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Moisture sorption, compressibility and caking of lactose polymorphs

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ABSTRACT

The aim of this study was to conduct storage studies on the moisture sorption and caking properties of lactose powder containing different polymorphs (i.e. α-monohydrate, α-anhydrous unstable, α-anhydrous stable, β-anhydrous) and spray-dried lactose. The dry sample was compacted using a texture analyzer in paper cylinders and stored at relative humidity (RH) of 33%, 43%, 57% and 75% (25 °C, for 3 months). The samples were monitored for weight gain, moisture content, α/β balance and hardness. A simple new method of powder compression for measuring the degree of hardness of caked lactose was developed using a texture analyzer. Clear distinctions were found in the storage behavior of the five different samples. Storage at various RHs caused severe caking to β-lactose anhydrous and spray-dried lactose. The β-lactose anhydrous was hygroscopic at 75% RH. The spray-dried lactose, which contained some amorphous lactose, was hygroscopic at all RHs studied. Its moisture sorption behavior differed from that of its major component, α-lactose monohydrate, by initially absorbing moisture then desorbing. α-Lactose monohydrate was less hygroscopic at 75% RH and it formed friable cakes. The α-lactose anhydrous stable was hygroscopic at 75% RH and initially formed hard cakes which became friable during storage. The unstable form of anhydrous α-lactose was hygroscopic at all levels of RH studied but did not cake.

1. Introduction

Lactose is one of the most used excipients in pharmaceutical dosage and is an important component in dairy powders and food ingredients. The presence of lactose in food and pharmaceutical powder is often related to stickiness and caking which causes blockages in pharmaceutical tabletting machines and reduces the shelf life of food ingredients by forming solid lumps. Moisture sorption and the presence of amorphous lactose have been related to caking (e.g. Lloyd et al., 1996; Bronlund, 1997; Foster et al., 2005; Paterson et al., 2005; Fitzpatrick et al., 2007), however caking is still a common problem. There are many disagreements about how to define the degree of caking in the literature. In addition, there is an inadequate understanding of the inter-relationship between caking and lactose polymorphism (the ability of lactose particles to exist in many solid forms that have different characteristics; Hancock and Shamblin, 1998). These disagreements lead to difficulties in studying and eliminating the problem of caking.

A standardized method for characterizing caking is not readily available in the literature. Paterson et al. (2005) indicated that caking is a two-step process. For a powder to cake, the particles involved must first bridge together (referred to as sticking or lumping) and the extent of stickiness before the solidification of these bridges will then determine the extent of caking in the powder. Listiohadi et al. (2005a) reviewed the available methods in the literature to describe caking. By summarizing and combining the various methods, it is clear that caking may be characterized and defined as the appearance of lumps of various sizes in powder materials. The lumps may be small, isolated and distributed through free flowing powder or they may connect throughout the bulk sample leaving little or no free flowing powder. This is the difference between small and large degrees of caking. Caking will be accompanied by energy changes. Caking may also be a slow or rapid process. The caked lumps may be held together by strong or weak attachments: this is the hardness of the cake. There is no readily accessible published data on the number, relative size of the lumps or hardness of the caked powder which may represent a bench-mark of a severe caking problem. To correctly define the term ‘caking’, a combination of the qualitative observations of the lumps and the quantitative examinations of the degree of hardness of the lumps are necessary.

Crushing is a commonly used method in the pharmaceutical industry for measuring the degree of hardness of tablets. The wide availability of instruments such as the Instron universal testing machine and texture analyzer in laboratories makes the crushing technique robust and convenient to use. However, the analytical results from this technique are dependent on the type of probes used.

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Caking, if it occurs in bulk packages, is likely to involve moisture sorption of lactose, lightly compacted by storage in stacked paper-walled bags. A bulk powder storage technique was described in the work of Lloyd et al. (1996) and Ozkan et al. (2003) in which the powder was contained in an aluminium cylinder to allow for robust handling during storage. However, the aluminium prevents uniform exposure of sample to the experimental conditions. Imitation of the bulk storage condition requires that a light compaction of a known quantity of powder would create sample uniformity and reduce the free movement of powder and crumbling during storage but still allow uniform exposure of sample to the experimental conditions.

It is important in studying the caking of lactose, to remember its polymorphic properties which may cause interconversion of lactose from one form to another (King, 1965; Walstra et al., 1999; Listiohadi, 2004; Kirk et al., 2007). This is even more important given that most processing techniques for commercially manufacturing lactose produce powder that contains mixtures of polymorphs. The currently known forms of lactose are: α-lactose monohydrate, α-lactose anhydrous unstable, α-lactose anhydrous stable, β-lactose anhydrous, the compound crystals of β/α-lactose and amorphous lactose (Lerk et al., 1984; Holsinger, 1988). Apart from amorphous lactose, the role of lactose polymorphs in caking has been neglected in the literature; yet there are large differences in their physical properties: hygroscopicity, solubility, melting point and crystal shape. Amorphous sugars sorb water into their bulk structure and may experience changes in their physicochemical properties as a consequence. Some workers (e.g. Herrington, 1934; Lerk, 1993; Lloyd et al., 1996; Bronlund, 1997; Darcy and Buckton, 1998; Bronlund and Paterson, 2004; Foster et al., 2005; Elmonsef Omar and Roos, 2007) have studied the moisture sorption properties of amorphous lactose. However, there is little study on the moisture sorption properties of the other forms of lactose in the literature.

The aim of this study was to investigate the moisture sorption and caking characteristics of powders that contained polymorphs of lactose and amorphous lactose upon exposure to various levels of relative humidity. The storage experiment was conducted on powders compacted in paper cylinders using the newly developed method described in this study in an attempt to imitate the common bulk storage condition in the industry. The moisture gain and loss was regularly monitored on the compacted powders in the paper cylinders and was not conducted on powders spread on Petri dishes as normally done for moisture sorption studies (e.g. Saltmarch and Labuza, 1980; Angberg et al., 1991; Bronlund, 1997). The moisture gain and loss were cross-correlated to the study of α- and β-lactose content to further examine the lactose polymorphic conversions and were related to the caking behavior described as the visual observation of lumps and the quantitative measurement of hardness.

2. Materials and methods

2.1. Materials

α-Lactose monohydrate (refined edible grade, Lactose New Zealand) was used in the study after being conditioned at 75% relative humidity at 25 °C to eliminate any incipient amorphous lactose (for at least 1 month; Buckton and Darcy, 1995; Bronlund and Paterson, 1997; Newell et al., 2001).

Spray-dried lactose Pharmatose DCL11 and anhydrous lactose Pharmatose DCL21 (pharmaceutical grade, produced by DMV International and supplied by Fernz Specialty Chemicals Australia), were used as supplied. The spray-dried lactose was the readily available commercial source for lactose powder, which contained amorphous lactose (5–12% amorphous lactose; Stubberud et al., 1996; Darcy and Buckton, 1998; Listiohadi et al., 2005b). The anhydrous lactose Pharmatose DCL21 was the readily available commercial source for lactose powder with a high β-lactose content (specified to contain between 78% and 100% β-lactose on anhydrous basis; DMV International, 2000). The anhydrous Pharmatose DCL21 will be referred to as "anhydrous β-lactose" in this paper to distinguish it from the anhydrous forms of α-lactose.

α-Lactose anhydrous stable was prepared by extracting the water of crystallization of α-lactose monohydrate in toluene using the Dean and Stark apparatus (Jones and McLachlan, 1927) for 5 h. α-Lactose anhydrous unstable was made by drying α-lactose monohydrate in a vacuum oven at 100–120 °C for 16 h (Holsinger, 1988; Kirk et al., 2007).

