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1 **Impurities enhance caking in lactose powder**

2 M. Carpin^{1,2,4}, H. Bertelsen², A. Dalberg², C. Roiland³, J. Risbo⁴, P. Schuck¹, R. Jeantet¹

3 ¹ UMR 1253, Science and Technology of Milk and Eggs, Inra-Agrocampus Ouest, 35042
4 Rennes cedex, France

5 ² Arla Foods Ingredients Group P/S, 6920 Videbæk, Denmark

6 ³ University of Rennes 1, UMR CNRS 6226, Campus de Beaulieu, Rennes, France

7 ⁴ Department of Food Science, University of Copenhagen, 1958 Frederiksberg C, Denmark

8 melanie.carpin@inra.fr

9 hans.bertelsen@arlafoods.com

10 anders.dalberg@arlafoods.com

11 claire.roiland@univ-rennes1.fr

12 jri@food.ku.dk

13 pierre.schuck@inra.fr

14 romain.jeantet@agrocampus-ouest.fr

15 Abstract:

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

26 Keywords:

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

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

38 Among the whey-derived ingredients, lactose is used in various food and pharmaceutical
39 applications. For example, lactose powder is the main ingredient of infant formulae and provides
40 an important source of carbohydrates to match the composition of human milk. Lactose can be
41 found in different forms, but the most common and stable form is crystallized α -lactose
42 monohydrate. α -lactose monohydrate is produced industrially by evaporation of whey followed
43 by slow cooling in a crystallization tank. Typically, the harvested crystals are then washed and
44 dried in a fluidised bed dryer. Different purification steps can make the process more complex,
45 depending on the type of lactose produced. For example, calcium and phosphate are usually
46 removed prior to evaporation in order to increase the running time of the evaporators and reduce
47 fouling. The lactose production process has been described in greater detail by Hourigan et al.
48 (2013).

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

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

79 2. Materials and methods

80 2.1. Production of lactose powders on a pilot scale

81 Decalcified and decolored ultrafiltered (UF) whey permeate was obtained from Arla Foods
82 Ingredients, Viby J, Denmark. The solids content was raised to 60% in a Centritherm CT2
83 evaporator (Flavourtech, Griffith, Australia). The concentrate was cooled in a tank from 79 °C to
84 11 °C in about 18 hours for lactose crystallization purposes. For the washing step, a Lemitec

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

95 Pharmaceutical grade lactose (Lactochem® Crystals, batch number 663108) was purchased
96 from DFE pharma (Goch, Germany) for comparison with the experimental lactose powders
97 produced at different washing grades. Pharmaceutical grade lactose is produced industrially
98 from edible grade lactose by re-dissolving the lactose in clean water followed by additional
99 purification steps (Paterson, 2009). It is therefore the most pure lactose available on the market.

100 Pharmaceutical grade lactose was mixed with distilled water to make a 15% (w/w) lactose
101 solution which was left to stand at 40 °C for one hour. The solution was then cooled to 20 °C and
102 spray dried on a pilot-scale spray dryer (GEA Niro A/S, Mobile Minor Dryer (MMD), Søborg,
103 Denmark) to obtain amorphous lactose. The inlet and outlet air temperatures were 200 °C and
104 90 °C, respectively, and the feed flow rate was 40 mL.min⁻¹.

105 2.2. Chemical composition

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

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

142 2.7. Quantification of caking

143 Caking, also known as time consolidation, was measured with a ring shear tester (RST-XS,
144 Schulze-Schüttgutmesstechnik, Wolfenbüttel, Germany). The measurement procedure has been
145 described in detail by Schulze (2008). First the yield locus of each powder was measured for a
146 normal stress at preshear σ_{pre} corresponding to a consolidation stress σ_c of around 9.3 kPa. This
147 value was chosen to simulate powder consolidation at the bottom of a flexible intermediate bulk
148 container (FIBC), also called a Big Bag. Three points of incipient flow were used to draw the
149 yield locus. Once the initial yield locus was established, the powder was preconditioned using
150 the same σ_{pre} as above and stored at 20 °C and 60% RH for four days. A temperature and
151 humidity data logger was used to check the storage conditions. Loads of 2 kg (corresponding to
152 a consolidation stress of 9.3 kPa) were applied to the samples for the duration of storage. After
153 storage the samples were sheared to obtain the time yield locus. From this, the unconfined yield
154 strength σ_1 and the ratio of σ_c to σ_1 , called *ffc*, were identified. By definition, a sample with an *ffc*
155 lower than 1 was considered to be caked (Jenike, 1964). For each powder except Wash 0.3, the
156 *ffc* was measured in triplicate. As the amount of Wash 0.3 was limited, the analysis could only be
157 performed in duplicate.

