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ScienceDirect
European Journal of Pharmaceutics and Biopharmaceutics 67 (2007) 476–484
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Stress relaxation test for the characterization of the viscoelasticity of pellets

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Received 5 December 2006; accepted in revised form 8 March 2007
Available online 21 March 2007

Abstract

The characterization of the mechanical properties of single uncoated pellets was performed in order to verify if these parameters could be used to predict the pellets aptitude to be compressed or utilized differently.

Different ratios of microcrystalline cellulose and lactose monohydrate were used for the preparation of four batches of pellets by an extrusion/spheronization process. The 0.6–0.71 mm pellet fraction was used for the tests. Crushing strength and stress relaxation tests were carried out on the single pellets. The first test provided information of both the mechanical strength and the fragmentation aptitude. The second test provided information about their deformation ability (viscous flow) and residual elasticity (stress relaxation modulus). The results obtained from these tests were then compared with those obtained from the Heckel analysis.

An excellent consistency was discovered between the parameters obtained from both the stress relaxation and crushing strength tests on one side and the Heckel parameters on the other side.

Tests performed on single pellets are very useful tools to predict their deformation and fragmentation aptitude under compression and can be used for early insight of the pellet aptitude to be compressed.

Keywords: Pellets; Extrusion; Spheronization; Mechanical properties; Viscoelasticity; Stress relaxation; Compression

1. Introduction

The formulation of multiple-unit controlled release dosage forms represents a preferable alternative to a single-unit system. According to some previously reported publications, the gastric emptying of multiple-unit forms is more uniform, more predictable and less influenced by food [1,2].

These units can be pellets, beads or microspheres. In some cases they are simply compressed into tablets but, very often, they are coated with a release rate controlling or enteric membrane before being used to fill hard gelatine capsules.

An interesting alternative is the compression of coated pellets into tablets, since it presents a series of advantages such as lower production cost, higher production rate, better patient compliance and the possibility to divide the dose into parts.

Unfortunately, the formulation of coated pellets into tablets is not an easy process since the compaction can damage the membrane and cause modification of the rate or loss of the release control.

Many papers report the influence of some parameters on the release kinetics from coated pellets after compaction: compression parameters [3,4], diluents properties and amount [3–6], pellets size and compression behaviour [7,8], kind of coating and related properties [6,8,9].

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doi:10.1016/j.ejpb.2007.03.013

However, very probably the integrity of the film does not only depend on its mechanical resistance and flexibility but also on the deformation ability of the pellets that support the film itself.

Single pellet mechanical properties like tensile strength (or crushing strength) or elastic modulus [9–18] and their influence on compression behaviour and tablets properties [19–26] have been studied however no findings were reported in the pharmaceutical field on the importance of the use of transient rheological parameters as factors for the prediction of the pellets ability to be compressed into tablets. Besides, among these parameters, those concerning the deformation ability could be used to distinguish among different formulations of pellets in order to choose the more suited to sustain the stress that a coating undergoes when coated pellets are compressed. In fact, as previously stated, pellets characteristics are fundamental. Deforming pellets are more suited than fragmenting pellets under this point of view.

Most pharmaceutical materials present a viscoelastic behaviour. In actual fact, viscoelastic behaviour can be studied by rheological analysis using transitory or oscillatory tests. These kinds of analysis are usually used to characterize liquid and semi-solid dosage forms however they do not represent a common approach in the development of solid dosage forms.

Rheological viscoelastic tests cannot be easily carried out on single pellets since the more or less spherical shape makes the stress applied during the test difficult to measure. Recently, some papers have been published about the use of dynamic mechanical analysis (DMA) in the study of the single pellet rheological behaviour [27–29] and the strength of this technique against conventional methods was illustrated.

The aim of this study is to find a reliable method to verify the rheological and mechanical properties of uncoated pellets in order to predict as early as possible their behaviour in further technological steps, such as compression. Besides, the classification of different batches of pellets according to their viscoelastic properties could be very helpful in the choice of the batch to use for being first film coated and then compressed into tablets with the minimal film breakage.

This method should characterize pellets in a simple, quick and effective manner and should need a small amount of material to be carried out.

Pellets of different composition but prepared using common pharmaceutical excipients such as microcrystalline cellulose (MCC), classified as ductile [30,31] and monohydrate lactose (LC), classified as brittle [32], could be indicated for this purpose.

Therefore, the work does not focus either on the optimization of the extrusion/spheronization process or on the effect of porosity on the mechanical properties of the pellets. This last aspect has already been assessed in previous studies [16,19].

