



Effect of milling on the plastic and the elastic stiffness of lactose particles

Samaneh Pazesh^{a,*}, Ann-Sofie Persson^a, Jonas Berggren^b, Göran Alderborn^a

^a Department of Pharmacy, Uppsala University, Uppsala, Sweden

^b Recipharm Pharmaceutical Development AB, Solna, Sweden

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ABSTRACT

The purpose of this study was to investigate the effect of degree of disorder of a series of α -lactose monohydrate powders, prepared by milling for different time periods, on the plastic and the elastic stiffness of the particles. As references, a series of physical mixtures consisting of original crystalline particles and amorphous particles obtained by spray-drying was used. In addition, the effect of powder pre-storage humidity on the mechanical properties was investigated.

For milled particles of a low degree of disorder, a decreased particle size increased the particle plastic stiffness. For milled particles of constant particle size, the plastic stiffness decreased with an increased degree of disorder while the elastic stiffness seemed nearly independent of the degree of disorder. The presence of moisture caused a recrystallisation of milled particles with low degree of disorder which increased their plastic stiffness.

For the physical mixtures of crystalline and amorphous particles, similar relationships between plastic stiffness and amorphous content as for the milled powders were obtained. A reasonable explanation is that the nature of the milled particles is represented by a two-state system with crystalline and amorphous domains.

1. Introduction

Mechanical processing during manufacturing of solid pharmaceuticals or other chemical products composed of crystalline particles may create disordered particles, especially processing involving high forces. It is today acknowledged that disordered solids may show different chemical and physical properties compared to the corresponding crystals which may be beneficial from a product formulation perspective, such as increased rate of dissolution (Bahl et al., 2008; Murdande et al., 2010), but may also be detrimental, such as reduced product physical and chemical stability (Guo et al., 2000). Due to the importance of the disordered state in the formulation of solid products, the physical nature of disordered particles have been discussed in the literature and two models have been proposed, namely the defective particle model and the two-state particle model (Chamarthy and Pinal, 2008; Luisi et al., 2012; Newman and Zografi, 2014; Pazesh, 2017). A defective particle model can be considered as a one-state particle where the degree of disorder depends on the concentration of defects or crystallographic imperfections of the particles. The two-state particle can be described as composed of a mixture of crystalline and amorphous domains and the degree of disorder depends on their relative proportion. Although both models are discussed in the literature, there seems not to be a consensus whether both models are applicable or not and the exact

physical nature of the disordered state still deserves to be studied.

The plasticity of particles is often considered as crucial for the physical structure and the tensile strength of tablets formed by powder compression. Plastic flow may be facilitated by the presence of defects in the crystal, such as dislocations (Acharya and Bassani, 2000; Feng and Grant, 2006), and a one-state defective particle may thus show a decreased plastic stiffness compared to a crystalline particle due to the increased number of potential slip planes. Regarding fully amorphous particles, it is reported (Fell and Newton, 1971; Sebhatu and Alderborn, 1999) that fully amorphous lactose particles showed a decreased plastic stiffness compared to their corresponding crystals. However, an increased hardness or plastic stiffness of a fully amorphous solid compared to the crystalline solid has also been reported (Hancock et al., 2002). Thus, the effect of disorder on the plastic stiffness of particles may depend on the physical nature of disordered particles and the relative hardness of fully amorphous and crystalline material. A two-state particle composed of crystalline and amorphous domains may hence show an increased or a decreased plastic stiffness compared to a crystalline particle. An improved understanding of the properties of mechanically disordered materials can provide information that may explain sources of variation in the handling of powders. In addition, such information may improve the controlled modulation of particle properties and give insight into the nature of the disordered state. To our

* Corresponding author at: Department of Pharmacy, Uppsala University, Box 580, SE-751 23 Uppsala, Sweden.
E-mail address: samaneh.pazesh@farmaci.uu.se (S. Pazesh).

knowledge, there are hitherto no reports in the literature on the sequential relationship between mechanical processing, process-induced degree of disorder and the plastic stiffness of disordered particles. The objective of this paper was hence to investigate the effect of degree of disorder of a series of α -lactose monohydrate powders, prepared by milling for different time periods, on the plastic and the elastic stiffness of the particles. A series of physical mixtures consisting of original crystalline particles and amorphous particles obtained by spray-drying was used as references. Moreover, the influence of powder pre-storage humidity on the mechanical properties was investigated. The particle plastic stiffness was assessed by analytical powder compression, i.e. a yield pressure was derived from the relationship between porosity of the powder column and the applied compression pressure during confined powder compression.

2. Materials and methods

2.1. Materials

Three qualities of α -lactose monohydrate with different labelled particle size, i.e. Pharmatos® 200M and 450M and Lactohale® LH300 (DFE Pharma, the Netherlands), hereafter denoted CL200, CL450 and LH300 respectively, were used. Magnesium stearate (Kebo, Sweden) was used as a lubricant. Phosphorus pentoxide (P_2O_5) and magnesium chloride ($MgCl_2$) were obtained from VWR, Sweden.

2.2. Powder preparations

Amorphous lactose was prepared by spray-drying a 10% (w/w) aqueous solution of CL200 using a Büchi MiniSprayDryer B-290 Advance (Büchi Labortechnik AG, Flawil, Switzerland). The solution was agitated for at least 15 h before spray-drying. A spray nozzle with a size of 0.7 mm and the high-performance cyclone were used. The aspirator rate was set to 100%, the spray gas flow rate to 40 L/min and the feed pump rate to 4 mL/min. The inlet and outlet temperatures were maintained at 155 °C and 98 °C, respectively. The spray-dried lactose is subsequently denoted SDL.