158 3. Results and discussion

159 3.1. Chemical composition

160 The results showed, as expected, that the higher the washing grade, the fewer the remaining
161 impurities measured in the final powder (i.e. nitrogen containing components expressed as
162 proteins, free moisture, ash and minerals) (Table 1 and Fig. 1). The remaining ash and protein
163 levels were highly correlated ($R^2=0.972$). Moreover, ash and protein levels were found to
164 correlate better with moisture measured by loss on drying at 87°C for 16 hours ($R^2=0.995$ and
165 $R^2=0.972$, respectively) than with moisture measured after drying at 105°C for 5 hours ($R^2=0.709$

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

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

182 Using a basic mass balance with simple assumptions, the expected amount of impurities in the
183 different washing grades after decantation was calculated from the amount measured in Wash 0.
184 The water content in the decanter output was considered the same for all washing grades (i.e.
185 10%) and it was assumed that no lactose was dissolved during the decantation process. The
186 calculated levels of protein and ash were in general lower than the measured amounts (data not
187 shown). The inclusion of droplets of mother liquor inside the crystals, as suggested by
188 Mathlouthi and Rogé (2003) for sucrose, could explain the limited effect of washing.

189 3.2. Moisture sorption

190 Sieving the powders led to standardization of particle size distribution (Fig. 2). Indeed it has
191 been shown that particle size can have a significant effect on moisture sorption (Stoklosa et al.,
192 2012).

193 Moisture sorption was highly dependent on the washing grade (Fig. 3). For the same particle
194 size fraction ($160 < x < 250 \mu\text{m}$), the sorption of the unwashed powder (Wash 0) was dramatically
195 enhanced from 30% RH and the final sorption was almost ten times higher than the most
196 washed powders (Wash 1 and Wash 2). Crystalline lactose is characterized by a very low
197 hygroscopicity, with a deliquescence relative humidity (DRH) value of 95% (Salameh et al.,
198 2006). However, Tereshchenko (2015) reported that, for a water soluble crystalline solid,
199 moisture sorption below the DRH was due to impurities. Enhanced sorption and reduced DRH
200 due to the presence of low levels of impurities have also been reported in a model deliquescent
201 pharmaceutical salt, in agreement with our results (Guerrieri et al., 2007). The sorption behavior
202 of the different lactose powders is thus likely to originate from differences in impurity contents
203 (Table 1). This was further evidenced by a comparison with pharmaceutical grade lactose. The
204 latter was found to contain about 20 times less ash and proteins than the most washed powder
205 produced during the pilot trial (Table 1). The difference in moisture sorption behavior between
206 Wash 2 and the pharmaceutical grade powder was very clear: indeed, Wash 2 powder adsorbed
207 almost 10 times more moisture than pharmaceutical grade lactose above 50% RH (Fig. 4).

208 As moisture sorption occurs primarily on the surface of crystals, a comparison of the surface of
209 the different washing grade lactose powders was undertaken by scanning electron microscopy
210 (Fig. 5). All samples from the pilot trial (Fig. 5A-D) presented a rough surface. Wash 0 powder
211 had many pores (Fig. 5A), which would provide greater possibilities for capillary condensation
212 and could therefore partly explain the enhanced moisture sorption previously reported (Fig. 3).
213 Compared to pharmaceutical grade lactose, which presented a smooth surface (Fig. 5E), Wash
214 0.5, 1 and 2 powders had significant amounts of fines agglomerated on the surface of their large
215 tomahawk crystals (Fig. 5B-D). Mathlouthi and Rogé (2003) showed that the presence of fines in
216 sucrose crystals enhanced moisture sorption and that the greater the number of fine particles,
217 the closer the sorption behavior of the sample to that of the amorphous state. Their findings are
218 consistent with the moisture sorption isotherms obtained in this study, showing less sorption for
219 pharmaceutical grade lactose (Fig. 4).

