Journal of Thermal Analysis and Calorimetry, Vol. 64 (2001) 731–738

CHARACTERIZATION OF LACTOSE POWDER SURFACES BY ISOTHERMAL MICROCALORIMETRY

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Abstract

Several lactose samples containing various amounts of amorphicity were studied with an isothermal microcalorimetric technique, which allow to detect the heat and the quantity of water sorption simultaneously. As interaction with vapor is characteristic of different surfaces, the samples were easy to be discriminated from each other by studying sorption behavior. With the crystalline lactose samples, the amount of sorbed water was too minor to be detected reliably with the technique, but differences were found when the energy values (J g^{-1}) were compared. In the future work, the measurement set-up will be improved so that sorption rates less than 0.1 nmol s^{-1} can be measured repeatably and reliably.

Keywords: isothermal microcalorimetry, lactose, molar sorption enthalpy, water sorption

Introduction

A few devices have been developed to measure the heat of sorption [1, 2] simultaneously with the amount of sorption [3, 4] with an isothermal microcalorimeter. A drawback of the twin double microcalorimeter introduced by Wadsö and Wadsö is that the sorption process cannot be manipulated from outside the calorimeter, but the progression of sorption is controlled by the diffusion of the vapor from the vaporization vessel to the sorption vessel. The partial pressure of the vaporized gas in the sample vessel is calculated according to the Fick's law. However, these techniques are sensitive tools to monitor dynamic changes in the sample caused by, e.g., humidity [5] and find out batch-to-batch variations in materials which are known to cause production problems by detecting solid surface energetics [6].

Corresponding calorimetric methods have been used in studying surface sites of silicon and zinc oxides [7], clays, carbon and zeolites [8], adsorption of water vapor on active carbons [9], adsorption of potassium gold cyanide from water to active carbons, graphites and carbon blacks [10], surface properties of gallium and tin oxides supported on alumina or titania [11], acid character of metal ion loaded zeolite and silica-alumina samples [12] and acid/base properties of oxide supports modified by additive ions [13], just to mention some latest publications. Most of these studies

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1418–2874/2001/ $ 5.00

Akadémiai Kiadó, Budapest
Kluwer Academic Publishers, Dordrecht

have been made in a gas phase where the adsorbed amounts have been measured by a volumetric line equipped with a differential pressure gauge (static conditions) or by a downstream detector (flow-through method). Both of these methods allow to perform adsorption-desorption cycles and thus the reversibility of the processes under study can be checked.

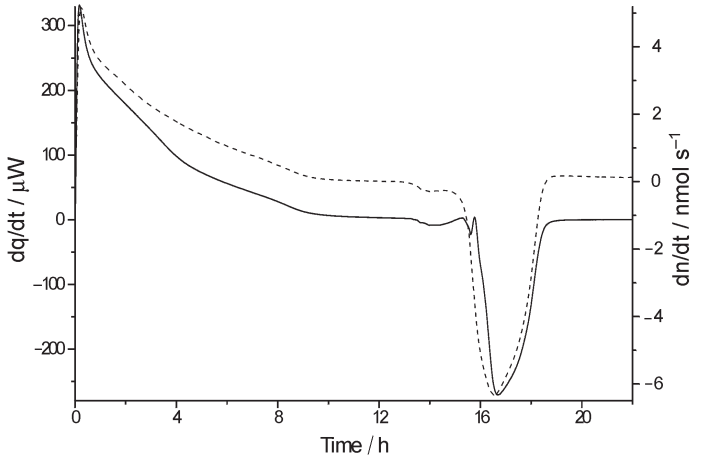

Fig. 1 Heat flow signal (solid line) and sorption rate (dashed line) for the recrystallization of amorphous lactose when the relative humidity of the air flow is raised from 0 to 54% RH at 25°C

However, with the later mentioned flow method the detection of small amounts of adsorbed vapor is limited and thus difficulties in investigation, e.g., of water adsorption on hydrophobic low surface area samples may arise. As microcalorimeter is a sensitive tool to measure the heat accompanied in the sorption processes, applying a microcalorimeter also in the quantitative determination of sorption would be attractive. In our previous work, a microcalorimetric technique to detect water sorption enthalpies and sorption uptakes simultaneously was introduced [14] and used to study, e.g., processes involved in recrystallization of amorphous lactose. The study showed the distinct phases of the recrystallization process revealing that right after the recrystallization takes place in the first particles the sample starts to expel water the processes being parallel for most of the time of the recrystallization (Fig. 1). In the present work, the same technique is tested in characterization of surfaces of lactose samples containing various amounts of crystallinity.

