Simultaneous Determination of the Heat and the Quantity of Vapor Sorption Using a Novel Microcalorimetric Method

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Purpose. In this study, instrumentation for measuring vapor sorption enthalpies and sorption uptakes simultaneously with an isothermal microcalorimeter is introduced. Various pharmaceutical model substances undergoing phase transitions when exposed to humid conditions (25°C), were employed to evaluate the usefulness and sensitivity of the constructed experimental method.

Methods. The sample is placed in the sample vessel of a RH cell and the moisture content of the air flow is controlled. From the RH cell the air flow is conducted into a subsequent perfusion cell in which a saturated salt solution has been loaded. The RH cell and perfusion cells are positioned in the sample sides of two twin calorimetric units. Depending on the moisture content in the outlet flow leaving the preceding RH cell, the heat flow signal from the subsequent perfusion cell will vary. By means of blank measurement with identical settings, the rate of water sorption can be calculated and, by integration, the amount of sorbed water is obtained.

Results. Amorphous lactose and cefadroxil undergo recrystallization when the moisture level in the surroundings exceeds the threshold values specific to each compound. During the sorption phase, heat is evolved fairly linearly as a function of consumed moisture, and also after the recrystallization, the heats indicate linear behavior. The heat values for the desorption phase of amorphous lactose and the adsorption of crystalline lactose coincide. With the different anhydrous forms of theophylline, the hydration takes place more rapidly in the metastable form I, and generally, the process is more energetic in form I. In all cases, the gravimetric results agree with the water sorption uptakes calculated from the calorimetric data.

Conclusions. The technique introduced offers a rapid and sensitive method to gain new insights into the transitions in which vapors are involved. In addition, different kinds of surfaces with various energetics can now be studied more closely.

KEY WORDS: vapor sorption; molar heat of adsorption; kinetics; isothermal microcalorimetry; recrystallization; hydration.

INTRODUCTION

Considering certain pharmaceutical formulations, particular emphasis should be given to controlling the surface energetics of powders, since all the interactions of the particles of a drug or an excipient take place in interfaces. Although it is well known that the chemical nature of the powder and its mechanical and thermal pretreatment will all play a role in controlling the surface energetics, the physical characterization methods are not always sensitive enough to detect the small variations in the surfaces, which produce problems in the final product. Many raw materials are exposed to processing to some extent during manufacturing; processing that may be sufficiently energetic to cause disruption to the crystal structure. Many articles have been published concerning characterization of surfaces (e.g., 1–3) in connection to the effects of water on solids which cannot be overestimated (4).

Interaction with a vapor is reported to be in many ways the best method to probe a surface. This is because the first layer of adsorbed vapor molecules gives the most significant information about the powder-probe interaction (5). The determination can be made with high sensitivity using an isothermal microcalorimeter (IMC) for both hydrophobic and hydrophilic powders of low surface area. However, with this method, the surface area must be determined separately so the various samples can be reliably compared.

Much attention has been paid to the effects of milling and spray drying on lactose. It has been recognized that lactose transforms to a disordered or amorphous state, depending on the treatment parameters. The recrystallization mechanism has been under intensive study (6–8) and various methods been applied to quantify the amorphous portions (9–11). A general discussion on the role of disordered structure in the solubility of hydrophilic substances has recently been published (12).

Wadso and Wadso (13,14) have introduced a calorimetric method to study vapor sorption. With this technique, a specially manufactured calorimetric unit was employed so both the sorbed amount of vapor and the heat of sorption could be detected. The progression of adsorption was controlled by the diffusion of the moisture from the vaporization vessel to the sorption (sample) vessel with no possibility to manipulate the progression from outside the calorimeter. The relative humidity in the sample vessel as a function of time was calculated according to Fick's law after the measurement.

In this paper, a new method is introduced to simultaneously determine the heat and the quantity of sorption with an isothermal microcalorimeter. The suitability of this method to investigate different kinds of phase transitions in the solid state is demonstrated. The model materials employed have been chosen because they have been studied extensively for years.

