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DVS Application Note 59

# Investigation of Channel Hydrate Formation and Loss Using the DVS

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***Dynamic Vapour Sorption (DVS) allows the fast and accurate determination of channel hydrate formation and loss. Channel hydrates typically exhibit characteristic water sorption isotherm behaviour. This paper illustrates channel hydration/dehydration using an active pharmaceutical ingredient (API).***

## Introduction

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].

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. These channels can vary in size, such that they could accommodate molecules of water. Additionally, channel hydrates can be stoichiometric, as the water tunnels fill to a defined manner with the lattice structure. Alternatively, non-stoichiometric channel hydrates occur when the lattice expands continuously (but remains isomorphic) over a wide range to accommodate additional water molecules.

This paper describes how the DVS can be used to detect and characterize channel hydrate formation and loss as a function of environment relative humidity.

## Method

An investigational drug, Compound X, was used as a model API for this study. Previous Powder X-Ray Diffraction (PXRD) analysis indicated presence of a channel hydrate at elevated humidity conditions at 25 °C.

Dynamic vapour sorption (DVS) is a well-established method for the determination of vapour sorption isotherms. The DVS-Intrinsic 1 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 high precision electronic mass flow controllers.

In particular to this study, it is important to have precise humidity control over a defined range. Many channel hydrates change water content in an isomorphic fashion only over a narrow temperature and humidity range [4]. Outside of this narrow range, the structure can collapse to a different phase or exhibit a polymorphic change to a different hydrate. The humidity generation available in the current SMS line of DVS instruments allows control of RH steps down to 0.2% RH. Additionally, channel hydrates typically hydrate/dehydrate at very low humidity conditions. Therefore, it is important to have a true zero relative humidity. Current SMS DVS instruments are equipped with positive wet flow restriction to ensure a true zero relative humidity. Without such restriction, water molecules can migrate from the water reservoir into the sample area; thus, maintaining a small, but important amount of humidity into the chamber. Some hydrates are extremely sensitive to small amounts of water vapour such that they will not dehydrate unless there is virtually no water vapour present.

## Results

The moisture sorption and desorption isotherms between 0 and 95% RH for Compound X are shown in Figure 1. 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. For this sample, once the channels are filled, further water sorption is limited to surface water (i.e. monolayer and multilayer water molecules). There is very little hysteresis between sorption and desorption isotherms. Hysteresis is almost negligible below 10% RH. In all, the resulting isotherm shape, has strong Langmuir behaviour (i.e. Type I isotherm). These isotherm characteristics are also often observed in vapour/gas sorption on rigid microporous materials (i.e. activated carbons, zeolites, and metal organic frameworks). Together, these results support the presence of a channel hydrate, which is fully hydrated by 15% RH.

Similar behaviour has been observed for other channel hydrates. For instance, the sodium salt of N-(3-aminosulfonyl)-4-chloro-2-hydroxyphenyl)-N'-(2,3-dichlorophenyl) urea contains 3 mol of water located in distinct channels of the sodium cation [4]. This material exhibited a similar water sorption profile to that in Figure 1. The confirmation of the structure of this channel hydrate was supported by complimentary thermal analysis, variable-RH PXRD, vibrational spectroscopy, and NMR analysis. Further, Cefaclor and Celiprolol HCl [5] had water sorption isotherms that exhibited strong Langmuir behaviour which was attributed to formation of channel hydrates. Finally, similar water sorption behaviour has been observed for an isomorphic clathrate of Cephalosporin [6]. The authors attributed this behaviour to the formation of a channel hydrate.

