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# Impurities enhance caking in lactose powder

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## Abstract:

Caking of lactose and other dry ingredients is a common problem in the dairy and food industries. The lactose production process includes different purification steps, depending on the type of lactose produced. The aim of this study was therefore to investigate how the remaining impurities (i.e. non-lactose components) affect the caking tendency of the final powder. The results from a combination of different methods, including dynamic vapor sorption, characterization of the physicochemical composition and assessment of caking with a ring shear tester, suggested humidity caking. Larger amounts of impurities in the lactose powder resulted in enhanced moisture sorption and greater caking tendency. These findings emphasize the importance of controlling the washing and purification steps throughout the production process in order to limit caking in the final product.

## Keywords:

Caking, lactose, impurities, amorphous, moisture sorption, ring shear tester

As a consequence of trade globalization and significant advances in drying and powder handling technology, the volume of food ingredients produced in powder form has dramatically increased in the past decade. Indeed, as dry ingredients have better storage stability and are easier to transport, a major part of the recent investments in the dairy sector has been focused on dry products (International Dairy Federation, 2015). In particular, whey, which was traditionally considered as waste, has gained considerable attention, and its different constituents (whey proteins, lactose, lactoferrin, milk salts, etc.) are now separated and sold as high value products in the dry state. The range of applications for whey-derived dry ingredients has thus expanded considerably.

Among the whey-derived ingredients, lactose is used in various food and pharmaceutical applications. For example, lactose powder is the main ingredient of infant formulae and provides an important source of carbohydrates to match the composition of human milk. Lactose can be found in different forms, but the most common and stable form is crystallized  $\alpha$ -lactose monohydrate.  $\alpha$ -lactose monohydrate is produced industrially by evaporation of whey followed by slow cooling in a crystallization tank. Typically, the harvested crystals are then washed and dried in a fluidised bed dryer. Different purification steps can make the process more complex, depending on the type of lactose produced. For example, calcium and phosphate are usually removed prior to evaporation in order to increase the running time of the evaporators and reduce fouling. The lactose production process has been described in greater detail by Hourigan et al. (2013).

The handling and storage of lactose and other dry food products can be complicated by a problem that is well known in the food industry, i.e. the unwanted agglomeration of powder particles observed as lumps of various sizes and hardness. This process, known as caking, results in non-conform products and significant economic loss. Although  $\alpha$ -lactose monohydrate is generally considered to be a stable product, caking of lactose is a major problem in the dairy industry. The three most relevant caking mechanisms in food powders have recently been reviewed (Carpin et al., 2016). Amorphous caking is the main mechanism in amorphous powders whereby a temperature increase above the glass transition temperature ( $T_g$ ) of the

material leads to viscous flow to contact points. Due to the plasticization effect of water, storage at relatively high relative humidity (RH) can lower the T<sub>g</sub> and initiate amorphous caking. Humidity is also a crucial factor in the second caking mechanism, called humidity caking. Water molecules are adsorbed on the surface of the particles and liquid bridges can be formed by capillary condensation. If the RH increases above the deliquescence relative humidity (DRH) of the material, the solid can dissolve in the surrounding water layer. A subsequent decrease in RH results in solid bridges and thus stronger links between particles. Finally, the third mechanism, mechanical caking, is an aggravating factor rather than a caking mechanism in itself. Mechanical pressure on a powder bed brings the particles closer to each other, thereby increasing the interactions between particles and the number of contact points. Mechanical caking therefore worsens any caking tendency due to humidity or the presence of amorphous material. In view of the above three mechanisms, it is obvious that caking can be influenced by several parameters such as water content, particle size and shape, amorphous content, etc. Several studies have investigated how these factors affect caking of  $\alpha$ -lactose monohydrate. Listiophadi et al. (2008, 2005a, 2005b) focused on the role of the different lactose polymorphs, amorphous lactose and the milling procedure. Bronlund and Paterson (2004) examined the effects of particle size and temperature on the moisture sorption characteristics of lactose powder and temperature-induced moisture migration in a bag of lactose (Paterson and Bronlund, 2009). As humidity has a crucial role in both amorphous and humidity caking, any impurity that can enhance lactose hygroscopicity, such as peptides and minerals, can be detrimental. This parameter has not been investigated to date. The aim of this study was therefore to characterize the effects of impurities on lactose caking.

## 2. Materials and methods

### 2.1. Production of lactose powders on a pilot scale

Decalcified and decolored ultrafiltered (UF) whey permeate was obtained from Arla Foods Ingredients, Viby J, Denmark. The solids content was raised to 60% in a Centritherm CT2 evaporator (Flavourtech, Griffith, Australia). The concentrate was cooled in a tank from 79 °C to 11 °C in about 18 hours for lactose crystallization purposes. For the washing step, a Lemitec

MD80 laboratory decanter centrifuge (Lemitec GMBH, Berlin, Germany) was used to produce five lactose powders with different washing grades. The slurry was first run through the decanter once without water for a pre-wash (Wash 0). The prewashed slurry was then mixed with water at different water / lactose slurry (w/w) ratios: 1/3 (Wash 0.3), 1/2 (Wash 0.5), 1/1 (Wash 1) and 2/1 (Wash 2). The different washing grades of slurry were run through the decanter once more, and then dried on an Anhydro SFD 47 spin flash dryer (SPX Flow Technology, Søborg, Denmark) with an inlet temperature of 105 °C and an outlet temperature of 82-87 °C. Finally the powders were packaged in two layers of plastic bags and a Kraft paper bag before transportation to the analysis laboratory where they were poured into airtight plastic containers of various sizes to minimize the headspace. The powders were stored at 20 °C before analysis.

