# Effect of Moisture Sorption on Tabletting Characteristics of Spray Dried (15% Amorphous) Lactose

Tesfai Sebhatu,[1] Amin A. Elamin,[1] and Claes Ahlneck[1,2]

Received September 30, 1993; accepted April 30, 1994

Spray dried (15% amorphous) lactose absorbs moisture when exposed to humidity. At 57% relative humidity (RH), the moisture uptake was 1.5%. It is suggested that the moisture is preferentially taken up in the amorphous regions, thereby increasing the actual moisture content in the amorphous parts up to 10%. The moisture uptake reduced the glass transition temperature below the operating temperature and thereby transformed the amorphous regions from a glassy to a rubbery state, setting up conditions for crystallisation of the lactose. Compaction of dry spray dried lactose led to a relatively low initial tablet strength. However, when pre-exposed to 57% RH for a short time period (2 to 4 hours) before compaction, the initial tablet strength increased markedly. This was due to moisture uptake which resulted in a higher molecular mobility of the amorphous spray dried lactose, and to an increase in plastic flow. Post compaction storage of tablets containing amorphous regions of spray dried lactose at 57% RH resulted in an increased tablet strength after 4 hours due to crystallisation. Spray dried lactose exposed to 57% RH for more than 6 hours before compaction led to the lowest initial tablet strength. Crystallisation of the amorphous regions of the spray dried lactose occurred before tabletting. No increase in tablet strength was noted on post compaction storage for these tablets.

KEY WORDS: amplification of moisture content; glass transition temperature; moisture sorption on storage; molecular mobility; tensile strength of tablets.

## INTRODUCTION

Spray dried lactose is a well known excipient for direct compression, with good binding properties and flow characteristics. Depending on the spray drying procedure, the product consists of either purely amorphous lactose, or a mixture of crystalline and amorphous lactose (1). Amorphous lactose is the result of rapid drying of dissolved lactose during spray drying.

An important property of amorphous lactose is its physical instability when exposed to moisture. Spray dried lactose differs from the other types of lactose in its moisture sorption behaviour (2). The amorphous regions of the spray dried lactose are known targets for moisture uptake, and such absorption may result in crystallisation depending on the amount of sorbed moisture, temperature and time. If an amorphous sample of lactose is stored at high relative humidities, there is a continued uptake of moisture until a maximum moisture content is reached, followed by a sharp loss of the sorbed moisture (3). The dramatic loss of water is the result of transformation of the amorphous material to the crystalline state. Such transformation is undesirable if it takes place during the powder storage before compaction, because the amorphous part of the spray dried lactose is responsible for good product quality as a filler/binder in direct compression. Spray dried, partially amorphous, lactose yields stronger tablets than the crystalline α-monohydrate (2,4), attributed to the presence of the lactose glass, which acts as a binder.

When water is absorbed into the amorphous regions of a solid, it can act as a plasticiser and greatly increase the free volume, due to breakage or rupture of hydrogen bonds between the solid molecules (5). This, in turn, leads to a reduction of the solids glass transition temperature Tg, to or below the operating temperature, with a change from an immobile glassy state to a rubbery state of a much higher molecular mobility.

Consider a situation where the total amount of water in a sample is 1% w/w and the sample consists of 10 mg of substance in an amorphous state and 40 mg in a crystalline state. With the knowledge of where the water is taken up, i.e., dissolved in the amorphous parts of the substance, the actual water content in the amorphous parts is amplified to 5% (6), which might be enough to transform the amorphous parts to the rubbery state. This could lead to an increased physical and/or chemical reactivity and to crystallisation of the amorphous material with consequent release of the sorbed water. It should be emphasised that the position of the amorphous regions in the solid, as well as the water content in the amorphous regions are the factors that determine the crystallisation temperature.

Transformation of amorphous regions of processed powders to the crystalline state is possible if the molecular mobility is high enough to permit crystallisation during powder storage. This would affect the bond formation during compaction. It may also lead to a decreased post compaction strength increase, since an already crystallised, i.e. "deactivated", system would exhibit a limited molecular mobility and re-arrangeability.