Ball milling of CL200 was performed in a planetary ball mill (PM 100 CM, Retsch, Germany). The milling operation was carried out in a stainless steel milling jar of a volume of 12 cm³ containing 50 balls with a diameter of 5 mm of the same material. Approximately 1 g of lactose (corresponding to a ball-to-powder mass ratio of 25:1) was milled for 10, 30, 60, 90, 150, 300, and 1200 min. The rotation speed was set to 400 rpm. Every 20 min of milling was followed by a pause period of 5 min in order to cool the jar. The milling experiments were performed in a humidity controlled room at 30 ± 5% relative humidity (RH) and at 22 ± 3 °C. Milled powders are subsequently denoted ML and the numbers are the milling times.

Binary physical mixtures of 2 g consisting of SDL and CL200 containing 1.37%, 8.93%, 10.7%, 22.2%, 41.1% and 79.1% (w/w) of SDL were prepared by mixing for 15 min in a 20 mL glass vessel using a Turbula mixer (W.A. Bachofen, Switzerland) operating at a rate of 46 rpm. The mixing was done at room temperature and at a RH of 30 ± 5%. The physical mixtures are subsequently denoted PM and the numbers are the percentage proportions of SDL.

2.3. Powder characterisation

The crystal structure of CL200, CL450, LH300 and SDL was investigated by X-Ray powder diffraction at room temperature using a Siemens D5000 powder diffractometer, theta-theta geometry (Germany) with $CuK\alpha$ anode; $\lambda = 1.5406 \text{ \AA}$. The sample was placed in a sample holder and scanned at 40 kV and 40 mA. Analysis was performed in a continuous mode with a step size of 0.01° and a step time of 0.2 s over an angular range of 8° to 60° 2 θ . The divergence and anti-scattering slit settings were set for illumination sample length of

20 mm. The diffractogram were collected using DIFRACT.SUIT software. The experimental diffraction patterns were compared with the theoretical patterns which were based on data from the Cambridge Crystallographic Data Centre (CCDC).

Images of ML and PM powders were prepared by scanning electron microscopy (SEM). A small amount of powder was attached to a metal stub using double-adhesive carbon tape and then sputtered with a thin layer of Au/Pd under argon in a sputter coater (Polaron, Quorum Technologies Ltd., Newhaven, U.K.). The images were captured at an accelerating voltage of 2 kV in the Scanning Electron Microscope (Leo (Zeiss), 1550 Schottky, Germany, equipped with SmartSEM software). The images were taken at 5 kX magnification.

The particle size distributions of the original crystalline powders CL200, CL450, LH300 and the lactose powder milled for 10 min (ML10) were measured using a laser diffraction instrument (Coulter LS230, small volume module plus, Coulter Corp, Miami, U.S.A.). Approximately 100 mg powder was poured into 5 mL of 2-propanol and sonicated in a water bath (Ultrasonic Cleaner Branson, B5210E-MT, Branson Ultrasonic Company, Danbury, U.S.A.) for 10 min at a frequency of 47 kHz ± 6% prior analysis. The sonicated sample was then added into the measuring cell containing 2-propanol and equipped with a magnetic stirrer. The sample was analysed with a dispersant refractive index of 1.378, a particle refractive index of 1.533 and an imaginary index of 0.1. The particle diameter was calculated according to the Fraunhofer theory. The median particle diameter of a volume distribution was determined and reported median particle diameters are the average of five measurements.

The apparent particle density (ρ_{app}) of each material was determined by helium pycnometry (Micromeritics AccuPyc II 1340, Micromeritics Instrument Corp, Norcross, U.S.A.). The powders were stored for two days in a desiccator above P_2O_5 prior to measurement. An average of five cycles was used for three independent measurements.

The apparent amorphous content (AAC) was determined after compression (see Section 2.4.) using Raman spectroscopy (Enwave Optronics Inc., SLSR-ProTT analyser, Irvine, U.S.A.) equipped with TE cooled CCD detector and a laser source with an excitation wavelength at 785 nm. The method used to quantify AAC of milled powders has been described in detail in a previous paper (Pazesh et al., 2016). Briefly, to construct a standard curve, Raman spectrum measurements were performed on a set of binary physical mixtures of crystalline and amorphous lactose. A straight baseline approach was used to subtract the background from the measured Raman spectra, after which the spectra were normalised to the integrated area. Principal component analysis (PCA) was employed for quantitative analysis of the Raman spectra after baseline correction and normalisation.

2.4. Powder compression

The powders were stored in a desiccator over P_2O_5 , corresponding to a nearly dry atmosphere and hereafter referred to as 0% RH, and in a desiccator over $MgCl_2$, hereafter referred to as 33% RH, for at least two days prior to compression. Approximately 400 mg of each powder was poured manually into the die and uniaxially compressed using materials tester (Zwick Z100, Zwick/Roell GmbH & Co, Ulm, Germany) equipped with 11.3 mm diameter flat-faced punches. The lower punch was stationary and the upper punch moved at a rate of 10 mm/min both during compression and decompression. Prior to die-filling, the punches and the die were lubricated with 1% magnesium stearate suspended in ethanol (95% w/w) in order to reduce powder to die wall frictional forces during compression. Five compacts of each powder were prepared at a pressure of 300 MPa. The compression experiments were performed in a humidity controlled room at 30 ± 5% RH and 22 ± 3 °C.

The system deformation was measured to be 0.4 $\mu\text{m}/\text{MPa}$ by pressing the upper and the lower punches together to 300 MPa as

described by Nordström et al. (Nordström et al., 2008) and was accounted for in the calculations of tablet height during compression analysis.

2.5. Compression analysis

The pressure–porosity relationship was used for calculation of the yield pressure (P_y) of the powders using the Heckel relationship (Heckel, 1961):

$$\ln \frac{1}{\varepsilon} = K \cdot P + A, \quad (1)$$

where ε is porosity of the powder column in-die, P is pressure, K and A are the slope and the intercept of the linear region, respectively. P_y was calculated as $1/K$ using linear regression with an R^2 -value > 0.999 . The pressure range of the linear region was determined using an Excel (Microsoft Corporation) macro locating the minimum value of the first derivative as the middle pressure and extending the linear region until the derivative increased by 25% in each direction. In addition, the minimum in-die porosity of the powder bed (ε_{\min}) was recorded from the compression-decompression profile of the powder compression experiments using ρ_{app} .