2. Materials

Microcrystalline cellulose (Avicel PH 101, FMC Europe, Brussels, Belgium), monohydrate lactose (Sorbolac 400, Maggle, Wasserburg, Germany), stearic acid (Acef, Fiorenzuola d'Arda, Italy); acetone and chloroform were standard reagent grade. All materials were used as supplied.

3. Methods

3.1. Pellets preparation

Microcrystalline cellulose and monohydrate lactose were manually sieved (600 μm sieve) and blended in a 12 litre cube mixer (Viani, Bresso, Italy) for 20 min at 10 rpm, according to the amounts presented in Table 1. The dry mixtures were wetted and extruded with a co-rotating screw horizontal extruder (TSA EF 21-20, Cernobbio, Italy), which was fitted with a 0.6 mm opening diameter axial screen and 1.8 mm screen thickness. The granulating liquid used was water, added in different amount for every batch, in order to obtain a suitable spheronization wet mass (Table 1).

The extrudate (300 *g*) was loaded in a spheronizer (Glatt P50), fitted with a friction plate and operated at 750 rpm for 3 min. The wet pellets were then dried at 45 °C in a fluid bed (Glatt GPGC-1), until the moisture content reached a value lower than 1%, determined by the halogen thermobalance (Mettler HR73). The value of the residual moisture was chosen very low in order to minimize the water effects on the material properties [33]. The 600–710 μm sieve fraction was used for this study and for this reason it was stored in sealed containers before analysis began.

3.2. Pellets shape

A stereomicroscope (Wild mod. M3C) equipped with a digital camera (Imagine & Computer mod. PCO CCD Imaging VC45) was used for the image analysis. For every batch, 50 pellets were photographed at 6.5× and then analysed with specific software (Image-Pro® Plus). This software is able to identify some objects inside an image when they are formed by continuous pixels of a specific intensity. Once identified, it can count them and measure the different types of parameters such as shape and size. Calibration of the stereomicroscope was carried out by using standard markers of known and adequate length.

In this study the parameters analysed were roundness and radius ratio.

Roundness is the ratio between the perimeter measured by the software, and that of a circular object of equivalent area [34]. For a sphere this ratio is 1. The more the value differs from 1, the more the object differs from sphericity and/or the surface is irregular.

Radius ratio is the ratio between the major and minor radius of the object [35]. The radii represent the maximal

Table 1
Composition and porosity of the four batches of pellets

Batch	Constituents of the dry mixture (%)		Water/powder ratio	Yield (%) of the 600–710 μm fraction	Porosity
	Sorbolac 400	Avicel PH101			
A	75	25	0.587	63.33	6.3
B	50	50	0.910	49.4	6.8
C	25	75	1.114	23.85	5.9
D	–	100	1.490	24.66	6.5

and minimal distance between the perimeter and the centroid of the object. Also, in this case, the ratio is 1 for a sphere and different from 1 for an ellypse.

Scanning electron microscopy analysis was carried out with a Stereoscan 360 (Cambridge Instruments Limited, Cambridge, UK) on all batches of pellets in order to obtain a visual image of their shape.

3.3. Pellets porosity

Pellets porosity was calculated, according to the method previously reported [16], by helium pycnometer as the ratio between the density of the entire pellets and the density of the powder mixture having the same composition of the pellets. Values are reported in Table 1.

3.4. Evaluation of the pellets rheological properties

3.4.1. Crushing test

For every batch the crushing strength of 10 pellets (mean and standard deviation of the obtained results were calculated) was determined using a texture analyser (Stable Micro System mod. TA-HD*i*® Texture Analyser), operating with a 5 kg load cell. The pellet was placed in the lower flat platen, centred under the 4 mm diameter upper punch, which then moved downwards at a constant rate of 0.7 mm/s until 50% of the strain was reached. Force-time plots were recorded using the texture analyser pc software (Texture Expert Exceed).

3.4.2. Stress relaxation test

The viscoelastic properties of a solid material can be determined by a uniaxial compression device using two kinds of transient test: creep and stress relaxation. In the first test one step of stress is applied and the change in strain is measured for a certain time; in the second test a constant strain is applied and the stress is measured for a period of time. The reason that the stress relaxation test was chosen in this study was because the contact surface between the pellet and the probe remains constant for the entire test (imposed strain is constant) so consequently, the stress is always proportional to the measured force. This statement is valid only when all the pellets are very similar in shape and size.

The test was performed using a texture analyser working with a 5 kg load cell. A constant strain was applied and the force was recorded for 15 s at room temperature. Of course this time was not enough to reach the equilibrium but most of the relaxation already occurred and, at the same time, water uptake is avoided. Both punch speed and strain applied are very important parameters. The punch speed should reach the fixed strain as quickly as possible (but without causing the pellets to crack), because ideally the strain function is a one-step function. The strain should be rather small (taking into account the sensitivity of the texture analyser) in order to be in the linear viscoelastic region. Preliminary experiments showed as suitable values a 0.7 mm/s probe speed and a 5% strain. Five pellets were analysed for each batch.