Pharmaceutical grade lactose (Lactochem® Crystals, batch number 663108) was purchased from DFE pharma (Goch, Germany) for comparison with the experimental lactose powders produced at different washing grades. Pharmaceutical grade lactose is produced industrially from edible grade lactose by re-dissolving the lactose in clean water followed by additional purification steps (Paterson, 2009). It is therefore the most pure lactose available on the market. Pharmaceutical grade lactose was mixed with distilled water to make a 15% (w/w) lactose solution which was left to stand at 40 °C for one hour. The solution was then cooled to 20 °C and spray dried on a pilot-scale spray dryer (GEA Niro A/S, Mobile Minor Dryer (MMD), Søborg, Denmark) to obtain amorphous lactose. The inlet and outlet air temperatures were 200 °C and 90 °C, respectively, and the feed flow rate was 40 mL.min<sup>-1</sup>.

## 2.2. Chemical composition

Protein, moisture and ash content were determined according to the methods described by Schuck et al. (2012). Total nitrogen content determined by Kjeldahl with a 6.38 conversion factor will be designated as protein content. Given the filtration steps in the lactose process, it is however unlikely that proteins remain in the final powder. Therefore, impurities formally expressed as protein may more likely be smaller nitrogen containing components such as peptides and amino-acids. Analysis of moisture and ash content was carried out in triplicate and the protein content was determined in duplicate. The lactose content was then calculated by

113 difference. Individual minerals (calcium, phosphorus, sodium, potassium and magnesium) were  
114 measured by inductively coupled plasma optical emission spectrometry (ICP-OES) on an  
115 Optima 2000 DV (PerkinElmer, Waltham, Massachusetts, USA). Chloride was determined by  
116 potentiometry. All minerals were analyzed in duplicate.

### 117 2.3. Sieving and measurement of particle size

118 The lactose powders of different washing grades were sieved to separate 80, 160, 250, 355 and  
119 500  $\mu\text{m}$  fractions. The particle size distribution of the powders was measured by laser light  
120 scattering using a Malvern Mastersizer 2000 equipped with a Scirocco 2000 dry dispersion unit  
121 (Malvern Instruments, Worcestershire, UK).

### 122 2.4. Moisture sorption measurements

123 Sorption isotherms of powders were obtained with a Dynamic Vapor Sorption (DVS) Advantage  
124 (Surface Measurement Systems Ltd., London, UK) equipped with a Cahn microbalance. The  
125 experiments were carried out in duplicate at a constant temperature (25  $^{\circ}\text{C}$ ) using a nitrogen  
126 flow rate of 200 standard  $\text{cm}^3\cdot\text{min}^{-1}$ . Approximately 40 mg of powder was subjected to ramping  
127 of RH from 0% to 95% in 10%–RH steps with water as solvent. Equilibrium was considered to be  
128 reached if the rate of change in mass was less than 0.0002  $\%\cdot\text{min}^{-1}$ .

### 129 2.5. Particle morphology — scanning electron microscopy (SEM)

130 The surface morphology of the lactose samples was examined using a scanning electron  
131 microscope (SEM, JEOL JCM-6000 - NeoScope II, Tokyo, Japan) operating at 15 kV. Samples  
132 were mounted on an aluminium stub and coated with a thin layer of gold (JEOL JFC-1300 auto  
133 fine coater) prior to analysis. The photomicrographs were taken at  $\times 1,000$  magnification.

### 134 2.6. Solid-state Nuclear Magnetic Resonance (NMR)

135  $^{13}\text{C}$  NMR spectra were obtained using proton decoupling, magic angle spinning (MAS) and  
136 cross polarization (CP). The spectra were recorded on a Bruker Avance I WB 300 MHz  
137 (7T) instrument (Bruker, Billerica, USA) at ambient temperature according to the method  
138 described by Gustafsson et al. (1998), with the following parameters: spinning rate 5 kHz,

contact time 2 ms, acquisition time 147 ms, sweep widths 2190 ppm and delay between pulses of 3 s. For each spectrum, about 150,000 transients were cumulated with 49k data points. The spectra were referenced to trimethylsilane (TMS).

## 2.7. Quantification of caking

Caking, also known as time consolidation, was measured with a ring shear tester (RST-XS, Schulze-Schüttgutmesstechnik, Wolfenbüttel, Germany). The measurement procedure has been described in detail by Schulze (2008). First the yield locus of each powder was measured for a normal stress at preshear  $\sigma_{pre}$  corresponding to a consolidation stress  $\sigma_c$  of around 9.3 kPa. This value was chosen to simulate powder consolidation at the bottom of a flexible intermediate bulk container (FIBC), also called a Big Bag. Three points of incipient flow were used to draw the yield locus. Once the initial yield locus was established, the powder was preconditioned using the same  $\sigma_{pre}$  as above and stored at 20 °C and 60% RH for four days. A temperature and humidity data logger was used to check the storage conditions. Loads of 2 kg (corresponding to a consolidation stress of 9.3 kPa) were applied to the samples for the duration of storage. After storage the samples were sheared to obtain the time yield locus. From this, the unconfined yield strength  $\sigma_1$  and the ratio of  $\sigma_c$  to  $\sigma_1$ , called *ffc*, were identified. By definition, a sample with an *ffc* lower than 1 was considered to be caked (Jenike, 1964). For each powder except Wash 0.3, the *ffc* was measured in triplicate. As the amount of Wash 0.3 was limited, the analysis could only be performed in duplicate.

## 3. Results and discussion

### 3.1. Chemical composition

The results showed, as expected, that the higher the washing grade, the fewer the remaining impurities measured in the final powder (i.e. nitrogen containing components expressed as proteins, free moisture, ash and minerals) (Table 1 and Fig. 1). The remaining ash and protein levels were highly correlated ( $R^2=0.972$ ). Moreover, ash and protein levels were found to correlate better with moisture measured by loss on drying at 87°C for 16 hours ( $R^2=0.995$  and  $R^2=0.972$ , respectively) than with moisture measured after drying at 105°C for 5 hours ( $R^2=0.709$

and  $R^2=0.840$ , respectively) (data not shown). The method to measure food moisture by loss on drying has been criticized for the lack of discrimination between the different types of water, distinguished by the extent of binding with solids (Isengard, 2001). “Free” and “bound” water can indeed be difficult to differentiate, and the results at 105 °C may overestimate the “free” water content of the samples.