The in-die elastic recovery ($ER_{\text{in-die}}$) was calculated from the expansion of the compacts during decompression prior ejection, relative to its height at maximum pressure (h_0):

$$ER_{\text{in-die}} = \left(\frac{h_1 - h_0}{h_0} \right) \times 100, \quad (2)$$

where h_1 is the height at each detectable pressure under decompression (Armstrong and Haines-Nutt, 1974). The system deformation during decompression was corrected for as described in Section 2.4.

An elastic modulus (E_M) was determined from the reciprocal of the slope of the relationship between $ER_{\text{in-die}}$ and pressure difference ($P_{\text{max}} - P$) using linear regression in the range 50–250 MPa with an R^2 -value > 0.987 .

In addition to the values of E_M , the maximum elastic recovery ($ER_{\text{in-die}}^*$) obtained during decompression is reported, i.e. a value based on the final recorded value of h_1 during decompression.

3. Results

3.1. Powder characteristics

The X-ray diffraction patterns of the original powders of the crystalline lactose materials (CL200, CL450, and LH300) were similar and corresponded to the theoretical diffraction pattern of α -lactose monohydrate (data not shown). The spray-dried lactose powder (SDL) showed a halo X-ray diffraction pattern characteristic of fully amorphous particles.

The CL200, CL450 and LH300 powders had a similar and irregular shape (images not shown). Adhered to the surfaces of the larger crystals were small crystals with a more elongated shape. The SDL particles displayed, as expected, a spherical shape with smooth surface.

In Fig. 1, images of ML300 (i.e. CL200 lactose particles milled for 300 min) and PM41.1% (i.e. the physical mixture of CL200 and SDL particles containing a proportion of amorphous particles equating the AAC of ML300) powders are presented. The ML300 particles were more irregular than the original CL200 particles. Also for the milled particles, small irregular particles adhered to the surface of the larger particles. For the physical mixture, the spherical SDL particles were located in-between or adhered to the surface of the CL200 particles.

Particle size distributions of CL200, CL450 and LH300 are presented as cumulative volume distributions in Fig. 2A. The original crystalline powders showed generally a spread in particle diameter and all powders consisted of a large number of small particles i.e. below 2 μm . The volume distributions showed a large difference in the width of the

distributions, corresponding to a marked difference in median particle diameter, i.e. 27.4 μm for CL200 particles, 17.2 μm for CL450 particles and 3.46 μm for LH300 particles.

Milling CL200 particles for 10 min (Fig. 2A) gave a narrower particle diameter distribution compared to the original CL200 particles, corresponding to a reduction in median particle diameter from 27.4 μm (CL200) to 5.37 μm (ML10).

The apparent particle densities (Table 1) of the original crystalline lactose qualities were similar, i.e. 1.545 g/cm^3 , 1.550 g/cm^3 and 1.558 g/cm^3 for CL200, CL450 and LH300, respectively. For the SDL, an apparent particle density of 1.489 g/cm^3 was obtained.

For the milled powders (the ML powders), the apparent particle density (Table 2) decreased gradually with increased milling time from 1.548 g/cm^3 for ML10 to 1.534 g/cm^3 for ML1200. However, an ANOVA-test did not indicate a significant ($p < 0.05$) difference between the measured densities of the ML powders.

For the physical mixtures (the PM powders), the apparent density (Table 2) decreased gradually with an increased proportion of SDL from 1.548 g/cm^3 for PM1.37% to 1.497 g/cm^3 for PM79.1%. An ANOVA-test indicated a significant ($p < 0.05$) difference between the measured densities of the PM powders.

Milling of CL200 gave an increase in apparent amorphous content (AAC) with increased milling time up to an AAC of about 80% (Table 2). The powder stored at 33% relative humidity (RH) gave generally lower AAC than the powders stored in a dry atmosphere before measurement.

3.2. Mechanical characteristics

The Heckel yield pressure (P_y) of CL200, CL450, LH300 and SDL are presented in Table 1. Although the crystal structure and the particle morphology of the original crystalline lactose powders were similar their P_y differed, i.e. the P_y increased (corresponding to an increased plastic stiffness) with a decreased median particle diameter (Fig. 2B). The RH during pre-storage of the powders (0% RH or 33% RH) had no effect on the P_y . The SDL powder showed a lower plastic stiffness than the crystalline powders and pre-storage at 33% RH decreased the P_y in comparison to the same powder pre-stored at 0% RH.

In Table 2, the P_y of all ML powders pre-stored at 0% RH and at 33% RH are presented. The highest value of P_y was observed for ML10 (202 MPa) pre-stored at 0% RH, i.e. milling CL200 powder for a short period of time increased the P_y . During longer milling times than 10 min, an increased milling time gradually decreased the P_y of the ML powders irrespective of the pre-storage RH of the powders. The lowest P_y was obtained for the ML1200 powder, i.e. 92 MPa, and was similar to the P_y of SDL. The increased AAC due to prolonged milling (Table 2) corresponded to a reduced P_y and the relationship between P_y and AAC was non-linear (Fig. 3).

The pre-storage humidity affected the AAC of the ML powders (Table 2). The ML powders of a low AAC (ML30–150) seemed to re-crystallise completely (ML30) or to a lower degree (ML60–150) during pre-storage at 33% RH whereas the ML powders with higher degree of AAC was less affected or unaffected by the pre-storage RH. As indicated in Fig. 4, the plastic stiffness was unaffected by the pre-storage humidity for ML powders as for the crystalline powders.