In order to compare the relaxation of every batch, the reduced stress, i.e. the ratio between the stress in function of time ($\sigma(t)$) and the initial stress (σ_0), was used to build the stress relaxation plot [36]. This kind of normalization converts absolute values in relative values, thereby minimizing errors and making a direct comparison easier. For a stress relaxation test, where the strain is constant and all the pellets have an almost identical size and shape, reduced stress is the same of the reduced forces ($F(t)/F_0$). Therefore, the real stress values lose their importance. In this work a ‰ reduced stress was used.

The viscoelastic behaviour can be represented using rheological models built using springs (describing elastic properties) and dashpots (describing viscous properties) linked in series or parallel. For a viscoelastic solid, the stress relaxation behaviour can be represented by the generalized Maxwell model (or Wiechert model) with n Maxwell units (a spring and a dashpot in series) in parallel with an isolated spring [37,38].

Preliminary tests showed that the simplest model able to accurately fit (ANOVA regression) the experimental data was the generalized Maxwell model with $n = 3$, represented by the following equation:

$$\sigma(t) = \sigma_e + \sigma_1 \, e^{-\frac{t}{\tau_1}} + \sigma_2 e^{-\frac{t}{\tau_2}} + \sigma_3 e^{-\frac{t}{\tau_3}}$$

where σ_e is the equilibrium stress, σ_1, σ_2 and σ_3 are the product between the elastic modulus of every spring in the Maxwell elements and the imposed strain, t is the time and τ_1, τ_2 and τ_3 are the relaxation times. They are the ratio between the viscosity of the dashpot and the elastic modulus of the spring for each Maxwell unit (η/E).

The regression analysis was performed on the reduced stress ‰/time data of the mean curve for every batch with the software TableCurve™2D v4.0.

3.5. Tablets preparation and analysis

Tablets were prepared for the only reason to compare the results of the rheological tests performed on the single pellet with the results of the Heckel analysis that was used as a countercheck.

The four batches of pellets were compacted in a 10 station rotary tablet press (Ronchi, Cinisello Balsamo, Italy) instrumented to measure both the force and the displacement of the upper and lower punches [39]. The tablet machine was equipped with 6 mm diameter round flat-faced punches, and the rotation speed of the turret was set at 25 rpm.

Tablets were prepared (five for each batch) at 180 MPa by manually filling the prelubricated (1% w/w stearic acid in acetone and chloroform 1:1) die.

Heckel plots were obtained starting from the force/displacement compaction data.

The Heckel equation [40,41] is:

$$\ln[1/(1-D)] = KP + A$$

where D is the relative density and $(1-D)$ the porosity, P is the applied pressure, K is the slope of the straight linear portion of the plot and the reciprocal of K is the mean yield pressure (P_Y), A is the intercept and is the sum of two densification terms:

$$A = \ln[1/(1-D_0)] + B$$

where D_0 is the initial relative density and B is the densification, due to the slippage and rearrangement of primary and fragmented particles.

The relative density at point A is $D_A = 1 - e^{-A}$ and the increase of relative density due to slippage and rearrangement is $D_B = D_A - D_0$.

In order to make a clearer distinction between densification due to the movement of the original particles and that due to the brittle fracture, D_0 and subsequently D_B were modified by using a relative precompression (1.5 MPa) density D'_0 term which includes the initial rearrangement of particles [42]. So, D'_B was calculated as follows:

$$D'_B = D_A - D'_0$$

where D'_B is only representative of the densification due to fragmentation.

Correction of the displacement transducers data for machine looseness was not necessary, since the transducers position in the turrets of the rotary machine [39] enabled the automatic detection of machine deflection.

The correction of punch deformation was carried out point by point according to the following equation:

$$D = FL/ES$$

where D is the punch deformation (mm), F is the applied force (kN), L is the punch length (mm), E is the steel rigidity modulus (kN/mm^2), and S is the punch section (mm^2).

The equation is valid below the limit of steel elasticity which is by far a lot higher than the pressures used to perform the analyses.

Besides, for a more precise correction, punch length was divided in two parts: punch stem (20 mm diameter) and punch neck (6 mm diameter).

Py was calculated between 50 and 100 MPa since in this interval the linear regression parameters (R^2 and P-value) were the best for all batches. The portion of the plot after the maximum value of $\ln[1/(1-D)]$ describes the decompression phase.