To minimize variations, particularly the effect of particle size on caking, the lactose powders were sieved (only particles retained on the sieve with screen sizes between 150 and 250 μm were collected). The particle size of the powders was measured using Malvern particle analyzer. The α-lactose monohydrate was confirmed by FT-IR analysis (Listiohadi, 2004; Kirk et al., 2007) and was measured to contain α- and β-lactose in the proportion of 94.8:5.2 (high-pressure liquid chromatography, HPLC). The lactose anhydrous produced by toluene distillation and that produced by vacuum oven drying had similar FT-IR spectra to α-lactose anhydrous stable and unstable respectively as reported by Kirk et al. (2007) and contained α- and β-lactose in the proportion of 89.4:10.6 and 91.2:8.8, respectively (HPLC). The anhydrous lactose Pharmatose DCL21 was confirmed to be mostly β-lactose anhydrous in the proportion of 16.2:83.8 (α- to β-lactose) by FT-IR (Listiohadi, 2004; Kirk et al., 2007) and HPLC. Spray-dried lactose Pharmatose DCL11 was measured to contain 4.9% amorphous lactose by thermal gravimetric analysis integrated with single differential thermal analysis (TGA/SDTA; Listiohadi, 2004) and α- to β-lactose in the proportion of 86.5:13.5 (HPLC). All powders (including the pre-conditioned α-lactose monohydrate) were stored in vacuum desiccators over phosphorus pentoxide at 25 °C (for a minimum of 1 week prior to experiment; Thomsen et al., 2006; Elmonsef Omar and Roos, 2007; Savolainen et al., 2007).

2.2. Powder compaction and compression methods

2.2.1. Powder compaction for the preparation of storage experiments

A texture analyzer (TA-XT2, Stable Micro Systems, England) fitted with a flat-ended cylinder probe (1.5 cm diameter) was used. A plastic tube lined with a cylinder made of filter paper (1.6 cm diameter and 5 cm height) was used as the die (Fig. 1).

Powder samples (approximately 3 g) in triplicates were uniformly compacted under 1.4 MPa (141,200 kg/m^2, corresponding to a load/force of 25 kg or 245 N over a standardized contact area 1.77×10^{-4} m^2) at 1.0 mm/s and then held at that pressure for 30 s to form the loose plug (test mode: hold distance-force relaxation). After compaction, the powder plug contained in the paper cylinder could easily be taken out of the plastic die and was ready for further analysis or storage experiment. The paper cylinder served as a protection to the powder plug from premature disintegration during handling and storage. The slits at the sides and the paper disc at the bottom of the paper cylinder allowed easy sampling of the powder plug. The filter paper which was permeable to moisture allowed uniform exposure of the sample to the experimental conditions. The plugs were readily amenable to examination of their hardness after storage.

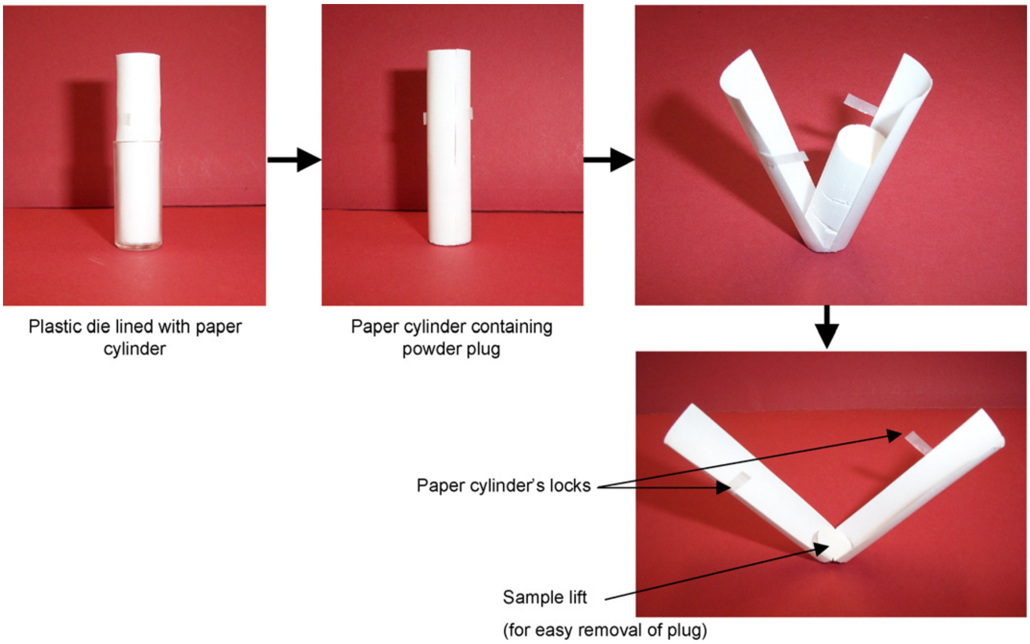

Fig. 1. Plastic die and paper cylinder for powder compaction and storage experiment.

2.2.2. Powder compression for the assessment of degree of hardness of caked plug

The powder compression for the analysis of the degree of hardness of the caked plug was carried out using a texture analyzer (TA-XT2, Stable Micro Systems, England) fitted with a flat-ended cylinder probe (1.5 cm diameter). A base with an indentation at the centre was designed to hold the sample plug in the test position (Fig. 2). The powder plug was analyzed by a compression method (test mode: return to start, measure force in compression) at 1.0 mm/s and was compressed until 50% of the height of the sample. The failure strength of the plug was characterized as breakage of the plug and disintegration of the powder. The degree of hardness was taken to be the pressure (force per unit area; kg/m^2 is the unit of pressure as read from the instrument) required to disrupt the plug. The compression profiles of the powder plugs and the visual observation were used to relate the degree of hardness of the caked powder to the degree of caking.

Fig. 2. Texture analyzer for the compression of powder plug for characterizing the crushing strength (degree of hardness).

2.3. Storage experiments on compacted lactose

The storage experiments on lactose that contained different polymorphs are illustrated in Fig. 3. Lactose powder was compacted using a texture analyzer in paper cylinders (method in Section 2.2.1) to model the storage of lactose in a 25 kg bag stacked in a pile. The storage studies were conducted on the compacted lactose (referred to as "lactose plugs") in the paper cylinders at 25 °C and at relative humidities of 33%, 43%, 57% and 75% (over saturated salt solutions of $MgCl_2$, K_2CO_3, NaBr, NaCl, respectively) for 3 months. It is noteworthy that this storage experiment was conducted on the plugs at ambient pressure whereas, industrially, the pressure of bags in a stack would be maintained for extended periods. Although not an exact duplication of the industrial situation, this experimental design was a closer representation than the studies typically found in the literature.

An empirical test was developed to assess caking. The formation of lumps was visually assessed while the hardness of caked lactose was analyzed by compression using the TA-XT2 texture analyzer (method in Section 2.2.2).

The initial moisture content of the lactose samples was analyzed using the Sartorius automated moisture detector. During storage, the moisture sorption of the compacted lactose in the filter paper cylinder, amongst other measures, was regularly monitored by weighing. The temperature and relative humidity of the room were carefully controlled at the stated settings and monitored daily during storage and sampling.

Data were statistically analyzed using Minitab Statistical software (Release 13.0, Minitab Inc., 1999, USA). For this study, the analysis of variances (ANOVA) for the general linear models (GLM) were carried out to investigate whether the time and relative humidity of storage had significant effects on the moisture content of the powder and the hardness of caked powder of the different forms of lactose.

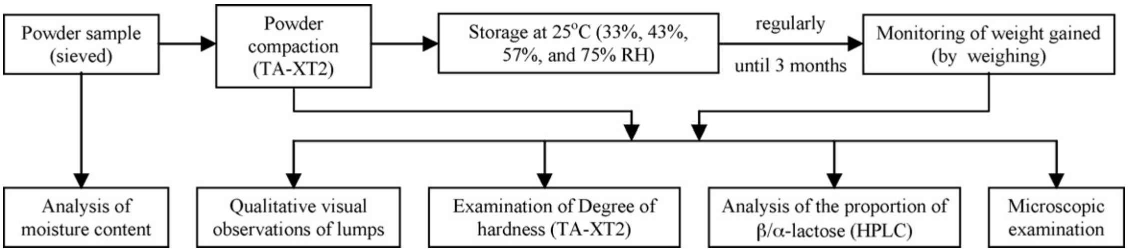

Fig. 3. Storage experimental procedure of lactose for the caking study.