MATERIALS

Lactose

Two different forms of α-lactose monohydrate were used. The commercial crystalline lactose was obtained from Leiras Oy, Finland, and was found to be totally crystalline according to x-ray diffraction (XRD) measurements. Determination with IMC also confirmed the lactose to be crystalline, since no exothermic recrystallization effect could be found in the heat flow signal when the humidity was raised from 0% RH to 80% RH during measurements (15–17). To obtain totally amorphous lactose, the starting material was spray-dried from a 15% w/w lactose-water solution with a Buchi Minispray dryer 190. XRD indicated the lactose was totally amorphous since the diffractogram showed only diffuse scattering, lacking the characteristic reflections.

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Cefadroxil

Cefadroxil, used as a second amorphous model compound, was also obtained from Leiras Oy, Finland. The material was from the same batch that was characterized in detail in our previous work (18). The amorphous form was obtained by ball-milling the monohydrate form for an appropriate length of time. XRD was used for verification.

Theophylline

The two anhydrous forms of theophylline were used to study the hydration of anhydrous compounds. The anhydrous theophylline (Sigma Chemicals, USA) was first hydrated by placing the powder under 97% RH for five days to obtain the monohydrate form. Form II, which is stable at room temperature, was prepared by heating the monohydrate at 110°C for 24 hours. Form I was obtained by heating form II additionally at 265°C for 4 hrs (19,20). The powders which were passed through a 125 μm sieve were used in all the measurements if not otherwise mentioned. The forms were identified with XRD.

METHODS

Isothermal Microcalorimetry (IMC)

The measurement system is designed to be used with a commercial isothermal heat conduction microcalorimeter, TAM 2277 (Thermometric AB, Sweden). 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 or desorption with the RH cell into which the sample is loaded, and the amount of the sorbed or desorbed vapor with the perfusion cell into which a saturated salt solution is placed. Thus, the heat of sorption/desorption can be obtained in J/mol units, i.e. the accompanying energy when a mole of water is sorbed/desorbed.

The moisture-free synthetic air from a gas tank is used as the gas flow, and the flow rate (100 ml/h) is controlled by a mass flow controller. The air flow enters the flow switch valve of the RH cell where the flow is divided into the dry and wet lines of the RH cell (Fig. 1). By means of the wet line (100% RH), the flow passes through two humidifiers into the sample vessel. Via the dry line (0% RH), the air flow is delivered into the sample vessel directly. The time proportion of the flow switch position sets the RH value in the sample vessel (21).

The gas flow is conducted from the RH cell into the perfusion cell into which the salt solution is loaded in a specially manufactured miniature chamber. The water content in the outlet flow from the preceding RH cell can be calculated, since the heat flow signal from the perfusion cell is directly related to the RH value of the flow when the flow of an unknown RH value is allowed to perfuse over a salt solution in the perfusion cell. The cells are connected with teflon tubing outside the calorimeter, and thus, the tubing is heated to ca. 20°C above the actual measurement temperature (25.00°C) to prevent condensation (Fig. 1). The miniature chamber into which the salt solution is loaded was designed so the changes in the surface level of the solution due to sorption or desorption during measurements would affect the rate of sorption or desorption as little as possible.

During the actual measurement, two independent twin calorimetric units, in whose sample sides the RH cell and perfusion cell are situated, are employed (Fig. 1). A small amount of the sample (10–40 mg) is placed in the ampoule of the RH cell and a saturated salt solution is placed in the ampoule of the perfusion cell. When a salt solution of, e.g., 54% RH ($Na_2Cr_2O_7 \cdot 2H_2O$) is employed, the vessel containing the solution must be designed so that the heat flow values for the flow of 0% RH and 100% RH do not exceed the setting of the amplifier. In this study, the measurements were started with a synthetic air flush of 0% RH until the heat flow signals from the RH cell reached baseline, and the signals from the perfusion cell showed steady negative values. The humidification was performed as a single step of 54% RH (for amorphous lactose), 80% RH (for crystalline lactose), or 95% RH (for cefadroxil and theophylline). After the signals became steady and the equilibrium was reached, the moisture content of the flow was reduced to 0% RH and corresponding heat flow curves for desorption were obtained.

