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The use of amorphous model substances to study mechanically activated materials in the solid state

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Abstract

Spray drying of aqueous solutions of sucrose and lactose produced amorphous solids that differed greatly from their crystalline counterparts in morphology, X-ray diffraction patterns, DSC scans and their water vapour uptake behaviour. Amorphous sucrose and lactose, being in high energy states, are thermodynamically and physically unstable. When exposed to high humidity, they took up moisture to a certain critical uptake level, depending on temperature, then crystallised and released the sorbed moisture. The crystallisation was described as a deactivation process as it ordered the constituent molecules as well as reduced the total energy content of the system. Water vapour uptake of amorphous sucrose and lactose reduced the glass transition temperature (T_g). The T_g was also affected by the heating rate during the DSC scan. When T_g was reduced to, or below, the operating temperature, transformation of the amorphous solids from the glassy state to the rubbery state occurred. The transformation set up conditions for crystallisation to occur. The time delay for crystallisation depended on the temperature difference between the operating temperature and T_g.

Keywords: Amorphous material; Crystallization; Disordered material; Glass transition temperature; Moisture sorption; DSC ; Thermomechanical analysis

1. Introduction

During the production of drugs in the solid state, solids are subjected to a variety of different processes such as comminution, mixing, drying and compaction. Many of these processes can introduce changes in the degree of disorder of the solid according to the concept of mechanical activation (Hüttenrauch, 1978; Hüttenrauch et al., 1985). Such structural changes can be manifested throughout the entire crystal (amorphous), or be localised to the particle surface, the so-called 'frictional hot spots' (Hersey and Krycer, 1980). It seems that the mechanical activation can affect the physical properties of drugs. Effects of processing have been reported on solubility (Florence and Salole, 1976; Waltersson and Lundgren, 1985; Elamin et al., 1994b), chemical stability (Waltersson and Lundgren, 1985; Ahlneck and Waltersson, 1986) and tablet strength (Elamin et al., 1994a).

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Non-crystalline (disordered) structures are thermodynamically and physically unstable and will, under favourable humidity and temperature conditions, transform to an ordered structure, i.e., crystallise. The crystallisation of disordered surface structures has been shown to lead to agglomeration of milled particles (Elamin et al., 1994a). The mechanism behind this process was suggested to be similar to the one reported for compacts (Ahlneck and Alderborn, 1989; Alderborn and Ahlneck, 1991). A lower critical relative humidity as well as the glass transition temperature (T_g) were considered to be important to understand the agglomeration of milled particles. T_g is the narrow temperature range over which the reversible transition from the amorphous glassy state to the rubbery state occurs. The two amorphous states differ greatly in free volume and molecular mobility. The increase in tablet strength of partially amorphous lactose due to moisture uptake during powder storage has also been related to T_g (Sebhatu et al., 1994a).

As mechanically induced surface effects are mainly manifested at the particle surface, they are often undetectable by many traditional bulk measurement techniques, such as differential scanning calorimetry (DSC) and powder X-ray diffraction. However, it is possible to study the stability and crystallisation of disordered structures, as well as factors affecting the glass transition temperature by DSC using totally disordered (amorphous) model samples. Of particular interest is the interaction of water vapour with amorphous solids, where considerably more water vapour is taken up relative to the crystalline form of the same chemical entity (Nakai et al., 1977; Pikal et al., 1978). Due to the disordered nature of the amorphous form, water vapour can be visualised as if it is dissolved in the bulk of the solid, in contrast to the surface adsorption in the case of crystalline solids (Ahlneck and Zografi, 1990). Absorbed (dissolved) moisture is known to be able to reduce the glass transition temperature of amorphous materials (Slade and Levine, 1988; Oksanen and Zografi, 1990).

The aim of this paper was to produce totally amorphous model substances to study the primary effect of storage conditions on water vapour uptake into totally disordered solids as well as to follow some fundamental changes in the glass to rubber phase transition, and the subsequent crystallisation process. Another objective was to scrutinise factors affecting measurements of glass transition and crystallisation temperatures.

2. Materials and methods

2.1. Materials

Sucrose (crystalline puriss, Kebo-Grave, Sweden) and α-lactose monohydrate (Pharmatose, DMV, Netherlands) were used as raw materials for spray drying. The amorphous spray dried forms of the two substances were used as models.

2.2. Methods

2.2.1. Preparation of spray dried materials

Crystalline sucrose and lactose to be spray dried were dissolved in water in a ratio of 1:4 and 1:6 at room temperature. The solutions were spray dried using an A/S Niro automiser (Copenhagen, Denmark) spray drier. The inlet temperatures were 150 and 170 ± 10°C, and the outlet temperature was 80 ± 10°C. The solutions' feed flow rate was about 0.6 l/h. The pressure used was 0.47 MPa/cm^2. The amorphous materials obtained were stored at 0% RH (P_2O_5) for at least 2 weeks before characterisation.

