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Assessment of the degree of disorder in crystalline solids by isothermal microcalorimetry

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Abstract

The use of isothermal heat-conduction microcalorimetry for assessment of degree of the disorder within crystalline material has been evaluated. Single entities, physical mixtures with varying contents of 100% amorphous lactose and 100% crystalline α-lactose monohydrate, and samples of spray dried lactose with varying degrees of disorder were analysed at 25°C. The technique monitors the heat flow from the crystallisation of the amorphous content of the powder, when the powder is exposed to a humid environment. The heat calculated from the heat flow curve by integration revealed good linearity. The technique was able to detect at least 2% disorder in a crystalline sample. Comparisons with X-ray analysis and DSC showed good agreement above 10% disorder. At lower degrees of disorder only microcalorimetry was able to measure the disorder with high accuracy.

Key words: Amorphous material; Crystallinity; Crystallisation; Disorder; DSC; Microcalorimetry; Moisture sorption; X-ray analysis

1. Introduction

Drugs used in the production of solid dosage forms are often recognized as crystalline. However, there are many processes, such as freeze drying, spray drying and comminution, which can transform particles or parts thereof to higher, disordered, energy states (Hüttenrauch, 1978, 1988; Hersey and Krycer, 1980). Many well-known excipients such as microcrystalline cellulose and spray dried lactose for direct compression are semi-crystalline, with regions of amorphous contents within their structure.

It seems as if a material can have a disordered structure throughout the entire particle, i.e., the whole particle is rendered amorphous, or that the disorder is located on the surface of the particle, as a surface layer or as so-called 'frictional hot spots'. In either case, the molecular mobility of the activated regions is increased (Ahlneck and Zografi, 1990). Materials that possess large quantities of disorder have been shown to have other properties than crystalline materials when compacted (Vromans et al., 1986, 1987; Sebhatu et al., 1994). Amorphism has also led to decreased chemical stability (Otsuka and Kaneniwa, 1990)

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and to increased dissolution rates (Chiou and Kyle, 1979; Hendriksen, 1990). Even if only the surface layers or parts thereof are in an activated state this may still have a pronounced effect on the physico-chemical properties, since many particle characteristics depend on the structure and state of the surface. Ground samples of alkali halides have been shown to be affected on storage at relative humidities below their critical relative humidity (RH_0) (Kaiho et al., 1973; Chikazawa et al., 1976). Kontny et al. (1987) showed that sodium chloride and sodium salicylate had a reduced surface area when stored at relative humidities below RH_0. Effects on milled particles by compaction have been reported on (Ahlneck and Alderborn, 1989; Alderborn and Ahlneck, 1991). Effects of comminution of pharmaceuticals have also been shown to affect the solubility of materials with low solubility (Florence and Salole, 1976; Elamin et al., 1992). The altered properties described above were all attributed to the disordered structure. It is therefore of the utmost importance to be able to measure the amorphous content in pharmaceuticals.

Measurements of the degree of crystallinity have been performed mainly by X-ray analysis (Klug and Alexander, 1974; Black and Lovering, 1977), infrared spectroscopy (Susi and Ard, 1973; Black and Lovering, 1977), solid-state NMR spectrometry (Murari, 1989) or by density (Duncan-Hewitt and Grant, 1986). The general problem these techniques exhibit is that they measure the average degree of order throughout the bulk and thus have limited capability when measuring small amounts of disorder. Techniques that utilize, directly or indirectly, the higher state of energy associated with the disordered state are preferable. One such technique, water vapour sorption, has been shown to be a useful method for measurements of amounts of disorder as low as 1% for milled samples of sucrose (Saleki-Gerhardt et al., 1994).

Another possibility is to measure the heat evolved during the transformation of an amorphous material to its crystalline state. The most widely used technique for such measurements is differential scanning calorimetry (DSC). From a scan of increasing temperature it is possible to detect and measure the heat of crystallisation of an amorphous material. However, the usefulness of DSC is limited to samples with high amounts of disorder (Saleki-Gerhardt et al., 1994). An interesting alternative to DSC is isothermal heat-conduction microcalorimetry, which has a higher sensitivity, for measurements of the transformation of amorphous materials to the crystalline state by the action of water vapour. Many pharmaceutical substances with amorphous contents are sensitive to moisture since the disordered parts are able to act as 'active centres' for the absorption of water vapour. This is the rationale behind the water vapour technique referred to above (Saleki-Gerhardt et al., 1994). The measurements will be performed at conditions that favour crystallisation, e.g., selection of a suitable vapour pressure and temperature. The amorphous material will crystallise when the water content in the total amorphous structure has reached a concentration at which the glass transition temperature has been decreased below the operation temperature (Ahlneck and Zografi, 1990; Oksanen and Zografi, 1990).