The amounts of all minerals decreased with a higher degree of washing, with the exception of calcium (Fig. 1). The decalcification and subsequent separation steps applied to the UF permeate reduced the initial calcium and phosphorus content (Hourigan et al., 2013). Thus the starting material for the trial already had low calcium and phosphorus content from the beginning. Fig. 1 shows that it was not possible to reduce the calcium content much further by washing the lactose crystals. This suggests that, as mentioned by Guu and Zall (1992), most of the remaining calcium formed strong complexes with lactose. Interestingly, phosphate did not follow the same trend as calcium. Guu and Zall (1991) reported that calcium phosphate precipitates may act as nuclei facilitating lactose crystallization. It was therefore expected that calcium phosphate could be trapped inside the crystals, thereby preventing it from being washed away. This was however not observed in the present study.

Using a basic mass balance with simple assumptions, the expected amount of impurities in the different washing grades after decantation was calculated from the amount measured in Wash 0. The water content in the decanter output was considered the same for all washing grades (i.e. 10%) and it was assumed that no lactose was dissolved during the decantation process. The calculated levels of protein and ash were in general lower than the measured amounts (data not shown). The inclusion of droplets of mother liquor inside the crystals, as suggested by Mathlouthi and Rogé (2003) for sucrose, could explain the limited effect of washing.

### 3.2. Moisture sorption

Sieving the powders led to standardization of particle size distribution (Fig. 2). Indeed it has been shown that particle size can have a significant effect on moisture sorption (Stoklosa et al., 2012).

Moisture sorption was highly dependent on the washing grade (Fig. 3). For the same particle size fraction ( $160 < x < 250 \mu\text{m}$ ), the sorption of the unwashed powder (Wash 0) was dramatically enhanced from 30% RH and the final sorption was almost ten times higher than the most washed powders (Wash 1 and Wash 2). Crystalline lactose is characterized by a very low hygroscopicity, with a deliquescence relative humidity (DRH) value of 95% (Salameh et al., 2006). However, Tereshchenko (2015) reported that, for a water soluble crystalline solid, moisture sorption below the DRH was due to impurities. Enhanced sorption and reduced DRH due to the presence of low levels of impurities have also been reported in a model deliquescent pharmaceutical salt, in agreement with our results (Guerrieri et al., 2007). The sorption behavior of the different lactose powders is thus likely to originate from differences in impurity contents (Table 1). This was further evidenced by a comparison with pharmaceutical grade lactose. The latter was found to contain about 20 times less ash and proteins than the most washed powder produced during the pilot trial (Table 1). The difference in moisture sorption behavior between Wash 2 and the pharmaceutical grade powder was very clear: indeed, Wash 2 powder adsorbed almost 10 times more moisture than pharmaceutical grade lactose above 50% RH (Fig. 4).

As moisture sorption occurs primarily on the surface of crystals, a comparison of the surface of the different washing grade lactose powders was undertaken by scanning electron microscopy (Fig. 5). All samples from the pilot trial (Fig. 5A-D) presented a rough surface. Wash 0 powder had many pores (Fig. 5A), which would provide greater possibilities for capillary condensation and could therefore partly explain the enhanced moisture sorption previously reported (Fig. 3). Compared to pharmaceutical grade lactose, which presented a smooth surface (Fig. 5E), Wash 0.5, 1 and 2 powders had significant amounts of fines agglomerated on the surface of their large tomahawk crystals (Fig. 5B-D). Mathlouthi and Rogé (2003) showed that the presence of fines in sucrose crystals enhanced moisture sorption and that the greater the number of fine particles, the closer the sorption behavior of the sample to that of the amorphous state. Their findings are consistent with the moisture sorption isotherms obtained in this study, showing less sorption for pharmaceutical grade lactose (Fig. 4).

Moreover, a higher concentration of impurities on the surface of the crystals would probably lead to enhanced sorption behavior. On the other hand, impurities trapped inside the crystals are not

expected to have a significant role in moisture sorption. This point requires further attention to identify which impurities (nature, concentration) are present on the surface of the particles.

### 3.3. Role of amorphous material

One particular kind of impurity is amorphous material, which is well known for its high hygroscopicity compared to the crystalline counterpart. Amorphous lactose can be formed on the surface of lactose particles during rapid drying and milling (Vollenbroek et al., 2010). As the samples were dried in a spin flash dryer in the present study, the possibility of formation of amorphous material due to rapid drying cannot be excluded. The impurities remaining after the washing process (e.g. minerals and protein fractions) were likely to retain some mother liquor which could turn into amorphous lactose upon drying. The presence of increasing, yet very low, amounts of amorphous lactose at lower washing grades could thus be another explanation for the enhanced hygroscopicity of the corresponding powders.

However, no recrystallization event was observed in the moisture sorption curves, contrary to previously reported sorption isotherms of predominantly crystalline materials containing some amorphous content (Sheokand et al., 2014). For example, a weight increase and subsequent decrease due to amorphous lactose absorbing moisture and crystallizing has been reported in samples containing between 0.125 and 0.5 w/w % amorphous material (Buckton and Darcy, 1995). However, the presence of amorphous material in our samples cannot be ruled out from the sorption isotherms. Residual amorphous lactose might be present at lower levels than those studied by Buckton and Darcy (1995). Moreover, Buckton and Darcy (1995) used physical mixes of spray-dried lactose and  $\alpha$ -lactose monohydrate in their study, which can facilitate the crystallization event compared to a situation where the amorphous material is in close contact with crystalline portions on the same particle.