Prior to the measurement with the sample, blank runs with identical settings must be performed for both the cells with the empty sample ampoule of the RH cell. The blank measurement of the RH cell is used to subtract the share of the adsorption of the stainless steel ampoule as such from the sorption signal for the sample. With the perfusion cell, the blank run provides the reference levels for each humidity value set. By means of

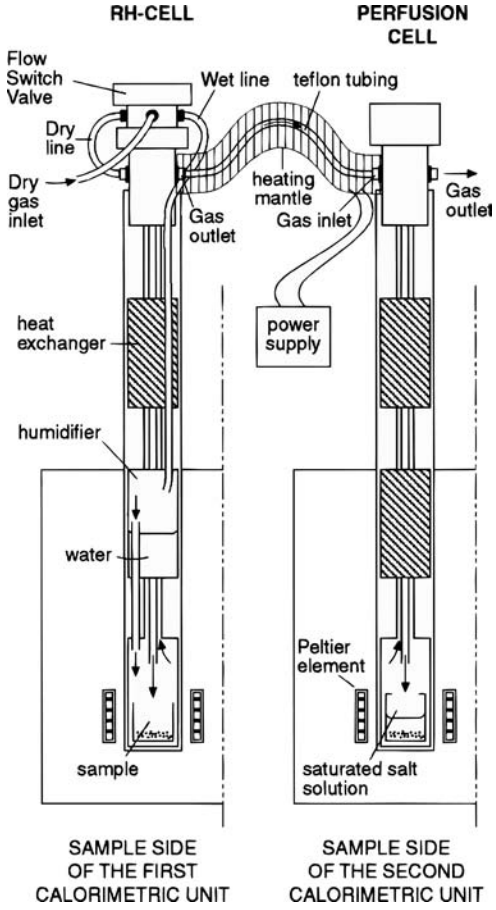

Fig. 1. A schematic drawing of the experimental set-up. The reference sides of the calorimetric units, three heat exchangers, and a humidifier are excluded from the drawing for the sake of legibility.

the blank measurement, the scale factor between the heat flow value and the RH value is obtained (cf., Theory section). When the heat flow signals from the blank and sample runs of the perfusion cell are subtracted from each other, the response to the variations in the moisture content of the gas flow due to sorption by the sample is achieved. The constant time shift between the heat flow signals from the RH and the perfusion cell is also achieved in this way. As the time shift depends on the length of the tubing between the cells, it must be evaluated every time the construction is altered. In this work the time shift was 170 s.

Gravimetric Hygroscopicity

The HMA apparatus (PuuMan OY, Finland) used for gravimetric hygroscopicity measurements has been described elsewhere (22). The humidity to which the samples were exposed was produced with saturated salt solutions (23). The temperature of the apparatus was kept constant at 25.0°C ± 0.1°C by Peltier elements attached to the wall of the measurement chamber. The samples (7–15 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 weight of each sample had stabilized the silica was replaced by the appropriate salt solution. When the samples reached steady values, the relative weight changes were calculated using the lowest weight reading.

THEORY

The calculations used to obtain the amount of water sorbed by the sample placed in the RH cell are based on the fact that the heat flow signal from the subsequent perfusion cell is directly related to the RH value of the air flow passing through the ampoule of the perfusion cell containing a salt solution. To calculate the amount of water, first, the difference between the RH values entering the RH cell ($RH_{in}(t)$) and coming out of the RH cell ($RH_{out}(t)$) must be calculated as

$$\Delta RH(t) = RH_{in}(t) - RH_{out}(t) = A \cdot (P_{nos}(t) - P_s(t)) \quad (1)$$

where $P_{nos}(t)$ and $P_s(t)$ are the heat flow signals without and with the sample, respectively. The correlation factor A is obtained by means of the identical blank run with the same RH setting when

$$A = \frac{X\%RH}{P_{X\%RH} - P_{0\%RH}} \quad (2)$$

where the heat flow signals $P_{X\%\,RH}$ and $P_{0\%\,RH}$ denote the values obtained with the settings of X% RH and 0% RH, respectively. In this work the correlation factor A was considered to be independent of time, since it is quite impossible to make an estimation of the $P_{0\%\,RH}$ course during the humidification run. The heat flow level just prior to the resetting of the RH value (humidification) was regarded as $P_{0\%\,RH}$, and the first steady heat flow values after the resetting were recorded as $P_{X\%\,RH}$. The rate of water sorption dn/dt can then be calculated as

$$\frac{dn}{dt}(t) = \frac{\Delta RH(t)}{100} \cdot \frac{P_{water} \cdot \frac{dv}{dt}}{RT} \quad (3)$$

where p_{water} is the vapor pressure of water at measurement temperature T, R is the gas constant and dv/dt is the flow rate. In this work T = 298.15 K and dv/dt = 100 ml/h, which yield the value of $3.549 \cdot 10^{-8}$ mol/s for the former part of Eq. (3). Here, the moisture content in the gas flow entering the sample vessel of the preceding RH cell was regarded as fixed by the setting of the flow switch valve as such, and no correction was made for the volume of water molecules entering the gas from the humidifier of the RH cell (24). The error would be at most 0.8% RH at 50% RH.