2.2.2. Characterisation of spray dried materials

2.2.2.1. X-ray powder diffraction. Diffraction patterns were obtained for the crystalline and the spray dried powders using an STOE position sensitive detector 'PSD', with Ge monochromatised Cu Kα. A curved wire detector ($r = 130$ mm) was used with an angular range of 45° in 2θ, operated in a stationary mode.

2.2.2.2. Differential scanning calorimetry (DSC). 4.5-5.5 mg samples were placed in sealed aluminium sample pans and scanned at a rate of 10°C/min in a differential scanning calorimeter (Mettler TC 3000, Hightstown, NJ, USA) to identify the glass transition temperature, crystallisation temperature and the melting temperature of the dried spray dried materials. Scanning rates between 5 and 25°C/min were used to study the effect of the scanning rate on the peaks obtained ($n = 3$).

2.2.2.3. Thermomechanical analysis (TMA). A Mettler TA4000 ThermoMechanical Analyser (Hightstown, NJ, USA) was used to analyse 300 mg compacts of the spray dried materials and the crystalline starting materials, in the temperature range 30–250°C at a scanning rate of 10°C/min.

2.2.2.4. Water content. The water contents were determined using the Karl Fisher method (Karl Fisher automat E 547 supplied with a multidosimat E415m Metrohm, Switzerland). Solvents used were dry methanol and formamide for sucrose and lactose, respectively, with the KF reagent ($n = 3$).

2.2.2.5. Scanning electron microscopy (SEM). The samples were sputter coated with a thin layer of gold and examined in a JEOL JSM T330 scanning microscope using secondary electron imaging, at an accelerating voltage of 10 kV.

2.2.2.6. Moisture uptake studies. Samples of 0.5 g (sucrose) and 1.0 g (lactose) were weighed in glass vials and exposed to different relative humidities, prepared with saturated salt solutions at different temperatures (Nyqvist, 1983). The vials containing the powders were taken out periodically and weighed to determine changes in weights ($n = 3$). Karl Fisher analysis, as described above, were performed simultaneously on some samples.

2.2.3. Phase transition studies

2.2.3.1. Dynamic glass transition studies. The Mettler TC 3000 DSC was used to study the effect of water content on the glass transition temperature. The DSC scans of the moist spray dried materials were performed in sealed aluminium sample pans to ensure a completely closed system, and scanned at a rate of 10°C/min ($n = 3$).

2.2.3.2. Isothermal crystallisation studies. Measurements of the time required for the spray dried material to crystallise were performed in the Mettler TC 3000 DSC by heating the samples at a rate of 10°C/min to a specific temperature above the T_g. When this temperature was reached, it was kept constant until crystallisation of the sample occurred ($n = 3$).

Isothermal storage was also performed in temperature controlled cabinets. Glass vials containing powders with different predetermined water contents were sealed and stored in different temperature controlled cabinets ($n = 3$). The isothermal temperature effects on the crystallisation of the amorphous materials were compared to that of the DSC. Eventual phase transitions of the powders were checked by DSC.

3. Results and discussion

3.1. Characterisation of the spray dried materials

The SEM photomicrographs of spray dried lactose (Fig. 1a) showed uniform spherical particles about 5–20 μm in diameter. For spray dried sucrose the particles were rounded but not totally spherical (Fig. 1c). This was due to the fact that a small quantity of absorbed moisture was present within the amorphous structure. Storage of the spray dried materials at high RH led to the formation of well-defined fine crystalline particles (Fig. 1b,d). The majority of these crystals were 1–5 μm in diameter and seemed to be connected to each other by solid bridges to form hard agglomerates.

The X-ray powder diffraction patterns of the spray dried lactose and sucrose (Fig. 2a,b) showed broad and diffuse maxima due to the relatively random arrangement of the constituent molecules which produced poor, coherent scatters. These patterns are quite distinguishable from those produced by the crystalline starting materials (Fig. 2a,b) which gave sharp and defined diffraction patterns. This difference was taken as evidence that the spray dried samples were amorphous, i.e., non-crystalline.

