ELSEVIER

European Journal of Pharmaceutics and Biopharmaceutics 51 (2001) 77–81

European
Journal of
Pharmaceutics and
Biopharmaceutics

www.elsevier.com/locate/ejphabio

Research paper

Comparison of three methods to find the vapor activity of a hydration step

Lars Wadsö[a,*], Natalia Markova[b]

[a]Division of Building Materials, Lund University, Lund, Sweden
[b]Division of Physical Chemistry 1, Lund University, Lund, Sweden

Received 27 July 2000; accepted 4 August 2000

Abstract

The formation of a stochiometric salt hydrate takes place at a well defined vapor activity. We have compared three methods to measure this vapor activity. In two of the methods we used a sorption balance in step mode and in ramp mode, respectively, and in one method we used a newly developed sorption microcalorimeter. The tests were made with the formation of morphine sulphate pentahydrate from its dihydrate at 25°C. With all three methods this transition was found to take place at a vapor activity close to 0.21. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Morphine sulphate; Water vapor; Sorption; Sorption balance; Microcalorimetry; Hydrate formation

1. Introduction

Many salts, both inorganic and organic, form stoichiometric hydrates, i.e. they take up well defined integer molar ratios of water. As an example, copper sulphate has an anhydrous form and three different hydrates: a monohydrate, a tri-hydrate and a pentahydrate [1]. At constant temperature the change from one of the hydrates to another takes place at well defined vapor activities a_{hyd}. At low water activities copper sulphate will take up one water to become a monohydrate and at a_{hyd} close to 0.22 and 0.33 the tri-hydrate and the pentahydrate will be formed. At even higher vapor activities, above $a \approx 0.97$ for copper sulphate, the deliquescence point is reached and the salt will dissolve.

A common way to study hydrates is by thermal analysis; usually thermal gravimetric analysis (TGA). When a fully hydrated salt is exposed to increasing temperatures it will loose the hydration waters at different temperatures. This is a simple way of finding which hydrates exist and it also gives information about at which temperatures a salt need to be dried to attain a certain hydrate form.

Most hydration processes during the development, production, storage and use of pharmaceutics take place at close to isothermal conditions. It is therefore advantageous to use isothermal methods to study hydration behavior when this is kinetically possible. With the isothermal methods described in this paper we try to assess the vapor activity of the hydration step, i.e. the equilibrium vapor activity of the two-phases system consisting of the two hydrate forms.

The measurements presented in this paper were made on morphine sulphate which has a dihydrate and a pentahydrate form. According to Merck index [2] morphine sulphate‘ ‘looses some H_2O at ordinary temperatures; about $3H_2O$ at 100°C, the remainder at 130°C’. In an earlier paper [3] we reported on a study on morphine sulphate hydration by a sorption calorimetric method. In this paper we use morphine sulphate as a test substance when we compare three different methods to evaluate the activities of hydration steps.

2. A note on nomenclature

In this paper we use relative water vapor activity (a) to describe the hygroscopic moisture state of a substance and relative humidity (ϕ) to describe the moisture state of a gas. Under the temperature and pressure conditions used (25°C, 1 atm) the relative humidity of a gas phase and the activity of a substance in equilibrium with the gas phase will for all practical purposes have the same numerical values. Both activity and relative humidity are expressed as ratios (not percent).

3. Methods

3.1. Lund sorption microcalorimeter

We have developed a sorption microcalorimeter [4] with

---

[*] Corresponding author. Department of Building Materials, Lund University, Box 118, 22100 Lund, Sweden Tel.: +46-46-2229592; fax: +46-46 2224427.

E-mail address: lars.wadso@byggtek.lth.se (L. Wadsö).

0939-6411/01/$ - see front matter
PII: S0939-6411(00)00134-X

which one may simultaneously measure both continuous sorption isotherms and continuous sorption enthalpies from dry conditions to $\phi = 0.97$. In this method a 20–100 mg sample is placed in a small chamber which is connected by a tube to another small chamber into which water is injected. The water will evaporate and by Fickian diffusion be transported through the tube to the sample chamber where it will be absorbed (adsorbed) by the sample. The rate of diffusion is limited by the tube geometry. An experiment that takes the sample from dry conditions to high relative humidities will take one or two days. During the whole experiment the thermal powers of vaporization in the water chamber and absorption in the sorption chamber are measured separately. From the thermal power of vaporization as a function of time the sorption isotherm may be calculated and from the thermal power of sorption the enthalpy may be found.

