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Lactose and thermal analysis with special emphasis on microcalorimetry

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Abstract

This paper reviews how isothermal microcalorimetry has been used to characterize the interaction between various lactose powders and water vapour. Microcalorimetry monitors the heat flow from processes proceeding in a sample. It has been shown that the rate of transformation of anhydrous lactose to the monohydrate depends strongly upon the content of anhydrous α- and β-lactose in the sample, in addition to the relative humidity. It has been further shown that microcalorimetry is an excellent technique for measuring small amounts of amorphous lactose. This was done by calculating the heat when the amorphous parts crystallized under humid conditions. Results obtained by differential scanning calorimetry are also discussed. Furthermore, references from other studies, in which lactose powders have been investigated by thermal analysis techniques, are given.

Keywords: DSC; Humidity; Lactose; Microcalorimetry; Water

1. Introduction

Lactose powder is one of the most extensively used pharmaceutical excipients, commonly used as fillers in tablets and capsules and as carriers for dry powder inhalation. Several commercial qualities with different properties are available and they are therefore used for various applications. Lactose in tablet manufacturing may, for example, be used in either granulation formulations or for direct compression.

Lactose is a disaccharide composed of galactose and glucose, which exists in two optically isomeric forms, α- and β-lactose. In aqueous solution, the lactose

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molecules mutarotate until an equilibrium is reached, consisting of 38% α- and 62% β-lactose at room temperature [1]. The crystalline α- and β-lactose differ in their physical properties, not only in their initial optical rotation after dissolution, but also their melting point, solubility and density values. Also within the α- and β-lactose solids, there are variations in the physical properties which are discussed below [2].

If a supersaturated lactose solution is crystallized below 93.5°C, a powder consisting almost completely of α-lactose monohydrate is obtained, i.e. with one molecule of water of crystallization in the α-lactose lattice. This is the most common of the lactose powders and it is used mainly for granulation formulations [1].

Crystalline lactose powders with a high content of anhydrous forms have been manufactured with the properties that make them suitable for direct compression. These powders consist of a mixture of anhydrous α- and β-lactose, usually also with a fraction of α-lactose monohydrate. One quality that has a large content of β-lactose is produced by letting a supersaturated lactose solution crystallize above 93.5°C utilizing the roller-drying technique. Another quality that has a large fraction of anhydrous α-lactose is produced by, for example, thermal dehydration of α-lactose monohydrate crystals at temperatures above 130°C [1].

Spray-dried lactose is made from a solution or suspension of lactose. The final powder contains a partly or totally disordered, amorphous, structure. Qualities of spray-dried lactose that are used for direct compression consist both of crystalline and amorphous lactose. Not only spray-drying, but also freeze-drying [3–5] and very often also mechanical activation such as, for example, milling and compaction, cause disordered structures [5–11]. That many other types of solid lactose forms can also be obtained, depending on the conditions during crystallization and subsequent treatments, has been reviewed [2]. There are reports of complexes consisting of both α- and β-lactose [1,5,12,13].

Lactose powders interact differently with water vapour, depending on crystalline structure (or lack of crystallinity), the relative humidity (RH) and the temperature and duration under which the powder is exposed. Since important properties may be influenced, for example, flowability, compactability and tablet strength, it is important to be able to characterize the starting material and possible changes that may proceed during processing and during various storage conditions.

Thermal analysis techniques, such as differential scanning calorimetry (DSC), differential thermal analysis (DTA) and thermogravimetry (TG), have been used to characterize lactose [1,4–6,9–12,14–20]. Some of these have been reviewed [21]. Lately, a less well-known thermal technique, isothermal microcalorimetry, has also been utilized [22–26].

This report will focus on how isothermal microcalorimetry has been used to characterize the interaction of various types of lactose with water vapour and crystallographic changes due to this interaction. Firstly, the transformation of crystalline anhydrous α- and β-lactose to the α-lactose monohydrate will be described, i.e. the incorporation of water of crystallization into the anhydrous structure. Secondly, the absorption of water vapour and subsequent crystallization of the amorphous fractions in spray-dried lactose will be presented.

2. Microcalorimetry and the interaction of powders with water or water vapour

2.1. The microcalorimeter system

In the studies reviewed here, the 2277 Thermal Activity Monitor (TAM) with the microcalorimeter model 2277-201 has been used [27] manufactured by Thermometric AB (Sweden). In isothermal microcalorimetry the heat flow (dQ/dt in μW) from proceeding processes is monitored as a function of time. The heat flow is ideally proportional to the rate of the process. By integrating the heat flow curve, the heat evolved or absorbed (Q in mJ) is obtained. As most reactions investigated by microcalorimetry have exothermic heat flows, they are given positive values. The experimental temperature for all the studies presented was 25°C and the measurements were performed as closed systems, i.e. there was no exchange of material (solid, liquid or gas) with the environment. Microcalorimetry in a range of pharmaceutical studies has been reviewed [28–30].