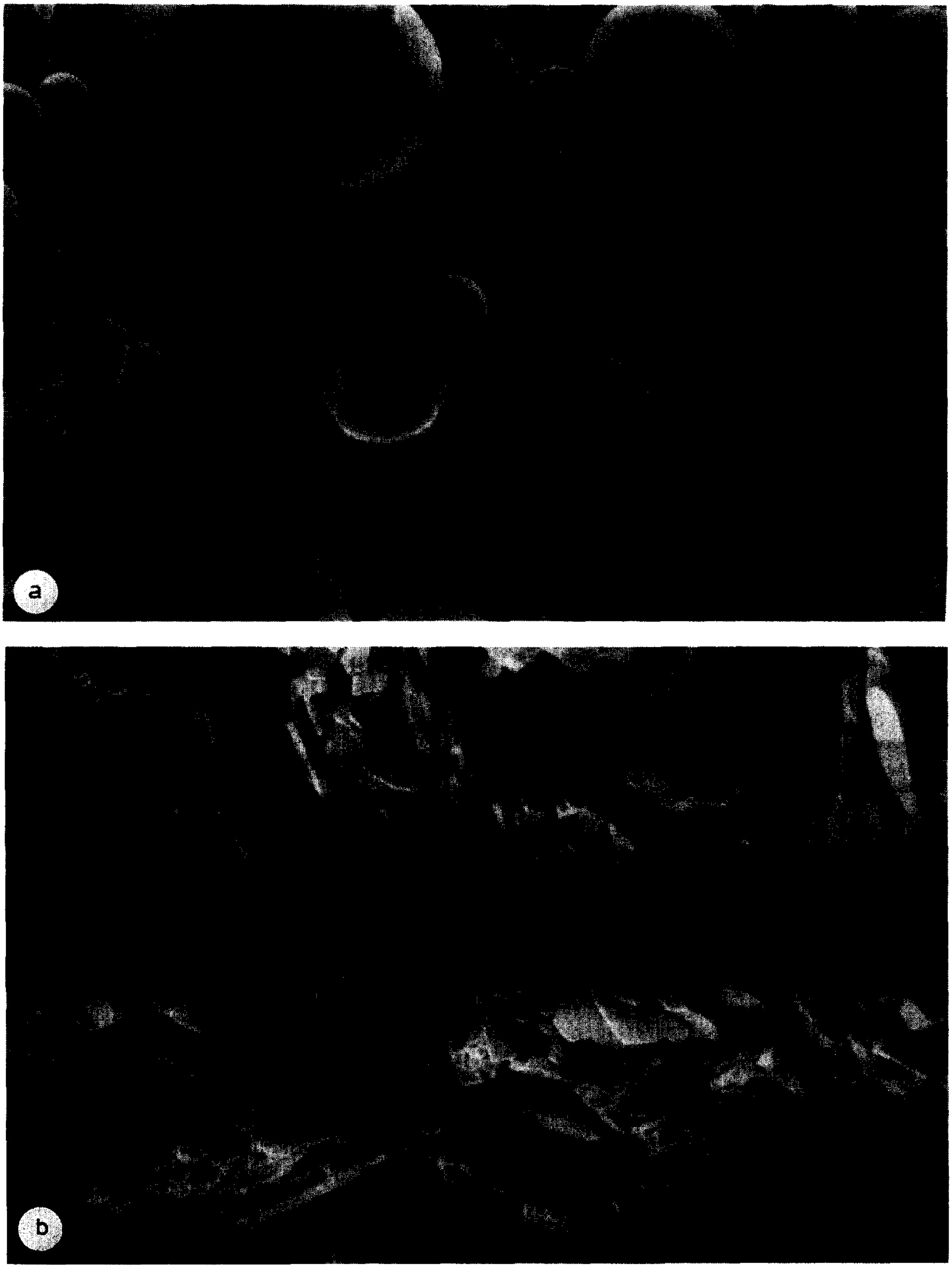

Fig. 1. SEM photomicrographs. (a) Spray dried lactose; (b) crystallised spray dried lactose; (c) spray dried sucrose; (d) crystallised spray dried sucrose.

