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European Journal of Pharmaceutics and Biopharmaceutics 58 (2004) 577–586
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Compaction of crystallographic forms of pharmaceutical granular lactoses. II. Compacts mechanical properties

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Received 28 August 2003; accepted in revised form 21 April 2004

Available online 11 June 2004

Abstract

It is well known that the choice of the crystal form affects the physicochemical properties such as compaction behaviour. In this work, the mechanical properties of compacts obtained from compaction of lactoses by using a micropress prototype are calculated. Tensile strength, Young's modulus, toughness and Brinell hardness were measured and used to compare the various crystalline forms: α-lactose monohydrate (LαM), anhydrous β-lactose (LβA), anhydrous α-lactose (LαA) and partly amorphous lactose (FF). With all the mechanical properties measured, the lactoses could be differentiated. Then, the specific energy of failure G_{IC}^{*} was obtained from the toughness and the Young's modulus for each lactose. LαM showed small specific energy of failure due to its low toughness which is not balanced by its Young's modulus. The highest values were obtained with the two anhydrous forms, LαA and LβA. Finally, these mechanical properties were linked with general compaction behaviour and cohesive energy density which is a characterization at a molecular level.

Keywords: Lactoses; Crystallographic forms; Compactibility; Tensile strength; Young's modulus; Brinell hardness

1. Introduction

It is well known that physical and physicochemical properties of a substance such as mechanical properties, solubility or stability, etc. are directly linked with the characteristics of the corresponding crystals, i.e. the crystalline structure [1]. Most of drugs can exist in different polymorphic forms [2], but, even isomorphic forms can have different crystal habit, and the choice of the crystal habit can also affect the physical properties of the product. This can be observed with the different forms of lactose: α-lactose monohydrate, anhydrous β-lactose, anhydrous α-lactose or partly amorphous lactose. In the first part of this work [3], the effect of the type of lactose on compressibility was studied with the use of Heckel's model and compaction energy parameters. It appears that compressibility is affected by the nature of lactose but much more by pseudopolymorphism than by anomerisation or partial amorphisation.

The aim of this second study is to evaluate the mechanical properties of parallelepipedical compacts. Tensile strength, Young's modulus, toughness and Brinell hardness can be measured using a micropress prototype [4]. From these mechanical properties, the general compaction behaviour was characterized, the specific energy of failure was calculated, and the cohesive energy density (CED) was also obtained.

2. Materials and methods

2.1. Materials

The materials used in this study were four lactoses: α-lactose monohydrate (EFK®, DMV GW960092, Germany) LαM; anhydrous β-lactose (DCL21®, DMV GW 940062, Germany) LβA; anhydrous α-lactose (Sheffield Products, MPP669641-93, USA) LαA; and partly amorphous lactose (crystalline particles of α-lactose monohydrate 'glued' by amorphous lactose obtained by spray-drying) (Fast-flo®,

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doi:10.1016/j.ejpb.2004.04.005

Nomenclature

FF	partly amorphous lactose
LαA	anhydrous α-lactose
LαM	α-lactose monohydrate
LβA	anhydrous β-lactose
a	notch length (toughness measurement)
CED	cohesive energy density
D	indentor diameter
d	diameter of the indentation imprint
d_{cr}	size of brittle–ductile transition
E	Young's modulus
E^*	reduce Young's modulus
F	maximal load applied in microindentation and Young's modulus measurement
F_r	maximal load applied in toughness measurement and tensile strength measurement
G_{IC}	specific energy of failure
G^*_{IC}	reduce specific energy of failure
H_0	Vickers hardness extrapolated at zero porosity
K_{IC}	critical stress intensity factor
P	Brinell hardness
p	distance between the two support of the three point single beam test
P_y	mean yield pressure obtained from Heckel plot
δ	central deflexion in the three point single beam test
ε	porosity of the compact
σ_{rf}	tensile strength

Foremost 8596091762, USA) FF. They are listed in Table 1 with their characteristics and some parameters obtained in the previous paper [3]. A granular fraction between 100 and 500 μm was obtained by sieving and was stored at 50% relative humidity (r.h.) for at least 3 days. Of these powders about 2 g, a mass suitable to obtain zero porosity at a theoretical compact thickness of 5 mm, were used to obtain compacts using an instrumented hydraulic press (Perrier Labotest, Montrouge, France) at maximum pressures between 42 and 210 MPa. These compacts were stored for at least 3 days at 50% r.h.

2.2. Compacts porosity

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).

Table 1
Characteristics of sieved lactoses

Substance	Apparent particle density (g cm^{-3})	Mean particle size (μm)	Specific surface area (m^2 g^{-1})	P_y (MPa)[a]
α-Lactose monohydrate (LαM)	1.5366 ± 0.0004	190.4	0.147 ± 0.001	105 ± 2
Anhydrous β-lactose (LβA)	1.5669 ± 0.0003	228.5	0.259 ± 0.010	125 ± 1
Anhydrous α -lactose (LαA)	1.5584 ± 0.0005	225.0	0.360 ± 0.006	151 ± 3
Partly amorphous lactose (FF)	1.5350 ± 0.0006	119.0	0.199 ± 0.002	120 ± 1

[a] Mean yield pressure from compaction to parallelepipedical compact.

The porosity ε of the compacts was calculated from the dimensions and the weight of the compact according to Eq. (1):

$$\varepsilon = 1 - \frac{\text{apparent density}}{\text{apparent particle density}} \quad (1)$$

Other works performed in the laboratory on cylindrical compacts made with these four lactoses has shown that the calculated porosity and the porosity measured by porosimetry were almost the same (data not shown).

2.3. Measurement of mechanical properties

Mechanical properties were studied on parallelepipedical compacts after total elastic recovery as described in part I [3], together with the calculation of the mean yield pressure of plastic deformation calculated after ejection, P_{yB}. A micropress prototype (No. MCC0300-01) conceived by DIGIPHARM [4] and developed for pharmaceutical application in our laboratory was employed. The instrumentation of the micropress allows easily to draw the force–displacement curves from raw data. It is possible to apply forces in a range of 0–500 N. The resolution of the force transducer is 0.01 N and its nominal sensitivity is 2 mV V^{-1}. The forces were calibrated using an external extensiometric gauged line. The accuracy of the displacement transducer is ±0.5 μm and its resolution is 0.05 μm. The acquisition frequency could be set with an accuracy of 0.4 s^{-1} [4]. The elastic deformation of the micropress was evaluated for all the range of pressures used and was taken into account before using the gross data.

