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Research paper

Compaction of crystallographic forms of pharmaceutical granular lactoses. I. Compressibility

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Abstract

Physico-chemical properties of a substance including the compaction behaviour are directly connected with the crystalline structure. The aim of this work is to compare the compaction behaviour in a group of excipient and in this first part, to display the influence of lactose structures on the compressibility.

α-Lactose monohydrate (LαM), anhydrous β-lactose (LβA), anhydrous α-lactose (LαA) and partly amorphous lactose (FF) were compressed using instrumented presses to investigate the densification behaviour under pressure. Force–displacement curves were associated to two energy parameters, specific cycle energy and specific expansion energy. This approach was used to class the four lactose species. It is possible to differentiate three groups with the specific energy cycle, FF, LαA/LβA and LαM in decreasing order of this energy. At the same time, the values of specific expansion energy are relatively low for FF and LαA contrary to LαM and LβA.

Then, Heckel's plots were obtained with two compact geometries and the mean yield pressure was calculated from the in-die-method and the out-of-die-method. Two lactoses seem to differ, LαM appears to be the most ductile whereas LαA is more brittle than the others.

Finally, it is concluded, that in the case of lactoses, pseudopolymorphism seems to affect the compressibility more than anomerisation or partial amorphisation.

Keywords: Lactoses; Crystallographic forms; Compressibility; Yield pressure; Force–displacement profile; Energy parameters

1. Introduction

In solid state, a crystalline solid is characterized by a regular and indefinite repetition of unit cells in three dimensions in space. The unit cell has a definite shape and specific properties of symmetry [1]. Because different crystalline forms differ in crystal packing, there are significant differences in their derived properties for pharmaceutical applications such as compactibility, wettability, solubility, dissolution rate, and then bioavailability. These differences which exist initially are directly linked with the primary characteristics of the crystals, i.e. the crystalline structure, internal (polymorphism, pseudopolymorphism, amorphous state) and external (habitus, facies) [2]. That is why the knowledge of the crystalline structure of the granular systems used in pharmacy is today essential. This set of problems is valid for active drugs and for excipients (for example, in the issue of dual sourcing). In this study, lactose was chosen because it is one of the most used excipients in pharmaceutical dosage forms and many grades are commercially available.

Lactose is a disaccharide, which can exist, in different forms in solid state. It is composed of one galactose unit and one glucose unit. Because of an asymmetric carbon due to cyclization of glucose, lactose can exist in an α or a β form which are two anomeric forms (Fig. 1). Depending on the manufacturing conditions, solid lactoses obtained are α-lactose monohydrate (LαM), anhydrous α-lactose (LαA), anhydrous β-lactose (LβA), α/β compounds, partly amorphous lactose (FF) or amorphous lactose. LαA and LβA are two anomer; LαA and LαM are pseudopolymorphs. In general, lactose monohydrate is an α form which could contain amorphous lactose and anhydrous lactose is a β form with sometimes LαA [3,4]. In pharmacopoeias, lactoses are

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Nomenclature

ε	porosity of the compact
FF	partly amorphous lactose
LαA	anhydrous α-lactose
LαM	α-lactose monohydrate
LβA	anhydrous β-lactose
Py_A	apparent mean yield pressure obtained from Heckel plot by in-die-method
Py_B	mean yield pressure obtained from Heckel plot by out-die-method
Py_e	$1/Py_e = 1/Py_A - 1/Py_B$
E_1	cycle energy (J)
E_2	expansion energy (J)
E_{1sp}	specific cycle energy (J g^{-1})
E_{2sp}	specific expansion energy (J g^{-1})

commonly differentiated by their moisturizing rather than the crystalline structure.

Despite the fact that it is widely used, there are few reports on structural properties of lactose. LαM and LβA crystallize in monoclinic system. Their space group are $P2_1$. The differences are in the crystal lattice volume and dimensions [5,6]. In the LαM, water molecules are inserted between disaccharides and are linked with them by hydrogen bonds [7]. LαA differs by the absence of water molecules in the disaccharide structure.

These various lactose forms show different compaction behaviour [8–11]. It was generally concluded that fragmentation predominate in consolidation of crystalline lactose [11], when amorphous lactose is considered to be more plastic [12,13]. Some differences in consolidation have been also shown between β-lactose and LαA [14].

This work proposed to study the variability of compressibility in one widely used family of excipient, lactose. Two approaches are proposed. First, lactoses were compared with the use of energetic parameters. And then, Heckel's model [15,16] was applied to four lactoses.