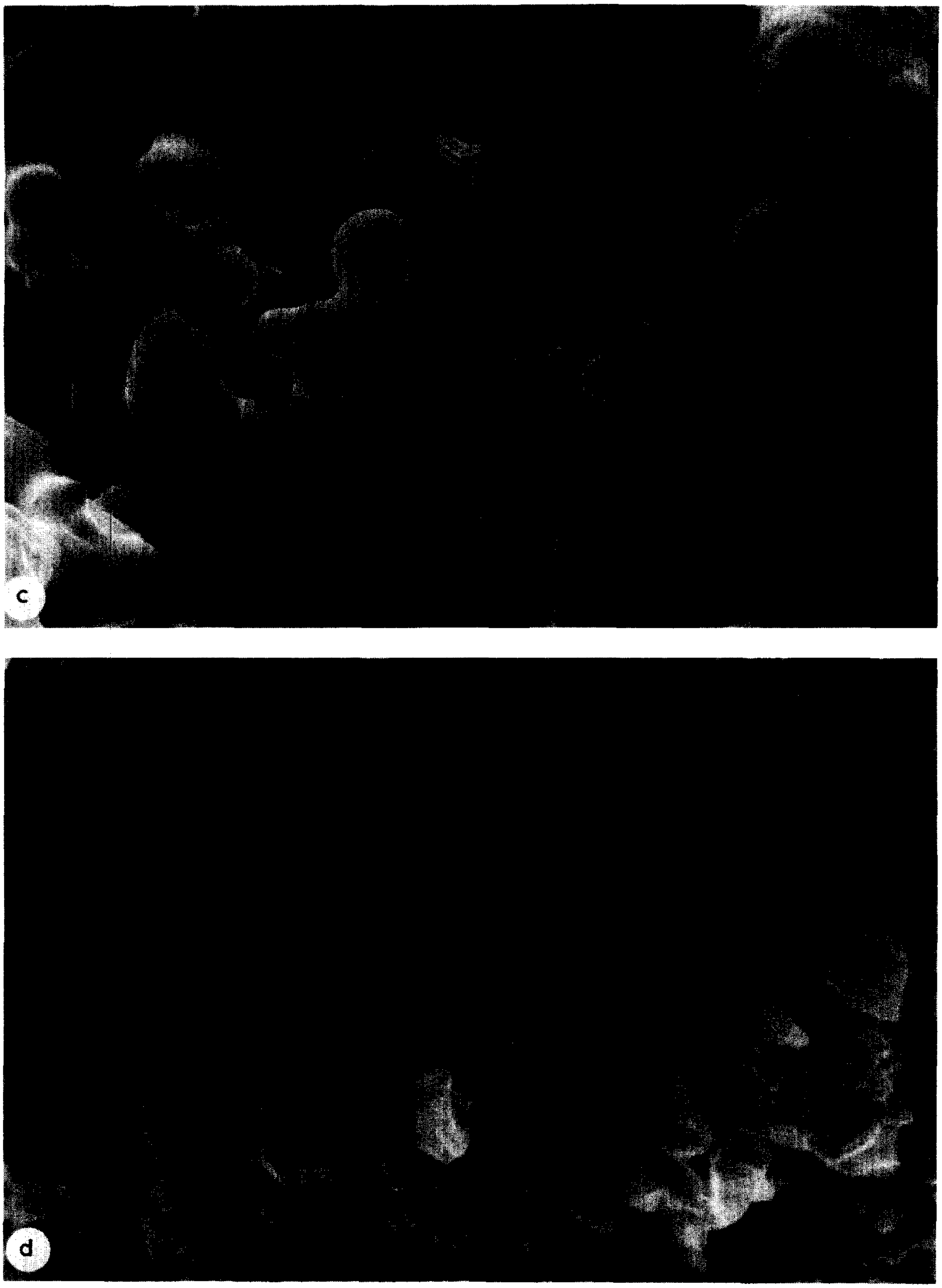

Fig. 1 (continued).

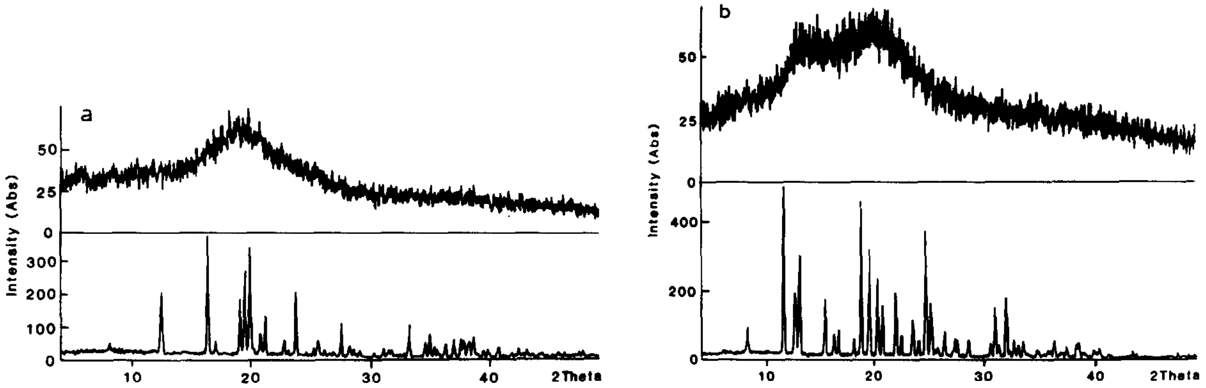

Fig. 2. X-ray powder diffraction patterns. (a) Spray dried lactose (top), crystalline α-lactose monohydrate (bottom); (b) spray dried sucrose (top), crystalline sucrose (bottom).