2.3.1. Three point single beam test

The compacts were placed and centred (using a XY micrometric table) on the three point system as shown in Fig. 1 and stressed using a 2 mm flat punch at constant velocity of 0.050 mm min^{-1}. The punch displacement

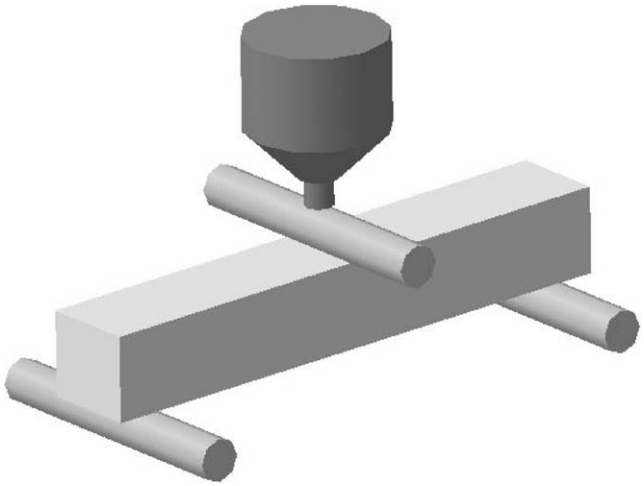

Fig. 1. Schematic representation of the three point single beam test.

and the force applied were recorded with a 0.1 s^{-1} acquisition frequency. In the case of lactoses, the speed of loading was 0.050 mm min^{-1}, the maximal depth of the punch was 0.500 mm and the relaxation time was 1 s.

2.3.1.1. Evaluation of the Young's modulus. To obtain only the elastic response of the compact, three loading/unloading cycles were applied. The maximum loading under these conditions was chosen to be lower than the loading which causes compact fracture. The Young's modulus, E (GPa), for a defined porosity level of the compact was calculated using the following equation [5]

$$E = \frac{Fp^3}{4\delta h^3 l} \tag{2}$$

where F is the load applied, p is the distance between the two supports (34.12 mm), δ is the central deflexion and h, l are the thickness and the width of the compact, respectively.

2.3.1.2. Measurement of the tensile strength. The load, F_r, that causes the compact fracture was also recorded and used to calculated the tensile strength σ_r (in MPa) by applying Eq. (3) [6]

$$\sigma_r = \frac{3F_r p}{2lh^2} \tag{3}$$

2.3.1.3. Measurement of the toughness as critical stress intensity factor, K_{IC}. The three point single beam test was applied on compacts with a calibrated V notch of 1 mm. Previous works performed in the laboratory on partly amorphous lactose (Fast-flo®) has shown the importance to make the notch after compaction rather than during compaction. Indeed, when partly amorphous lactose was compacted using a punch with a V form, like those used for dividable tablet, the tensile strength calculated for the compacts with a notch were higher or equal than that obtained for compacts without the notch (data not shown). This is in contradiction with the fundamentals of solid mechanic and crack propagation. A possible explanation could be a local concentration of the stresses around the notch during the compaction, followed by further densification inside the granular system near or in continuation of the V notch. The scanning electron microscopy (SEM) observation of the upper side of a compact and of the surface of the notch (Fig. 2a and b) seems to confirm such a hypothesis. Therefore, the notch was made after compaction with a specific equipment developed in the laboratory, which consists of a little circular saw of known dimensions and a micrometer to control the width of the notch. The rate of sawing the notch may also be adjusted considering the material properties. Contrary to other techniques used by Roberts et al. [7] (e.g. pressing a razor blade into the beam or using a small saw blade), this equipment enabled to have a high reproducibility of the notch. This standardization is necessary due to the impact of notch depth and shape on the critical stress intensity factor [7].

The load, F_r, that caused the compact fracture was recorded and used to calculate the toughness, K_{IC} in MPa $m^{1/2}$, in accordance with the equation described by Brown and Srawley [8] applied to the parallelepipedical geometry

$$K_{IC} = \frac{3\gamma F_r a^{1/2} p}{2lh^2} \tag{4}$$

where F is the load that causes the compact fracture, a is the notch length, p is the distance between supports (34.12 mm), l and h represent the compact dimensions, and γ is a polynomial function of the parameter a/h, for non-infinite medium, given by Eq. (5)

$$\gamma = 1.93 - 3.07(a/h) + 14.53(a/h)^2 - 25.11(a/h)^3 + 25.8(a/h)^4 \tag{5}$$

2.3.2. Microindentation test

The compacts are placed on a flat support. A maximal displacement of 0.080 mm is imposed and a stress applied on the top side of the compact by a 2.38 mm spherical indentor, descending at a rate of 0.06 mm min^{-1}. The indentor is kept on the compact at the maximal penetration during 3 min to ensure the stress relaxation [4]. The acquisition frequency during the test is 0.2 s^{-1}. The force–displacement curves were recorded and then, the response of the compact was quantified by the Brinell hardness P (in MPa) which was calculated by Eq. (6) [9]

$$P = \frac{2F}{\pi D(D - \sqrt{D^2 - d^2})} \tag{6}$$

where F is the maximal load applied, D is the indentor diameter and d represents the diameter of the indentation surface.