Isothermal heat-conduction microcalorimetry measures the heat flow (dQ/dt) from ongoing processes. With the so-called miniature humidity chamber technique, the processes are allowed to proceed at a specified relative humidity in a sample vessel. This technique has been utilized to characterise the incorporation of crystal water in anhydrous lactose and the absorption of water vapour in microcrystalline cellulose (Angberg et al., 1992a,b). Utilisation of this technique to monitor the crystallisation processes has been described briefly by Byström (1990). However, a thorough evaluation of its applicability has not yet been published.

The aim of this study was to evaluate the use of isothermal microcalorimetry at 25°C for assessments of the degree of disorder in processed solids. The substance used was spray dried lactose, which is converted from the amorphous to the crystalline state when exposed to water vapour within the microcalorimetric sample vessel. Results obtained from microcalorimetry were compared with measurements by X-ray analysis and DSC.

2. Materials and methods

2.1. Materials

α-Lactose monohydrate (Pharmatose, DMV, The Netherlands) was used for preparation of lactose solutions and suspensions for the spray drying process and as a reference material corresponding to 100% crystalline lactose. β-Lactose (AB Svenskt Mjölksocker, Sweden) was used for the X-ray diffraction measurements.

2.2. Spray drying

A solution or a suspension of α-lactose monohydrate was spray dried in an A/S Nitro automiser (Anhydro, Denmark). To obtain samples with different degrees of disorder various spray drying parameters were altered (Table 1). After spray drying, the samples were dried at 70°C for 24 h to remove residual water. Thereafter the samples were stored over P_2O_5 before characterisation. The obtained particle sizes ranged between 3 and 10 μm approximately.

2.3. Microcalorimetry

The microcalorimeter system used was the 2277 Thermal Activity Monitor (TAM) (Thermometric AB, Sweden), consisting of four independent isothermal heat-conduction microcalorimeters (Suurkuusk and Wadsö, 1982). The heat flow signal (dQ/dt in μW) is monitored as a function of time. By integrating the heat flow curve over a specific time interval the heat (Q in J) evolved or absorbed can be obtained. Exothermic signals are given positive values. The experimental temperature used was 25.0°C.

The spray dried lactose (100% amorphous) and α-lactose monohydrate were investigated alone, sample weights ranging between 16 and 60 mg, or in physical mixtures with a spray dried lactose content ranging between 2 and 100%. The total sample weight for the physical mixtures was 100 mg for mixtures with up to 60% spray dried lactose and 60 mg for the mixtures consisting of 70 and 90% spray dried lactose. For the samples described in Table 3, a sample weight range of 30–250 mg was used.

The measurements were performed according to the miniature humidity chamber technique (Angberg et al., 1992a,b). A powder sample was placed in a sample vessel, a 3.3 ml glass vial, together with a small container filled with a saturated salt solution or water. After the closure of the vial a specified relative humidity (RH), 57, 75, 84 or 100% RH (Nyqvist, 1983), was created within the sample vessel. The reference vessel only contained a sample of α-lactose monohydrate. The sample and reference vessels were temperature equilibrated for 20 min within the TAM, before the vessels were lowered into the measurement position and the monitoring of the heat flow signal and the computer program were started. This time is referred to as $t = 0$. The measuring principles, the calibration procedure and the temperature equilibration, etc., are described by Angberg (1992).

Table 1
Parameters used in spray drying to obtain various contents of disorder in lactose

Sample	Inlet temperature (°C)	Outlet temperature (°C)	Feed flow (l/h)	Concentration ratio lactose/water (g/g)
100% amorphous	185	85	0.6	1:7
I	160	75	1.0	1:3.5
II	150	70	1.2	1:2.5
III	150	65	1.2	1:2
IV	140	65	1.5	1:1.5
V	125	60	1.5	1:1

2.4. X-ray analysis

Samples were analysed with an XDS2000 diffractor (Scintag, U.S.A.) using Cu-Kα radiation 45 kV, 30 mA and a germanium detector. The samples were scanned in steps of 0.03° from 5 to 35° (2θ) with 2 and 4 mm primary slits. Quantitative estimates were made using the peaks at 10.5° (β-lactose) and multipeaks (α-lactose monohydrate).