On the basis of these considerations, the properties of spray dried lactose were studied when exposed to moisture before and after tabletting. The effect of glass transition temperature, as a function of moisture content of amorphous lactose, was studied in relation to the initial tablet strength (measured immediately after compaction) and the post compaction tablet strength (measured after storage of tablets) of the 15% amorphous lactose.

## MATERIALS AND METHODS

### Materials

*Pharmatose, Spray Dried Lactose.* (DMV, Netherlands) a mixture of α-lactose monohydrate and amorphous lactose. The content of amorphous lactose was approximately 15%.

*Pharmatose, lactose 96% α-monohydrate.* (DMV, Netherlands). This quality of lactose was used as a reference material for crystalline α-lactose monohydrate.

[1] Department of Pharmacy, Biomedical Center, Uppsala University, Box 580, S-751 23 Uppsaka (Sweden).

[2] Present affiliation: Astra Draco AB, Box 34, S-221 00 Lund (Sweden).



0724-8741/94/0900-1233$07.00/0 

*Spray Dried Amorphous Lactose.* Approximately 100% amorphous lactose was prepared by spray drying a solution of lactose. The procedure and characterisation of the spray dried material is presented (3).

## Methods

*Preparation of Powders.* The size fractions 45–125 μm (I) and 125–250 μm (II) were prepared by sieving. The sieved fractions were stored in a desiccator over $P_2O_5$ for not less than three weeks. The smaller size fraction was used in all experiments except for the sorption studies shown in Fig. 1.

*Density.* The true density of the material was determined with an air comparison pycnometer (Beckman model 930, USA) (n = 5).

*Microcalorimetry.* The degree of disorder of the starting materials was measured by isothermal microcalorimetry (2277 Thermal Activity Monitor (TAM), Thermometric AB, Sweden), using saturated salt solutions in the miniature sample vessels to control the relative humidity. The technique for assessment of the degree of disorder by microcalorimetry has been described earlier (7).

*Surface Area Measurement of Powders.* The specific surface areas for the size fraction 45–125 μm of the material was determined by air permeametry using a Blaine apparatus (Ton industries, F.R.G.). A weighed amount of powder was compacted by hand in the permeability cell using a plunger to a porosity of 40–45%. The weight specific surface area corrected for slip flow was calculated (8).

*Moisture Content.* The moisture content was determined by the Karl Fisher method (Karl Fisher automat E 547 applied with multi dosimat E 415, Metrohm, Switzerland). The solutions used were Karl Fisher solution and dry methanol. Although lactose is practically insoluble in alcohol it showed sufficient solubility in dry methanol to allow the determinations.

*Moisture Sorption.* One gram samples of the prestored material (II) were weighed in glass vials and exposed to RH chambers of 22%, 33%, 57%, 75% and 84% RH using saturated salt solutions, for a time period of two weeks. The glass vials containing the samples were periodically taken out of the humidity chambers and weighed on an analytical balance to determine any changes in weight as a result of the moisture sorption at room temperature.

As a reference, the moisture sorption properties of the approximately 100% amorphous spray dried lactose are included (3).

*Differential Scanning Calorimetry (DSC).* Mettler TC 3000 DSC differential scanning calorimeter (Hightstown, NJ, USA) was used to observe the thermal properties of the spray dried lactose in the temperature range 80–270°C. 4,5-5,0 mg samples were weighed in 'open' aluminum sample pans and scanned at a programmed rate of 10°C/min.

*Storage of Powder Before Compaction.* Spray dried lactose was stored at about 0% RH for not less than three weeks. Samples were moved to 57% RH and were stored for 0, 1, 2, 4, 6, 8, 16 hours and for 20 days before compaction. The moisture uptake of the prestored material was monitored.