The α- and β-anomer proportion of the lactose samples was determined using high-pressure liquid chromatography. The agglomeration of the particles of lactose after storage was visually observed under a microscope with polarized light.

The methods of compaction of powder, compression of caked powder plug and storage experiment developed in this study have also been applied to the caking of amorphous lactose, skim milk powder and whey powder and processed lactose powders (Listiohadi et al., 2005b,c,d).

2.4. Methods of analysis for the characterization of lactose powder

2.4.1. Water content analysis using Sartorius automated moisture detector

The total water content of the samples was determined using Sartorius automated moisture detector (model: MA30, Sartorius AG, Germany) according to the method described by Listiohadi (2000). Samples of lactose powder (5 g) were heated at 140 °C for 10 min. The instrument readout is shown as "moisture" and will be reported as such here. It is recognized that this is, strictly speaking, the loss on drying.

2.4.2. Analysis of α/β-anomer proportions in lactose

The proportion of α and β-lactose anomer in lactose was analyzed using high-pressure liquid chromatography based on Listiohadi (2000). The system used in the analysis was made up of a pump (model no. SP8810-020, Spectra-Physics, USA), a C18 column (Aqua 5 μ 125A, Phenomenex, Australia) 250 mm × 4.6 mm internal diameter, and a refractive index detector (Shodex, model: RI se-61, Showa Denko K.K, Tokyo, Japan). The HPLC was run using Delta Chromatography Data Systems software version 5.0 (1999, DataworX, Digital Solutions Pty. Ltd., Australia).

Lactose powder was dissolved rapidly into distilled water (lactose concentration was 0.1–1%) and injected into the C18 HPLC column (sample size: 20 μL) through a filter (pore size: 0.45 μm). The analysis was carried out at 25 °C. Distilled water was used as the mobile phase at a flow rate of $0.7 \pm 0.02\,\mathrm{mL\,min^{-1}}$. The peak of β-lactose anomer appeared first with a retention time of 4.10 min and that of α-lactose anomer appeared at 4.37 min (Listiohadi, 2000). The chosen conditions ensured a clear separation between these two peaks. The size of the areas under the peaks was used to calculate the proportions of these anomers in the lactose sample.

2.4.3. Microscopic analysis of powder using a microscope with polarized light

A method described by Roetman and Van Schaik (1975) was followed. Lactose powder (<1 mg) was dispersed in paraffin oil and examined under a microscope with polarized light (model: Wetzlar, Leica Mikroskopie & Systeme GmbH, Germany). Under polarized light, crystalline lactose appears as shiny particles whereas amorphous lactose appears as a transparent and dark material. Images of the microscopic examination were recorded using Twain 32 camera (model: WV-CP410/G, Panasonic).

2.4.4. Particle size analysis of powder using Malvern particle analyzer

The particle size distribution of the lactose powders was measured by a laser diffraction method using Malvern particle analyzer (model: MSX-EX, Malvern Instruments Limited, UK, 1998) fitted with 1000 mm range lens to provide 2.4 mm active beam length. Lactose powder (<1 g, refractive index of α-lactose monohydrate is 1.333–1.361; Malvern Instruments Ltd., 1997) was dispersed in dry alcohol (refractive index is 1.360; Malvern Instruments Ltd., 1997) in a small volume dispersion unit (model: MS1, Malvern Instruments Limited, UK). The analysis was run using Malvern Mastersizer X-long bed software version 2.18 (Malvern Instruments Ltd., 1992–1998) and set at the polydisperse mode. At least 5000 scans were recorded in a single analysis.

2.4.5. FT-IR for the identification of crystalline lactose

FT-IR spectra of lactose powder (±2 mg) in dry KBr disks (±0.3 g) were recorded with Avatar 360 FT-IR E.S.P.$^{\mathrm{TM}}$ (Nicolet Instrument Corporation, USA). An average of 32 scans was recorded at a resolution of $4\,\mathrm{cm^{-1}}$. The spectra were analyzed using OMNIC 5.1 software (Nicolet Instrument Corporation, USA). Each sample was analyzed in duplicates.

2.4.6. Amorphous lactose analysis using TGA/SDTA

Thermal analysis was conducted using thermal gravimetric analysis integrated with single differential thermal analysis instrument (model: 851e/LF1100, Mettler-Toledo GmbH, Switzerland) equipped with a robotic arm (model: TSO801RO) for automated sampling. Lactose powder (10 ± 1 mg, accurately weighed into open 70 μL aluminum oxide crucibles using the TGA/SDTA microbalance) was heated from 25 to 300 °C at a heating rate of $5\,^{\circ}\mathrm{C\,min^{-1}}$, under a nitrogen flush ($50\,\mathrm{mL\,min^{-1}}$). The analysis was conducted in four replicates. The instrument was calibrated using indium. Data of TGA and SDTA were analyzed using Star$^{\mathrm{e}}$ Base Software for Windows NT Service Pack 4 (Mettler-Toledo GmbH, Switzerland).

3. Results and discussion

3.1. Lactose moisture sorption characteristics and polymorphic transformations

The moisture sorption characteristics of the lactose samples that contained generally more than one polymorphic forms of lactose followed the moisture sorption characteristic of the major component (Fig. 4). The analysis of variance (Table 1, $p < 0.05$) shows that the various forms of lactose possessed significantly different moisture sorption characteristics. The amount of moisture absorbed