2.2. Exposure of powders to water in combination with microcalorimetry

Exposure of powders to water or water vapour in isothermal calorimeters can be achieved by different approaches. Below are some examples that have been accomplished mainly on the TAM, but also on other types of calorimeters. One possibility is to equilibrate the powders at various humidities before the microcalorimetric measurement [22,23,31]. Another approach is to have a source of water vapour within the sample vessel to create a humid atmosphere [24–26,32]. With this technique the heat of vaporization is also monitored. To avoid this, the microcalorimeter has to be equipped so that the water vapour comes from a position separated from the sensitive measuring position [33–35]. The most drastic approach is to immerse [36] or dissolve the powder in water [37].

3. Anhydrous lactose exposed to water vapour

To calculate the amount of water of crystallization in a powder sample, DSC is probably the most commonly used technique. For an anhydrous sample that transforms to a hydrate, it can be a valuable complement or even more informative to follow the direct process of hydration, i.e. the incorporation of water of crystallization, by microcalorimetry, and to compare it with the opposite process, dehydration by DSC.

3.1. Prestored samples

The first approach was to let a series of powder samples interact with water vapour at various relative humidities for different lengths of time before the microcalorimetric measurement [22]. This meant that each measurement represented a "point" measure of the proceeding process. 2.2 g of roller-dried β-lactose samples

Table 1
The approximate proportions (in %) of anhydrous β-lactose, anhydrous α-lactose and α-lactose monohydrate in the various lactose types studied

Lactose type	β-Lactose	α-Lactose	
	Anhydrous	Anhydrous	Monohydrate
Roller-dried β-lactose [a]	69	22	9
α-Lactose anhydrous [b]	20	71	9
Crystalline β-lactose [c]	94	5	1
Commercial α-lactose monohydrate [d]	4	0	96

[a] Lactose N.F. anhydrous direct tableting 59009 (called roller-dried β-lactose), Sheffield products, Norwich, NY, USA. [b] α-Lactose anhydrous (called α-lactose anhydrous). [c] β-Lactose (called crystalline β-lactose). [d] Pharmatose^{R} 200M (referred to as commercial α-lactose monohydrate). The last three samples were obtained from De Melkindustrie Veghel bv (DMV), Veghel, The Netherlands.

(Table 1) were prestored at 33–94% RH. After prestorage, the samples were rapidly transferred to 4.4 ml steel vessels and inserted into the measuring position (after 30 min temperature equilibration). The exothermic heat flow curves showed that the highest response was obtained for the highest humidity (94% RH), after the shortest storage time (1 day) and at the beginning of each measurement. For powders stored at 33% RH no response was seen indicating that no reaction was in progress.

To be able to present all measurements in one figure, the heat flow values after 2 h measurement time were plotted as a function of prestorage time (Fig. 1). The

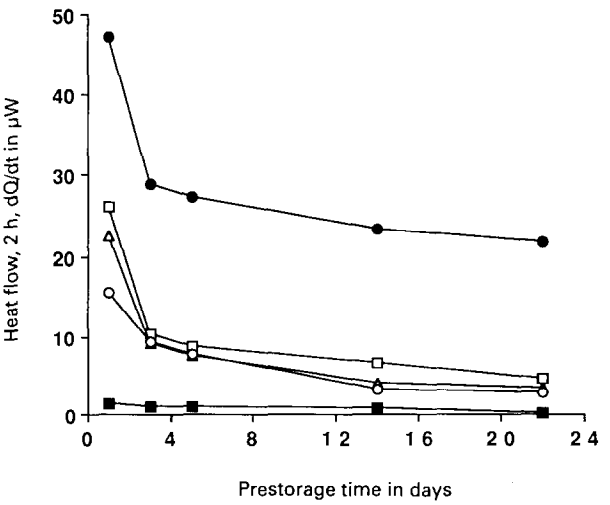

Fig. 1. Heat flow values after 2 h as a function of prestorage time for roller-dried β-lactose (Table 1) at ■, 58% RH; ○, 75% RH; △, 81% RH; □, 84% RH; and ●, 94% RH. Sample mass 2.2 g. Results for 1, 3 and 5 days are mean values ($n = 5$).

2 h values, instead of those at $t = 0$, were chosen due to disturbances directly after the start of the measurement.

It is known that the β-lactose cannot exist as the monohydrate [1,4] and the first interpretation was that the heat flow signals resulted only from incorporation of water into anhydrous α-lactose. Anhydrous α-lactose shows varying stability towards water vapour depending on the manufacturing conditions, often referred to as stable and unstable α-lactose, respectively. These show different physical properties also resulting in different DSC scans [1,2,12,20].