In Table 2, the P_y of all PM powders pre-stored at 0% RH and at 33% RH are presented. The pre-storage of only SDL powders at 33% RH indicated no tendency to a moisture induced crystallisation and the degree of amorphous content was hence assumed to be equal to the proportion of SDL powder in the mixture. The PM with the lowest proportion of SDL (1.37%) showed a similar P_y as the CL200 powder (Tables 1 and 2). Thereafter, an increased proportion of SDL of the PM powders decreased the P_y and a proportion of SDL of 79.1% gave the same P_y as the SDL powder. The P_y values of the PM powders compared favourably with the P_y values of ML powders of an AAC that corresponded to the proportion of SDL of the PM powders (Fig. 3).

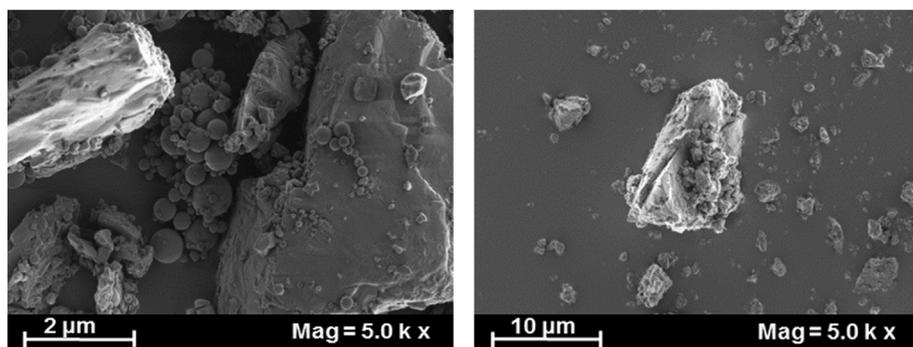


Fig. 1. Scanning electron microscopy images of lactose milled for 300 min (right) and physical mixture containing 41.1% amorphous content (left).

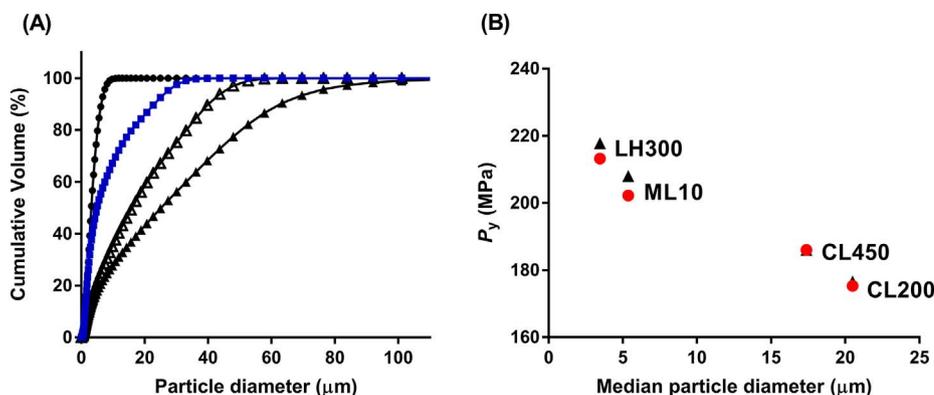


Fig. 2. (A) Volume distribution of particle diameter of lactose CL200 (closed black triangles), CL450 (open black triangles), LH300 (black circles) and lactose milled for 10 min (blue squares). (B) Heckel yield pressure (P_y) as function of median particle diameter of lactose particles. The powders were pre-stored at 0% RH (red circles) and at 33% RH (black triangle).

For the PM powder of the lowest proportion of SDL (1.37%), the pre-storage humidity had no effect on the P_y . For the PM powders of a higher proportion of SDL (8.93%–79.1%), pre-storage in a humid atmosphere (33% RH) gave generally lower P_y values in comparison to the same PM powders stored in a dry atmosphere (Table 2) which is consistent with the effect of moisture on the P_y of SDL particles. Since the PM powders in contrast to the ML powders showed a dependency of the pre-storage RH, the measured P_y of the ML powders pre-stored at 33% RH were higher than the corresponding P_y for PM powders pre-stored at 33% RH (Fig. 3B).

In Table 1, the indications of the elastic properties of the compacts formed from CL200, CL450, LH300 and SDL are presented, i.e. the maximum in-die elastic recovery (ER^*_{in-die}) and the elastic modulus (E_M). For compacts of the crystalline powders, the same ER^*_{in-die} were obtained and the median particle diameter had thus no effect on ER^*_{in-die} . For the E_M , there was a tendency to a reduced modulus, corresponding to a reduced elastic stiffness, with a reduced median particle diameter. There was no effect of pre-storage humidity on the calculated values. The SDL powder showed a lower ER^*_{in-die} and tended to have a higher E_M than the crystalline powders which indicates that SDL formed tablets that were slightly less elastic than the crystalline powders. Pre-storage of SDL powder at 33% RH decreased the ER^*_{in-die} and increased the E_M in comparison to the same powder pre-stored at 0% RH. Thus, an increased moisture content of the SDL powder reduced the elasticity of the compacts in-die.

In Table 3, ER^*_{in-die} and E_M are presented for the ML powders pre-stored at 0% RH and at 33% RH together with values of the minimum compact porosity (ϵ_{min}) recorded during the compression-decompression cycle. The values of elasticity were similar for compacts of all ML powders. One may note a trend however with a decreased ER^*_{in-die} and an increased E_M with increased milling time, i.e. an increased AAC tended to reduce the elasticity of the compacts in-die. There was no effect of pre-storage humidity on the calculated values of elasticity. An increased milling time gave a gradual reduction in ϵ_{min} .