2. Materials and methods

2.1. Materials

The materials used were four lactoses: LαM (EFK®, DMV GW960092, Germany); LβA (DCL21®, DMV GW940062, Germany); LαA (Sheffield Products, MPP669641-93, US); FF (crystalline particles of α-lactose monohydrate 'glued' by amorphous lactose obtained by spray-drying [12]) (Fast-flo®, Foremost 8596091762, US). From all raw lactoses, a fraction between 100 and 500 μm was obtained by sieving in order to minimize the size effect. Two sieves with a screen opening size of 100 and 500 μm were used under vibration for 15 min (vibrator sieve with an amplitude of 70, Tamisor, France). Depending on the lactose, the collected fraction could consist of aggregates of polycrystals (e.g. anhydrous lactoses and lactose FF). Before use, these fractions were stored at 50 ± 4% of relative humidity for at least 3 days (saturated solution of $Na_2Cr_2O_7$, $2H_2O$ put in a close space). The size distributions in volume were obtained by laser diffraction (Coulter LS 230) in conditions of validity of Fraunhofer's theory. Fig. 2 shows the size distribution in volume % after sieving for each fraction. The apparent particle density of each sieve fraction was measured by helium pycnometry (Acupyc 1330, Micromeritics, Norcross). The bulk densities were obtained from the mass of powder used to fill manually a defined die volume which has a normalized value of 1 cm^3 (diameter of 1.13 cm and height of 1 cm). The surface area of the powders was determined by gas adsorption technique (Coulter SA 3100) based on the BET adsorption theory of a gas (nitrogen) on a solid surface at reduced temperature. Table 1 summarizes the main characteristics of the four lactoses.

2.2. Formation of compacts

2.2.1. Parallelepipedical compacts

An instrumented hydraulic press (Perrier Labotest, Montrouge, France) equipped with three-dimensional demountable die (40 × 6 mm^2) was used to form parallelepipedical compacts under a constant compaction speed of 0.1 mm s^{-1}. The surfaces of the die and punches were

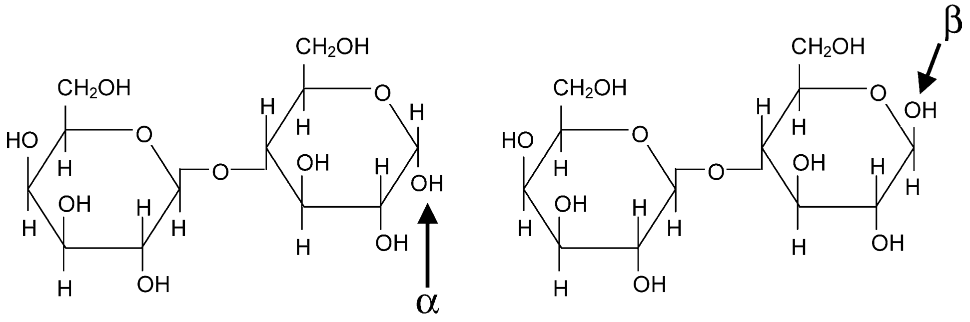

Fig. 1. Structural formula of α-lactose and β-lactose.

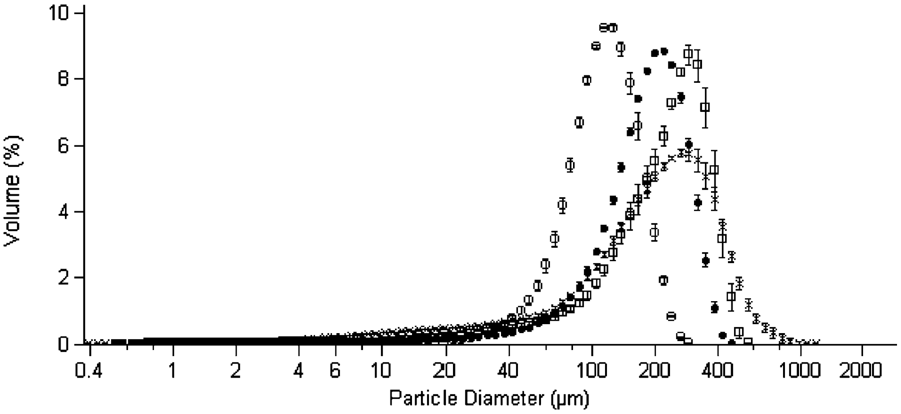

Fig. 2. Size distribution in volume % obtained by laser diffraction for lactose fractions of 100–500 μm. Key: (●) LαM, (×) LαA, (□) LβA, (○) FF.

lubricated with magnesium stearate (NF-BP-MF2 039445, Akcros Chemicals v.o.f., Netherlands). The mass of powder used was calculated for each lactose from the apparent particle density to have a 5 mm high compact at zero porosity (about 2 g for each lactose manually filled into the die). The applied forces varied between 10 and 50 kN in increments of 10 kN, corresponding to compaction pressures between 42 and 210 MPa.

