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Form conversion of anhydrous lactose during wet granulation and its effect on compactibility

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Abstract

The purpose of this study was (a) to evaluate the factors affecting the form conversion of anhydrous lactose to the monohydrate form during wet granulation using water as the granulating agent and (b) study the effect of lactose form conversion on its compaction properties. A two-level full factorial design with two center points was used to evaluate the factors affecting form conversion. The three variables evaluated were percentage of microcrystalline cellulose (low 0 and high 20), water to intragranular solids ratio (low 0.10 and high 0.18) and drying conditions (tray drying and fluid bed drying). The presence of microcrystalline cellulose in the formulation did not provide any benefit in reducing the percent lactose conversion. But, the conversion was significantly reduced by decreasing the amount of water added to the granulation and/or by decreasing the drying time, using a fluid bed dryer compared to a tray dryer. In the second part of the study, complete conversion of the anhydrous lactose to monohydrate was achieved by storing the anhydrous form under 25 °C/97% RH for 4 weeks. Physical characterization (compactibility, surface area and surface morphology) was performed on the form converted material and compared to the as received anhydrous lactose. The physical characterization results indicated that even though anhydrous lactose undergoes complete form conversion to monohydrate form under high humidity and/or during wet granulation, it retains its inherent higher as received material compactibility and the BET surface area and porosity of the form converted material are higher than that of the as received anhydrous lactose.

Keywords: Lactose conversion; Granulation; Lactose anhydrous; Wet granulation; Compactibility

1. Introduction

Lactose is one of the most frequently used fillers in tablet formulations. Lactose is available in different forms depending upon the crystallization conditions and in various grades with different particle sizes and different compaction properties. α-Lactose monohydrate and β-anhydrous lactose are among the most commonly used forms of lactose. Even for the same crystal form, different lactose grades from different suppliers exhibit different powder properties and therefore could not be treated as interchangeable in direct compression formulations (Whiteman and Yarwood, 1998). In particular, compactibility behavior is different for the various forms of lactose. In contrast to α-lactose monohydrate, roller dried β-anhydrous lactose has significantly superior compaction properties which have been attributed to the very irregular particle surfaces resulting in higher tendency of the particles to fracture during compaction (Vromans et al., 1985, 1987; Lerk, 1993). Therefore, anhydrous lactose would be the lactose form of choice in tablet formulation where an improvement in compactibility is required, including wet granulated tablet formulations. However, anhydrous lactose can undergo partial form conversion to α-lactose monohydrate in presence of water used during granulation. In addition to its possible impact on compactibility, this form conversion should be monitored closely as it could cause dilution of the active in the formulation. Since batching is based on the weight of anhydrous material, water acquired by the lactose during form conversion results in increase in the weight of the lactose diluent and hence reduces the potency of the tablets. Preliminary studies in our lab indicated, that wet granulated blends containing anhydrous lactose showed better compactibility than lactose monohydrate granulations despite partial conversion of β-anhydrous lactose to α-lactose monohydrate during granulation. This form conversion and its consequence on the formulation performance need to be further investigated.

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Microcrystalline cellulose (MCC) is another commonly used excipient in the wet granulated tablet formulations. MCC is hygroscopic and has the ability to absorb large quantity of water. It is relatively stable and has few incompatibilities (Handbook of Pharmaceutical Excipients, 1986). Anberg et al. (1991a) demonstrated that MCC protects anhydrous lactose when water vapor is abundant by slowing down the rate of hydration, because water is preferentially absorbed by MCC. Put together, the addition of MCC in the wet granulated tablet formulation along with anhydrous lactose could influence the incorporation of water into the anhydrous lactose crystal and reduce form conversion of anhydrous lactose to monohydrate. The objective of the first part of this study was hence to evaluate the effect of three factors on form conversion of anhydrous lactose: (1) inclusion of MCC along with anhydrous lactose in the formulation; (2) amount of water used for granulation; and (3) drying conditions of the granulation (tray drying versus fluid bed drying). Fluidized bed drying has been shown to be significantly faster in both drying and handling time than tray drying (Gao et al., 2000; Rankell et al., 1991).