In Table 3, the ER^*_{in-die} , the E_M and the ϵ_{min} are presented for all PM powders pre-stored at 0% RH and at 33% RH. In the same way as for the

Table 1

Apparent particle density (ρ_{app}), yield pressure (P_y), maximum in-die elastic recovery (ER^*_{in-die}) and elastic modulus (E_M) of the original crystalline lactose powders and the spray-dried lactose. Relative standard deviations are given in parentheses ($n = 3$ for ρ_{app} and $n = 5$ for mechanical characteristics).

	CL200	CL450	LH300	SDL
ρ_{app} (g/cm ³)	1.545 (0.001)	1.550 (0.001)	1.558 (0.001)	1.489 (0.002)
P_y^a (MPa)	175 (0.00)	187 (0.00)	213 (0.01)	102 (0.05)
P_y^b (MPa)	177 (0.00)	186 (0.01)	218 (0.02)	86.9 (0.02)
$ER^*_{in-die}^a$ (%)	3.1 (0.01)	3.0 (0.01)	3.0 (0.01)	2.2 (0.02)
$ER^*_{in-die}^b$ (%)	3.1 (0.01)	3.0 (0.00)	3.0 (0.02)	1.8 (0.06)
E_M^a (GPa)	14.3 (0.005)	13.3 (0.008)	11.8 (0.006)	14.4 (0.019)
E_M^b (GPa)	14.4 (0.022)	13.3 (0.004)	12.0 (0.012)	17.6 (0.038)

CL200: Crystalline α -lactose monohydrate 200M.

CL450: Crystalline α -lactose monohydrate 450M.

LH300: Crystalline α -lactose monohydrate LH300.

SDL: Spray-dried lactose.

^a Powder pre-stored at 0% RH.

^b Powder pre-stored at 33% RH.

ML powders, the ER^*_{in-die} and the E_M were similar for compacts of all PM powders. However, for compacts of the PM powders of the two highest proportions of SDL (41.1% and 79.1%), the ER^*_{in-die} seemed to decrease with increased proportion of SDL and approaching the value of SDL. This tendency was valid for powders pre-stored both at 0% and at 33% RH. In a similar way, the E_M of compacts of the PM powders of the two highest proportions of SDL tended to increase and to a higher level for powders pre-stored at 33% RH. One may note that the PM powders containing a low and an intermediate proportion of SDL particles (up to 41.1%) formed compacts of a higher ER^*_{in-die} compared to the corresponding ML powders, i.e. ML10 to ML300. In addition, the effect of pre-storage humidity on the E_M was more obvious for the PM powder of the highest proportion of SDL particles in comparison to the ML powder of highest AAC. An increased proportion of SDL in the PM powders gave a reduction in a similar way as for the ML powders.

Table 2

Apparent particle density (ρ_{app} , $n = 3$), yield pressure (P_y , $n = 5$) and apparent amorphous content (AAC, $n = 5$) of the milled lactose powders and physical mixtures pre-stored at 0% RH and at 33% RH. Relative standard deviations are given in parentheses.

	ρ_{app} (g/cm ³)	P_y^a (MPa)	AAC ^a (%)	P_y^b (MPa)	AAC ^b (%)
ML10	1.548 (0.001)	202 (0.01)	0 (0.23)	208 (0.02)	0 (0.11)
ML30	1.547 (0.001)	179 (0.02)	1.37 (1.22)	202 (0.00)	0 (0.90)
ML60	1.546 (0.002)	163 (0.01)	8.93 (0.20)	171 (0.02)	4.90 (0.24)
ML90	1.545 (0.001)	160 (0.04)	10.7 (0.18)	188 (0.01)	3.51 (0.26)
ML150	1.545 (0.001)	139 (0.04)	22.2 (0.07)	171 (0.01)	9.42 (0.12)
ML300	1.537 (0.001)	115 (0.01)	41.1 (0.07)	115 (0.01)	37.5 (0.07)
ML1200	1.534 (0.002)	92.0 (0.01)	79.1 (0.01)	91.7 (0.01)	77.9 (0.01)
PM1.37%	1.548 (0.001)	178 (0.00)	–	178 (0.01)	–
PM8.93%	1.541 (0.001)	159 (0.01)	–	153 (0.03)	–
PM10.7%	1.540 (0.002)	159 (0.01)	–	151 (0.02)	–
PM22.2%	1.533 (0.001)	140 (0.02)	–	131 (0.01)	–
PM41.1%	1.525 (0.001)	123 (0.07)	–	109 (0.02)	–
PM79.1%	1.497 (0.001)	101 (0.08)	–	85.4 (0.00)	–

ML: Milled powder, the numbers are the milling times in minutes.

PM: Physical mixtures, the numbers are the percentage proportions of spray-dried lactose.

AAC: Apparent amorphous content.

^a Powder pre-stored at 0% RH.

^b Powder pre-stored at 33% RH.