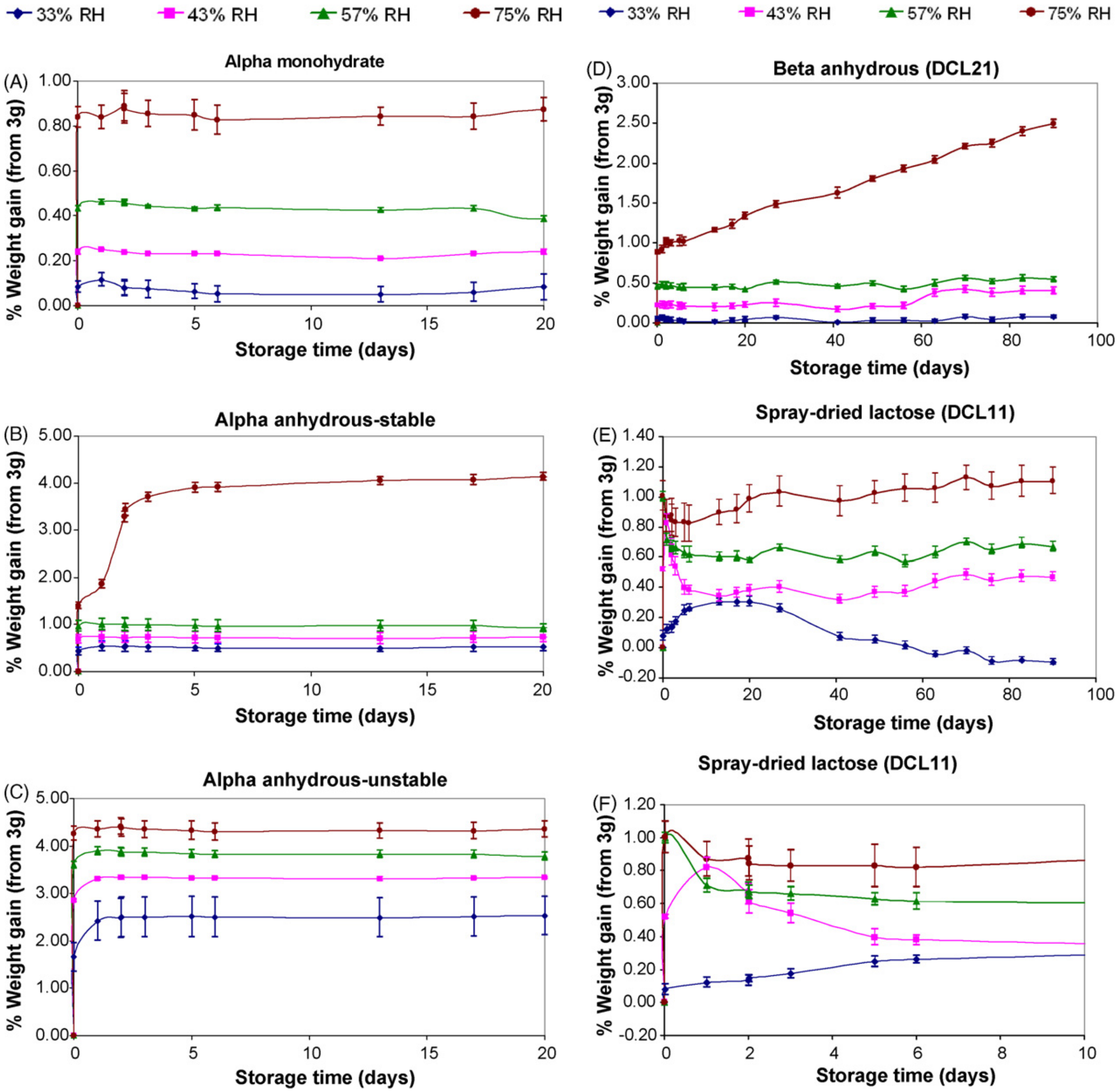

Fig. 4. Moisture sorption characteristics of (A) α-lactose monohydrate, (B) α-lactose anhydrous stable, (C) α-lactose anhydrous unstable, (D) anhydrous β-lactose Pharmatose DCL21, (E) and (F) spray-dried lactose Pharmatose DCL11 stored at 33%, 43%, 57% and 75% relative humidities at 25 °C ($n = 3$). (F) is an enlargement of the initial 10 days of storage of spray-dried lactose Pharmatose DCL 11. Standard deviations are represented by error bars.

by the lactose samples was significantly dependent on the relative humidity of storage and time (Table 1, $p < 0.05$). In general, the higher the relative humidity of storage, the higher was the amount of moisture absorbed and the faster was the process. It is shown that the relative humidity of storage had more effect on the moisture sorption than the time of storage (*F*-values in Table 1).

Table 1

Analysis of variance (general linear model) of the moisture sorption characteristic of the various polymorphic forms of lactose

Analysis of variance (general linear model)		
Factors	*p*-Value	*F*-value
Time	0.016	2.28
Humidity	<0.010	74.40
Sample type	<0.010	197.71

Note: *p*-Value < 0.050 is significant.

In Fig. 4, while all samples started at zero on the weight gain scale, within a day they all quickly absorbed the amount of water shown. The data in Fig. 4 for α-monohydrate, α-anhydrous stable and α-anhydrous unstable are shown only for the initial 20 days where the weight gains were most pronounced. The remaining 70 days of the study revealed little change in the mass of these three samples. For the other two samples, β-lactose anhydrous DCL21 and spray-dried lactose DCL11, data are shown for the full 90 days of the study as noteworthy changes in the mass of these samples occurred throughout the study.

α-Lactose monohydrate absorbed moisture quickly during storage at all levels of relative humidity achieving a weight gain of 0.1–0.9% in less than 10 days and maintained it throughout the experiment (Fig. 4A and Table 2). This is in accordance with the water adsorption isotherm in which only a few layers of water molecules would form on the surface so the total mass change

Table 2
Water content of the various polymorphic forms of lactose before and after 3 months storage at various levels of relative humidity at 25 °C

Sample	% Total water content				
	Initial[a]	Final (after 3 months storage)[b]			
		33% RH	43% RH	57% RH	75% RH
α-Monohydrate	5.26 ± 0.04	5.35 ± 0.01	5.57 ± 0.01	5.72 ± 0.02	6.17 ± 0.02
α-Anhydrous stable	0.99 ± 0.06	1.51 ± 0.02	1.71 ± 0.01	2.05 ± 0.02	5.18 ± 0.02
α-Anhydrous unstable	1.34 ± 0.03	3.89 ± 0.01	4.79 ± 0.01	5.18 ± 0.02	5.73 ± 0.03
β-Anhydrous (DCL21)	0.31 ± 0.01	0.38 ± 0.00	0.71 ± 0.01	0.86 ± 0.01	2.81 ± 0.01
Spray-dried (DCL11)	4.99 ± 0.08	4.89 ± 0.01	5.46 ± 0.01	5.66 ± 0.02	6.09 ± 0.02

Note: RH means relative humidity of storage environment. Maximum moisture sorption by paper cylinder was 0.29%, 0.33%, 0.44% and 0.68% at 33% RH, 43% RH, 57% RH and 75% RH, respectively.

[a] Initial total water was analyzed using automated Sartorius moisture analyzer (mean ± standard deviation, $n = 3$).

[b] Final total water content is the sum of the initial total water content and the %moisture gained (mean ± standard deviation, $n = 3$).

throughout an adsorption isotherm is small (generally much less than 1% (w/w); Buckton, 2000).

The stable form of α-lactose anhydrous was less hygroscopic below 57% relative humidity and very hygroscopic at 75% relative humidity (Fig. 4B). The unstable form of α-lactose anhydrous exhibited a considerable monotonic increase in weight with the increase in the levels of the relative humidity of storage from 33% to 75% (Fig. 4C).

Below 57% relative humidity (at 25 °C), α-lactose anhydrous stable achieved a weight gain of 0.5–1.0% (in less than 10 days) and maintained it throughout the experiment (Fig. 4B and Table 2). The weight gain at 33% relative humidity was slightly less than that at 43%, which was in turn, slightly less than that at 57% relative humidity. This suggests that the sorption of free moisture by α-lactose anhydrous stable at 25 °C happened at and below 57% relative humidity. This is not in agreement with Figura and Epple (1995) who stated that α-lactose anhydrous stable was more hygroscopic at relative humidities above 50%. The less hygroscopic behavior of α-lactose anhydrous stable at 57% relative humidity (at 25 °C) observed in this study may be due to the different methods of sample preparation between Figura and Epple (1995) and in this study. Figura and Epple (1995) prepared their α-lactose anhydrous stable by dehydration in an oven (a less controllable process to produce α-lactose anhydrous stable than the toluene distillation method used here). The thermal dehydration forms α-lactose anhydrous unstable from α-lactose monohydrate as a precursor to α-lactose anhydrous stable (Figura and Epple, 1995; Kirk et al., 2007) which might potentially produce a considerable proportion of the more hygroscopic α-lactose anhydrous unstable in the final sample. The thermal method may also be more prone to sugar damage during heating than the toluene distillation (Figura and Epple, 1995; Kirk et al., 2007).

At 75% relative humidity (at 25 °C), the stable and unstable forms of α-lactose anhydrous showed an initial weight gain of approximately 4% (in less than 20 days and 10 days, respectively, Fig. 4B and C), which changed a little for the duration of the experiment. The α-lactose anhydrous stable finished the 3 months storage with a weight gain of 4.19% and the unstable form with 4.39% (Table 2). The final total water contents of the α-lactose anhydrous stable and unstable after storage were close to the theoretical moisture content of α-lactose monohydrate (5%) suggesting the possibility that a good proportion of these samples absorbed water to convert to crystalline α-lactose monohydrate. Holsinger (1988) stated that α-lactose anhydrous unstable might convert to α-lactose monohydrate because it has the same crystal lattice as α-lactose monohydrate allowing absorbed water to easily accommodate the vacant space within the crystal lattice and forming α-lactose monohydrate. However, Holsinger (1988) suggested that α-lactose anhydrous stable could not convert to α-lactose monohydrate without first dissolving in water because its crystal structure is different from that of α-lactose monohydrate.