The second part of the study investigated the effect of form conversion from anhydrous to monohydrate on compactibility of lactose, since lactose monohydrate is less compactable than anhydrous lactose. Complete form conversion of lactose anhydrous to monohydrate form was induced by exposure to high humidity condition. It has been widely cited in the literature that anhydrous β-lactose at higher humidity incorporates water and undergoes form conversion to crystalline α-lactose monohydrate (Berlin et al., 1971; Ford and Timmins, 1989; Anberg et al., 1991b; Shukla and Price, 1991). However, none of those studies evaluated the effect of this conversion on physical characteristics of the material, particularly as they relate to compactibility. Since compactibility of lactose is known to depend on particle size and surface area, it is difficult to obtain a consistent and complete picture from the literature regarding the effect of form conversion on compactibility.

2. Experimental

2.1. Materials

Anhydrous lactose (60 M grade) and lactose monohydrate (310 grade) were acquired from Kerry Bio-Sciences (Norwich, NY, USA) and Foremost Farms (Baraboo, WI, USA), respectively. Microcrystalline cellulose (Avicel® PH102) and croscarmellose sodium were obtained from FMC Corporation (Philadelphia, PA, USA). Hydroxypropyl Cellulose (Klucel® EXF) was obtained from Aqualon (Wilmington, DE, USA).

2.2. Methods

2.2.1. Factors affecting lactose form conversion during wet granulation

A two-level full factorial design with two center points (Table 1) was used to study the effect of three variables: percentage of MCC (low 0% and high 20%), water to intragranular solids ratio (low 0.10 and high 0.18) and drying conditions (tray drying versus fluid bed drying). All formulations contained, 3% hydroxypropyl cellulose, and 2% croscarmellose sodium (1% intra- and 1% extra-granular). Percent lactose conversion (see below) was the response variable evaluated. Statistical analysis of the data was carried out in SAS JMP® 4.0 (SAS Institute Inc., Cary, NC, USA). Preliminary data analysis using a regression model with main effects and two-way interactions indicated that the magnitude of some of interaction terms was insignificant. As a result, data were subsequently analyzed with the regression model that excluded those interaction terms.

2.2.1.1. Granulation batches in the high shear mixer. Granulation of the different experimental design batches was carried out in a 10 L Fielder (PMA-10, Aeromatic-Fielder AG, Bubendorf, Switzerland) high shear granulator at a batch size of 1.5 kg using water as the granulating liquid. Anhydrous lactose, hydroxypropyl cellulose, intragranular croscarmellose sodium, and MCC (when applicable) were added to the granulator bowl and blended for 2 min at impeller speed of 330 rpm and chopper speed of 1800 rpm. The specified amount of water for the batch was then added to the blend in the granulator using a peristaltic pump over a period of 2 min, with the impeller speed maintained at 330 rpm and the chopper speed at 1800 rpm. After complete addition of water, the granulation was wet massed for 30 s while maintaining the same impeller and chopper speeds. The wet granulation was screened through a 12-mesh screen (1680 μm) and dried either in a hot air oven at 50 °C or in a Glatt fluid bed dryer GPCG1 (Glatt Air Techniques Inc. Ramsey, NJ, USA) to a Loss on drying (LOD) at 105 °C of <1.5%. The inlet temperature of the fluid bed dryer was maintained at 65–70 °C. The dried granulation was milled using a conical mill (Comil® 197S, Quadro Inc. Millburn, NJ, USA) through 18-mesh screen (1000 μm).

2.2.1.2. Percent (%) lactose conversion. The percent lactose conversion in the milled granulation was measured by determining the loss on drying of the granulation at two different temperatures, 105 and 150 °C, using a Halogen Moisture Analyzer, Model HR 73 (Mettler Toledo, Columbus, OH, USA). At 105 °C only the unbound water would be lost as compared to

Table 1
Full factorial design with two center points

Run#	% (w/w) of MCC in the formulation	% (w/w) of granulating water[a]	Drying conditions
1	0	18	Tray
2	20	10	Tray
3	0	10	FBD
4	10	14	Tray
5	20	18	Tray
6	0	10	Tray
7	10	14	FBD
8	20	18	FBD
9	0	18	FBD
10	20	10	FBD

[a] % (w/w) of granulating water = 100 × weight of granulating water/weight of solids in the granulator.

the loss of bound water (water of hydration) at 150 °C. The difference between the two LOD values at 105 and 150 °C were calculated and the percent form conversion from lactose anhydrous to monohydrate was determined by the following formula:

$$\%\ \text{lactose form conversion} = \frac{\langle \text{LOD at 150 °C} - \text{LOD at 105 °C} \rangle \times 100}{\text{wt. fraction of lactose in formulation} \times 4.7}$$

where 4.7 is the theoretical % water (w/w) in the crystal of α-lactose monohydrate.