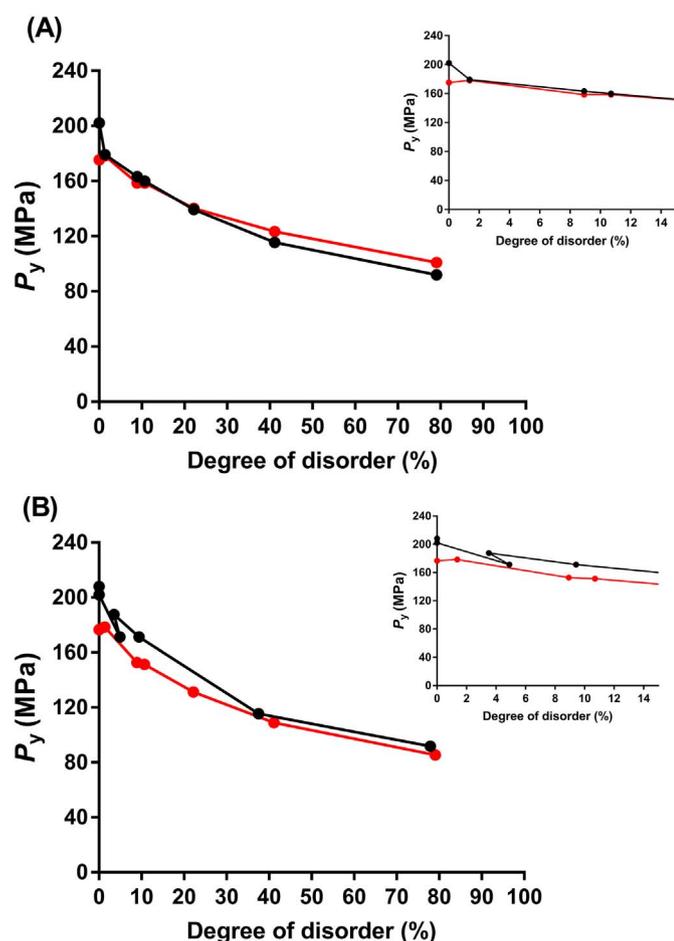


Fig. 3. Heckel yield pressure (P_y) as function of degree of disorder for milled lactose (black circles and line) and physical mixtures (red circles and line). The powders were pre-stored at 0% RH (A) and at 33% RH (B) prior compression.

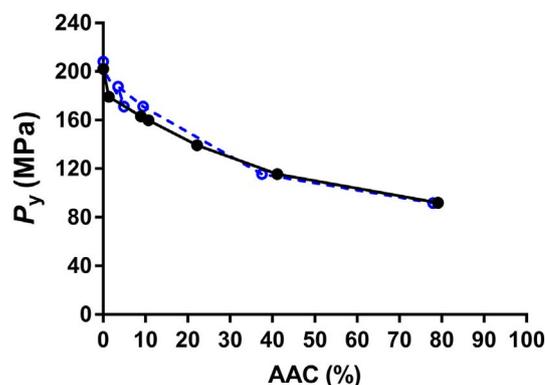


Fig. 4. Heckel yield pressure (P_y) as function of apparent amorphous content (AAC) for milled lactose pre-stored at 0% RH (black circles and line) and at 33% RH (blue open circles and blue dashed line).

4. Discussion

The measure used to indicate the particle plastic stiffness in this study was the Heckel $1/K$ parameter, commonly denoted the yield pressure (P_y) (Heckel, 1961; Roberts and Rowe, 1987; Roberts et al., 1989). The P_y is an indication of the compressibility of a powder and may thus reflect both plastic and elastic deformation of the particles during compression (Duberg and Nyström, 1986). However, based on a comparison between P_y and another theoretically derived compression parameter it was proposed (Mahmoodi et al., 2013) that for pharmaceutical powders, the P_y represents a measure of the plastic stiffness of the particles. More on, it is also argued (Hassanpour and Ghadiri, 2004) that above a critical ratio between Young's modulus of elasticity and yield pressure the Heckel relationship reflects yield pressure and the authors concluded that for lactose, the P_y is reflecting the plastic deformation of the particles and their elastic deformation has a limited contribution.

In this paper, the relationship between process-induced degree of disorder and mechanical properties, primarily particle plastic stiffness, of lactose particles has been studied. Milling in a planetary ball mill was used as a means to prepare particles of different degree of disorder. As reference powders to the milled powders, three crystalline powders of different median particle size were used (CL200, CL450 and LH300) as well as a completely amorphous particle prepared by spray-drying (SDL). It has earlier been reported, e.g. (Fell and Newton, 1971), that P_y is affected both by the dimensions of the particles, i.e. small particles may have a higher P_y than large particles, and by the solid state of the particles, i.e. amorphous lactose particles tend to have a lower P_y and thus be softer than crystalline particles (Sebhatu and Alderborn, 1999). For the CL200, CL450 and LH300 powders used in this study, the P_y seemed to depend on the median particle diameter in an approximately linear way (Fig. 2B) with a relatively marked effect of median particle diameter on the particle plastic stiffness. For the amorphous reference powder SDL, a considerably lower P_y was obtained in comparison to the crystalline reference powders (Table 1). Thus, the compression analysis of the reference lactose powders used in this study is consistent with earlier findings on the importance of particle dimensions and solid state for their plastic stiffness.

It was recently proposed (Pazesh et al., 2017) that the relationship between comminution and degree of disorder, expressed as an apparent amorphous content (AAC), for lactose could in a simplified way be generalised as consisting of two stages. In the first stage, comminution occurred with minute disordering of the particles and in the second stage, the particles became disordered and the AAC increased without any further particle size reduction. In this study, it was found that also

Table 3

Maximum in-die elastic recovery (ER^*_{in-die}), elastic modulus (E_M) and minimum in-die porosity (ϵ_{min}) of the milled lactose powders and physical mixtures pre-stored at 0% RH and at 33% RH. Relative standard deviations are given in parentheses ($n = 5$).