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

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

224 3.3. Role of amorphous material

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

234 However, no recrystallization event was observed in the moisture sorption curves, contrary to
235 previously reported sorption isotherms of predominantly crystalline materials containing some
236 amorphous content (Sheokand et al., 2014). For example, a weight increase and subsequent
237 decrease due to amorphous lactose absorbing moisture and crystallizing has been reported in
238 samples containing between 0.125 and 0.5 w/w % amorphous material (Buckton and Darcy,
239 1995). However, the presence of amorphous material in our samples cannot be ruled out from
240 the sorption isotherms. Residual amorphous lactose might be present at lower levels than those
241 studied by Buckton and Darcy (1995). Moreover, Buckton and Darcy (1995) used physical mixes
242 of spray-dried lactose and α -lactose monohydrate in their study, which can facilitate the
243 crystallization event compared to a situation where the amorphous material is in close contact
244 with crystalline portions on the same particle.

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

249 material was detected in our samples (Fig. 6). It can therefore be concluded that if any
250 amorphous material was present in the samples, the amorphous content was probably below
251 0.5%. However, the analysis of very low levels of amorphous material is always challenging in
252 terms of sample storage and sampling. Indeed, amorphous material can crystallize during
253 storage before analysis, thus preventing its identification.

254 3.4. Caking tendency

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

260 It is clear from these results that higher levels of impurities lead to greater risk of caking. In the
261 present study, the samples were stored at 20 °C and 60% RH for four days in the ring shear
262 cells before measurement of caking tendency. Amorphous lactose stored at room temperature
263 (20-25 °C) has been reported to crystallize at about 40% RH (Jouppila and Roos, 1994;
264 Thomsen et al., 2005). Amorphous caking was therefore expected to occur if the samples
265 contained amorphous lactose. However, as mentioned in section 3.3., the solid state NMR
266 analysis did not indicate the presence of disordered structures, meaning that the amorphous
267 content of the samples was probably below 0.5%. Thus amorphous caking cannot be considered
268 to be the main mechanism responsible for the caking tendency observed here. In his work on
269 caking of crystalline lactose, Bronlund (1997) also showed that amorphous caking was only
270 marginal for amorphous content below 5%, and that the major contribution to caking from the
271 amorphous material occurred through moisture sorption.

272 The sorption isotherms of Wash 0, 1, 2 powders and pharmaceutical grade lactose showed that
273 the difference in sorption behavior was important at 60% and room temperature (Fig. 3 and Fig.
274 4). During the caking experiments, the samples were given time to equilibrate with ambient air at
275 60% RH. Due to humidity caking, the caking tendency was therefore expected to be enhanced
276 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}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 $20 \text{ }^\circ\text{C}$. 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 ⁻¹)	Moisture (g.100g ⁻¹)	Ash (g.100g ⁻¹)	Lactose (g.100g ⁻¹)
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.