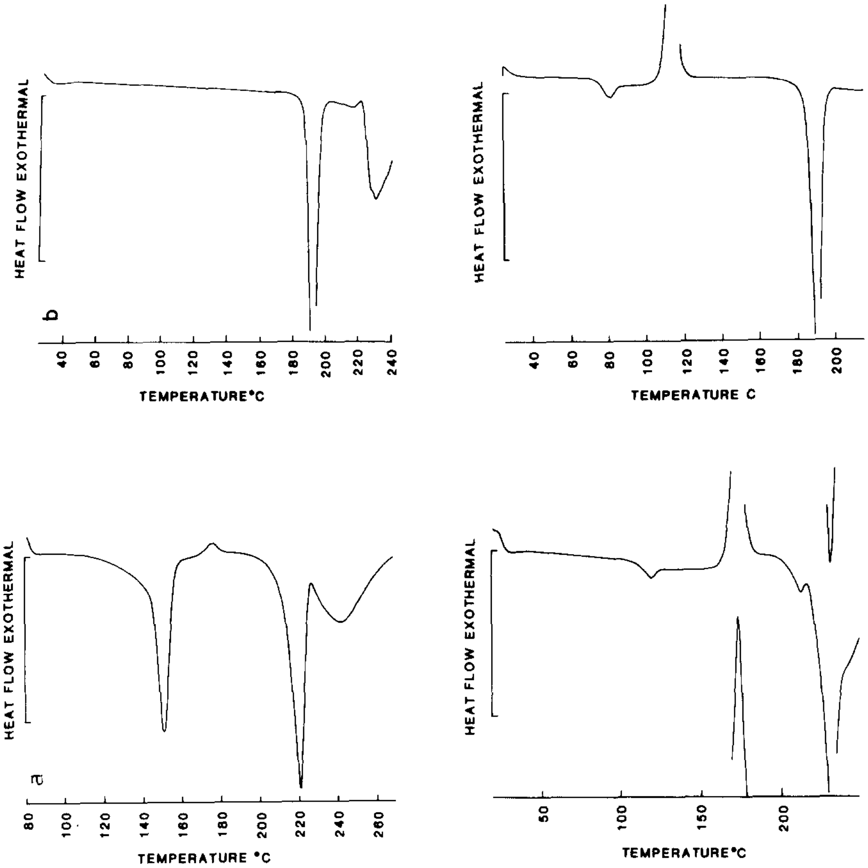

Fig. 3. DSC scans at 10°C/min. (a) Spray dried lactose (right), crystalline α-lactose monohydrate (left); (b) spray dried sucrose (right), crystalline sucrose (left).

The DSC scans of the spray dried lactose and sucrose (Fig. 3a,b) showed typical amorphous behaviour, with glass transition temperatures (T_g) at about 104 and 79°C, respectively. The transition is followed by exothermic peaks at about 173 and 112°C, respectively, due to the transformation of the samples to the crystalline state at the crystallisation temperature (T_c). Finally, sharp endothermic melting peaks (T_m) were registered at about 190°C for sucrose, and two melting peaks at about 220 and 230°C for lactose indicating that following crystallisation a mixture of α- and β-lactose was present (Sebhatu et al., 1994b).

Crystalline sucrose showed no heat effects registered as a function of temperature in the temperature range of 25–250°C, except at 192°C (Fig. 3b) where a sharp endothermic melting peak was registered. However, α-lactose monohydrate crystals showed a broad endothermic peak at about 150°C due to the loss of crystal water (Fig. 3a), and no further heat effects were registered below the melting peak at 220°C. The scans presented are consistent with published scans (Shukla and Price, 1991; Te Booy et al., 1992; Figura, 1993).

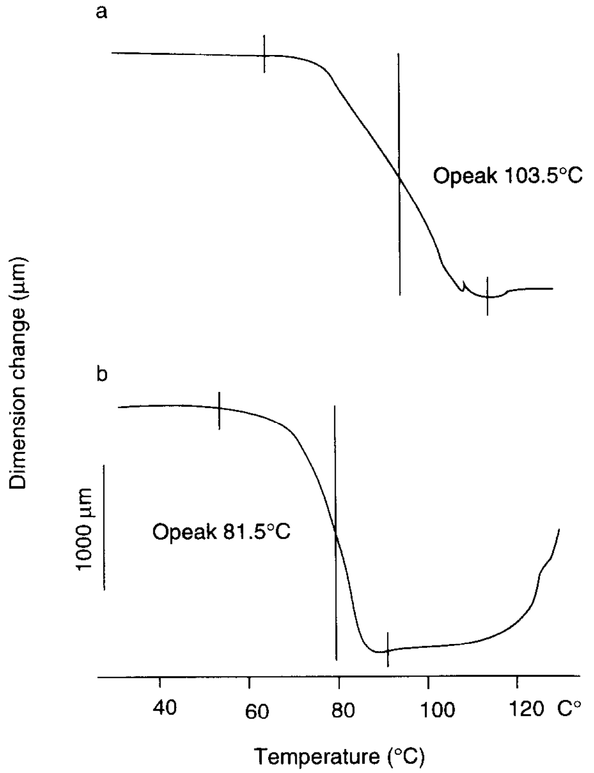

Fig. 4. TMA scans at 10°C/min. (a) Spray dried lactose; (b) spray dried sucrose.

The values of T_g and T_c increased with increasing scanning rates. This indicates that the T_g values reported above are only apparent values registered at a scanning rate of 10°C/min, which was the rate used throughout this study. At lower scanning rates, the T_g detection became increasingly difficult.

The DSC measurements of T_g were supported by thermomechanical analysis (TMA) (Fig. 4), which showed dramatic dimension changes at, or slightly above, T_g. In Fig. 4a and b the dramatic softening effect is shown for the amorphous materials when they undergo glass-to-rubber phase transitions. TMA as well as dynamic mechanical thermal analysis (DMTA) are alternatives to DSC for measurements of T_g. Since TMA measures changes in mechanical properties whereas DSC the heat changes compared to a reference, TMA can be an alternative to DSC, especially if complex DSC scans are obtained.

