Dynamic vapour sorption (DVS) characterisation and MVTR properties in pharmaceutical materials

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Introduction

Traditional methods of analysing moisture sorption in pharmaceutical materials are labour intensive both in operation and maintenance as well as providing information of limited accuracy. Modern automated gravimetric Dynamic Vapour Sorption (DVS) analysers can accurately measure both the equilibrium capacity and the kinetics of the uptake process. These systems provide high accuracy with low maintenance costs and a flexible approachto characterisation both in R&D and QA/QC applications.

Why is the pharmaceutical industry interested in DVS?

Moisture is constantly present in our environment and can affect solid state forms due to its influence on their structural phase. This may be due to the formation of a hydrate phase or an induced amorphous to crystalline phase transition. These moisture induced phase changes can affect mechanical properties, cause chemical interactions and alter yield, purity and dosage calculations and therefore it is important to accurately characterise the effect of moisture on pharmaceutical materials.

DVS analysers

The DVS data presented were measured using analysers manufactured by Hiden Isochema Ltd. The IGAsorp, shown in fig 1, is a fully automated and computer controlled GVS instrument, which continuously monitors the moisture content of the sample whilst accurately controlling both the temperature and relative humidity. A schematic of the IGAsorp is presented in Fig. 2. A sensitive microbalance (0.1μg resolution) is utilized to measure changes in the moisture content of the sample. The sample temperature is regulated, in the range 5-85 °C, to +/-0.05 °C by a water bath which pumps water through a network of channels in the sample block. An additional internal heater is situated in the sample chamber for rapid drying temperatures up to 350 °C. From an equilibrium state, the relative humidity is rapidly changed to a new set-point and then regulated at this new value. The sample will react by altering its adsorbed capacity. The trend of the data (mass versus time) is analysed in real-time as the sample capacity approaches the new equilibrium condition. This relaxation is used to determine when the new equilibrium condition has been achieved.

Figure 1: IGAsorp Dynamic Vapour Sorption Analyser

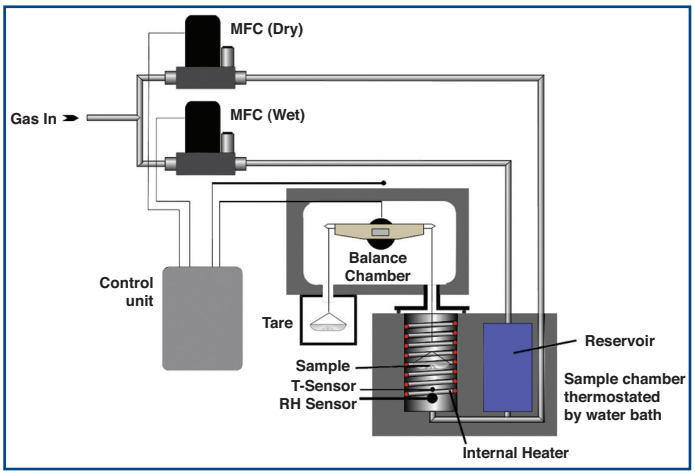

Figure 2: Schematic representation of the IGAsorp

Once attained, the equilibrium uptake values can be recorded. The method provides a consistent analysis from sample to sample thus removing human subjectivity and the kinetic data usually discarded or not measured with other techniques is readily available, which can prove to be just as valuable as the equilibrium data.

Applications of DVS in the pharmaceutical industry.

DVS analysers are very versatile instruments and are becoming an essential tool in analytical laboratories. The IGAsorp is capable of characterising moisture sorption isotherms, investigating hydrate phases and deliquescence, detecting and quantifying amorphous phases and measuring kinetics such as diffusion rates and Moisture Vapour Transmission Rates (MVTR's). The kinetic analysis is of great interest as the most important question is often 'how quickly' not just 'how much'.

Below are several examples of studies performed using the IGAsorp.

Hydrate analysis

One of the crucial challenges in the development of new pharmaceutical products is the stability of active compounds within an excipient, and their ability to be stored without degradation. Any observed polymorphism or the formation of amorphous structures may adversely affect dissolution kinetics and contravene licensing conditions. Such effects in novel medicines may prevent certification. Many pharmaceuticals form hydrate phases as the RH and temperature are varied.DVS can be used to study the stability and availability of such phases. Characterising the hydrate phases can indicate what type of storage and packaging is necessary. The kinetics of reactions are automatically measured, yielding information about the speed of the reaction.

The investigation was performed using an IGAsorp Gravimetric Vapour Sorption (GVS) instrument from Hiden Isochema Ltd, Warrington, England. This system performs isothermal measurements at atmospheric pressure at relative humidity (RH) levels in the range 0-98 % RH, measuring weight changes due to absorbed vapour with high resolution (from 0.05 μg). The humidity is set by bubbling dry nitrogen (99.999 % purity) through distilled water to provide a 100 % humidity gas stream, which is then combined with another stream of dry nitrogen as necessary to supply the required RH. This is passed over the sample at a rate of 100 ml/min. Isotherms can be determined with a temperature stability of ±0.05 °C. Kinetic data for each isotherm point is recorded at intervals down to 0.1 seconds. This is analysed in real-time by the IGAsorp software to predict the asymptotic equilibrium point, allowing the instrument to record the predicted value and move to the next RH set-point once user-defined criteria have been satisfied. These equilibrium points are then used to plot an isotherm over the selected RH range.