2.5. DSC

A differential scanning calorimeter, DSC 220 (Seiko instruments, Japan), was used together with oscillating differential calorimetry software (ODSC). The sample was exposed to a linear heating ramp which had a superimposed sinusoidal ripple. The sample weight was 5–8 mg. Scanning was performed at a heating rate of 10°C/min in the temperature range 20–280°C in a nitrogen atmosphere. The oscillating frequency used was primarily 0.02 Hz and the amplitude 1–3°. Aluminium oxide was used as a reference. Exothermic signals are given positive values.

3. Results and discussion

3.1. Characterisation of the reference materials

When evaluating the microcalorimetric technique for its ability to measure the degree of disorder in crystalline materials it is important to investigate reference samples. Fig. 1a shows the X-ray diffraction pattern of an amorphous sample (hereafter referred to as 100% amorphous lactose). It is evident that this sample has no signs of crystalline α-lactose monohydrate, but a small content of crystalline β-lactose of about 1% is shown at 10.5°. Fig. 1b shows the typical diffrac-

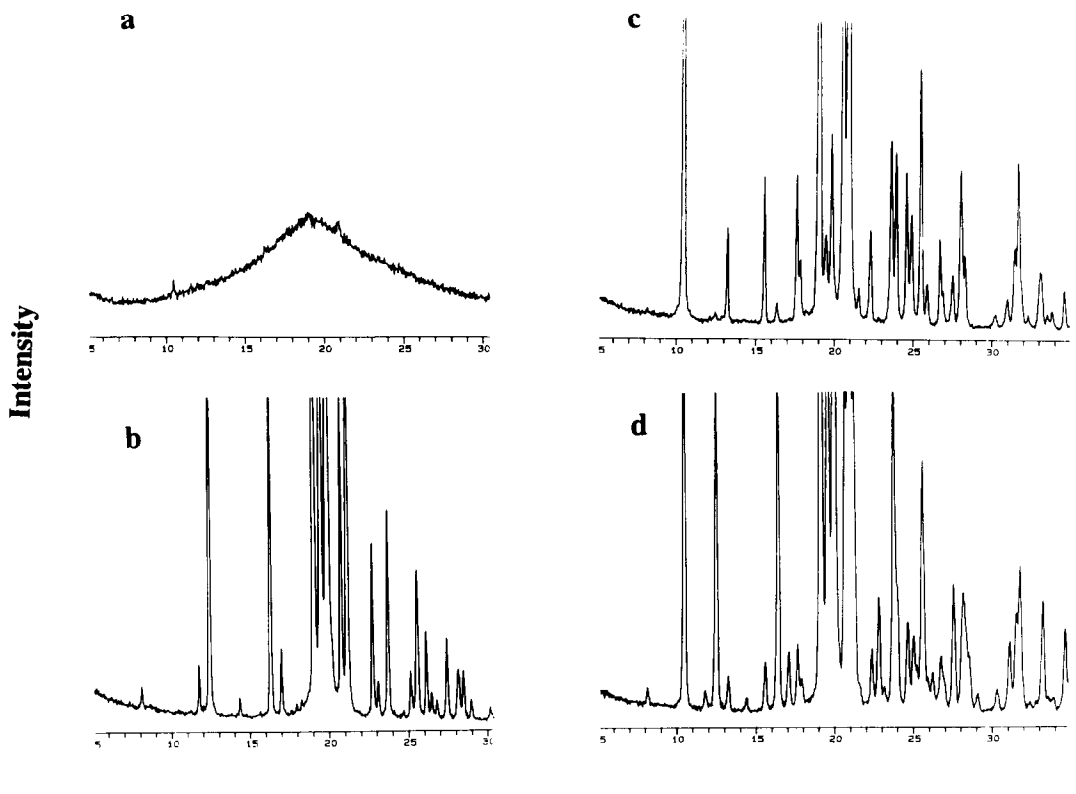

Fig. 1. X-ray powder diffraction patterns for (a) spray dried amorphous lactose (referred to as 100% amorphous lactose), (b) crystalline α-lactose monohydrate (referred to as 100% crystalline lactose), (c) crystalline β-lactose, and (d) spray dried lactose crystallised at 75% RH.