*Compression of Tablets.* Tablets were compressed in an instrumented single punch tablet press (Korsch EkO) at a maximum upper punch pressure of 150 MPa. Flat faced punches with a diameter of 1.13 cm were used with a distance of 3mm between the punch faces at the lowest position of the upper punch at zero pressure. The powder for each compact was weighed separately and poured into the die. A 1% magnesium stearate suspension in ethanol was used as external lubricant.

*Storage and Characterisation of Compacts.* Some of the compacts were characterised immediately after compaction and the measured tablet strength will be referred to as the initial tablet strength. The rest of the tablets were stored for 1h, 2h, 4h, 16h, 24h and 10 days at room temperature at 57% RH before characterisation. This tablet strength will be referred to as post compaction tablet strength. The diametral crushing strength was measured (Erweka TBH, F.R.G.) for compacts of each storage condition. The tensile strength was calculated from a mean of six compacts (9). The initial air permeametry surface area of tablets, compacted by hand at 50 MPa, was measured in the die with a Blaine apparatus (8).

## RESULTS AND DISCUSSION

### Characterisation of the Material on Storage

*Moisture Sorption Analysis.* Moisture sorption of the spray dried lactose as a function of storage time at various relative humidities (Fig. 1) showed an increase in the amount of moisture sorbed up to 33% RH. At 33% RH a plateau level of about 0.8% was reached after 36 hours. Storage at 57% RH led to a rapid increase in moisture uptake reaching a peak level followed by a sharp drop to a lower plateau level, which is due to crystallisation of the amorphous parts. Storage at higher relative humidities for shorter time periods led to a faster moisture uptake before the crystallisation took place. From these findings 57% RH was chosen as the storage RH for further studies.

The 15% amorphous sample stored at 57% RH showed an uptake of moisture up to about 1.5% after 8 hours (Fig. 2). After longer storage there was a sharp loss of water content due to crystallisation of the amorphous regions, as determined by DSC (see below). Beyond this point there was no sorption of water. The actual moisture uptake in the amor-

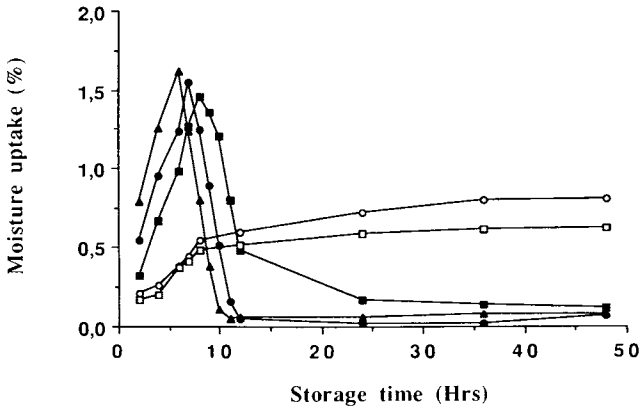


Fig. 1. Moisture sorption of spray dried (15%) amorphous lactose as a function of storage time at different relative humidities. ▲ 84%; ● 75%; ■ 57%; ○ 33%; □ 22%.

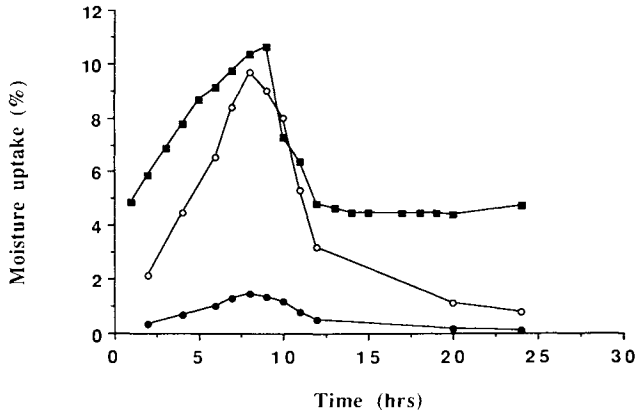


Fig. 2. Moisture sorption as a function of time for spray dried amorphous lactose, 15% and 100%, when stored at 57% RH and room temperature. ■ Spray dried (100%) amorphous lactose; ● Spray dried (15%) amorphous lactose; ○ Amplified spray dried (15%) amorphous lactose.

phous regions is amplified to about 10% (Fig. 2), since almost all the sorbed water is taken up by the amorphous parts (5). This level corresponds well to that of the 100% amorphous spray dried lactose (Fig. 2). The reason for the different moisture levels after crystallisation is due to the larger total incorporation of hydrate water in the crystallised 100% amorphous lactose.