2.2.2. Cylindrical compacts

The powders were mixed with 0.5% by weight of magnesium stearate (NF-BP-MF2 039445, Akcros Chemicals v.o.f., Netherlands) in a Turbula mixer (type T2C, Willy A Bachofen, Basel, Switzerland) at 50 rpm for 5 min (100 g of powder in a 550 ml vessel). An eccentric instrumented Frogerais OA tabletting press with a compaction speed of about 80 mm s^{-1} (speed when the punch enter the die) was used to form cylindrical compacts. The compression forces were measured with sensors at the upper and the lower punches. The accuracy of the force measurements was 10 N. The forces were calibrated using an external extensiometric gauged line. The displacement sensors mechanically hung on the upper and lower punches were calibrated using wedges with a height exactly known. The accuracy of the punches displacement was 0.001 mm. The sampling rate was 1000 Hz. The elastic deformation of the punches was 0.002397 mm kN^{-1} (this factor of elasticity was taken into consideration when the Heckel model was used). The volume of the die was constant, 1 cm^3 (section of 1 cm^2 and height of 1 cm) and it is filled manually. The compaction pressures were 40, 80, 120, 160 and 210 MPa. The forces applied and the punch displacements were recorded using PECAMEC software (4.1 version, 2002, J2P instrumentation, France); the force–displacement profile and the ejection forces were obtained (for the ejection, this is the same sensor than those used to record the compaction force at the lower punch).

After compaction, the compacts were stored for at least 3 days at 50 ± 4% of relative humidity. This humidity was generated in a close space with a saturated solution of $Na_2Cr_2O_7$, $2H_2O$ [17]. The compacts were measured with a micrometer (Digimatic 293, Mitutuyo, Japan, with a resolution of 1 μm) after total elastic recovery and exactly weighted on an analytical balance (Sartorius BP 2215, Germany). The porosity ε of the tablet was calculated from the dimensions and the weight of the compact according to:

$$\varepsilon = 1 - \frac{\text{apparent density}}{\text{apparent particle density}} \tag{1}$$

Table 1
Physical properties and characteristics of the lactose powders (values are expressed as mean ± standard deviation)

Substance	Apparent particle density (g cm^{-3})[a]	Powder bulk density (g cm^{-3})[b]	Mean particle size (vol.%) (μm)[c]	Specific surface area (m^2 g^{-1})[d]
α-Lactose monohydrate, LαM	1.5366 ± 0.0004	0.794 ± 0.006	190.4 ± 83.8	0.147 ± 0.001
Anhydrous β-lactose, LβA	1.5669 ± 0.0003	0.674 ± 0.008	228.5 ± 113.3	0.259 ± 0.010
Anhydrous α-lactose, LαA	1.5584 ± 0.0005	0.583 ± 0.009	225.0 ± 148.4	0.360 ± 0.006
Partly amorphous lactose, FF	1.5350 ± 0.0006	0.627 ± 0.006	119.0 ± 45.6	0.199 ± 0.002

[a] Helium pycnometry (Acupyc 1330, Micrometics); $n = 3$.

[b] $n = 60$.

[c] Laser diffraction granulometry (Coulter LS 230, $\lambda = 750$ nm); $n = 3$.

[d] Gas adsorption, BET method (Coulter SA 3100); $n = 3$.

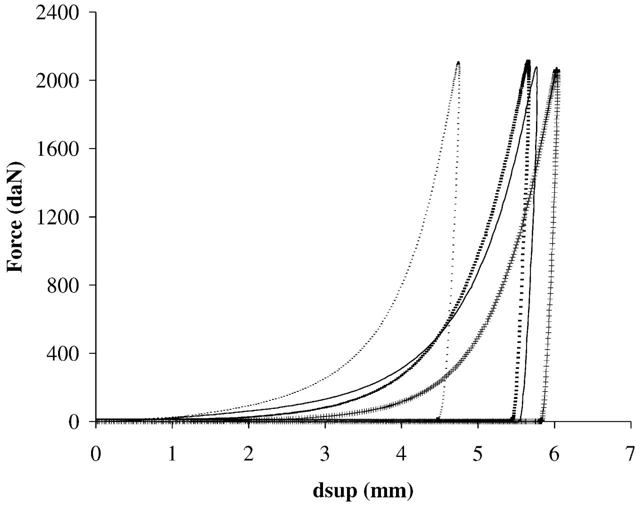

Fig. 3. Compression cycle (force–displacement curve) of lactoses for compaction pressure of about 210 MPa. Key: (···) LαM, (+++) LαA, (- - -) LβA, (—) FF.

3. Results and discussion

3.1. Compression cycles

Compression cycles or force–displacement curves exhibit three steps as shown in Fig. 3. The first one corresponds to a rearrangement and a packing of the powder in the die. The second phase, corresponds to a fragmentation and/or a plastic deformation of the powder particles. When the applied pressure is released (last phase), the compact may more or less instantaneously recover elastically.