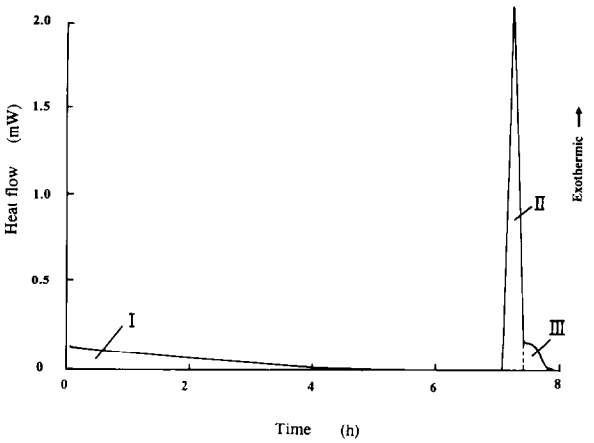

Fig. 2. Schematic microcalorimetric heat flow curve for a 31 mg sample of 100% amorphous lactose monitored at 57% RH. Phases I, II and III are explained in the text.

tion pattern for α-lactose monohydrate (hereafter referred to as 100% crystalline lactose) with no signs of β-lactose (shown in Fig. 1c). It was decided that these samples would be used as reference samples.

Fig. 1d shows a 100% amorphous sample which has crystallised after exposure to 75% RH. The diffraction pattern at 10.5° shows that a large content (40%) of β-lactose is present in the sample. It can be concluded that crystallisation of the spray dried amorphous lactose used in this study crystallises to a mixture of α-, and β-lactose.

3.2. Microcalorimetric measurements of the reference samples

The heat flow curve for the 100% amorphous lactose reference when exposed to 57% RH is shown in Fig. 2. For the 100% crystalline reference no signal was obtained. The curve in Fig. 2 shows three phases. Phase I starts directly with an exothermic heat flow, which shows that a process has started before it could be monitored by the microcalorimeter due to the necessary temperature equilibration period. The signal then descends slowly to a minimum value approximately superimposing the basclinc until phase II begins. Phase I represents absorption of water vapour into the amorphous structure, presumably also during the time period of zero heat flow, but with the vaporisation and absorption processes cancelling each other out (Angberg et al., 1992a,b). In phase II the signal gives a high and narrow exothermic peak, representing crystallisation of the amorphous lactose.

Finally, the curve shows a phase III until the signal reaches zero again. What this phase represents has not been investigated. There is a release of water vapour from the powder sample as a consequence of the crystallisation of the amorphous regions. However, the vapour ought to condense into the small container with solution in it. The heat flow from these two processes ought to cancel each other out or show an endothermic heat flow, which was discussed above for the opposite process in phase I. One probable explanation is that the α-lactose formed after crystallisation, in addition to the β-lactose, is anhydrous and that water is incorporated to form the monohydrate. Such a conversion is also possible at 57% RH for unstable anhydrous α-lactose (Berlin et al., 1971). The X-ray analysis (Fig. 1d) showed clearly both the content of α-lactose monohydrate and β-lactose in crystallised samples. However, in that case the supposed conversion from

Table 2
Data from microcalorimetric measurements of 100% amorphous lactose at various relative humidities (standard deviation in parentheses)

Relative humidity (%)	Sample weight (mg)	Number of samples	Peak time (h)	Heat Phase II (J)	Specific heat of crystallisation (J/g)
57	30.4 (0.67)	7	7.2 (0.76)	0.951 (0.051)	31.3 (1.20)
75	29.9 (0.73)	6	4.6 (0.43)	0.954 (0.059)	31.9 (1.47)
84	30.0 (0.48)	6	3.1 (0.30)	0.975 (0.019)	32.5 (0.85)
100	29.9 (1.0)	4	2.3 (0.17)	0.923 (0.019)	30.9 (1.30)
57–100 (total)	30.1 (0.71)	23	–	0.953 (0.044)	31.7 (1.28)

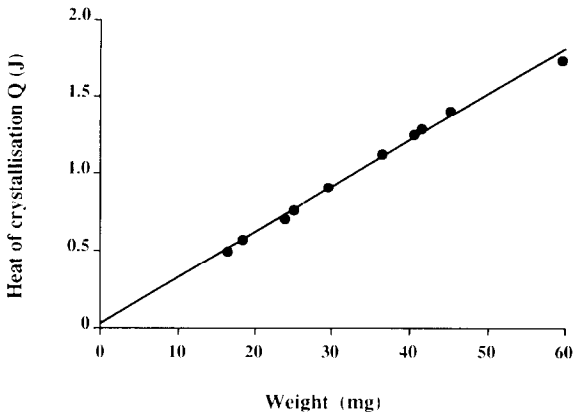

Fig. 3. Heat of crystallisation obtained by microcalorimetry (phase II) at 57% RH as a function of sample weight for 100% amorphous lactose.

the anhydrous α-lactose to the monohydrate had already taken place.