Further, spray dried lactose was stored at different time intervals at 57% RH to reach various moisture uptake levels and then compacted. These tablets were stored after compaction as described above, and in some cases also at 0% or 33% RH before characterisation.

*Differential Scanning Calorimetry (DSC).* The heat effects registered as a function of temperature for the 15% amorphous lactose (Fig. 3, line b) shows the presence of crystalline α-monohydrate (Fig. 3,c) as indicated by the peak at about 150°, which represents the release of water of hydration and the melting peak at 220°C. The energy required to release the water of hydration for the sample stored at 0% RH (Fig. 3,b) was 103 J/G. However, more energy was required (130 J/G) when the powder had been stored at 57% RH for more than 8 hours (Fig. 3,d), which is in good agreement with the crystalline α-monohydrate reference material (Fig. 3,c). The increase in energy is due to the incorporation of crystal water following crystallisation of the amorphous lactose. The ratio between the energy required to release the water of hydration from the starting material and the one stored for more than 8 hours at 57% RH is 21% which is in fairly good agreement with the declared 15% degree of disorder.

The crystallised 15% amorphous lactose (Fig. 3,d) showed a second melting peak at about 230°C, probably due to the presence of anhydrous α- or β lactose, which is not the case for the reference crystalline α-monohydrate. This finding corresponds well with the fact that crystallised 100% amorphous lactose holds less than 1 mole of $H_2O$ (5%) (Fig. 2) (10).

The thermogram for the approximately 100% amorphous lactose is shown in Fig. 3,a. The exothermic peak in the thermogram at 170°C is a result of crystallisation of amorphous lactose. A trace of this exothermic peak is also shown for the 15% amorphous material (Fig. 3,b).

It has earlier been shown that water vapour sorption reduces the glass transition temperature (Tg) for poly(vinylpyrrolidone) measured by DSC using hermatically sealed sample pans (11). For the dry amorphous lactose sample, the apparent Tg-value is 104°C (Fig. 3,a). When the moisture content is increased, the difference Tg-T, where T is the operating temperature, is drastically reduced (Table I) (3).

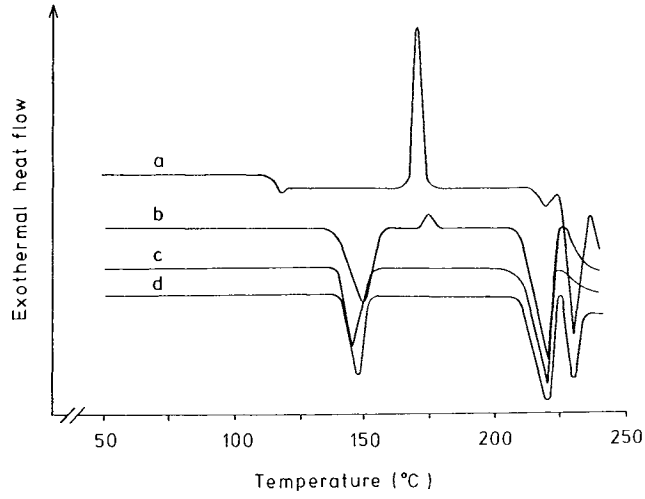


Fig. 3. DSC thermograms of a) spray dried (100%) amorphous lactose; b) spray dried (15%) amorphous lactose; c) crystalline α-monohydrate lactose; d) crystallised spray dried 15% amorphous lactose.