As reported in the literature, lactose monohydrate contains ~5.2% total moisture while lactose anhydrous contains less than 0.5% moisture (Shukla and Price, 1991; Reier and Shangraw, 1966; David and Augsburger, 1977). As a positive control, the difference in LOD between 105 and 150 °C for a formulation with 70% lactose monohydrate was determined and was found to be 3.4%. This is in close agreement to the theoretical water of hydration for the lactose monohydrate which supports the validity of the method used for assessing lactose conversion in this study. In addition, pre-blend containing anhydrous lactose showed only minimal difference between the two LOD values.

2.2.2. Form conversion of anhydrous lactose under high humidity conditions

2.2.2.1. Storage under high humidity. Preliminary experiments demonstrated that under high humidity (97% RH) at room temperature, anhydrous lactose converts to monohydrate form completely. Based on the preliminary experiments, anhydrous lactose (~15.0 g) was placed in desiccators filled with saturated solution of potassium sulfate, resulting in an equilibrium humidity of 97% for a period of 4 weeks to induce the form conversion of anhydrous lactose to the monohydrate form. The difference between the LOD values at 105 and 150 °C, as described earlier, was used to calculate the percent conversion in the sample. The as received samples and the samples stored at high humidity were subjected to the tests below.

2.2.2.2. Thermogravimetric analysis (TGA). TGA was used to confirm the conversion of anhydrous lactose to the monohydrate form. Samples were weighed into tared aluminum crucible and heated from 25 to 180 °C at a rate of 10 °C/min in a stream of nitrogen gas, using TGA Q500, TA Instruments (New Castle, DE, USA). The acquired data of the weight change was then plotted as the function of temperature to give the total weight loss curve.

2.2.2.3. Powder X-ray diffraction (PXRD). X-ray diffraction patterns of the samples were measured using a Rigaku MiniFlex® powder X-ray diffractometer (The Woodlands, TX, USA). The samples were scanned at room temperature (25 °C) using a 2θ range from 2° to 40°, with increments of 0.1°, and measuring time was 1 s/step (1°/min).

2.2.2.4. Compactibility. The compaction profiles of the different lactose samples of same size fraction (88–149 μm) were obtained using an ESH Tablet Compaction Simulator (Huxley Bertram Engineering, Cambridge, UK). Only the material passing through 100 mesh (149 μm) and retained on 170 mesh (88 μm) screens was used for analysis. The similar size fraction removes particle size bias and facilitates comparison of compactibility. A 260-mg sample of each batch was compressed on the simulator using 3/8″ flat face tooling to a pre-determined in-die thickness. Each batch was compressed to five different thickness targets with two to three tablets obtained at each thickness. Actual thickness achieved for each compressed tablet was determined by the Linear Variable Displacement Transducer (LVDT) of the Compaction Simulator. Compression and ejection forces were determined for each tablet. The hardness of each tablet was determined by a diameteral compression test on a hardness tester (Key International, Englishtown, NJ, USA) and converted to a tensile strength. Compaction profiles were then constructed using the compression pressure (obtained by dividing the compression force by punch tip surface area) and corresponding compact tensile strength. The compactibility parameter was calculated as the slope of the line obtained by linear regression of the data points in the compaction profile. The other compaction parameters calculated from the Compaction Simulator data were the yield pressure and bonding. The yield pressure was obtained from the slope of the linear portion of the natural logarithm of the reciprocal tablet porosity versus compression pressure. The Bonding parameter was calculated as the *Y*-intercept of the plot of tensile strength versus tablet porosity and represents theoretical tablet tensile strength at zero porosity.

2.2.2.5. Particle size distribution (PSD). The particle size distribution was determined by mesh analysis using an Allen Bradley Sonic Sifter (Allan Bradley, Milwaukee, WI, USA) equipped with a series of six screens and a pan. About 5.0 g of the sample was tested with a pulse setting of "5", sift setting of "5", and total sifting time of 5 min. The percent fines was calculated by the summation of the percent material retained over the mesh #325 (44 μm) and dust collected in the pan of the sonic sifter.

