Surface Measurement Systems
World Leader in Sorption Science

DVS Application Note 36

Investigation of Hydrate Formation and Loss Using the DVS

Dan Burnett and Frank Thielmann, Surface Measurement Systems Ltd.

Dynamic Vapour Sorption (DVS) allows the fast and accurate determination of hydrate/solvate stoichiometry for a wide range of solid-vapour systems. This paper describes hydrate loss and formation on naloxone HCl and nedocromil sodium samples.

Introduction

For many materials, phase transitions can be influenced by the amount of water vapour surrounding the sample. Water vapour can associate with a solid in many ways, such as adsorb only on the surface, absorb deep into the bulk structure, chemisorb to the surface, act as a plasticizing agent forcing a glass transition and potentially inducing spontaneous recrystallization, or chemically react with the solid. In the case of hydrates, water is incorporated into the lattice structure, often in stoichiometric proportions. Further, a sample may form several different stoichiometric hydrate species, depending on the conditions surrounding the sample. Also, hydrates are typically only stable over well defined humidity and temperature environments.

The ultimate hydration state of a material may influence several physicochemical properties including physical and chemical stability. The hydration state of crystalline substances is of particular concern in the pharmaceutical industry [1]. 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 pharmaceutical actives are capable of forming crystalline hydrates [2]. For these reasons above, there has been increased regulatory pressure to fully characterise and control the physical form of excipients and active drugs [3]. This paper describes how the DVS can be used to detect and characterize hydrate formation as a function of environment relative humidity.

Theory

An isotherm describes the equilibrium vapour uptake as a function of vapour partial pressure. If a material forms a stoichiometric hydrate species at distinct vapour pressures, then the corresponding equilibrium uptake and resulting isotherm can be used to calculate the stoichiometry of the hydrated species. To illustrate, consider an anhydrous material, Sample A with molecular weight, MW. If Sample A forms a hydrated species at a particular vapour partial pressure, then the percentage weight gain





at that partial pressure, WG, can be used to calculate the stoichiometry, S, of the hydrate as in equation (1) below:

$$S = \frac{WG}{100\%} \times \frac{MW}{18.01 amu / watermolecule} = HydrateStoichiometry \quad (1)$$

The above equation assumes formation of a stoichiometric, or true hydrated species. Similar analysis could be applied for solvate stoichiometries. Simply replace the molecular weight of a water molecule (18.01 amu) with the molecular weight of the vapour used.

Method

Dynamic vapour sorption (DVS) is a well-established method for the determination of vapour sorption isotherms. The DVS instrument used for these studies measures the uptake and loss of vapour gravimetrically using a SMS ultra-balance with a mass resolution of ±0.1 µg. The high mass resolution and excellent baseline stability allow the instrument to measure the adsorption and desorption of very small amounts of probe molecule. The vapour partial pressure around the sample is controlled by mixing saturated and dry carrier gas streams using electronic mass flow controllers. The temperature is maintained constant ±0.1 °C, by enclosing the entire system in a temperature-controlled incubator.

Naloxone HCl, a well-characterized drug used to prevent or reverse the effects of narcotic pain relievers, was used as a model hydrate-forming pharmaceutical material. Naloxone HCl can be obtained from Aldrich as a dihydrate species with the following molecular formula: $C_{19}H_{21}NO_4 \cdot HCl \cdot 2(H_2O)$; atomic weight 399.88 amu. The dihydrate species was placed into the DVS sample pan and dried under a stream of dry nitrogen at 25 °C. Then, the humidity was increased in 10% RH steps to 90% RH. Finally, the humidity was decreased in a similar fashion for the desorption phase.

The hydrate formation/loss for nedocromil sodium, a common drug used to inhibit the activity of inflammatory cells associated with asthma, was also studied using the DVS. Nedocromil sodium ($C_{19}H_{15}NO_7Na_2$; 415.29 amu) is known to have a number of hydrate states including a monohydrate, trihydrate, and heptahemihydrate [4]. At 22 °C and 50% RH (approximate ambient conditions) nedocromil sodium exists as a trihydrate species, but will lose two water molecules to form a monohydrate species below 6% RH at 22 °C. Above 80% RH at 22 °C, nedocromil sodium will form a heptahemihydrate species and finally form a solution above 90% RH [4]. For the DVS experiments, the trihydrate species was placed in the pan at 0% RH and 25 °C under a stream of dry nitrogen followed by 10% increasing humidity steps to 90% RH, plus a final 95% RH step. The humidity was then decreased in a similar fashion for the desorption phase.

Results

Naloxone HCL

The moisture sorption kinetics for the Naloxone sample over the 0 to 90% RH range are displayed in Figure 1. The red line traces the percentage change in mass (based on the dry value) as a function of time, while the blue line traces the relative humidity as a function of time. The corresponding isotherm is shown in Figure 2, where the red line follows the sorption phase and the blue trace follows the desorption phase.