### Effect of Moisture Sorption on the Initial Tablet Strength

The initial radial tensile strength is a function of the powder precompaction storage time at 57% RH is presented in Fig. 4. The initial compact strength of the 15% amorphous lactose increased with increasing prestorage time of the powder, up to 4 hours. Storage for 6 hours led to a reduced initial tablet strength. For longer precompaction storage times more than 6 hours, no further change in the initial tablet strength was noted.

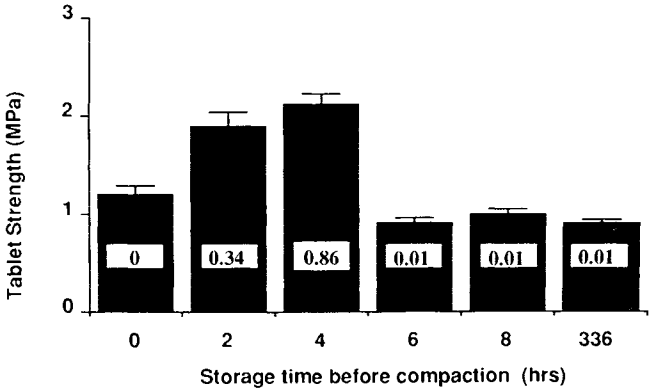


Fig. 4. The initial radial tensile strength of tablets of spray dried (15%) amorphous lactose as a function of powder precompaction storage time at 57% RH and room temperature. The values in the inserted boxes represents the calculated moisture content in the powder at the time of compaction. (The bars indicate the standard deviation.)

To determine if a relationship between Tg and the initial tablet strength exists, Tg-T values for the 100% amorphous lactose at various moisture contents were plotted as a function of the corresponding tablet strength of the 15% amorphous lactose taking the moisture concentration amplification in consideration (Fig. 5). The tablet strength increased as the value of Tg - T became smaller. When Tg = T, i.e. Tg − T = 0, the criteria for crystallisation are met. Further storage of the powder at 57% RH did not produce any changes either in the initial tablet strength (Fig. 4) or in the moisture content.

From the moisture sorption studies, storage for 2 hours yielded 0.34% and for 4 hours 0.86% moisture uptake. Since the moisture content of the material is different, the degree of plasticisation and compactibility are different, probably due to differences in Tg-values. The Tg values of 100% amorphous lactose were reduced as the moisture content increased (Table I), i.e. lower temperatures are required to transform amorphous lactose from the glassy state to the rubbery state with increasing moisture content. When enough moisture is taken up to reduce Tg, to or below T, crystallisation of the amorphous lactose will take place.

It seems that a material in its rubbery (amorphous) state can cause increased initial strength when compacted. It is probable that the water present in the amorphous phase can act as plasticiser and thereby increase the plastic deformation during compaction. The increased tablet strength can be due to either greater fusion of particles with layers of amorphous (rubbery) material during compaction, or to an increased plastic flow leading to a closer packing of the particles and thus increase the available bonding surface area within the tablet (12).

The above mechanistic explanation is also valid in explaining the results of moisture sorption effects on tabletting of spray dried lactose by Vromans et al. (4). Where the degree of plasticisation depends on both the amount of moisture taken-up and the degree of crystallinity, i.e. it takes five times more moisture to plasticise 100% amorphous material compared to 20% amorphous material to the same extent.