It might be possible to estimate the degree of disorder by integration of the heat flow signal obtained due to the water vapour uptake (I) and crystallisation (II). However, since the uptake of water started almost immediately after preparation of the sample, it was decided that no measurements of water uptake for estimation of the degree of disorder should be performed. Furthermore, the time period with zero heat flow in phase I but with continuous absorption of water vapour will not be included in the calculation. Instead, it was decided to integrate only the second phase, where heat is evolved from the crystallisation process, for assessment of the degree of disorder (Table 2). The specific heat of crystallisation has a mean value of 32 J/g. When all measurements are accounted for the relative standard deviation is $\pm 4.0\%$. The precision seems to be acceptable. The accuracy of the specific heat of crystallisation obtained is dependent on the accuracy of the electrical calibration (Angberg, 1992). The narrow peak indicates that the crystallisation proceeds simultaneously for the total amorphous content within the sample. For a rapid process, as in this case, the microcalorimetric curve may show a small displacement from the real event. However, this will not influence the calculation of the heat evolved.

The specific heat of crystallisation should naturally be independent of the RH during the measurements, as shown in Table 2. However, the time to reach the crystallisation process varies with the humidity. Here it took between 2.3 and 7.2 h to reach the peak maximum (Table 2). From the data reported in Table 2, 57% RH was chosen as suitable for the other measurements.

For the evaluation of the microcalorimetric technique it is important to investigate its sensitivity, e.g., to find the lowest detectable amount of amorphous material that can be measured. For this evaluation samples of 100% amorphous lactose with varying weights were analysed (Fig. 3). As seen, good linearity was obtained in a plot of

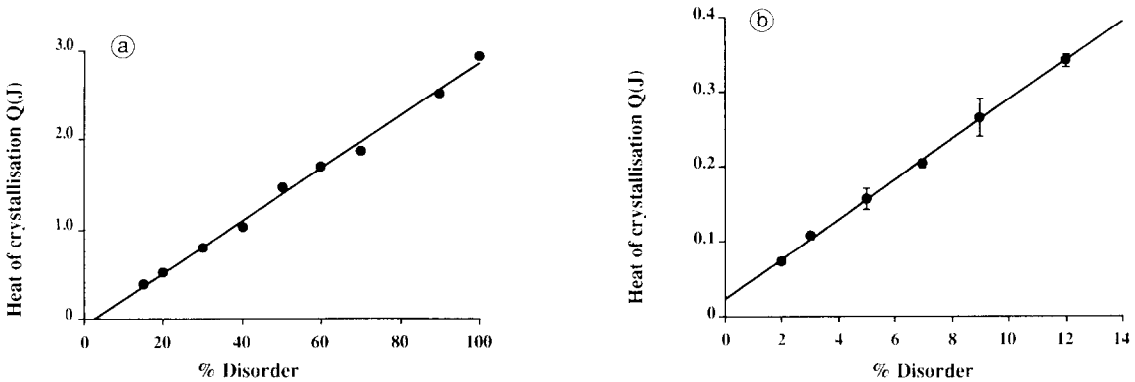

Fig. 4. Heat of crystallisation obtained by microcalorimetry (phase II) at 57% RH as a function of % disorder in physical mixtures between 100% amorphous and 100% crystalline lactose at 57% RH. (a) Mixtures with a degree of disorder above 15% ($n = 2$); (b) mixtures with a degree of disorder between 2 and 12% ($n = 3$). The error bars represent standard deviation.

heat of crystallisation vs the amount of amorphous lactose. The intercept is close to 0 and the correlation coefficient is 0.994. The slope is 32 J/g, which corresponds to the specific heat of crystallisation obtained at different RH (Table 2). The restricting factor for lowering the sample weight further is the time at which the crystallisation peak appears. The shortest time to reach the peak for the 100% amorphous lactose samples measured was 2 h (16 mg). For samples that contain a very low amount of amorphous material the crystallisation may come within the time for the temperature equilibration or when the sample and reference vessels have just been lowered to the measurement position, which will disturb the heat flow signal. To avoid this a lower RH can be used, as indicated above.

3.3. Microcalorimetric measurements of physical mixtures of amorphous and crystalline lactose

The heat flow signals for the crystallisation of lactose in a physical mixture consisting of 100% amorphous and 100% crystalline lactose were monitored when exposed to 57% RH in the sample vessels. As before, phase II was integrated to obtain the heat of crystallisation. From Fig. 4a it is evident that for mixtures containing large amounts of amorphous lactose (more than 15%) there is no problem in estimating the degree of disorder in a sample. Only a few measurements were performed in duplicate in this region due to the good linearity (correlation coefficient = 0.995). A careful evaluation was instead made in the region of less than 15% disorder, where other techniques such as DSC and X-ray analysis have earlier had problems to detect small amorphous contents in 'crystalline' samples (Saleki-Gerhardt et al., 1994).