The maximal relative density (D_{max}) during the compression cycle was calculated as the point of minimal distance between upper and lower punches. Relative density at the end of the compression cycle (D_{fin}) was calculated from the last point of the decompression portion of the curve.

The immediate elastic recovery (E_R) can be evaluated from the corresponding D_{max} and D_{fin} values (which are proportional to the respective strain) according to the following equation:

$$E_R = \frac{D_{max} - D_{fin}}{D_{max}} 100$$

This index slightly underestimates the immediate elastic recovery due to the fact that the plastic flow occurs even during the decompression phase (stress does not drop immediately to zero) but in any case it is extremely indicative of the elastic decompression phenomena.

Mean and standard deviation (5 replicates) of the obtained results were calculated for each batch.

The ejected tablets were tested for weight, thickness and crushing strength (Erweka TBH 30). The strain rate of the Erweka probe was 0.5 cm/s. Tablets failed in tension. The tensile strength values were calculated from the crushing strength data, according to the equation given by Fell and Newton [43]:

$$T_S = \frac{2 \cdot F_C}{\pi \cdot d_E \cdot H_E}$$

where F_C is the crushing strength, d_E is the ejected tablet diameter and H_E is the ejected tablet thickness.

4. Results and discussion

4.1. Pellets analysis

4.1.1. Microscopy

A direct comparison between the crushing strength values and the parameters obtained from the stress relaxation test is possible only if no appreciable size and shape differences exist among the pellets. In our case, pellets size was rather uniform since the same fraction (600–710 μm) was used for all the tests. The shape was evaluated by an imaging analysis (optical microscope).

Roundness and radius ratio values (Table 2) show that the pellets shape is similar to that of a sphere, these values being nearly 1. At the same time, the ANOVA test (not shown results) revealed no significant differences in shape among the four batches. SEM image of the four batches of pellets is reported in Fig. 1a–d.

Table 2
Roundness and radius ratio values for the different batches of pellets

Batch	Roundness		Radius ratio	
	Mean	Std. Dev.	Mean	Std. Dev.
A	1.093	0.021	1.135	0.087
B	1.085	0.023	1.079	0.046
C	1.093	0.024	1.071	0.041
D	1.076	0.022	1.110	0.080

4.1.2. Pellets crushing strength

The crushing strength value is given by the maximal force corresponding to the peak of the force–time plot. In the presence of plural peaks or notches, some authors adopted different approaches to assume the correspondence between a peak and the real crushing strength value. In some cases the last one was chosen [15], whereas in other cases the highest one [4] and yet in other works the first peak giving a preset drop of force was taken into account [10,19].

Tests performed in this work revealed more than one peak and two different trends (Fig. 2). When the amount of lactose in the pellets is considerable (A and B batches) then a well-defined first peak is present. However, on the contrary, when cellulose prevails in the composition of the pellet (C and D batches), only a notch can be noticed in the plot. Indeed, for these batches there is a continuous pellet deformation until the completion of the test, which is represented by the second peak (the higher one). Therefore, the second peak is not a real crushing peak but it is just the completion of the test (prefixed 50% of strain reached).

In order to interpret more clearly these different behaviours, pellets were observed under the stereomicroscope after having stopped the test immediately after the first peak or notch (Fig. 2). The images show that pellets fragment when the first type of plot is observed and deform in the second type of plot. In this last case, only some fracture lines are present. In any case, the crushing force always corresponds to the first drop of force or to the notch [9].