The 22% anhydrous α-lactose contained in the roller-dried β-lactose sample (Table 1) ought to be transformed to the monohydrate most rapidly for the highest humidity and hence should be the first to decrease to a zero signal. However, a continuous high heat flow signal was observed for samples that had been stored at 94% RH (Fig. 1). The response could be explained by the fact that even if β-lactose cannot form a monohydrate, at high humidities it can mutarotate to α-lactose with subsequent incorporation of water. The explanation, proposed by Berlin et al. [4], was that β-lactose has a higher density than α-lactose, i.e. a more compact structure that cannot accommodate a water molecule. As the energy expenditure is too large to allow expansion, the monohydrate cannot be formed. At very high humidities (they investigated 97% RH), water vapour was taken up rapidly to form a concentrated solution in which β-lactose mutarotated to α-lactose and subsequently water was incorporated to form the crystalline α-lactose monohydrate.

It was concluded that the consistently high heat flow signals at 94% RH (Fig. 1) came from the incorporation of water into former β-lactose that had mutarotated to α-lactose. No dissolution of the powder sample was seen, but it was proposed that the adsorbed water increased the molecular mobility to allow mutarotation. The effect of water on the molecular mobility in solids has been reviewed [38].

Hence, the change to the monohydrate of a sample containing both anhydrous α- and β-lactose will have a biphasic appearance, at least at very high humidities: the α-phase corresponds to the incorporation of water in the original α-lactose where the relative humidity determines the incorporation rate; the β-phase corresponds to the incorporation of water in the former β-lactose where the mutarotation is rate limiting. At humidities lower than 94% RH, mutarotation also proceeds, but at a much slower rate. This means that it is primarily the change from anhydrous α-lactose to the monohydrate that is monitored.

DSC measurements were performed on a DSC 20 (Mettler, Switzerland) to show the increase of the monohydrate content and to follow the crystallographic changes that appeared. Open aluminium pans were used, the samples were in an atmosphere of nitrogen and the heating rate was 10°C min^{-1}. Fig. 2 shows the DSC scans for untreated roller-dried β-lactose (scan A) and a similar powder stored for 22 days (scan B) and 101 days (scan C) at 94% RH, respectively. Also included is a scan for commercial α-lactose monohydrate (scan D). For the untreated sample (scan A), there is a small deviation at 132°C representing the release of water of crystallization, the dehydration. The fusions of α- and β-lactose are represented by the peaks around 220°C and 235°C, respectively. However, DSC is not actually suitable for the calculation of the ratio of α- and β-lactose, even though it has been carried out

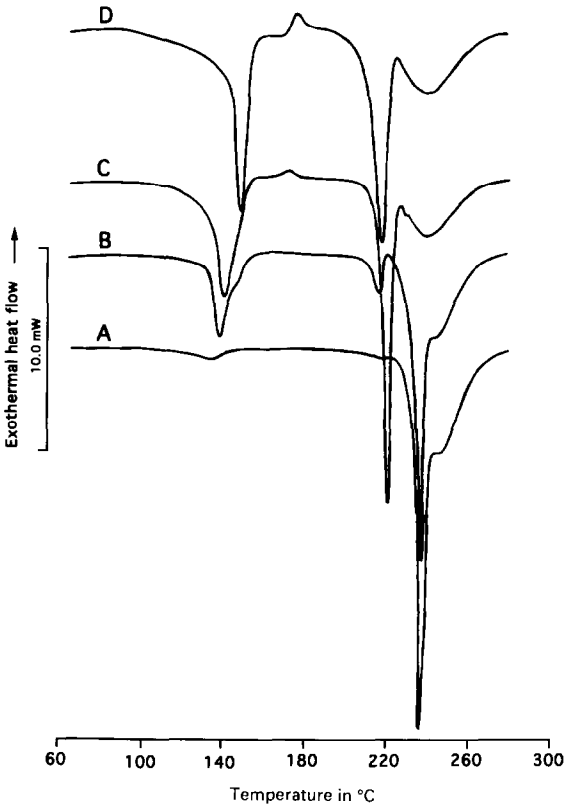

Fig. 2. DSC scans for roller-dried β-lactose: curve A, untreated; curve B, prestored for 22 days at 94% RH; and curve C, prestored for 101 days at 94% RH. The scan D represents untreated commercial α-lactose monohydrate. The dehydration peak temperatures range between 132°C and 147°C. The heat of fusion peaks are for α-lactose around 220°C and for β-lactose around 235°C. The broad low peak behind the β-lactose peak represents charring and decomposition of the lactose.