Otherwise, it is also possible to calculate a reduced modulus of superficial elasticity E^* [10]. E^* is classically

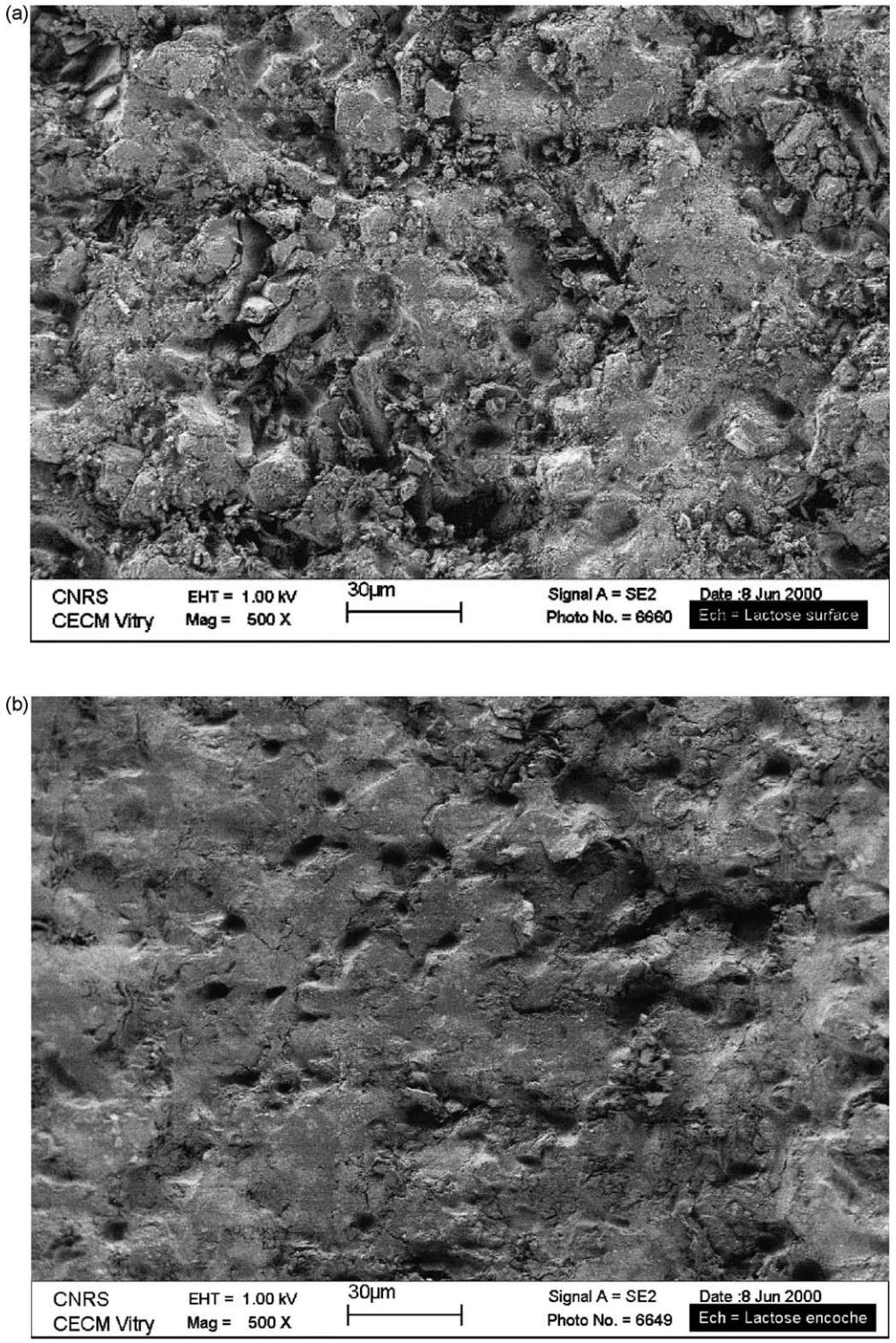

Fig. 2. SEM photographs of upper flat part (a) and notch (b) of a parallelepipedical compact of amorphous FF.

obtained as the slope of the linear zone during unloading. It should be noted that there is an uncertainty on the E^* values because of the difficultly in the use of experimental data, since, the linear zone limits are chosen graphically and few points are used to calculate E^*.

2.3.3. Mechanical properties versus porosity relationship

The mechanical properties previously described may be plotted versus compaction pressure or versus compact porosity. A mechanical property A may be plotted versus the porosity ε by the use of the following empiric

exponential model [11]:

$$A = A_0\, e^{-b\varepsilon} \quad (7)$$

The evaluation of mechanical properties at zero porosity was recommended by some authors for tensile strength [11,12], Young's modulus [13,14], critical stress intensity factor [15,16] and hardness [17].

In Sections 3 and 4, lactoses mechanical properties are compared using the 20% porosity point and the extrapolated values at zero porosity. The choice of the 20% porosity could be justified because it was not possible to obtain compacts with porosities lower than 10%. This choice allowed to compare the systems one to another in a range of porosity where it is possible to calculate mechanical parameters from experimental values. But to get information on the continuous solid, the value at zero porosity is necessary, keeping in mind that it is only extrapolated and not accurate value.

3. Results

3.1. Tensile strength σ_{rf}

Data of tensile strength versus compaction pressure and porosity for the different lactoses are shown in Figs. 3 and 4 and some values obtained for each product are reported in Tables 2 and 3. The extensiometric slope (Fig. 4) obtained for the two anhydrous forms are about twice (0.0259 and 0.0243) than those of LαM (0.0103) and partly amorphous lactose FF is intermediate (0.0188). LαM gives compacts with relatively lower cohesion than other grades even at high compaction pressures, and for these pressures, i.e. higher than 170 MPa, capping was observed. On the other hand, if we consider that an acceptable tensile strength is in a range of 1–2 MPa, all the lactoses studied are convenient but with a upper limit only in the case of LαM (with about 2 MPa at 170 MPa).

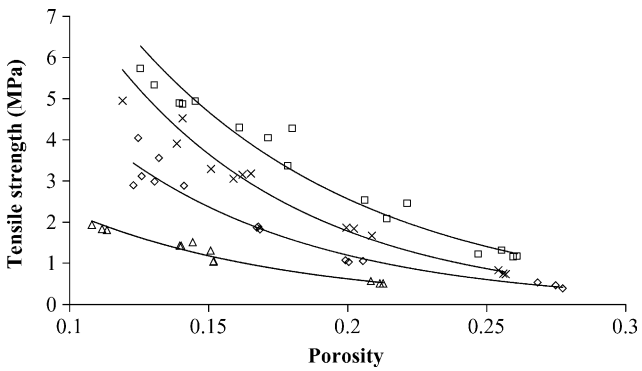

Fig. 3. Relationship between porosity and tensile strength for the compacts composed of the different grades of lactoses studied (FF: $y = 18.451\, e^{-13.682x}$, $R^2 = 0.9803$; LαA: $y = 28.384\, e^{-12.022x}$, $R^2 = 0.9600$; LαM: $y = 8.131\, e^{-12.864x}$, $R^2 = 0.9708$; LβA: $y = 31.505\, e^{-14.365x}$, $R^2 = 0.9868$). Key: (△) LαM, (□) LαA, (×) LβA, (◇) FF.