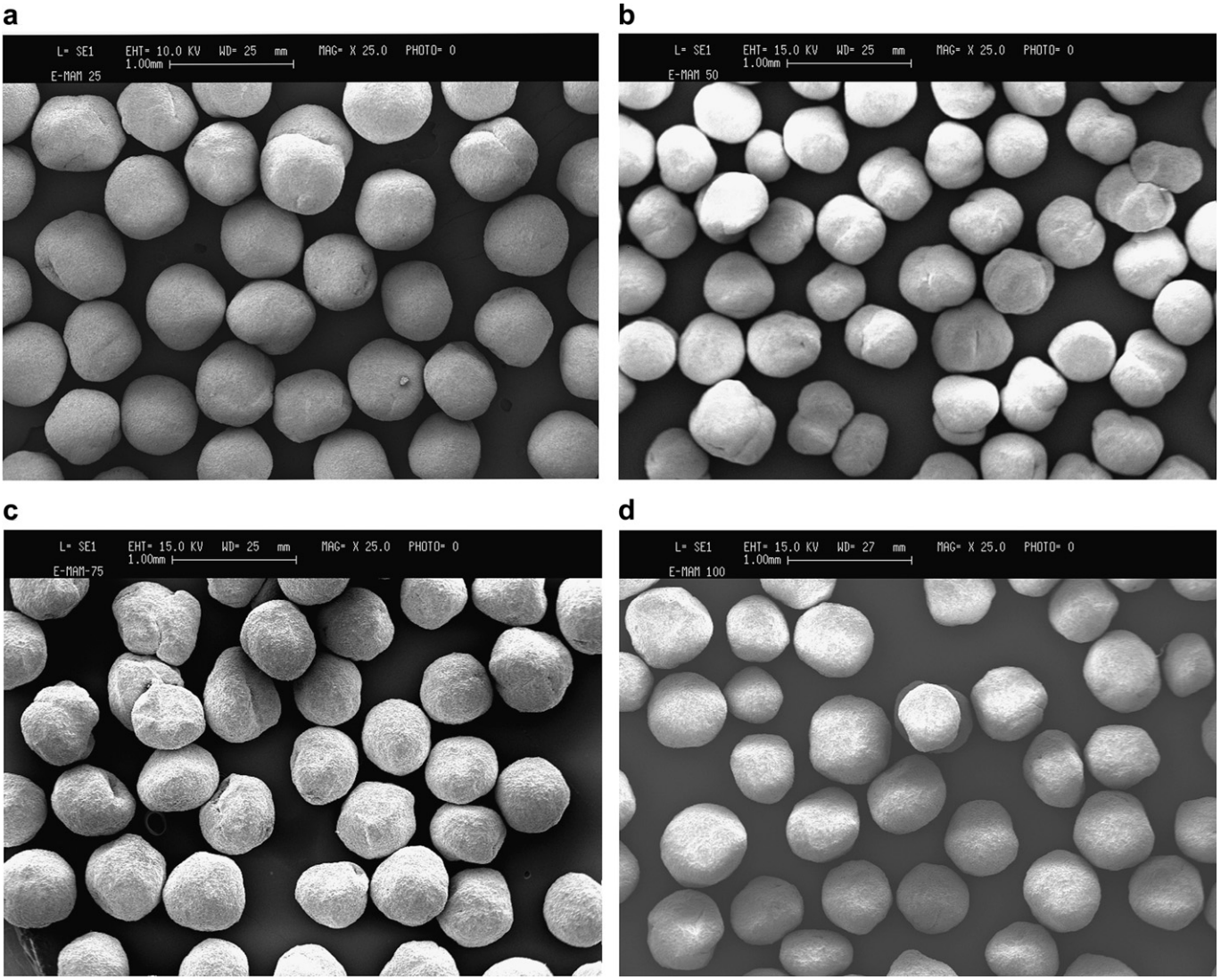

Fig. 1. (a–d) SEM images of the 600–710 μm batches of pellets.

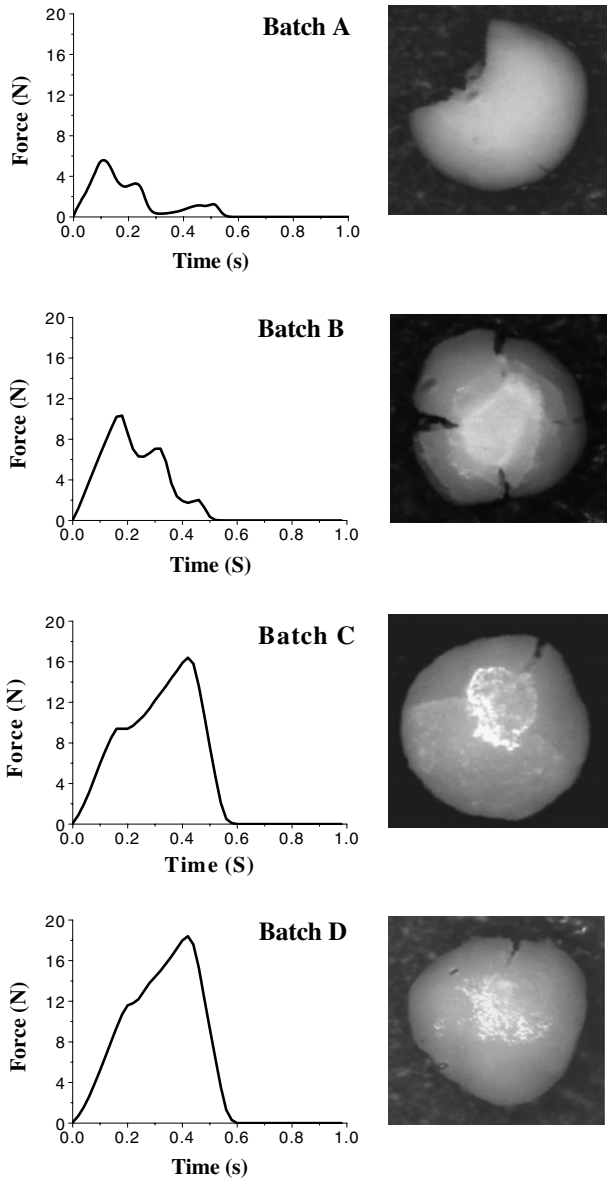

Fig. 2. Examples of crushing strength plots and the corresponding images of the crushed pellets for the four batches of pellets. Images were taken after the first peak or notch.

