative humidities are generated by accurately mixing dry and saturated vapour gas flows in the correct proportions using mass flow controllers. Humidity and temperature probes are situated just below the sample and reference holders to give independent verification of system performance. The microbalance mechanism is very sensitive to sorption and desorption of moisture, therefore a constant dry gas purge to the balance head is provided to give the best performance in terms of baseline stability. The purge flow is manually controlled such that in the event of a power failure, condensation of moisture in the balance head cannot occur.

The DVS instrument is fully automated under control from a dedicated IBM compatible PC microcomputer. The DVSWIN software package supplied with the instrument provides a flexible and easy to use interface for setting up and running moisture sorption /desorption experiments on the DVS instrument. In addition, the DVS Data Analysis Suite, which runs from within Microsoft Excel, provides a powerful environment for rapid plotting and quantitative analysis of data.

Results and Discussion

The following results, obtained using a DVS-1 instrument, highlight the versatility and power of Dynamic Vapour Sorption method.

Moisture Sorption of Microcrystalline Cellulose RM 302

Microcrystalline cellulose (RM 302) is an EC reference material for measuring moisture sorption isotherms on pharmaceutical and food materials and has been the subject of an extensive EC-wide study using the COST 90 procedure [6]. Figure 2 shows the kinetic data for a water sorption isotherm measured on RM 302 at 25°C using a DVS-1 instrument. These data demonstrate the rapid establishment of equilibrium using this technique; the *whole sorption isotherm* was measured accurately within 33.5 hours using the DVS instrument, whereas *each point* on a similar sorption isotherm took a minimum of 7 days to measure using the COST 90 procedure. Table 1 shows the certified equilibrium moisture content for RM 302 measured by the COST 90 procedure together with the mean of 4 sets of DVS-1 data from two different laboratories. The DVS-1 data agrees well with the COST 90 data and the small standard deviation for the DVS data demonstrates the very good reproducibility of the instrument. RM-302 is increasingly being used as a standard material for validating the performance of the DVS instrument within pharmaceutical laboratories.

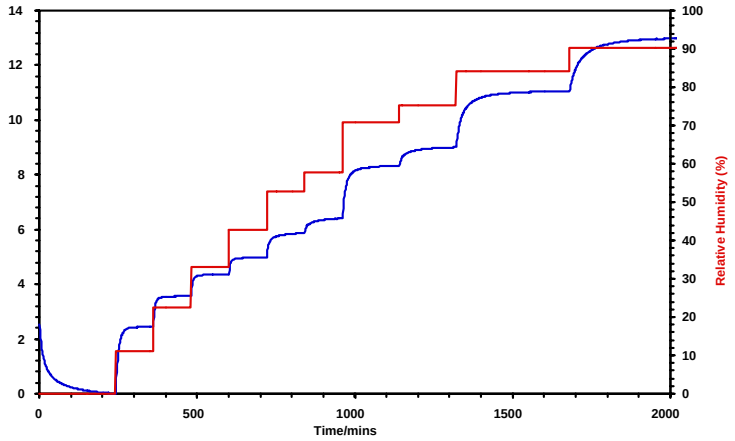

Figure 2. Kinetics of moisture sorption of RM302.

Polymorphism in Spray Dried Lactose

The collapse of amorphous spray dried materials above a certain critical humidity is a recognised problem within pharmaceutical product development. Recently a DVS methodology has been used to estimate the amorphous contents of lactose powders for amorphous contents as low as 0.125% (compared to 10% detection limit for X-Ray Diffraction) [7].

Table 1. COST and DVS isotherms for RM302.

Relative Humidity (%)	Mean % H_2O Content COST 90	Mean % H_2O Content DVS-1	Standard Deviation DVS-1
11.05	2.13 ± 0.11	2.45	0.026
22.45	3.24 ± 0.12	3.59	0.041
33.00	4.15 ± 0.09	4.40	0.029
42.76	5.16 ± 0.09	5.02	0.027
52.86	5.97 ± 0.14	5.89	0.026
57.70	6.48 ± 0.15	6.43	0.029
70.83	8.25 ± 0.17	8.29	0.060
75.28	8.90 ± 0.24	8.84	0.081
84.26	11.00 ± 0.33	10.98	0.071
90.19	13.27 ± 0.43	12.82	0.160

Automated computer control of the DVS instrument allows novel experimental approaches to be adopted for rapidly investigating such materials. The data in Figure 3 demonstrates the physico-chemical behaviour of a highly amorphous lactose sample by using a rapid humidity ramping methodology. After an initial drying period, the sample was subjected to a linear humidity ramp of 10% RH per hour from 0 to 100% RH at 25°C. The sample was then dried and a second ramping cycle performed. The first cycle data shows the rapid uptake of moisture by the amorphous powder up to a critical moisture content at around 60% RH above which rapid loss of moisture is observed. This observed loss of moisture might be attributed to recrystallisation of amorphous material caused by a moisture induced lowering of the glass transition temperature (T_g) of the amorphous regions in the sample to below 25°C. The data for the second cycle shows very little moisture uptake and is similar to that observed for crystalline α-lactose monohydrate, indicating that virtually all of the amorphous content of the sample recrystallised in the first cycle. These data therefore demonstrate the power of the DVS instrument to detect polymorphism in certain pharmaceutical materials.