Anhydrous β-lactose Pharmatose DCL21 (containing 80.2% β-lactose) had initial rapid moisture absorption and achieved a constant weight gain of maximum 0.5% at relative humidities below 57% in less than 10 days (at 25 °C, Fig. 4D and Table 2). Similar to α-lactose anhydrous stable, storage below 57% relative humidity (at 25 °C) might allow free moisture absorption by the anhydrous β-lactose. At 75% relative humidity (at 25 °C), anhydrous β-lactose absorbed moisture at a constant rate of approximately 0.5% per 30 days throughout the 3 months storage without stabilizing (Fig. 4D and Table 2). This is similar to the observation done by Angberg et al. (1991) for 22 days. It is possible for β-lactose anhydrous to slowly convert to α-lactose monohydrate during storage as moisture was absorbed at high relative humidity as was also reported by Briggner et al. (1994), Angberg (1995) and Cal et al. (1996). Fig. 5 shows that the β-lactose content of anhydrous β-lactose Pharmatose DCL21 decreased when stored at 75% relative humidity

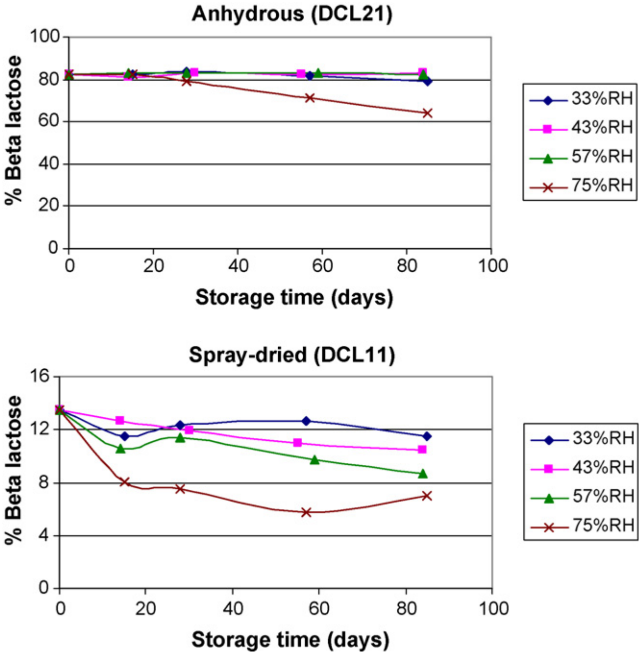

Fig. 5. β-Lactose content of anhydrous β-lactose Pharmatose DCL21 and spray-dried lactose Pharmatose DCL11 after storage at various relative humidities at 25 °C ($n = 2$).

Table 3
The β content of α-lactose samples after storage at 33%, 43%, 57% and 75% relative humidities (at 25 °C)

	Sample											
	α-Monohydrate				α-Anhydrous stable				α-Anhydrous unstable			
	%Relative humidity											
	33	43	57	75	33	43	57	75	33	43	57	75
%β (Initial)	5.15				10.60				8.75			
%β (After)												
15 days	3.65	3.86	3.99	3.92	8.95	10.52	8.85	7.88	8.00	7.94	7.72	7.62
28 days	4.40	4.36	5.12	4.56	10.04	11.26	9.57	8.22	9.03	8.74	8.51	8.21
57 days	3.95	4.43	5.20	4.32	9.31	9.78	8.76	7.33	7.44	7.95	7.42	7.37
85 days	4.45	3.95	4.15	4.65	9.10	10.95	7.80	8.00	7.35	7.85	7.65	7.75
Average	4.11	4.15	4.62	4.36	9.35	10.63	8.75	7.86	7.95	8.12	7.83	7.74
S.D.	0.38	0.29	0.64	0.33	0.48	0.64	0.73	0.38	0.77	0.42	0.47	0.35

Note: Average and S.D. indicate the means and standard deviations of %β-lactose in the samples initially and after storage ($n = 2$, from 15 days to 85 days storage).

(at 25 °C). However, the conversion of β-lactose anhydrous to α-lactose monohydrate was much slower than the conversion of the α-lactose anhydrous forms to the monohydrate form described earlier perhaps because it may involve the transformation of β-anomer to α-anomer before the conversion of the anhydrous form to the monohydrate form could proceed. These data suggest that a complete dissolution of β-lactose, described earlier by Holsinger (1988), might not be required to initiate the mutarotation to α-lactose by the ring opening. Lloyd et al. (1996) and Bronlund and Paterson (2004) did storage experiments of lactose and dairy powders under a broader range of relative humidity to develop a moisture sorption isotherm, but their storage studies were shorter (3 h and 3 weeks, respectively) than the study done here and their data were taken only at the end of the storage study, not monitored throughout the study. The present experiments complement these earlier studies and show the importance of monitoring sorption over a longer period which was more representative of bulk storage in industry.

Spray-dried lactose Pharmatose DCL11 exhibited different moisture sorption characteristics to its major component, α-lactose monohydrate (Fig. 4E and F). The spray-dried lactose initially absorbed then desorbed moisture at 33–75% relative humidity (25 °C). The moisture absorption and desorption happened in less than 10 days for the samples stored at 43–75% relative humidity but they happened in more than 30 days at 33% relative humidity. It appears that the moisture sorption characteristic of the spray-dried lactose might have followed that of amorphous lactose as suggested by Sebhatu et al. (1994), Buckton et al. (1995), Listiohadi et al. (2005b) and Elmonsef Omar and Roos (2007), when it passed through the different stages of glass–rubber–crystal.

Fig. 5 shows that spray-dried lactose Pharmatose DCL11 initially contained some proportion of β-lactose (13.5%) and the content of this β-lactose reduced during storage at relative humidity as low as 33% (at 25 °C). The β-lactose content of the spray-dried lactose reduced with the increase in the relative humidity of storage (33–75% relative humidity). The initially high moisture absorption by the amorphous lactose in the spray-dried lactose might be sufficient for the transformation of amorphous to crystalline lactose and the β-anhydrous to the monohydrate lactose. Table 3 shows that the samples of α-lactose monohydrate, α-lactose anhydrous stable and α-lactose anhydrous unstable initially contained a small proportion of β-lactose. The moisture sorption during storage at all levels of relative humidity studied did not markedly change the content of β-lactose in these samples.

In this study, all powder samples were compacted prior to the storage experiment to imitate the storage of bulk powder. However, comparing our results to the previous studies on uncompacted lactose (e.g. Darcy and Buckton, 1998), the results of the studies are similar suggesting that compaction does not make a major difference to water sorption.

3.2. *Observation on the compaction of powder and compression of lactose plugs*

The typical curve of powder compaction is shown in Fig. 6. All lactose powders compacted in the paper cylinders prior to the storage experiments (i.e. α-lactose monohydrate, α-lactose anhydrous stable, α-lactose anhydrous unstable, anhydrous β-lactose Pharmatose DCL21 and spray-dried lactose Pharmatose DCL11) exhibited a smooth compaction curve. The compacted powder (referred to as “lactose plug”) formed a loose cake of the cylinder shape. The height of the plug varied between 1.5 and 3 cm depending on the type of powder.