Fig. 3 displays an isotherm measured on a pharmaceutical

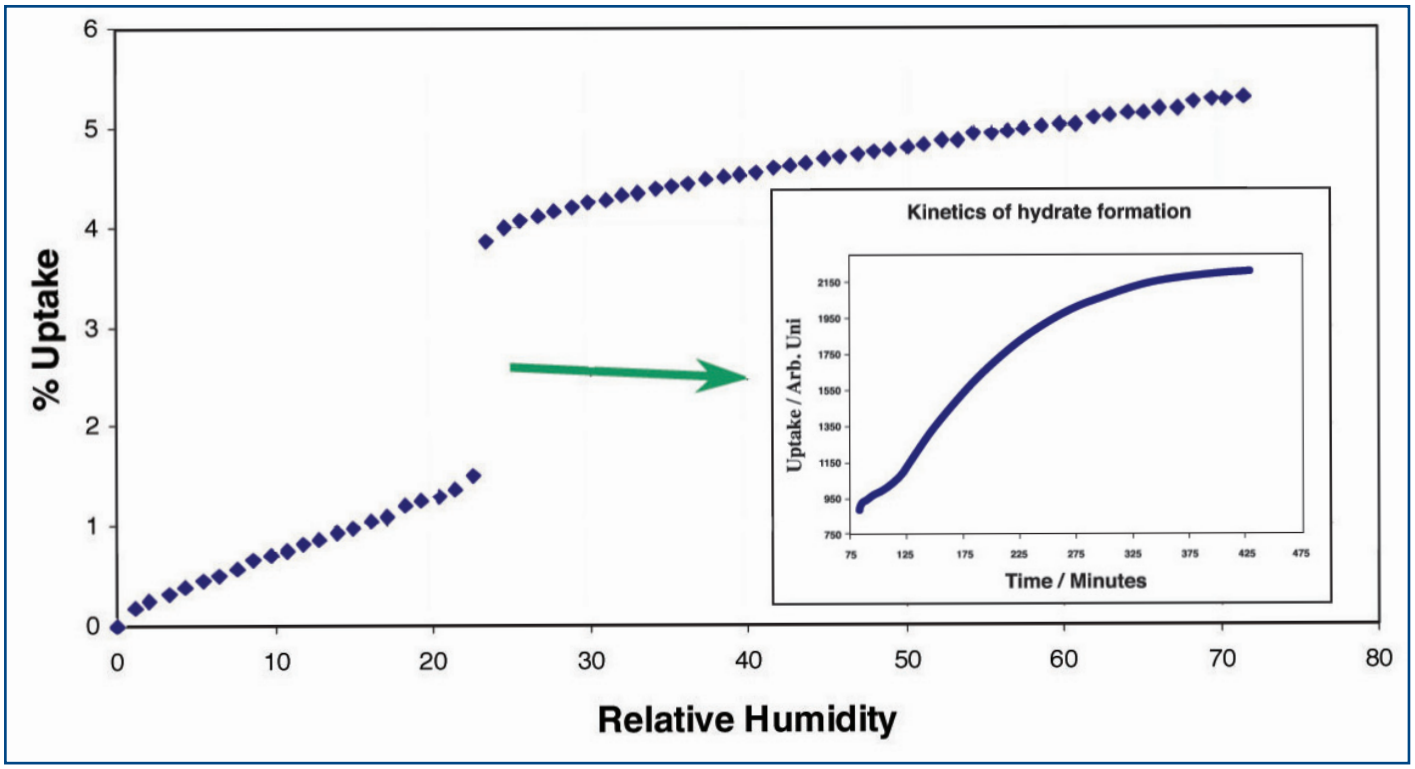

Figure 3: Monohydrate formation observed with the IGAsorp

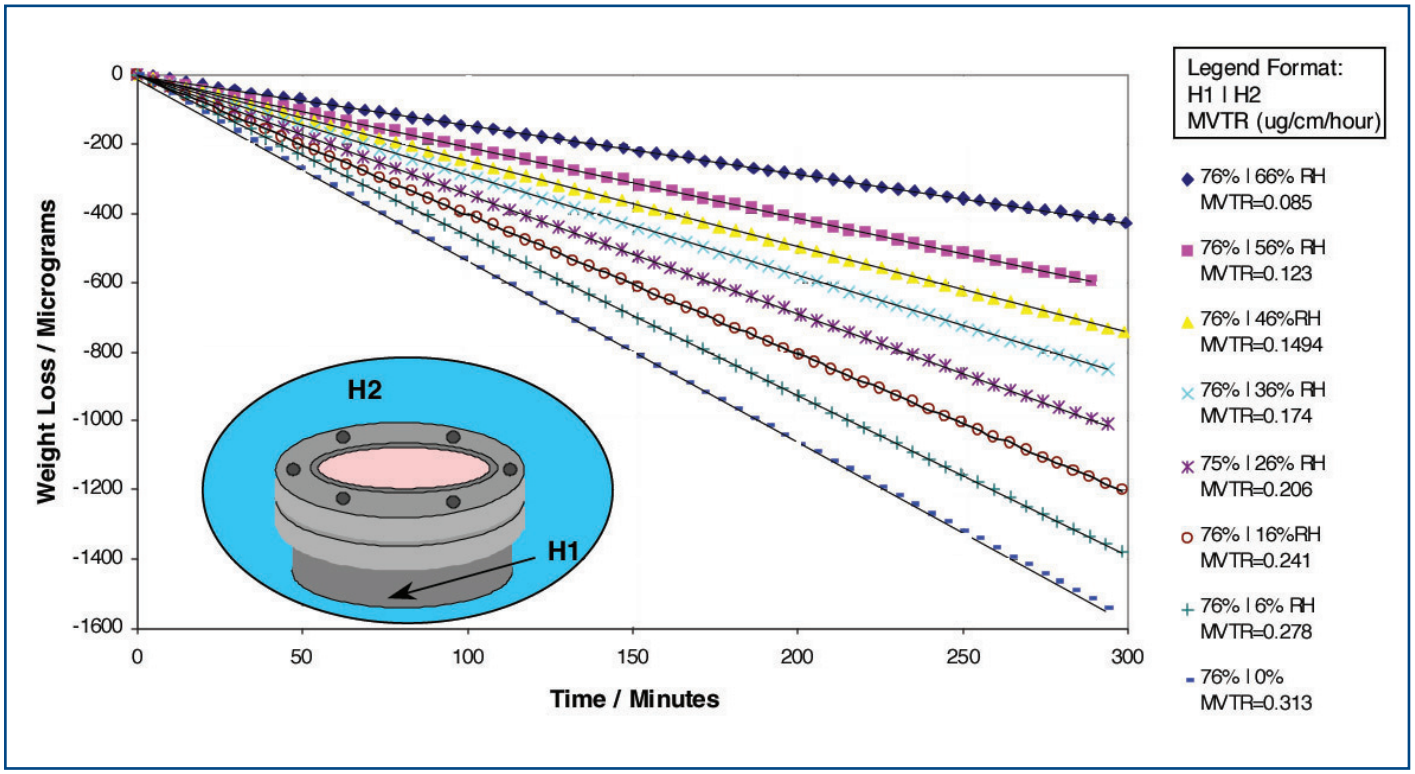

Figure 5: MVTRs measured through a polymer film

solid powder. This study shows the formation of a mono-hydrate. The kinetics of the hydration process are also shown in the inset.

MVTR and diffusivity determination

The IGAsorp can be utilised to measure diffusion coefficients and moisture vapour transmission rates (MVTR's). The most common type of samples to be studied in this manner are polymer films used for packaging and membranes. The IGA-sorp allows diffusivity and MVTR's to be easily studied as a function of uptake, RH and temperature, indicating the regions in which the films are most and least efficient. Fig. 5 shows a series of data from which MVTR's are calculated under differ-ent operating conditions. Fig. 4 shows the special permeation cell used for this type of analysis.