The double twin microcalorimeter [5] used was developed from a TAM microcalorimeter (Thermometric, Järfälla, Sweden). It is calibrated electrically and the mass flow resistance through the system is found from experiments with water in one chamber and a drying agent in the other.

This method has the advantage of giving almost continuous absorption isotherms from dry conditions to high relative humidities. This makes it possible to accurately determine the vapor activity of en event like hydrate formation. In comparison, with the commonly used technique with exposure over saturated salt solutions one often measures only five points on an isotherm and this is not enough to determine the vapor activity of hydrate formation.

3.2. DVS ramp method

The DVS (Surface Measurement Systems, London, UK) is a sorption balance in which the mass of a small sample is measured with an analytical balance while it is exposed to a programmed relative humidity. One way to find the vapor activity with such an instrument is to ramp the relative humidity and look for the activity at which the mass starts to change. If only one ramp is made it will, however, be difficult to assess the activity of hydration (a_{hyd}) because there is no well defined starting point of the mass change. Here, we have instead made one absorption run and one desorption run and then mirrored the desorption graph in different relative humidities (ϕ) until it overlapped the absorption curve (cf. Fig. 3 in Section 4). Then $a_{\mathrm{hyd}} = \phi$. The relative humidity scan rate $\mathrm{d}\phi/\mathrm{d}t = 0.00333$ 1/min.

In the DVS the relative humidity of the gas stream is controlled by two mass flow controllers for dry and saturated gas, respectively. These mass flow controllers are stable and provide good repeatability. In connection with the experiments we ran two validations in which the relative humidity was slowly ramped passing the deliquescence points of LiCl and $MgCl_2$, respectively. This is a good way of checking the equipment because these deliquescence points are well known (0.113 and 0.328, respectively, at 25°C). We found that the true relative humidities were 0.010 and 0.012 higher than the set target relative humidities of the instrument and have therefore added 0.011 to all DVS target relative humidities. It should be noted that this is a standard procedure to calibrate the DVS. In the DVS gas streams the relative humidities are measured, but this is only used as a check of the instrument; the relative humidity sensors are not used to control the instrument.

3.3. DVS step method

A second way to use the DVS is to make step changes in the relative humidity and when a_{hyd} is passed a mass increase is measured. However, by itself this is not a good way to find a_{hyd} as it cannot be found with greater accuracy than the size of a step (and sometimes not even that). Here we have instead evaluated the mass change rates during a series of different steps past a_{hyd} with the same sample. In the DVS the sample is placed in a glass pan which is suspended from the balance in a glass tube through which the humidified gas flows. For each such arrangement of pan, sample and gas flow the mass change rate of the sample $\mathrm{d}m/\mathrm{d}t$ (which equals the mass flow rate between the gas stream and the sample) is related to the difference between the relative humidity of the gas stream (ϕ_{gas}) and the activity of the sample surface (a_{surf}) by

$$\frac{\mathrm{d}m}{\mathrm{d}t} = K(\phi_{\mathrm{gas}} - a_{\mathrm{surf}}) \tag{1}$$

Here, K (g/s) is a mass transfer coefficient that is constant for each experiment. This equation will hold as the only resistance to mass flow between the gas stream and the sample surface is the flowing gas which remains at a dynamic steady-state (cf. boundary layer theory). A rough estimate of $K = 1$ mg/min may be made by calculating the mass transfer coefficient of water vapor over a stagnant boundary layer of 5 mm air and through 100 mm^2 area (the approximate surface area of the sample).

During at least the first part of a relative humidity step that passes a_{hyd}, a_{surf} will equal a_{hyd}, so from a plot of $\mathrm{d}m/\mathrm{d}t$ against a_{gas} it will be possible to find a_{hyd}. In practice $|\mathrm{d}m/\mathrm{d}t|$ will decrease during a step as the upper part of a sample will be hydrated and then present a mass flow resistance to the vapor hydrating the lower parts of the sample. In our evaluation we have therefore used the maximum $|\mathrm{d}m/\mathrm{d}t|$ at the beginning of each step when the sample surface is still absorbing or desorbing.