2.2.2.6. Surface area. The surface area for the entire sample and the size fraction (between 88 and 149 μm) sample for all the lactose samples was determined using a nitrogen adsorption technique by Gemini™ 2380 V series surface area analyzer (Micromeritics, Norcross, GA, USA). The sample (1.0–1.5 g) was degassed by nitrogen flow at 55 °C for at least 2 h using Vac Prep™ 061 (Micromeritics, Norcross, GA, USA). The amount of nitrogen adsorbed was determined at partial nitrogen pressure (P/P_0) ranging from 0.05 to 0.30. Surface area was determined using the Brunauer–Emmett–Teller's (BET) calculation for the nitrogen data in the P/P_0 range from 0.05 to 0.3.

2.2.2.7. Mercury intrusion porosimetry (porosity). Pore volume distributions of the samples were determined for a size fraction passed through 100 mesh (149 μm) and retained on 170 mesh (88 μm), by mercury intrusion porosimetry (Autopore III 9420, Micromeritics, Norcross, GA, USA). Incremental pore volume and total pore volume were determined in the pressure range from 1 to 60,000 psi cor-

responding to pore diameters between 148 to 0.003 μm. Equilibrium time was 5 s at each pressure. Plots of incremental pore volume and cumulative pore volume were constructed against diameter for pore diameters between 10 and 0.1 μm.

2.2.2.8. Scanning electron microscopy (SEM). The images of the size fraction (between 88 and 149 μm) samples were taken through XL30 ESEM FEG (environmental scanning electron microscope, field emission gun) instrument (FEI/Philips, Hillsboro, OR, USA) in vacuum mode. Material samples were sputtered with a thin conductive layer of platinum to prevent charging of the sample, using a Sputter coater Pelco SC-7 (Pelco International, Redding, CA, USA).

3. Results and discussion

3.1. Factors affecting lactose conversion during wet granulation

Table 2 shows the data for wet granulation experiments. The percent form conversion for all the runs ranged from 22.8 to 37.7%. Table 3 depicts the regression analysis of the percent form conversion during the wet granulation. Statistical analysis demonstrated that the formulation granulated with a higher percent of water showed a higher tendency for form conversion during the wet granulation as indicated by the positive sign of the parameter estimate ($p = 0.0122$). Higher percent form conversion would eventually lead to dilution of the active in the formulation and could potentially lower the potency of the tablets. Therefore, it is desirable to use minimum amount of water needed to achieve acceptable granulation, in order to avoid dilution in formulations containing anhydrous lactose.

Table 2
Response data for the factorial design evaluating factors affecting percent lactose form conversion during wet granulation

Run#	Difference between LOD at 105 and 150 °C (%)	Percent lactose conversion
1	1.47	33.1
2	0.92	26.3
3	1.03	23.2
4	1.42	35.8
5	1.32	37.7
6	1.23	27.7
7	1.04	26.2
8	0.95	27.1
9	1.21	27.2
10	0.8	22.8

Table 3
Regression analysis of percent lactose form conversion during wet granulation

Parameter	Parameter estimate	*P* value
% (w/w) of MCC	0.3375	0.7165
% (w/w) of water	3.1375	0.0122
Drying conditions (FBD)	−3.41	0.0051

Granulation subjected to fluidized bed drying demonstrated a significantly lower percent form conversion than those subjected to convective tray drying ($p = 0.0051$), as indicated by the negative sign of the parameter estimate. A fluid bed dryer significantly reduces drying time compared to tray dryer or vacuum dryer (Gao et al., 2000). The fluid bed dryer took approximately 45 min to dry a granulation to the target moisture content of <1.5% as compared to 6–8 h for tray drying. Hence, the residence time during which moisture is available to interact with the anhydrous material is much higher in tray drying as compared to the fluidized bed dryer.

Effect of MCC on percent form conversion was not statistically significant ($p = 0.7165$) as per the regression analysis of percent form conversion (Table 3). MCC is known to have high affinity for water and hence its presence in the formulation could make granulating water less available for form conversion. However, levels of MCC up to 20% used in this study did not reduce the percent form conversion.