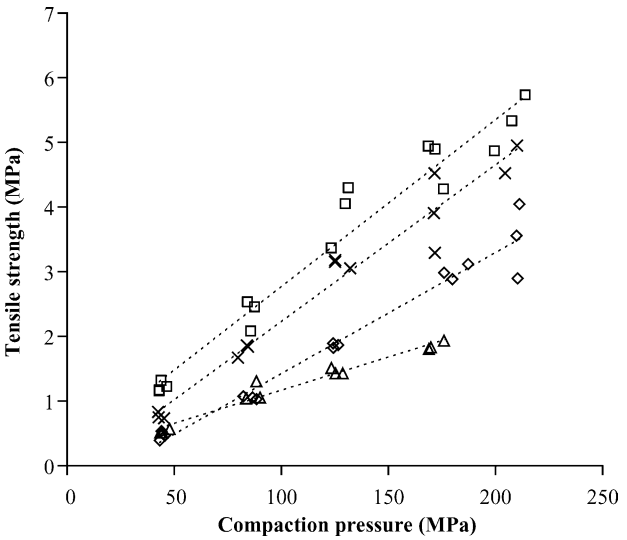

Fig. 4. Relationship between compaction pressure and tensile strength for the compacts composed of the different grades of lactoses studied (FF: $y = 0.0188x - 0.4551$, $R^2 = 0.9627$; LαA: $y = 0.0259x + 0.1787$, $R^2 = 0.9587$; LαM: $y = 0.0103x + 0.1369$, $R^2 = 0.9637$; LβA: $y = 0.0243x - 0.1999$, $R^2 = 0.9607$). Key: (△) LαM, (□) LαA, (×) LβA, (◇) FF.

This hierarchy is kept with the plot of tensile strength versus porosity. At a porosity of 20%, the ratio between the tensile strength of FF, LαA, LβA versus the tensile strength of LαM are 2, 4 and 3, respectively, and confirm the worst compaction behaviour of LαM. The ratio between the tensile strength of the LαM and LαA is in the same order than those obtained previously with the crushing strength [18] (a binding capacity for the anhydrous α-lactose which was almost four times higher than the α-lactose monohydrate was found). The same scale of compaction pressures lead to lower values of porosity for compacts of LαM. In the same time, it is necessary to go down to a porosity lower than 12% to obtain a tensile strength of about 2 MPa.

3.2. Young's modulus E

The increase in Young's modulus with the decrease of porosity is shown in Fig. 5. The extrapolated values at zero porosity are listed in Table 2. As suggested by Bassam et al. [19], the analysis of Young's modulus at zero porosity thus provides a means of quantifying the elastic behaviour.

Table 2
Extrapolated values of mechanical properties obtained by exponential relationship between a mechanical property, A, and porosity, ε, according to $A = A_0\, e^{-b\varepsilon}$

	σ_{rf0} (MPa)	E_0 (GPa)	K_{IC0} (MPa m$^{1/2}$)	P_0 (MPa)	E_0^* (GPa)
LαM	8.13	7.7	0.201	203	28.7
LβA	31.50	21.4	0.578	808	131.9
LαA	28.38	27.8	0.609	2876	185.7
FF	18.45	13.2	0.322	234	28.5

Table 3
Interpolated values of mechanical properties obtained by exponential relationship between a mechanical property, A, and porosity, $\varepsilon = 20\%$, according to $A = A_0\, e^{-b\varepsilon}$

	$\sigma_{rf20\%}$ (MPa)	$E_{20\%}$ (GPa)	$K_{IC20\%}$ (MPa $m^{1/2}$)	$P_{20\%}$ (MPa)	$E^*_{20\%}$ (GPa)
LαM	1.18	0.8	0.016	8.3	3.1
LβA	3.65	2.5	0.033	31.7	11.0
LαA	4.67	3.0	0.046	27.5	11.6
FF	2.37	1.1	0.024	33.8	10.8

Independent of the porosity, the lowest Young's modulus values were obtained for compacts of LαM. For a porosity of 20% (Table 3), its value is less than one-third of the moduli of the two anhydrous forms. The anhydrous lactoses LβA and LαA are the most rigid lactoses with higher Young's modulus at all porosity levels. The partly amorphous lactose FF is intermediate but closer to LαM than the others, since at a porosity of 20%, its Young's modulus ($E = 1.1$ GPa) is not very far from the modulus of LαM ($E = 0.8$ GPa). The lower Young's modulus for the LαM's compacts means that it is more prone to the deformation. However, due to its tensile strength, its limit of elasticity is lower than in the case of the other lactoses.

3.3. Critical stress intensity factor K_{IC} (representative of the material toughness)

An exponential model [7,15,16] was used to show the evolution of critical stress intensity factor versus compact porosity in Fig. 6. High values of toughness represent materials which are able to highly support crack propagation.

For all porosity levels, the toughness of LαM compacts appears to be low. The two anhydrous lactoses and particularly LαA are characterised by the highest critical stress intensity factors. Like with the other mechanical properties, the hierarchy is the same and compacts composed of FF have an intermediate behaviour. It is interesting to note that LβA has a critical stress intensity factor either at zero porosity or at porosity of 20% which is about twice the value of LαM as Roberts et al. [7] had reported it previously. The differences between our values and those obtained by these authors (0.7597 MPa $m^{1/2}$ for LβA and 0.3540 MPa $m^{1/2}$ for LαM) may have several origins. In both cases, the minimum porosity obtained is about 10% and in this case, the extrapolation is very considerable. The differences may be also due to the method and the tester used (with the micropress, the machine elasticity is greatly reduced).

The LαA's critical stress intensity factor is about three times those obtained with LαM at zero and 20% porosity.