Figure 4: MVTR permeation cell with calibration salt solutions

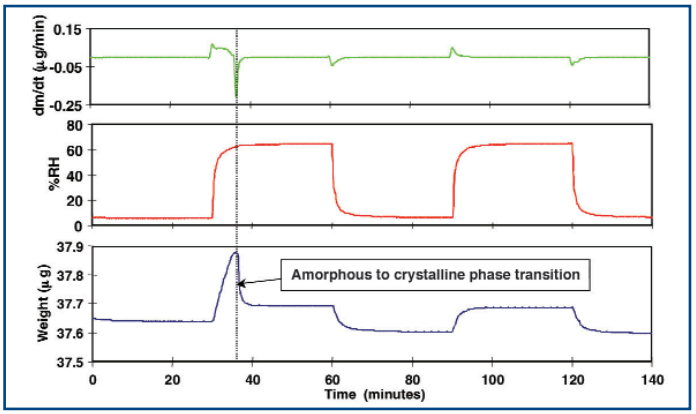

Figure 6: Identification of an amorphous phase transition within a pharmaceutical product.

Amorphous phase detection

Large differences often occur in the properties of amorphous and crystalline phases. Amorphous phases tend to be more bioavailable than their crystalline counterparts. This means it is important to know exactly how much of each phase you have present for dosage purposes. Amorphous phases are often much more hydroscopic than crystalline phases and therefore the IGAsorp can be used to detect and quantify even very small amounts of amorphous phases. Fig. 6 displays data showing a simple test designed to detect amorphous phases.

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