3.2. Form conversion of anhydrous lactose under high humidity condition

Anhydrous lactose converted completely to the monohydrate form when stored under high humidity (97% RH/25 °C) for 4 weeks. The difference between the LOD values at 105 and 150 °C for the anhydrous lactose material stored under those conditions was approximately 4.8%, which is in close agreement with theoretical water of hydration for lactose monohydrate (Berlin et al., 1971; Brittain et al., 1991). In addition, the unexposed anhydrous lactose (as received) material showed only minimal difference between the two LOD values. Thermogravimetric analysis performed on the anhydrous lactose stored under the high humidity condition, demonstrated a weight loss of 4.721% between 105 and 150 °C (Fig. 1A) as compared to the weight loss of 4.924% for as received lactose monohydrate (Fig. 1B). This further confirmed the complete conversion of anhydrous lactose to monohydrate under high RH. PXRD was also performed on the different samples of lactose to confirm the conversion of anhydrous lactose to monohydrate under high RH. The X-ray pattern of anhydrous lactose subjected to high RH was similar to the pattern of lactose monohydrate control and different from the control anhydrous lactose (Fig. 2). This establishes the conversion of anhydrous lactose to monohydrate under high RH.

Sieve analysis revealed that anhydrous lactose, when stored under high RH, agglomerates and the mean geometric diameter increased from 81.9 μm for control anhydrous lactose to 135.9 μm. The % fines also decreased from 36.8 to 17.6 (Table 4). Since the three different lactose materials exhibited different particle size distribution, further physical characterization of these materials, which included BET surface area, mercury porosimetry and compactibility measurements, were performed on the same size fraction materials (88–149 μm), which would eliminate any bias due to particle size differences.

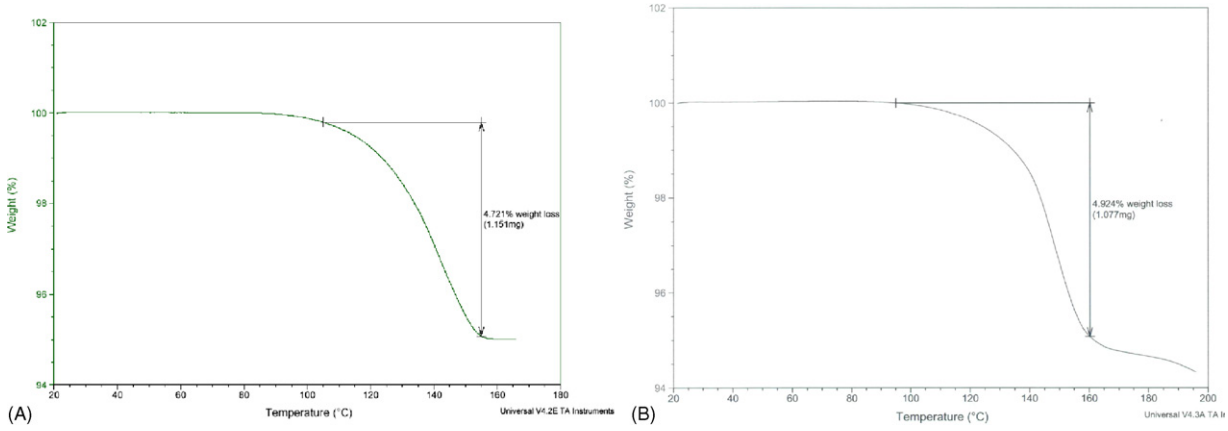

Fig. 1. Thermogravimetric analysis. (A) Anhydrous lactose stored at 97% RH for 4 weeks (form converted material). (B) As received lactose monohydrate.

Table 4
Physical characterization and compaction data for the different samples of lactose

Sample	Particle size by mesh analysis		Compaction parameters			BET surface area (m^2/g)	Mercury porosimetery total intrusion volume (mL/g) from 0.1 to 10.0 μm pore diameter
	Geometric mean diameter (μm)	% fines (<75 μm)	Compactibility (kPa/MPa)	Bonding (MPa)	Yield pressure (MPa)		
Lactose monohydrate (as received)	57.4[b]	58.8[b]	5.2[a]	2.2[a]	281.3[a]	0.256[a]/0.350[b]	0.0598[a]
Anhydrous lactose (as received)	81.9[b]	36.8[b]	11.0[a]	4.3[a]	182.5[a]	0.284[a]/0.453[b]	0.1383[a]
Form converted material	135.9[b]	17.6[b]	11.8[a]	5.4[a]	258.3[a]	0.906[a]/0.884[b]	0.3318[a]

[a] Size fraction between 88 and 149 μm.
[b] Entire sample.