One can further speculate that, even at very low moisture contents, a material that has regions in an amorphous glassy state before compaction could convert to the rubbery

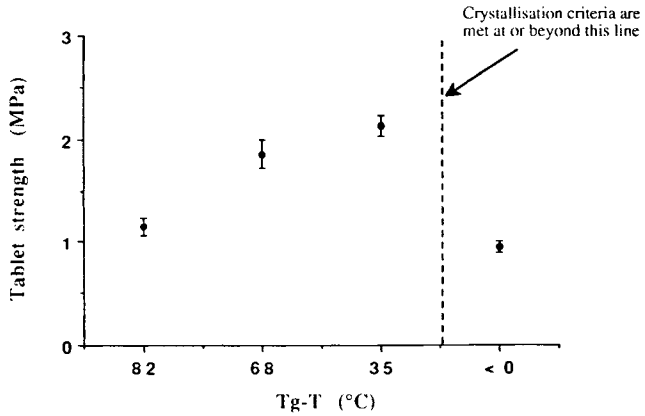


Fig. 5. The initial radial tensile strength of tablets of spray dried (15%) amorphous lactose as a function of Tg-T. (The bars indicate the standard deviation.)

Table I. Effect of moisture uptake on the glass transition temperature of spray dried 100% amorphous lactose as measured by DSC. (Compiled from (3)).

| Moisture content (%) | Glass transition temperature, Tg. (°C) | Tg-T (°C) |
|---|---|---|
| 0 | 104 | 82 |
| 1,95 | 91 | 69 |
| 5,76 | 57 | 35 |
| 7,17 | 37 | 15 |

state, due to the increased local temperature and/or pressure during the compaction phase. Since plasticisation is an effect of interaction between moisture and temperature, disordered (plastic) regions at the particle surfaces may come in contact during compaction and fuse. The possible amorphous bridges formed may solidify, i.e. revert back to the glassy amorphous state on the release of the pressure and the subsequent temperature drop at the end of the compaction cycle.

This mechanism may in some cases lead to crystallisation of fused amorphous regions if high enough temperatures, due to friction or pressure, are reached. However, for spray dried lactose this possibility is less likely to occur due to its high Tg.

The initial tensile strength decreased dramatically for the material stored for 6 hours—2 weeks before compaction (Fig. 4). This decrease occurred as a result of transition of the amorphous regions of lactose to the crystalline state during precompaction storage. In the absence of the amorphous parts, the plasticity of the material is reduced, and with it the ability to form strong compacts. The tablet strength of the crystallised material had approximately the same tablet strength as crystalline α-monohydrate, i.e. about 1 MPa at the same compaction pressure. Similar findings were obtained for sodium chloride, which was rendered partially amorphous by milling (activated), where both the initial and the post compaction tablet strength were reduced due to the storage of the milled powder at medium and high relative humidities before compaction (13).

### Effects of Moisture Uptake on Tablet Surface Area

Results for initial permeametry surface area of compacts, showed clear differences in tablet surface area (Table II). In relation to the results discussed earlier, the most probable explanation is that the increase obtained for the compacts of spray dried lactose, stored 6-336 hours as a powder, is probably due to particle fragmentation during compaction. Thus, formation of cracks could be possible which in turn can lead to a larger surface area. Crystalline α-monohydrate lactose has earlier been shown to undergo fragmentation (8). Air permeametry measurements of the powder when stored for various times at 57% RH did not show differences in the permeametry surface area of the powders.

### Effects of Moisture Sorption on Post Compaction Tablet Strength

The tensile strength of tablets made from powder stored for more than 6h at 57% RH before compaction does not

Table II. Initial air permeametry tablet surface area, pore diameter and porosity for spray dried (15%) amorphous lactose tablets compacted at 50 MPa from powders stored for different time periods at 57% RH before compaction.

| Powder storage time at 57% RH (h) | Surface area ($cm^2/g$) | Porosity (%) |
|---|---|---|
| 0 | 3020 | 34.8 |
| 2 | 3894 | 33.0 |
| 4 | 3495 | 33.3 |
| 6 | 5624 | 32.4 |
| 8 | 5563 | 32.5 |
| 336 | 4949 | 33.0 |

increase with increasing post compaction storage time (Fig. 6). This is because the amorphous parts of the spray dried lactose had already crystallised. The small tendency of an increased post compaction tablet strength with increasing tablet storage time might be due to fragmentation of the crystalline material during compaction creating some regions of disorder which might, in turn, crystallise during the post compaction storage. However, this tendency is not significant at the 95% confidence level as tested by the student t-test, even though studies on sucrose indicate such possibilities (13–16).