The samples with different washing grades were therefore analyzed by solid-state NMR. A detection limit of 0.5% amorphous lactose has been reported for this technique (Gustafsson et al., 1998), which is among the lowest levels for the detection of amorphous material in predominantly crystalline materials (Giron et al., 2007). No disorder indicating amorphous

material was detected in our samples (Fig. 6). It can therefore be concluded that if any amorphous material was present in the samples, the amorphous content was probably below 0.5%. However, the analysis of very low levels of amorphous material is always challenging in terms of sample storage and sampling. Indeed, amorphous material can crystallize during storage before analysis, thus preventing its identification.

### 3.4. Caking tendency

For the different particle size distributions investigated, the unwashed powder was characterized by a poorer flowability and hence a higher tendency to caking than the washed powders (Fig. 7). Moreover, a *ffc* after storage of  $0.6 \pm 0.1$  was obtained for non-sieved Wash 0.3 while non-sieved pharmaceutical grade lactose still flowed easily after the four-day storage. It was not straightforward to discriminate Wash 1 and Wash 2 powders from each other.

It is clear from these results that higher levels of impurities lead to greater risk of caking. In the present study, the samples were stored at 20 °C and 60% RH for four days in the ring shear cells before measurement of caking tendency. Amorphous lactose stored at room temperature (20-25 °C) has been reported to crystallize at about 40% RH (Jouppila and Roos, 1994; Thomsen et al., 2005). Amorphous caking was therefore expected to occur if the samples contained amorphous lactose. However, as mentioned in section 3.3., the solid state NMR analysis did not indicate the presence of disordered structures, meaning that the amorphous content of the samples was probably below 0.5%. Thus amorphous caking cannot be considered to be the main mechanism responsible for the caking tendency observed here. In his work on caking of crystalline lactose, Bronlund (1997) also showed that amorphous caking was only marginal for amorphous content below 5%, and that the major contribution to caking from the amorphous material occurred through moisture sorption.

The sorption isotherms of Wash 0, 1, 2 powders and pharmaceutical grade lactose showed that the difference in sorption behavior was important at 60% and room temperature (Fig. 3 and Fig. 4). During the caking experiments, the samples were given time to equilibrate with ambient air at 60% RH. Due to humidity caking, the caking tendency was therefore expected to be enhanced for samples which could adsorb more moisture. This was confirmed by the flowability results

277 after storage (Fig. 7). Only Wash 1 and Wash 2 showed similar flowability values, although  
278 Wash 1 was found to adsorb twice as much moisture as Wash 2 at 60% RH according to the  
279 DVS measurements. The difference in the impurity levels and thus moisture sorption between  
280 these two powders was probably too small for the ring shear tester to detect a difference  
281 between the caking tendencies of the two powders.

282 As humidity caking could be evidenced by the caking measurements with the ring shear tester,  
283 the repeatability of the measurement was considered acceptable. In order to discriminate  
284 between samples with similar sorption behaviors (such as Wash 1 and Wash 2), it might be  
285 helpful to increase the repeatability even further. As pointed out by Hartmann and Palzer (2011),  
286 one drawback of the ring shear cells is that they are almost closed, which hampers moisture  
287 exchange between the powder and the surrounding atmosphere. If the impurities are not  
288 homogeneously distributed in the powder, moisture sorption might be heterogeneous at a local  
289 level, leading to various degrees of consolidation. It is however interesting to note the low  
290 standard deviation associated with the results for Wash 0 and Wash 0.3. It seems therefore that  
291 once humidity caking has reached a certain level, it systematically proceeds to strong and  
292 repeatable caking. This level may be associated with the DRH which, as explained in section  
293 3.2., can be significantly decreased by the presence of impurities. Moreover, a critical step in the  
294 experimental procedure is relieving the shear cells from the consolidation pressure and moving  
295 them from the humidity controlled chamber to the ring shear tester. This operation requires care  
296 as interactions between the powder particles can be damaged. It is thus consistent that the  
297 stronger the interactions between particles, the better the caking reproducibility.

#### 298 4. Conclusions

299 Time consolidation experiments with a ring shear tester constitute an appropriate method to  
300 discriminate between samples with different caking tendencies. Combined with DVS  
301 measurements and characterization of the physicochemical composition, including the  
302 amorphous content, the caking test results suggested a humidity caking mechanism. The  
303 presence of impurities in lactose powder was found to greatly enhance moisture sorption and

304 caking. It is therefore critical to control the washing and purification steps in the process in order  
305 to prevent caking in the final product.

306

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**Table 1: Composition of lactose powders as a function of degree of washing of the crystals. Results are given as average  $\pm$  standard deviation. Number of repeats = 3 for moisture and ash and 2 for proteins.**

*Figure 1: Variations in the mineral content (potassium (K), chlorine (Cl), sodium (Na), phosphorus (P), calcium (Ca), and magnesium (Mg)) of lactose powder as a function of degree of washing of the lactose crystals.*

*Figure 2: Particle size distributions of lactose powders for three different washing grades (0, 1, 2) but with the same particle size fraction ( $160 < x < 250 \mu\text{m}$ ).*

*Figure 3: Moisture sorption isotherms of lactose powders with three different washing grades but the same particle size fraction ( $160 < x < 250 \mu\text{m}$ ): Wash 0 (squares), Wash 1 (circles), Wash 2 (triangles).*

*Figure 4: Moisture sorption isotherms of non-sieved pharmaceutical grade lactose (circles) and the most washed lactose from the pilot trial (Wash 2) (squares).*

*Figure 5: SEM images showing details of particle surface of different washing grade lactose powders: (A) Wash 0; (B) Wash 0.5; (C) Wash 1; (D) Wash 2; (E) Pharmaceutical grade lactose.*

*Figure 6:  $^{13}\text{C}$  CP/MAS NMR spectra of (A) Wash 0; (B) Wash 0.3; (C) pharmaceutical grade lactose; (D) amorphous lactose.*

*Figure 7: ffc of non-sieved (crosses) and sieved (triangles) lactose powders between  $160 \mu\text{m}$  and  $250 \mu\text{m}$  as a function of the washing grade. The ffc was measured after storage for four days at 60% RH and  $20^\circ\text{C}$ . Each sample was consolidated under a pressure of 9.3 kPa. The flowability of pharmaceutical grade lactose after storage is included for comparison purposes.*

Table 1: Composition of lactose powders as a function of degree of washing of the crystals.