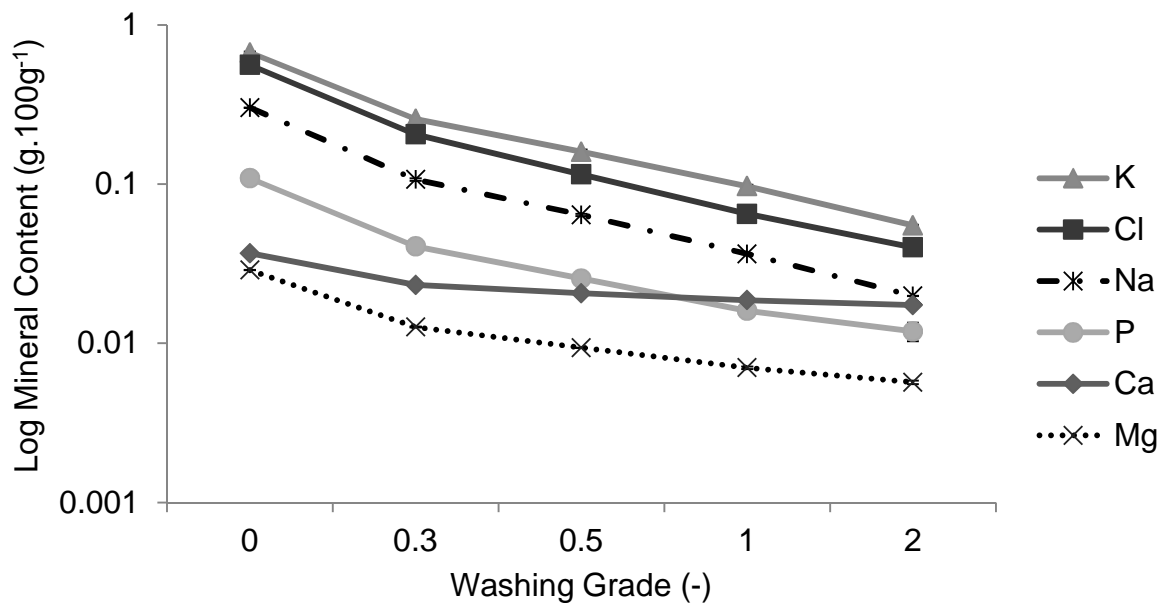


Figure 1: Variations in the mineral content (potassium (K), chlorine (Cl), sodium (Na), phosphorus (P), calcium (Ca), and magnesium (Mg)) of lactose powder as a function of degree of washing of the lactose crystals.

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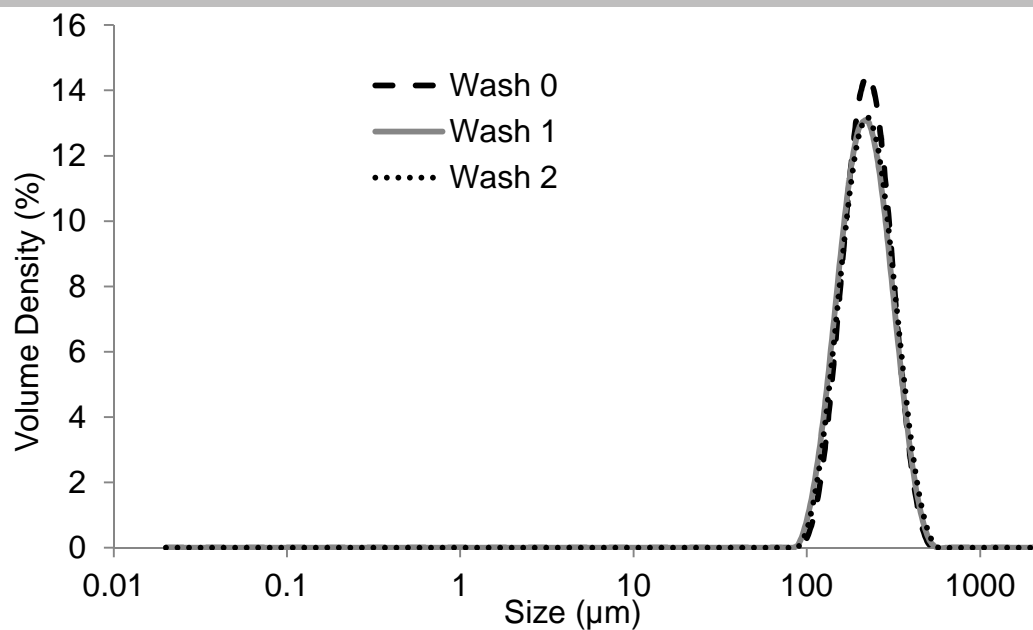


Figure 2: Particle size distributions of lactose powders for three different washing grades (0, 1, 2) but with the same particle size fraction ($160 < x < 250 \mu\text{m}$).