RESULTS

Lactose

Amorphous lactose has, on many occasions, been found to give an exothermic response due to recrystallization when the crystallization process has been monitored by an isothermal microcalorimeter. In these experiments, the miniature technique has been utilized (25,26), where the moisture content of the surroundings of the sample is raised so that the glass transition point T_g is reduced to below the measurement temperature (usually 25°C), and the recrystallization occurs spontaneously. The time for the recrystallization depends on the humidity level and the sample size. The process has also been studied gravimetrically (27,28), showing the recrystallization process to be followed by expulsion of the excess water sorbed by the amorphous portion.

In this work, the amorphous sample (~10 mg) is placed in the sample vessel of a RH cell. The moisture content of the air flow is raised from 0% RH to 54% RH at t = 0 s (Fig. 2a). A saturated salt solution of $Na_2Cr_2O_7 \cdot 2H_2O$ (54% RH) is placed in the subsequent perfusion cell. Depending on the moisture content in the outlet flow from the preceding RH cell, the heat flow signal obtained from the subsequent perfusion cell will vary (Fig. 2b). To calculate the RH value of the flow, an identical blank measurement without a sample in the RH cell is also performed (dotted lines, Fig. 2). The signals (dashed

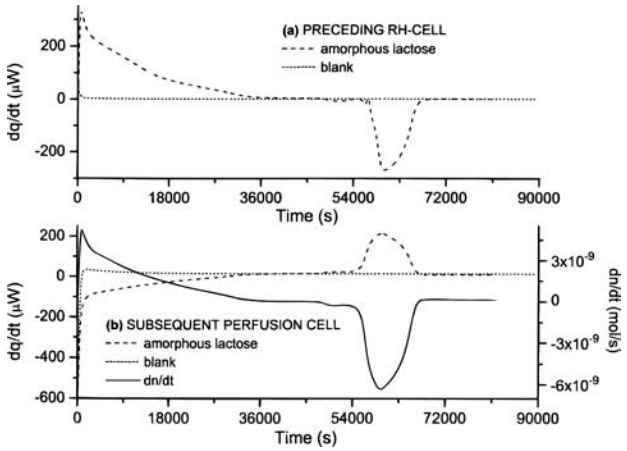

Fig. 2. (a) The heat flow signals from the preceding RH cell for amorphous lactose (m = 11.512 mg, dashed line) and the empty sample vessel (blank measurement, dotted line) when the RH value of the air flow is raised from 0% to 54%. (b) The corresponding heat flow signals from the subsequent perfusion cell containing the salt solution of 54% RH. The solid line shows the rate of water sorption/desorption as a function of time.

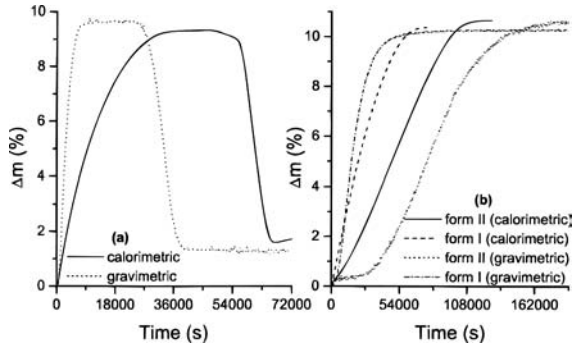

Fig. 3. (a) The mass increase curves of amorphous lactose determined calorimetrically (solid line) and gravimetrically (dotted line). (b) The mass increase curves for the anhydrous theophylline forms determined with the microcalorimeter (form II: solid line, form I: dashed line) and with the gravimeter (form II: dotted line, form I: mixed dashed line).