Results are given as average  $\pm$  standard deviation. Number of repeats = 3 for moisture and ash and 2 for proteins.

Washing Grade	Protein (g.100g <sup>-1</sup> )	Moisture (g.100g <sup>-1</sup> )	Ash (g.100g <sup>-1</sup> )	Lactose (g.100g <sup>-1</sup> )
0	0.640 $\pm$ 0.014	1.12 $\pm$ 0.01	2.14 $\pm$ 0.05	96.09
0.3	0.332 $\pm$ 0.005	0.89 $\pm$ 0.00	0.79 $\pm$ 0.04	97.99
0.5	0.227 $\pm$ 0.006	0.77 $\pm$ 0.02	0.52 $\pm$ 0.02	98.49
1	0.152 $\pm$ 0.006	0.36 $\pm$ 0.02	0.43 $\pm$ 0.04	99.05
2	0.082 $\pm$ 0.001	0.31 $\pm$ 0.01	0.19 $\pm$ 0.00	99.42
Pharmaceutical grade lactose	0.004 $\pm$ 0.002	n.d.	0.01 $\pm$ 0.00	n.d.

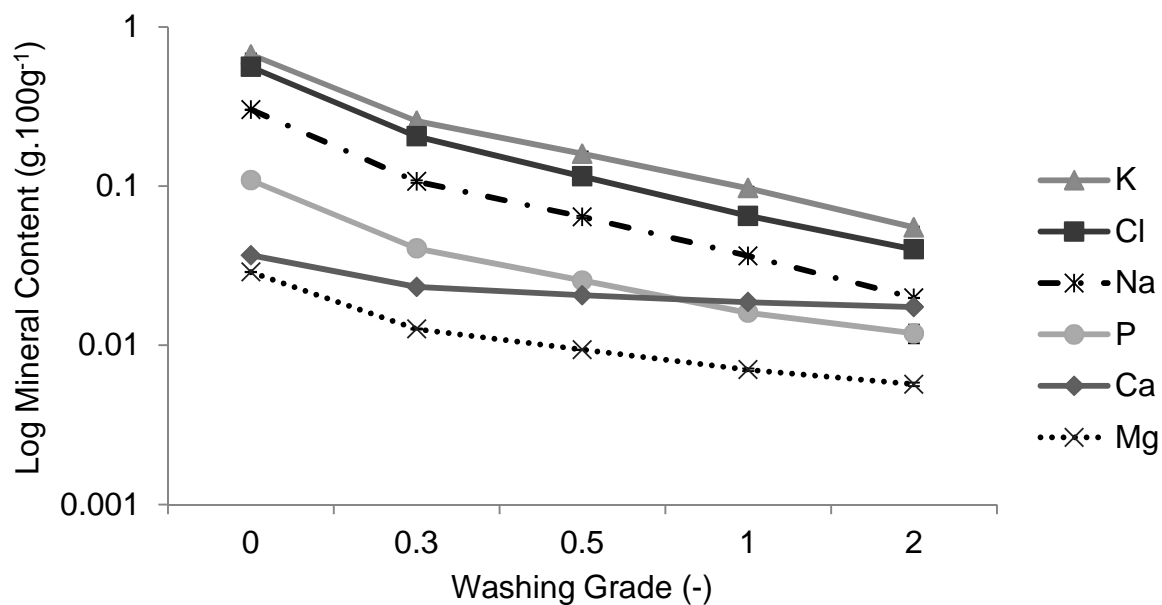


Figure 1: Variations in the mineral content (potassium (K), chlorine (Cl), sodium (Na), phosphorus (P), calcium (Ca), and magnesium (Mg)) of lactose powder as a function of degree of washing of the lactose crystals.

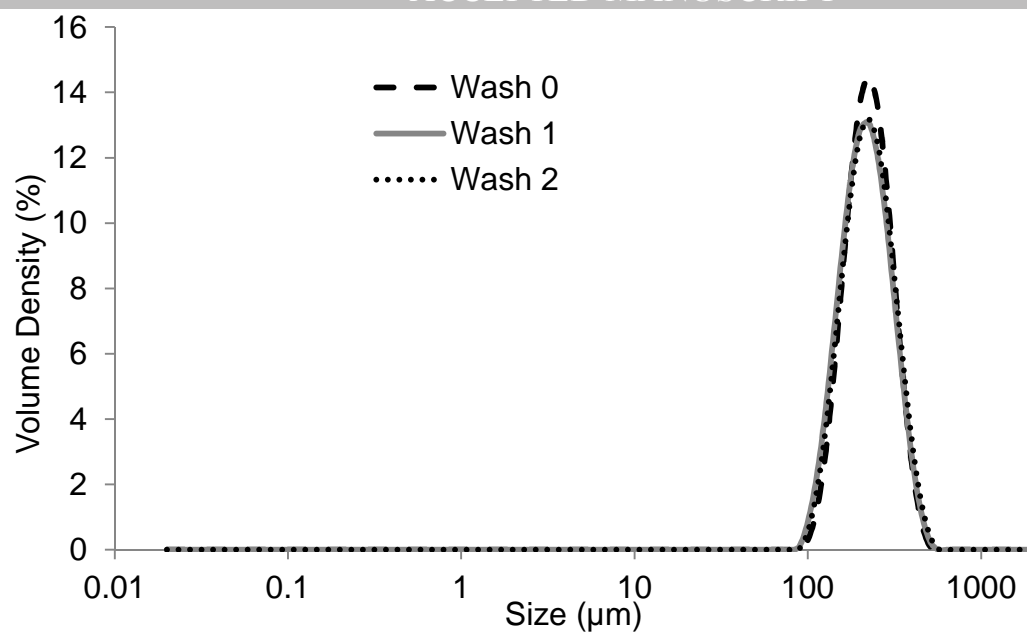


Figure 2: Particle size distributions of lactose powders for three different washing grades (0, 1, 2) but with the same particle size fraction ( $160 < x < 250 \mu\text{m}$ ).