	$ER^*_{in-die}{}^a$ (%)	$E_M{}^a$ (GPa)	$\epsilon_{min}{}^a$ (%)	$ER^*_{in-die}{}^b$ (%)	$E_M{}^b$ (GPa)	$\epsilon_{min}{}^b$ (%)
ML10	2.6 (0.03)	14.6 (0.008)	4.9 (0.02)	2.6 (0.01)	14.7 (0.006)	5.1 (0.03)
ML30	2.5 (0.02)	14.8 (0.005)	4.3 (0.02)	2.6 (0.01)	14.3 (0.006)	5.2 (0.01)
ML60	2.6 (0.03)	14.6 (0.007)	3.7 (0.01)	2.6 (0.02)	14.4 (0.004)	3.9 (0.03)
ML90	2.4 (0.02)	14.9 (0.023)	3.8 (0.13)	2.4 (0.01)	14.7 (0.007)	4.7 (0.03)
ML150	2.2 (0.02)	15.4 (0.014)	2.7 (0.12)	2.4 (0.02)	14.6 (0.004)	3.9 (0.03)
ML300	2.3 (0.05)	16.0 (0.012)	0.8 (0.14)	2.3 (0.07)	15.7 (0.007)	0.6 (0.28)
ML1200	2.3 (0.03)	15.5 (0.008)	0 (0.98)	2.3 (0.07)	15.7 (0.022)	0 (0.30)
PM1.37%	3.2 (0.01)	13.5 (0.020)	3.8 (0.01)	3.2 (0.00)	13.6 (0.011)	3.8 (0.01)
PM8.93%	3.0 (0.01)	14.6 (0.004)	3.0 (0.02)	3.1 (0.01)	14.8 (0.024)	2.8 (0.04)
PM10.7%	3.1 (0.01)	13.8 (0.017)	3.0 (0.03)	3.2 (0.01)	14.1 (0.015)	2.8 (0.03)
PM22.2%	3.1 (0.00)	13.8 (0.015)	2.1 (0.06)	3.1 (0.01)	14.4 (0.013)	1.9 (0.04)
PM41.1%	2.8 (0.03)	14.9 (0.027)	1.1 (0.36)	2.8 (0.01)	16.1 (0.016)	0.7 (0.26)
PM79.1%	2.3 (0.03)	15.1 (0.023)	0 (0.46)	1.9 (0.02)	17.5 (0.013)	0 (0.44)

ML: Milled powder, the numbers are the milling times in minutes.

PM: Physical mixtures, the numbers are the percentage proportions of spray-dried lactose.

^a Powder pre-stored at 0% RH.

^b Powder pre-stored at 33% RH.

the P_y was affected by the milling in two ways, i.e. an initial increased P_y was followed by a slow gradual decrease with milling time. The initial increase in P_y was obtained after 10 min of milling, i.e. ML10 vs CL200. The P_y of ML10 seemed to obey the relationship found between P_y and median particle size of the crystalline reference powders (Fig. 2B). For the ML10 powders, no measurable increase in AAC was obtained (Table 2). Thus, the increase in P_y after milling CL200 for 10 min is explained by the decreased particle size rather than a change in particle morphology or in the disordering of the particles.

For the milled powders pre-stored at 0% RH, milling for longer times than 10 min gave an increase in AAC with milling time (Table 2). The P_y for these ML powders was also influenced by milling and decreased with increased milling time. Thus, the decrease in P_y after milling CL200 for at least 10 min is explained by the increased AAC of the particles, i.e. a decrease in particle plastic stiffness is associated with the creation of structural defects or amorphous regions of the particles. The two stages of the comminution-amorphisation relationship corresponded thus to different effects on the particle plastic stiffness, i.e. comminution with minute disordering increased the particle plastic stiffness while low and substantial disordering of the particles of constant diameter decreased the particle plastic stiffness. In the second stage, the relationship between P_y and AAC was non-linear (Fig. 3A) with a faster rate of change in P_y with AAC at low AAC followed by a somewhat slower rate at high AAC. At an AAC of about 80%, the plastic stiffness of the milled particles (ML1200) became similar to the plastic stiffness of the fully amorphous reference powder SDL (Tables 1 and 2).

The moisture content and the state of the moisture of a solid may affect the compressibility of the powder. More on, absorbed moisture may increase the risk of recrystallisation of a disordered or amorphous solid (Bronlund and Paterson, 2004; Elamin et al., 1995). Due to the potential influence of sorbed moisture on both the plastic stiffness and the degree of disorder of the particles, the effect of pre-storage RH (0% and 33% RH) on the properties of the particles was studied.

It was earlier reported (Ahnebeck and Alderborn, 1989) that water adsorbed to the surface of crystalline α -lactose monohydrate particles had a minor effect on the powder compressibility and thus the plastic stiffness of the particles. Also in this study, the pre-storage RH did not affect the P_y of the three crystalline reference powders (Table 1). However, for the amorphous reference powder SDL, the pre-storage of the powder at the higher RH markedly decreased the P_y as reported earlier for spray-dried lactose (Sebhatu et al., 1997). It was proposed that disordered particles absorb moisture that function as a plasticizer and facilitates relative movement of molecules in the amorphous phase and thus decreases the plastic stiffness of the particles.

The series of milled powders (ML) was also pre-stored at 33% RH and thereafter analysed with respect to particle plastic stiffness and AAC. The P_y for the ML10 to ML150 powders were higher compared to the same ML powders pre-stored at 0% RH. The AAC for these ML powders pre-stored at 33% RH were lower than the corresponding ML powders pre-stored at 0% RH, i.e. the powders recrystallised to some degree during pre-storage in the humid atmosphere. It is proposed that this recrystallisation increased the P_y of the ML powders, as supported by the fact that the ML30 powder, that became crystalline after pre-storage at 33% RH, had a similar P_y as the crystalline ML10 powders pre-stored at 0% and at 33% RH. For the powders milled for the longest milling times (ML300 and ML1200), neither P_y nor AAC was affected by the pre-storage RH. Since the SDL particles became softer due to moisture sorption (Table 1) it is possible that also the disordered domains of the milled particles may become somewhat softer after exposure to 33% RH. Thus, the change in particle plastic stiffness due to moisture sorption may depend on a combined effect of hardening due to crystallisation and softening due to moisture sorption in amorphous domains. However, since the relationships between P_y and AAC for the ML powders pre-stored at 0% and at 33% RH nearly coincided (Fig. 4) it is concluded that the moisture content had a limited effect on the plastic stiffness of the disordered particles prepared by milling, i.e. in contrast to the SDL particles. The SDL particles were considered to be fully amorphous and they had a hollow structure. The shell is thus the load bearing part of such a particle and a slight softening of the solid shell may be expressed as a higher degree of particle deformation during compression compared to a dense amorphous particle.