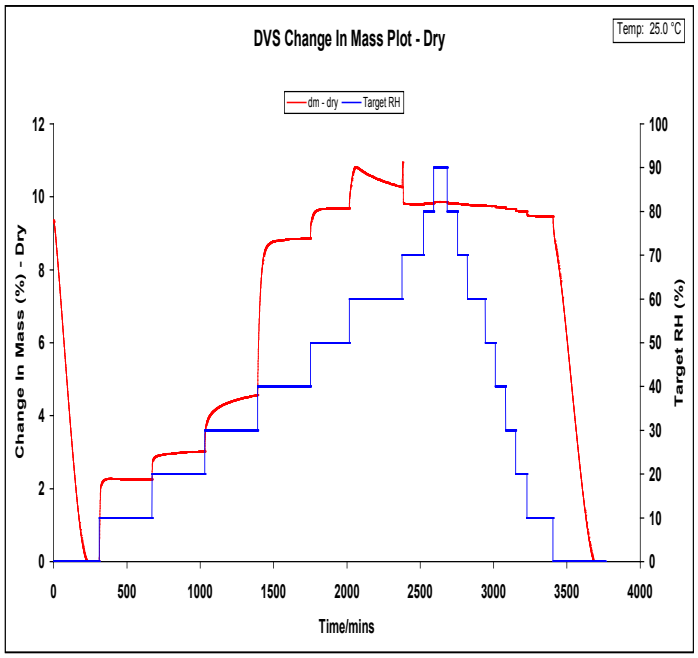

Figure 1. Water sorption kinetics for a naloxone HCl dihydrate sample at 25.0 °C.

During the initial drying stage, the sample loses approximately 9.6% of its dry mass weight. naloxone HCl dihydrate has a molecular weight of 399.88 amu. If the sample was to lose its two water molecules (36.02 amu), this would represent a 9.9% weight loss (based on dry value, 363.86 amu). Therefore, the sample most likely loses its two water molecules upon drying.

As the humidity is increased up to 50% RH, the sample uptakes significant amounts of water vapour and the weight approaches equilibrium. During the 60% RH step, the sample mass initially increases, but then steadily decreases. This phenomenon is even more dramatic during the 70% RH step, where there is a short, initial increase followed by a sharp decrease in mass, before the mass finally reaches equilibrium. This type of behaviour is typical for a water-induced recrystallization event. Similar behaviour has been observed for amorphous lactose [5,6]. Water acts as a plasticizing agent, thus lowering the glass transition and inducing spontaneous recrystallization. The initial starting material was a crystalline dihydrate. Therefore, the evidence of this amorphous to crystalline transition at 60% RH indicates that the initial sample became amorphous when it lost the two water molecules during the drying stage. Similar behaviour has been observed for other hydrate species [1]. As the humidity is increased further to 90% RH, the sample uptakes very little water and approaches equilibrium rapidly. The fast kinetics and small uptake are indicative of surface water adsorption on the now crystalline material.

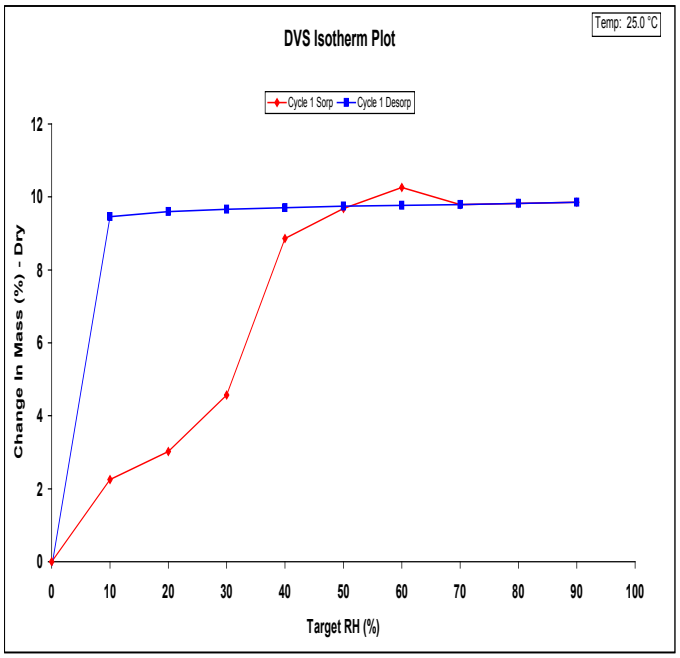

Figure 2. Water sorption (red) and desorption (blue) isotherms on naloxone HCl dihydrate at 25 °C.