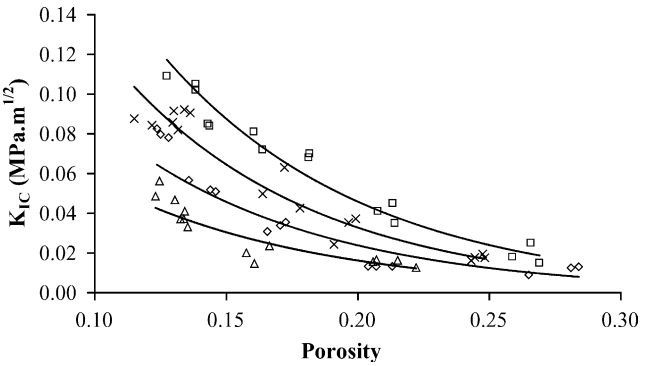

Fig. 6. Relationship between porosity and critical stress intensity factor for the compacts composed of the different grades of lactoses studied (FF: $y = 0.3219\, e^{-13.01x}$, $R^2 = 0.8460$; LαA: $y = 0.6092\, e^{-12.945x}$, $R^2 = 0.9548$; LαM: $y = 0.2009\, e^{-12.584x}$, $R^2 = 0.8057$; LβA: $y = 0.5776\, e^{-14.287x}$, $R^2 = 0.9427$). Key: (△) LαM, (□) LαA, (×) LβA, (◇) FF.

3.4. Brinell hardness P and reduced modulus of elasticity E^*

Brinell hardness traduces the surface elastoplasticity of the compact. The evolution of Brinell hardness versus porosity is plotted in Fig. 7 and extrapolated values are

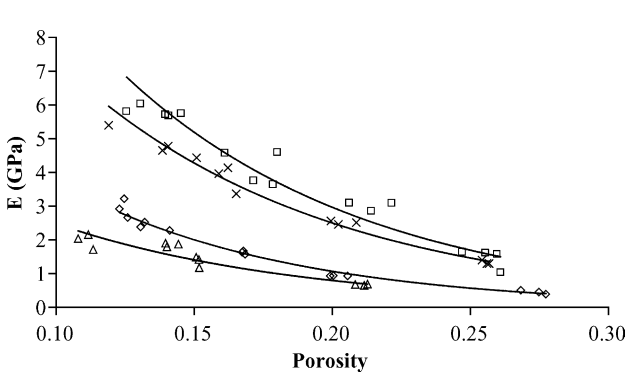

Fig. 5. Relationship between porosity and Young's modulus for the compacts composed of the different grades of lactoses studied (LβA: $y = 21.352\, e^{-10.721x}$, $R^2 = 0.9877$; FF: $y = 13.183\, e^{-12.561}$, $R^2 = 0.9866$; LαA: $y = 27.779\, e^{-11.187x}$, $R^2 = 0.9285$; LαM: $7.7217\, e^{-11.354x}$, $R^2 = 0.9120$). Key: (△) LαM, (□) LαA, (×) LβA, (◇) FF.

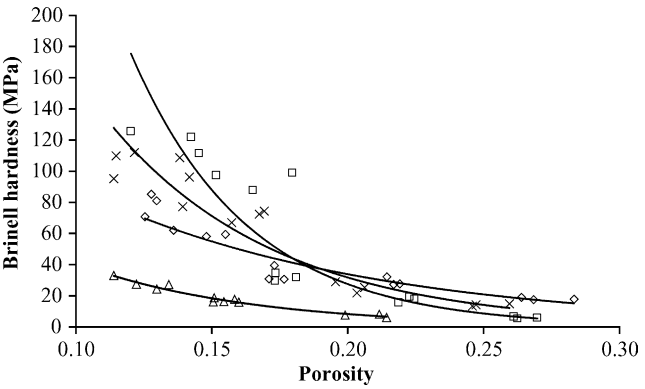

Fig. 7. Relationship between porosity and Brinell hardness for the compacts composed of the different grades of lactoses studied (FF: $y = 234.33\, e^{-9.6739x}$, $R^2 = 0.9041$; LαA: $y = 2876.4\, e^{-23.248x}$, $R^2 = 0.9143$; LαM: $y = 203.05\, e^{-16.011x}$, $R^2 = 0.9703$; LβA: $y = 807.66\, e^{-16.184x}$, $R^2 = 0.9351$). Key: (△) LαM, (□) LαA, (×) LβA, (◇) FF.

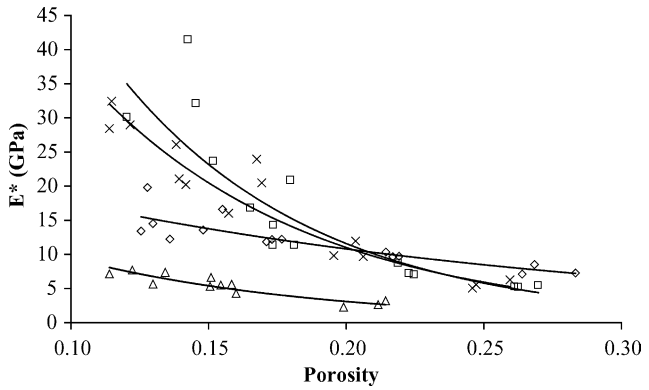

Fig. 8. Relationship between porosity and reduce Young's modulus for the compacts composed of the different grades of lactoses studied (FF: $y = 28.472\,e^{-4.847x}$, $R^2 = 0.8327$; LαA: $y = 185.71\,e^{-13.873x}$, $R^2 = 0.8855$; LαM: $y = 28.749\,e^{-11.147x}$, $R^2 = 0.8425$; LβA: $y = 131.86\,e^{-12.414x}$, $R^2 = 0.9287$). Key: (△) LαM, (□) LαA, (×) LβA, (◇) FF.

reported in Table 2. The exponential extrapolation at zero porosity is not as accurate as expected due to the large dispersion of the data especially for LαA and LβA when the porosity becomes low. Beyond the differences in the experimental conditions, that is one reason why it is not really possible to compare the values obtained with those of other authors [17]. The compacts of LαM present a lower Brinell hardness than all other lactoses with a very little change when the porosity decreases, i.e. three or four times lower than the anhydrous forms and the partly amorphous form at a porosity of 20%. The hardness of FF is intermediate for porosities lower than 20% and the anhydrous forms, LβA and LαA, are characterised by the highest hardness, markedly decreasing with increasing porosity. Porosity of 17% seems to be a critical value since for porosities higher than 17% the Brinell hardness of FF becomes the highest and those of the two anhydrous forms are inversed.