The force–displacement profiles obtained with the instrumented Frogerais OA press for the different lactoses (internal lubrication with 0.5% of magnesium stearate) are shown in Fig. 3. The rearrangement step is the lowest for LαM when the volume reduction of LαA is more important. This could be linked with the differences observed in the bulk densities for the various lactoses.

3.2. Energy measurements

The areas associated to the compression cycles could be expressed as energies [18]. The area under the curve corresponds to the compression work or cycle energy E_1 that is the energy used to rearrangement, fragmentation, and/or ductile deformation giving rise to interparticulate bonding. The integral calculus was made between the displacement corresponding to the beginning of the increase of the force and the maximal displacement of the punch. E_2, expansion energy is the energy lost by instantaneous elastic recovery of the compact during pressure releasing. The integral calculus was made between the displacement corresponding to the return of the force to zero and the maximal displacement. The compression conditions were normalized by using the same volume of powder, 1 cm^3, but for an equal volume, the mass used during compaction is different for each lactose (Table 2). In order to compare lactoses, each energy measured during compaction, is divided by the mass of the compact. Then, the values are expressed as specific energy E_{sp} in J g^{-1}. The comparison of the raw energies and their specific values shows that the hierarchy is not the same in the two cases. For the cycle energy, there is a reversal between LαM and LαA, whereas, in the case of the expansion energy, LαM and LβA are reversed. This justified the use of a specific energy to be able to compare with accuracy the systems one to an other.

Figs. 4 and 5 plot the E_{1sp} and the E_{2sp} values versus the maximal pressure of compaction, respectively. The values of E_{1sp} for the pressures of 40, 80 and 120 MPa, are almost in the same order for the different lactoses (around 5–13 J g^{-1}), except for FF. For higher pressures of compaction (160 and 210 MPa), the specific energy E_{1sp} (Table 2) becomes lower for LαM (below 20 J g^{-1}) than for the other lactoses and it is possible to distinguish three groups: FF, LαA/LβA and LαM. It is also remarkable that the evolution of E_{1sp} on the compaction pressures range is linear for all the materials and it may be possible to classify the lactoses with the slopes of this representation. A similar linear evolution have been observed with apatitic phosphate powders [18].

For all products, the phase of decompression on the force–displacement cycle is close to a vertical line for lower pressure of compaction (40 MPa) which is shown by a zero E_{2sp} value for LαA, FF and LβA. It means that the elastic recovery is logically limited for this level of pressure, except for LαM ($E_{2sp} = 0.502 \pm 0.003$ J g^{-1}). Above 80 MPa for LαM and 160 MPa for the other lactoses, this instantaneous elastic recovery is no longer negligible

Table 2
Characteristic energies of lactoses calculated from the compression cycles at 210 MPa on the Frogerais OA tabletting press ($n = 12$; values are expressed as mean ± standard deviation)

	Powder mass (g)	Cycle energy, E_1 (J)	Specific cycle energy, E_{1sp} (J g^{-1})	Expansion energy, E_2 (J)	Specific expansion energy, E_{2sp} (J g^{-1})	E_{2sp}/E_{1sp}
LαM	0.789 ± 0.006	15.1 ± 0.5	19.1 ± 0.5	2.2 ± 0.1	2.8 ± 0.1	0.148
LβA	0.670 ± 0.007	16.6 ± 1.0	24.7 ± 1.2	2.1 ± 0.2	3.1 ± 0.2	0.128
LαA	0.583 ± 0.007	13.6 ± 1.0	23.3 ± 1.4	1.1 ± 0.1	1.8 ± 0.2	0.080
FF	0.626 ± 0.005	18.6 ± 0.9	29.7 ± 1.1	1.3 ± 0.1	2.1 ± 0.2	0.071

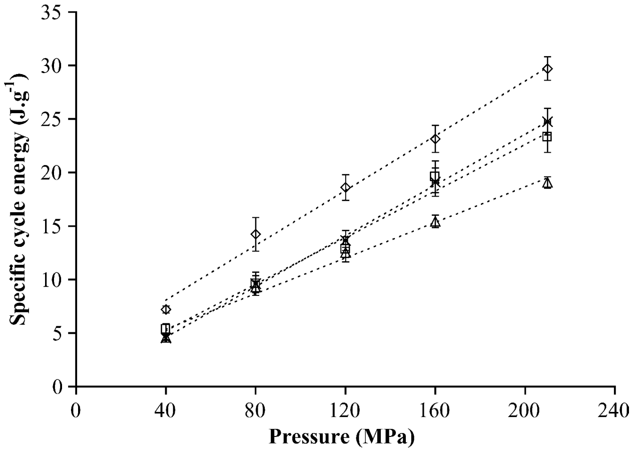

Fig. 4. Evolution of specific cycle energy (E_{1sp}) of cylindrical compacts versus compaction pressure(LαM: $y = 0.0834x + 2.0058$, $R^2 = 0.9887$; LαA: $y = 0.1090x + 0.8380$, $R^2 = 0.9854$; LβA: $y = 0.1188x - 0.1691$, $R^2 = 0.9987$; FF: $y = 0.1283x + 2.9260$, $R^2 = 0.9932$). Key: (△) LαM, (□) LαA, (×) LβA, (◇) FF.