BET surface area and total intrusion volume measurements of the different lactose materials for similar size fraction (88–149 μm) are also listed in Table 4. The BET surface area for the form converted material was 0.906 m^2/g, compared to 0.284 and 0.256 m^2/g for control anhydrous lactose and lactose monohydrate, respectively. Similar surface area measurements were also performed on the entire sample and showed increased surface area in the following order: lactose monohydrate < anhydrous lactose < form converted material (Table 4), which is in agreement with the literature stating that β-anhydrous lactose has more pronounced particle surface irregularities than the α-lactose monohydrate, leading to higher surface area.

Fig. 3A and B illustrate the pore distribution of different lactose materials for similar size fractions between 88 and 149 μm. The total intrusion volume (total pore volume) for anhydrous lactose, determined by mercury porosimetry, increased from 0.1383 to 0.3318 mL/g, upon conversion to monohydrate form. The total

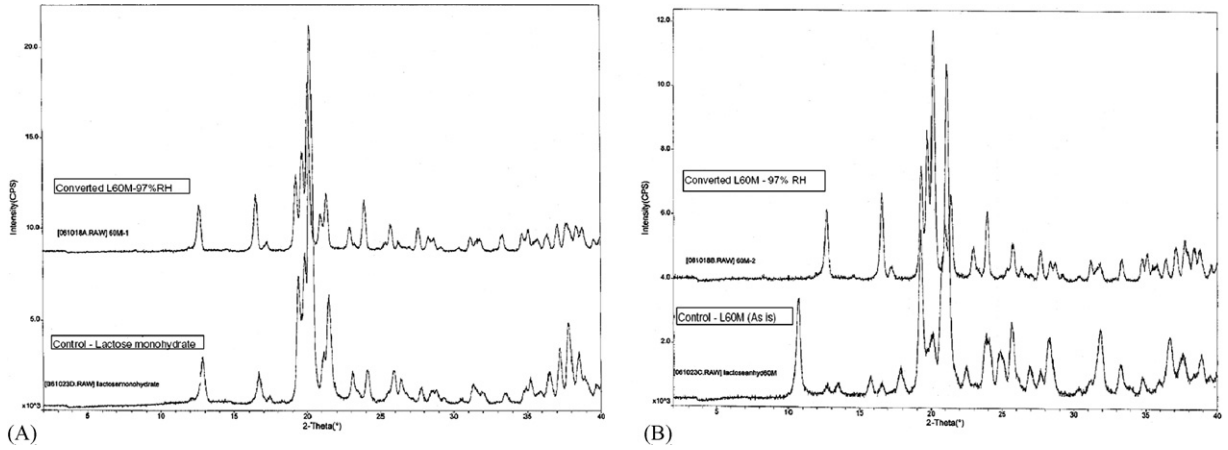

Fig. 2. Powder X-ray diffraction (PXRD) patterns for different grades of lactose. (A) Comparison of PXRD patterns of anhydrous lactose stored 97% RH for 4 weeks (top) vs. as received lactose monohydrate (bottom). (B) Comparison of PXRD patterns of anhydrous lactose stored at 97% RH for 4 weeks (top) vs. as received anhydrous lactose.