For compacts made from powder stored at 57% RH for shorter time periods than 6 hours before compaction, changes in the post compaction tablet strength were monitored, showing an increased post compaction strength with increasing post compaction storage time (Fig. 6). Apart from the findings a decrease in post compaction tablet strength was noticed for powders stored for 4 hours before compaction.

To further explore the effects of moisture on the reduction in the post compaction tablet strength of spray dried lactose, additional compacts were made using a new batch of spray dried lactose. Unfortunately, there was a variation in the degree of disorder between this new batch (19%) and the batch used earlier (15%), as measured by microcalorimetry (7), which led to differences in the values of the tablet strength. The initial tablet strength of tablets made from powders of 0.64% moisture content was 2.9 MPa (s.d. 0.1 MPa). Storage of the tablets at 57% RH for 2 hours reduced the tablet strength (2.3 ± 0.2 MPa). At this stage some of the tablets were moved to either 0% RH or 33% RH. The rest of the tablets were maintained at 57% RH. After 16 hours of post compaction storage at 0% RH, the tablet strength tended to increase (2.4 ± 0.2 MPa) probably due to drying of the amorphous parts and the possible transformation to the amorphous glassy (solidified) state. At 33% RH spray dried lactose takes up moisture to a plateau level (Fig. 1) which is higher than the uptake of 0.3% after two hours at 57% RH. This uptake is not enough to cause crystallisation. Thus, the amorphous parts of lactose are maintained in the amorphous rubbery state with an increased molecular mobility which is manifested as a reduction in tablet strength (2.0 ± 0.06 MPa). The tablets stored at 57% RH for 16 hours showed an increase in strength (3.2 ± 0.05 MPa) Mpa which is due to crystallisation of the amorphous parts of the lactose.

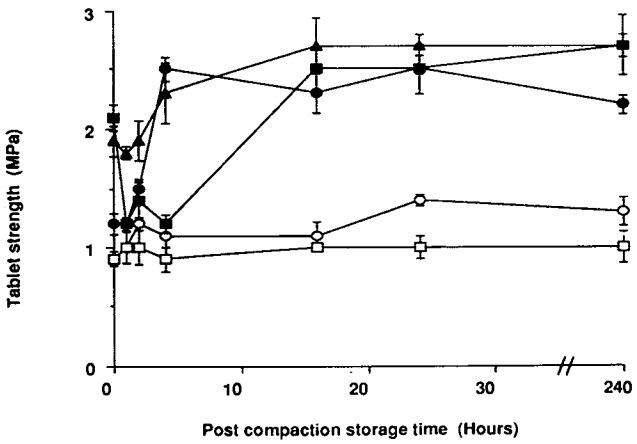


Fig. 6. The radial tensile tablet strength of tablets of spray dried (15%) amorphous lactose as a function of post compaction storage time at 57% RH and room temperature. The spray dried lactose powder was stored for various times at 57% RH before compaction (The bars indicate the standard deviation): ● 0 h; ▲ 2 h; ■ 4 h; ○ 6 h; □ 336 h.

The observed reduction is suggested to be due to a continued moisture sorption after compaction. In this case the sorbed moisture will continue to plasticise the amorphous lactose regions and increase the free volume of the material, i.e. continue to break or rupture hydrogen bonds in the amorphous lactose. By this action moisture can soften the solidified amorphous bridges previously formed between neighbouring lactose particles. Another alternative is that the moisture acts as a filter for van der Waals forces within the tablets (15,17).

The increase in post compaction tablets strength for the approximately 15% amorphous lactose is similar to earlier findings of milled materials (13,15–16). It is therefore suggested that the finding of a glass-to-rubber transformation of the amorphous lactose followed by crystallisation on post compaction storage is also valid for materials undergoing processes of mechanical activation, such as milling, mixing etc. In these cases it is not always possible to measure the amount of amorphous material (degree of disorder) with conventional techniques (7,18). This study implies that spray dried materials might be of value as model materials for understanding reactions occurring in processed materials.