[16]. As seen in scan A, the α-lactose area peak does not correspond to 31% α-lactose (Table 1). The reason for this is that α-lactose may mutarotate to β-lactose due to the increasing heat during a DSC measurement [1,2,5,12]. The opposite process from β- to α-lactose is also possible. This will happen in closed DSC sample pans, where the release of the water of crystallization will dissolve the lactose powder resulting in mutarotation [2]. That mutarotation in lactose can proceed without dissolution has been shown after grinding and compression [5,10,11] when the lactose passes through a state of amorphous structure.

The peak that represented the heat of dehydration increased, as did also the peak temperature, with prestorage time and the relative humidity, exemplified at 94% RH by scans B and C in Fig. 2. On the whole, the increase of the hydrate content corresponded well with the microcalorimetric result. For samples that had been prestored at 94% RH for 76 days and longer the hydrate content did not increase

further (scan C), indicating that the total anhydrous lactose content had changed to the monohydrate. However, the microcalorimeter monitored a small heat flow response, showing that there was a process still going on. For scans C and D, it can be noticed that when the samples are almost completely in the form of α-lactose monohydrate, there seems to be no mutarotation from α- to β-lactose when the temperature increases during a DSC measurement.

The results presented above have been published [22]. In a succeeding study [23], where the roller-dried β-lactose was mixed with a hygroscopic excipient, microcrystalline cellulose (MCC), it was shown that the rate of incorporation of water decreased. This was explained by the fact that the water vapour was absorbed and retained by the MCC instead of being available directly for the lactose.

3.2. The miniature humidity chamber (MHC) technique

Even if the microcalorimetric response with the prestorage technique could be interpreted, this technique had the disadvantage that most of the process of incorporation was not monitored by the microcalorimeter. Furthermore, the sample mass for each measurement was very large. To be able to monitor the whole incorporation process continuously, a technique was developed that includes a source of water vapour within the microcalorimetric sample vessel converting it to a miniature humidity chamber, referred to here as the MHC technique [24]. A small container is filled with water to obtain 100% RH, or saturated salt solutions to obtain humidities lower than 100% RH. The container is placed in the powder bed (usually 100 mg) in the sample vessel (3.3 ml glass vials).

3.3. The MHC technique at 100% RH

In Fig. 3, the heat flow curves are shown at 100% RH for three samples with large contents of anhydrous lactose (curves a, b and c). The curve for commercial α-lactose monohydrate (curve d) is also included [24]. The powders are specified in Table 1. The curve representing commercial α-lactose monohydrate (d) has almost no heat flow, which is an important fact in further evaluation. It means that the endothermic heat of vaporization from the small container is cancelled by the exothermic heat of condensation, i.e. the adsorption of water, for a crystalline sample. If it is desirable to measure the heat of adsorption, a technique has to be used where the heat of vaporization will not be monitored [33–35].

The biphasic appearance, i.e. the α- and β-phases referred to earlier, of the incorporation of water in anhydrous lactose are clearly visible for curves a and b. The area under the curve of the α-phase ought to correspond approximately to the amount of anhydrous α-lactose originally in the sample, because it represents the direct incorporation of water into the original α-lactose which is a rapid process at 100% RH. However, a large part of the α-phase could not be monitored due to the fact that it proceeded during the necessary temperature equilibration period. The area under the curve of the β-phase corresponds approximately to the amount of anhydrous β-lactose in the sample (curves a–c). The larger the β-lactose content

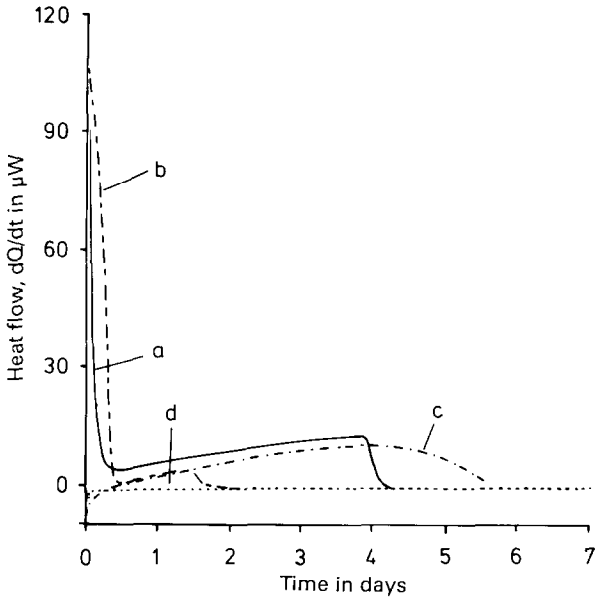

Fig. 3. Heat flow curves for 100 mg lactose at 100% RH utilizing the MHC technique. Only the proportions of the anhydrous lactose forms are listed (Table 1). Curve a, roller-dried β-lactose (——), 22% α- and 69% β-lactose; curve b, α-lactose anhydrous (– – – –), 71% α- and 20% β-lactose; curve c, crystalline β-lactose (–·–·–), 5% α- and 94% β-lactose; and curve d, commercial α-lactose monohydrate (····), 0% α- and 4% β-lactose.