The microindentation technique gives also the possibility to calculate a reduce modulus of elasticity (Fig. 8), E^* (however, there is an uncertainty on the E^* values because the selection of the linear zone limits is made on the force–displacement curves and few points are used to calculate E^*). The values obtained by interpolation at a porosity of 20% are shown in Table 3. The hierarchy observed is the same than those of E except for FF compacts with a porosity higher than 0.22. The highest values obtained for anhydrous forms indicate a higher stiffness in surface.

4. Discussion

4.1. Mechanical properties and general compaction behaviour

In order to better understand the compaction behaviour of the four lactoses tested, it seems to be interesting to match the different mechanical properties measured.

Table 4
H_0/P_y and E_0/P_y ratios used to characterize material behaviour according to Roberts and Rowe classification [20]

H_0/P_y	E_0/P_y	Classification
1.5–2	11–25	Elastic material
2–2.2	25–35	Brittle material
3	132	Plastic material
>3	>132	Rigido-plastic material

4.1.1. Compaction behaviour classification

First, the classification defined by Roberts and Rowe [20] was used to compare the products (Table 4). This classification is obtained from Eq. (8) [20–22]

$$\frac{H_0}{P_y} = 0.07 + 0.6 \ln \frac{E_0}{P_y} \quad (8)$$

where H_0 is the Vickers hardness extrapolated at zero porosity and expressed in MPa, P_y is the yield pressure in MPa and E_0 represents the Young modulus in MPa extrapolated at zero porosity.

For the four lactoses, the E_0/P_y ratios were calculated from the evaluated values of P_y and E_0.

The results of E_0/P_y ratio are shown in Table 5. The presence or the absence of water molecules in crystal lattice, i.e. pseudopolymorphism, seems to be the most important effect on the general compaction behaviour of lactoses. The E_0/P_y ratio value of 73 for LαM confirms an intermediate behaviour between brittle and plastic behaviour. The values for LβA and LαA are very close, 170 and 184, respectively, corresponding to a rigido-plastic behaviour, and point out the lesser influence of the anomeric change α/β on compaction behaviour in regard to pseudopolymorphism. An intermediate behaviour for the partly amorphous form, FF is observed with a E_0/P_y value of 110.

4.1.2. Capping tendency

It is also interesting to link the mechanical properties with real use properties such as cleavage phenomenon or capping which is experimentally observed with LαM for high compaction pressures. This technical issue may be quantified by the specific energy of failure G_{IC} which may be calculated with the following equation in case of a failure in mode I [23]:

$$G_{IC} = \frac{1 - \nu^2}{E} K_{IC}^2 \quad (9)$$

Table 5
Mechanical properties and general compaction behaviour of lactose

	E_0/P_y	G_{IC0} (J m^{-2})	$G_{IC20\%}$ (J m^{-2})	d_{cr} (μm)
LαM	73	5.23	0.33	39
LβA	170	15.62	0.44	228
LαA	184	13.36	0.71	173
FF	110	7.86	0.53	77

For pharmaceutical products, it is generally considered that the Poisson's ratio ν is about 0.3 [24]. If the square of the Poisson's ratio is either neglected in comparison with unity, then an approximation of the specific energy of failure defined by Eq. (10) may be calculated and used to compare the compacted materials

$$G^*_{IC} = \frac{(K_{IC})^2}{E} \tag{10}$$

where K_{IC} is the critical stress intensity factor and E is the Young's modulus. The relationship between porosity and the specific energy of failure was recalculated using the relationship obtained for the critical stress intensity factor and for the Young's modulus (Fig. 9). The extrapolated values of G^*_{IC} at zero porosity are reported in Table 5. In the general mechanic of solid medium, a flaw leads to a stress concentration when a solicitation is applied on the solid. Such a flaw will be able to propagate if the surface energy in the flaw is smaller than the energy of failure. The energy of failure is the energy which is needed to form some new surfaces near the flaw. This justifies that G^*_{IC} is related to K_{IC} and the cleavage tendency. In the same way, a solid medium characterized by a low Young's modulus (i.e. high recoverable elastic deformation) may be able to support high deformation before breaking. This justifies that G^*_{IC} is related to the reciprocal of E. Finally, a low value of specific energy of failure means a high tendency to cleave, since it corresponds to a product with a low toughness and/or a high modulus of elasticity. In the case of lactoses, the specific energy of failure for the compacts of LαA is the most important because of its especially high value of toughness even if its Young's modulus is also important. At 20% of porosity, the specific energy of failure of compacts of LαA ($G^*_{IC}20\% = 0.71\ J\ m^{-2}$) is twice the value of compacts of LαM ($G^*_{IC}20\% = 0.33\ J\ m^{-2}$). The lower G^*_{IC} values obtained with LβA and FF than those of LαA may be due to lower values of the toughness. This values are intermediate between the G^*_{IC} of the two α forms with a little superiority for FF if a porosity higher than 15% is considered (0.44 and 0.53 for a porosity of 20%). At zero porosity, this order seems to be inverse (7.86 for FF and 13.36 for LβA). LαM is characterized by the lowest Young's modulus but at the same time by the lowest toughness, which lead to a poor value of G^*_{IC} ($G^*_{IC0} = 5.23\ J\ m^{-2}$). This G^*_{IC} value should be linked with the cleavage phenomenon observed systematically for the highest compaction pressures. The best compactibility of the two anhydrous forms is confirmed by the highest value of G^*_{IC} ($G^*_{IC0} = 15.62\ J\ m^{-2}$ for LβA and 13.36 for LαA). The comparison of the G^*_{IC0} calculated with the values of E_0 and K_{IC0} with those obtained by extrapolation (Table 5) shows acceptable correlation (except for LαA).