and dotted lines) are subtracted from each other and, in the case of the signals from the perfusion cell, the difference in the moisture content of the inlet and outlet flow of the RH cell is calculated using the correlation factor obtained on the basis of the blank measurement (dotted line, Fig. 2; cf., Theory section). Using Eq. (3), the sorption rate dn/dt is obtained. Thus, the sorption and recrystallization processes are monitored thermally (Fig. 2a) and quantitatively (Fig. 2b), simultaneously, as a function of time. Integration of the dn/dt curve gives the amount of sorbed moisture, which is in good agreement with the gravimetric determination (Fig. 3). The difference in the shapes of the moisture uptake curves could be due to the different measurement design of the two systems (different ways of generating the humidity in the measurement chamber), and the sample size. However, the moisture uptake levels are practically the same in these measurements. When the heat of sorption is expressed as a function of the sorbed moisture, the energies associated with various parts of the process can easily be verified (Fig. 4).

Identical measurements with the RH value of 80% were also performed for the crystalline lactose. Since only adsorption takes place here, the heat flow values are much lower and no

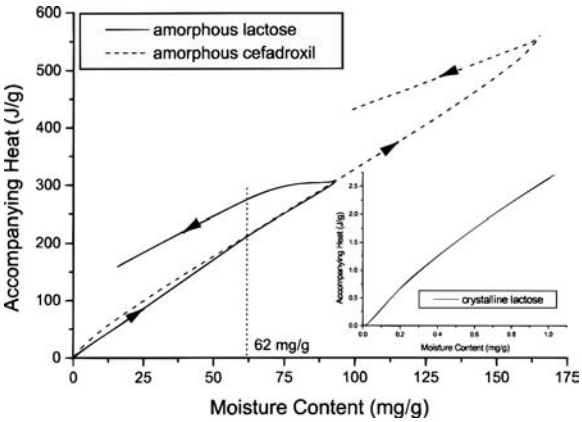

Fig. 4. The progress of the recrystallization of amorphous lactose (solid line) and amorphous cefadroxil (dashed line) when the accompanying heat is expressed as a function of sorption uptake. The corresponding curve for the crystalline lactose is shown in the insertion.

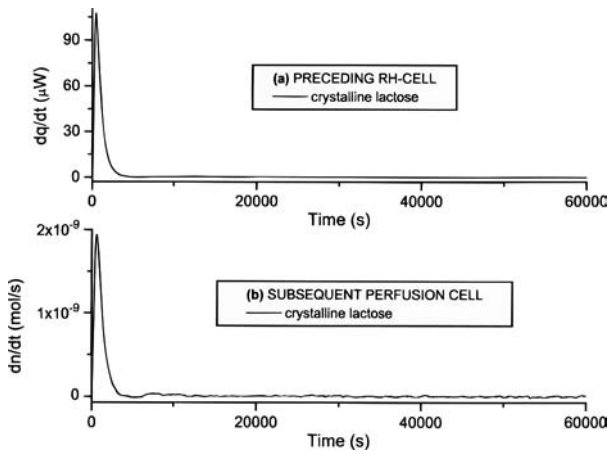

Fig. 5. (a) The blank-corrected heat flow signal from the preceding RH cell for crystalline lactose (m = 40.777 mg) when the humidity is changed from 0% RH to 80% RH. (b) The corresponding rate of water adsorption by crystalline lactose calculated from the heat flow data of the subsequent perfusion cell.

recrystallization can be noticed, as was to be expected, (Fig. 5). According to these IMC determinations, lactose takes up moisture to the extent of only ca. 0.10% of its weight. The heat of adsorption is expressed as a function of moisture content in the insertion in Fig. 4.

Cefadroxil

Another model amorphous material used in the sorption studies was cefadroxil. As was reported in our previous study (18), the crystallization process of the amorphous form to monohydrate was found to consist of the subsequent steps of crystallization of the plasticized regions and expulsion of the excess water. The thermal responses to the sorption and the desorption phases of the recrystallization process behave in a way similar to that for the sorption and desorption rate of water (Fig. 6). Figure 4 shows the heat values for various parts of the recrystallization process.