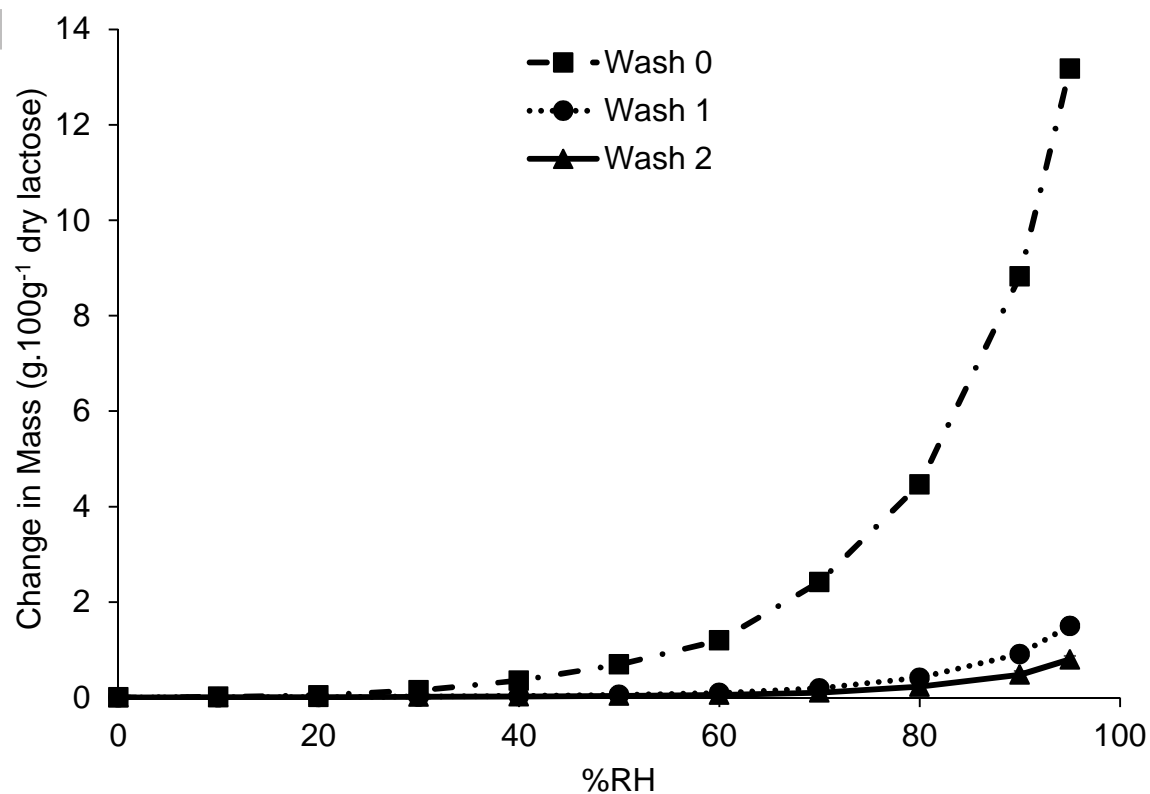


Figure 3: Moisture sorption isotherms of lactose powders with three different washing grades but the same particle size fraction ( $160 < x < 250 \mu\text{m}$ ): Wash 0 (squares), Wash 1 (circles), Wash 2 (triangles).