In Fig. 4b it is shown that samples containing a low degree of disorder, between 2 and 12%, also give excellent linearity (correlation coefficient = 0.999), with usually only small standard deviations at each point ($n = 3$). These measurements show how sensitive the microcalorimetric technique is in estimating low amounts of amorphous content. The two slopes can nevertheless be used to calculate the amorphous content in unknown samples.

3.4. Comparisons between microcalorimetry and other measuring techniques

Five samples of lactose with varying degrees of disorder were prepared by altering the spray drying parameters (Table 1). These samples were used for comparisons of the microcalorimetric results with X-ray analysis and DSC measurements.

The X-ray diffraction patterns obtained for the five samples showed that all samples contained a large but varied portion of crystalline α-lactose monohydrate. No β-lactose was found. The measured degree of disorder for the samples is listed in Table 3. X-ray analysis is a good method for assessing the degree of disorder for samples containing relatively high amounts of amorphous content, above 10%. When the degree of crystallinity is higher than 90% problems arise. For the values given for most crystalline samples, IV and V, the results are only rough estimates. However, it is possible to make preliminary assessments by careful monitoring. For samples containing less than 85% crystallinity X-ray analysis is often a better choice than microcalorimetry since it can provide information about the structure of the material. Comparisons of the degree of disorder for the samples were also performed by a new DSC technique using oscillating heat flow (ODSC – sometimes also referred to as

Table 3
Comparisons of the degree of disorder between different measurement techniques (samples according to Table 1; standard deviation for microcalorimetry in parentheses)

Sample	X-ray	ODSC		Microcalorimetry	
	Degree of disorder (%)	Specific heat of crystallisation (J/g)	Degree of disorder (%)	Specific heat of crystallisation (J/g)	Degree of disorder (%)
Amorphous	99	170	100	31.3 (1.2)	100
I	54	85.2	50	15.7 (0.8)	50
II	32	54.7	32	10.3 (0.3)	33
III	16	32.5	19	5.49 (0.3)	18
IV	7	[a]	[a]	2.39 (0.03)	7.6
V	5	[a]	[a]	0.98 (0.06)	3.1

[a] Not measurable by this technique.

modulated DSC, MDSC). The heat flow signal obtained by ODSC is equivalent to the heat flow data collected by conventional DSC. However, the heat flow can be separated into a heat capacity (C_p) component, which gives information on reversible events such as glass transitions, and a kinetic component, which provides data on irreversible transformations such as crystallisation and dehydration. These combined components together give additional information compared to conventional DSC. In Fig. 5, the scan for a conventional DSC profile is shown together with the C_p and kinetic components. The endothermic peak below 100°C, shown by the kinetic component, is the desorption of absorbed water in the amorphous lactose. By separation of the conventional DSC scan it is possible to see that the crystallisation peak at 173°C is a combined effect of a large irreversible exothermic peak and a smaller reversible endothermic peak. The exothermic peak gives the heat of crystallisation whereas the endothermic peak probably reflects a conversion between two crystalline forms. In evaluation of the degree of disorder, the heat of crystallisation measured for the exothermic peak by ODSC was used. The data obtained are in very close agreement with X-ray analysis and microcalorimetry when the samples are not too highly crystalline (Table 3).

Even if both microcalorimetry and DSC are calorimetric methods the crystallisation is provoked in different ways. In DSC it is the temperature increase that leads to the transformation while in microcalorimetry it is mainly the water uptake when ambient temperatures are used. Due to the different mechanisms the heat of crystallisation obtained by the two techniques will be different (Table 3). The values of the degree of disorder measured by microcalorimetry are often in close agreement with the values from X-ray analysis and ODSC (Table 3). However, while these methods could not accurately determine the amorphous content in the samples with the lowest degree of disorder, it was possible with