3.2. *Water vapour sorption of spray dried materials*

3.2.1. *Effect of relative humidity*

The water vapour sorption studies (Fig. 5a,b) showed that amorphous lactose and sucrose are capable of sorbing large amounts of water vapour at room temperature compared to their crystalline counterparts. Exposure of amorphous sucrose at 22% RH and lactose at 33% RH resulted in moisture uptake up to equilibrium levels of about 4% w/w for sucrose and 6% w/w for lactose. These levels were maintained for a long period of time without crystallisation. Exposure to higher RH led to moisture uptake of about 10% w/w for lactose and 6% w/w for sucrose. After the peak level was reached, a fast decrease in the moisture content followed. In the case of lactose the new moisture level was about 2%, corresponding to a water content less than the crystal water content of α-lactose monohydrate (5%). This finding agrees with the results from the DSC, scans in that following crystallisation a

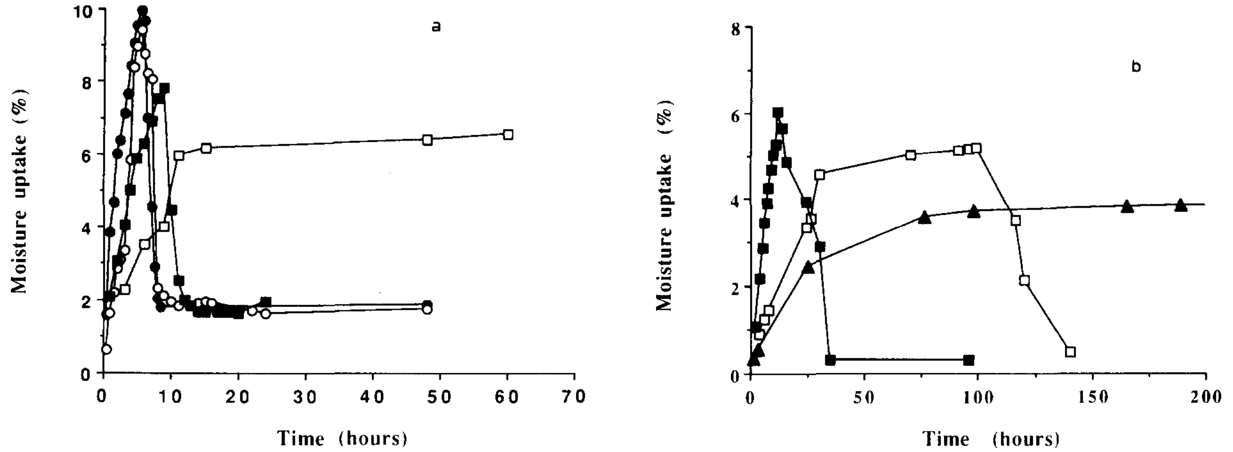

Fig. 5. Moisture sorption of spray dried materials as a function of storage time at different relative humidities. (a) Spray dried lactose; (b) spray dried sucrose. (▲) 22%, (□) 33%, (■) 57%, (○) 75%, (●) 84%.

mixture of α-lactose monohydrate and anhydrous lactose is formed. The loss of the sorbed moisture is due to the transformation of the amorphous lactose to the crystalline state.

Water vapour sorption has been reported to increase the molecular mobility of the amorphous solids (Levine and Slade, 1988; Ahlneck and Zografi, 1990) by breaking intermolecular hydrogen bonds in the solid, and replacing them by labile water-solid hydrogen bonds. The increased molecular mobility resulted in the transformation of the spray dried sucrose and lactose to their crystalline states. This process can be thought of as a 'deactivation' process, since it involves both ordering of the constituent molecules, as well as lowering of the total energy content of the system.

The relatively long initial induction time required by the amorphous sucrose stored at 33% RH before crystallisation occurred was interpreted to be the time required for a build-up of sufficient nuclei to initiate an appreciable rate of crystallisation (Makower and Dye, 1956). This time delay was probably due to the high viscosity caused by the relatively small amount of water vapour sorbed, which slowed the molecular rearrangement, and thus stabilised the amorphous state for a relatively long time.

The results of the water vapour sorption studies for sucrose and lactose indicated that there is

Table 1

Effect of temperature on the amount and rate of water vapour uptake by spray dried sucrose and lactose at 57% RH

	Temperature (°C)	Maximum water uptake (% w/w)	Peak time (h)
Sucrose	10	8.2	45
	21	6.0	12
	35	3.2	3
Lactose	10	12.8	19
	21	7.8	9
	35	7.6	2.5

Note that different weights were used for sucrose and lactose and thus affect the peak time necessary for crystallisation to occur.

a critical amount of water vapour or vapour pressure, i.e., RH, that has to be present for crystallisation to take place.