The method will not work if the sample is changed between runs as it is probable that K will then also change. It is also important that one does not pass the deliquescence point as the morphology of the sample then will change drastically. For morphine sulphate the deliquescence point is above $a = 0.95$ and we never went above $\phi = 0.42$ in the

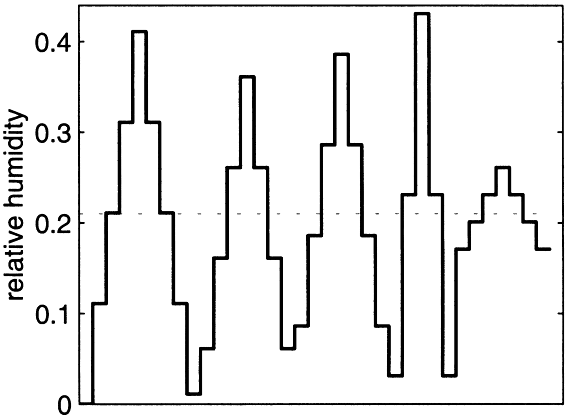

Fig. 1. The relative humidity program used for the DVS step method.

experiments. There was no visible changes in the sample during the runs.

The relative humidity program for the experiment is given in Fig. 1. The relative humidity passed a_{hyd} ten times and at each of these there was absorption or desorption from which we have determined the maximal mass change rate. The next step was made when the mass change rate $|dm/dt| < 0.002$ mg/min after a minimum of 10 min at each level, or after 10 h at the same relative humidity. The relative humidity was corrected in the same way as described for the DVS ramp method above.

4. Material

A fine powder of morphine sulphate (99.6% pure, Macfarlan Smith, Edinburgh, UK) was used in the present experiments. Before the measurements with the sorption microcalorimeter the morphine sulphate was dried in vacuum at 100°C for 2 days. It was then present in its anhydrous form at the start of the measurement. In the DVS measurements the sample was dried in the instrument in dry nitrogen at 25°C as part of the relative humidity programs. This milder drying did not remove the last two waters from the morphine sulphate, so the DVS measurements started with the dihydrate.

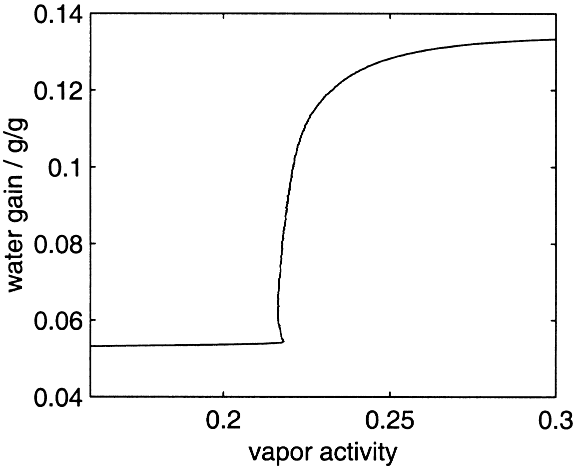

Fig. 2. Detail of the sorption isotherm measured with the sorption microcalorimeter. Note that the measurement started with an anhydrous sample.

5. Result

5.1. Lund sorption microcalorimeter

Fig. 2 shows the sorption isotherm calculated from the result of a run with the sorption calorimeter. The hydration step is not a perfect step because of the dynamic nature of the method. At the beginning of the step there is a slight overshoot that may reflect a delayed start of the sorption. Later the calculated activity increases gradually as the internal resistances in the sample increases (the water vapor has to diffuse through the already hydrated top part of the sample). The lowest calculated activity during the hydrate formation should be closest to the true value of the hydration activity. It was found to be $a_{\mathrm{hyd}} = 0.216$.

5.2. DVS ramp method

Fig. 3 shows the result of one absorption ramp and one desorption ramp past the activity of interest. Because of the time lag in the sorption there is not much sorption at a_{hyd} (the vertical dotted line in the figure). When the desorption graph is mirrored in $a = 0.207$ the resulting curve overlaps the absorption curve. As we expect the absorption and desorption processes to be each other's mirror images this gives us $a_{\mathrm{hyd}} = 0.207$ with the ramp method.