The compressibility characteristics of the lactose plugs are illustrated in Fig. 7. The height of the initial significant high peak where the plug fractures or fails to maintain its integrity was taken as the degree of hardness (the instrument reads the force in kg, the area of the probe is 1.77 mm^2). The width of the peak indicates the resistance of the plug to fracture. A narrow peak (Fig. 7A, first peak)

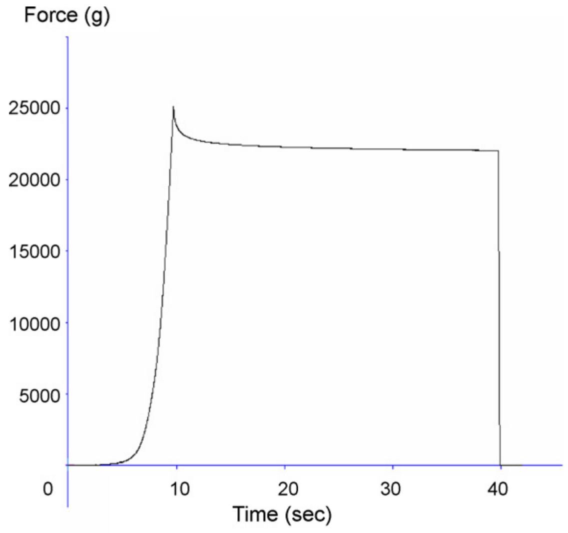

Fig. 6. Compaction profiles of lactose powder under 1.4 MPa using TA-XT2 texture analyzer.

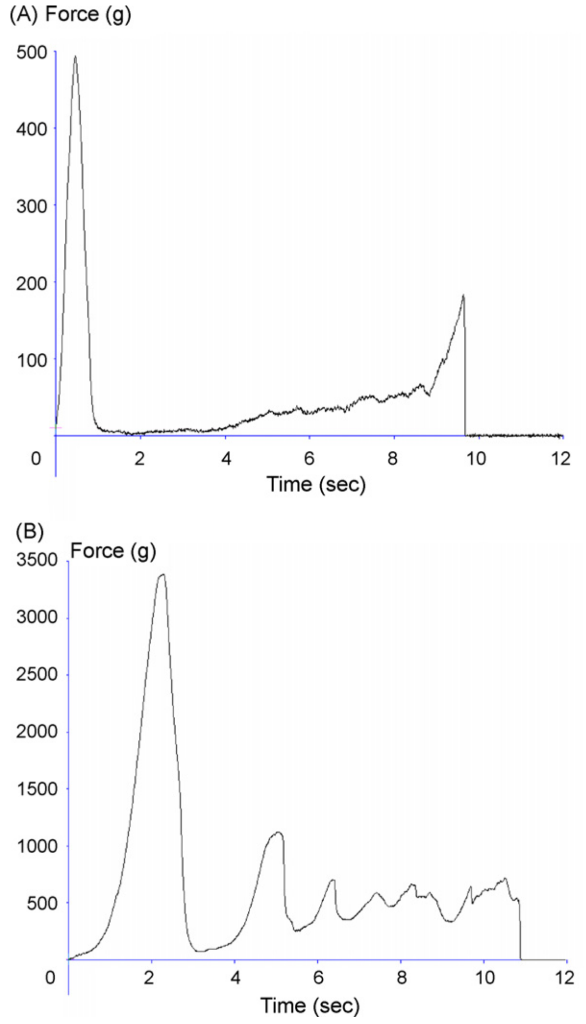

Fig. 7. Examples of the compression profiles of lactose plugs characterized using a texture analyzer. The examples above are of (A) α-lactose monohydrate after storage and (B) anhydrous β-lactose Pharmatose DCL21 plugs after storage.

means the plug was brittle, whereas a broader peak (Fig. 7B, first peak) means the plug was more elastic (i.e. more resistant to deformation). The number of well-defined peaks indicates the intactness of the plug. More peaks (clearly shown in Fig. 7B) mean that the plug was broken into pieces and was difficult to compress into powder.

The compression characteristic of the lactose plugs examined in this study before and after storage (Table 4) may be classified into two groups illustrated in Fig. 7. Powder of α-lactose monohydrate, α-lactose anhydrous unstable, α-lactose anhydrous stable, anhydrous β-lactose Pharmatose DCL21 and spray-dried lactose Pharmatose DCL11 after compaction and before storage were either free flowing or formed into loose plugs (loose caked powder). The compression characteristic of the powder plugs was indicated by an initial fracture followed by a collapse into powder (illustrated in Fig. 7A as a single distinctive peak followed by almost flat peaks).

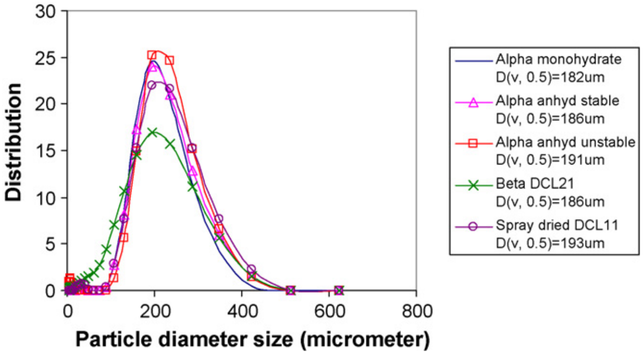

Fig. 8. The particle size distributions of the lactose powders after sieving. $D(v, 0.5)$ is the mean diameter of particle as resulted from Malvern instrument data statistical analysis on the particle distribution (5000 scans).

After storage, the plugs of α-lactose monohydrate, α-lactose anhydrous unstable and α-lactose anhydrous stable had similar compression characteristics to their plugs before storage. However, after storage, anhydrous β-lactose Pharmatose DCL21 and spray-dried lactose Pharmatose DCL11 formed plugs with different compression characteristics to the plugs before storage. Under compression, the plugs had an initial fracture followed by more fractures (illustrated in Fig. 7B as a single high distinctive peak followed by other well separated distinctive peaks smaller than the first one). The plug was broken into intact portions, which depending on the hardness of the plug, could be further crushed into smaller intact pieces or into powder.

The lactose plugs that exhibited the compression profiles illustrated in Fig. 7 are listed in Table 4. The magnitude of hardness, brittleness/plasticity and cohesiveness may vary among the powder plugs of the various forms of lactose. The hardness of the plug could be used to further classify whether the plug was friable, soft or hard. Particle size differences should not contribute to the caking characteristics since the lactose powders were sieved to produce uniform particle size prior to the experiments (Fig. 8, average particle size was 182–193 μm) and the sieved powders were compacted under identical mild conditions. A preliminary study shows that for the small plugs of the same type of powder used in this study, the small variation in the height of the plugs after compaction did not result in noticeable effect on the degree of hardness, measured using the texture analyzer.

Table 4
Examples of lactose plugs with similar compression profiles illustrated in Fig. 7

Compression profile	Fresh (before storage)	After storage
Fig. 7A Plug disintegrated easily into powder (non-cohesive)	• α-Lactose monohydrate • α-Lactose anhydrous stable • α-Lactose anhydrous unstable • Anhydrous β-lactose DCL21 • Spray-dried lactose DCL11	• α-Lactose monohydrate • α-Lactose anhydrous stable • α-Lactose anhydrous unstable
Fig. 7B Plug was brittle, broken into intact portions, and non cohesive		• Anhydrous β-lactose DCL21 • Spray-dried lactose DCL11

Table 5
Analysis of variance (general linear model) of the hardness of plugs (pressure required to break lactose plug, kg/m^2) of the various polymorphic forms of lactose stored at various levels of relative humidity

Analysis of variance (general linear model)		
Factors	*p*-Value	*F*-value
Time	0.983	0.47
Humidity	<0.010	8.18
Sample type	<0.010	23.8

Note: p-Value < 0.050 is significant.

3.3. Hardness of caked lactose after storage

The polymorphic forms of lactose significantly affected the hardness of the caked lactose plugs ($p < 0.05$, Table 5, Fig. 9). Humidity ($p < 0.05$) not time ($p > 0.05$) was the significant factor contributing to the degree of hardness of the plugs during storage (Table 5 and Fig. 9).

α-Lactose monohydrate, α-lactose anhydrous unstable and α-lactose anhydrous stable formed friable plugs after the 3 months storage (Fig. 9 and Table 6). The hardness of the plugs of α-lactose monohydrate increased monotonically with the increase in humidity and time of storage (Fig. 9A). The hardness of the plugs of α-lactose anhydrous unstable slightly increased with the increase of relative humidity but decreased with the increase of storage time (Fig. 9C).