3.2.2. Effect of temperature

The temperature effect on the water vapour sorption behaviour of amorphous lactose and sucrose at 57% RH and 10, 21 and 35°C (Table 1) showed that the amount of water vapour needed to crystallise amorphous materials was very much dependent on the temperature at which the sorption studies were performed. The lower the temperature the higher the water uptake level required to cause crystallisation. The apparent uptake rate was also increased as a function of temperature.

These findings suggest that crystallisation of the amorphous materials can be looked upon as an energetically driven process. The energy needed to cause crystallisation is supplied either by an increase in temperature, or in water vapour uptake, or in both. Hence, a critical water content exists at each given temperature which leads to a molecular mobility at which processes such as crystallisation can occur.

In this context, the sorbed moisture by amorphous solids can cause sufficient molecular mobility to cause a 'liquid-like' behaviour, thus, making it unnecessary to invoke dissolution of the solid surface, or melting of the surface to support crystallisation of amorphous materials in the solid state. The behaviour of lactose and sucrose stored at low RH might be explained by the molecular mobility caused by the water vapour uptake at those RH not reaching the critical molecular mobility level required to readily support nucleation and the commencement of crystallisation.

3.2.3. Effect of water vapour uptake on glass-to-rubber phase transition

Increasing the amount of water vapour sorbed by amorphous lactose and sucrose led to a reduc-

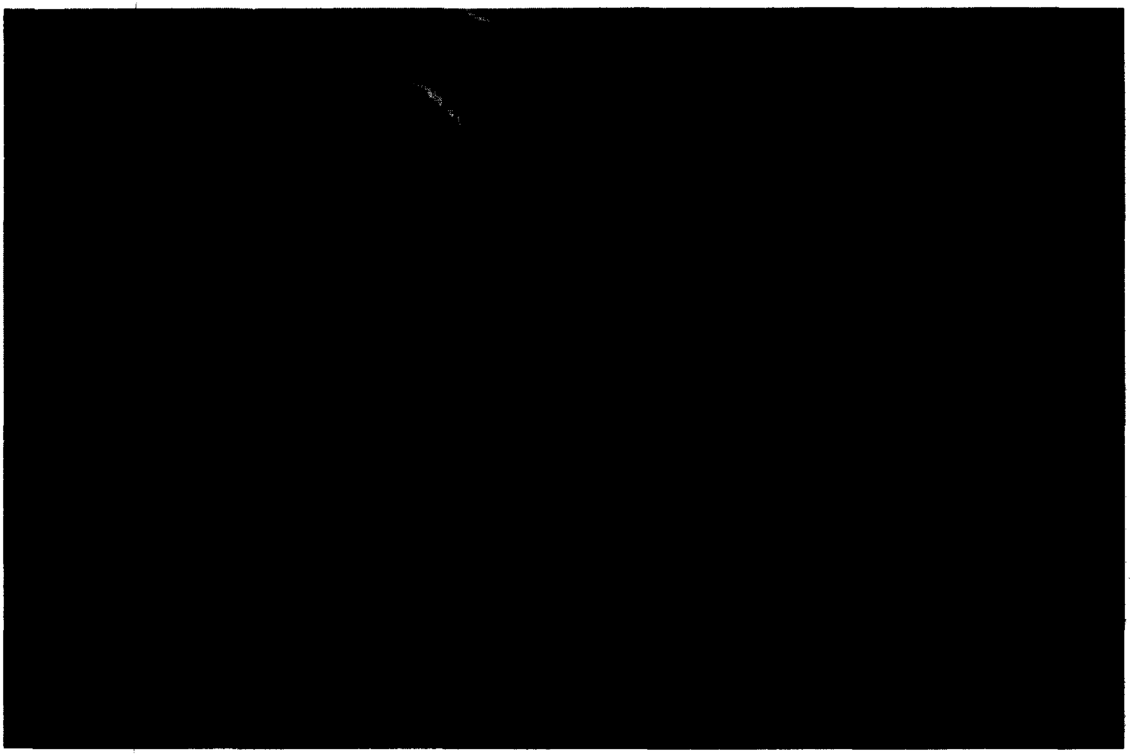

Fig. 6. SEM photomicrograph of spray dried lactose in the rubbery state.

Table 2
Effect of moisture content on T_g and T_c for sucrose and lactose by DSC

Sucrose			Lactose		
M.C (%)	T_g (°C)	T_c (°C)	M.C (%)	T_g (°C)	T_c (°C)
0.0	76.9	113.2	0.0	104.0	173.0
0.5	65.7	110.1	2.0	91.0	141.2
0.7	62.8	103.0	2.8	88.0	138.0
1.0	58.8	95.9	3.1	78.0	125.6
1.8	53.0	87.1	4.5	60.0	109.8
1.9	42.6	82.9	5.7	57.0	85.5
2.0	41.3	80.2	7.2	37.0	77.9
2.5	41.3	77.8	8.0	[a]	67.5
3.3	33.3	68.0			
3.6	[a]	65.0			
3.8	[a]	63.0			

[a] Not measurable.

tion in their apparent T_g values from 79 and 104°C, respectively, to T_g values below 35°C when 3.5 and 7.5% water vapour was sorbed (Table 2), i.e., when the T_g of the amorphous materials was brought to or below the operating temperature by water vapour uptake a phase transition from the glassy to the rubbery state occurred. The T_c values also decreased as the moisture content of the sample increased, in much the same way as T_g.