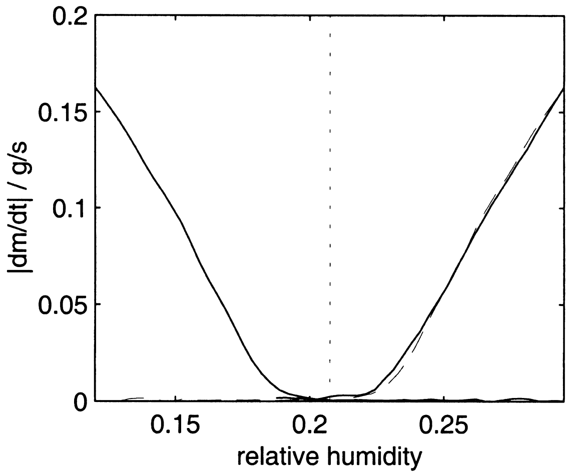

Fig. 3. The rate of mass change during the DVS ramp measurements plotted against the gas stream relative humidity. The absorption graph starts at low values on the left and then rises to the right; the desorption graph starts on the right with low values and then rises to the left. The dashed line is the desorption graph mirrored in the dotted line (0.207).

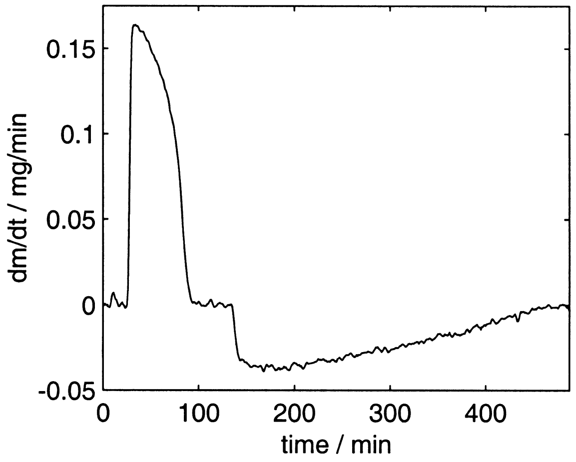

Fig. 4. Part of the results from the measurement with the DVS step method which shows the mass change rate during the steps 0.186 → 0.286 and 0.286 → 0.186.

5.3. DVS step method

The relative humidity program (Fig. 1) was constructed so that the relative humidity would pass a_{hyd} ten times at different $\phi_{\mathrm{gas}} - a_{\mathrm{surf}}$. Fig. 4 gives as an example the mass change rate during the relative humidity steps from 0.186 to 0.286 and from 0.286 to 0.186. The maximum of the peak up and the minimum of the peak down shown in this figure were used together with the other eight peaks to construct Fig. 5. From the linear regression line in Fig. 5 the relative humidity at zero mass flow change rate was found to be 0.210. Thus, $a_{\mathrm{hyd}} = 0.210$. From the slope of Fig. 5 we have also calculated an approximate value of $K = 2$ mg/min that is in good agreement with the rough estimate of $K = 1$ mg/min given above.

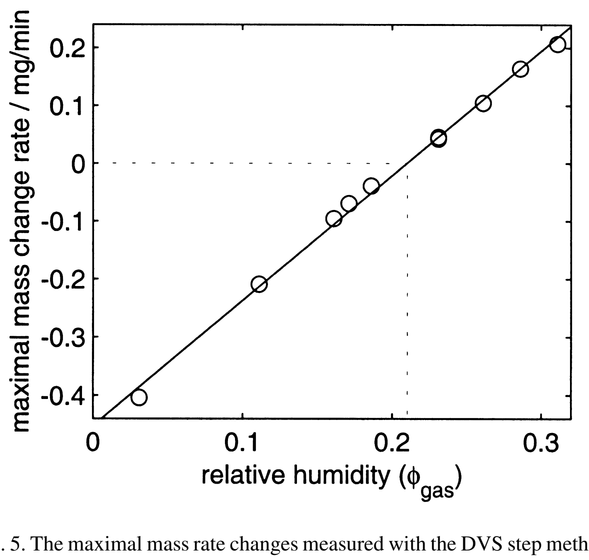

Fig. 5. The maximal mass rate changes measured with the DVS step method plotted as a function of the gas stream relative humidity. The relative humidity at zero mass rate change is the hydration activity (0.210).