During storage, the hardness of plugs of α-lactose anhydrous stable decreased (Fig. 9B). This type of lactose initially formed a hard plug, which became more friable after storage at 43% relative humidity and above (at 25 °C). This result suggests that if lactose particles have a coating of α-lactose anhydrous stable, then hard lumps would form in the packaging which would become friable after exposure to humid atmospheres. The cause of this phenomenon needs to be further studied.

Anhydrous β-lactose Pharmatose DCL21 and spray-dried lactose Pharmatose DCL11 formed noticeable harder plugs after the 3 months storage at all levels of relative humidity studied (Fig. 9 and Table 6). The hardness of the plugs of the anhydrous β-lactose increased with the increase of storage time and humidity, which is in accordance with its moisture sorption characteristic as illus-

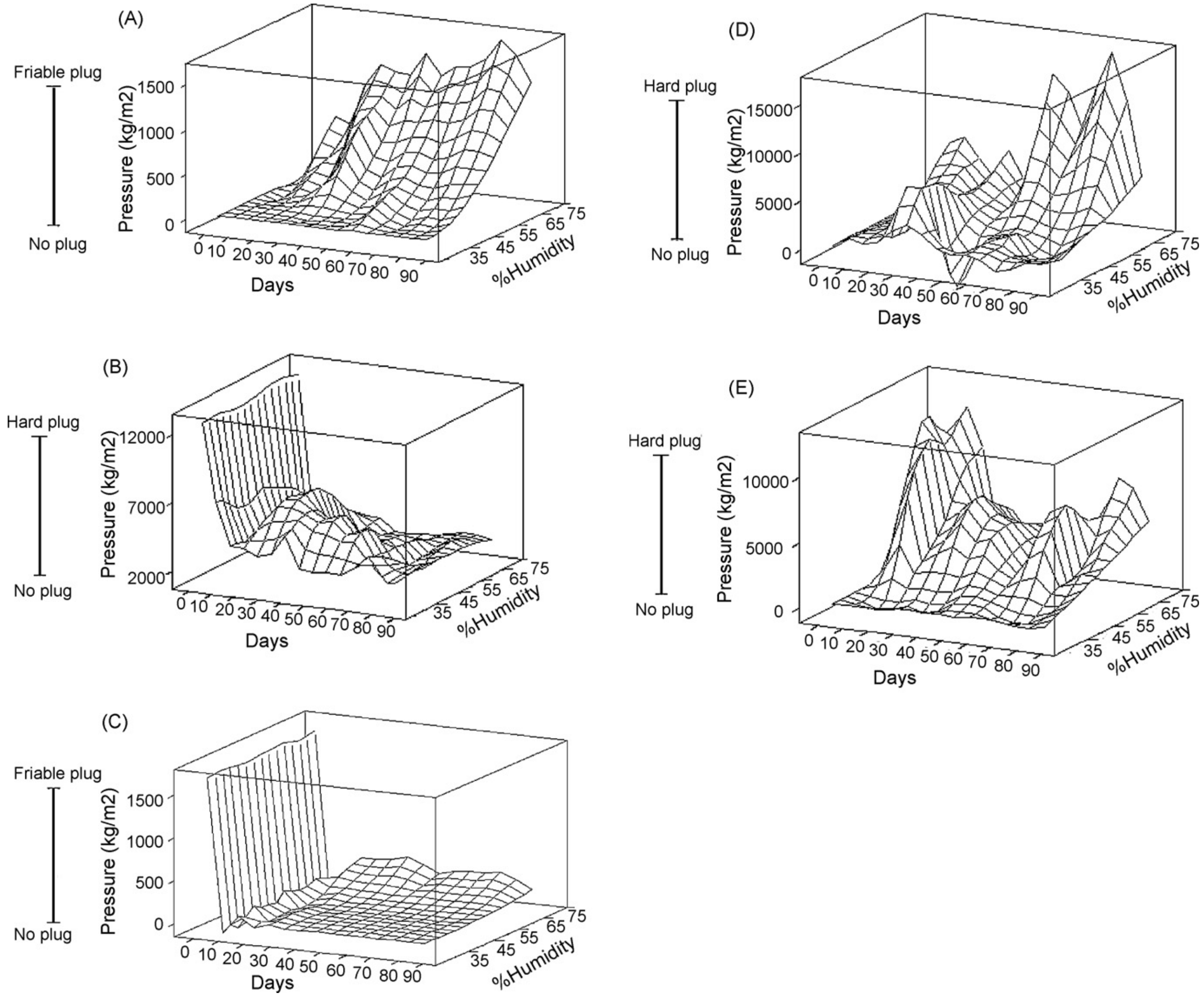

Fig. 9. Degree of hardness of some lactose plugs (measured as the pressure in kg/m^2, as resulted from the TA-XT2 instrument, $n = 3$) after storage at various levels of relative humidity at 25 °C. (A) α-Lactose monohydrate; (B) α-lactose anhydrous stable; (C) α-lactose anhydrous unstable; (D) β-lactose anhydrous Pharmatose DCL21; (E) spray-dried lactose Pharmatose DCL11.

Table 6
Hardness of powder plugs of the various polymorphic forms of lactose before and after 3 months storage at 33%, 43%, 57% and 75% relative humidities (at 25 °C)

Lactose sample powder	Initial hardness (kg/m^2)		Final hardness after storage (kg/m^2)							
			33% RH		43% RH		57% RH		75% RH	
α-Monohydrate	0	NP	0	NP	0	NP	455	F	1,232	F
α-Anhydrous unstable	1,664	F	0	NP	0	NP	0	NP	80	NP
α-Anhydrous stable	12,601	H	4,340	H	2,555	F	2,730	F	2,264	F
β-Anhydrous (DCL21)	0	NP	930	F	852	F	1,677	F	4,478	H
Spray-dried (DCL11)	0	NP	284	F	155	F	2,664	F	4,309	H

Note: RH means relative humidity of storage environment. Hardness data $n = 3$. NP (no plug), F (friable), H (hard). Consult Table 7 for complete descriptions.

trated in Fig. 4D. The anhydrous β-lactose formed hard plug at 75% relative humidity (25 °C).

The caking characteristic of spray-dried lactose Pharmatose DCL11 (Fig. 9E) was different from the other lactose samples analyzed and in particular, it differed from that of α-lactose monohydrate, the major component of this spray-dried lactose. In general, the hardness of the plugs of spray-dried lactose increased with the increase of storage relative humidity. However, during storage (more obvious at higher relative humidities), the hardness of the plug of spray-dried lactose initially (at early storage time