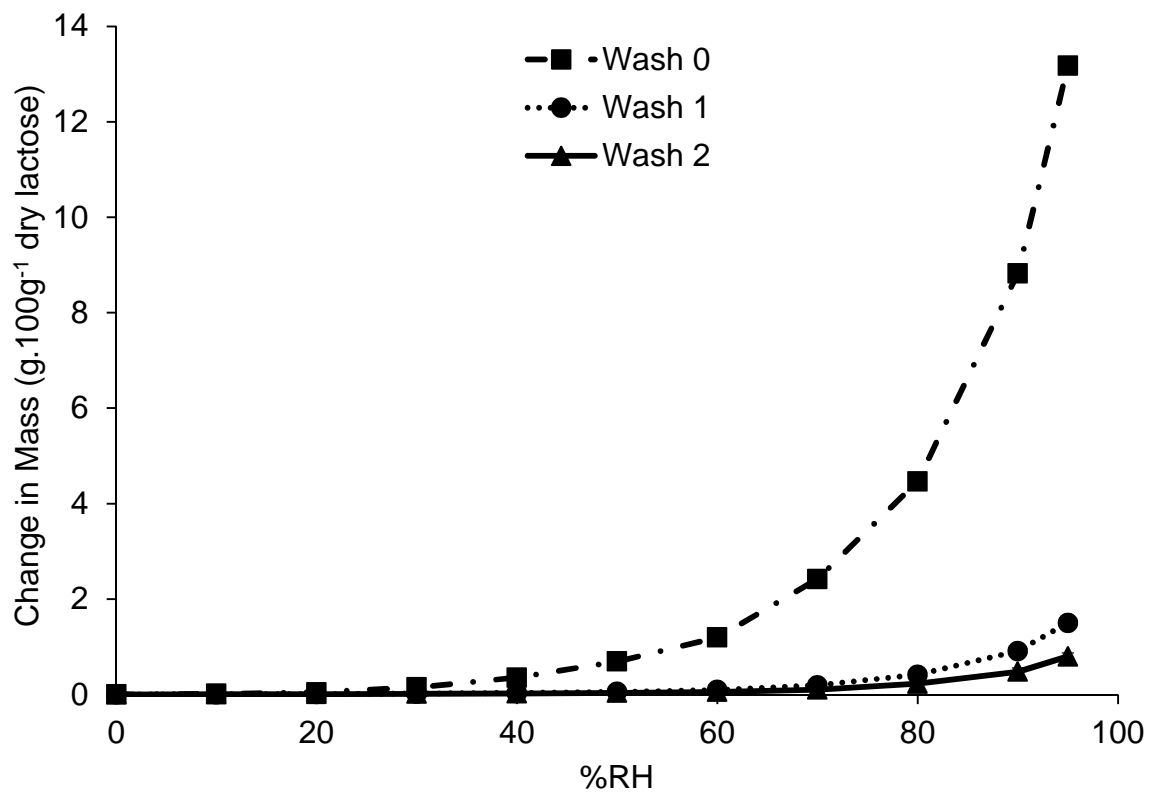


Figure 3: Moisture sorption isotherms of lactose powders with three different washing grades but the same particle size fraction ($160 < x < 250 \mu\text{m}$): Wash 0 (squares), Wash 1 (circles), Wash 2 (triangles).