Experimental

Spray drying

α-Lactose monohydrate (Pharmatose b.v., the Netherlands) passed through a 325 mesh sieve was used as the starting material to prepare samples containing various degrees of amorphism. Spray drying was chosen as the preparation method since it is

well known and widely used method in the pharmaceutical industry to produce small spherical particles, which may be partially or totally amorphous depending on the drying conditions. Spray drying was performed using a Büchi Minispray Dryer 190 (Büchi Laboratorium-Technic AG, Switzerland) from a water/ethanol solution or suspension containing 15% mass/mass lactose. When the ethanol concentration in the feed solution was changed, samples with crystallinity between 0 and 100% were obtained. The samples used in the present study were prestored for at least eight months in a silica desiccator at room temperature prior to the measurements. The values for crystallinity were also determined for those samples.

Surface area measurements

The BET surface areas were measured with a TriStar 3000 (Micromeritics, Norcross, USA) instrument as a single determination of eight-point measurement using partial pressure of nitrogen between 0.06–0.20 p/p_0.

Gravimetric hygroscopicity

The HMA apparatus (PuuMan OY, Finland) used for gravimetric hygroscopicity measurements has been described elsewhere [15]. The humidity to which the samples were exposed was produced with saturated salt solutions. The temperature of the apparatus was kept constant at 25.0±0.1°C by Peltier elements attached to the wall of the measurement chamber. The samples (9–35 mg) were prestored in a silica-desiccator prior to the measurements. At the beginning of the measurements, the samples were placed into the apparatus containing silica, and when the mass of each sample had stabilized the silica was replaced by the appropriate salt solution. When the samples reached steady values, the relative mass changes were calculated using the lowest mass reading.

Crystallinity determination

The amorphism of lactose was measured with an isothermal heat-conduction microcalorimeter TAM 2277 (Thermometric AB, Sweden) at 25°C. Calibration was performed as described in the users manual. The miniature humidity chamber technique [16, 17] was employed to detect the thermal response for the recrystallization of amorphous lactose. As widely recognized, the extent of heat evolution was supposed to be directly related to the amorphous degree. During the measurement, the samples were recrystallized by loading a small container filled with a saturated salt solution (ca 54% RH) together with the sample in the hermetically sealed 3 ml glass ampoule. The samples were prestored in a silica desiccator at room temperature and were accurately weighed (6–100 mg) just prior to the measurements. After preparation, the samples and the identical reference ampoules with no lactose samples were immediately placed in the equilibrium position of the TAM for 15 min before lowering into the measuring position. Each spray dried lactose batch was measured in duplicate. The lactose, spray dried from pure water, was regarded as totally amorphous sample since X-ray diffraction (XRD) studies

showed only diffuse scattering with no characteristic reflections in the diffractogram of the sample. The corresponding heat (55.4 J g^{-1}) for recrystallization process was regarded to as the reference value. Furthermore, XRD was used to verify the relative orders in the crystallinities determined with TAM.

Sorption studies

The measurement system is designed to be used with a commercial isothermal heat conduction microcalorimeter, TAM 2277. The system consists of a preceding commercial RH cell and a subsequent perfusion cell connected in series. The idea is to measure the heat of sorption with the RH cell into which the sample is loaded, and the amount of the sorbed vapor with the perfusion cell into which purified water is placed. Thus, the molar heat of sorption/desorption can be obtained in J mol^{-1} units.

The experimental set-up has been introduced in our previous work [14] in detail. The only differences from that work are that the salt solution was replaced with purified water, moisture-free nitrogen of 110 ml h^{-1} was used as gas flow and the humidification was performed as subsequent steps of 0, 1, 5, 10, 20, 30 and 40% RH at 25°C.

Results and discussion

The effect of ethanol concentration in the feed solution on crystallinity and surface areas is represented in Table 1. The values behave logically except that the surface area for the most amorphous lactose is smaller than that for the next two lactose samples. It should be noticed that the crystallinity has remarkably reduced during the storage, and the prestored samples have been used in the present study.