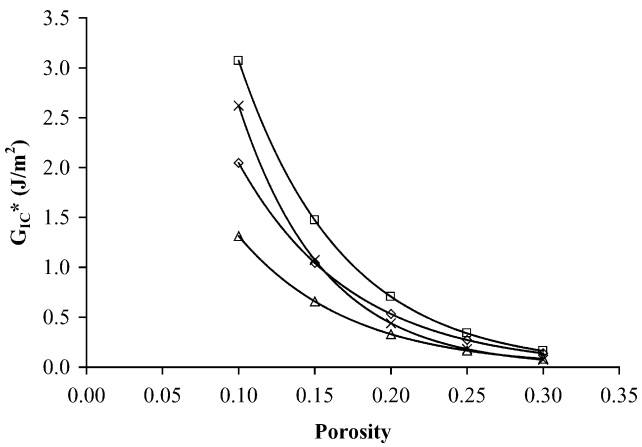

Fig. 9. Relation between porosity and breaking specific energy for the compacts composed of the different grades of lactoses studied (LαA: $y = 13.3599\ e^{-14.7030x}$; LβA: $y = 15.6248\ e^{-17.8530x}$; FF: $y = 7.8601\ e^{-13.4590x}$; LαM: $y = 5.2269\ e^{-13.8140x}$). Key: (△) LαM, (□) LαA, (×) LβA, (◇) FF.

4.1.3. Brittle–ductile transition

The calculation of the particle size where the brittle–ductile transition takes place, brings out the complexity of the behaviour of lactoses particles under pressure. This dimension d_{cr} could be calculated for a rectangular geometry with a relationship between the critical stress intensity factor at zero porosity K_{IC0} and yield stress pressure P_y [20,25]:

$$d_{cr} = \frac{32}{3}\left(\frac{K_{IC0}}{P_y}\right)^2 \tag{11}$$

The values give a rough estimate (Table 5) because d_{cr} were calculated with ratio of proportionality (32/3) which correspond to perfect rectangular individual particles. Nevertheless, they could be used in order to compare lactoses.

The critical diameter calculated for LαM is not in contradiction with the previous results, i.e. it is the most ductile of the lactoses studied. It is even in line with the compaction behaviour classification (Section 4.1.1). In fact, LαM is characterized by a very little toughness. It means that the particles of LαM have the tendency to reduce in size quickly at low compaction pressures. The brittle to ductile transition begins at intermediate pressures corresponding to low values of P_y. For the same pressures, the particles of the anhydrous forms keep a higher size due to higher toughness and higher critical stress intensity factor/P_y ratio. This is consistent with the rigido-plastic behaviour of the previous classification.

4.2. Mechanical properties and cohesive energy density (CED)

The cohesive energy density (CED), expressed in MPa, is the strength required to break the network of a crystalline solid. Roberts and Rowe [26] gave a relationship between Young's modulus and CED. This relationship generalizes that given by Tobolsky [27] for a simple

Table 6
Mechanical properties of lactoses derived from cohesive energy (CED) and general compaction parameters

	CED (MPa)	σ_{rf0}/CED	K_{IC0}/CED ($m^{1/2}$)	G_{IC0}/CED (μm)
LαM	615	0.013	0.00033	0.0085
LβA	1415	0.022	0.00041	0.0110
LαA	1798	0.016	0.00034	0.0074
FF	938	0.019	0.00034	0.0084
Average ratio		0.018 ± 0.004	0.00035 ± 0.00004	0.0088 ± 0.0015

system corresponding to a face-centred cubic lattice

$$E_0 = (0.01699)\text{CED} - 2.7465 \quad (12)$$

with E_0 expressed in GPa and CED in MPa.

This relation gives the highest values of CED for the two anhydrous forms, LαA and LβA, with 1798 and 1415 MPa, respectively (Table 6). The CED of LαA is higher than the CED of LβA. For FF and especially LαM, the results are lower, 938 and 615 MPa. These differences are due to the changes of molecular interaction with the inclusion of water molecules in the crystal lattice (LαM) or with the partial amorphisation (FF). It should be noted that the application of Eq. (12) in the case of FF is quite tedious since the CED notion must be applied to a crystalline solid. However, lactose FF is primarily amorphous at its surface and mainly composed of LαM. This could explain that the calculated values for CED of FF and LαM are quite similar. Moreover, α-lactose monohydrate is known to be the most stable form of lactose [28], and its lowest value of CED could be explained by the unit cell volume which is lower for the anhydrous β-lactose [29] than for the α-lactose monohydrate [30].

The calculated values of the others mechanical properties σ_{rf0} and K_{IC0} were also used to check the experimental relationship obtained by Roberts et al. [31] for pharmaceutical solids. These relationships are the following:

$$\sigma_{rf0} = (0.0183 \pm 0.011)\text{CED} \quad (13)$$

$$K_{IC0} = (0.000260 \pm 0.000016)\text{CED} \quad (14)$$

For the four lactoses studied, the relations between the tensile strength and the CED are the same, i.e.

$$\sigma_{rf0} = (0.018 \pm 0.004)\text{CED} \quad (15)$$

In case of critical stress intensity factor, the relation obtained with the lactose is in the upper limit of the interval suggested ($K_{IC0} = (0.00035 \pm 0.00004)$CED).

A similar relationship could be obtained for G^*_{IC0} and CED. The values obtained with the four lactoses give the following relation:

$$G^*_{IC0} = (0.0088 \pm 0.0015)\text{CED} \quad (16)$$

5. Conclusion

In this work, the importance of the crystalline nature of a product on its compaction behaviour has been shown with the example of one of the most important excipients in pharmacy, the lactose. In this case, the crystalline nature affects considerably the properties during compaction and the mechanical properties of the obtained compacts. For lactoses, pseudopolymorphism appears to more affect these properties than the use of a partly amorphous form or changing of anomer. The first part of this work has pointed out the impact on compressibility with the yield pressures and energy measurements. Then, this effect is found on the mechanical properties (tensile strength, toughness, Young modulus and Brinell hardness) too. LαM is characterized by a high instantaneous elasticity and an important viscoelasticity which show a tendency to expansion. Moreover, the LαM's toughness is very low and is not sufficiently balanced by the Young modulus even if it is low. This leads to a little specific energy of failure. In the case of LαM, all parameters contribute to promote the cleavage phenomenon. On the contrary, the risk of cleavage is lower for the two anhydrous forms, LαA and LβA.

With the example of the lactose, it appears that it is important to consider physical parameters of the products (polymorphism, pseudopolymorphism, polyamorphism, partial amorphisation) and not only the chemical characteristics (purity, etc.). These aspects may be considered even if the reference like USP and the European Pharmacopoeia do not define the structural aspects in the monograph. This study takes an interest in the problematic of the dual sourcing and shows that an accurate definition of the physical parameters of a product is essential to the suppliers specifications.