(Table 1), the longer is the time to end the incorporation process. It is obvious that the β-lactose is more stable against water vapour than the anhydrous α-lactose.

The increase of the heat flow level seen for the β-phase (Fig. 3) indicated that the incorporation rate increased with time. This was proved by a series of microcalorimetric measurements with roller-dried β-lactose that were terminated after different lengths of time before the transformation to the monohydrate was complete. On each sample the heat of dehydration could be measured by DSC and the mass increase could be measured gravimetrically. The heat evolved during each microcalorimetric measurement was calculated by integrating the heat flow curve.

The microcalorimetric data (the heat of hydration) and the DSC data (the heat of dehydration) developed similarly, which showed that the incorporation rate really increased with time. However, there was a small discrepancy that was accounted for by a small endothermic contribution to the microcalorimetric heat flow curve, which comes from the mutarotation process from β- to α-lactose. The increasing incorporation rate was explained by the total water uptake. It was shown that it was much larger than the amount actually incorporated as water of crystallization. Instead the amount of condensed water increased with time resulting in an increased mutarotation rate.

Also with the MHC technique, physical mixtures consisting of roller-dried β-lactose and microcrystalline cellulose (MCC) were investigated. At higher humid-

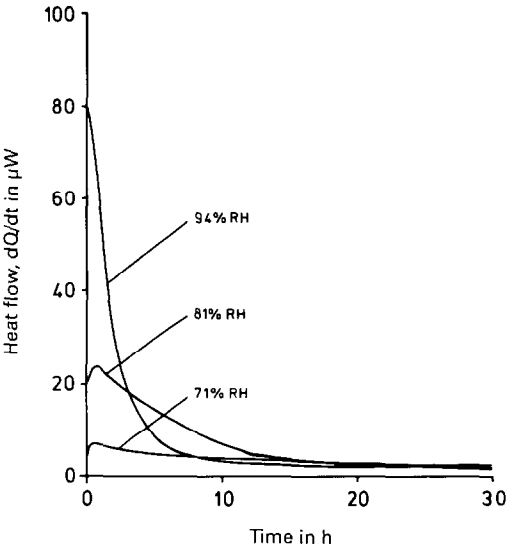

Fig. 4. Heat flow curves for 100 mg roller-dried β-lactose (Table 1) monitored at 75, 81 and 94% RH utilizing the MHC technique. The measurements proceeded for a longer time than shown in the figure.

ities it was clearly shown that the water vapour was preferentially absorbed by the hygroscopic MCC before the incorporation process started [25].

3.4. Humidities lower than 100% RH with the MHC technique

Results for the same experimental technique, but at lower humidities [25], are shown in Fig. 4 for the roller-dried β-lactose (Table 1) for the first 30 h. The longest investigated microcalorimetric measurement time was 14 days, but the incorporation process had, as expected, not terminated within this time for any of the investigated humidities. An increase of the β-phase could not be seen, which corresponds to the results in Fig. 1. The reason is that water vapour did not condense on the powder surface in such abundance as at 100% RH [24].

3.5. Prestorage of samples followed by the MHC technique at 100% RH

The MHC technique may be used to characterize lactose qualities that consist of different amounts of anhydrous α- and β-lactose (Fig. 3). It may also be used to show if a powder, normally giving a well-known heat flow curve, has been exposed to water vapour during storage or processing [24]. This was investigated by prestoring the powders for 3 months at 58–94% RH. Samples of 100 mg were thereafter monitored with the MHC technique at 100% RH. In Fig. 5 the heat flow curves for roller-dried β-lactose show that the areas of both the α- and the β-phase decrease in size as the prestorage humidity increases. For a powder that has been

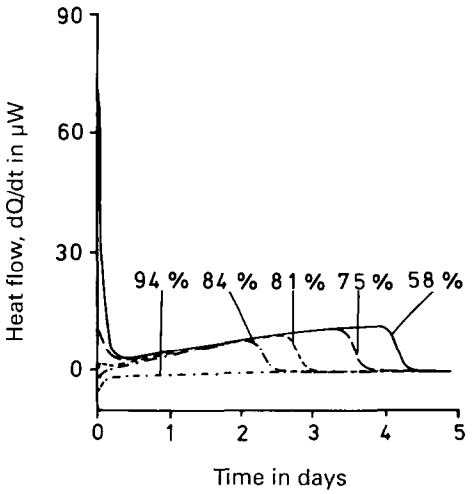

Fig. 5. Heat flow curves for 100 mg roller-dried β-lactose (Table 1) monitored at 100% RH utilizing the MHC technique after prestorage for 3 months at (——) 58% RH, (– – – –) 75% RH, (- - - -) 81% RH, (–·–·–) 84% RH and (·–·–) 94% RH.

stored at 94% RH there is no heat flow, indicating that the powder has been transformed totally to the monohydrate.