## ACKNOWLEDGMENTS

The authors are very grateful to Dr. Göran Alderborn for valuable discussions. The authors are also grateful to AB R. Lundberg, Malmö, Sweden for providing Pharmatose.

## REFERENCES

1. J. T. Fell and J. M. Newton. The production and properties of spray dried lactose. Part 2. *Pharm. Acta Helv.* 46:425–430 (1971).
2. H. Vromans, G. K. Bolhuis, C. F. Lerk, K. D. Kussendrager and H. Bosch. Studies on tableting properties of lactose. VI. Consolidation on tableting properties of spray dried lactose. *Acta Pharm. Suec.* 23:231–240 (1986).
3. A. A. Elamin, T. Sebhatu and C. Ahlneck. Effect of water content on glass transition temperature and tablet strength of spray dried lactose. *Swed. Ann. Pharm. Conf.* 1992, p. 92.
4. H. Vromans, G. K. Bolhuis, C. F. Lerk, H. van de Biggelaar

and H. Bosch. 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**:29–37 (1987).
5. C. Ahlneck and G. Zografi. The molecular basis of moisture effects on the physical and chemical stability of drugs in the solid state. *Int. J. Pharm.* **62**:87–95 (1990).
6. C. Ahlneck. Chemical and physical stability of drugs in the solid state. In E. Sandell (ed) *Industrial Aspects of Pharmaceutics*, Swedish Pharmaceutical Press, Stockholm, 1993, pp. 80–92.
7. T. Sebhatu, M. Angberg, and C. Ahlneck. Assessment of the degree of disorder in crystalline solids by isothermal microcalorimetry. *Int. J. Pharm.* **104**:135–144 (1994).
8. G. Alderborn, M. Duberg and C. Nyström. Studies of direct compression of tablets X. Measurement of tablet surface area by permeametry. *Powder Technol.* **41**:49–56 (1985).
9. J. T. Fell and J. M. Newton. Determinations of tablet strength by the diametral compression test. *J. Pharm. Sci.* **59**:688–691 (1970).
10. A. Otsuka, T. Wakimoto and A. Takeda. Moisture sorption and volume expansion of amorphous lactose tablets. *Chem. Pharm. Bull.* **26**:967–971 (1978).
11. C. Oksanen and G. Zografi. The relationship between glass transition temperature and water vapor absorption by poly(vinylpyrrolidone). *Pharm. Res.* 7:654–657 (1990).
12. C. Nyström and P. G. Karehill. Studies of direct compression of tablets XVI. The use of surface area measurements for the evaluation of bonding surface area in compressed powders. *Powder Technol.* 47:201–209 (1986).
13. A. A. Elamin, G. Alderborn and C. Ahlneck. The effect of precompaction processing and storage conditions on powder and compaction properties of some crystalline materials. *Int. J. Pharm.* In Press.
14. C. Ahlneck and G. Alderborn. Moisture adsorption and tabletting. I. Effect on volume reduction properties and tablet strength for some crystalline materials. *Int. J. Pharm.* **54**:131–141 (1989).
15. C. Ahlneck and G. Alderborn. 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**:143–150 (1989).
16. G. Alderborn, and C. Ahlneck. Moisture adsorption and tabletting. III. Effect on tablet strength—post compaction storage profiles. *Int. J. Pharm.* 73:249–258 (1991).
17. P. G. Karehill and C. Nyström. Studies on direct compression of tablets XXI. Investigation of bonding mechanisms of some directly compressed materials by strength characterisation in media with different dielectric constants (relative permittivity). *Int. J. Pharm.* **61**:251–260 (1990).
18. A. Saleki-Gerhardt, C. Ahlneck and G. Zografi. Assessment of disorder in crystalline solids. *Int. J. Pharm.* **101**:237–247 (1994).