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A MICROCALORIMETRIC STUDY OF WATER VAPOR SORPTION ON MORPHINE SULPHATE

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Abstract

Water vapor sorption on morphine sulphate was studied in a twin double sorption microcalorimeter at 25°C. The vapor sorption isotherm and the differential heats of sorption were determined simultaneously from dry condition to a water activity of 0.99. Two well resolved hydration steps were obtained on the sorption isotherm at water activities of 0.01 and 0.22 corresponding to the formation of dihydrate and pentahydrate of morphine sulphate. They were accompanied by constant values of the differential heats of sorption: -24 kJ mol^{-1}(H_2O) for the dihydrate formation and -10 kJ mol^{-1}(H_2O) for the pentahydrate formation.

The calorimetrically obtained sorption isotherms were compared with the results of Karl Fisher titrations of morphine sulphate samples equilibrated at different water activities. The appearance of a liquid phase in the morphine sulphate at high water activities is discussed on the basis of the obtained differential heats of sorption and measured heat capacities of morphine sulphate at different water activities.

Keywords: differential heat of sorption, microcalorimetry, morphine sulphate, sorption isotherm

Introduction

Sorption of water vapor by solid compounds may influence their physical and chemical properties such as density, crystal structure, heat capacity, solid state reactivity and rate of dissolution. Stability and performance of pharmaceuticals may be strongly affected by hydration [1, 2].

A number of methods have been developed for studying water vapor sorption and for characterizing hydrates [2]. However, for a better understanding of the hydration process, methods are needed by which both vapor sorption isotherms and differential heats of sorption may be obtained simultaneously. In the present work, water vapor sorption of morphine sulphate, an extensively used pharmaceutical, was studied by such a method.

Methods and materials

A twin double sorption microcalorimeter [3, 4] was used to study water vapor sorption of morphine sulphate. The calorimetric cell consists of two vessels con-

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nected by a steel tube. At the start of the measurements the bottom vessel contains 100 μl of water and the top vessel 50–200 mg of a dry sample. During the measurements water vaporizes in the bottom vessel and diffuses through the tube to the top vessel where it is sorbed by the sample. The thermal powers of vaporization and sorption are measured simultaneously and separately in the double calorimeter. The method allows for simultaneous determination of vapor sorption isotherms and differential heats of sorption. It provides a continuous monitoring of near equilibrium moisture uptake in a broad range of water activities.

A fine powder of morphine sulphate $(C_{17}H_{19}NO_3)2H_2SO_4$ (M_w= 668.77 g mol^{-1}, 99.6% pure, Macfarlan Smith Ltd., Edinburgh, LTK) was used in the present experiment. According to the Merck Index (1996) morphine sulphate has a pentahydrate form under normal conditions and it looses about three water molecules at 100°C and the rest at 130°C.

For the sorption measurements the samples were dried at 100°C in vacuum for 40 min and then kept under vacuum for one day at room temperature. Charging of the cell with the sample was carried out in a glove bag (Instruments for Research and Industry, Cheltenham, PA, USA) purged and inflated with dry nitrogen (relative vapor pressure less than 0.02%). Two sorption measurements were made with 66.33 and 54.32 mg of dry morphine sulphate, respectively.

Solid morphine sulphate samples for Karl Fisher titrations (20–40 mg) and for heat capacity measurements (90–100 mg) were equilibrated at 25±1°C for two weeks in tightly closed jars over saturated salt solutions (LiCl, $CaBr_2$, CH_3COOK, $MgCl_2$, K_2CO_3, $(NH_4)_2SO_4$, $C_7H_5O_2Na$, K_2SO_4). The samples with the highest water activity of 0.99 were taken directly from the calorimetric sorption cell at the end of a sorption measurement. The conditioned samples were then titrated in a Karl Fisher titration unit without diaphragm (Metrohm, Switzerland) to obtain absolute values of water content. Salts for the conditioning of the samples were of analytical pure grade and provided relative vapor pressures constant within less than 2% in the temperature range from 20 to 30°C [5, 6].

The heat capacities of the morphine sulphate samples at 25°C were measured in a drop calorimeter [7]. During a measurement the sample in a steel ampoule was first equilibrated in the ‘furnace’ at 30°C and than dropped into the calorimeter kept in a water bath thermostated at 20°C.

Results and discussion

Sorption isotherms

Two well resolved vertical steps were obtained on the vapor sorption isotherms at water activities of 0.01 and 0.22 (Fig. 1). The first step corresponds to the formation of morphine sulphate dihydrate stable within 0.01–0.22 water activity range. The slight slope observed at the first vertical step of the isotherm may be a result of the water activity gradient over the sample; the moisture uptake takes place at slightly different time in different parts of the sample. The second vertical step is the transition to the pentahydrate form. The number of moles of water per mole of morphine sulphate was calculated as 1.95 and 4.95 for the dihydrate and pentahydrate, respectively.

The water activities close to 0.99 corresponds to the appearance of a liquid phase in the crystalline sample. This two-phase system is comprised of pentahydrate of morphine sulphate and its saturated aqueous solution.