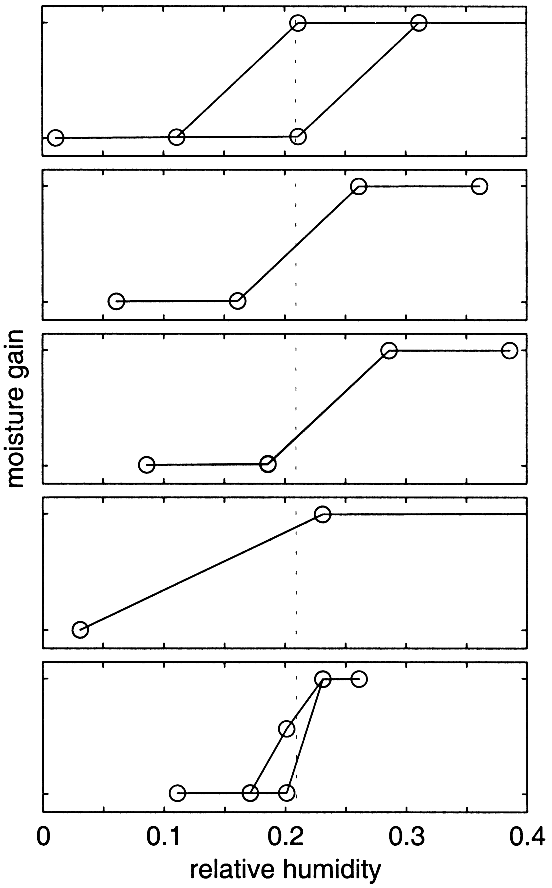

Fig. 6. The sorption isotherms calculated from the measurements made with the DVS in step mode (cf. Fig. 1).

6. Discussion

The three methods gave a_{hyd}:s of 0.216, 0.207 and 0.210. The closeness of the results suggests that all methods are useful for measuring hydration step activities.

Fig. 6 shows the five isotherms calculated from the DVS step method result. In the second, third and fourth isotherms no hysteresis is seen, just as expected for hydrate formation. In the top isotherm, however, a marked hysteresis is seen resulting from the absorption isotherm not going up when the relative humidity of the gas stream is increased to a value above a_{hyd}. The reason is that the gas stream relative humidity is just a little higher than a_{hyd}, so the mass change rate quickly becomes insignificantly low, both with respect to the $|dm/dt|$-criterion of 0.002 mg/min and the mass change of the sample before the DVS changes to a new relative humidity. In the top isotherm in Fig. 6 $\phi_{gas} - a_{hyd} = 0.002$, and this only gives a maximum mass change rate of 0.004 mg/min (Eq.(1)) which in a short time drops below the equilibrium criterion used in the present measurements (0.002 mg/min). A lower dm/dt-criterion may be used, but this will give longer measurement times.

The last isotherm in Fig. 6 shows a similar situation, but here $\phi_{gas} - a_{hyd} = 0.008$ for the first desorption step that passes a_{hyd}. This is high enough for the $|dm/dt|$-criterion not to be fulfilled until after 10 h. During this time half the water of the hydration was taken up. In the evaluation the second sharper peak resulting from the next step was used. This worked well because, as the sample was desorbing so slowly, there was no pronounced gradient in the sample and the surface remained at essentially a_{hyd} until the start of the next step. During the other steps $|\phi_{gas} - a_{hyd}|$ was equal to or higher than 0.024, which was high enough for essentially the whole sorption step to be completed before $dm/dt < 0.002$ was fulfilled.

We have tested the three methods on morphine sulphate which readily absorbs and desorbs water vapor as it changes between its dihydrate to pentahydrate forms. For other salts the sorption processes may be kinetically hindered and extremely slow at low temperatures. The tested methods will then not work as well. We have for example used the above methods without success on copper sulphate which is known to remain in non-equilibrium hydrate forms for long periods of time.

7. Conclusions

The three methods tested for determining the vapor activity of a hydration step gave the same result for the morphine sulphate dihydrate-pentahydrate equilibrium of 0.21. The closeness of the results suggests that all three methods are useful for measuring hydration step activities.

Acknowledgements

We thank the Swedish Building Research Council and the Troëdsson Research Foundation for their support (LW).

References

[1] Gmelin Handbuch. Der Anorganischen Chemie, Verlag Chemie, Weinheim, 1958, Teil 60, Kupfer B1, p. 592.

[2] The Merck Index, Merck Research Laboratories, Whitehouse Station, NJ, USA. 1996.

[3] L. Wadsö, N. Markova, A microcalorimetric study of water vapor sorption on morphine sulphate, J. Thermal Anal. 57 (1999) 133–137.

[4] I. Wadsö, L. Wadsö, A second generation twin double microcalorimeter for measurements of sorption isotherms, heats of sorption and sorption kinetics, J. Thermal Anal. 49 (1997) 1045–1052.

[5] L. Wadsö, N. Markova, A double twin isothermal microcalorimeter, Thermochim. Acta. 360 (2000) 101–107.