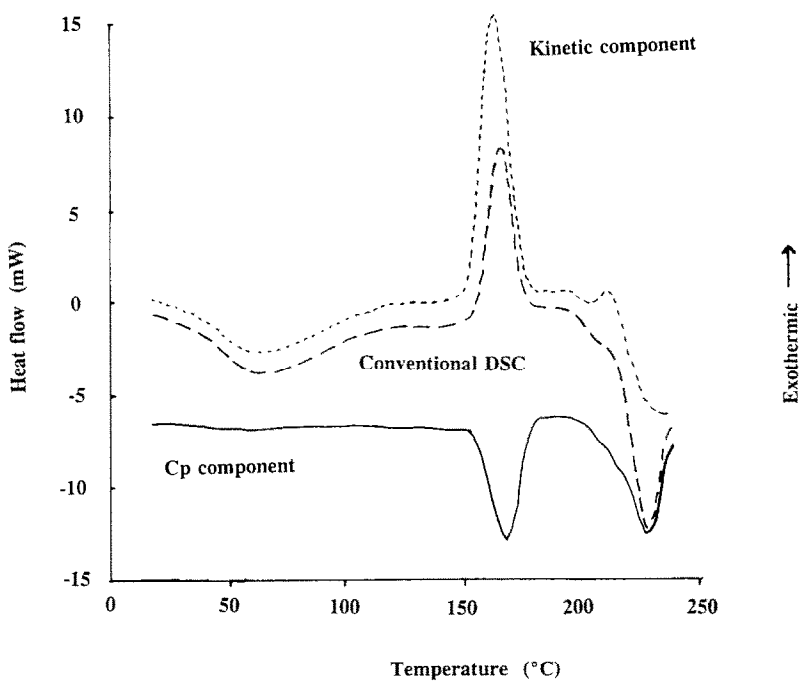

Fig. 5. DSC scan with oscillating heat flow for 100% amorphous lactose. A conventional scan is shown together with its separated kinetic and C_p components, showing irreversible and reversible transformations, respectively.

microcalorimetry to measure the amorphous content. The measured degree of disorder was 3.1% for sample V, for which X-ray analysis gave approx. 5%. This demonstrates the suitability of microcalorimetry for detecting low amounts of disorder in processed samples.

There are several parameters that can be changed to improve the assessment of the degree of disorder in a 'crystalline' material. As described earlier it is not until all amorphous regions have reached a certain condition that it will crystallise, e.g., the water concentration. The time taken to reach this water concentration will depend, for example on the amount of amorphous material in the sample, the relative humidity, how the water source is placed within the sample vessel and the water surface area. All these variables can be changed to obtain optimal measurement conditions. Furthermore, the sensitivity level of the microcalorimeter can be increased and the integration of phase II can be improved. There is no doubt that the lowest detectable amount of disorder could be very small, probably less than 1%.

4. Conclusions

Measurements with microcalorimetry have advantages when estimating the degree of disorder for highly crystalline samples (less than 10% of disorder) compared to methods such as X-ray analysis and DSC. The lowest measured degree of disorder in this study was 2%. However, by improving the measurement conditions further analysis of amorphous contents less than 2% will be possible. Furthermore, when checking for small differences in the amorphous content of materials after purchase or in house processing, microcalorimetry will be a valuable addition to other techniques.

5. Acknowledgement

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6. References

Ahlneck, C. and Alderborn, G., Moisture adsorption and tabletting: II. The effect on tensile strength and air permeability of the relative humidity during storage of tablets of three crystalline materials. *Int. J. Pharm.*, 56 (1989) 143–150.

Ahlneck, C. and Zografi, G., The molecular basis of moisture effects on the physical and chemical stability of drugs in the solid state. *Int. J. Pharm.*, 62 (1990) 87–95.

Alderborn, G. and Ahlneck, C., Moisture adsorption and tabletting: III. Effect on tablet strength – post compaction storage profiles. *Int. J. Pharm.*, 73 (1991) 249–258.

Angberg, M., Evaluation of isothermal heat-conduction microcalorimetry in pharmaceutical stability studies. Ph.D. Thesis, Dept of Pharmaceutics, Uppsala University, Sweden (1992).

Angberg, M., Nyström, C. and Castensson, S., Evaluation of heat-conduction microcalorimetry in pharmaceutical stability studies: V. A new approach for continuous measurements in abundant water vapour. *Int. J. Pharm.*, 81 (1992a) 153–167.

Angberg, M., Nyström, C. and Castensson, S., Evaluation of heat-conduction microcalorimetry in pharmaceutical stability studies. VI. Continuous monitoring of the interaction of water vapour with powders and powder mixtures at various relative humidities. *Int. J. Pharm.*, 83 (1992b) 11–23.

Berlin, E., Kliman, P.G., Anderson, B.A. and Pallansch, M.J., Calorimetric measurements of the heat of desorption of water vapor from amorphous and crystalline lactose. *Thermochim. Acta*, 2 (1971) 143–152.

Black, D.B. and Lovering, E.G., Estimation of the degree of crystallinity in digoxin by X-ray and infrared methods. *J. Pharm. Pharmacol.*, 29 (1977) 684–687.