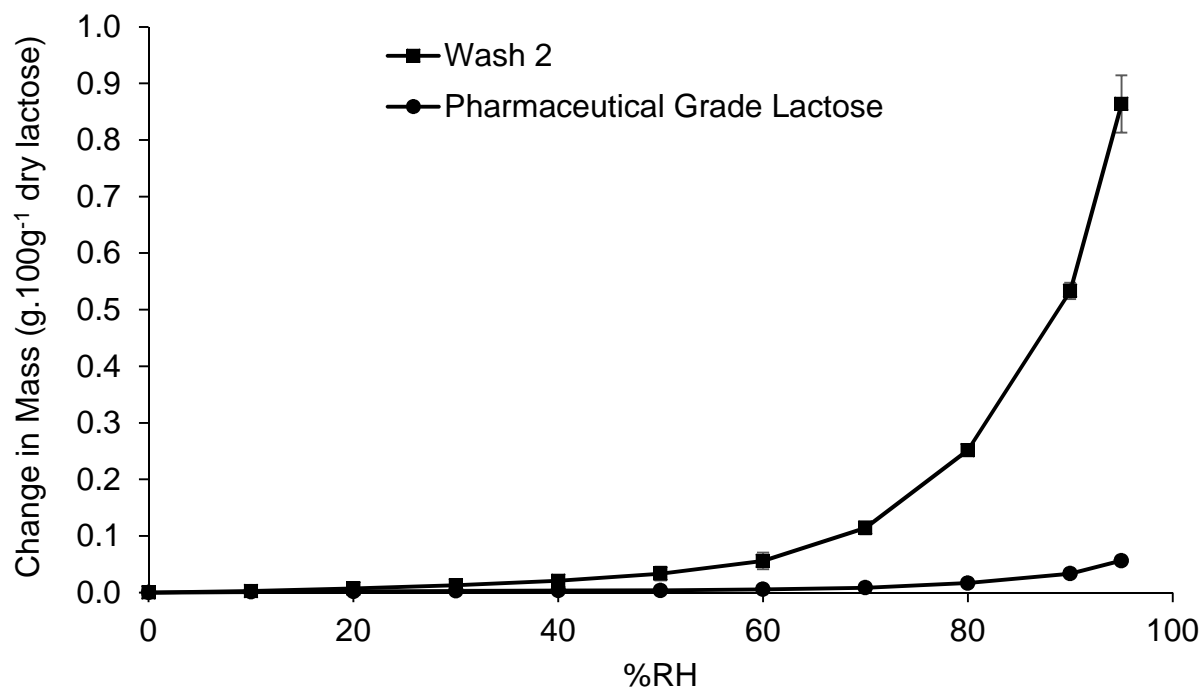
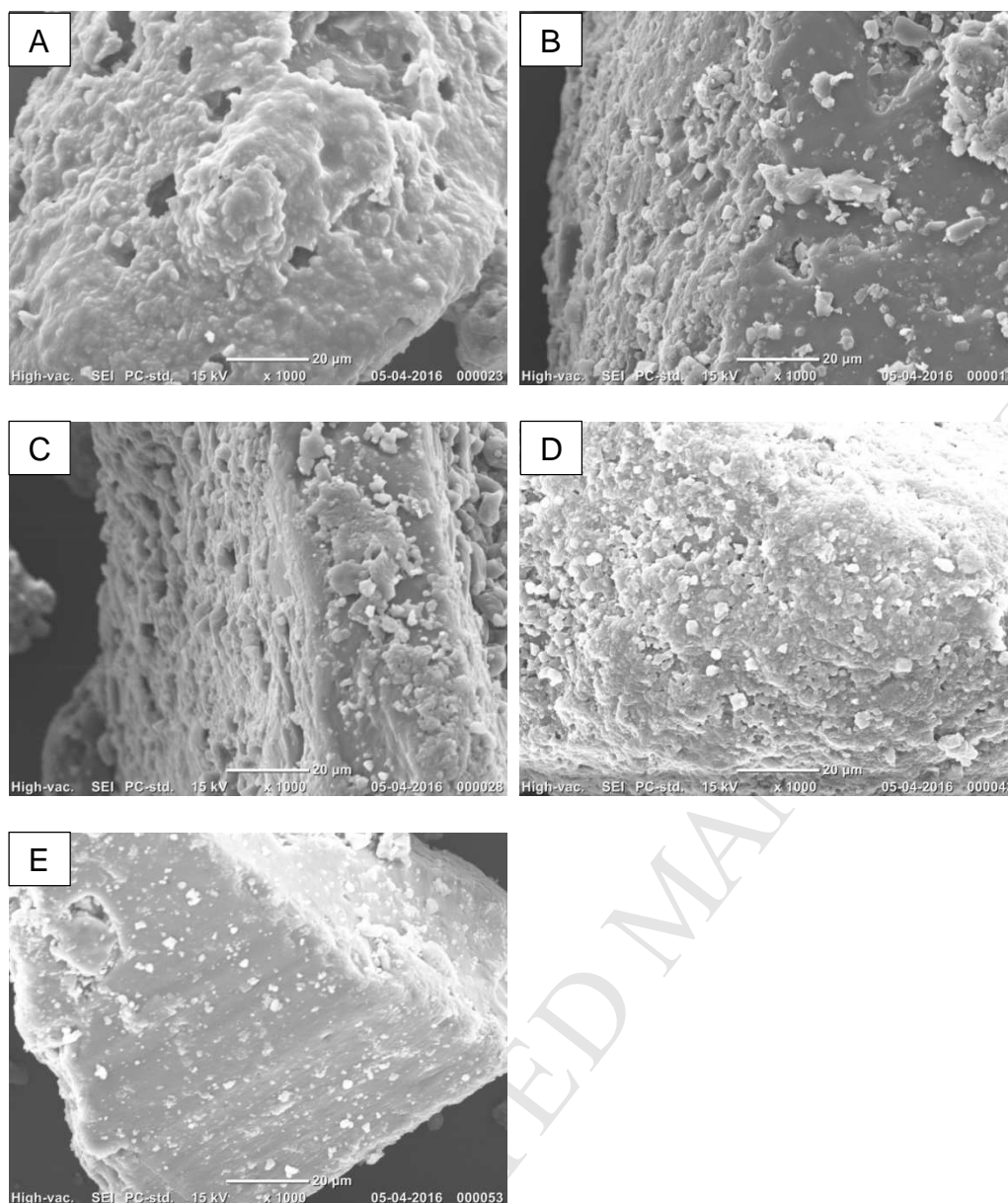


Figure 4: Moisture sorption isotherms of non-sieved pharmaceutical grade lactose (circles) and the most washed lactose from the pilot trial (Wash 2) (squares).