Fig. 3 reports the crushing strength of the pellets (first peak or notch). Sample resistance seems function of the microcrystalline cellulose content, even if for the B and C batches, containing the 50% and 75% of cellulose, respectively, the crushing strength values are similar.

4.1.3. Stress relaxation

Stress relaxation, like the creep test, allows the characterization of the macroscopic viscoelasticity of a material as the sum of every single contribution due to all the time dependent molecular rearrangements.

Every single contribution to the stress relaxation can be represented by one unit of the Maxwell model with a specific relaxation time, intended as the time necessary for the stress to relax to 1/e of its initial value when the strain is held constant.

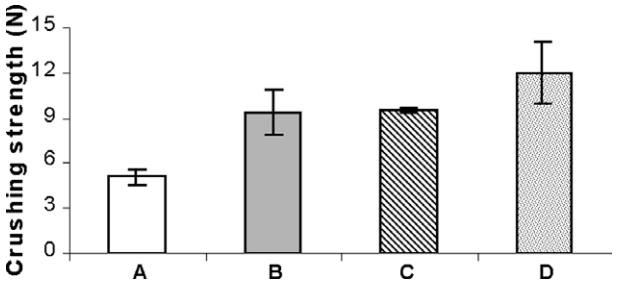

Fig. 3. Crushing strength of the four batches of pellets.

In the case of viscoelastic solids, the stress does not completely relax but settles to an equilibrium value after a sufficiently long time. Rearrangements stop when the viscous flow of the material is exhausted and no further energy can be dissipated. An elastic response persists and it is characterized by an equilibrium stress (σ_e).

Before analysing the results it is essential to verify if the test is discriminant for the different batches of pellets. Fig. 4 shows that the relaxation curves of the four batches are distinct, despite a certain variability within the batch being noted. This is inevitable, since pellets are not perfectly spherical and probably also because of the instrument sensitivity.

According to its composition, each batch shows characteristic kinetics of stress relaxation.

Characteristic parameters such as the relaxation times (τ_n) and the reduced stress at equilibrium ($\sigma_e/\sigma_0‰$) have been calculated by the regression analysis of the stress relaxation curves, using the previously described generalized Maxwell model.

The calculated but not reported relaxation times do not allow a comparison of the different batches behaviour, probably because a model with a reduced n value ($n = 3$) cannot be representative of the whole distribution of the contributions to the relaxation. On the other hand, an increase of the n number is difficult to manage on the basis of the actual computer software and hardware.

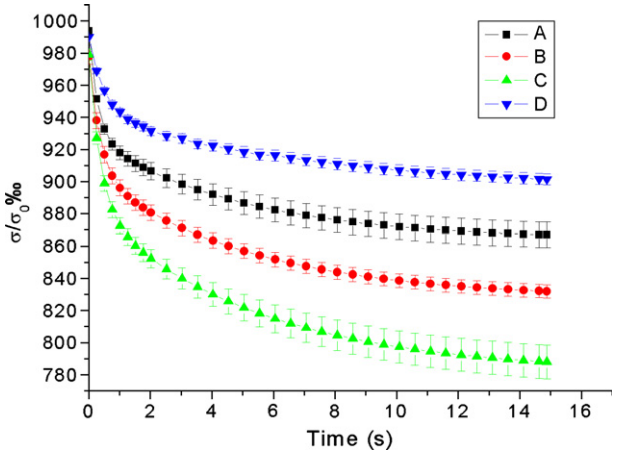

Fig. 4. Stress relaxation curves of the four batches of pellets.

Nevertheless, a comparison of the different relaxation kinetics can be performed by calculating the time necessary to reach a certain stress decay. In this study the authors chose the amount of time necessary for the stress to relax to 1/e of its initial value ($\tau_{1/e}$), which corresponds to a 63% fall of stress. This empirical parameter was chosen because it represents the relaxation time of a single Maxwell unit. This of course is a considerable approximation compared to the whole relaxation times spectrum however it could be extremely useful in distinguishing and classifying different materials.