Byström, K., Microcalorimetric testing of physical stability of drugs in the solid state. *Thermometric Application Note 22004*, Thermometric AB, Järfälla, Sweden, 1990.

Chikazawa, M., Kaiho, M. and Kanazawa, T., Changes in surface properties of sodium bromide due to moisture absorption. *Nippon Kagaku Kaishi*, (1976) 410–414.

Chiou, W.L. and Kyle, J., Differential thermal, solubility and aging studies on various sources of digoxin and digitoxin powder. Biopharmaceutical implications. *J. Pharm. Sci.*, 68 (1979) 1224–1229.

Duncan-Hewitt, W.C. and Grant, D.J.W., True density and thermal expansivity of pharmaceutical solids: comparison of methods and assessment of crystallinity. *Int. J. Pharm.*, 28 (1986) 75–84.

Elamin, A.A., Alderborn, G., Nyström, C. and Ahlneck, C., Effects of mechanical processing on the solubility of griseofulvin. *AAPS Annual Meeting*, San Antonio, p. 163 (PT 6196) (1992).

Florence, A.T. and Salole, E.G., Changes in crystallinity and solubility on comminution of digoxin and observations on spironolactone. *J. Pharm. Pharmacol.*, 28 (1976) 637–642.

Hendriksen, B.A., Characterization of calcium fenoprofen: 1.

Powder dissolution rate and degree of crystallinity. *Int. J. Pharm.*, 60 (1990) 243–252.

Hersey, J.A. and Krycer, I., Biopharmaceutical implications of technological change. *Int. J. Pharm. Technol. Prod. Manuf.*, 1 (1980) 18–21.

Hüttenrauch, R., Molekulargalenik als grundlage moderner arzneiformung. *Acta Pharm. Technol.*, (Suppl.) 6 (1978) 55–127.

Hüttenrauch, R., Fundamentals of pharmaceutics. *Acta Pharm. Technol.*, 34 (1988) 1–10.

Kaiho, M., Chikazawa, M. and Kanazawa, T., Influence of adsorbed water on surface state of sodium chloride powder. *Nippon Kagaku Kaishi*, (1973) 914–917.

Klug, H.P. and Alexander, L.E., *X-ray Diffraction Procedures for Polycrystalline and Amorphous Materials*, Wiley, New York, 1974.

Kontny M.J., Grandolfi, G.P. and Zografi, G., Water vapour sorption of water-soluble substances: studies of crystalline solids below their critical relative humidities. *Pharm. Res.*, 4 (1987) 104–112.

Murari, R., Solid state NMR: Correlation with other techniques. *31st Annu. Int. Ind. Pharm. Res. Conf.*, Wisconsin, 1989.

Nyqvist, H., Saturated salt solutions for maintaining specified relative humidities. *Int. J. Pharm. Technol. Prod. Manuf.*, 4 (1983) 47–48.

Oksanen, C.A. and Zografi, G., The relationship between the glass transition temperature and water vapour absorption by poly(vinylpyrrolidone). *Pharm. Res.*, 7 (1990) 654–657.

Otsuka, M. and Kaneniwa, N., Effect of grinding on the crystallinity and chemical stability in the solid state of cephalotin sodium. *Int. J. Pharm.*, 62 (1990) 65–73.

Saleki-Gerhardt, A., Ahlneck, C. and Zografi, G., Assessment of disorder in crystalline solids. *Int. J. Pharm.*, 101 (1994) 237–247.

Sebhatu, T., Elamin, A.A. and Ahlneck, C., Effect of moisture sorption on tabletting characteristics of spray dried (15% amorphous) lactose. *Pharm. Res.*, (1994) submitted.

Susi, H. and Ard, J.S., Determination of crystallinity of α-D-lactose by far infrared spectroscopy. *J.A.O.A C.*, 56 (1973) 177–180.

Suurkuusk, J. and Wadsö, I., A multichannel microcalorimetry system. *Chem. Scr.*, 20 (1982) 155–163.

Vromans, H., Bolhuis, G.K., Lerk, C.F., Kussendrager, K.D. and Bosch, H., Studies on tableting properties of lactose: VI. Consolidation on tableting properties of spray dried lactose. *Acta Pharm. Suec.*, 23 (1986) 231–240.

Vromans, H., Bolhuis, G.K., Lerk, C.F., Van de Biggelaar, H. and Bosch, H., Studies on tableting properties of lactose: VII. The effect of variations in primary particle size and percentage of amorphous lactose in spray dried lactose products. *Int. J. Pharm.*, 35 (1987) 29–37.