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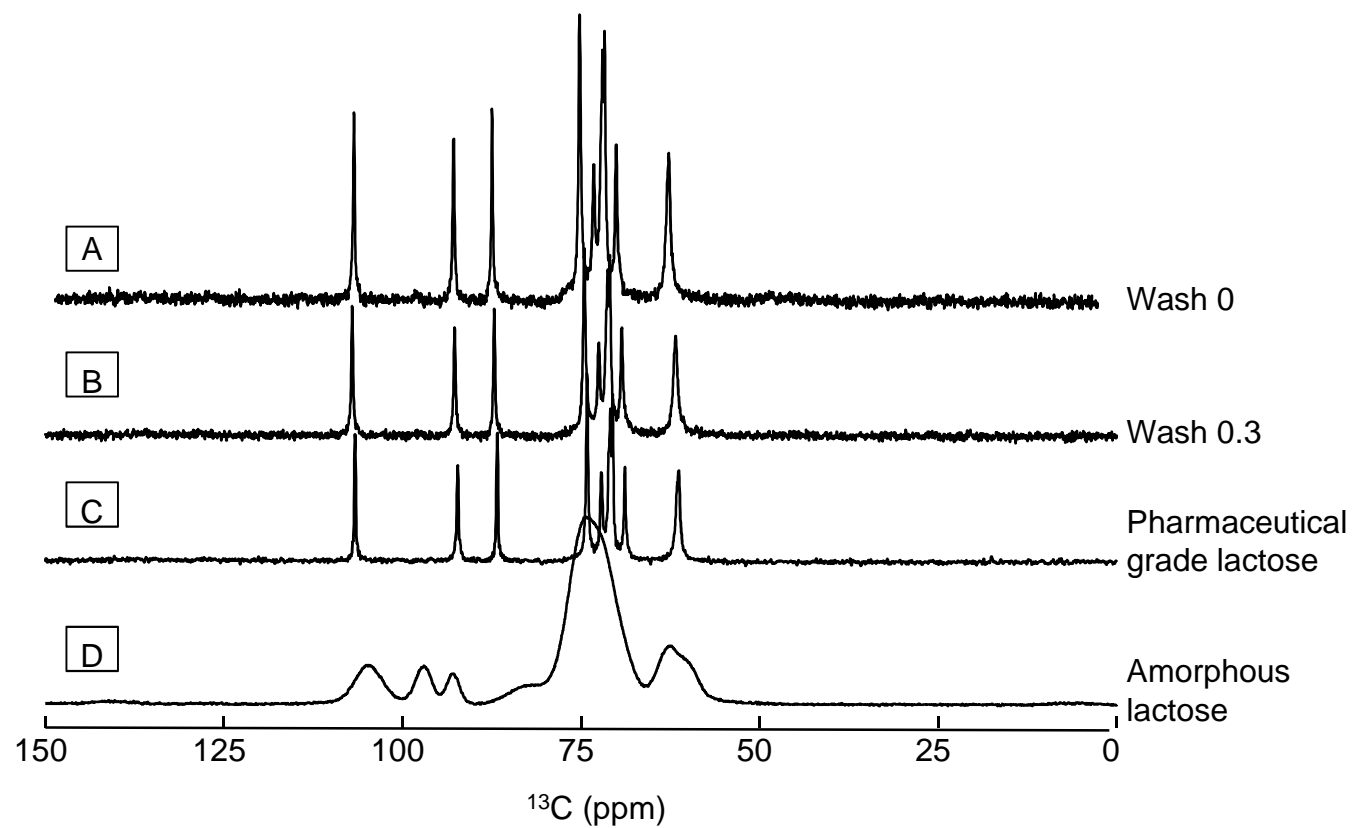


Figure 6:  $^{13}\text{C}$  CP/MAS NMR spectra of (A) Wash 0; (B) Wash 0.3; (C) pharmaceutical grade lactose; (D) amorphous lactose.

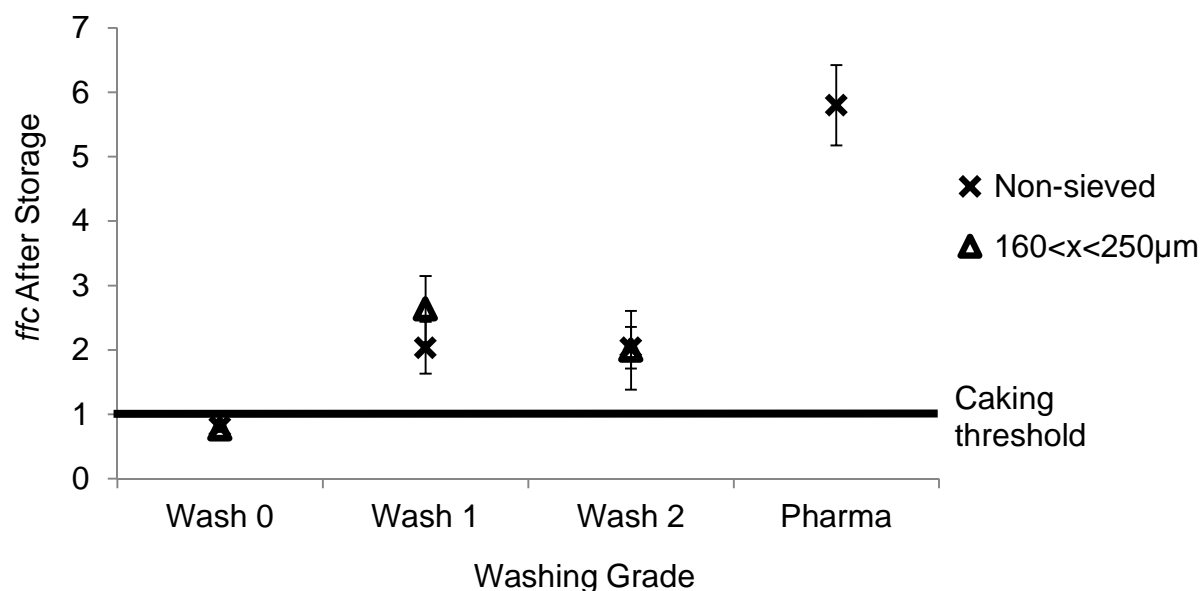


Figure 7: ffc of non-sieved (crosses) and sieved (triangles) lactose powders between 160  $\mu\text{m}$  and 250  $\mu\text{m}$  as a function of the washing grade. The ffc was measured after storage for four days at 60% RH and 20 °C. Each sample was consolidated under a pressure of 9.3 kPa. The flowability of pharmaceutical grade lactose after storage is included for comparison purposes.

- Caking of lactose results in non-conform products and significant economic loss.
- Impurities in the lactose powder increased moisture sorption and caking tendency.
- The ring shear tester is a valuable tool to assess caking.
- The washing and purification steps should be closely monitored to limit caking.