Similar measurements were performed with α-lactose anhydrous and crystalline β-lactose (Table 1) prestored for 3 months. DSC measurements were performed after the prestorage. The scans for α-lactose anhydrous are shown in Fig. 6(a). The dehydration peaks did not develop in such a consistent manner as seen for roller-dried β-lactose (Fig. 2). The dehydration peaks are split for powders that have been prestored at 75% RH (curve B), 81% RH (curve C) and 84% RH (curve D) (Fig. 6(a)), indicating that there are stages when possibly two types of hydrates are present, with one hydrate more loosely bound than the other. Split dehydration peaks for lactose have also been shown by other workers; in closed sample pans [4,5], for different particle sizes [19], after grinding [6,9] and for powders that have repeatedly been dehydrated and rehydrated [20]. The heat of dehydration was calculated, but the heat did not increase as a function of the relative humidity during storage. The powder prestored at 84% RH (curve D) had a lower value than at 75% RH (curve B), 81% RH (curve C) or 94% RH (curve E). However, the microcalorimetric measurements at 100% RH, that followed the prestorage at 84 or 94% RH, did not give any heat flow response that could be correlated with an incorporation process. Both the dehydration peaks and the fusion peaks show that the transformation to the α-lactose monohydrate was a complex process.

For crystalline β-lactose (Fig. 6(b)) the DSC scans are shown after prestorage at 58% RH (curve A), 84% RH (curve B) and 94% RH (curve C). The scan for the sample after 7 days microcalorimetric measurement at 100% RH (curve D) is also

included. The dehydration peaks changed little in size between 58% RH (curve A) and 84% RH (curve B), but there was a change in the appearance of the scans. The scan for a sample stored at 94% RH (curve C) had changed considerably showing that the powder had partly transformed to the monohydrate. It is clear that it will take time to change totally to the monohydrate. The DSC results were consistent with the microcalorimetric measurements utilizing the MHC technique at 100% RH.

It was also shown that the α-lactose monohydrate formed from the different starting materials gave both somewhat different appearances of the scans and different heat of dehydration values: 181 J g^{-1} (roller-dried β-lactose, Fig. 2, scan C), 167 J g^{-1} (α-lactose anhydrous, Fig. 6(a), similar appearance as at 94% RH, scan E) and 155 J g^{-1} (crystalline β-lactose, scan D, Fig. 6(b)). The commercial α-lactose monohydrate (Fig. 2, scan D) had a value of 157 J g^{-1}. Previously, a value of 144 J g^{-1} was published [4,19]. That several factors may influence values obtained by DSC is well known [21]. However, it is obvious that there are physical differences between the various α-lactose monohydrates formed.

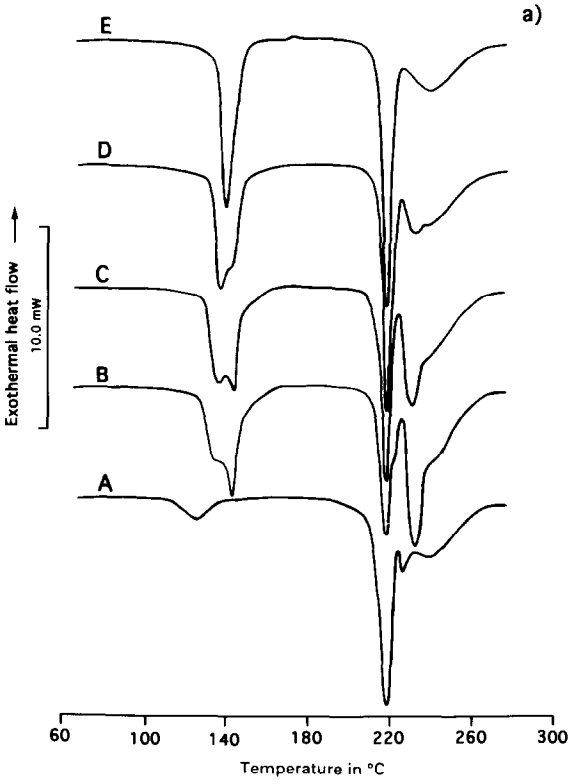

Fig. 6. (a).