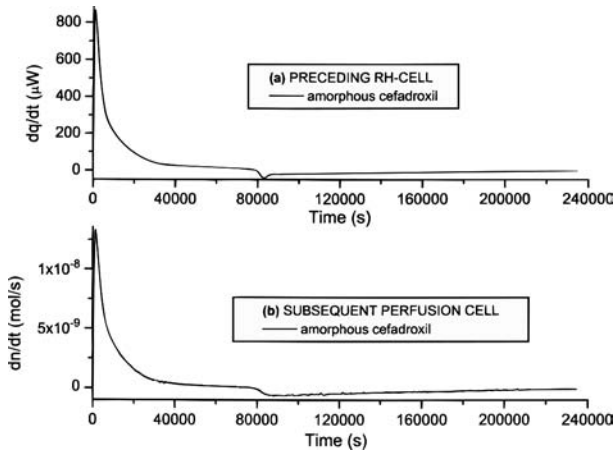

Fig. 6. (a) The blank-corrected heat flow signal from the preceding RH cell for amorphous cefadroxil (m = 12.999 mg) when the humidity is changed from 0% RH to 95% RH. (b) The corresponding rate of water sorption by amorphous cefadroxil calculated from the heat flow data of the subsequent perfusion cell.

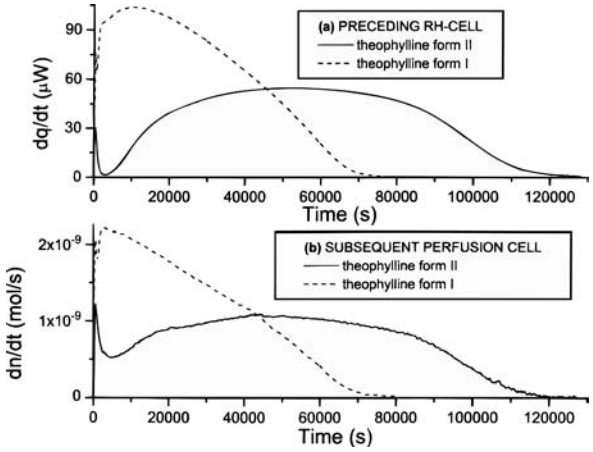

Fig. 7. (a) The heat flow signals from the preceding RH cell for the anhydrous theophylline form II (m = 15.270 mg, solid line) and form I(m = 15.361 mg, dashed line) when the RH value of the air flow is raised from 0% to 95%. (b) The corresponding heat flow signals from the subsequent perfusion cell containing the salt solution of 54% RH.

Theophylline

The stable anhydrous form of theophylline is form II, and the metastable form I transforms spontaneously to the stable form at room temperature. Caffeine (29) and theophylline (30) are essentially isomorphous compounds in terms of the crystal structures of the hydrate forms, the anhydrous forms of the compounds behaving similarly under humid conditions, resulting in the hydrate form. In our experiments, both the anhydrate forms of theophylline show the same phases during the hydration process, namely, the rapid adsorption of free water and the subsequent slow transformation to the hydrate form (Fig. 7). The magnitude of the adsorption depends on the surface area of the powder (the smaller the particles, the more energetic adsorption), but the energy of the hydration phase is independent of the surface area. Both part processes happen more rapidly for the metastable form I, which is the same result as for caffeine (29). The mass increase curves show the equilibrium moisture content (EMC) values to be ca. 10.3% and ca. 10.6% for form I and form II, respectively (Fig. 3). As the adsorption corresponds to the 0.4% mass increase for form II (Figs. 3 and 8) and the mass portion of the hydrate water is 10.0%, the EMC values conform with each other. Figure 8 represents the heat evolved in the hydration process as a function of sorbed moisture. The hydration itself is more energetic for the metastable form I, and at the end of the reaction, the total heats evolved are 299.7 J/g (0.5 J/g) and 288.1 J/g (1.7 J/g) (means of three measurements with the standard deviation in parentheses) for form I and form II, respectively. When the corresponding heats for the adsorption of free water are approximated as 6.7 J/g and 2.4 J/g (Fig. 7), the transition enthalpy between the polymorphic forms can be calculated to be −7.3 J/g. According to the curves in Fig. 8, the hydration mechanism (sites for the hydrogen bonds) after the adsorption phase is the same although the kinetics differ.