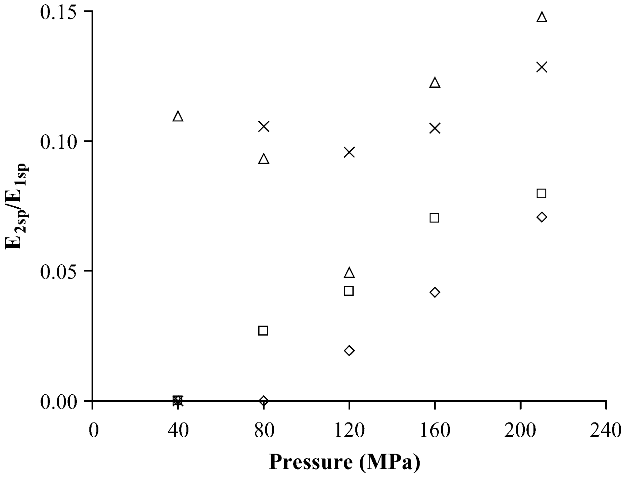

Fig. 6. E_{2sp}/E_{1sp} ratio (specific expansion energy divided by specific cycle energy) versus compaction pressure. Key: (△) LαM, (□) LαA, (×) LβA, (◇) FF.

(Fig. 5). E_{2sp} values increase with the enhancement of the pressure of compaction starting at a pressure threshold which depends on the type of lactoses.

The E_{2sp}/E_{1sp} ratio could be studied to characterize the behaviour during compaction [18]. This ratio expresses the distribution of the total compression energy into instantaneous elastic recovery energy and compaction energy. It is an index of the ability of the product to use the given energy of compaction in order to establish permanent interparticulate bonding. For a same E_{1sp} value, a higher ratio value means a higher loss of energy into elastic recovery. The ratio values are reported in Table 2 for a compaction pressure of 210 MPa and plotted versus the applied pressures in Fig. 6. The values of E_{2sp} are relatively low for FF and LαA and the specific expansion energy represents about 7% of the specific cycle energy at 210 MPa. For LαM and LβA, the impact is more important since E_{2sp} represents more than 10% of the cycle energy for these products at 210 MPa. This confirms the important loss of energy into instantaneous elastic recovery for LαM (above a pressure of 40 MPa) and LβA (for pressures above 80 MPa).

The relatively high elastic recovery can be directly linked with the values of maximal ejection force which are more important for LβA especially beyond 120 MPa (Fig. 7). This elastic recovery has a tendency to hold the compact in the die. This is less evident for LαM except for a pressure of 40 MPa.

As the instantaneous elastic recovery after unloading is linked with the capping tendency [19], the approach with energy measurements can be used to class the products and to predict the capping phenomenon after compaction. In view of the compressibility results obtained with lactoses, LβA and LαM seems to be more prone to cap at high

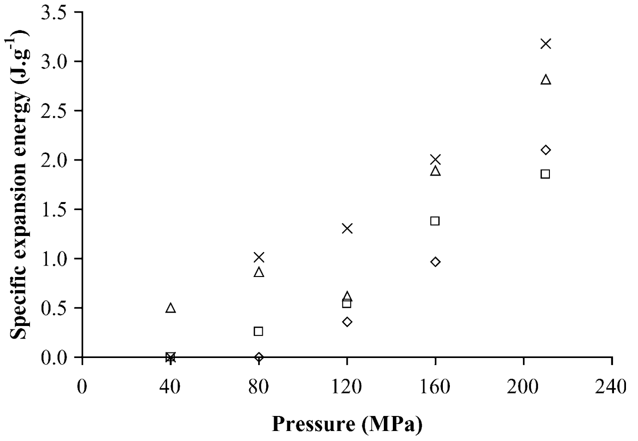

Fig. 5. Evolution of specific expansion energy (E_{2sp}) of cylindrical compacts versus compaction pressure. Key: (△) LαM, (□) LαA, (×) LβA, (◇) FF.