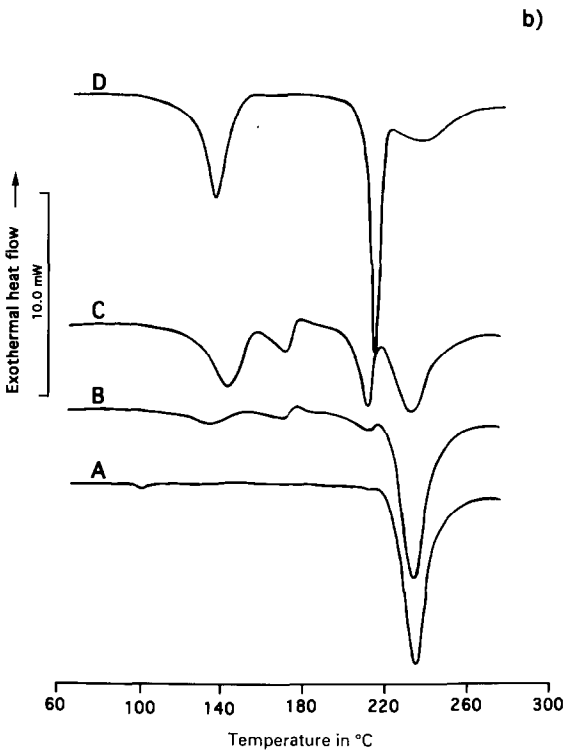

Fig. 6. DSC scans for (a) α-lactose anhydrous after storage for 3 months at (curve A) 58% RH, (curve B) 75% RH, (curve C) 81% RH, (curve D) 84% RH and (curve E) 94% RH and (b) crystalline β-lactose after storage for 3 months at (curve A) 58% RH, (curve B) 84% RH, (curve C) 94% RH and after 7 days microcalorimetric measurements at 100% RH (curve D). The dehydration peak is around 140 C, the fusion of α-lactose around 220°C and the fusion of β-lactose around 235°C. The broad, low peak behind the β-lactose peak, represents charring and decomposition of the lactose. The powders, before the prestorage, are specified in Table 1.

4. Amorphous lactose exposed to water vapour

The last study presented will show that isothermal microcalorimetry is an excellent technique for measuring small amounts of amorphous material in lactose [26]. Several processes, such as freeze-drying [4,5], spray-drying [1,5], milling and compression [5–11] may render the lactose powder partly or totally amorphous, i.e. it has a disordered structure. In the studies referred to above, conventional thermal analysis techniques were utilized. The amorphous parts are in a higher energy state, and will therefore more easily absorb water vapour than the crystalline parts. When the water content in the total amorphous structure has reached a concentration at which the glass transition temperature has decreased below the experimental temperature, the amorphous parts will crystallize [38]. In a sorption isotherm the crystallization will be shown as a rapid drop in the curve, because the formed

crystalline parts desorb the superfluous water [3]. The amount of water vapour absorbed before the crystallization can be measured to calculate small amounts of amorphous material, e.g. see studies on sucrose [39].

Thermal analysis can also be used to measure the amorphous content by utilizing the higher energy state of the amorphous structure. When DSC is used, the increasing temperature will eventually lead to crystallization of the amorphous lactose associated with an evolution of heat. However, the amorphous content must usually be above 10% to enable a reliable result to be obtained [39].

As indicated above, it is also possible to get a measure of the amorphous content by isothermal microcalorimetry. This application has briefly been described for drugs that have become partly amorphous due to milling [32]. For the lactose studies, the MHC technique was used as described above, varying the sample size and the relative humidity [26]. The samples consisted of a spray-dried lactose powder, either almost totally in the amorphous form and thus referred to as 100% amorphous, or of mixtures consisting of amorphous and crystalline lactose.

In Fig. 7, a schematic microcalorimetric heat flow curve is shown for a 100% amorphous sample at 57% RH. The curve is divided into three phases. Phase I represents the heat flow when the amorphous parts absorb water vapour. Phase II corresponds to the actual crystallization process. Phase III is still obscure, but may