From the compression pressure – porosity relationships, the minimum compact porosity (ϵ_{min}) was recorded for all ML powders (Table 3). The P_y related nearly linearly to the ϵ_{min} which compared favourably with an earlier report (Duberg and Nyström, 1986). Thus, the plastic stiffness of the particles controlled the ϵ_{min} obtained during powder compression.

As a means to study if the elastic properties of the particles were affected by the AAC, the elastic expansion of compacts during the decompression cycle in-die was studied using two measures, the maximum in-die elastic recovery (ER^*_{in-die}) and the elastic modulus (E_M). In general terms, a high degree of elastic recovery during decompression may be detrimental to the mechanical strength of tablets due to risk of capping and lamination (Hiestand, 1997). For the ML powders, the ER^*_{in-die} and the E_M were similar (Table 3) although a tendency to a stiffer compact with increased AAC was obtained. The pre-storage RH had no effect on the measures of elastic expansion. This was again in contrast to the fully amorphous SDL for which an increased pre-storage

RH gave a lower elastic expansion (Table 1). An elastic expansion is probably affected by the mechanical strength of the compact in the die and a high strength may have an inhibitory effect on the elastic expansion. Thus, the interpretation of measures based on compact elastic expansion is, although commonly used, not straight forward. More on, it is reported that the Young's modulus measured by beam bending (Rowe and Roberts, 1996) may increase with a decreased beam porosity. Thus, the effect of AAC on the E_M may also be a result of the decreased ϵ_{\min} . It seems however reasonable and it is concluded that the elastic stiffness of the particles used in this study were to a minor extent affected by the AAC of the disordered particles.

As discussed above, the physical nature of mechanically disordered particles may be complex. One physical model is that particles are composed of two states, an amorphous and one crystalline. Thus, the relationship between P_y and AAC for the milled particles was compared to the relationship between P_y and amorphous content for a series of powders in the form of binary physical mixtures of crystalline particles (CL200) and fully amorphous particles (SDL) in different proportions (the PM powders). For a powder mixture, the P_y represents an indication of the compressibility of the blend which will be a function of the P_y of the respective component and the blend composition. One may speculate that the same situation is applicable to a single disordered particle if such a particle is composed of a blend of amorphous and crystalline domains, i.e. the expressed particle deformation is a function of the deformation of the respective domains. The binary powder mixture may hence be viewed as a model of a two-state disordered particle, i.e. the binary powder consisting of crystalline and amorphous particles (CL200 and SDL particles) is a model of a two-state micro-particle consisting of crystalline and amorphous grains or domains on the nano-scale.

Similar to the ML powders, the P_y of the PM powders decreased with an increasing proportion of SDL in the mixture (Table 2 and Fig. 3). In general the relationship between P_y and degree of disorder for the ML powders and the PM powders showed a clear similarity both for powders pre-stored at 0% RH and at 33% RH. For the former powders, the relationships almost coincided while for the latter, the relationships were somewhat displaced along the P_y -axis, i.e. the PM powders gave a lower P_y . This is explained by the different effect of pre-storage RH on the plastic stiffness of ML particles and SDL particles as discussed above.

Regarding the effect of pre-storage RH for the PM powders with a proportion of SDL powder below about 10% the pre-storage RH did not affect the P_y (Table 2). However, for the PM powders with a proportion of SDL powder above about 10%, the P_y was lower than the same PM powders pre-stored at 0% RH. It is assumed that the theoretical amorphous content of the PM powders pre-stored at 0% RH and 33% RH is similar since the SDL powder appeared to be stable during short-term storage at 33% RH. The reduction in P_y due to moisture exposure is explained by a decreased plastic stiffness of the SDL particles in the PM powders due to moisture sorption, as demonstrated for the reference SDL powder (Table 1).

In summary, for both the PM powders and the ML powders, an increased degree of disorder (due to the presence of discrete amorphous particles or due to milling) gradually lowered the P_y and the relationship between the P_y and the degree of disorder was similar between the two types of powders. A reasonable explanation is that the nature of the milled particles is a two-state system with crystalline and amorphous domains. A difference in behaviour of the ML powders and the PM powders was however the effect of sorbed moisture on their compressibility, which may be a result of the untypical hollow structure of SDL particles.

Regarding the elastic stiffness, as assessed by the $ER^*_{\text{in-die}}$ and the E_M , the effect of degree of disorder was similar for the ML powders and the PM powders pre-stored at 0% RH (Table 3). This also supports that the nature of the milled particles is a two-state system with crystalline and amorphous domains. However, the pre-storage RH caused a slight

increase in the elastic stiffness of the PM powders while the pre-storage RH did not affect the elastic stiffness of the ML powders. Thus, the effect of moisture on the elastic stiffness is consistent with the effect of moisture on the particle plastic stiffness for the two types of powders.

5. Conclusions

In this paper, the effect of milling of lactose particles on their plastic and elastic stiffness was studied. A reduced particle size contributed to an increased plastic stiffness in a linear way while an increased degree of disorder of the particles gave a reduced plastic stiffness in a non-linear way. In contrast to the plastic stiffness, the particle size and the degree of disorder had a limited effect on the elastic stiffness of the particles. The compressibility of the milled particles of different degree of disorder compared favourably with the compressibility of binary physical mixtures of crystalline and amorphous particles in different proportions. Thus, the functional behaviour and the nature of the milled particles could be described as a two-state system composed of crystalline and amorphous domains. It was however observed that sorbed moisture had no effect on the plastic stiffness of milled disordered particles while sorbed moisture reduced the plastic stiffness of fully amorphous particles prepared by spray-drying. This difference in moisture sensitivity between disordered particles prepared by different procedures is explained by the hollow structure of the spray-dried amorphous particles in contrast to the dense milled particles.

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