During the desorption phase, there is almost no change in mass from 90% to 10% RH. Again, this is due to surface water desorption from the crystalline material. During the 0% desorption step, there is a dramatic decrease in mass and the sample mass returns to a value slightly below the initial 'dry' value. This may be due to loss of HCl during drying or moisture sorption.

The isotherms in Figure 2 show a wide hysteresis gap below 50% RH. This is often indicative of hydrate formation, where the sample will lose the water molecules at a lower RH than it gains them. Based on the uptakes we can estimate the stoichiometry of the hydrated species. At the 10% RH desorption step, the sample retains approximately 9.6% of its dry weight in water. Using equation (1) we can

estimate the stoichiometry of this hydrated species:

$$S = \frac{9.6\%}{100\%} \times \frac{363.86 amu}{18.01 amu / watermolecule} = 1.9 \quad (2)$$

As equation (2) indicates, the stoichiometry of the hydrated species at the desorption 10% RH step is 1.9, suggesting a dihydrate species. This has the same stoichiometry as the Naloxone HCl dihydrate starting material. The calculated stoichiometry is not quite an integer, which could be due to HCL loss during the sorption cycle.

Overall, the naloxone HCl dihydrate sample exhibits complex hydrate/dehydrate behaviour over the 0% to 90% relative humidity range at 25.0 °C. The sample begins as a dihydrate crystal. Upon drying, the sample loses it two hydrated water molecules and becomes amorphous. When exposed to water vapour, the sample uptakes significant water and passes through an amorphous to crystalline transformation over the 60% to 70% RH range, resulting in a dihydrate, crystalline species. During the desorption phase, the sample maintains a dihydrate stoichiometry until it is dried at 0% RH where it again loses its two water molecules.

Nedocromil Sodium

Figure 3 displays the moisture sorption kinetics for a ~5 mg sample of nedocromil sodium. As before, the red line traces the percentage change in mass (based on the dry value) as a function of time, while the blue line traces the relative humidity as a function of time. Figure 4 shows the resulting sorption (red) and desorption (blue) isotherms.

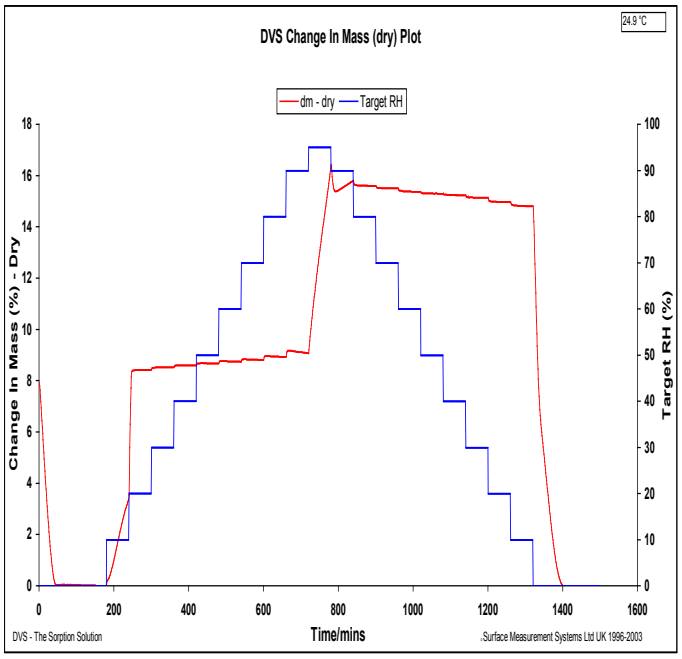

Figure 3. Water sorption kinetics for a nedocromil sodium sample at 25.0 °C.

As reported previously, nedocromil sodium trihydrate (species as loaded into the sample pan) will lose two water molecules to form a monohydrate species a low RH values. This is clearly shown during the drying stage in Figure 3. Based on the dry value for the monohydrate species (433.30 amu), two water molecules would represent an 8.3% change in mass. This value corresponds well with the approximately 8% loss in mass during the drying stage.

By 20% RH the sample sorbs approximately 8.4% of its dry, monohydrate weight in mass. Using equation (1), this mass increase corresponds to 2.0 moles of water, corresponding with the formation of the trihydrate species:

$$S = \frac{8.4\%}{100\%} \times \frac{433.30 amu}{18.01 amu / watermolecule} = 2.0 \quad (3)$$

The sample uptakes relatively little water until a large mass uptake is observed at 95% RH where there is a sharp increase in mass. The mass uptake is not completed by the end of the 1-hour, 95% RH step, as the mass has not approached equilibrium. Under these conditions, the sample is expected to form a heptahemihydrate species followed by solution formation. Because the

sample mass did not reach equilibrium any hydrate formation would not be complete.