Values of $\tau_{1/e}$ are reported in Table 3 and show that the relaxation does not vary in proportion to that of the amount of cellulose within the pellets. A specific cellulose–lactose ratio exists where the relaxation speed is maximal and the viscosity of the material is minimal. This corresponds to the 50–50 cellulose–lactose ratio (batch B). In particular, viscosity is maximal in batch B and minimal in batch A, the latter being the most viscous among the four batches. There is no evidence of any significant differences between batches C and D. Probably, above a certain amount of cellulose the relaxation time does not undergo a significant variation.

The $\sigma_e/\sigma_0‰$ modulus obtained from the regression analysis describes the residual elasticity of the material when the viscous flow is complete. Results show that the stress relaxation modulus is lower in batch C. Therefore, these pellets seem to be the less elastic ones. There is little difference in elasticity present between batches A and B. On the other hand, pure cellulose pellets (batch D) are the most elastic. It seems that a gradual decrease of lactose in the pellets composition reduces gradually the residual elasticity but below a certain lactose amount the phenomenon is inverted. So, a certain amount of lactose, however small, must be present.

Interestingly, batches having rather different residual elasticity (C–D) can present the same relaxation kinetics. This can happen since the residual elasticity is referred to the isolated spring and the relaxation time is related to the Maxwell element of the model.

4.2. Pellets compression

Tensile strength and Heckel parameters obtained from the compression of the four batches of pellets are presented in Table 4 as mean and standard deviation of five replicates.

Tensile strength values clearly indicate that mechanically resistant tablets can be obtained only from the compression of the batch A pellets that possesses elevated lactose content. Tablets from C and D batches disintegrate as they are ejected out of the die and only deformed pellets can be retrieved. Since the pellets relative humidity was very low (less than 1%), this different behaviour most probably depends on the different tendency to fragment of the four batches. Fragmenting pellets under compression should generate a wider contact surface between particles, consequently a higher number of bonds compared to the non-fragmenting pellets. The higher tensile strength of batch A tablets compared to that of the batch B tablets is related to the respective values of the pellets crushing strength. Less resistant pellets (batch A) require a lower pressure to be fragmented. So, if the same compression pressure is used fragmentation will be more relevant in those pellets that have a lower crushing strength value.

Table 3
Parameters obtained from the regression of the mean stress relaxation curves

Batch	R^2	$\tau_{1/e}$ (s)	$\sigma e/\sigma_0‰$
A	0.999	1.88 ± 0.05	853.8 ± 7.92
B	0.999	1.00 ± 0.04	835.5 ± 4.20
C	0.999	1.25 ± 0.07	788.8 ± 10.50
D	0.999	1.26 ± 0.03	901.8 ± 3.45

Table 4
Tensile strength and Heckel parameters

Batch	Tensile strength (MPa)	D'_B	Py (MPa)	E_R (%)
A	3.34 ± 0.17	0.305 ± 0.005	132.3 ± 3.13	3.3 ± 0.003
B	0.86 ± 0.07	0.189 ± 0.040	88.5 ± 4.13	4.8 ± 0.013
C	/	0.018 ± 0.010	70.4 ± 1.12	6.9 ± 0.012
D	/	0.019 ± 0.021	84.0 ± 3.80	9.9 ± 0.002

Obviously, the interparticulate bonding usually depends on plastic deformation as well, however in this case the batch A shows the greater Py value (the least ductile among the four batches), the lowest immediate elastic recovery (E_R) and the highest relaxation time τ (higher viscosity than the other three batches) that is a lower and slower plastic deformation. At the same time, the tensile strength of the batch A tablets is higher than that of batch B and tablets from the non-fragmenting C and D batches do not form whatsoever. It is clear that at the moisture conditions used by the authors, fragmentation gives the fundamental contribution to interparticulate bonds formation.

Yet, tablet porosity can also affect tablet tensile strength, however at a constant maximum stress applied, the porosity of the final tablet is a consequence of both the densification mechanism and the viscoelastic behaviour of the material. Both parameters have been studied in the present work.

These considerations are confirmed by the D'_B values obtained from the Heckel analysis. An example of the trend of the Heckel plots is shown in Fig. 4. D'_B value expresses the increment of relative density due to particle fragmentation occurring at the beginning of the compression cycle.