Table 1 Values of the amorphicities and the surface areas for the spray dried lactose samples

Ethanol/% (mass/mass)	Amorphism/%		BET surface area/m^2 g^{-1} (8-points method)[#]
	after preparation	after ca 8 months	
0	100[*]	95	0.64 (±0.01)
20	82	79	2.30 (±0.06)
30	38	33	0.95 (±0.01)
50	6	5	0.39 (±0.01)
80	0.4	0.3	0.26 (±0.05)
100	0	0	0.19 (±0.03)
325 Mesh	0	0	0.29 (±0.01)

[*]Equals to the net heat value of 55.4 J g^{-1}
[#]The confidence intervals of 99.7% are in parentheses

The heat flow curves measured with the RH cell and the perfusion cell for the lactose sample of 5% amorphous content, and also the corresponding blank runs, are represented in Fig. 2. The measurement was started by perfusing the sample with moisture free nitrogen. After the signal from the RH-cell reached the baseline, the hu-

midity was increased stepwise to the values of 1, 5, 10, 20, 30 and finally 40% RH. The whole humidifying cycle with TAM went through in 25 h. At higher humidity values no steady state, or equilibrium, was reached due to the short time duration of the steps. Indeed, according to gravimetric determination the samples containing amorphism take up moisture for several hours at the humidities of 20 and 30% RH before equilibrium will be obtained (Fig. 3). However, at 40% RH the maximum water absorption was attained in ca 2 h after which the mass started to decrease.

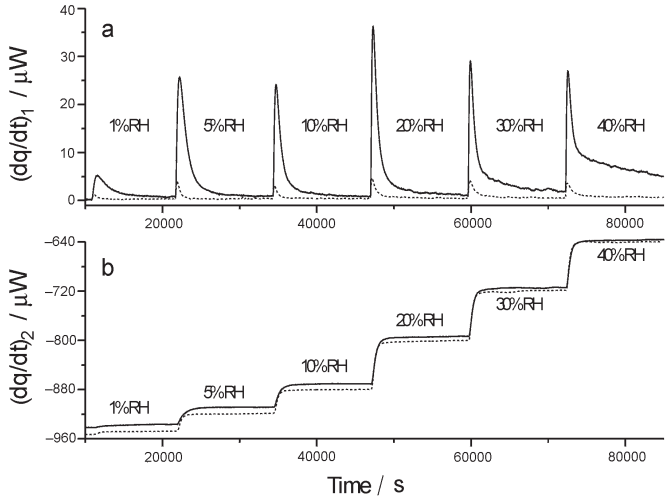

Fig. 2 Thermal responses from the RH cell (a) and the subsequent perfusion cell (b) for the spray dried lactose of $\alpha_{amorph.}$=0.05 (solid line) and the corresponding blank runs (dashed lines)

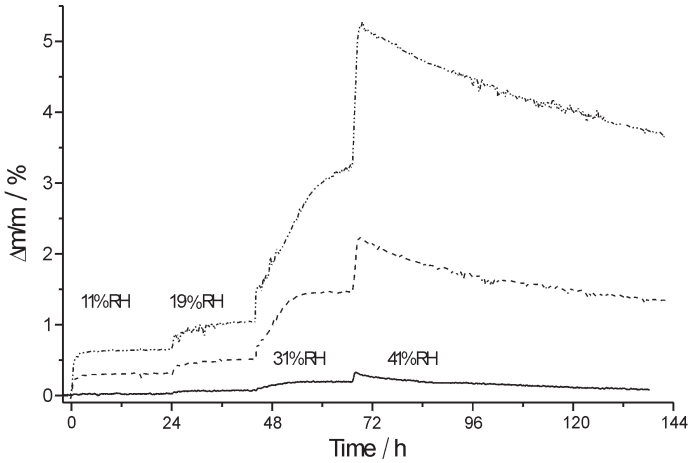

Fig. 3 Gravimetric mass increase curves for amorphous lactose samples of $\alpha_{amorph.}$=0.79 (dotted line), $\alpha_{amorph.}$=0.33 (dashed line) and $\alpha_{amorph.}$=0.55 (solid line)

In the lower graph of Fig. 2, it can be seen that the levels for certain RH values vary from one measurement to another although the measurement procedure remains the same throughout the study. This drawback made us complicated to obtain repeatable results since when the curves are subtracted from each other the baseline is not at zero level and not a straight line. In Fig. 4 the baseline was estimated and the values for the sorbed amounts were calculated.