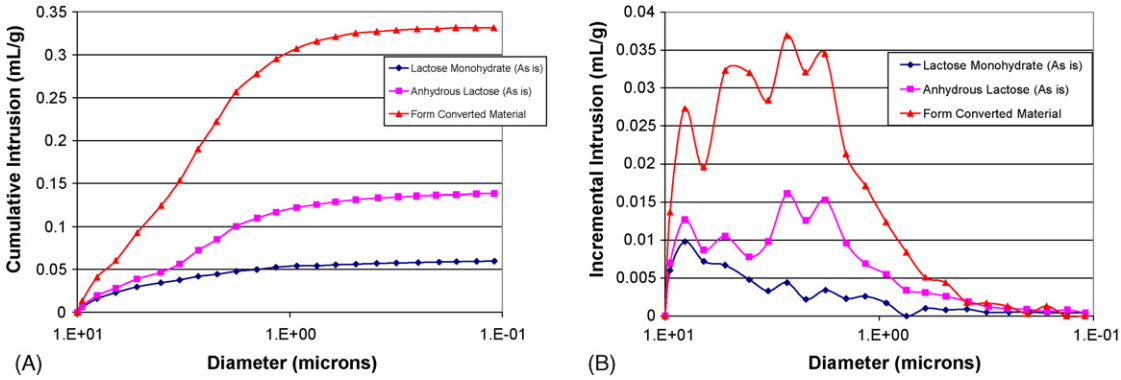

Fig. 3. Mercury intrusion porosimetry plots for different grades of lactose for size fraction between 88 and 149 μm. (A) Cumulative intrusion volume vs. diameter. (B) Incremental intrusion volume vs. diameter.

intrusion volume for the different samples of lactose increases in the following order: lactose monohydrate < anhydrous lactose < form converted material. This is consistent with the results from the BET surface area measurements.

The scanning electron micrograph imaging (Fig. 4) illustrates the difference in the surface morphology between the different samples of lactose. The pictures confirmed the rougher and irregular surfaces of control anhydrous lactose particles as compared to lactose monohydrate. Anhydrous lactose upon exposure to high RH undergoes form conversion to monohydrate. Upon conversion, the anhydrous lactose particles change their morphology. Each particle of the resulting monohydrate form is an aggregate of small crystals with subsequently higher surface area and higher porosity. Thus, while both have the same crystal form, the commercial and converted lactose monohydrate materials have very different particle morphology.

Anhydrous lactose also demonstrated increase in surface area upon wet granulation. For the granulation (Run 1 of Table 1) containing high level of anhydrous lactose, granulated with 18% (w/w) water and dried using a tray dryer, the percent of lactose conversion was 33.1% (Table 2). The surface area for this granulation was 0.756 m^2/g as compared to 0.453 m^2/g for the starting material anhydrous lactose. It can therefore be inferred that form conversion of anhydrous lactose during wet granulation is also accompanied by similar morphological changes as the form converted material under high humidity.

Table 4 demonstrates the compaction parameters of the three different samples of lactose, for the same size fraction