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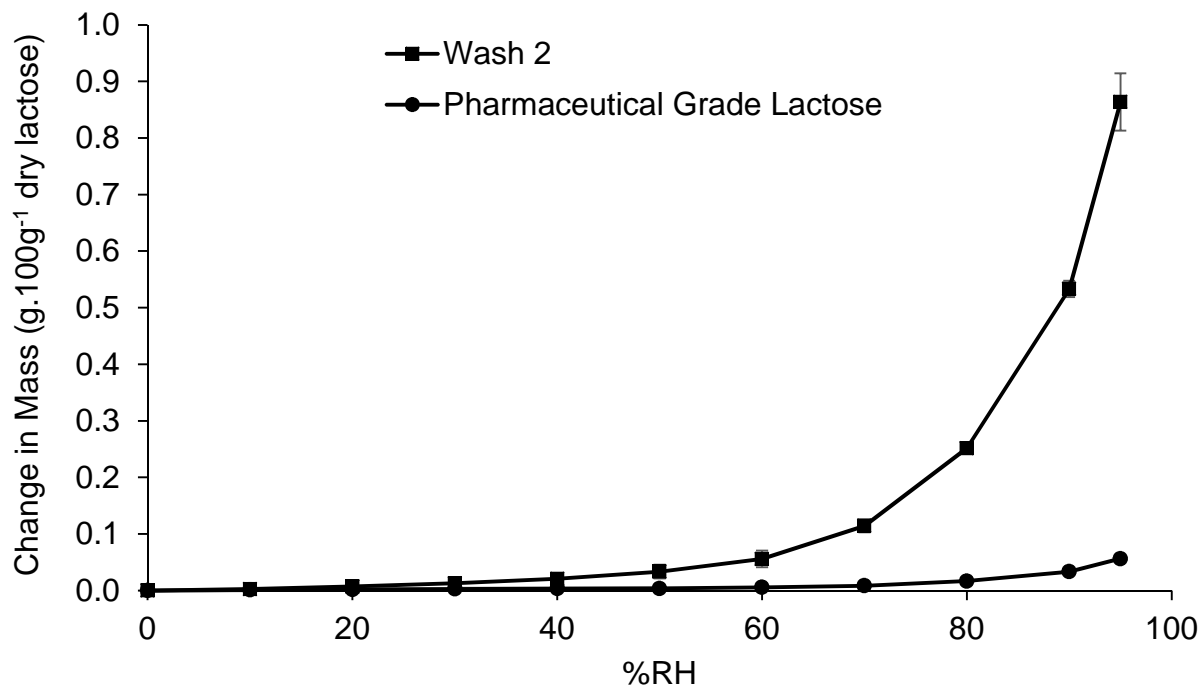


Figure 4: Moisture sorption isotherms of non-sieved pharmaceutical grade lactose (circles) and the most washed lactose from the pilot trial (Wash 2) (squares).

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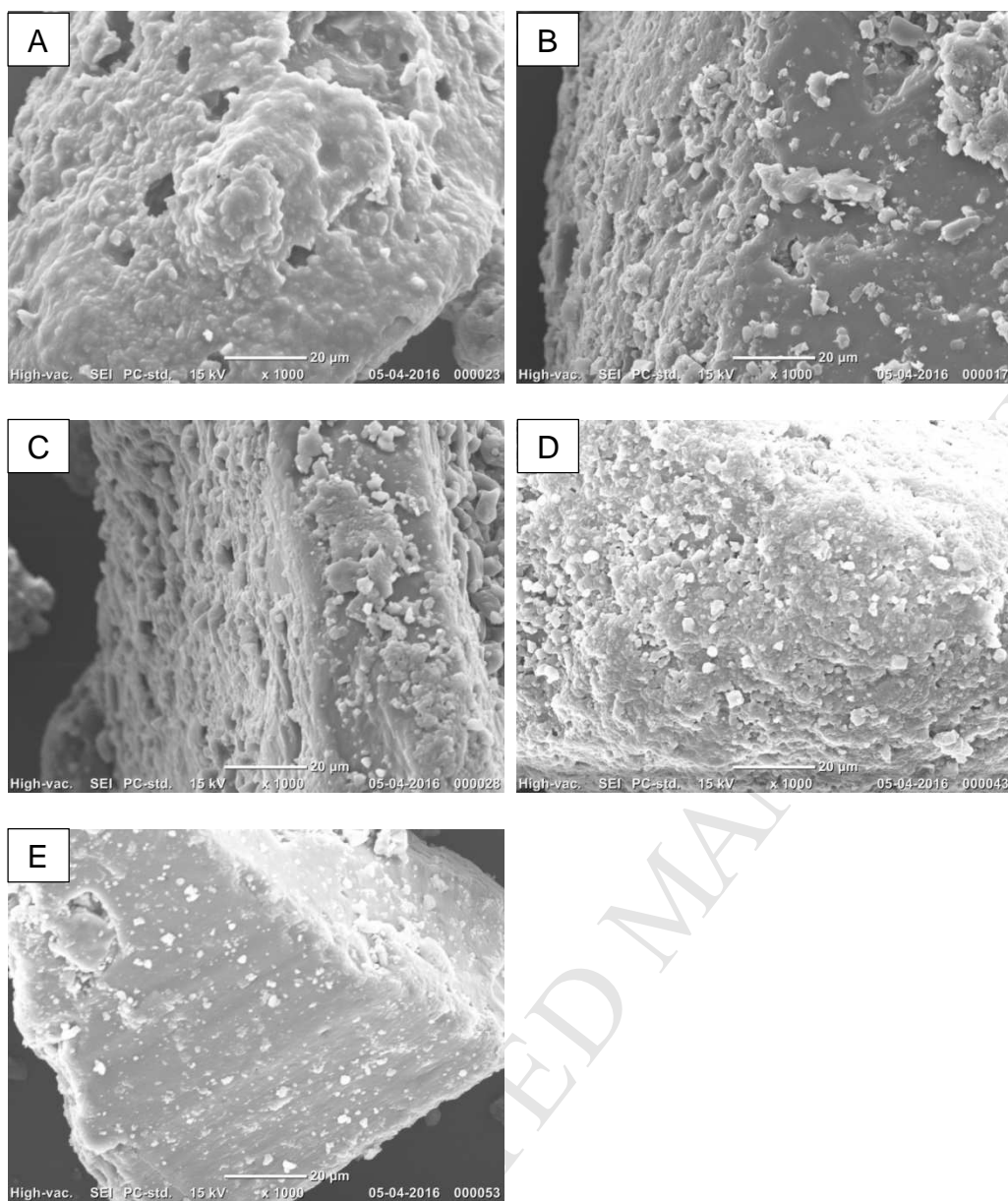