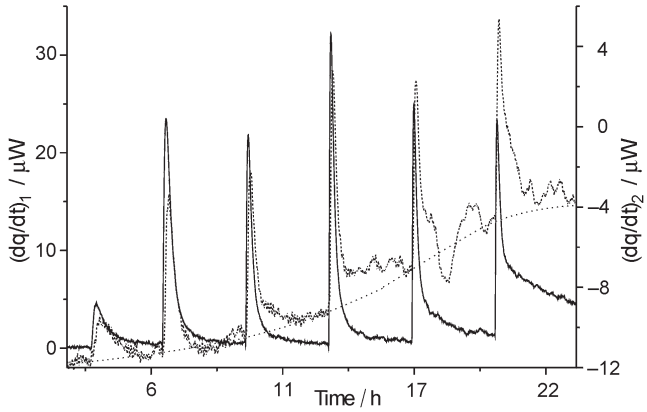

Fig. 4 The curves of the heat flow signal (solid line) and the sorption rate (dashed line) after subtraction of the blank runs. The dotted line denotes the estimated baseline for the sorption rate curve

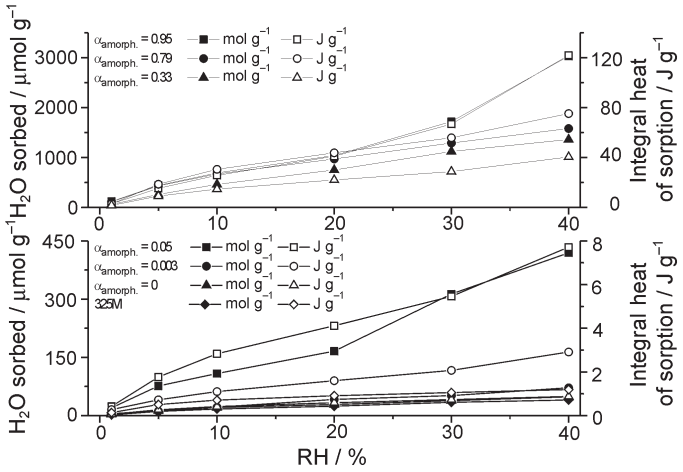

Fig. 5 Heats and amounts of sorption for lactose samples as a function of relative humidity

Figure 5 shows both the sorbed amounts of water and the corresponding heats as a function of relative humidity. For the sample of the highest degree of amorphism, the curves are of the same shape, but with other samples the shapes differ from each other. The sample that was spray dried from pure ethanol and the starting material

should both be totally crystalline, but the relative differences of the curves are remarkable indicating differences in the sorption behavior.

Maybe, the most convenient and informative way to express the results is to look at the differential heat values (kJ mol^{-1}) as a function of cumulative water uptake (μmol g^{-1}). In this way, finding differences between samples should be easy, but this also provides excellent quality from the data. The measurements of the amorphous lactose implied that the heat of sorption approached the condensation heat of water (44 kJ mol^{-1}). The subsequent runs of the same sample revealed, that the sorption was enhanced in the second run. As the measured values were not the same for the repeated cycles, it can be concluded that sorption process was not reversible already with the humidities below the critical value of about 50% RH where the recrystallization happens spontaneously.

The water uptake was also measured gravimetrically using various salt solutions (Fig. 3), and the values at ca 40% RH are compared with calorimetric results in Table 2. The calorimetric determinations made in duplicate usually differed from each other especially with the samples of high amorphous content indicating the heterogeneity of the samples. This is one reason why the calorimetric and gravimetric results do not coincide, but the most significant source of errors is caused by the difficulties how to draw the baseline for the signal from the subsequent perfusion cell (Fig. 4).

Table 2 Gravimetric and calorimetric results for the moisture uptake of the spray dried lactose samples at ca 40% RH

Amorphism/%	$\Delta m/m_{gravimetric}$ */%	$\Delta m/m_{calorimetric}$/%
95	7.4	5.9
79	5.2	3.0
33	2.2	2.5
5	0.33	0.54
0.3	0.06	0.14
0	0.02	0.09
325 M	–	0.07

*Maximum values; dry atmosphere refers to the conditions generated by silica gel at 25°C

Conclusions

The technique enabled us to distinguish the totally crystalline lactoses even though the water uptake was extremely small. This was also the main reason why the results were not reliable and repeatable enough. The disturbances were caused mainly by two factors: the samples itself were not homogenous, and the set-up for the detection of water uptake in the perfusion cell was not properly carried out, which allowed variation between measurements.

As an overall conclusion, it can be said that the microcalorimetric vapor sorption technique is valuable in the characterization of surfaces of pharmaceuticals, at least

after requisite improvements. Especially, when various probe molecules are employed, much information can be obtained concerning hydrophobicity, hydrophilicity, acidity and basicity of surfaces, for example. However, it should be kept in mind when a new technique is introduced, the results must be verified with other methods especially in this case where quantifying the vapor sorption rates less than 0.1 nmol s^{-1} is a very delicate activity.

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The authors thank Leiras Oy, Finland for donating lactose and M. Sc. Päivi Harjunen for spray drying the lactose samples.

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