The SEM photomicrographs of spray dried lactose (Fig. 6) showed that water vapour uptake, above the amount needed to reduce T_g below T, led to the swelling of the particles, and the individual particles tended to fuse together forming a continuous viscous mixture of the amorphous material and absorbed water vapour. In this phase, the surface of the particles became sticky, and when two particles touched, they tended to fuse. The rubbery state has earlier been described as a 'stickiness' related to viscous flow (Tsourouflis et al., 1976; To and Flink, 1978) and sometimes as a supercooled liquid state that occurs before caking or structural collapse of lyophilised or spray dried powders (Islesias and Chirifi, 1978; Van Scoik and Carstensen, 1990). Spray dried sucrose showed a similar behaviour.

3.2.4. The significance of T_g on crystallisation

To understand the significance of the glass-to-rubber phase transition on the crystallisation of the amorphous materials used, four sets of amorphous samples with known amounts of moisture uptake were prepared and stored at four different temperatures. This gave an opportunity to place each category of samples with the same moisture content at positions above and below the apparent T_g. The samples which were stored at temperatures that placed them above or very near the T_g crystallised readily, while the ones below the T_g stayed in their original state for about 6 months.

This finding suggests that for crystallisation to occur, the material has to be in the amorphous rubbery state. This seems reasonable since the rubbery state provides the molecular mobility required for molecules to orient, form sufficient stable nuclei and to create the liquid-like condition needed for molecular diffusion and the commencement of an appreciable rate of crystallisation.

The above explanation is supported by the results from the isothermal crystallisation experiment performed in the DSC for the spray dried sucrose (Fig. 7), which shows a positive exponential relationship between the time in the rubbery state required for the material to crystallise, and the temperature at which the experiment was conducted. The results suggest that crystallisation will be most likely to occur when $T_g < T$, and the time required for crystallisation to occur depends on the difference between T and T_g. Therefore, the difference between T_g and T_c is a difference due to kinetic events.

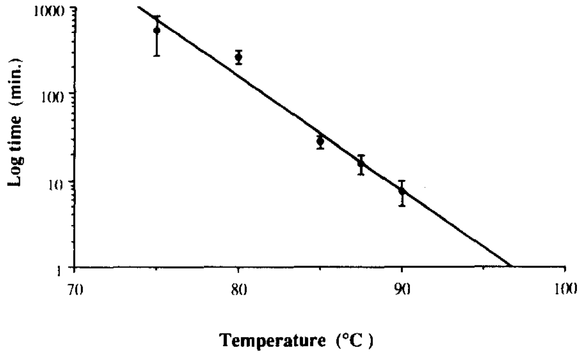

Fig. 7. Time required for crystallisation to occur within the DSC during a isothermal temperature scan. The bars represent standard deviation.

4. Conclusions

Technological and processing operations such as milling and compaction of pharmaceuticals produces mechanical activation phenomenon, which are probably, manifested mainly at the surfaces of crystals. These regions of disorder are unidentifiable by a variety of techniques, and thus might go unnoticed. Studying the amorphous forms of such pharmaceuticals might prove to be a valuable tool in understanding the properties and/or the reactions and interactions of such surfaces.

Many water-soluble amorphous materials are thermodynamically and physically unstable. When exposed to high humidity, they take up moisture and undergo a transition from the glassy to the rubbery amorphous state before crystallisation and the release of the sorbed moisture. When a material is in a crystalline, amorphous glassy state or rubbery state, it has a distinctly different set of properties associated with that particular physical state. In the rubbery state the disordered surfaces swell, become sticky and tend to fuse with the neighbouring disordered surfaces in the powder bed. The fused surfaces may crystallise with time and thus create solid bridges. This process requires a certain amount of molecular mobility, which explains its dependency on water vapour uptake and temperature.

The T_g values of amorphous lactose and sucrose were shown to vary according to the DSC scanning rate used, as well as to the moisture content of the sample. The use of TMA was shown in this study to be an alternative way of determining T_g on compacts. It seems that for these amorphous materials to be physically stable, they have to be in their glassy amorphous state below T_g. Thus, T_g determination can serve as a valuable stability indicating tool for amorphous solids, as it is possible to estimate the maximum temperature that the material can be exposed to during storage, handling or transport and still be maintained in the amorphous stable glassy state.

This explanation might be applicable to the effects on tablet strength (Elamin et al., 1994a; Sebhatu et al., 1994a) as well as on solubility (Elamin et al., 1994b). Thus studies on an amorphous model sample may increase an understanding of the behaviour of mechanically activated materials under different conditions.

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