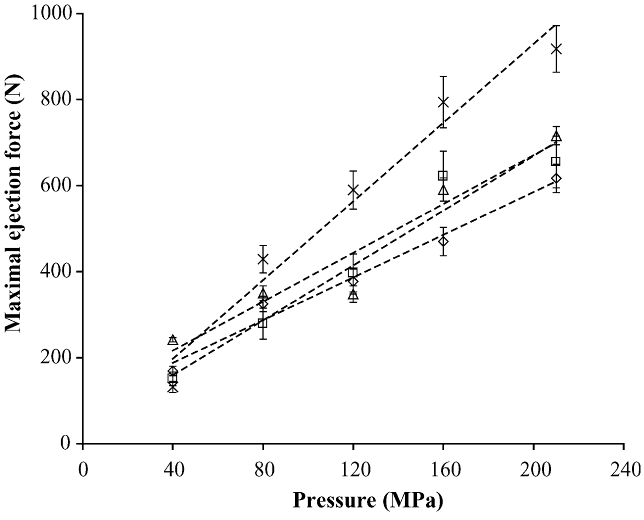

Fig. 7. Maximal ejection force of lactose cylindrical compacts obtained during compaction versus compaction pressure. Key: (△) LαM, (□) LαA, (×) LβA, (◇) FF.

compaction pressures than the others. Moreover, it seems that the specific cycle energy increases linearly with the compaction pressure applied (in a given range of pressures).

3.3. Heckel plots

Heckel plots give information about the compressibility behaviour of powders. They are defined by the following equation [15,16]:

$$\ln(1/\varepsilon) = b \times P + A \qquad (2)$$

where ε is the porosity of the compact, P is the compressional pressure and b, A are constants.

The Heckel plots of the different lactoses (for the two types of compacts) are shown in Fig. 8a and b. All the lactoses show a non-linear step corresponding to rearrangement and/or fragmentation for the lowest pressures (below 50 MPa) and then a linear curve imputed to indicate plastic deformation. The reciprocal of the slope (1/b) in the linear zone is classically defined as the apparent mean yield pressure corresponding to plastic deformation Py_A (in-die-method) or the mean yield pressure Py_B (out-of-die-method, after totally elastic recovery). When there is a lake of accuracy on the linear zone (i.e. correlation coefficients not close to 1), Sonnergaard [20] suggests to estimate the apparent yield pressure as R^2/b. In our case, the correlation coefficients on the linear zone were higher than 0.99 (higher than 0.992 in the case of the parallelepipedical compacts and higher than 0.997 for the cylindrical compacts), then,

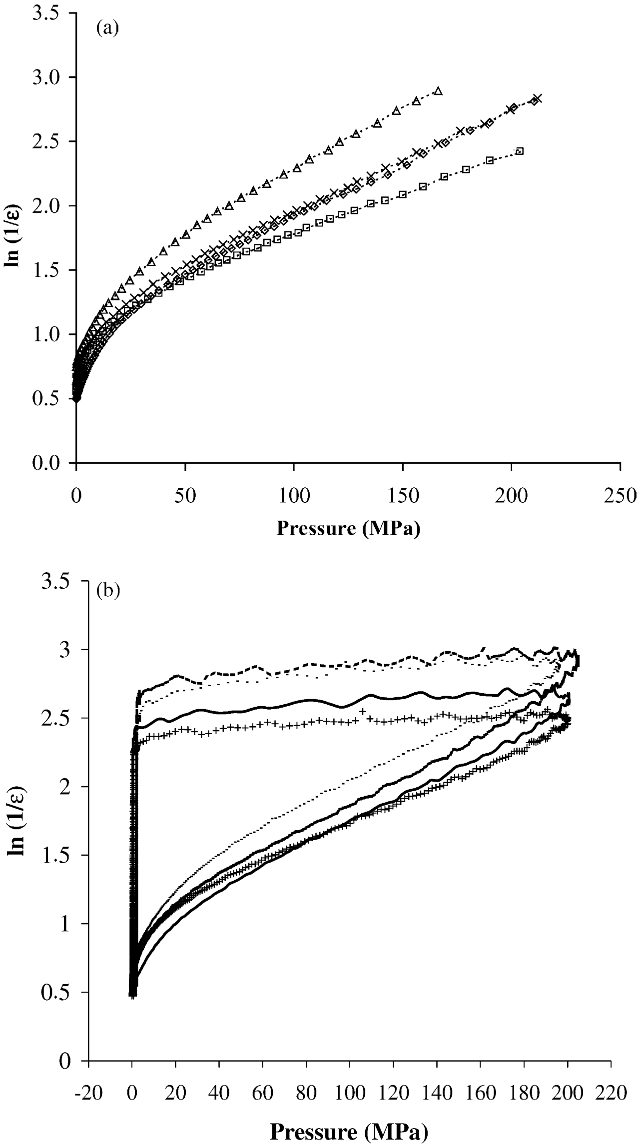

Fig. 8. Heckel's plot with the in-die-method (compaction pressure: 210 MPa). (a) Parallelepipedical compacts, key: (△) LαM, (□) LαA, (×) LβA, (◇) FF. (b) cylindrical compacts, key: (···) LαM, (+++) LαA, (- - -) LβA, (—) FF.