Figure 5: SEM images showing details of particle surface of different washing grade lactose powders: (A) Wash 0; (B) Wash 0.5; (C) Wash 1; (D) Wash 2; (E) Pharmaceutical grade lactose.

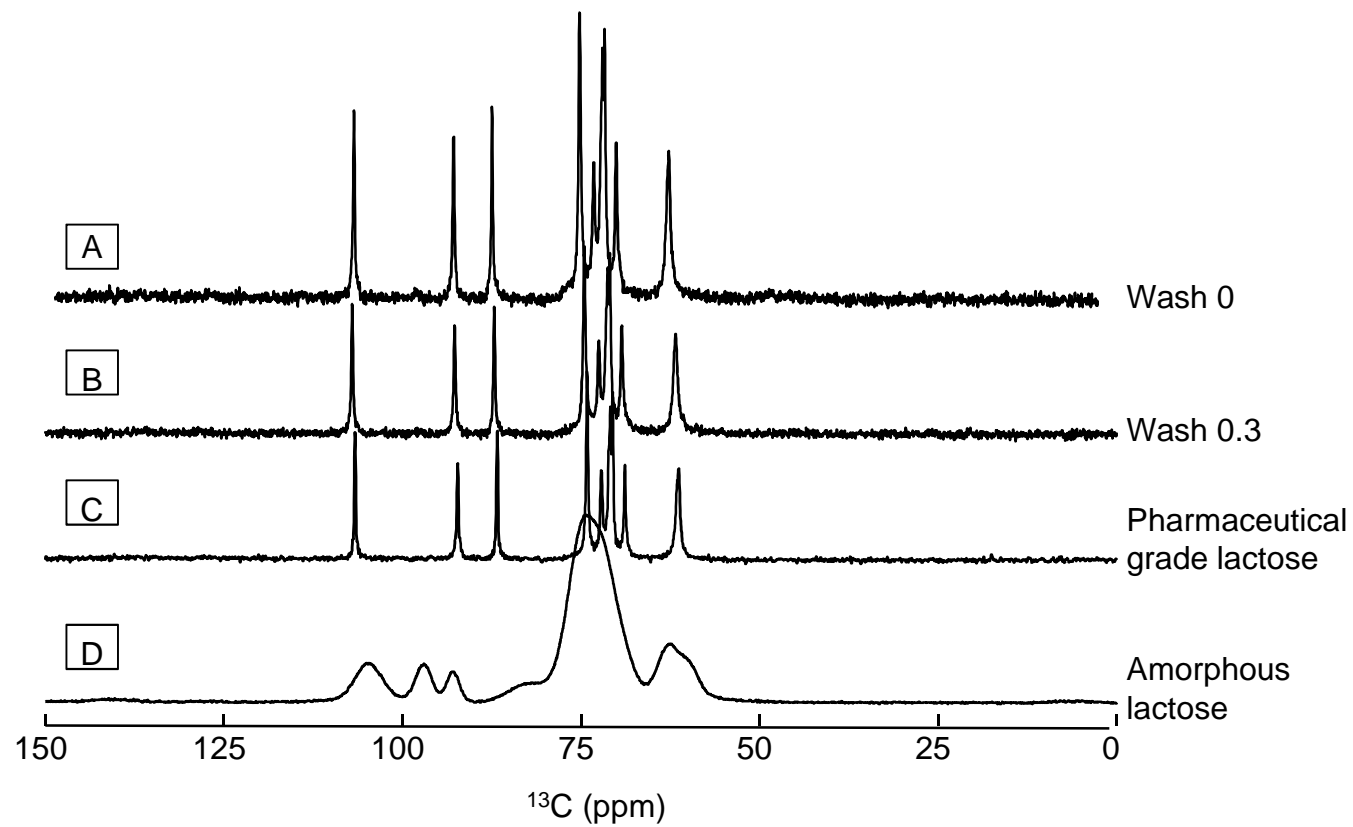


Figure 6: ^{13}C CP/MAS NMR spectra of (A) Wash 0; (B) Wash 0.3; (C) pharmaceutical grade lactose; (D) amorphous lactose.

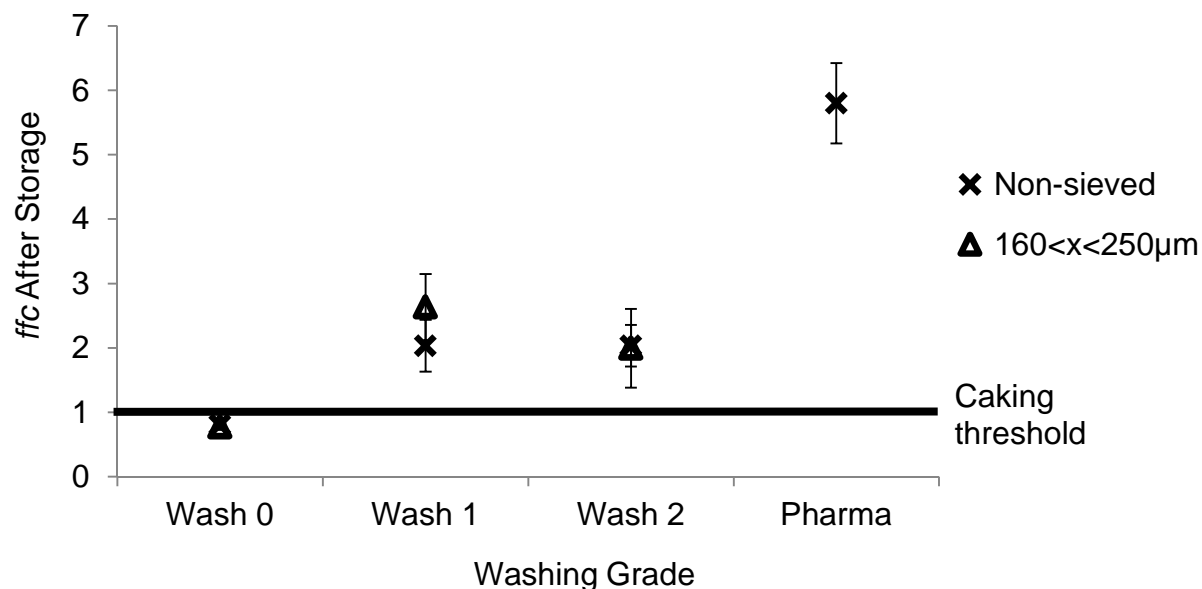


Figure 7: *ffc* of non-sieved (crosses) and sieved (triangles) lactose powders between 160 μm and 250 μm as a function of the washing grade. The *ffc* was measured after storage for four days at 60% RH and 20 $^{\circ}\text{C}$. Each sample was consolidated under a pressure of 9.3 kPa. The flowability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

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- 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.

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