Diffusion of Moisture Through Polymer Films

The measurement of diffusion and permeation of vapours and liquids through polymer films is of interest to many sectors of the pharmaceutical industry. Such measurements are particularly pertinent in the development of primary and secondary packaging devices such as capsules or blister packs as well as thin films such as tablet coatings. A novel diffusion cell has been developed by Surface Measurement Systems to facilitate DVS measurements on polymer films and packaging devices. Figure 4 shows kinetic moisture sorption data for cellulose and PVC coated cellulose films at 25°C measured by DVS. The

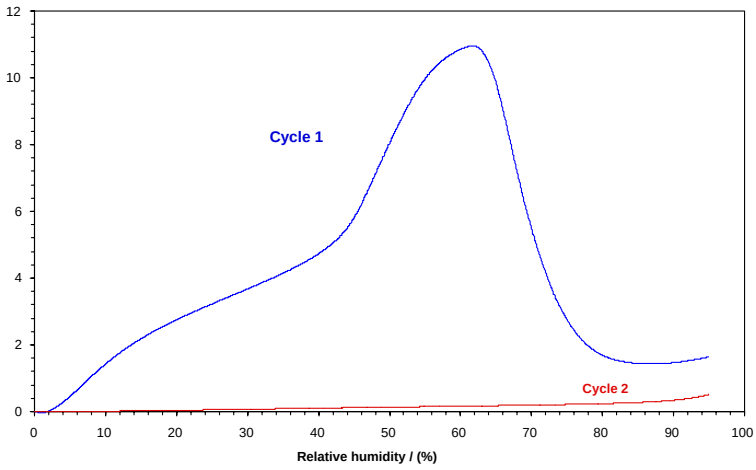

Figure 3. Humidity ramping experiment for 100% amorphous lactose.

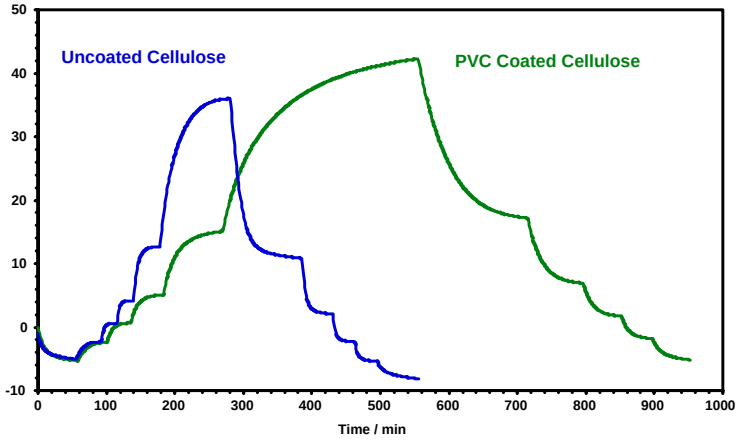

Figure 4. Diffusion of moisture through uncoated and PVC coated cellulose films.

films were subjected to the following humidity profile: 0% RH, 20% RH, 40% RH, 60% RH, 80% RH, 95% RH, 80% RH, 60% RH, 40% RH, 20% RH and 0% RH. The DVS data clearly demonstrates the barrier effect of the PVC coating to diffusion of moisture into the film. The kinetics of moisture sorption are significantly slower at all humidities for the PVC coated film. Thus, in this case the PVC coated film would be expected to enhance product shelf life where moisture ingress is a problem. In addition to the above methodology, a novel diffusion cell method has been developed by SMS in to allow absolute measurement of diffusion constants through thin polymer films and is discussed in detail elsewhere [8].

Conclusions

The DVS technique has been demonstrated to provide the following major advances in moisture sorption measurement to the pharmaceutical researcher;

(1) Much faster equilibration times - typically 10 to 100 times faster than traditional experimental approaches.

(2) High precision and sensitivity - samples sizes less than 1mg may be readily studied.

(3) Full automation - removes labour intensive nature of sorption measurements.

(4) Flexible and easy to use computer interface - allows complex and novel experiments to be executed automatically without supervision.

The data discussed above clearly demonstrates the power of the DVS technique over a wide range of sectors in the pharmaceutical industry. The instrument has already proved very useful in many industrial laboratories, with typical applications being the characterisation of excipients and formulations, salt and polymorph selection studies and the measurement of diffusion in packing films and materials.

References

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