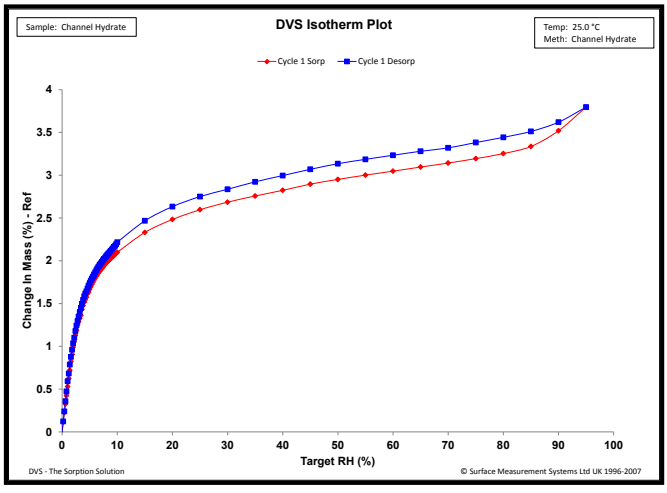


*Figure 1. Water sorption kinetics Compound X at 25.0 °C.*

Expanding the isotherm below 15 % RH shows the very low hysteresis in this range. Also, it illustrates the sensitivity of the sample with respect to small changes in humidity. The small RH steps (0.2% RH) between 0 and 10% RH

allow a more complete understanding of the water sorption properties in this range.

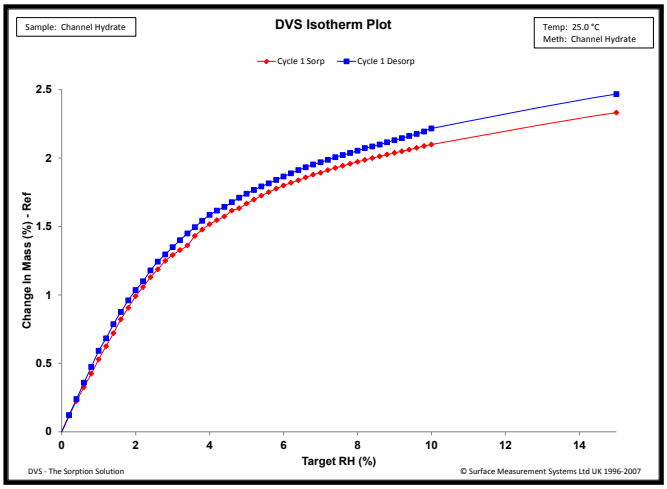


Figure 2. Expanded view of Compound X water sorption isotherm below 20% RH at 25 °C.

Also, the numerous RH steps in the pore-filling regime allow the application of different porosity isotherm models. One such model is the Dubinin-Radushkevich (DR) model [7], which is part of the SMS Isotherm Analysis Suite. The DR model allows the determination of total micropore volume. In this instance, it would yield the volume in the lattice channels. Figure 3 displays the DR analysis fit for Compound X between 0.4 and 20 % RH. The DR equation is typically only applicable to the low vapour concentration regime of the isotherm (i.e. less than 20%). Therefore, it is important to take many steps in this range to allow for accurate micropore volume determination. For Compound X, the total micropore volume was 0.0353 $cm^3/g$. For this channel hydrate, this would represent the volume of the channels, once filled with water.

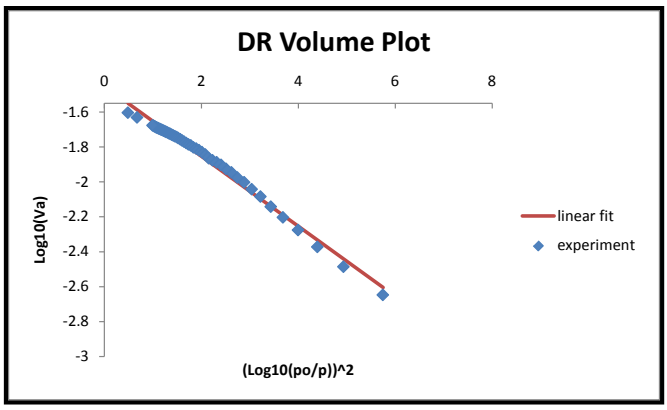


*Figure 3. DR analysis for Compound X at 25.0 °C.*

## Conclusion

Hydrate formation and loss were studied on a channel hydrate using DVS. The resulting isotherm exhibited strong Langmuir/Type I behaviour. DR analysis was used to determine a channel pore volume of 0.0353 $cm^3/g$. The ability of the DVS instruments to perform 0.2% RH steps below 10% RH and true zero RH functionality greatly enhanced the isotherm quality for these types of materials. Similar analysis could be applied to a wide range of channel hydrate and solvate systems. This information can give vital information for the processing and storage conditions of these types of drugs and their subsequent formulations.

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