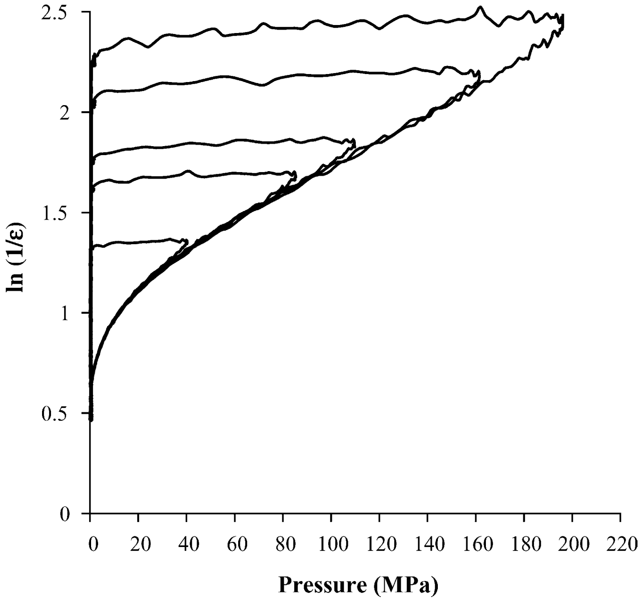

Fig. 9. Superposition of LαA's Heckel plots obtained for increasing compaction pressure (cylindrical compact).

Table 3
Apparent mean yield pressure and mean yield pressures in MPa obtained from Heckel plots of the two compact geometries using the in-die-method and the out-of-die-method (values are expressed as mean ± standard deviation)

	Parallelepipedical compact (Py in MPa)			Cylindrical compact (Py in MPa)		
	Py_A ($n = 8$)	Py_B	Py_e	Py_A ($n = 12$)	Py_B	Py_e
LαM	105 ± 2	208	212	125 ± 1	200	333
LαA	151 ± 3	238	413	151 ± 2	204	581
LβA	125 ± 1	217	295	121 ± 1	182	361
FF	120 ± 1	222	261	127 ± 1	208	326

Py_A, apparent mean yield pressure obtained from Heckel plot by in-die-method in the range of 50–210 MPa for LαA, LβA, FF compacts and in the range of 50–170 MPa for LαM parallelepipedical compacts. Py_B, mean yield pressure obtained from Heckel plot by out-of-die-method (obtained with 15 compacts compacted in the range of 50–210 MPa for LαA, LβA, FF compacts and in the range of 50 and 170 MPa for LαM parallelepipedical compacts). Py_e, $1/Py_e = 1/Py_A - 1/Py_B$.

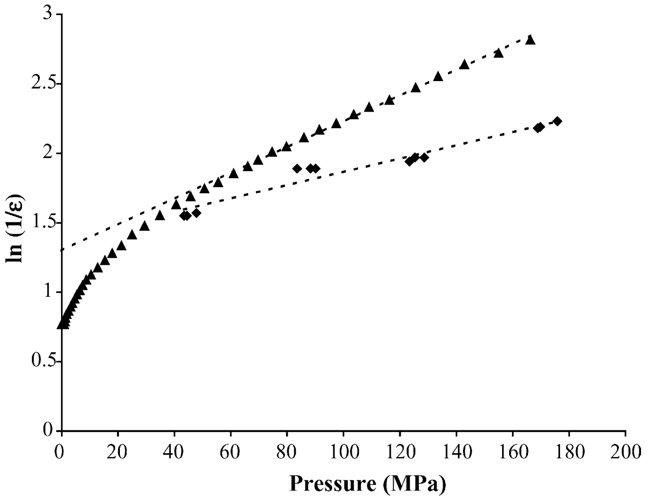

Fig. 10. Heckel plots obtained from the in-die-method (▲) and the out-of-die-method (◆) for LαM parallelepipedical compacts.