As the compression pressure increases, pellets can either deform or fragment. These two possibilities are well represented in the Heckel plots obtained from the four batches of pellets (Fig. 5). In the first case (batches C and D), the Heckel plot is a straight line and the D'_B values are either at zero or very close to it. This means that fragmentation phenomena are not present. In the second case (batches

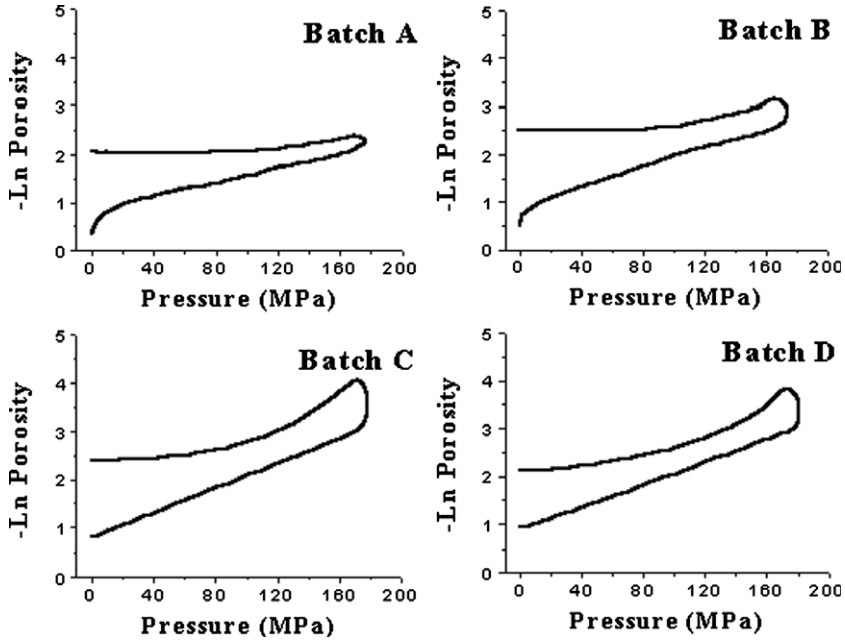

Fig. 5. Heckel plots of the four batches of pellets.

A and B), when pellets fragment, D'_B can reach considerable values.

From the D'_B values reported in Table 4 it is clear that the C and D batches do not fragment whatsoever, however batch A, containing the 75% of lactose, undergoes a remarkable fragmentation. These results are in agreement with the force/time plots of the granules.

The Py value expresses the aptitude of a material to deformation during the compression cycle, without discriminating between plastic and elastic deformation. Values presented in Table 4 show that B, C and D batches deform better than batch A. Yet, only entire pellets deform in C and D batches, while for B and particularly A batches, a solid block deforms, previously generated by the pellets fragmentation.

Before the beginning of the decompression phase, the typical trend of the plot obtained in a rotary tablet machine is visible. It is related to the dwell time and is even more remarkable in ductile materials [37].

E_R quantifies the immediate elastic recovery occurring during the decompression step. E_R value increases proportionally to the amount of microcrystalline cellulose in the pellets. So, under the relative humidity conditions used, cellulose seems to increase the elasticity of the material. Nevertheless, also in this case, one should consider that for the compression of A and B batches the elastic recovery is related to a solid block (the final tablet) but in the case of the compression of C and D batches the elastic recovery depends on the properties of the single pellets.

Interestingly, batches A and D, which are the most different in composition, show similar porosity values at the end of the compression cycle. This is a simple coincidence as shown by the Py and E_R values.

Batch D is more ductile but also more elastic. So, cellulose, at very low moisture content, makes material more ductile but also more elastic. This is also in agreement with the corresponding residual stress relaxation moduli.

5. Conclusion

Granule crushing strength was extremely useful in predicting the fragmentation aptitude of the pellets. It was pointed out that the presence of an elevated amount of lactose induced fragmentation in the pellets (A and B batches) and, at the same time, decreased the pellet crushing strength. The same consideration can be drawn from the D'_B values of the Heckel analysis and the tensile strength of the ejected tablets.

The stress relaxation test performed on the four batches of pellets allowed a direct comparison of their deforming behaviour. The relaxation time and the relaxation modulus are not proportional to the pellets composition but they are minimal at a particular lactose–cellulose ratio.

Since the stress relaxation test was carried out on the native pellets, a direct comparison between these and the deformation parameters from the Heckel analysis (Py and E_R) was possible only for the non-fragmenting C and D batches. In fact, it was only in these two cases that the yield pressure depended on the rheological properties of the single pellets.

When this comparison was possible, consistency was found between the stress relaxation and the Heckel parameters. In fact, batch C showed from the Heckel analysis a lower than batch D index of elastic recovery (E_R). Yet, batch C showed a lower index of residual elasticity (σ_e/σ_0‰) in the single pellet than the batch D from the stress relaxation test. At the same time, an identical relaxation time ($\tau_{1/e}$) for the C and D batches corresponded to similar Py values. These Py values are not exactly identical

like the $\tau_{1/e}$ values but it must be taken into account that Py is the expression of both elastic and plastic deformation.

In conclusion, tests performed on the single pellets can be extremely helpful in predicting their deformation and fragmentation aptitude under compression.

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