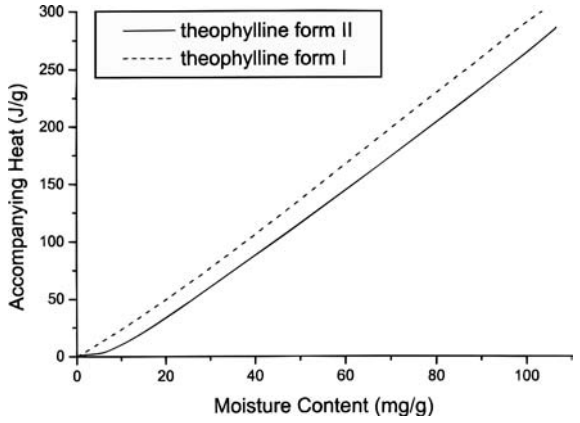

Fig. 8. The progress of the hydration of anhydrous theophylline form II (solid line) and form I (dashed line) when the accompanying heat is expressed as a function of sorption uptake.

DISCUSSION

The recrystallization process of the amorphous lactose starts with adsorption and proceeds as absorption up to a value of 62 mg/g (Fig. 4), the corresponding heat of absorption being 3.40 kJ/g. Thereafter, the recrystallization takes place along with the ongoing absorption until the expulsion of the excess water starts to dominate. Recrystallization continues until the moisture content has been decreased back to the value of 62 mg/g_{H2O}, after which the mass decrease continues as desorption. The heat of desorption is −2.52 kJ/g_{H2O}, that is practically the same value as the heat of adsorption (2.51 kJ/g_{H2O}) for the crystalline lactose (inserted figure, Fig. 4).

The different phases of the recrystallization process of the amorphous cefadroxil are more difficult to distinguish from each other than those of lactose. Also the mass increase curve reaches a plateau before it starts to decrease, the result being consistent with the gravimetric study (18) and with the results for lactose. However, this time, in contrast to lactose, the recrystallization seems not to start before the expulsion of the free water and to be over in a short time, while the desorption is prolonged for a longer period of time. The heat values for the absorption and desorption are 3.08 kJ/g_{H2O} and −1.86 kJ/g_{H2O}, respectively (Fig. 4).

The particle size plays an important role in the hydration of anhydrous theophylline since the process is prolonged for days with the powders that are not milled after their heat treatments. In these cases, the adsorption phase is rather minor when compared with that of the milled powder. However, the heat evolved in the hydration process is unaltered. Hydration proceeds more slowly with the stable form II, and the heat of adsorption is also less marked, which might be due to the difference in the surface areas. Indeed, the mean Martin's particle diameters for the theophylline powders passed through a 100 μm sieve were found to be 25.4 μm and 15.9 μm for the forms II and I, respectively. However, according to Fig. 8, the surface energetics evidently differ from each other for the two polymorphs. The recrystallization process proceeds energetically with the same mechanism on the basis that the heats for the hydration, 2.90 kJ/g_{H2O} (form II) and 2.95 kJ/g_{H2O} (form I), can be taken as equal (Fig. 8). The kinetics for the two forms varies, which is obviously due to the different capability of water molecules to penetrate through the crystal. This might be contributed to by the smaller particles of form I, or by the longer crystal parameters when the water tunnels along the c-axis are larger. Despite this, the sites for the hydrogen bonds are the same for both forms.

CONCLUSIONS

The main problem of the technique introduced was the variations in the reference heat flow level obtained from the subsequent perfusion cell. These were caused by the variations in the surface level of the salt solution. Thus, it is essential to verify the results calculated (mass increase curves) with the gravimetric method. The results presented in this paper were generally in excellent agreement with each other, while the disagreements were fully explained by the different ways of generating the moisture atmosphere and the different sample sizes in the IMC and the gravimeter.

The technique gave relevant information on the studied transformations where water was involved. Having a parallel knowledge of the heat and amount of sorption accompanying these processes is of great importance to be able to calculate the energies of various phases of the processes. In this work, the main emphasis was on the dynamic processes, i.e., recrystallization and hydration, but with this technique, the energetics of different surfaces can also be easily and reliably determined. For example, even very small variations in the surface energies of the inhalation powders due to different batches or comminution can affect the performance of the dry powder inhalator. It is extremely important to determine these differences in the drug formulation, and to characterize the powder materials well enough so that the stability problems of the product can be avoided.

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