$1/b$ is used instead of R^2/b to calculate Py_A. The Py values are calculated in the linear zone of the plot between 50 and 210 MPa (170 MPa for LαM parallelepipedical compacts). This range of pressure is used to have a good precision on the Py values. It should be noted that the superposition of the Heckel plots for an increasing compaction pressure leads to Py values highly comparable for a same product, as shown in Fig. 9 for LαA. The values of the Py obtained for the two different kinds of compacts (parallelepipedical and cylindrical) and for the four studied lactoses are presented in Table 3. For the two compact geometries, the Py_A values are in the same order except for parallelepipedical compacts of LαM. The obtained Py values, depending on the lactose, are in the range of 120–150 MPa, in good accordance with compressional behaviour of lactoses described previously in Refs. [13,21]. These values confirm that lactoses have an intermediate behaviour and consolidate primarily by particle fragmentation. The differences observed for the two kinds of compacts may be explained by the geometry of the compact [22], the compression speed [23], and more, the internal lubrication in cylindrical compacts, even in little proportions which could modified the Py values [24]. The lowest Py values were obtained by using LαM and the parallelepipedical geometry. The difference of the Py between the two geometries is the most important for LαM. This could be due to a higher sensitivity of LαM to compaction speed. Lactoses have an intermediate behaviour between totally plastic products and brittle products. Now, if we consider only this intermediate product category, LαM seems to be slightly more ductile than other lactoses. It is in line with conclusions of Humber-Droz et al. [21] who found that crystalline α-lactose monohydrate has the highest plasticity. At the opposite, LαA is slightly more brittle than the other lactoses. It is in line with the results of Wong et al. [25] on monocrystals which showed that the anhydrous form is very brittle but it undergoes brittle fracture much more readily and at lower stresses than the monohydrate.

In regard to the results, it seems that an anomeric transformation LαA/LβA or the presence of amorphous lactose LαM/FF have not many impacts on the brittle/ductile behaviour. On the other hand, the consequence of pseudopolymorphism, LαA/LαM, seems to be more important especially for the parallelepipedical beams. Such a difference may be due to the fact that during dehydration, the removal of water of crystallisation results in the partial disruption of the crystalline order [25,26]. This process may introduce cracks in the crystal [9] and then explain the differences in the degree and the nature of the fragmentation mechanisms of the two crystal types.

Otherwise, the values obtained from the in-die-method (Py_A) are logically lower than those obtained from the out-of-die-method (Py_B) because of the visco-elastic recovery [27]. In the case of the out-of-die-method, the Heckel plot is obtained from experimental porosities of compacts obtained at compaction pressures between 50 and 170/210 MPa. Fig. 10 shows as an example the plots obtained in both conditions for LαM parallelepipedical compacts. It is possible to calculate Py_e ($1/\mathrm{Py}_e = 1/\mathrm{Py}_A - 1/\mathrm{Py}_B$) which describes the tendency of a material to recover visco-elastically (Table 3) [28]. Py_e which is the reflect of a time-dependent property characterizes the visco-elasticity of a material. Py_e is the reciprocal of the difference of the reciprocal Py values obtained from the in-die-method and from the out-of-die-method. The lowest values were obtained with LαM ($\mathrm{Py}_e = 212$ MPa for parallelepipedical compact) and are comparable with those of starches (Py_e between 150 and 196 MPa [28]) which imply for a visco-elastic tendency of LαM. Otherwise, LαA presents

Table 4
Estimation of the differences between the energetic parameters values and estimation of the differences between the Heckel parameters for the lactose forms studied

	E_{1sp}	E_{2sp}	E_{2sp}/E_{1sp}	Parallelepipedical compact			Cylindrical compact		
				Py_A	Py_B	Py_e	Py_A	Py_B	Py_e
LαM-LαA	+	+	+	++	++	++	+	−	+
LαM-FF	++	+	++	+	+	−	−	−	−
LαA-LβA	−	+	+	+	+	++	+	+	+

Key: (−) small difference, (+) large difference, (++) very large difference. Energetic parameters calculated from the compression cycles at 210 MPa.

the lowest visco-elastic recovery ($Py_e = 413$ and 581 MPa for the two geometries). These statements are valid for the compaction conditions considered, since the values for Py_e are dependent on the degree and on the rate of densification.

4. Conclusion

This work has shown the impact of the crystalline structure of lactose on the properties during compaction.

The calculation of energies using the force–displacement curves is a means to understand the use of the energy by the lactoses during compaction. These energies are supplemented by the ratio E_{2sp}/E_{1sp} which expresses the sharing out of the total compaction energy into instantaneous elastic recovery and compaction cycle energy. Then, the specific expansion energy which characterizes the instantaneous elastic recovery, can be linked to the capping tendency.

This was linked with the Heckel's plots and the mean yield pressures calculated from two methods. All these parameters were used to classify the different lactose species.

Looking at energy measurements, the degree of crystallinity (amorphic conversion) should highly influence the energy parameters and not the Heckel results (Table 4). More, the pseudopolymorphism and the anomery should influence the Heckel parameters (with a little superiority for pseudopolymorphism). This comment seems to be valid especially for the parallelepipedical compacts.

In a second part, we will study the impact of crystalline structure on the compactibility of lactoses by investigating the mechanical properties of compacts.

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