During the desorption phase, there is little mass change as the humidity decreases to 10% RH. The sample retains approximately 14.8% of its dry mass at 10% RH. During the desorption 0% RH step, the sample loses significant amounts of water and the mass returns to the sorption 0% RH level, indicating the sample returns to the monohydrate form. Note, the trihydrate species observed during the sorption phase is not observed over the conditions studied. The resulting large hysteresis gap (see Figure 4) is characteristic of hydrate formation. The stoichiometry of this hydrate formed between 90 and 95% RH is 3.6%:

$$S = \frac{14.8\%}{100\%} \times \frac{433.30 amu}{18.01 amu / watermolecule} = 3.6 \quad (4)$$

The sample should have a heptahemihydrate stoichiometry (7.5 water molecules), but the mass did not reach equilibrium during the 90 to 95% RH step, so hydrate formation was probably not complete.

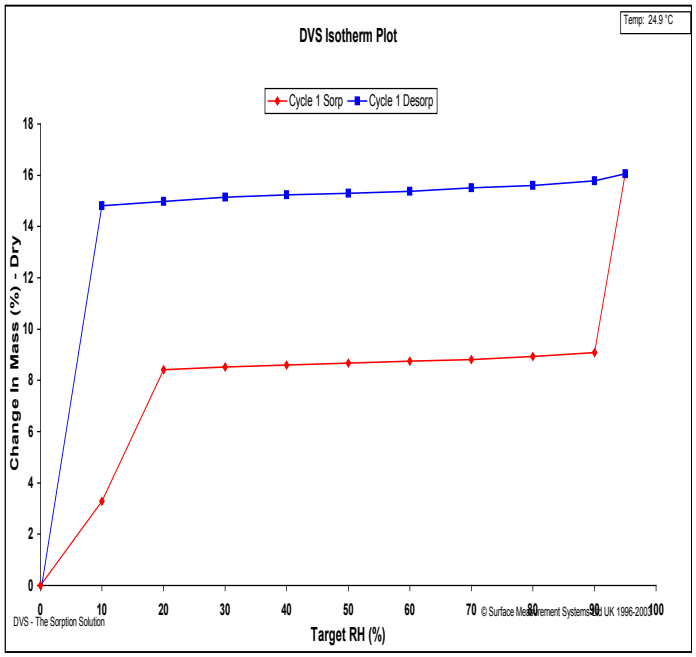

Figure 4. Water sorption (red) and desorption (blue) isotherms on nedocromil sodium at 25 °C.

Overall, the nedocromil sodium sample starts as a trihydrate species at ambient conditions. During the 0% RH drying stage it loses two water molecules forming a monohydrate species. By 20% RH, the sample returns to the trihydrate species where it remains until 90% RH. Above 90% RH, the nedocromil sample forms a higher stoichiometry hydrate species. During desorption, this hydrated species remains stable through the 10% RH step. During the desorption, 0% RH stage the sample returns to the monohydrate species.

Conclusion

Hydrate formation and loss were studied on naloxone HCl dihydrate and nedocromil sodium compounds. The samples exhibit complex hydrate/dehydrate behaviour over the conditions studied. The stoichiometry of the hydrated species were determined by the corresponding weight increases. Similar analysis could be applied to a wide range of hydrate and solvate systems. This information can give vital information for the processing and storage conditions of drugs and their excipients.

References

[1] Brittain, H.G. editor, *Polymorphism in Pharmaceutical Solids*, Marcel Dekker: New York (1999).
[2] Braimer. D.D., editor, Towards Better Safety of Drugs and Pharmaceutical Products, Elsevier/North-Holland Biomedical Press (1980).
[3] Office of the Federal Register. Q6A-Specifications. Test procedures and acceptance criteria for new drug substances and drug products: Chemical substances. Federal Register, Vol. 62. Washington, DC: Office of the Federal Register (1997) 62889-62910.
[4} Khankari, R.K., Chen, L., Grant, D.J.W., J. Pharm. Sci. 87 (1998) 1052-1071.
[5] Saleki-Gerhardt, A., Zografi, G., Pharm. Res. 11 (1994) 1166-173.
[6] Buckton, G., Darcy, P., International Journal of Pharmaceutics 179 (1999) 265-275.

Head Office:
Surface Measurement Systems, Ltd
5 Wharfside, Rosemont Road
LondonHA0 4PE, UK
Tel: +44 (0)20 8795 9400
Fax: +44 (0)20 8795 9401
Email: science@surfacemeasurementsystems.com

United States Office:
Surface Measurement Systems, Ltd, NA
2125 28th Street SW, Suite I
Allentown PA, 18103, USA
Tel: +1 610 798 8299
Fax: +1 610 798 0334