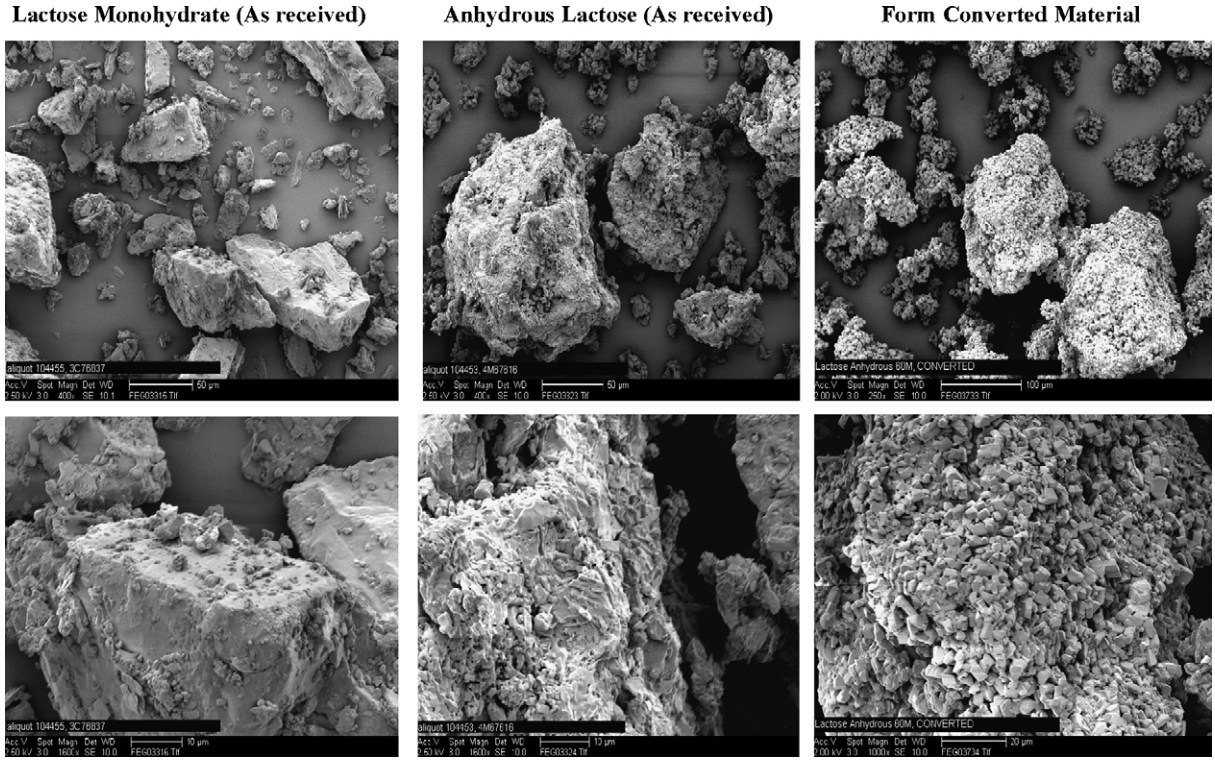

Fig. 4. SEM Imaging of different grades of lactose.

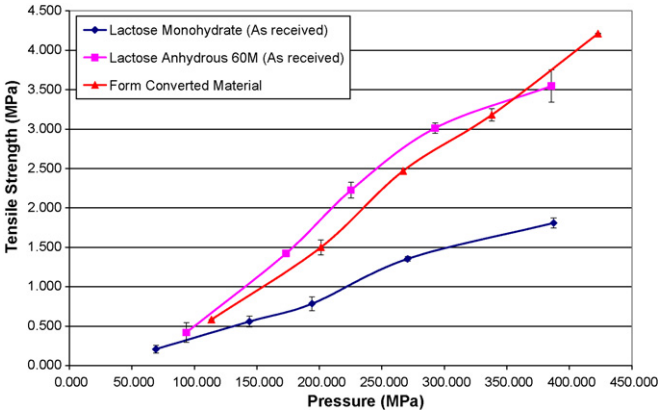

Fig. 5. Compactibility profiles of different lactose materials with similar size fraction (between 88 and 149 μm).

(88–149 μm). Compaction profiles are shown in Fig. 5. As expected, the compactibility of 'as received' anhydrous lactose material (11.0 kPa/MPa) was significantly higher than the compactibility of 'as received' lactose monohydrate (5.2 kPa/MPa), which is in agreement with the literatures (Vromans et al., 1985, 1987; Lerk, 1993). The compactibility of the form converted material (11.8 kPa/MPa) was comparable to the starting material, despite its conversion from anhydrous to monohydrate form during storage at high relative humidity. Compactibility of a given material depends upon two factors (1) bonding strength and (2) compressibility, which is the ability to undergo volume reduction with pressure (densification tendency). Even though the compactibility of control anhydrous lactose and the form converted material is similar, considerable differences were observed in bonding and yield pressure. The form converted material demonstrated a higher bonding of 5.4 MPa compared to 4.3 and 2.2 MPa for the control anhydrous lactose and control lactose monohydrate, respectively. The Yield pressure for the form converted material, which is inversely related to densification tendency, was 258.3 MPa as compared to 182.5 MPa for control anhydrous lactose . This points out that the form converted material requires more pressure to densify to a given solid fraction during compression than the control anhydrous lactose, indicating a lower compressibility for the converted material. The form converted material being an aggregate of very fine particles, is expected to have higher fragmentation tendency. The fine particles resulting from fragmentation of primary particles of the form converted material appear to be more resistant to densification compared to the anhydrous starting material and may be responsible for higher yield pressure and lower the compressibility. However, the higher fragmentation tendency leads to a higher bonding surface area per unit volume and hence the higher bonding strength observed for the form converted material as compared to the control anhydrous lactose. Although the bonding strength increases, there is no increase in the compactibility as the lower compressibility tends to act in an opposite direction, leading to similar compactibility to that of starting anhydrous lactose material.

4. Conclusion

Anhydrous lactose provides compactibility advantage compared to lactose monohydrate in tablet formulations. The higher compactibility of anhydrous lactose is expected to be maintained despite partial form conversion to lactose monohydrate during wet granulation. However, the wet granulation process should employ conditions that minimize form conversion in order to avoid any significant reduction in the final tablet potency. These conditions include minimal amount of water to achieve desired granulation and use of short drying times.

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