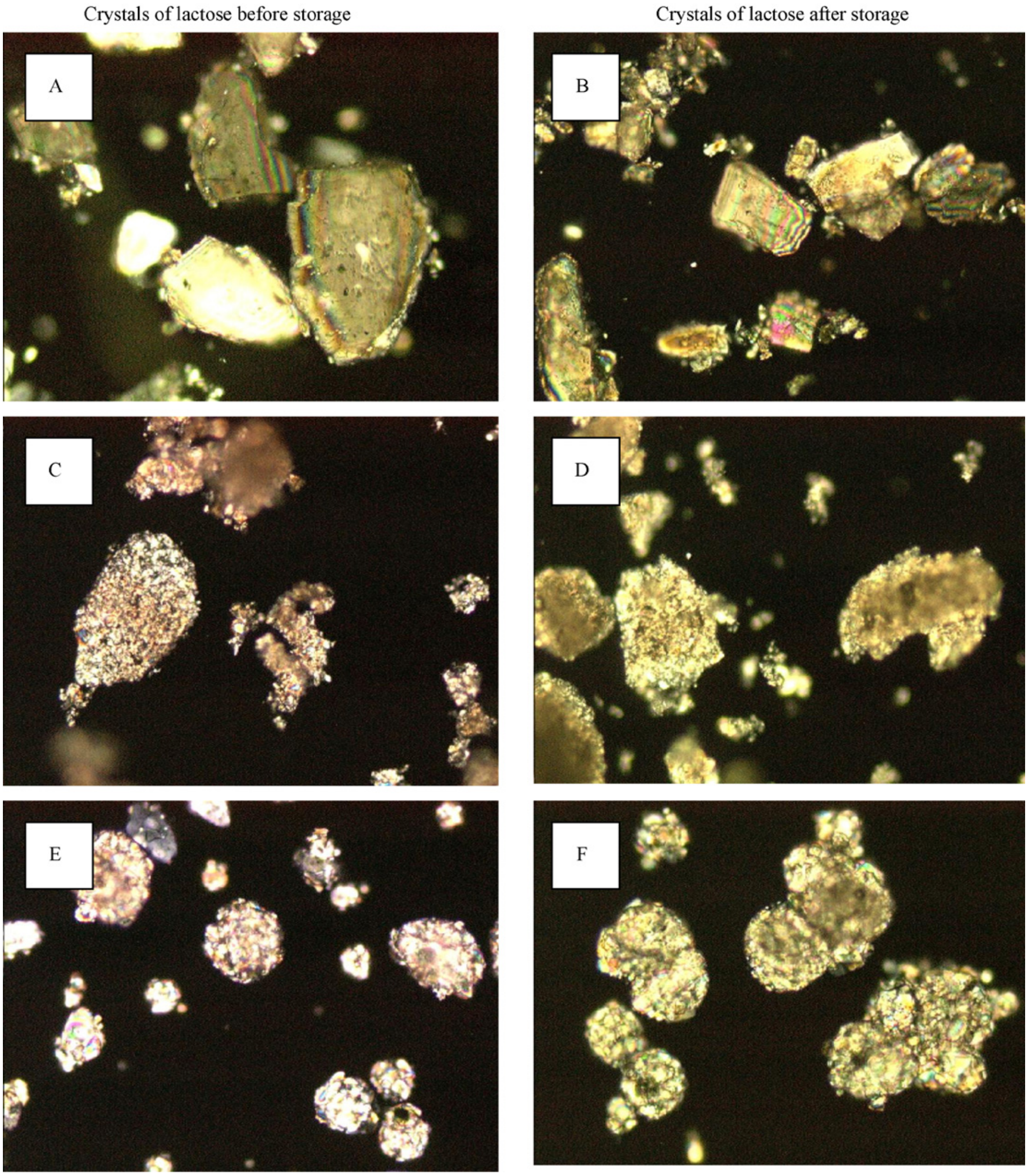

Fig. 10. Lactose particles as observed under a microscope with polarized light (100× magnification, dispersed in paraffin oil). Parts (A and B) are α-lactose monohydrate; (C and D) are anhydrous β-lactose Pharmatose DCL21; (E and F) are spray-dried lactose Pharmatose DCL11. Storage of samples was done at 75% relative humidity (at 25 °C) for 3 months.

Table 7
Description of the degree of hardness of lactose powder plugs

Pressure required to break plug (kg/m^2)[a]	Pressure required to break plug (kPa)[b]	Force (g) required to break plug (probe area 1.77 cm^2)[a]	Suggested scale of caking	Caked lactose plug	Qualitative description
<150	<2	<26	0	No plug	Free flowing
>150	>2	>26	1	Friable	A slightest touch with finger was sufficient to break the plug back into powder
<3,000	<30	<531			
>3,000	>30	>531	2	Hard	Plug was broken into smaller lumps, which could be further crushed back into powder
<25,000	<245	<4,425			
>25,000	>245	>4,425	3	Very hard	Plug was broken into smaller very hard intact portions
<150,000	<1,470	<26,550			

[a] Data obtained from the analysis using the texture analyzer.

[b] Data calculated from the first column.

between 1 and 15 days) increased rapidly then decreased. This caking characteristic was not reported in the literature for the study of amorphous lactose by previous workers (Lloyd et al., 1996; Ozkan et al., 2003). The amorphous content of lactose had been reported by the previous workers to significantly contribute to the hardness of caked lactose but the changes in the degree of hardness of the cake were not monitored during storage. The spray-dried lactose formed hard plug after 3 months storage at 75% relative humidity (25 °C).

Based on the examinations of the degree of hardness (Fig. 9), the compression profiles (Fig. 7 and Table 4) of the various lactose plugs and the qualitative observations, caking may be classified as listed in Table 7.

3.4. *Particle morphology after storage*

The agglomeration of crystals after storage was clearly illustrated for spray-dried lactose Pharmatose DCL11 (Fig. 10E and F). Although not clearly visible in the micrographs (Fig. 10A–D), the observation under the microscope showed that transverse movements of the microscope slides caused some crystals of α-lactose monohydrate and anhydrous β-lactose Pharmatose DCL21 to move in groups attached together in the paraffin oil. This indicates that after storage, the crystals of caked α-lactose monohydrate and anhydrous β-lactose were lightly attached to each other. The stronger attachment within crystals of spray-dried lactose in comparison to α-lactose monohydrate and anhydrous β-lactose crystals was due to the amorphous content of spray-dried lactose as was also reported by some workers (e.g. Lloyd et al., 1996; Darcy and Buckton, 1998).

The crystals of α-lactose anhydrous unstable and stable did not show any agglomeration. The crystals moved freely in paraffin oil when the microscope slides were moved in a transverse direction. This is in accordance with the decrease in the hardness of the plugs of α-lactose anhydrous unstable and α-lactose anhydrous stable after storage.

4. Conclusion

The moisture sorption and caking characteristics of various polymorphic forms of lactose were studied in a 3-month storage experiment. Simple methods of powder compaction for storage experiments and compression for measuring the degree of hardness of caked lactose were developed using a common texture analyzer. The degree of caking was described as a combination of the degree of hardness measured as the pressure (force per unit area) to break the caked lactose and the qualitative observations.

The polymorphic and isomeric properties of lactose play a significant role in its hygroscopicity and caking profile. α-Lactose monohydrate was less hygroscopic at 75% relative humidity and below (at 25 °C) absorbing <1% moisture. α-Lactose monohydrate formed friable cakes after 3 months storage at relative humidities of 57% and above that were easily broken with minimal pressure.

α-Lactose anhydrous unstable was hygroscopic and monotonically absorbed substantial amounts of moisture (2.5–4.5% at 33–75% relative humidity, 25 °C) but did not cake. α-Lactose anhydrous stable and anhydrous β-lactose Pharmatose DCL21 were hygroscopic at 75% relative humidity with α-lactose anhydrous stable absorbing moisture quickly almost reaching the final theoretical moisture content of α-lactose monohydrate and anhydrous β-lactose constantly absorbing moisture during the 3-month storage. The absorbed moisture was able to induce the transformation of the anhydrous form of lactose to α-lactose monohydrate and the β-anomer to α-anomer. The α-lactose anhydrous stable formed hard cake at the early time of storage, which became friable during storage. The anhydrous β-lactose formed permanent hard cake, which could not be easily broken back into powder.

The spray-dried lactose Pharmatose DCL11 exhibited the moisture absorption and desorption characteristics of amorphous lactose at 33–75% relative humidity. The spray-dried lactose formed hard cake after 3 months storage at 75% relative humidity but at the early storage time, it initially formed harder cake. Its strong cake was due to the apparent partial fusion between the crystals as seen under a polarizing microscope.

Powder compaction before storage to the levels done in this study did not make a major difference to the water sorption by the various forms of lactose.

The results suggest that to understand the moisture sorption of commercial lactose samples one needs to appreciate the α/β balance, the anhydrous/monohydrate balance and the amorphous/crystalline balance in the sample, and their interconversions, at the start, during and at the conclusion of the exposure to the moist environment. The way these processes play out will determine whether the sample cakes, the hardness of the cakes and how to minimize the caking. The results on various commercial samples might provide useful information for industrial production and distribution of lactose.

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