Due to the abundance of parameters obtained with the lactoses and the micropress prototype, it appeared more interesting to combine these parameters to characterize the general compaction behaviour and even attain a characterization at a molecular level with the CED.

Finally, all of these methods and parameters could be adapted to active drugs and should be subjected to an exhaustive evaluation.

Acknowledgements

The authors are grateful to Digipharm and D. Bielawski for experimental support.

References

[1] E. Doelker, Caractères physicochimiques des principes actifs. Leurs conséquences sur la faisabilité et la stabilité des formes galéniques, S.T.P. Pharma Pratique 9 (5) (1999) 399–409.

[2] L. Borka, Review on crystal polymorphism of substances in the European Pharmacopoeia, Pharm. Acta Helv. 66 (1) (1991) 16–22.
[3] V. Busignies, P. Tchoreloff, B. Leclerc, M. Besnard, G. Couarraze, Compaction of crystallographic forms of pharmaceutical granular lactoses. I. Compressibility, Eur. J. Pharm. Biopharm. (2004) in press.
[4] D. Bielawski, G. Couarraze, B. Leclerc, P. Tchoreloff, Procédé et micropresse pour caractériser les propriétés mécaniques des solides pharmaceutiques, vol. World Patent WO 02084254, 24 Oct., 2002.
[5] S. Timoshenko, Elements of strength of materials, fifth ed., Van Nostrand, Wokingham, UK, 1968.
[6] J.T. Fell, J.M. Newton, The prediction of tensile strength of tablets, J. Pharm. Pharmacol. 22 (1970) 247–248.
[7] R.J. Roberts, R.C. Rowe, P. York, The measurement of the critical stress intensity factor (KIC) of pharmaceutical powders using three point single edge notched beam (SENB) testing, Int. J. Pharm. 91 (1993) 173–182.
[8] W.F. Brown, J.E. Srawley, ASTM Special Tech. Publ. 410 (1966).
[9] H. Leuenberger, B.D. Rohera, Fundamentals of powder compression. I. The compactibility and compressibility of pharmaceutical powders, Pharm. Res. 3 (1) (1986) 12–22.
[10] N. Huber, D. Munz, C. Tsakmakis, Determination of Youngs modulus by spherical indentation, J. Mater. Res. 12 (9) (1997) 2459–2469.
[11] E. Ryshkewitch, Compression strength of porous sintered alumina and zirconia, J. Am. Ceram. Soc. 36 (2) (1953) 65–68.
[12] J.M. Newton, A.B. Mashadi, F. Podczeck, The mechanical properties of an homologous series of benzoic acid esters, Eur. J. Pharm. Biopharm. 39 (1993) 153–157.
[13] J.C. Kerridge, J.M. Newton, The determination of the compressive Young's modulus of pharmaceutical powders, J. Pharm. Pharmacol. Suppl. 38 (1986) 79.
[14] R.M. Spriggs, Expression for effect of porosity on elastic modulus of polycrystalline refractory materials, particularly aluminium oxide,, J. Am. Ceram. Soc. 44 (1961) 628–629.
[15] R.J. Roberts, R.C. Rowe, Determination of the critical stress intensity factor (KIC) of microcrystalline cellulose using radially edge-cracked tablets, Int. J. Pharm. 52 (1989) 213–219.
[16] P. York, F. Bassam, R.C. Rowe, R.J. Roberts, Fracture mechanics of microcrystalline cellulose powders, Int. J. Pharm. 66 (1990) 143–148.
[17] H. Leuenberger, The compressibility and compactibility of powder systems, Int. J. Pharm. 12 (1982) 41–55.
[18] C.F. Lerk, Consolidation and compaction of lactose, Drug Dev. Ind. Pharm. 19 (17–18) (1993) 2359–2398.
[19] F. Bassam, P. York, R.C. Rowe, R.J. Roberts, Young's modulus of powders used as pharmaceutical excipients, Int. J. Pharm. 64 (1990) 55–60.
[20] R.J. Roberts, R.C. Rowe, Brittle/ductile behaviour in pharmaceutical materials used in tabletting, Int. J. Pharm. 36 (1987) 205–209.
[21] D.M. Marsh, Plastic flow in glass, Proc. R. Soc. Lond. A279 (1964) 420–435.
[22] D. Tabor, The hardness of solids, Rev. Phys. Technol. 1 (1970) 145–179.
[23] D. François, A. Pineau, A. Zaoui, Comportement mécaniques des matériaux, Viscoplasticité, endommagement, mécanique de la rupture, mécanique du contact, Hermès Ed., Paris, 1995, pp. 115–178.
[24] R.J. Roberts, R.C. Rowe, P. York, The Poisson's ratio of microcrystalline cellulose, Int. J. Pharm. 105 (1994) 177–180.
[25] K. Kendall, The impossibility of comminuting small particles by compression, Nature 271 (1978) 710–711.
[26] R.J. Roberts, R.C. Rowe, The relationship between Young's modulus of elasticity of organic solids and their molecular structure, Powder Tech. 65 (1991) 139–146.
[27] A.V. Tobolsky, Properties and Structure of Polymers, Wiley, New York, 1962, p. 1.
[28] M. Morita, Y. Nakai, E. Fukuoka, S. Nakajima, Physicochemical properties of crystalline lactose. II. Effect of crystallinity on mechanical and structural properties, Chem. Pharm. Bull. 32 (10) (1984) 4076–4083.
[29] K. Hirotsu, A. Shimada, The crystal and molecular structure of beta-lactose, Bull. Chem. Soc. Jpn 27 (5) (1974) 994–1005.
[30] J.H. Noordik, R.A. Visser, R.O. Gould, Crystal structure, polarity and morphology of 4-*O*-beta-D-galactopyranosyl-alpha-glucopyranose monohydrate (alpha-lactose monohydrate): a redetermination, Z. Kristallogr. 168 (1–4) (1984) 59–65.
[31] R.J. Roberts, R.C. Rowe, P. York, The relationship between the fracture properties, tensile strength and critical stress intensity factor of organic solids and their molecular structure, Int. J. Pharm. 125 (1995) 157–162.