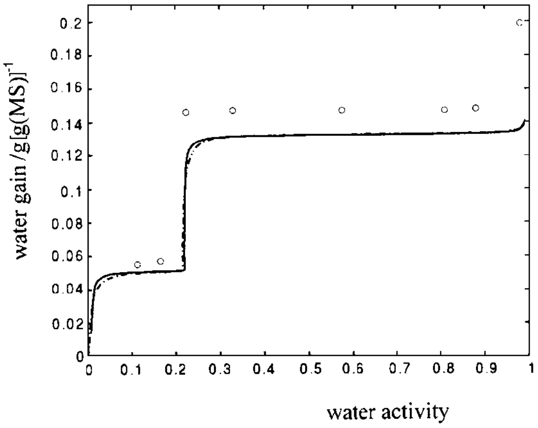

Fig. 1 Sorption isotherms of morphine sulphate (MS) at 25°C: 66.33 mg sample (solid line); 54.32 mg sample (dashed line); Karl Fisher titration data (circles)

Calorimetrically obtained sorption isotherms were compared with the results of Karl Fisher titration of the solid morphine sulphate samples (Fig. 1). The shape of the isotherm was reproduced although Karl Fisher titration gave higher absolute values of the amount of water in morphine sulphate (2.1 and 5.4 moles of H_2O per mole of morphine sulphate for the dihydrate and pentahydrate, respectively). The short time (10–20 s) of exposure of the titration cell to the ambient conditions could not

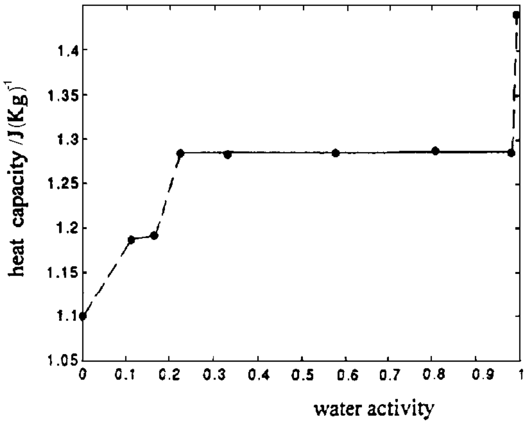

Fig. 2 Heat capacity of morphine sulphate at 25°C *vs.* water activity

account for such a deviation. It could be a result of a poor solubility of morphine sulphate in the Karl Fisher solution or a side reaction. Morphine sulphate precipitate was observed on the anode at the end of the measurements and the Karl Fisher solution was slightly brown. This could be an indication that the method is not suitable for quantitative determination of water in morphine sulphate.

Heat capacity isotherm

The heat capacity isotherm of the morphine sulphate was obtained in the water activity range from 0 to 0.99 (Fig. 3). The heat capacity was fairly constant at the water activities corresponding to the stability ranges of the two pseudopolymorphs. The heat capacity of the dihydrate (1.191 J K^{-1} g^{-1}) is lower than that of the pentahydrate (1.285 J K^{-1} g^{-1}). A pronounced increase in the heat capacity was observed at 0.99 water activity.

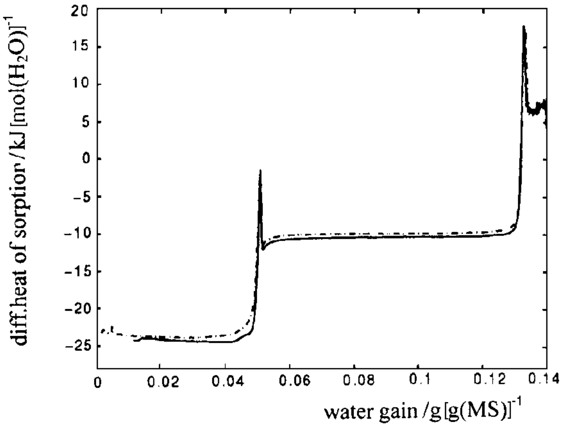

Fig. 3 Differential heat of sorption of water vapor on morphine sulphate (MS) *vs.* water gain: 66.33 mg sample (solid line); 54.32 mg sample (dashed line)

The heat capacity is affected by the state and the amount of the water in the sample. When the water content increases the heat capacity goes up. The pronounced increase of the heat capacity observed at 0.99 water activity is certainly caused by the appearance of a liquid phase in the system which is consisting of saturated solution of morphine sulphate in addition to the bound water in the pentahydrate.

Differential heats of sorption

The differential heat of sorption is referred to the liquid state of pure water. Thus, the heat of condensation is subtracted from the values of the heat measured at the sorption side of the calorimeter. The hydration steps observed on the sorption isotherm of morphine sulphate are characterised by constant differential heats of sorption, –24 kJ $mol^{-1}(H_2O)$ for the dihydrate and –10 kJ $mol^{-1}(H_2O)$ for the pentahydrate (Fig. 3), which is also an indication of the stability of the two hydrates.

Reproducible peaks are observed on the plots of differential heats of sorption *vs*. water gain at the end of the dihydrate and pentahydrate regions. The peak at 0.22 water activity could be caused by the recrystallization of the dihydrate and the peak at 0.97 water activity could be an artifact caused by the water condensation.

The differential heat of sorption for the formation of morphine sulphate pentahydrate is less exothermic than that for the dihydrate formation. Further vapor sorption by the pentahydrate is accompanied by a change in the sign of the differential heat of sorption. The endothermic differential heat values suggest the appearance of a liquid phase in the system. Hence, the heat measured at high water activities cannot be regarded as heat of sorption only, but rather as an effective value of a complex process including sorption and dissolution.

Conclusions

Reproducible sorption isotherms and differential heats of sorption were obtained by a new sorption microcalorimetric technique. Formation of two hydrates of morphine sulphate was observed. The phase transitions take place at 0.01 water activity from the anhydrous form to the dihydrate and at 0.22 water activity from the dihydrate to the pentahydrate. The dihydrate and pentahydrate formations are characterized by differential heats of sorption of –24 kJ $\text{mol}^{-1}(H_2O)$ and –10 kJ $\text{mol}^{-1}(H_2O)$, respectively.

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