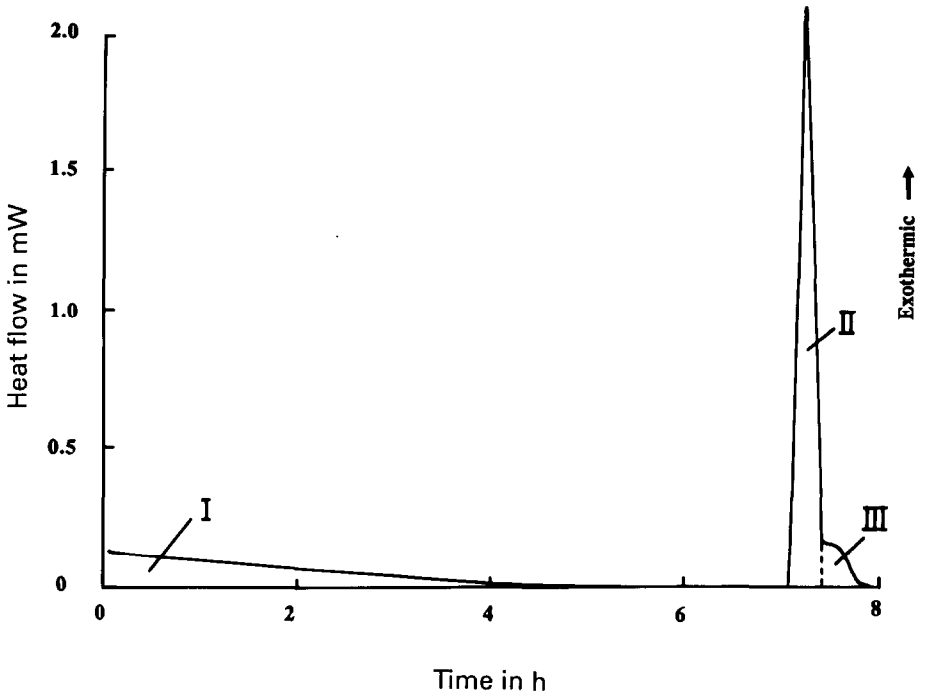

Fig. 7. Schematic microcalorimetric heat flow curve for a 31 mg sample of 100% amorphous lactose monitored at 57% RH utilizing the MHC technique. Phases I, II and III are explained in the text.

composition of α-lactose monohydrate, anhydrous α-lactose and β-lactose may vary after spray-drying [40]. This ought to influence the appearance of the heat flow curve like phase III. The peak (phase II) is integrated and the heat evolved becomes a measure of the amorphous content, as described below.

Samples of 100% amorphous lactose were measured at 57% RH, 75% RH, 84% RH and 100% RH, respectively. The time to reach the necessary concentration of water vapour in the powder naturally differed for the various humidities and thus the time for the crystallization event varied. The time until the maximum peak value was reached ranged between 7.2 and 2.3 h for a sample mass of 31 mg (100% amorphous). The heat of crystallization had a mean value of 32 J g^{-1}.

The value calculated for the slope was also 32 J g^{-1} when the heat evolved was plotted as a function of sample mass (correlation coefficient, 0.994). The sample mass of 100% amorphous lactose was varied between 16 and 60 mg and investigated at 57% RH. The result showed that microcalorimetry could detect and measure small amounts of amorphous lactose. This was further evaluated by monitoring physical mixtures of 100% amorphous and α-lactose monohydrate (referred to as 100% crystalline). In Fig. 8, the measurements are shown for samples that have less than 12% disorder, the content where other techniques such as X-ray diffraction analysis and DSC often can only give rough estimates of the amorphous content. An excellent linearity was obtained (correlation coefficient, 0.999). This curve was later used as a standard curve for spray-dried samples prepared to contain various amounts of amorphous lactose. For high contents (above 20%) agreement was shown with DSC and X-ray diffraction data, but at lower contents these two methods could not compare with the microcalorimetric result.

Microcalorimetry can probably be used down to an amorphous content of 1% when the experimental conditions have been further improved. Microcalorimetry could thus possibly become the standard method for such characterizations in the future.

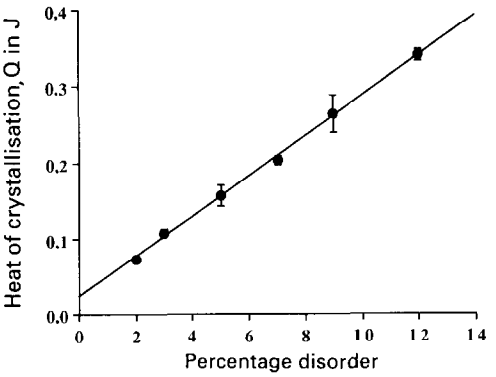

Fig. 8. The heat of crystallization obtained by microcalorimetry (phase II) at 57% RH as a function of percent disorder in physical mixtures between 100% amorphous and 100% crystalline lactose. The error bars represent standard deviation ($n = 3$).

5. Conclusions

Lactose powders can be obtained in a number of qualities that interact differently with water vapour, possibly leading to changed properties. Of the thermal analysis techniques, DSC has especially been used in the characterization of lactose. Isothermal microcalorimetry has been shown to be a valuable complement to DSC and, for certain applications, is more informative than DSC.

The miniature humidity chamber technique has been shown to be a simple technique which allows continuous measurements at constant relative humidities. Anhydrous α- and β-lactose both transform to α-lactose monohydrate when exposed to water vapour. However, the β-lactose must first mutarotate to α-lactose, which is a rate-limiting process. Microcalorimetry may, in the future, be the technique of choice for measuring small amorphous contents of lactose and other semicrystalline materials.

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